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MESSAGES

Now more than ever, international indexing and online publication ensures that locally produced research studies are globally cited. This year, the Journal of the Philippine Medical Association will start publishing bi-annual issues of quality original articles in compliance with the minimum requirements for indexing with the Western Pacific Region Index Medicus. The Western Pacific Region Index Medicus (WPRIM) is a project of the WHO Western Pacific Regional Office in collaboration with several institutions in its Member States. This is the Region's contribution to the Global Health Library (GHL) initiative which aims to extend to all the benefits of the knowledge that is essential to the fullest attainment of health. WPRIM will be deployed and hosted, along with the index medici of other WHO Regions, at the Global Index Medicus portal under the GHL platform, where searches can be conducted individually or simultaneously through a federated search engine.

MARIA MINERVA P. CALIMAG, M.D.
President

This first issue of the Philippine Medical Association's Journal would not have been possible with out the unconditional support given by the editorial board under the Chairmanship of Dr. Arnel Asino. Keeping in mind that a medical journal is a forum for the exchange of ideas and valuable information, it is with pride that this journal is presented to all members of the PMA.

We wish to acknowledge all physicians who have participated by submitting their research papers and case presentations to the PMA. It is to them that we attribute the success of this journal. We fully appreciate their having contributed their work.

A second issue of the PMA Journal will be forthcoming by May, 2016. We encourage all other physicians to have their research papers and case presentations published. The PMA Journal follows the Research Ethics of the Declaration of Helsinski, and we enjoin all participating doctors to do so.

We dedicate this journal to all members of the Philippine Medical Association!
Our sincerest gratitude to all!

MARIANNE L. ORDOÑEZ-DOBLES, M.D.
Secretary General
Chair, Committee on Publications

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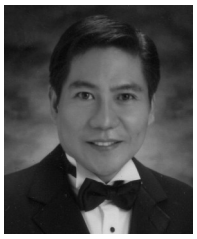

Greetings!

The world is a pocket of mystery where things evolve in a very complicated dimension finding solutions to understand unresolved ideas and events. I agree with John F. Kennedy when he said that, "Things do not happen. Things are made to happen." Probably the reason why systematic scientific research are encouraged not to only to harness our curiosity to discover new concepts and modalities, but also to offer new insights, intelligent opinion and strategies. An outcome-based contribution to the human knowledge which may be used as a tool to improve the healthcare system.

Embarking in a research will uncover hidden evidence and encourage investigators to make use of their critical thinking particularly in building theories and conclusion to validate a certain fact in question. It is true that research leads to progress and reduce the rate of errors while improving treatment. According to Thomas Edison, "Our greatest weakness lies in giving up. The most certain way to succeed is always to try just one more time."

I strongly believe that a well-driven researcher always dwell with his work in a formulated thought which reminds me of what Confucius once said that, "The more man meditates upon good thoughts, the better will be his world and the world at large."

God bless us all!

Arnel M. Asino, MD, FPBA
Chair, Sub-Committee on PMA Journal

Journal of the

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Instruction for Authors

General Information

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In the conduct and reporting of research, the JPMA adheres to the ethical considerations set forth by the ICMJE with respect to authorship and and contributorship, editorship, peer review, conflicts of interest, right to privacy and confidentiality of patients, study participants as well as authors and reviewers; and, the protection of human subjects and animals in research.

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Manuscript Preparation

(This section is primarily based on the previous and existing JPMA Instructions to Contributors but with some modifications based on the ICMJE recommendations. A completely revised version based on the guidelines of the ICMJE will be published in the next issue.

Accompanied by a cover letter from the principal author, the manuscripts, figures, tables, photographs, and references should be submitted in duplicate (an original and a copy) and typed double-space (including legends and footnotes) on one side of a white bond paper, 8.5 and 11 inches properly numbered consecutively on the upper right-hand corner of each page beginning with the title page. Illustrations must also be in duplicates. An electronic copy of the articles in a CD must be submitted.

The first page should contain the title, subtitle (if any, all authorsí full names and highest earned academic degrees, and hospital or institutional affiliations. It must also include disclaimer, if any.

For the original article, an abstract must be type at the beginning of each paper after the title. It must contain, in structured format, the following: background or context of the study, objectives, methods, results and conclusions of the study, as appropriate. It must not be more than 300 words. No footnotes/references must be in the abstract. For other articles, an unstructured abstract may be preferred. Below the abstractr, identify three to ten keywords or short phrases that will assist in indexers in cross-indexing the article.

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Generic names of drugs are preferred. Trade names may be given only once at the end of the paper or in the acknowledgement and should follow the generic name in parenthesis.

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Delayed Emergence After Hepatic Cyst Aspiration and Sclerosis Under Intravenous Sedation

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Prolonged recovery from anesthesia is a cause of concern among anesthesiologists. Time to emerge from anesthesia is multifactorial and associated with patient factors, anesthetic administered and the type and duration of procedure or surgery. In this case, dexmedetomidine drip with local infiltration of lidocaine was used to afford a cooperative sedation for hepatic cyst aspiration and sclerosis with ethanol. On handover to the post anesthesia care unit, the patient was found to be asleep and barely responsive to any stimulus. Analysis of factors that could have caused delayed emergence in this case pointed to ethanol intoxication as the most probable cause. Continuous attention in monitoring and support of the airway, breathing and circulation until the cause is ascertained remains the primary management. The importance of vigilance and continuous monitoring is highlighted.

Keywords: delayed emergence, aspiration and sclerosis of hepatic cyst, dexmedetomidine, ethanol

INTRODUCTION

In otherwise healthy patients who have undergone a relatively short procedure, the incidence of delayed awakening is practically zero.[1] In this case, we have a patient who underwent hepatic cyst aspiration and ethanol sclerosis with ultrasound guidance under conscious sedation. The delay in return to full consciousness was disconcerting.

The aim of this paper is to make healthcare workers aware that even minimally invasive procedures under monitored anesthesia care can still have potentially life threatening complications. The factors that may have contributed to the delay to full awareness are presented. In particular, acute ethanol intoxication was highly suspected.

Case Presentation

A.O. is an 82 y/o female who was admitted due to complaints of one year history of gradual abdominal enlargement, early satiety and weight loss. She was a known cirrhotic with Child Pugh A. There was no history of change in sensorium, disorientation, jaundice or hematemesis. On physical examination, she was awake, alert, conversant, oriented to three spheres, normosthenic with normal cardiovascular, respiratory, neurologic findings, globular abdomen without asterexis or any other signs of cirrhosis. CT scan of the abdomen showed hepatic cysts with hepatomegaly and absence of splenomegaly and ascites. She was scheduled for percutaneous aspiration of hepatic cyst with possible ethanol injection. Pre-operatively, laboratory exams showed normal hemoglobin (118g/L), thrombocytopenia (95 x 10^9/L), normal creatinine (0.62mg/dL), normal bleeding time (3 minutes), normal prothrombin time (15.9 seconds), normal INR (1.17), 75% activity, and elevated alanine aminotransferase (275 U/L). She was given 3 doses of vitamin K 10mg/IV and 2 units of platelet concentrate 1 hour prior to the procedure. Cardiovascular clearance was granted after an unremarkable 2D echo result.

Upon arrival at operating room 20 minutes before the procedure, dexmedetomidine drip at 0.5mcg/kg/hour was started, and nalbuphine 10mg/IV was given. Intraoperatively, blood pressure was maintained at 110-120/70-80 with a heart rate of 60's. She had a Richmond agitation sedation score of -1 to -2 and was able to follow command to shift body sideways. Aspiration of 1800cc straw colored fluid from two cysts was done under ultrasound guidance. After confirming that no communication existed between the cysts and the biliary tree through fluoroscopy, a total volume of 550cc 99.9% ethanol was injected into and remained in the two cysts for 15 minutes then subsequently aspirated. The procedure lasted for 1 hour and 15 minutes. Dexmedetomidine drip was discontinued at the end of the procedure.

She was transferred to the post anesthesia care unit (PACU) responsive but unable to maintain wakefulness. Vital signs at the time of arrival at the PACU was BP 100/60 mmHg, heart rate 57 bpm, RR 19 cpm, temperature 35.9ºC, 100% oxygen saturation with oxygen supplement of 4 LPM via nasal cannula. She was kept normothermic (36.4-36.8ºC). Oxygen supplementation was continued. One hour after PACU admission, she was noted to be flushed, bradycardic (HR 50's) and hypotensive (BP 80/50) for 30 minutes. Blood pressure and heart rate normalized after 2 doses of atropine 0.5mg/IV and ephedrine 10mg/IV were given. On the 2nd hour of the PACU stay, she was noted to be unresponsive. Glasgow coma scale score was 8 (E1V2M5). Pupils were isocoric at 3-4mm and equally reactive to light. Respiratory rate was at 18-19/minute and respiratory depth seemed adequate. Oxygen saturation ranged from 97 -100%. A capnograph was connected and nasal cannula was shifted to an oxygen face mask to monitor end tidal carbon dioxide level ($ETCO_2$). $ETCO_2$ ranged from 35- 40 mm Hg.

During the 5th hour of the PACU stay, a total of 800mcg naloxone boluses were given but she remained unconscious. Capillary blood glucose was 179 mg/dL. A foley catheter was inserted and urine output was monitored. Repeat CBC (Hgb 148, Hct 0.45, platelets 128 x 10^9/L), serum sodium (142), potassium (3.6), chloride (110) and arterial blood gas showed wide anion gap metabolic acidosis with good oxygenation (pH 7.28, pCO_2 29.4, HCO_3 13.5). Sodium bicarbonate 100 meqs divided into 2 doses were given. After one hour, she regained consciousness.

She was observed for 6 more hours with episodes forof drowsiness and was eventually discharged to the room awake with stable vital signs. While in the room, she had recurring episodes of drowsiness with disorientation for 24 more hours after ethanol injection. She remained anicteric with stable vital signs. Intravenous branched chain amino acid, rifaximin and lactulose were given since concurrent hepatic encephalopathy cannot be entirely ruled out. She was eventually discharged oriented, awake, without episodes of bleeding at the post-op site, 2 days after the procedure.

Discussion

Delayed Emergence

Delayed emergence from anesthesia is often multifactorial. Factors that delay emergence from anesthesia can be grouped into four, namely: patient factor, pharmacologic, surgical, and metabolic factors. [1,2]

Patient Factor

In our case, the patient is a geriatric who has liver cirrhosis with Child Pugh A score without signs of portal hypertension. She has no other comorbidity other than hypertension. Pre-operative history taking, physical examination, laboratory exams, chest xray and 2d-echo showed no evidence of hepatic encephalopathy, pleural effusions, hepatopulmonary syndrome, hepatopulmonary hypertension, hepatorenal syndrome, cirrhotic cardiomyopathy, and coagulation disorders which are associated with chronic liver disease.[3]

Geriatric patients have an exaggerated response to CNS active drugs due to an underlying age related decline in CNS function as well as increased pharmacodynamics sensitivity towards benzodiazepines, general anesthetics and opioids.[4] Old age is also associated with changes in drug pharmacokinetic due to decreased hepatic blood flow and liver mass with reduced hepatic microsomal enzyme function.[5]

Postoperative delirium and cognitive dysfunction (POCD) are topics of special importance in the geriatric surgical population. It is associated with longer hospital stays and increased mortality. Benzodiazepines can precipitate delirium in this population while dexmedetomidine can prevent it.[6,7]

Liver disease affects drug pharmacokinetics as a result of alterations in protein binding, reduced serum albumin, altered volume of distribution and reduced metabolism secondary to abnormal hepatocyte dysfunction.[8,9]

Pharmacologic

Dexmedetomidine was introduced two decades ago as a sedative hypnotic in intubated ICU patients. Its safety and efficacy in sedation of non-intubated patients during surgical and diagnostic procedures has since been studied prospectively.[10] Uses now include sedation for: 1) patients undergoing small or minimally invasive procedures where tracheal intubation is not needed 2) procedures requiring sudden awakening from sedation such as for cooperative clinical examination. [11] When used in therapeutic doses, it is very effective in surgeries that require awake and communicative patients.[12,13] It is metabolized in the liver into inactive metabolites with a mean elimination half-life of 2-2.5 hours with an extraction ratio of 0.71. [14] Use of dexmedetomidine is not contraindicated in hepatic disease but dose adjustments are indicated. In general, the effect of hepatic disease in drugs with high extraction ratio, like dexmedetomidine is predictably altered. Clearance is primarily dependent on hepatic blood flow which is in turn dependent on systemic blood flow. [8,15,16]

Nalbuphine is an agonist-antagonist opioid that binds to μ-receptors, as well as to κ- and δ-receptors. It is a potent analgesic with low side effect profile. It produces few overt behavioral or autonomic affects even in higher doses. [16] Plasma elimination half-life is 5 hours.[8]

Our patient remained unconscious well over the plasma half-life of both nalbuphine and dexmedetomidine. The age and liver pathology of the patient were taken into consideration but only sedation caused by nalbuphine could be reversed. Naloxone is an opioid antagonist that is used to treat opioid overdose including nalbuphine. [17,18,19,20] It reverses all signs of opioid toxicity. It was given at the 5th hour of the PACU stay.

Classic symptoms of opioid toxicity include apnea, stupor and miosis. Although not all three are always present, respiratory depression is considered the sine qua non of opioid intoxication.[18,19] The patient is stuporous but had normal-sized pupils and adequate respiratory rate. These observations made nalbuphine toxicity unlikely.

Surgical

The procedure entails the insertion of a catheter into the cyst with complete emptying of the contents. A volume of ethanol usually equivalent to 25% of the drained fluid is instilled. Ethanol is often used to destroy the secreting epithelial layer of the cyst wall with marked inflammatory reaction.[22] Patients are rolled from side to side to ensure adequate contact of the ethanol to the entire cyst wall and ethanol is then aspirated out.

Our patient underwent this minimally invasive procedure that lasted for 1.25 hours under sedation with dexmedetomidine infusion and one dose of nalbuphine 1.17mcg/kg. Intra-operative vital signs were stable with no episodes of desaturation with oxygen supplementation via nasal cannula.

Metabolic

Some of the metabolic factors causing delayed emergence from anesthesia include the following: hypoglycemia, hyperglycemia (DKA, hyperosmolar nonketotic coma), electrolyte imbalance (hypo or hypernatremia), hypothermia, hypoxemia, hypothyroidism, hepatic or renal failure, and acidosis.

Capillary blood glucose monitoring did not show hypoglycemia or elevated blood glucose levels enough to cause DKA or hyperosmolar nonketotic coma. Repeat electrolytes showed normal serum sodium and potassium. She was kept normothermic. There was no episode of desaturation. Urine output was adequate. Acute on chronic liver failure (ACLF) leading to hepatic encephalopathy could have been a consideration.

Pre-operatively, she was fully awake and had no changes in sensorium. Physical exam was essentially normal except for enlarged abdomen with palpable slightly tender epigastric mass extending to RUQ._Laboratory exams showed evidence of liver dysfunction. According to the Eastern criteria for ACLF (proposed by either Asia–Pacific Association for the Study of the Liver and Chinese Medical Association), liver failure alone is focused on, and the lower cutoff levels of INR (i.e., >1.5) and serum bilirubin (i.e., 5 mg/dL defined by APASL or 10 mg/dL defined by CMA) are taken to define liver failure.[23] In this patient, these laboratory exams as well as blood ammonia levels were not taken during the comatose state. Hepatic encephalopathy could not have been totally ruled out. The investigation was focused on finding possible precipitating factor and other etiologies instead.

Arterial blood gas showed wide anion gap metabolic acidosis with good oxygenation. Among the causes of wide anion gap metabolic acidosis, ethanol intoxication was the most probable. A blood ethanol concentration would have confirmed the diagnosis; however, the test was unavailable.

Ethanol Intoxication

Hepatic cysts are usually asymptomatic and are detected incidentally by imaging examinations. Symptoms usually arise due to the compression effects of large hepatic cysts on surrounding structures including pain, nausea, vomiting, early satiety and obstructive jaundice.[23] Aspiration-sclerotherapy is an effective means of achieving liver volume reduction and relief of symptoms.[24,25,26,27] It is easy to perform, can be performed on an outpatient basis and leads to few complications. [28]

Ethanol destroys the lining epithelium of the cyst and leads to fibrosis and impedance production of fluid. [29] As a treatment agent, ethanol combines the benefits of being widely available, inexpensive, efficacious, and relatively easy to administer.[30] Complications commonly reported include mild pain, transient increase in temperature, nausea and vomiting. [28] Only one incident of ethanol induced coma after ethanol injection into a hepatic cyst was reported by Wernet in 2008.

This may be secondary to ethanol systemic absorption or unintentional intravascular injection.[30] Wernet et al [31] proposed that ethanol can be directly

absorbed through the cyst wall formed by an epithelium which resembles biliary epithelium and a stroma made of thin layer of connective tissue. The high volume (550cc) of ethanol used could have contributed to the volume absorbed even if contact time with the cysts wall only lasted for 15 minutes each.

Van Sonnenberg et al (1994)[32], reported a maximal ethanol blood level of 1.02g/L 1 hour after injection. Blood alcohol concentration needed to produce intoxication varies due to different levels of tolerance to it. CNS depression is produced by binding the GABA receptor and by acting as an antagonist of the NMDA receptor.

The patient is a geriatric with liver dysfunction and no history of alcoholic beverage drinking. Ninety-five percent of ethanol is metabolized in the liver. Impaired metabolism and minimal tolerance to alcohol may have produced the comatose state.

Ideally, a blood ethanol concentration level and blood ammonia levels can be taken to differentiate between acute ethanol intoxication and hepatic coma; however, blood ethanol level determination was not available in the hospital. We believed our geriatric patient initially had ethanol intoxication over hepatic encephalopathy since she remained anicteric with Child Pugh A score with no signs of coagulopathy. Serum electrolytes and blood glucose were taken to rule out any other underlying cause. When she then had episodes of disorientation back in her room, concurrent hepatic encephalopathy could not be ruled out. Measures (rifaximin, lactulose) to lower blood ammonia level were instituted.

Treatment of ethanol intoxication is primarily supportive. Most feared complication of ethanol intoxication includes hypoglycemia and respiratory depression.[33] Patients' respiration and ability to maintain the airway should be closely monitored. Intubation and mechanical ventilation should be done as indicated. Hypoglycemia occurs secondary to ethanol's inhibition of gluconeogenesis. Blood glucose monitoring should be done. The patient in this case was breathing adequately with no signs of respiratory depression. Capillary blood glucose levels ranged from 160-179.

In addition to the two complications, serum electrolyte determination was also done because other metabolic derangements such as hypokalemia, hypomagnesemia, hypocalcemia and hypophosphatemia may be present in alcohol intoxication.[26] Acetaldehyde acetate, a metabolite of ethanol, may also produce hypotension by inducing peripheral vasodilatation. Intermittent hemodialysis is the most efficient way of rapidly lowering serum alcohol levels.[34]

Wide anion gap metabolic acidosis in ethanol intoxication can occur from lactic acidosis or alcoholic ketoacidosis. The management of metabolic acidosis is by treating the underlying cause. Alcoholic ketoacidosis on the other hand, occurs in the background of chronic alcoholic abuse with binge drinking and starvation. Treatment is giving dextrose and saline for hydration. Our patient was not starved and she was hooked to a dextrose containing fluid from the preoperative period making alcoholic ketoacidosis unlikely.

Conclusion

Aspiration of hepatic cyst and sclerosis is minimally invasive requiring a short procedural time, virtually no blood loss and no incision. Monitored anesthesia care with sedation using dexmedetomidine was used to keep the patient comfortable and cooperative without the propensity for respiratory depression; however, she became unarousable in the PACU. Vigilance and continuous monitoring of patients are essential roles of anesthesia providers even in seemingly simple cases. In this case, the interplay of the patient's age, hepatic dysfunction, drugs, drug interaction and ethanol use were contributory to the adverse event. Continuous, meticulous, and vigilant monitoring together with supportive care is again emphasized for a good outcome.

Ethical Considerations

The authors declare no conflict of interest. A written informed consent was obtained from the patient prior to writing the draft of this case report. (consent forms attached)

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Can Video Laryngoscopy Be considered As An Alternative Airway Management Strategy In Obese Patient For Thyroid Surgery With A History Of Failed Fiberoptic Intubation?

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Abstract

Expertise in managing the airway is the prime clinical skill that defines anesthesiologists. A 45 year old female, 110 kg with a BMI of 45, diagnosed with multinodular non-toxic goiter consults an anesthesiologist if she could be successfully intubated. Her elective thyroidectomy was cancelled twice because of difficult laryngoscopy and failure of endotracheal intubation despite the use of awake flexible fiberoptic laryngoscopy. Fiberoptic intubation of the spontaneously breathing patient is the current gold standard and technique of choice for the elective management of an anticipated difficult intubation. What should be done if the gold standard fails? According to the failed airway management algorithm, cricothyrotomy is the most rapid and accepted means of gaining access to the airways in a "cannot intubate, cannot oxygenate situation" [1][2]. How a surgical airway was circumvented will be discussed in this case report.

Keywords: Anticipated Difficult Airway, Management of Difficult Airway, Obese airway management, Anterior neck mass airway management

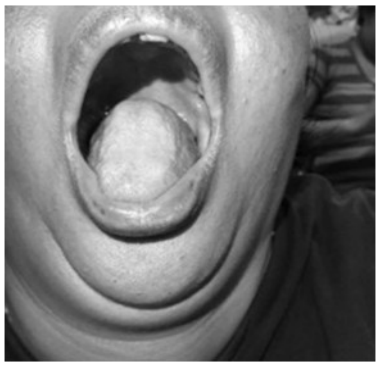
INTRODUCTION

Expertise in managing the airway is the prime clinical skill that defines anesthesiologists. An obese patient with a huge thyroid mass presenting with a history of two cancelled elective thyroidectomies in previous institutions consulted if she could be intubated without having to undergo surgical airway. Further history noted that flexible fiberoptic intubation was done in the second institution but there was difficulty in inserting the tube to the larynx due to the extreme deviation of the trachea.

Fiberoptic intubation of the spontaneously breathing patient is the current gold standard and technique of choice for the management of an anticipated difficult intubation. What should be done if the gold standard has failed? According to the airway management algorithm, the next step would be a surgical airway but it is not without problems especially among obese patients with huge goiters and unidentifiable landmarks.

Case Summary

Patient M.B is a 45 year old female with a weight of 110 kg, and a BMI of 47.6 kg/m^2. She is hypertensive maintained with Losartan 100 mg once a day and metoprolol 50 mg twice a day. She has no other disabilities, with good functional capacity and works as a teacher. Other Physical Exam findings were essentially normal. Airway assessment showed macroglossia, mallampati grade 4, small mouth opening, adequate length of mandible, short thyromental distance, submental fat pads, short thick neck with a palpable anterior neck mass approximately 10-12 cm and limited neck extension.

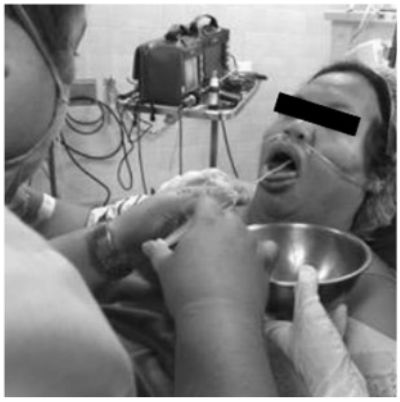


Four years prior to admission, she underwent open cholecystectomy. She was told that she was difficult to intubate and that her thyroid gland was enlarged. She had no assoicated symptoms until six months prior to admission when she started to have palpitations and heat intolerance, leading to a consult. On neck ultrasound, an enlarged right thyroid gland with diffuse parenchymal nodules were seen. CT scan also revealed the same finding and a left deviated trachea. Eight weeks prior to admission, she was admitted to undergo elective thyroidectomy at the 1st institution. On induction, after 5 attempts at intubation, they were not only unsuccessful but her right front tooth was fractured. Conventional laryngoscopy was not able to view her glottic opening thus surgery was cancelled. She was advised to transfer to another hospital with an available flexible fiberoptic intubating scope because it was not available at the initial institution. She was admitted at the 2nd institution where flexible fiberoptic scope was available however intubation was still not successful due to "softness" of the scope and the difficulty of advancing the tube through the vocal cords. The procedure was again cancelled. Distressed, she decided to consult another anesthesiologist. Consequently, she was admitted, for a third attempt to have her elective total thyroidectomy.

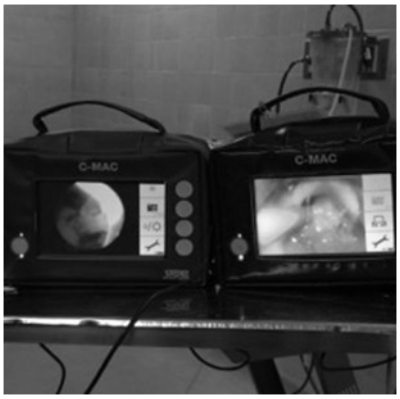
Upon admission at our institution, a thorough history and physical examination was done. CT scan result in the 2nd institution was studied with a radiologist revealing a narrowing at the level of the trachea. Further examination showed a 1 cm outer diameter endotracheal tube would fit this constriction. Due to the anticipated difficulty in intubation, she was appraised with the possibility of a surgical airway especially if a 'can't intubate, can't oxygenate' situation would ensue. She insisted against a surgical airway because of her profession. After a long explanation, she later consented reluctantly. An airway expert was called in to assist in the difficult airway management and the difficult airway cart was brought to the Operating Room. Preoperatively, she was given Pantoprazole 40mgIV and her due Metoprolol 50mg/tab as pre-op medications.

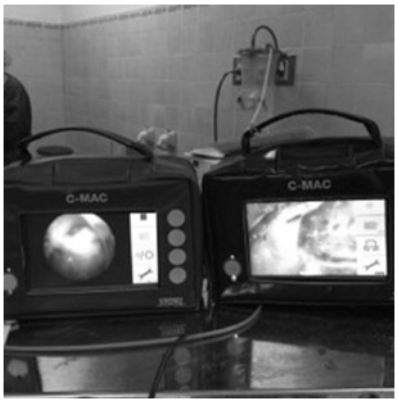
Upon arrival at the operating room, she was wide awake and had the following vital signs:

BP 140/80, HR 88, RR 18, SpO_2 97%. She was hooked to oxygen per nasal cannula and was placed on a semi-recumbent position. Lidocaine 2% using atomizer was sprayed liberally over the tongue and all around the laryngotracheal mucosa. With the patient awake,x` a CMAC blade 4 was inserted for a quick look, however, a cormack lehane 4 was the only view seen on the monitor. The airway team decided to use the Bonfils™. This time, CMAC D-blade was inserted gently, and a size 7 endotracheal tube preloaded Bonfil™ was inserted laterally into the mouth provided with a jaw thrust manuever. A better view of the glottic opening was seen on the monitor. The Bonfils™ was advanced into the glottic aperture but the tracheal tube could not be inserted into the trachea despite a good view of the vocal cords. She was reactively biting and became uncooperative. Since there was a good view with the bonfils™, she was given a slow bolus of 100 mg Propofol until she was sedated with spontaneous ventilation.



Oxygenation was continued this time with a facemask at 6 lpm. She was then given another 100 mg propofol slowly. With two hands trying to keep a tight fit and another anesthesiologist bagging, ventilation was possible. Still maintaining spontaneous ventilation, sevoflurane at 8% was administered. A nasal trumpet was inserted and then connected to the breathing circuit. On the second attempt, a gum elastic bougie was preloaded on the D-blade's suction port. Once the D-blade was in position and the glottis is in full view, the bougie was pushed towards the trachea. The endotracheal tube size 7 was then railroaded successfully through the trachea. Succinylcholine 150 mg/IV was given. The tube was secured at level 20. This was further verified with a positive $ETCO_2$ (30 mm Hg). A five-point auscultation was done to assure equal breath sounds bilaterally.





Intraoperatively, the patient was stable all through out with the following vital signs: BP 100-110/80-70, HR 80s, SpO_2 100, $ETCO_2$ 30-38. She was given diclofenac 75mg/IV and Tramadol 50 mg/IV on closing and reversal of the neuromuscular blocker was done using neostigmine 0.5 mg and atropine 0.5 mg intravenously. She was fully awake with spontaneous eye opening. After extubation, no difficulty of breathing, hoarseness or cardiopulmonary distress noted. Prior to removing the endotracheal tube, a ventilating tube exchanger was inserted to serve as a guide for possible reintuabtion. However, the patient did not tolerate the device so it was eventually removed. Post-operatively, patient was comfortable in the semi-recumbent position with minimal pain and was discharged stable, improved and thankful.

Discussion

Airway evaluation is one important aspect of pre-operative assessment especially on how to approach airway management. For a patient requiring tracheal intubation, an airway evaluation is performed primarily to help decide if intubation can be safely done after the induction of general anesthesia or with the patient awake[3].

Many factors can predict a difficult airway. The following variables were found in this patient: A thyromental distance less than 6 cm[4], fractured front tooth, inability to move the lower teeth in front of the upper teeth, inability to extend and flex the neck more than 90º, mallampati 4, neck circumference of more than 47 cm[5], short neck with limited extension [4] and the history of two failed endotracheal intubations. This patient is undoubtedly an anticipated difficult airway.[4.5.6]

The fundamental goal of airway management is ensuring alveolar oxygen delivery. Achieving this requires both a patent airway and a mechanism for delivering oxygen to the alveoli. Finding out if facemask ventilation can maintain and keep the patient's airways patent is valuable [8].

Obesity per se may not indicate a difficult airway, but anatomic changes associated with this condition may contribute to challenges in maintaining airway patency. For instance, neck circumference has been identified as the single leading predictor of problematic intubation in morbidly obese patients [9]. Genta et. al. (2014) revealed that upper airway collapsibility is associated with obesity (BMI, neck and abdominal circumferences) and hyoid position related to tongue length, volume, and pharyngeal length. A high BMI may not necessary predict a difficult airway, but a BMI more than 26 kg/m^2 is an independent predictor of difficult facemask ventilation. [7] It is also a predictor of extraglottic airway insertion failure[10]. Landmark identification can be hard in doing a cricothyrotomy or standard tracheostomy with a thick neck due to the failure of the cannula to reach the trachea[11]. Physiologic factors such as rapid oxygen desaturation and increased risk of aspiration, must be considered. Therefore, careful airway evaluation is warranted in the morbidly obese patient.

Another factor that may have contributed to the difficulty of airway management is the presence of a huge neck mass. Thyroid swelling has been considered a risk factor for difficult direct laryngoscopy, intubation and respiratory complications. The incidence of difficult endotracheal intubation defined as inadequate exposure of the glottis by direct laryngoscopy has been shown as 5.3% and 8.5% by Bouaggad A. et. al. (2006) to as high as 10%, Rios et al (2007) and 11.1% by Amathieu R et al (2008). Sedation may precipitate complete airway closure and make mask ventilation and tracheal intubation almost impossible. The use of muscle relaxants may also cause collapse of the airway because of pressure of the huge neck mass.

In formulating the airway strategies, we need to know what was done in the two institutions and why their airway management may have failed.

In the first institution, intubation employed conventional rigid laryngoscopy. There was difficulty viewing the glottic opening because in conventional laryngoscopy, the upper airway anatomy needs to be distorted in order to bring the glottis in a straight line. The thyroid mass and the obese airway may make this necessary distortion impossible. Furthermore, anesthesiologist looks through a "keyhole" while keeping this line of sight straight. Delivering the endotracheal tube to the glottic opening may even make this "keyhole" view narrower. Thus, she was advised to transfer to an institution with a flexible fiberoptic scope for intubation.

Awake flexible fiberoptic intubation is the gold standard for management of anticipated difficult tracheal intubation. This does not require an unobstructed straight view from the upper incisors to the larynx. Anatomic abnormalities such as a limited mouth opening, a huge neck mass and redundant pharyngeal tissue would be better managed with a flexible fiberoptic scope. In the 2nd institution, they did several attempts, both nasal and oral. They were able to see the glottic opening but could not advance the tube pass the glottic aperture. A surgical airway was then suggested to the patient but she refused.

With these in mind, the team formulated different plans on how to intubate a patient with a previous history of a failed flexible fiberoptic intubation.

Plan A

Considering the patient's history, an awake intubation with combined videolaryngoscope aided by the bonfils™ was contemplated.

Awake airway management remains a mainstay of the ASA's difficult airway algorithm. An awake approach can potentially confer a safety benefit by having the patient maintain airway patency, gas exchange, and protection of the airway against aspiration of gastric contents or blood during the intubation process [3]. It also provides the assurance that the patient would have no interruption in alveolar oxygen delivery. Nevertheless this needs cooperation and good communication between the physician and the patient[12].

Video laryngoscopy provides an electronically projected image on a monitor from a video chip set at the distal end of a conventional-like laryngoscope blade, but with a wider angle of view (60°). The operator therefore "sees" at a position behind the tongue, and displacement as with direct laryngoscopy may not be necessary. The C-MAC was employed because Gaszynski (2014) found it improves laryngeal view in morbidly obese patients, and allows a fast endotracheal intubation [13]. It has a better clinical performance in normal [14] and difficult airways [15] and less need for adjuncts (e.g. stylet). Also, less force on the upper teeth was noted during intubation using CMAC videolaryngoscopy compared to conventional laryngoscopy [16].

An adult Bonfils™ fiberscope is a rigid 40 cm long endoscope with 40˚ distal curved end. A tracheal tube with an internal diameter of at least 5.5 mm can be loaded[17]. The Bonfils fiberscope's rigid body can lift up large epiglottises and push away airway masses to gain access to the glottis[18]. It allows easy routing through the oral cavity, and will be able to displace collapsed soft tissues and other obstructions. Railroading the endotracheal tube using a Bonfils™ will be more straightforward than railroading the tube through a flexible fiberscope[19,20]. It is especially useful in patients who have limited or no neck mobility. For failed fiberoptic intubation, the Bonfils fiberoptic would be very appropriate.

The flexible fiberoptic bronchoscope may provide a good view but it may be too pliable to advance the endotracheal tube in the desired direction. C-MAC videolaryngoscopy can be used to achieve the best possible view of the space of the laryngeal inlet. The Bonfils™ would serve as a stylet for the insertion and easy maneuvring of the Bonfils™ -pre-loaded-endotracheal tube [11] to facilitate insertion of the tube through the glottic opening.

Plan B

CMAC-D blade, bougie assisted

D-blade was used in our patient. Compared with a regular macintosh video laryngoscopy, the D-blade's 40˚ angle (macintosh blades angulated at 18˚) conferred an even better glottis visualization [21]. It also has a suction port providing a channel for the bougie for easier passage of the endotracheal tube past the glottic opening.

The gum elastic bougie is a reliable adjunct for difficult endotracheal intubation. It can be used for direction control or when the laryngeal inlet cannot be seen. In this case, because the bougie is less rigid than the bonfils, this allowed it to be directed deeper. It is also steadier than a flexible fiberoptic scope which supported the force of the endotracheal tube.

Plan C

Awake Flexible fiberoptic intubation

Awake fibreoptic intubation is still regarded by many as the gold standard technique for a difficult airway. The ability to maintain spontaneous ventilation and bypass an upper airway obstruction, such as a neck mass, are the main advantages of awake fiberoptic intubation. An adult flexible fiberoptic intubation would still be attempted on this patient even if the two earlier plans would fail. A scope that will provide a smaller gap (not greater than 1.5 mm) between the scope shaft and the tube will less likely allow the tube to be caught on the arytenoids[22,23] or the tracheal mass.

Plan D

Surgical Airway

According to the ASA difficult airway algorithm, in the event that intubation, xawake or not, has failed after multiple attempts, the next step is to cancel the case or do invasive airway access. However our patient specifically requested that invasive surgical airway be not done due to her livelihood.

Tracheostomy under local anesthesia by the surgeon is the last option in case the airway strategy and the back up plans fail. However, this shall be decided upon early on before airway is compromised. All attempts at securing the airway shall be limited to three attempts. Considering her obesity and its associated anatomical changes, this procedure may be difficult and not without adverse effects. Tracheostomy would require the patient to lie flat for at least 30 minutes, which may make her very uncomfortable. Not only will it leave an unsightly hole in the throat, but it may also render the patient aphonic. Pain, bleeding, infection, airway obstruction, dislodgement, pneumothorax, recurrent laryngeal nerve injury, and persistent percutaneous fistula are also some of its complications [24]. These are the reasons why surgical airway was not the first management considered.

Intraoperative Management

Initially, a "quick look" with a CMAC videolaryngoscope was done awake, in an adequately topicalized patient to see if the glottic opening can be viewed through the monitor. Laryngeal viewgrade 4 was appreciated. The airway team proceeded to plan A but the patient became uncooperative while doing laryngoscopy with CMAC and bonfils. Thus, she had to be sedated. Despite sedation, difficulty was still noted with the advancement of the tube through the opening even if there was a perfect view. The airway team then proceeded to the next plan. With the D-Blade providing the best view of the glottic opening and the bougie guiding the insertion of the endotracheal tube, the trachea was successfully intubated, and succinylcholine was administered to make sure laryngospasm does not occur.

Extubation

Lastly, extubation in patients with difficult airway should be an integral part of overall airway management. Decisions has to be made regarding the following: awake extubation versus extubation before the return of consciousness, factors that may affect ventilation after the patient has been extubated, management plan if patient is not able to maintain adequate ventilation after extubation, and a device that can serve as a guide for expedited reintubation.[25]. Mort (2008) suggested the following strategies to manage extubation in a difficult airway patient: a. standard extubation; b. extubation and evaluation via a fiberoptic bronchoscope; c. extubation followed by a placement of an extra-glottic device; and d. extubation over an airway exchanger[26]. For this patient, a ventilating airway exchange catheter was left inside the tracheal lumen after extubating awake in the postanesthesia care unit (PACU). The patient kept coughing on the presence of the catheter and verbalized her desire to have the catheter removed. With all airway management tools ready, the airway exhange catheter was removed. She was spontaneously breathing with a mask on, with no episodes of desaturation at the PACU.

Lastly, other considerations that may have helped in the management of this difficult airway: Firstly, adequate local topicalization is important most especially in awake intubation. Sedation cannot substitute a poor topicalization because this might cause an airway obstruction. Secondly, limit airway interventions to 2 attempts, more attempts would increase complications previously mentioned, and that succeeding attempts can produce more secretions, blood and swelling from trauma and injury.

Conclusion and Recommendations

There is one skill above all that an anesthesiologist should exhibit and that is to maintain the airway. The most compelling effort among anesthesiologists should be to reduce the frequency and severity of complications. Preparedness, assessment, planning, communication, teamwork, skill with multiple techniques, and situational awareness are key factors in reducing airway complications. The focus

should be on alveolar oxygen delivery at all times in order to prevent the patient progressing to the point of critical oxygen desaturation. To make the gold standard work, Anesthesiologists must train and be updated in the constantly developing tools because airway interventions should "First Do No Harm".

A successful induction of anesthesia and intubation heavily relies on good pre-operative assessment and planning, alongside teamwork. But it is also important to note that the anesthesiologist should be comfortable with the techniques and instruments he uses. They should always anticipate failure and know the next necessary step should the first attempt at airway management fail. Doing the same things that didn't work the first time may cause more complications. With the right attitude, right preparation, right state of mind and attention to the continuing innovations in airway devices anaesthesiologists can now choose from, an anticipated difficult airway can no longer be as stressful as they used to be.

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An Atypical Presentation of Pulmonary Tuberculosis in an Asthmatic Adolescent: A Case Report*

Geannagail O. Anuran, MD, MBA**

Abstract

Pulmonary tuberculosis (PTB) screening is conventionally done with the use of a chest radiograph. However, immunocompromised patients with PTB could present with a normal chest finding. It is therefore important to probe through the patient's history to determine if sputum smear microscopy would be needed even for screening.

A 15-year-old female, a known asthmatic since 3 years old, with history of receiving high cumulative doses of systemic corticosteroid for asthma exacerbations, consulted the emergency room for a 3-day history of worsening dyspnea. The patient was managed as a case of asthma in acute exacerbation and was also screened for PTB due to identified risk factors. Her chest radiograph turned out normal, but sputum smear microscopy were twice positive for acid-fast bacilli (AFB). This atypical presentation of PTB could be due to the patient's immunosuppressed state, brought about by her history of systemic steroid use, which predisposed her to the absence of a parenchymal or nodal involvement in her chest x-ray. The patient was maintained on a combined beta$_2$-agonist and inhaled corticosteroid for her asthma, and she was also started on anti-Koch's medications. Repeat sputum smear microscopy after two months of anti-Koch's treatment were twice negative for AFB. There were also no recurrence of her asthma symptoms.

Asthma patients with history of systemic steroid use are considered immunocompromised. PTB screening in this population should include sputum smear microscopy aside from the usual chest x-ray, because imaging could be normal, as what this patient exhibited. Inhaled steroids may also be given safely to this group of patients.

KEYWORDS: Pulmonary Tuberculosis, Asthma, Adolescent, Chest X-ray Negative

*Selected for competition, Inter-hospital Interesting Case Contest, Philippine Academy of Family Physicians - Manila Chapter

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INTRODUCTION

In screening for pulmonary tuberculosis (PTB), most physicians customarily request for a chest radiograph (CXR), wherein the disease would typically present with opacities, consolidations, cavities, and nodules (Kisembo, et al., 2012). Owing to its high sensitivity (at 97%) in detecting PTB (Piccazzo, et al., 2014), CXR-negative patients are deemed normal and further laboratory tests are seldom requested. However, there have been reports of false negative examinations, which amount to about 1% among the immunocompetent population, and increased to 7% to 15% in individuals seropositive for human immunodeficiency virus (HIV) (Piccazzo, et al., 2014). Further, among those who were immunocompetent, it was observed that CXR-negative PTB was commonly identified in those who were symptomatic or through contact tracing for PTB (Marciniuk et al., 1999).

Clinicians, therefore, must have a high index of suspicion in order to catch this group of patients who tend to present with CXR-negative PTB. Probing the patient's history is essential to identify the presence of co-morbid diseases, history of corticosteroid use, past medical history of PTB, and exposure to an active PTB case – factors that would increase the patient's risk for developing PTB and would therefore prompt the clinician to request for further laboratory tests in screening the patient.

This report looks into the case of an asthmatic adolescent who developed pulmonary tuberculosis presenting with a normal chest radiograph and positive sputum smear.

CASE PRESENTATION

A 15-year-old female was seen at the emergency room on February 2015 for difficulty of breathing. She is a known asthmatic since 3 years old, with persistent symptoms, but with no maintenance medications, and relies only on daily Salbutamol nebulization. For the past 12 years, she had monthly emergency room visits for intravenous steroid administration if her symptoms were unrelieved by nebulization. Thus far, she has had six confinements, without having been intubated or put in intensive care.

Her symptoms were uncontrolled until three days prior to consult, she had worsening dyspnea, triggered by cigarette smoke exposure, and associated with chest tightness, shortness of breath, and productive cough, which were all not relieved by more than six Salbutamol nebulization at home nor by four doses of intravenous Hydrocortisone administered at the local district hospital. Persistence of symptoms thus prompted consult.

The patient has a history of Primary Complex at 10 years old, and she is allergic to *"Tulingan"* and to Cotrimoxazole. Her immunization status is complete only up to 9 months of age, and no booster doses have been given. Her father, who smokes at home, also has asthma and allergy to crabs. She has a close contact exposure to PTB through her paternal uncle. Please see Figure 1 for the family genogram.

The patient is an average year level eight student, who had to repeat levels two and five, because she had to stop in the middle of the school year due to her inability to tolerate climbing the stairs to attend her classes. The patient shares that she regrets having to repeat this two school years, because of the undue financial strain it caused their family, and she has also been feeling anxious that she might not be able to finish school because of her illness. Meanwhile, she reports that currently, she could exercise during her physical education classes without having an exacerbation.

On physical examination, the patient was conscious, coherent, spoke in sentences, with a blood pressure of 110/80 mm Hg, tachycardic at 101 beats per minute, tachypneic at 26 breaths per minute, with an O_2 saturation of 92%. Patient was underweight with a body mass index (BMI) of 15.52, with poor air entry and wheezing over all lung fields. The rest of the physical exam findings were unremarkable.

Assessment at this time was "Bronchial Asthma, in moderate acute exacerbation, rule out Pulmonary Tuberculosis." The patient was immediately nebulized with Salbutamol/Ipratropium for three doses every 20 minutes. There was decrease in dyspnea, though she still had wheezes, but no crackles. Her final O_2saturation was at 95%, which she was

able to maintain after three hours of observation. Patient was then sent home with requests for a chest radiograph and sputum smear microscopy, and with prescriptions for Budesonide/Formoterol 160/4.5 mcg, two puffs once a day; Montelukast 10 mg/tab, one tablet once a day; and Salbutamol/Ipratropium nebulization every six hours for three days then as needed for dyspnea.

The patient's chest radiograph revealed normal findings, while her sputum smear were positive for acid-fast bacilli (AFB) for days 1 and 2. The patient was then started on anti-Koch's treatment, Isoniazid-Rifampicin-Pyrazinamide-Ethambutol (HRZE) tablets, two tablets once a day for two months and HR tablets for four months through the Tuberculosis-Directly Observed Shortcourse (TB-DOTS) Program. Repeat sputum smear microscopy after two months of anti-Koch's treatment were twice negative for AFB. The patient had no adverse reaction to the medications. The patient then gained weight, with a BMI of 17.35.She also had no recurrence of dyspnea, chest tightness, shortness of breath, and cough.

CASE DISCUSSION

Presented with a case of a 15-year-old female consulting for a 3-day history of dyspnea associated with chest tightness, shortness of breath, and productive cough, differential diagnoses for the patient's case include cardiovascular, psychogenic, and respiratory diseases. The cardiovascular causes include heart failure, anemia, and deconditioning. However, the patient does not have any history of congenital or acquired cardiac diseases, and she does not present with other heart failure signs and symptoms; she does not have physical exam findings indicative of anemia; and she is able to exercise without respiratory discomfort; so these conditions are unlikely in the patient's case.

Psychogenic causes of dyspnea like panic attacks and hyperventilation syndrome may also be ruled out, since the patient does not have any ongoing psychosocial stressor and does not complain of any anxiety or panic attacks.

The respiratory causes of dyspnea include disorders of the respiratory controller or the brainstem, the ventilatory pump, and the gas exchanger (Schwartzstein, 2012). Drugs, like aspirin or progesterone, and diabetic ketoacidosis can stimulate the brainstem and cause dyspnea; however, the patient is not taking these drugs, and she does not present with other symptoms of hyperglycemic crisis like nausea and vomiting, abdominal pain, or mental status changes. Similarly, the ventilatory pump, composed of the ventilatory muscles and bones of the chest wall, the pleura, and the airways could be affected by neuromuscular weakness as in Myasthenia Gravis or Guillain-Barre Syndrome. However, the patient did not present with the characteristic weakness and muscle fatigue of Myasthenia Gravis nor with the characteristic weakness and numbness of Guillain-Barre Syndrome.

There may also be dyspnea if there is reduced compliance of the chest wall as in kyphoscoliosis, or if there is reduced compliance of the lungs as in interstitial fibrosis; however, the patient also did not present with an abnormal curvature of the spine, likewise, the patient does not have any drug, radiation, or environmental exposure, nor does she have any comorbid autoimmune disease that may cause damage to her lungs; thus, these disease entities as the cause of her dyspnea are not considered. Pleural effusion as well as pneumothorax from any cause could result in dyspnea, but the patient's clinical picture does not fit with the usual presentation of these conditions. On the other hand, the patient does meet the criteria for bronchial asthma, and there are valid points to suspect pulmonary tuberculosis; thus, both diseases are considered in this patient.

The patient's asthma, previously diagnosed only by virtue of her dyspneic episodes being relieved by nebulization, could be validated using the criteria defined in the Global Initiative for Asthma (GINA) guideline (2014). This guideline states that asthma presents with "episodic wheezing, shortness of breath, chest tightness, and cough; symptoms often occur or worsen with viral infections; such occur variably over time; and they often occur or are worse at night or on waking;" which are all present in the patient's case.

On initial consult, a co-morbid pulmonary tuberculosis was considered because of the persistence of the patient's symptoms despite receiving systemic steroids, her history of Primary Complex during childhood, and her immunosuppression from receiving high cumulative doses of intravenous corticosteroids. In addition, the patient is a close contact of a pulmonary tuberculosis index case, and because of this, according to the 2013 Manual of Procedures for the National Tuberculosis Control Program, the patient should be investigated as part of the case finding process for contact investigation.

How common does PTB coexist with asthma? The association between bronchial asthma and PTB is rare, with a prevalence rate of 0.3% (Fekih et al., 2010). Pulmonary tuberculosis was found to be more commonly associated with Type 2 Diabetes Mellitus (DM) with 29.63% prevalence (Jimenez-Corona et al., 2013) and with HIV, having an 18.86% prevalence (Kamath, 2013). Common among DM and HIV patients is their immunosuppressed state, which could also be the reason for the development of PTB in this asthmatic adolescent, given that she has been receiving high cumulative doses of systemic corticosteroids.

This assertion is consistent with the findings in a case-control study by Jick, et al., (2006), that asthma is not necessarily a risk factor for the development of pulmonary tuberculosis. Asthma was found to be inconsistently associated with an increased risk for tuberculosis with an adjusted odds ratio of 1.4 and a 95% confidence interval of 1.0-2.0. The authors suggest that asthma appears to increase the risk for tuberculosis, particularly if the asthmatic patient would be dependent on systemic steroids for control of symptoms, as in this patient's case.

Moreover, the risk for tuberculosis appears to increase with cumulative doses of glucocorticoids (Jick, et al., 2006), which could be significant for this patient, since she has been having systemic corticosteroids for most years of her life, and though she does not use such medications continuously, she must have already accumulated a large concentration. According to the aforementioned case-control study, the adjusted odds ratios for current users with a cumulative dosage of <1,000 mg, 1,000-2,999 mg, and ≥3,000 mg, are 4.1 (95% CI 1.8-9.3), 8.3 (95% CI 2.1-33.5), and 3.9 (95%CI 1.5-9.7), respectively. This suggests that regardless of the dose, patients with cumulative steroid use are at in increased risk for developing pulmonary tuberculosis compared with patients who are unexposed.

Thus, the patient's immunosuppressed state, which is due to her cumulative systemic steroid use, predisposes her to the absence of a parenchymal or nodal involvement in her chest x-ray, because of her inability to mount an immune response to the pulmonary TB infection. Various authors thus agree that among immunocompromised patients, and particularly in those who are symptomatic and in those with tuberculosis exposure, a normal chest x-ray finding should not preclude further diagnostic evaluation in this population.

How should patients with coexisting asthma and PTB be managed? This adolescent patient was given combined $beta_2$-agonist and inhaled corticosteroid as maintenance medication for her asthma, since GINA guideline states that, "inhaled glucocorticosteroids are not contraindicated in patients with active tuberculosis."

Use of inhaled steroids for asthma among those with concomitant PTB infection is considered safe in clinical practice, as reported by Horton et al. (1977), since its use did not adversely affect the resolution of PTB in their cohort. Moreover, in the event of an asthma exacerbation, systemic steroids may also be safely given for those with concomitant PTB who are already receiving effective anti-Koch's treatment, as seen in the case series reported by Fekih et al. (2010), although they noted that a higher dose might be necessary, since rifampicin is a hepatic enzyme inducer, and thus would increase drug clearance.

Preventive measures imparted to this patient include avoidance of asthma triggers especially that of exposure to irritant smoke, which led to the motivation of the family to encourage the patient's father to stop smoking. Other measures consisted of putting emphasis on the patient's adherence to PTB and

asthma medication regimen, and updating of her immunization status. For the psychosocial intervention, Catharsis-Education-Action (CEA) was done to determine the impact of her illnesses on her quality of life, and to support her on the implementation of treatment and wellness plans.

CONCLUSION

This case exemplifies the holistic approach in managing a patient with atypical presentation of pulmonary tuberculosis in an asthmatic adolescent.

The physician as a health care provider must be adept at obtaining the patient's medical history to determine the patient's immune status. Thus, when screening for PTB in an immunosuppressed patient, the physician could make a clinical decision to request for sputum smear microscopy in order to catch PTB patients who would present with a normal chest radiograph.

As an educator, the physician should ensure patient and family's understanding of the condition in terms of the risks, etiology, and pathophysiology, to empower them to adhere to the treatment and wellness plans.

As a counselor, the physician caring for an adolescent afflicted with comorbid illnesses should be able to empathize with the patient and his/her family, and to reassure them that specific measures can be taken to improve the patient's quality of life.

As a researcher, the physician should be able to apply evidenced-based information on clinical decision-making, and at the same time, to document his/her own experiences in caring for his/her patients.

Lastly, as a health manager, the physician should be able to coordinate patients with available resources in the community, such as the TB-DOTS program for PTB treatment, to minimize the financial burden put on the family and to further promote treatment adherence.

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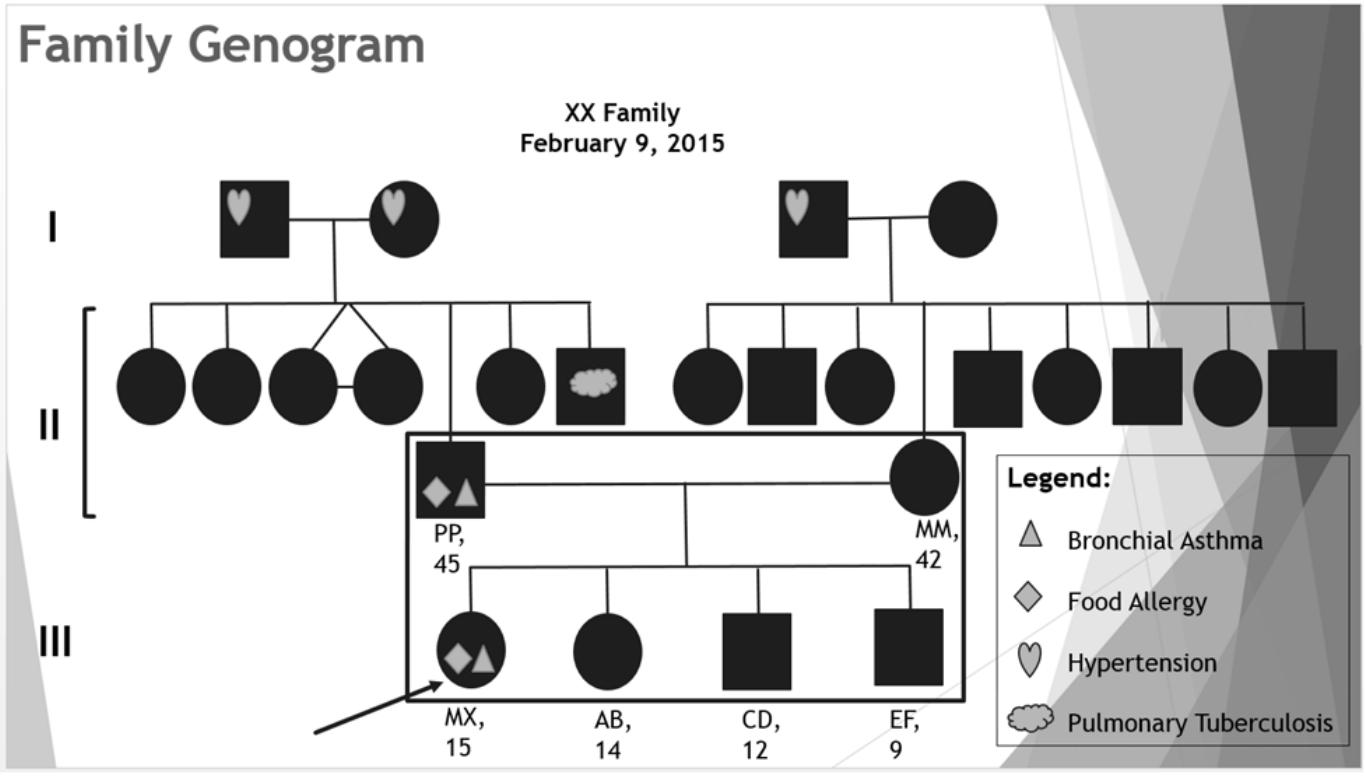
TABLES

Summary of Diagnostic Findings		
Date	**Diagnostic Test**	**Results**
February 16, 2015	Sputum AFB x 1	+4, More than 10 AFB/visual field in at least 20 fields
February 17, 2015	Sputum AFB x 2	+2, 10-99 AFB/100 visual field
February 18, 2015	Chest X-ray, PA	Normal chest
March 12, 2015	Chest X-ray, PA	No significant chest findings
March 13, 2015	AST	19 – normal
March 13, 2015	ALT	13 – normal
March 13, 2015	PPD Skin Test	13mm
June 16, 2015	Repeat Sputum AFB x 1	Negative
June 17, 20915	Repeat Sputum AFB x 2	Negative
June 26, 2015	Repeat ALT	35.5 – Normal
June 26, 2015	Repeat AST	33.4 – Normal

ILLUSTRATION



Family Case Report

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INTRODUCTION

In the Philippines, most Filipinos are living in a "sandwich generation." This is a generation wherein an adult is stuck between the responsibilities of raising their children and taking care of their elderly parents. There is absolutely nothing wrong for children to take care of their old parents, especially in our culture, where placing our parents in an old's home is met with negative regard. This set up, however, can potentially be problematic if the middle generation adult is not adequately equipped to handle such a balancing act. It would be good if the children have the means to support their parents financially, but what if they are not able to do so? Will they view their elderly parents as a burden? Today, we are all sons and daughters and maybe some of us are already parents. Some of us might be in this kind of situation right now or some might experience this in the future. So let us look at the journey this family went through to get a clearer picture on what might happen if you get **caught in the middle.**

OBJECTIVES

1. To present and discuss a family in a "sandwich generation"
2. To describe the family structure and analyze the family psychodynamics using the family assessment tools
3. To address the identified biomedical and psychosocial issues of the family in a "sandwich generation" using appropriate family interventions
4. To formulate a wellness plan for the family

RATIONALE

Caregivers are the therapeutic allies of family physicians. They are our potential patients in the future if their biomedical and psychosocial issues are not addressed properly. I chose this case to highlight the situation of a loving daughter, a very efficient caregiver to her parents who, in the process, began to neglect her own family.

EPIDEMIOLOGY

From a report of the Economist Intelligence Unit 2010, based on the total population data from the United Nations, an estimated 20% of the working -age population across Australia, China, Hong Kong, Japan, Singapore, South Korea and Taiwan are members of the Sandwich Generation. The sandwich generation is biggest in China and smallest in Australia and Japan. Although there is no available data on the proportion of Filipinos who belong to the sandwich generation, we can already surmise that they comprise a significant portion of our population just based on our daily patient encounters.

Figure 5
Asia's Sandwich Generation

Country	Total population	Working-age population*	Prevalence of Sandwich Generation in working-age population**	Implied number of people in Sandwich Generation
Australia	20.4m	16.3m	6%	1.0m
China	1.3b	1.0b	37%	370m
Hong Kong	6.9m	5.5m	27%	1.5m
Japan	127.4m	89.2m	6%	5.4m
Singapore	4.3m	3.4m	26%	0.9m
South Korea	47.6m	38.1m	18%	6.9m
Taiwan	23.1m	18.5m	19%	3.5m

* Over 21 and under 70, estimated at 80% of total population except for Japan (70%). NB, The incidence of survey respondents over 60 years of age meeting the definition of Sandwich Generation member is 0.4%.
** See "About the research", above, for explanation of Sandwich Generation socioeconomic classification.
Sources: Economist Intelligence Unit calculation based on survey response rate. Total population data from United Nations Department of Economic and Social Affairs/ Population Division, World Population Prospects 2008, except Taiwan (National Statistics).

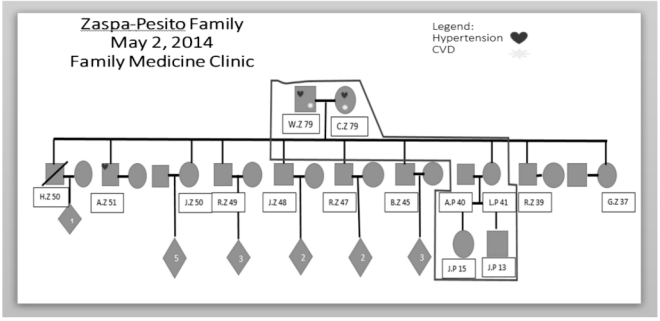
FAMILY PROFILE

Tatay William, who was my initial patient in the family, is a 79 year old married man from Davao, an Aglipayan Catholic, and father of ten children. He currently resides in Sta. Rosa, Laguna with one of his daughters while he seeks regular medical care at the Philippine General Hospital's Outpatient Department. Tatay William has been my patient and has been enrolled in my continuity service since May 2014. He is being treated as a case of Congestive Heart Failure Functional Class II secondary to Hypertensive Heart Disease, Hypertension Stage 2, controlled, s/p Cer brovascular Infarct with right-sided hemiparesis, Broca's Aphasia and dysarthria (2012).

Tatay William was always accompanied by Ate Luningning, his 8th child, whenever he would come for his outpatient visits. Ate Luningning serves as Tatay William's primary caregiver; thus,

Tatay William's illness has had the greatest impact on her. Ate Luningning is a 40 year old Aglipayan Catholic mother of two. Although born in Davao, she has been living in Sta. Rosa Laguna with her husband, Kuya Angel, for the past 16 years. They have been blessed with 2 children, Jansen and Jemsean, who are both in their adolescent years.

FAMILY GENOGRAM



TIMELINE:

Ate Luningning was born in Davao and was raised by her farmer parents. She finished her primary and secondary education at a school in their town. She has always been deemed a responsible daughter and she never got tired of helping out with household chores. **In 1994**, when she was 21 years old, she went to Sta. Rosa Laguna, where she was recruited by her cousin to work in a canteen. During her stay in Laguna, she regularly send money to her parents to help provide for their needs in Davao. She would go and visit her family in Davao only once a year because sending them money would be of more help to them than if ate Luningning went home frequently.

In 1997, Ate Luningning met Kuya Angel who was a seafarer during that time. The shipping agency where he worked at happened to be the same agency which housed the canteen where Ate Luningning was employed as a helper.

In 1998, they became a couple but when the news came to the knowledge of Tatay William and Nanay Carmen, they told Ate Luningning that they were against her relationship with Kuya Angel. Nanay Carmen and Tatay William believed that Ate Luningning was just one of Kuya Angel's "girl in every port". Despite her parents' disapproval, Ate Luningning's relationship with Kuya Angel thrived. They eventually got married only after 6 months of being a couple. Gradually, Ate Luningning's family began to accept Kuya Angel.

In 1999, the couple had their first baby, and she was named Jansen. At that time, Kuya Angel was also scheduled to go overseas but he decided to forgo this job because he did not want to leave his family. Ate Luningning agreed and supported Kuya angel's decision. She never blamed Kuya Angel whenever they would experience financial difficulties. Ate Luningning continued to work hard in the canteen to support the family's financial needs.

In 2002, their 2nd child was born, Jemsean. During this time, Ate Luningning and Kuya Angel realized that their income was no longer sufficient to support the needs of their growing family. They opened a small sari-sari store beside their house in Sta Rosa Laguna. While working at the canteen, Ate Luningning also started to sell AVON products for extra income. Kuya Angel stayed at home to take care of their children and man their small sari sari store.

In 2004, they were able to save enough money and bought a tricycle. During this time, the couple began to shift their roles in the family. Ate Luningning resigned from her job, stayed at home to take care of their children, and man their sari-sari store. Kuya Angel, on the other hand, became a full time tricycle driver. This was also the time when Jansen started to go to school. Right from the start, Jansen excelled academically, and she consistently became the topnotcher of her batch.

Ate Luningning worked full-time in taking care of her family. She played the role of a mother, a friend, and a tutor to her children. She would always take time to check on Jansen and Jemsean's assignments and supported them in most of their school activities.

In 2012, Tatay William suffered a cerebrovascular accident. He developed right sided hemiparesis, aphasia and dysarthria. He became bed bound and needed a caregiver to watch over him. Nanay Carmen

asked Ate Luningning to be the caregiver, since she is the closest to her father. She did not think twice, and brought her whole family to Davao in order to take care of tatay William. They had to close their sari-sari store in Laguna, and they left the tricycle to the care of the barangay. Ate Luningning's family stayed in Davao for 2 months, but they had to return to Laguna since school was starting real soon. Kuya Angel, Jansen and Jemsean went back to Laguna and left Ate Luningning in Davao.

In early 2013, Ate Luningning went back to Laguna to rejoin her family. They reopened their sari-sari store and Kuya Angel continued to work as tricycle driver. Ate Luningning became more lax with her growing adolescents. It was noticeable that Jansen became aloof and stubborn, but Ate Luningg did not pay much attention to the changing behavior of her child. On the other hand, Jemsean remained the same playful but obedient child. He was also consistently the batch topnotcher since he started going to school.

In early 2014, Tatay William was transported to Ate Luninging in Laguna since Rene, the 4th sibling is experiencing a hard time taking care of their father. Once again, she accepted taking care of Tatay William with open arms.

On May of 2014, Tatay William was brought to PGH and this was the time that I had started managing him.

Upon performing a comprehensive geriatric assessment (CGA), it became evident that Tatay William was suffering from severe cognitive impairment. In terms of functional activity, he required assistance in most of the basic and instrumental Activities of Daily Living (ADL's).

CGA Component	Elements	Tatay William
Medical Assessment	Problem List	1. Congestive Heart Failure Functional Class II secondary to Hypertensive Heart Disease 2. Hypertension stage 2, controlled 3. Post Cerebrovascular Infarct with right- sided hemiparesis, Broca's aphasia and dysarthria (2012)
	Medication Review	Losartan 50mg/tab OD, Aspirin 80mg/tab OD Simvastatin 20mg/tab OD, Multivitamins tab OD Vitamin B complex tab OD
Assessment of Functioning	Basic ADL's Instrumental ADL's Activity/exercise Gait and balance	**Katz score: 1 (Very dependent to caregiver)** **Lawton: 0 (completely unable to do instrumental ADLS Unable**
Psychological Assessment	Mental Status (Cognitive) Testing Mood/depression testing	**MMSE: 4/30: Severe Cognitive Impairment** **Geriatric Depression Scale: 0/30: NO DEPRESSION**
Social Assessment	Informal Support needs and assets Care resource Eligibility/Financial assessment	**Primary Caregiver: Luningning Pesito**

In August 2014, Nanay Carmen also moved to Sta. Rosa Laguna to live with Luningning. It was Nanay Camen's choice to live with her because she knew that she would be well taken care of. At a glance, this new set-up seemed to be beneficial for Tatay William's recovery since he was now going to be together with his wife. In addition, Nanay Carmen could serve as an additional caregiver for tatay, thus sharing care-giving responsibilities with Ate Luningning.

As it turned out, Nanay Carmen had actually suffered a mild stroke some months before. Because of her condition, her son Rene had difficulty taking care of her especially whenever conflict would arise between her and Rene's wife. Rene actually wanted to pass on the responsibilities of taking care of Nanay Carmen to Ate Luningning. Since the stroke, Nanay Carmen seemed to be having problems with memory as she became noticeably more forgetful, much to the irritation of Rene's wife.

Ate Luningning brought Nanay Carmen into her family's home. Eventually, she brought her to PGH for medical care. Nanay Carmen was also enrolled in my continuity clinic and was managed as a case of Hypertension stage 2 controlled. A Comprehensive Geriatric Assessment was also performed on her.

CGA Component	Elements	Tatay William
Medical Assessment	Problem List Medication Review Nutritional Status	Hypertension stage 2-controlled t/c Vascular dementia Amlodipine 5mg/ tab OD, Multivitamins tab OD, Vitamin B complex tab OD MNA
Assessment of Functioning	Basic ADL's Instrumental ADL's Activity/exercise Gait and Balance	**Katz score: 6 (Full function)** **Lawton: Needs help and supervision with instrumental ADL's** **Stable gait, no history of fall**
Psychological Assessment	Mental Status (Cognitive) Testing Mood/depression testing	**MMSE: 2/30: Severe Cognitive Impairment** **Geriatric Depression Scale: 0/30: NO DEPRESSION**
Social Assessment	Informal Support needs and assets Care resource Eligibility/Financial assessment	**Primary Caregiver: Luningning Pesito**

Nanay Carmen had better functionality than Tatay William. Unfortunately, in terms of mental capacity, they both suffer from severe cognitive impairment.

Clearly, Ate Luningning has her hands full. She is now tasked to take care of both her parents, both elderly, both of whom are highly dependent, both with cardiovascular complications due to uncontrolled hypertension, and both requiring intensive supervision and chronic medical care. Ate Luningning might be at risk for developing caregiver fatigue as she now had to play multiple roles as daughter, primary caregiver, and mother and wife to her own family. Thus, she was asked to accomplish the modified caregiver strain index.

MODIFIED CAREGIVER STRAIN INDEX (MCSI):

Madalas (3) Paminsan-minsan (2) Halos hindi(1)

QUESTIONS	SCORE
1. Naaabala ang aking pagtulog dahil sa pag-aasikaso sa pasyente.	2
2. Ang pag-aalaga sa aking pasyente ay nakakapagod dahil sa pagkarga, pag-alalay at pag-asikaso.	**3**
3. Ang pag-aalaga sa aking pasyente ay nagdulot ng mga pagbabago sa buhay ng aking pamilya dahil sa nagulong pang-araw-araw na gawain.	**3**
4. Nauubos ang aking pansariling oras sa pag-aalaga ng aking pasyente.	**3**
5. Ang pag-aalaga sa aking pasyente ay nagdulot ng mga pagbabago sa aking mga plano sa buhay tulad ng pagpalit o pagtigil sa trabaho o pag-aaral, paglabas-labas, pagbabakasyon, at iba pa.	**3**
6. Bukod sa pag-aalaga sa aking pasyente, mayroon pang dumagdag na responsibilidad na nangangailangan din ng aking oras.	**3**
7. Ang pag-aalaga sa aking pasyente ay nangailangan ng tibay ng loob dahil sa hindi naiiwasang mga alitan at hindi pagkakaunawaan.	2
8. Ako ay nalulungkot dahil malaki na ang ipinagbago ng aking pasyente mula ng siya ay magkasakit	2
9. May mga pagkakataon na nauubos ang aking pasensiya at ako ay naiinis dahil sa ikinikilos ng aking pasyente.	2
10. Lubos akong nag-aalaala kung paano ko makakayanan ang sitwasyong ito .	2
11. Malaki na ang aking gastusin dahil sa pag-aalaga sa pasyente.	**3**
TOTAL	**28**

A score of **28 in the MCSI** means that Ate Luningning is predisposed to having strain. During this time, I realized that Ate Luningning is a potential patient if her issues will not be addressed properly. In addition, this might further affect the biomedical and psychosocial issues faced by the family since Ate Luningning plays such a crucial role in the family.

I decided to explore further on the questions that she answered "Madalas" to in the Modified Caregiver Stain Index.

I asked her about the most stressful situation for her at that moment. Ate Luningning told me that since she became the primary caregiver of her parents, she has never received financial support from her older brothers. Josephine, her eldest sister, and Gina, her youngest sister, would send their parents monthly allowance ranging from 1,000-1,500 pesos which was still not enough to cover for maintenance medications and other necessities. Because of the increasing financial demand in the family, Ate Luningning and Kuya Angel opened a new sari-sari store in a nearby small market. Aside from driving the tricycle, Kuya Angel started to repack charcoal and deliver it to different houses in the neighborhood for extra income. Ate Luningning continued her AVON business, and the sarisari store beside their house remained operational.

We computed for an estimate of the monthly expenses for Tatay William's and Nanay Carmen's medical care in order to get a clearer picture of the family's financial situation.

	Tatay William	**Nanay Carmen**	**Total (30 days)**
Food: Breakfast, Lunch, Dinner	50x3 = 150.00 / day	50x3 = 150 / day	9,000.00
Medications (Generics drugs)	Losartan 50mg = 11.00 Aspirin 80mg = 2.00 Simvastatin 20mg = 14.00 Multivitamins tab = 3.00 Vitamins B complex = 2.00 Total: **32.00/day**	Amlodipine 5mg = 11.00 Multivitamins = 3.00 Vitamins B complex = 2.00 Total = **16.00/day**	**1,440.00**
Electricity: 1 bulb, 1 electric fan	-	-	**500.00**
Drinking water (Mineral)	-	-	**150.00**
Toiletries (Bathing soap, laundry soap, shampoo, toothpaste, toothbrush)	-	-	**400.00**
Total			**11,490.00**

The estimated monthly expenses for Tatay William and Nanay Carmen's medical care and basic necessities amounted to 11,490.00. If Gina and Josephine would send allowance regularly on a monthly basis, Ate Luningning's family would only have to **shoulder 8,000-10,000.00** added to the monthly expenses of Ate Luningning and her family. The SCREEM tool was then utilized to assess for other extra familial resources that may be tapped to help this family.

SCREEM

	RESOURCES	PATHOLOGY
SOCIAL	The family has well balanced lines of communication with extra-familial social groups and other community organizations such as: **Homeowners' Association**	
CULTURAL	The family has cultural satisfaction and does not feel cultural inferiority or shame	
RELIGIUOS	The family has satisfying spiritual experiences	
ECONOMIC	Their source of income: angel's work as a **tricycle driver, sari-sari store**	The family is having financial problems making it difficult to meet the monetary demands of crisis
EDUCATIONAL	The educational background of the family members is adequate to understand the illness and the care for the patient	
MEDICAL	Medical care is available through channels that are easily established and have previously been experienced satisfactorily **Such as: Local Health Center, use of Barangay's Ambulance on follow-up consults at PGH**	

After doing the family SCREEM, we have together identified the resources of the family that would help them in their current crisis. We also listed the programs that the government offers for senior citizens.

1. Senior Citizens Benefits applicable to them:
   - 20% discount on medications, recreation areas, restaurants
   - Free medical and dental services in government facilities
   - Free vaccinations for indigent senior citizens
   - 5% discount on water and electric bill provided that the meters are registered in the name of the senior citizen residing in the household

2. DANGAL (Damayan Damayan Ang Nayon Gabayan Ang Lungsod): A program in the 1st District of Laguna (Sta. Rosa included) that provides medical assistance/support, scholarship programs, livelihood programs

3. Available free medications at the barangay health centers: I advised them that most of the medicines that Tatay William and Nanay Carmen were taking are available at their barangay for free

Apart from the financial problem that bothers her, Ate Luningning also had less time for her family. She became busy taking care of her parents, and she was also preoccupied with earning money to support their family. She is thankful that Kuya Angel understands their current situation and is doing his best to help and support her.

Meanwhile, Ate Luningninig was having problems with Jansen. They seldom get the chance to talk as Jansen spends most of her time outside their house with her friends. She would only stay inside the house to eat, sleep and take a bath. Ate Luningning first took note of this when she returned from Davao. I asked her to tell me more about the changes that she noticed with Jansen. She said that she also got

dismayed when Jansen ranked 3rd in the class, where she was consistently the topnotcher for the past years. When she asked Jansen what happened, she would just stare at her and will not give an answer. I then realized that there is an ongoing conflict between Jansen and ate Luningning. Ate Luningning would also seek Jansen's help in watching over the elderlies but she would only give excuses not to follow ate Luningning. Since this became evident during the time she came back from Davao, I asked Ate Luningning what could have been the reason for Jansen's attitude. Ate Luningninig was quiet and seemed apprehensive to give out a reply. I asked her again about the changes in the family that would make Jansen act differently towards the other family members.

Ate Luningning said that since her parents got sick, she had less time to bond with her family and even less attention to her children. Ate Luningning realized that she might not be delegating the tasks among the family members properly and her time was taken up by the different roles that she needed to perform. From her realizations, we agreed on a plan to improve on her time management. And since it was near Christmas Vacation that time, I asked Ate Luningning to bring Jansen with her on the next follow up.

Last December 2014, Ate Luningning came back for follow up with Kuya Angel and Jansen. I asked ate Luningning how she was able to convince Jansen to come with her and she said that she did not find it hard to do so. This was a sign than Jansen was willing to cooperate.

Before I conducted a separate interview with Jansen, I first did a family APGAR to help me assess each member's satisfaction or dissatisfaction with their family's current state of function.

FAMILY APGAR

		Ate Luningning	**Kuya Angel**	**Jansen**
ADAPTATION	Ako'y nasisiyahan dahil nakakaasa ako ng tulong sa aking pamilya sa oras ng problem	2	2	2
PARTNERSHIP	Ako'y nasisiyahan sa paraang nakikipag-talakayan sa akin ang aking pamilya tungkol sa aking problem	2	2	1
GROWTH	Ako'y nasisiyahan at ang aking pamilya ay tinanggap at sinusuportahan ang aking mga nais na gawin patungo sa mga bagong landas para sa aking ikauunlad	1	2	1
AFFECTION	Ako'y nasisiyahan sa paraang ipinadadama ng aking pamilya ang kanilang pagmamahal at nauunawaan ang aking damdamin katulad ng galit, lungkot at pag-ibig	1	2	1
RESOLVE	Ako'y nasisiyahan na ang aking pamilya at ako ay nagkakaroon ng panahon sa isa't-isa	1	1	0
TOTAL		**7**	**9**	**5**

With the result of their APGAR, we can say that Ate Luningning's Family is Moderately Dysfunctional. After doing the APGAR, I asked ate Luningning and Kuya Angel to wait outside. Since Jansen is an Adolescent, I did the Home, Education Activity, Drugs, Spiritual, Sexuality, Safety (HEADSSS) to get a good overview of her psychosocial history. Based on her HEADSSS, Jansen had balanced her academics and extracurricular activities in school, has time to go out with friends and no history of any delinquencies. She was cooperative and answered the questions appropriately. But when the questions were about her relationship and satisfaction with her family, she would only smile and say that everything is okay. I asked her to elaborate what "OK" means for her. She did not say any word but just smiled at me. During my interview with her, I sensed that Jansen is experiencing issues that she hasn't disclosed with the family. She might not be aware of the reasons why she is experiencing those feelings. I was thinking of an intervention that would bring her to awareness of her actions and feelings. So I decided to use the Gestalt Therapy.

INTERVENTION: GESTALT – THE EMPTY CHAIR TECHNIQUE

I explained to her that I will ask her questions and her answers will be based on what is she is feeling and experiencing at that very moment.

Since she cannot elaborate what "OK" is for her, I asked her to tell me what she was feeling at that moment. She asked me if I really wanted to know the truth, asked me to keep it a secret from her parents. She told me that she feels sad because she feels neglected and unappreciated by her mom. I asked her how Ate Luningning made her feel that way. She was quiet for a moment, and said that Ate Luningning does not love her and the only thing important to Ate Luningning is to earn money and she is irritated about this. As I was listening to her, I also observed her reactions, gestures and mannerisms. I let her ventilate her feelings and remained silent.

When she was done expressing her feelings, I asked her to stay on her feelings. I asked her to close her eyes and imagine Ate Luningning sitting in front of her, listening to her. I then told her to tell Ate Luningning everything that she was feeling during that moment.

Jansen closed her eyes. She started talking to the empty chair. She said that she feels that she is unloved. All her efforts to be a good daughter is unrecognized. Jansen also told the empty chair that Ate Luningning has neglected her family and that she has no time for them because all she does is work and earn money, which frustrates her.

After Jansen expressed her feelings on the empty chair, I asked her to open her eyes and sit on the empty chair. I told her to imagine that she is Ate Luningning and what could have been Ate Luningning's reply to everything that she said. Jansen was quiet. When she started talking, her voice cracked. Jansen said that ate Luningning would have said that it's not true that she is not loved and unappreciated. The reason for all her hardwork is for their future. She also said that Ate Luningning would also say that they don't have financial or material inheritance to leave the family. They can only support their education and that is the best thing that she can give her children to prepare them for the future. As she finished her statement, I felt that Jansen was slowly developing self-awareness. I paused and gave her time to ponder on the things that we have talked about. After a few minutes, I asked Jansen what she became aware of after the experience. Jansen said that she realized that she was wrong, thinking that her mother does not love her. She also realized that her parents are working extra hours and their family time is compromised just because they want the family to have a decent life.

After her Gestalt experience, I asked her about her plans regarding the conflict between her and Ate Luningning. She said that she will try to be more understanding about their situation. I then called Ate Luningning and Kuya Angel for the schedule of their follow up.

On March 2015, I did a Home Visit with them at Sta. Rosa Laguna. It was noticeable that Ate Luningning has a happier aura. She told me that Tatay William and Nanay Carmen were approved by the DANGAL foundation, and the 2 elderly will receive a

Quarterly monetary allowance from the foundation. Nanay Carmen and Tatay William also joined the Senior Citizens' Club in their Barangay where medical assistance are rendered monthly. The Senior Citizens' Club also offers morning exercises and other weekly/ monthly activities, where Nanay Carmen and Tatay William are now regular attendees. I asked her how Jansen was doing after their consult with me. She said that Jansen changed a lot and was then helping in the household chores and is now more actively involved in caring for Tatay William. Ate Luningning was also proud of Tatay William's improvement in functionality. She attributes this to the patience of Jansen and Jemsean in assisting their grandfather in performing the prescribed rehabilitation exercises.

I then asked Jansen how she was doing and if there were changes she noticed in their family. Jansen told me that Ate Luningning has allotted more time for the family. They now go to church every Sunday and eat at Mang Inasal after going to church. She is now content with the time and attention that she is receiving from her family. As I heard the things that they said, I did a reassessment of the Ate Luningning's Caregiver Strain, Tatay William's functionality, and their family APGAR.

REASSESSMENT OF FAMILY APGAR

		Ate Luningning	**Kuya Angel**	**Jansen**
ADAPTATION	Ako'y nasisiyahan dahil nakakaasa ako ng tulong sa aking pamilya sa oras ng problem	2	2	2
PARTNERSHIP	Ako'y nasisiyahan sa paraang nakikipagtalakayan sa akin ang aking pamilya tungkol sa aking problem	2	2	2
GROWTH	Ako'y nasisiyahan at ang aking pamilya ay tinanggap at sinusuportahan ang aking mga nais na gawin patungo sa mga bagong landas para sa aking ikauunlad	2	2	2
AFFECTION	Ako'y nasisiyahan sa paraang ipinadadama ng aking pamilya ang kanilang pagmamahal at nauunawaan ang aking damdamin katulad ng galit, lungkot at pag-ibig	2	2	2
RESOLVE	Ako'y nasisiyahan na ang aking pamilya at ako ay nagkakaroon ng panahon sa isa't-isa	2	2	2
TOTAL		**10**	**10**	**10**

REASSESSMENT OF FUNCTIONALITY of Tatay William

	May 2014	**March 2015**
Katz score	2	4
Lawtons Score	0	0

REASSESSMENT OF CAREGIVER STRAIN of Ate Luningning

	August 2014	**March 2015**
Modified Care Giver Strain Index	**28**	**17**

POSSIBLE REASONS FOR DECLINE IN SCORE OF MODIFIED CAREGIVER STRAIN INDEX:

1. Time management
2. Delegation of Tasks
3. Cooperation of other members of the family
4. Open communication
5. The family might have adapted to the changes and current situation

DISCUSSION

The term Sandwich Generation was coined by Dorothy Miller in 1981. It refers to a generation that is simultaneously caring for two generations. The members of the sandwich generation face difficulties in allocating time and money and often describe themselves as being pulled in two directions or caught in between generations.

In the family that was discussed, Ate Luningning was caught between taking care of her parents and supporting her growing children. Conflicts arise due to gap in generations, and in their case, lack of communication.

According to a 2013 report by the Pew Research Center, financial planning will help in surviving sandwich generation. Here are the tips that may help in coping with being in a sandwich generation:

1. Keep saving for retirement
2. Fund a college savings plan
3. Purchase long-term care insurance
4. Get legal paperwork in order
5. Inventory assets and consolidate accounts
6. Look for outside help
7. Keep saving

Obviously, most of the things listed are pertaining to the financial concerns of the sandwich generation. This is may be applicable to some patients. But in the case of Ate Luningning and her they have little left to save since their total expenses is greater than their income. This family is able to survive their financial crisis through their hardwork and with the support coming from the other family members and government programs.

Pesito family has also undergone conflicts in the relationship with each other. They were able to hurdle this because they were able to adjust to change through improvement in communication, time management and proper task delegation.

Pesito Family is in the stage of **Family with Adolescent.** Identifying the first order and second order changes helps provide anticipatory guidance for stressful changes that are expected to happen in each stage of life cycle. These may require adjustments and readjustments to maintain the viability of the family.

1st Order Change (Need to Do)	2nd Order Change (Need to Be)
• Shifting of parent-child relationships to permit the adolescent to move in and out of the system • Refocus on mid-life, marital and career issues • Beginning shift towards concern for the older generation	• Providing facilities for widely different needs • Working out money matters in the family with teenagers • Sharing the tasks of responsibilities of family living • Putting the marriage relationship into focus • Keeping the communication system open • Maintaining contacts with the extended family • Growing into the wood as a family and as a person • Reworking and maintaining a philosophy of life

PROBLEMS ENCOUNTERED IN THIS STAGE OF LIFE CYCLE

ADOLESCENT:

MEDICAL	EMOTIONAL AND SOCIAL
• Drug and other substance • STD • Acne, bad odor • Gynecologic problems • Menstrual problems • Allergies and other skin disease • Circumcision	• Sexual experimentation leading to teenage pregnancy • Homosexuality • Conflict with parents • Juvenile delinquency • Depression secondary to peer pressure identity crisis and secondary sex characteristics • Child prostitution • Suicide tendencies

PARENTS

MEDICAL	EMOTIONAL AND SOCIAL
• Common medical problems • OB-gyne problems • Pre-menopausal symptoms • Alcoholism and vices	• Middle life crisis • Male climacteric • Extra-marital affairs • Insecurities secondary to changing appearance

FAMILY WELLNESS PLAN

My interaction with this family does not end here. As a Family Physician, it is imperative that short and long-term wellness plans be agreed upon and implemented among the family members.

FAMILY MEMBER	MEDICAL & PSYCHOSOCIAL CONCERN	RECOMMENDATION
Luningning Pesito (40)	**Psychosocial:** Care-giver fatigue	Repeat caregiver strain index as the need arises
Angel Pesito (41)	**Psychosocial:** care-giver fatigue	Screen for caregiver strain
Jansen Pesito (15)	**Psychosocial:** Conflict with parents	Immunization Anticipatory Guidance
Jemsean Pesito (13)		Immunization Anticipatory Guidance Screening for psychosocial and biomedical issue as an adolescent
William Zaspa (79)	Medical: Hypertension, Congestive Heart, FC II Cerebrovascular Infarct Right sided hemiparesis	Immunization BP Monitoring Continue Rehabilitation Exercises
Carmen Zaspa (79)	Medical: Hypertension To consider Vascular Dementia	Immunization BP Monitoring Refer to neurology for further assessment: Acetylcholinesterase inhibitors can be used to treat vascular dementia

INSIGHT

Family physicians have a different perspective in taking care of patients. Managing the physical signs and symptom is as important as looking into the contribution of the family in maintaining the health of all members. There are family tools that are seldom used but were of big contribution in changing the life situation of this family. Indeed, a biopsychosocial approach enables family physicians to see the patient beyond the physicality of his symptoms and to explore and discover the origin of the symptoms which are mostly psychoemotional issues. Most of the time, we only see the tip of the iceberg but allowing ourselves to listen to our patients and their issues reveals the depth and magnitude of the patient's story.

An Evaluator-Blinded Pilot Study Comparing the Efficacy and Tolerability of Intralesional Bleomycin versus Intralesional Triamcinolone Scetonide in the Treatment of Small Keloids

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An evaluator-blinded pilot study comparing the efficacy and tolerability of intralesional bleomycin versus intralesional triamcinolone acetonide in the treatment of small keloids

Background: In recent years, considerable interest has evolved over the use of chemotherapeutic agents for the treatment of scars. At present, there is currently no locally published trial comparing intralesional (IL) bleomycin and IL triamcinolone for the treatment of keloids.

Objective: This single center, pilot study aims to assess the efficacy and safety of IL bleomycin versus IL triamcinolone acetonide in the treatment of small keloids.

Methods: Six subjects aged 11 to 36 years old with two or more small keloids on the trunk or extremities were included in the study. A blinded evaluator assessed the study scars using the Vancouver Scar Scale (VSS) at the beginning and at the end of the trial period. The experimental keloid was injected with 0.1 mL of 1.5 U of bleomycin, while the control keloid was injected with 0.1 ml of 10 mg/mL of triamcinolone every 2 weeks. The incidence of adverse events, and self-assessed changes in pruritus, pain, erythema, softness, and size of the treated keloids were considered. Participant's satisfaction was also measured.

Results: The keloids that received IL bleomycin showed a significant improvement in the VSS at the end of the trial, which was not seen in the triamcinolone group. None of the patients were dissatisfied with the treatment outcomes. Adverse reactions were hyperpigmentation and crusting in the bleomycin group, and telangiectasia and hyperpigmentation for the triamcinolone group.

Conclusions: This pilot study shows that IL bleomycin is an effective and safe treatment for keloids. In addition to improving the cosmetic appearance of the keloids, it also improved pruritus and pain, and was perceived by the subjects as a satisfactory treatment. In addition, it may be used an alternative treatment for those non-responsive to IL triamcinolone. Larger and longer studies may follow this research to assess whether bleomycin could result in faster improvement and a prolonged time to recurrence, thereby resulting in fewer treatments over time.

Keywords: bleomycin, keloid, scar, triamcinolone acetonide

INTRODUCTION

Keloids are the result of abnormal wound healing responses, which lead to benign fibrous growths in predisposed individuals from certain ethnic groups[1]. Patients with keloids frequently seek consultation in dermatology clinics for aesthetic reasons. In addition, bothersome symptoms such as pain and pruritus are commonly reported. Functional disability may result from a large keloid, leading to difficulties in mobility and an adverse effect on one's activities of daily living. The negative impact that scars have on many individuals has prompted several researchers to continually seek prevention and treatment strategies. A review for the management of scars reveals the following armamentarium: scar revision surgery, compression therapy, topical silicone gel, laser therapy, radiation, corticosteroids, and other pharmacologic therapies, such as 5-fluorouracil, imiquimod 5% cream, onion extract, interferons, and immunotherapy, or a combination of these[2]. Success rates in clinical trials vary, mostly according to sample size, the length of study period, as well as the length of post-treatment surveillance. It is not uncommon for a dermatologist to be faced with a patient who has tried numerous therapeutic approaches, but without acceptable clinical response.

Among all the methods of treating keloids, perhaps the most accepted and most commonly used is IL triamcinolone acetonide, a corticosteroid. Its success in the treatment of scars lies in its ability to prevent excessive scarring by decreasing collagen synthesis, glycosaminoglycan synthesis, the proliferation of fibroblasts, and by downgrading the expression of inflammatory mediators[3]. Although success rates are pegged at 50% to 100%, the rate of recurrence of keloids after treatment ranges from 9% to as high as 50%[4]. Unfortunately, effective treatment is not guaranteed and typically requires many sessions Side effects include the pain of the injections, thinning and at-rophy of the skin and subcutaneous tissues, the development of steroid acne, capillary dilation, and hypopigmentation[5]. These concerns have led the investigators to look for an alternative treatment that will result in less recurrence and better outcomes in a shorter period of time.

In recent years, considerable interest has evolved over the use of chemotherapeutic agents for the treatment of keloids. Bleomycin is an antitumor, antibacterial, and antiviral agent that was first isolated in 1962 by Umezawa and colleagues from the actinomycotic soil fungus *Streptomyces verticillus*. This drug is most commonly used as a chemotherapeutic agent in the treatment of various kinds of malignancy such as squamous cell carcinoma of the head and neck, skin, penis, cervix, vulva, lymphoma, testicular carcinoma, and in malignant pleural effusion. In the field of dermatology, there are currently no approved United States Food and Drug Administration (US FDA) indications for the use of IL bleomycin. Its off-label use for dermatologic diseases however, is quite common, and includes treatment for tumors, vascular anomalies, cutaneous malignancies, and verruca[6].

In 1996, the first clinical trial using IL bleomycin as therapy for scars was published. The researchers, Bodokh and Brun[7], administered three to five IL injections of bleomycin to 5 hypertrophic scars and 31 keloids within a period of one month. Complete regression of the scars was seen in 69.4% of patients. These promising results prompted a more recent study done by España et al[8]. In their trial, 1.5 IU/mL of bleomycin was drizzled onto the scars of 13 patients. Using a 25-gauge needle, the medication was introduced into the skin via a multiple-puncture method, where 40 punctures/ 5 mm^2 was given. After approximately 1 to 5 sessions spanning 1 to 4 months, primary outcome measures (size, symptomatic improvement, color, and thickness of the scars) were measured. 53.8% of patients had complete flattening of their lesions; 38.4% had highly significant flattening, and the remaining 1 patient had significant flattening.

To the best of the authors' knowledge, there is currently no locally published trial comparing IL bleomycin and IL triamcinolone for the treatment of small keloids.

OBJECTIVES

General Objectives:

1. To assess the efficacy of IL bleomycin in the treatment of keloids.
2. To evaluate the safety of IL bleomycin in the treatment of keloids.
3. To determine the tolerability of IL bleomycin in the treatment of keloids by examining the subjects' post-treatment satisfaction.

Specific Objectives:

1. To compare changes in the vascularity, pigmentation, pliability, and height between the control lesion (triamcinolone) versus the experimental lesion (bleomycin) using the VSS.
2. To determine the incidence of adverse events related to both groups.

METHODOLOGY

Study Design

This was an 8-week, left-right comparison study on subjects with 2 or more small keloids.

Patient Selection and Randomization

Subjects were recruited from May to July 2011 from the outpatient department of the Department of Dermatology, Jose R. Reyes Memorial Medical Center, Sta. Cruz, Manila, Philippines. Those with known allergies to components of triamcinolone acetonide or bleomycin, pregnant women, lactating mothers, subjects with active comorbid illnesses, and those incapable of giving a written informed consent were excluded from the study. A total of six participants aged 11 to 36 years old with two or more keloids measuring not more than 2 cm^3 on the trunk or extremities were included in the study.

Personal data forms were collected regarding their sex, age, occupation, cause of the keloid, site, length of time the keloids have been present, associated symptoms, and any previous treatments for their scars. Toss coin method was used to determine which of the subject's keloid received bleomycin or triamcinolone.

The study was approved by the Institutional Review Board of the said institution and was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent from the patients and/or guardians was obtained before the start of the trial.

Treatments and Evaluations

Bleomycin sulfate (Bloicin-S) 15 IU/mL was dissolved in 10 mL of 2% lidocaine to make a concentration of 1.5 IU/mL. The area of the first keloid (experimental lesion) was given IL bleomycin 0.1 mL while 0.1 mL triamcinolone (Kanolone) 10 mg/mL was given to the area of the 2^{nd} keloid (control lesion). Sessions were repeated every 2 weeks for 2 months, for a total of 4 sessions.

An evaluator assessed the scars using the VSS at the beginning and at the end of the study. The VSS is an evaluator-based scale that measures four scar parameters: pigmentation, vascularity, pliability, and height (Table 1). Photographs were taken at baseline and at each visit using a digital camera (Panasonic Lumix LX3). Any adverse events were recorded.

At the end of the study period, participants were asked to answer a questionnaire regarding subjective changes in the following symptoms: pain, pruritus, erythema, pliability, and scar size, whether these improved (I), worsened (W), did not change (NC), or was not present (NA). Overall satisfaction was also measured using a 5-point Likert scale, where: 1 (dissatisfied), 2 (somewhat dissatisfied); 3 (neither satisfied nor dissatisfied); 4 (somewhat satisfied); and 5 (very satisfied).

Table 1. Vancouver Scar Scale

Score	Pigmentation	Vascularity	Pliability	Height
0	Normal (Closely resembles the color of nearby skin)	Normal	Normal	Normal (Flat)
1	Hypopigmentation	Pink (Slight increase in local blood supply	Supple (Flexible with minimal resistance)	<2 mm
2	Hyperpigmentation	Red (Significant increase in local blood supply)	Yielding (Giving way to pressure, offering moderate resistance, but does not behave as a solid scar mass)	>2 & <5 mm
3	-	Purple (Excessive local blood supply)	Firm (Solid/inflexible unit, not easily moved, resistant to manual pressure)	>5 mm
4	-		Banding Rope-like tissue that blanches with extension of scar but does not limit range of motion)	-
5			Contracture (Permanent shortening of scar producing deformity or distortion; limits range of motion	

Statistical Methods

Data were analyzed using the Mann-Whitney U test and Pearson's chi-squared test. A level of significance of 5% was adopted.

RESULTS

Patient Disposition and Baseline Characteristics

A total of 6 subjects were included in the study. Table 2 shows a summary.

Table 2. Patient demographics and scar characteristics

Subject	Age	Sex	Occupation	Scar Age	Location	Cause	Symptoms	Prior Treatment
1	36	M	Logistic officer	< 1 yr	Foot/Arm	Trauma	Pruritus, erythema	None
2	23	M	Promodizer	> 1yr	Chest	Trauma	Pruritus, erythema	None
3	23	M	Loans Assistant	> 1 yr	Chest	Acne	Pruritus, erythema	None
4	11	F	Student	< 1 yr	Chest/Shoulder	Varicella	Pruritus, erythema	None
5	15	M	Student	> 1 yr	Back	Varicella	Erythema	IL steroid
6	27	M	Writer/researcher	> 1 yr	Chest	Acne	Pruritus, Pain, increasing size, erythema	IL steroid Topical allantoin gels

Assessment of Scar Height, Vascularity, Pigmentation and Pliability using the VSS

The total VSS for the studied keloids were recorded at baseline and at the end of the trial (Table 3). Results show that for the bleomycin group, there was a significant improvement in the VSS (p = 0.05), whereas no statistically significant improvement was seen in the triamcinolone group (p = 0.34). The results also show that there were no statistically significant changes in the individual parameters of height, vascularity, pigmentation, and pliability.

Table 3. Comparison of initial and final total VSS scores

	Bleomycin		Triamcinolone	
Subject	**Initial**	**Final**	**Initial**	**Final**
1	9	7	4	3
2	7	4	8	4
3	9	7	9	8
4	7	4	3	0
5	6	6	6	7
6	7	4	9	7
Mean	7.5 ±1.2	5.3 ± 1.5	6.5 ± 2.6	4.8± 3.1
z score	**1.92**		0.96	
p-value	**0.05**		0.34	

Table 4. Height scores of the keloids before and after treatment

	Bleomycin		Triamcinolone	
Subject	**Initial**	**Final**	**Initial**	**Final**
1	3	2	0	0
2	3	1	3	1
3	2	2	2	2
4	1	0	0	0
5	0	2	1	2
6	2	1	2	2
z score	0.80		0.16	
p-value	0.42		0.87	

Table 6. Pigmentation scores of the keloids before and after treatment

	Bleomycin		Triamcinolone	
Subject	**Initial**	**Final**	**Initial**	**Final**
1	2	2	2	2
2	2	1	2	1
3	2	2	2	2
4	0	2	0	0
5	1	1	0	2
6	2	2	2	2
z score	-0.08		-0.08	
p-value	0.93		0.94	

Table 7. Pliability scores of the keloids before and after treatment

	Bleomycin		Triamcinolone	
Subject	**Initial**	**Final**	**Initial**	**Final**
1	3	2	1	1
2	1	1	2	1
3	3	2	3	3
4	3	1	0	0
5	3	1	3	1
6	1	1	3	2
z score	1.52		0.88	
p-value	0.12		0.38	

Subject's Self-Assessment

At the end of the study period, participants were asked to answer a self-assessment survey regarding changes in pruritus, pain, erythema, softness, and size. Although not statistically significant, all patients reported an improvement in the softness and size of the keloid that was treated with bleomycin. The single patient who reported keloid pain reported this pain to have improved with the bleomycin treatment. Only 1 subject reported a worsening of erythema, and only 1 noted no change in pruritus after bleomycin treatment (Table 8).

Subjects were also asked to grade their satisfaction with the treatments they received (Table 9). None of the patients were dissatisfied with the treatment outcome. Mean satisfaction for the bleomycin treatment was lower than the triamcinolone treatment. There was no significant difference in satisfaction between these two (p = 0.55).

Table 1. Vancouver Scar Scale

Subject	Pruritus		Pain		Erythema		Softness		Size	
	Bleo	**Triam**	**Bleo**	**Triam**	**Bleo**	**Triam**	**Bleo**	**Triam**	**Bleo**	**Triam**
1	NC	NC	NA	NA	W	W	I	NC	I	I
2	I	I	NA	NA	I	W	I	I	I	I
3	I	I	NA	NA	I	I	I	I	I	I
4	I	I	NA	NA	I	I	I	I	I	I
5	NA	NA	NA	NA	I	NC	I	I	W	I
6	I	I	I	NA	I	I	I	I	I	I
Total improved	4/6	4/6	1/6	0/6	5/6	3/6	**6/6**	5/6	**6/6**	5/6

Bleo, bleomycin; Triam, triamcinolone; NC, no change; NA, not present; W, worsened; I, improved

Table 9. Subject satisfaction with end result of the treatments

Subject	Bleomycin	Triamcinolone
1	4	4
2	3	3
3	3	3
4	5	5
5	4	5
6	3	4
mean	**3.6 ± 0.81**	**4 ± 0.89**
p-value	0.55	

Adverse Reactions

For the keloids that were given triamcinolone, 1 subject exhibited telangiectasia and another had hyperpigmentation. In the bleomycin group, 1 subject showed both hyperpigmentation and minimal crusting at the injection site of the treated area.

DISCUSSION

Disfiguring and bothersome keloids are one of the most common reasons for consultation in dermatology clinics. The general consensus on the guidelines for the management of these scars is through a multi-modality approach, where IL triamcinolone as a first-line treatment for scars has been well established. A study done by Anthony et al comparing different strengths of triamcinolone concluded that a dosage of 10 mg/mL followed by 40 mg/mL was most effective, with the lowest recurrence rate[8]. Furthermore, studies suggest that treatment periods of as long as 4 – 6 months are needed before any noticeable improvement can be observed. Because of these drawbacks, recent studies using IL bleomycin have been done to assess its efficacy in the treatment of keloids. Although its exact mechanism remains unknown, recent experimentation on cultures of human dermal fibroblasts have found that bleomycin directly inhibits the formation of collagen of these cells. It has also been postulated that bleomycin has the capability to reduce the levels of lysyl-oxidase, the cross linking enzyme involved in collagen maturation[9].

In the present investigation, the initial VSS of the scars in the triamcinolone group did not statistically improve, while VSS of the scars that received IL bleomycin did. This result suggests that bleomycin has the potential to be a successful alternative in patients not responsive to the usual therapy with triamcinolone.

The present study parallels earlier studies done where bleomycin was effective in decreasing scar size. Saray and Gülec[10] investigated a different method of introducing bleomycin into scars in 2005 when they applied intralesional dermojet injections of the drug to 14 patients who were unresponsive to intralesional steroid injection in the past. 0.1 mL of 1.5 IU/mL bleomycin was injected 0.5 mm apart into each lesion in sessions that were repeated monthly. Measurements of scar height, scar pliability, and erythema were taken during the treatment and follow-up periods. The results showed that 73.3% of lesions showed complete flattening, 6.7% showed highly significant flattening, 13.3% had significant flattening, and only 6.7% moderate flattening. Mean scar height was significantly lower, and both the mean scar pliability as well as erythema scores were significantly better at the end of the treatment period.

The participant's self-assessment is also integral to any study on keloid treatment. Statistics of the present study revealed that there was no significant difference in the patients' self-assessments between the bleomycin and triamcinolone groups. It appears patients considered both drugs as equally effective in improving the appearance of the scars and their associated symptoms. Interestingly, the subjects' satisfaction did not parallel the objective findings – although bleomycin contributed to better results, the satisfaction means were higher in the triamcinolone group. Perhaps other factors (such as pain from the procedure) made bleomycin less desirable than triamcinolone.

Adverse effects observed with bleomycin were hyperpigmentation of the treatment site and minimal hemorrhagic crusting, which may have been due to the effect of bleomycin or due to scratching of the patient. The crusting resolved spontaneously within a week. As for triamcinolone, 1 patient was observed to have telangiectasia and another had slight hyperpigmentation of the lesion. The present study did not assess for systemic adverse effects of the drug, since these types of problems are seen usually in intravenous usage of much higher concentrations, i.e. 150 mg, of the drug[6]. In previous studies using similar concentrations, no systemic toxicity has been reported.

Limitations of the Study

Measuring keloid height and surface area are often challenging in keloid studies due to the irregular shapes of these scars. Gradated measuring devices, like rulers and calipers, are prone to intra-observer variability. To this end, the most precise and accurate means of measuring scar height at present is through ultrasonography[10], while planimetry by digital photography has been recommended as the standard of choice for measuring surface area[11]. Color evaluations may benefit from the use of certain tools (e.g. laser-Doppler flowmeter, etc.), but these were not accessible to the investigators.

This pilot study encourages trials with a bigger sample size, with a uniform location of keloids, with a longer study period, and that includes medium to large keloids, in order to assess time to improvement and rate of recurrence when using IL bleomycin for the treatment of keloids.

CONCLUSIONS

The results of the present study are promising - we can conclude that IL bleomycin is an effective and safe treatment for keloids. Scar height, pigmentation, vascularity, and pliability of scars showed a decreasing trend, approaching the appearance of normal skin. Subjects were generally satisfied with the outcome, and adverse events were mild, cutaneous in nature, and resolved spontaneously. The present study also suggests that IL bleomycin may be used an alternative treatment for those who have a slow response or are non-responsive to IL triamcinolone.

ACKNOWLEDGMENTS

The investigators would like to thank Anne Salcedo and Edgardo Tolentino, DMD of Qualimed Pharma, Inc. for their generosity in providing Bloicin-S.

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A Systematic Review on the Effectiveness of Hemorrhoidal Artery Ligation (Transanal Hemorrhoidal Dearterialization) vs the conventional hemorrhoidectomy for Adult Patients with Grades II and III Internal Hemorrhoids

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A systematic review was by Giordano et al in 2009 showed that transanal hemorrhoidal dearterialization (THD) would appear to be a potential non-excisional technique for the treatment of second-degree and third-degree haemorrhage, the main advantages being minimal postoperative pain and quick recovery. However, it included mostly poor quality studies available at that time, so that the conclusion may be an overestimate of the effectiveness of the technique and did not include trials that have completed and reported after 2009. The aim of this systematic review is to synthesize the best current evidence on the effectiveness of transanal hemorrhoidal dearterialization as compared to the conventional hemorrhoidectomy with post-operative pain, post-operative bleeding and recurrence rate as primary outcomes, and operative time and urinary retention as secondary outcomes, among adult patients with Grades II and III internal hemorrhoids. PubMed was searched for randomized controlled trials done from 1995 up to 2014. Four out of 221 trials met the criteria for inclusion. There was no evidence of any difference between conventional open hemorrhoidectomy and transanal hemorrhoidal dearterialization in terms of post-operative pain, post-operative bleeding (P=0.76), operative time, urinary retention (P = 0.57), post-operative prolapse/recurrence (P=0.38) in adult patients with grades II and III internal hemorrhoids. Because the confidence interval of the summary statistics (Risk Ratio) are very wide, it just shows that not enough data is available to show a precise result. Thus, one cannot conclude whether one technique is better than the other or if they are truly the same.

KEYWORDS: *Hemorrhoidal artery ligation, Transanal hemorrhoidal dearterialization, internal haemorrhoids, hemorrhoidectomy, postoperative complications*

INTRODUCTION

Hemorrhoidal disease is a common form among anal disorders. It is caused by anal cushion descent or abnormal congestion of the internal hemorrhoidal venous plexus.[1] There are different approaches in treating hemorrhoidal disease, including pharmaceutical, instrumental and surgical methods in various therapeutic schemes. The gold standard in treating hemorrhoidal disease is hemorrhoidectomy which includes well-established procedures such as Milligan-Morgan, Parks, and Ferguson. Hemorrhoidectomy is the most effective treatment for hemorrhoids with the lowest rate of recurrence compared to other modalities. It can be performed using scissors, diathermy, or vascular-sealing device such as Ligasure and Harmonic scalpel. Indications for hemorrhoidectomy include failure of non-operative management, acute complicated hemorrhoids such as strangulation or thrombosis, patient preference, and concomitant anorectal conditions such as anal fissure or fistula-in-ano which require surgery. [3] It is a good method to eliminate the pathophysiological factors which causes hemorrhoids, but has disadvantages of having an approximately 10% postoperative complication rate, requiring time for treatment, and requiring significant time to return to daily living.[1]

The arterial blood supply of the internal hemorrhoidal plexus is commonly believed to be associated with the pathogenesis of hemorrhoids. Ultrasound-supported proctoscopic techniques with Doppler-guided ligature of submucosal rectal arteries have been introduced for the therapy of hemorrhoids. The present investigation focuses on caliber and flow changes of the terminal branches of the superior rectal artery supplying the corpus cavernosum recti in patients with hemorrhoids.[4] Transanal hemorrhoidal dearterialization (THD) is an effective treatment for hemorrhoidal disease. It is based on two technical steps: the targeted ligation of hemorrhoidal arteries (called ''dearterialization''), using a very sensitive continuous Doppler probe able to identify the maximal flow; and the plication and lifting of redundant and prolapsing rectal mucosa/submucosa (called ''mucopexy''). Transanal hemorrhoidal dearterialization is a valid therapeutic option in patients with hemorrhoidal disease. The limited number and severity of complications makes THD very safe.[5]

The researchers are in a constant search of new methods of treating hemorrhoidal disease that would offer not only high effectiveness and low morbidity, but also short recovery and good postoperative comfort. It has long been a challenge to surgeons to meet the patient's expectations of resolution of preoperative symptoms such as pain, bleeding and prolapse and also of minimal postoperative pain and bleeding. During the last two decades, nonexcisional surgical approaches to hemorrhoidal disease have shown a high potential for cure with a theoretically reduced morbidity. In 1995, Morinaga, a Japanese surgeon, developed a technique based on Doppler-guided selective ligation of the main hemorrhoidal arteries, branches of the inferior rectal arteries. This technique allows for restoration of normal anatomy using minimally invasive surgery with substantially reduced pain and discomfort. [2] This procedure has grown in popularity because it is easy to perform, has a short learning curve, is minimally invasive, and is associated with positive outcomes, low levels of pain and a low risk of fecal incontinence.

A systematic review was done in 2009 by Giordano, et al which included 17 articles including a total of 1996 patients analyzed. This showed that THD would appear to be a potential non-excisional technique for the treatment of second-degree and third-degree haemorrhage, the main advantages being minimal postoperative pain and quick recovery.[6] However, the limitation of this review is that it included mostly poor quality studies available at that time, so that the conclusion may be an overestimate of the effectiveness of the technique. Also, it does not include trials that have completed and reported after 2009. In the light of the above, the need to do a systematic review that includes new studies, but is limited to randomized controlled trials (which are the best evidence of treatment efficacy / effectiveness) may establish the true effectiveness of the procedure compared with other interventions available for the treatment of haemorrhoids.

The aim of this systematic review is to synthesize the best current evidence on the effectiveness

of transanal dearterialization/hemorrhoidal artery ligation as compared to the conventional hemorrhoidectomy in terms of post-operative pain, post-operative bleeding, length of hospital stay and recurrence rate among adult patients with Grades II and III internal hemorrhoids.

OBJECTIVES

This review made the comparison of hemorrhoidal artery ligation/transanal hemorrhoidal dearterialiazation versus the conventional hemorrhoidectomy under any kind of anesthesia in terms of post-operative pain, post-operative bleeding, operative time, urinary retention, post operative prolapse/ recurrence in adult patients with grades II and III internal haemorrhoids.

METHODOLOGY

The review utilized an electronic search of literature to identify randomized control trials comparing hemorrhoidal artery ligation/transanal hemorrhoidal dearterialiazation versus conventional hemorrhoidectomy under any kind of anesthesia in adult patients with grades II and III internal haemorrhoids.

SEARCH FOR IDENTIFICATION OF STUDIES

Database searched: PubMed was searched for randomized controlled trials and systematic reviews done from 1995 up to September 2014.

Simple search was done in PubMed limiting the search to include randomized controlled trials and systematic reviews only. The search terms used were "(hemorrhoidal artery ligation) or (transanal hemorrhoidal dearterialization)". The initial search yielded 221 articles. These articles were screened based on the content of their abstracts by two reviewers working independently of each other. Out of 221 articles, 205 were excluded because these were either older than 1995, and/or with interventions and outcomes not relevant in our study. Out of 16 full-text articles (15 randomized controlled trial and 1 systematic review) eligible for study, 12 studies were excluded due to following reasons: 9 studies were not randomized controlled trials, 1 study had study population that did not meet the inclusion criteria (had previous surgery/intervention), 1 study had interventions not relevant to this study, and 1 article was not available for retrieval. From the review of references in the included systematic review, titles were screened. One out of 17 articles is a randomized controlled trial, hence was included in this review. Once deemed eligible, full text was retrieved and information was abstracted as in the other trials picked up by the electronic search. Articles that were excluded included those older than 1995, and those with interventions and outcomes not relevant in our study.

Search Sequence and terms:

1. Hemorrhoidal artery ligation
2. Transanal hemorrhoidal dearterialization
3. Internal haemorrhoids
4. Hemorrhoidectomy
5. Postoperative complications
6. Adults
7. 1 or 2 and 3 or 4 and 5 and 6

CRITERIA FOR SELECTION

The criteria used for the inclusion of studies in this review included :

TYPES OF PARTICIPANTS

Studies included adult patients with grades II and III internal hemorrhoids

TYPES OF INTERVENTION

One arm of the study included patients who underwent hemorrhoidal artery ligation/transanal hemorrhoidal dearterialization which involves selective ligation of the inferior rectal hemorrhoidal arteries with or without the aid of Doppler transducer followed by a mucopexy under any kind of anesthesia while another arm underwent the conventional

hemorrhoidectomy which includes procedures such as Milligan-Morgan, Parks, and Ferguson under any kind of anesthesia.

TYPES OF OUTCOMES

Primary outcomes included incidence of postoperative pain, postoperative bleeding and recurrence rate. Secondary outcomes included operative time and urinary retention.

TYPES OF STUDIES/METHODOLOGIES

Randomized controlled trials and systematic reviews

PROCESS OF SELECTION

Published reports of all potentially eligible studies were evaluated by two reviewers independently, without prior consideration of the results. First screen was done by sorting through the titles and abstracts to know which full text articles to get. Second screen was done by selecting among the full text articles. This only included studies in English language

STUDY APPRAISAL/ASSESSMENT OF THE RISK OF BIAS

The risk of bias in eligible trials was assessed independently by two reviewers using the Cochrane risk of bias tool. Factors that were considered include quality of random allocation and concealment (where appropriate), description of drop-outs and withdrawals and missing data, blinding during intervention and at outcome assessment (where appropriate), description of and protection against possible contamination (where appropriate).

DATA ABSTRACTION

Standardised data extraction forms were used by two reviewers independently and cross-checked. In cases where insufficient data were reported (i.e. standard deviation was not reported) such as in studies done by Elmer et al and De Nardi et al, these authors were contacted through email for further information. However, no response from Elmer noted. De Nardi was able to respond to the correspondence via email wherein she stated that the resident who collected the database of their study is working in another country and not available at the moment.

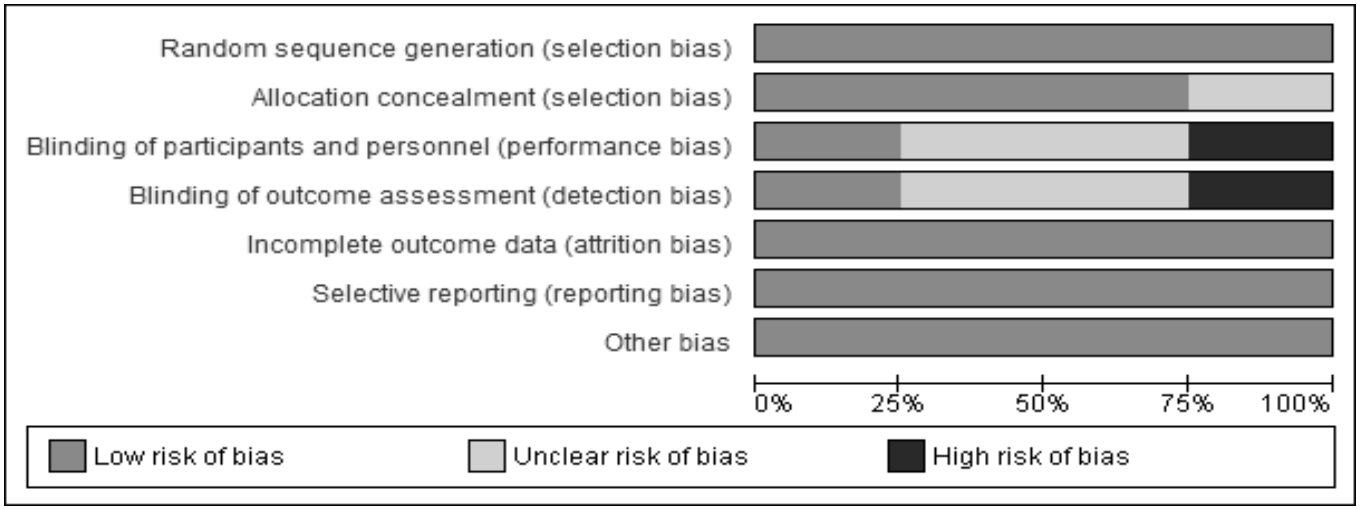
RESULTS

Two hundred twenty-one studies were identified through database search using PubMed. Out of 221 studies, 205 were excluded because these were either older than 1995, and/or with interventions and outcomes not relevant in our study. Out of 16 full-text articles eligible for study, 12 studies were excluded due to following reasons: 9 studies were not randomized controlled trials, 1 study had study population that did not meet the inclusion criteria (had previous surgery/intervention), 1 study had interventions not relevant to this study, and 1 article was not available for retrieval. Four trials met the criteria for inclusion. A total of 198 patients were enrolled from the four trials, from which 190 patients were included in the results. The reasons for withdrawal will be discussed in the summary of quality assessment of the studies included (Table 1.1). Ninety-six patients underwent Hemorrhoidal Arterial Ligation/Transanal hemorrhoidal dearterialization while Ninety-four patients underwent conventional hemorrhoidectomy.

Table 1.1 Summary of Quality Assessment of Included Studies

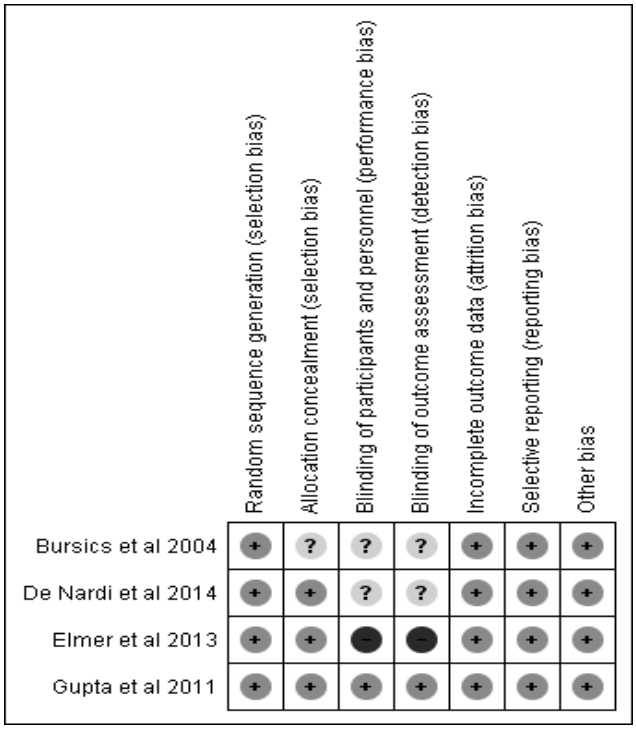
STUDY	RANDOMIZATION	ALLOCATION CONCEALMENT	BLINDING	WITHDRAWALS	ALL OUTCOMES REPORTED	REMARKS
De Nardi et al 2014	An allocation list, which was based on the block random assignment of 5 patients, was used.	For every consecutively enrolled patient, a sealed envelope, with the randomization arm written on a paper that was folded twice, was prepared by a physician who was not involved in the study. The envelope was assigned after the patient provided this consent, and it was opened before the surgical procedure began.	Not mentioned	3 Reasons: 1 patient from the EOH group and 1 from the DM group were lost to follow up. 1 patient from EOH group excluded from analysis (patient because of a stroke that had occured 6 months before)	Yes	The principal weaknesses of the study are that the follow-up, although longer than the majority of the available studies, was not very long; a cost analysis was not performed; and the questionnaires used in the follow-up were not validated
Elmer et al 2013	Randomization between THD and OH was done by a research nurse.	Sealed envelopes were used and opened in the operating room.	None	2 Reasons: 2 patients in open hemorrhoidectomy arm. One did not receive allocated intervention (1 patient did not want to undergo surgery). One patient did not wish to take part in follow-up	Yes	No blinding was possible because it is a surgical intervention. Since there was no blinding in the study, there might be a possible bias in reporting of outcomes
Gupta et al 2011	A single person performed all randomizations, which were done in blocks so that the number of patients in the two groups was balanced over the course of the trial	Recruited patients were randomly allocated, by means of sealed envelopes, to one of the two study arms: (1) ligation and mucopexy [SL group] or (2) DGHAL plus ligation and mucopexy [DSL group]	Yes	2 in DSL group and 1 in SL group Reason: After 1 year, 2 patients from the DSL group and one patient from the SL group were lost to follow up.	Yes	This is a double-blinded randomized control study. There was no reporting bias. No other sources of bias in the study
Bursics et al 2004	Patients were randomized based on the date of the first visit to outpatient department	Not mentioned	Not mentioned	No	Yes	Potential sources of bias would be the allocation concealment and were not mentioned

Figure 1.1 Risk of bias graph



Based on the graph shown above (Figure 1.1), generally, there was a low risk of bias in all the criterias except for blinding of participants and personnel and also the blinding of outcome assessment which is either not mentioned or is not possible since the intervention on both arms are surgical. There is one study (Bursics et al 2004) wherein allocation concealment was not mentioned in the study, hence can be a potential source of bias

Figure 1.2 Risk of bias summary

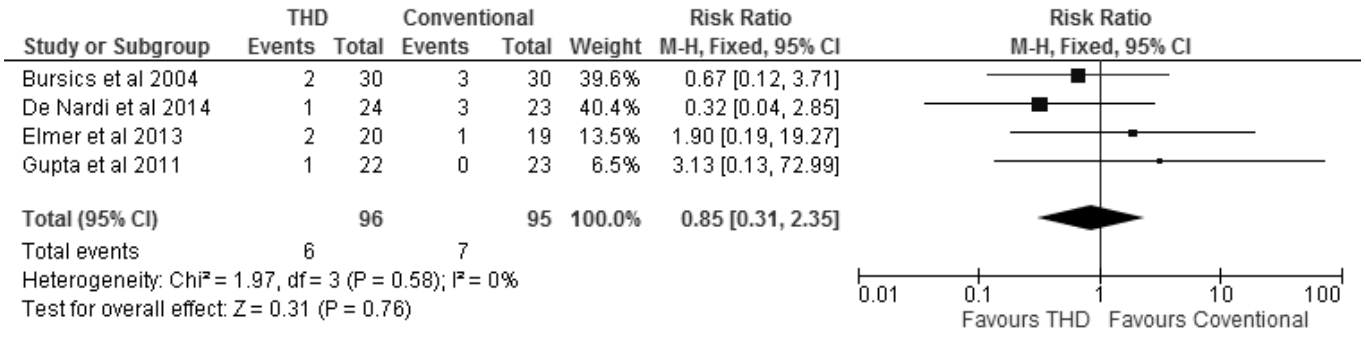


As seen in Figure 1.2, there was generally a low risk of bias in all 3 studies. In the study done by De Nardi et al (2014), blinding was not mentioned which gave the study a Unclear Risk for blinding. In contrary, blinding was not done in the study of Elmer et al (2013), therefore there is a high risk of bias in the study done. In the study done by Bursics et al (2004), allocation concealment was not mentioned.

All the three studies reported on the comparison of postoperative pain between the two interventions. However, a metaanalysis could not be done since standard deviation was not reported in these studies. Gupta et al reported that the postoperative pain score was significantly higher in the Doppler group (VAS of 4.4) than in control (VAS of 2.2) with P value less than 0.002. The mean total analgesic dose and duration of pain control using analgesics were greater and longer for the Doppler group (17 vs 11 tablets, and 13 day vs 9 days), respectively. In the study done by De Nardi et al (2014), one gram of paracetamol was administered every 8 hours, and the patients were discharged with 10 mg ketoprofen or 50mg tramadol, as needed. The following mean postoperative VAS pain scores were recorded in the open hemorrhoidectomy and dearterialization groups: 7 vs 5.5 (p=0.67) on first postoperative day, 3 vs 2.5 (p = 0.71) on 7^{th} postoperative day, 1 vs 0 (p = 0.71) on 14^{th} postoperative day and 0 vs 0 (p = 0.98) on the 30^{th} postoperative day. The mean VAS pain score during defecation was 5 vs 3 (p=0.07) on 7^{th} postoperative day and 2 vs 1 (p = 0.51) on the 14^{th} postoperative day.

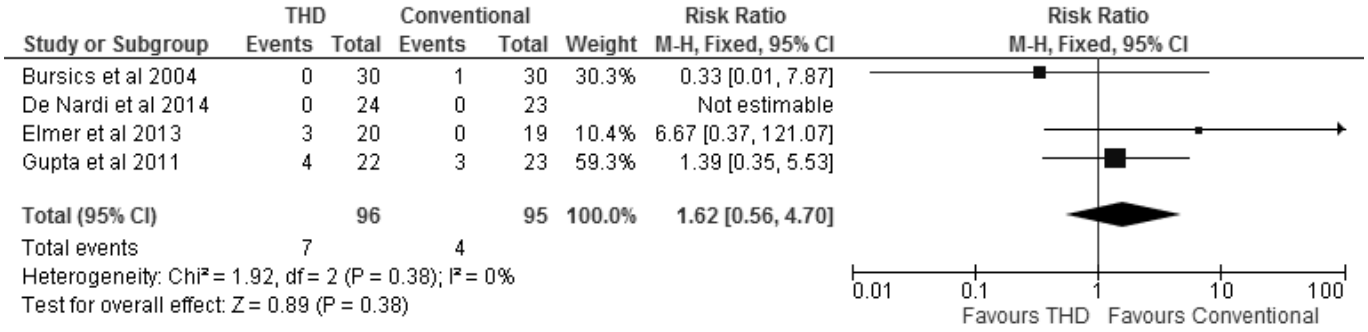
In the study done by Elmer et al (2013), The peak pain scores were significantly lower in the THD group for 5 days during the first week ($p < 0.05$). A peak pain score of more than 3 was reported for a median of 7 days (range of 0 to 13 days) in the THD group in comparison with 12 days (range of 5 to 14 days) in the open hemorrhoidectomy group. The overall pain did not differ between the two groups. The use of analgesics was similar among the groups.

Figure 1.3 Postoperative Bleeding



There was no significant difference (P = 0.76) in the risk of postoperative bleeding between conventional hemorrhoidectomy and transanal dearterialization. Risk ratio was 0.85 (95% CI 0.31, 2.35).

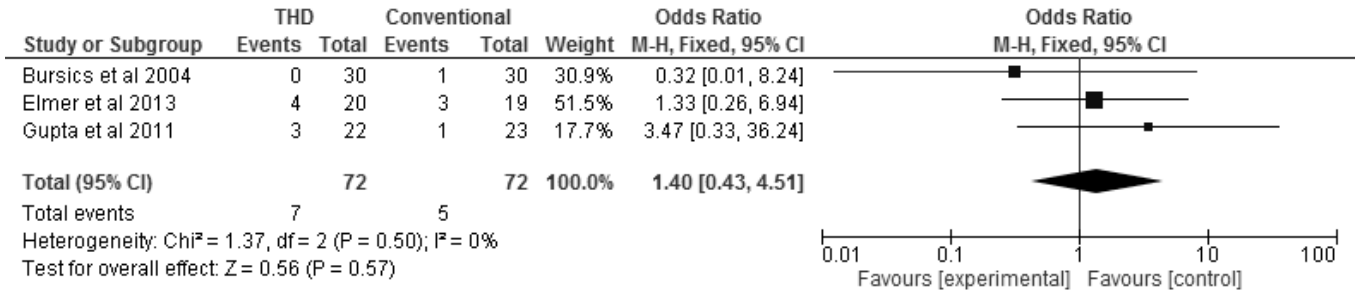
Figure 1.4 Prolapse/Recurrence



There was no significant difference (RR = 1.62, 95%CI 0.56, 4.70) in prolapse/recurrence between the conventional hemorrhoidectomy and THD.

Three out of four included studies had data on duration of surgery. However, metaanalysis was not possible because standard deviation was not reported. All studies reported longer operative time with THD. Gupta et al (2011) reported that the duration of surgery was significantly higher in the Doppler group (31 minutes vs 9 minutes with P value of less than 0.003. In the study done by De Nardi et al (2014), mean operative time was 25 ± 10 minutes in the open hemorrhoidectomy and 35 ± 20 minutes in dearterialization and mucopexy group with P value less than 0.001. In the study done by Elmer et al (2013) operative time was longer for THD (36 minutes) as compared to Open hemorrhoidectomy (20minutes) with p value < 0.001.

Figure 1.5 Urinary Retention



Only three out of the four studies had data regarding urinary retention (Elmer et al and Gupta et al). There was no significant difference (RR= 1.40, 95%CI 0.43, 4.51) in urinary retention between THD and conventional hemorrhoidectomy.

DISCUSSION

Summary of main results

The overall postoperative pain did not differ between the hemorrhoidal artery ligation and the conventional hemorrhoidectomy. There was no significant difference in postoperative bleeding between the 2 interventions.

There was no significant difference in urinary retention, prolapse/recurrence between the conventional hemorrhoidectomy and THD. There was generally a longer duration of surgery in THD as compared to the conventional method.

Limitations of the study

Our study was limited since there were only few randomized controlled studies comparing the two interventions. Majority of the available studies were either prospective or retrospective cohorts, or observational studies consisting of case series of surgeons pioneering the technique, which were excluded in this study. The size of population analyzed in this study is small, therefore, randomized controlled trials with larger population are recommended to come up with better results. Authors of these trials should be encouraged to report mean and standard deviation data (or make them available on request) to allow accurate representation of summary data within a meta-analysis or systematic review when required. Well-designed methodology of randomized controlled trials is recommended which includes the population excluded in these trials .

Potential biases in the review process

The potential sources of bias in the review process would include the limitation of the selection of studies to English language papers only, the failure to get the necessary missing information from the authors which included important elements in the raw data of their studies which are essential in the metaanalysis.

Agreements and disagreements with other studies or reviews

A systematic review on transanal hemorrhoidal dearterialization was done in 2009 by Giordano et al which included all published studies on dearterialization without language restrictions. Seventeen articles including a total of 1,996 patients were analyzed. In general, the quality of the studies was low. Primary outcome measures were postoperative pain and hemorrhoidal recurrences. In this systematic review, transanal hemorrhoidal dearterialization appeared to be a potential treatment option for second-degree and third-degree hemorrhoids.

The present systematic review included only randomized controlled trials in English language wherein there was no significant difference was noted between the two interventions. However, more randomized trials with larger population is needed to establish a possible role and to further evaluate the advantages and disadvantages of this technique.

Implications to Practice

Since there was no significant difference noted between conventional hemorrhoidectomy and hemorhoidal artery ligation/transanal hemorrhoidal dearterialization, it is still recommended not to change the conventional method of performing hemorrhoidectomy.

Implications to Research

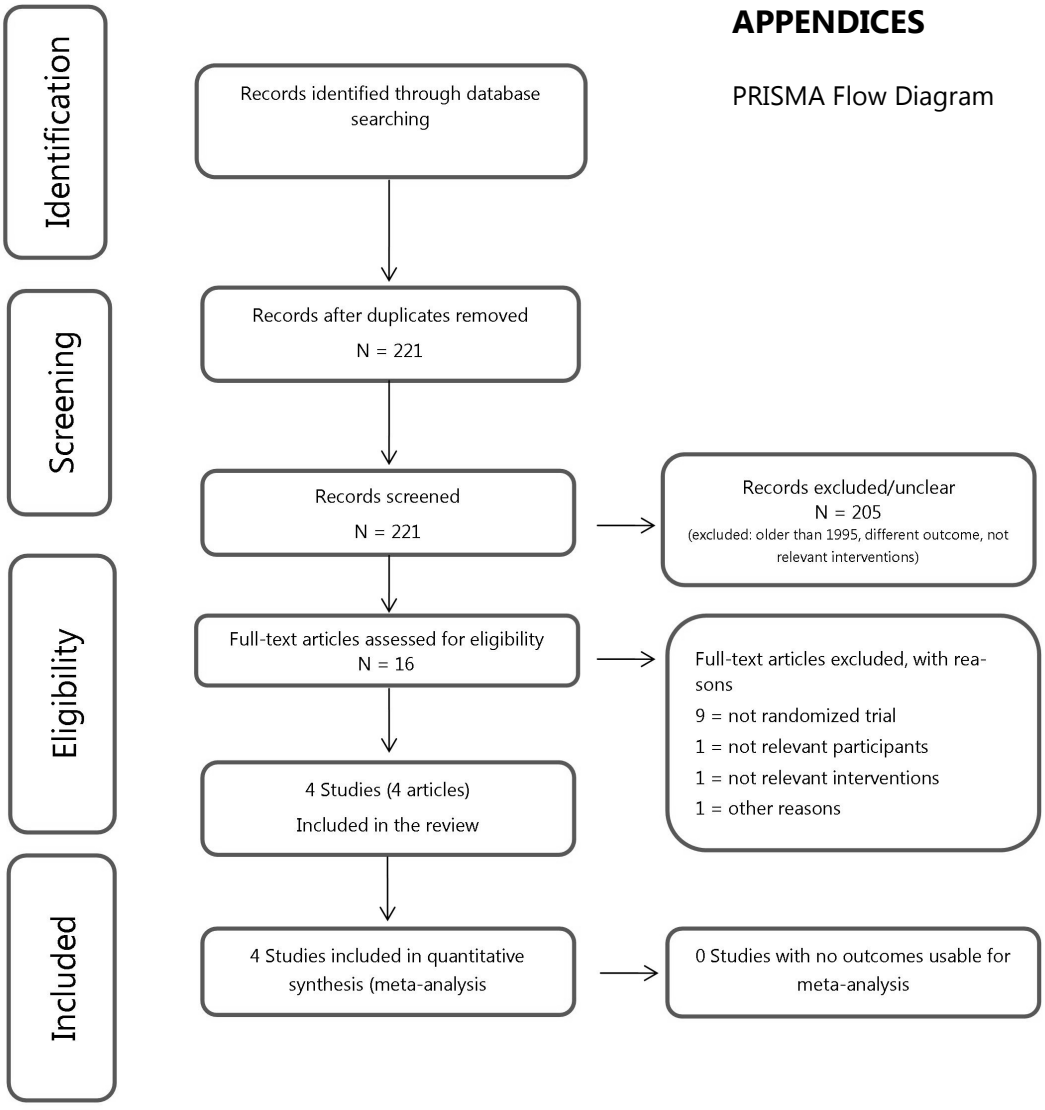
More randomized controlled trials regarding transanal hemorrhoidal dearterialization/hemorrhoidal artery ligation are needed with larger population in each study to yield better results.

CONCLUSION

In conclusion, there was no evidence of any difference between conventional open hemorrhoidectomy and transanal hemorrhoidal dearterialization in terms of post-operative pain, post-operative bleeding, operative time, urinary retention, post-operative prolapse/recurrence in adult patients with grades II and III internal hemorrhoids. Because the confidence interval of the summary statistics (RR) are very wide, it just shows that not enough data is available to show a precise result. Thus, one cannot conclude whether one technique is better than the other or if they are truly the same.

APPENDICES

PRISMA Flow Diagram



DATA ABSTRACTION

1. De Nardi et al 2014

STUDY IDENTIFIER	De Nardi et al 2014
STUDY TITLE	A Prospective, Randomized Trial Comparing the Short- and Long-term Results of Doppler-Guided Transanal Hemorrhoid Dearterialization With Mucopexy Versus Excision Hemorrhoidectomy for Grade III Hemorrhoids
AUTHORS	Paola De Nardi, M.D., Giovanni Capretti, M.D., Antonino Corsaro, M.D., Carlo Staudacher, M.D.
CITATION	Dis Colon Rectum. 2014 Mar;57(3):348-53. doi: 10.1097/DCR.0000000000000085.
PARTICIPANTS	
Description	From July to November 2010, 50 consecutive patients, with Goligher grade III hemorrhoids and prolapse, occurring in at least 80% of their bowel movements, were randomly assigned to undergo excisional hemorrhoidectomy (EOH) or Doppler-guided dearterialization and mucopexy (DM)
Total Number enrolled (exp/ctrl)	25/25
INTERVENTION	
Experimental	
Description	In the DM group, the arterial ligation of the terminal branches of the superior rectal artery was performed with 2-0 absorbable polyglycolic acid suture and a 5/8 curved needle after identifying the blood flow approximately 3 cm above the dentate line by using Doppler guidance. Subsequently, a running suture was added from the suture point to 1 cm above the dentate line to lift the prolapsing tissue. A transanal hemorrhoidal dearterialization instrument (THD S.p.a., Medical Division, Correggio, Reggio Emilia, Italy) was used.
Number (enrolled/analyzed)	25/24
Control	
Description	The EOH patients underwent a conventional, 3-quadrant open, diathermy hemorrhoidectomy.
Number (enrolled/analyzed)	25/23
OUTCOMES	The primary end point was postoperative pain on the first postoperative day. The secondary outcome measures were postoperative morbidity, resumption of social and working activity, patient satisfaction, and relapse of symptoms at 1 and 24 postoperative months..
METHODOLOGY/DESIGN	Prospective Randomized Trial
REMARKS	

STUDY IDENTIFIER	De Nardi et al 2014
RANDOMIZATION (Description)	An allocation list, which was based on the block random assignment of 5 patients, was used.
ALLOCATION CONCEALMENT (Description)	For every consecutively enrolled patient, a sealed envelope, with the randomization arm written on a paper that was folded twice, was prepared by a physician who was not involved in the study. The envelope was assigned after the patient provided this consent, and it was opened before the surgical procedure began.
BLINDING (yes/No)	Not mentioned
WITHDRAWALS	
Yes/No	Yes
How many?	3
Reasons for withdrawal	1 patient from the EOH group and 1 from the DM group were lost to follow up. 1 patient from EOH group excluded from analysis (patient because of a stroke that had occured 6 months before)
ALL OUTCOMES REPORTED?	Yes
Remarks	The principal weaknesses of the study are that the follow-up, although longer than the majority of the available studies, was not very long; a cost analysis was not performed; and the questionnaires used in the follow-up were not validated.

STUDY IDENTIFIER	De Nardi et al 2014	
OUTCOME	Excisional hemorrhoidectomy	Transanal Hemorrhoidal Dearterialization
Mean Operative time	25 ± 10 minutes	35 ± 20 minutes
Mean Postoperative VAS pain scores (First postop day)	7	5.5
Mean Postoperative VAS pain scores (7th postop day)	3	2.5
Postoperative compications	0/23	0/24
Pain on 24th month	1/23	4/24
Bleeding on 24th month	3/23	1/24
Work or normal activity resumed	22 ± 21 days	10 ± 11 days
Prolapse/Recurrence	0/23	0/24

2. De Nardi et al 2013

STUDY IDENTIFIER	Elmer et al 2013
STUDY TITLE	A Randomized Trial of Transanal Hemorrhoidal Dearterialization With Anopexy Compared With Open Hemorrhoidectomy in the Treatment of Hemorrhoids
AUTHORS	Solveig E. Elmér, M.D. • Jonas O. Nygren, M.D., Ph.D. • Claes E. Lenander, M.D., Ph.D
CITATION	Dis Colon Rectum. 2013 Apr;56(4):484-90. doi: 10.1097/DCR.0b013e31827a8567.
PARTICIPANTS	
Description	All eligible patients with symptomatic second- to third-degree hemorrhoids were considered for a randomized study comparing THD/A with OH. Inclusion criteria were symptomatic (bleeding, pain, pruritus, soiling, and prolapse) hemorrhoids grades 2 to 3 requiring surgical treatment. Exclusion criteria were acutely thrombosed hemorrhoids, anal fissure, anal abscesses, anal fistulas, inability to understand the study instructions, age more than 80 years, continuous consumption of analgesics, IBD, fecal incontinence, anal stenosis, bleeding disorder, and rectal prolapse. Patients who had undergone rubber band ligation or sclerotherapy in the past 3 months, OH within 3 years, or any previous operation with HAL, THD, or stapled anopexy were excluded.
Total Number enrolled (exp/ctrl)	20/20
INTERVENTION	
Experimental	Transanal hemorrhoidal dearterialization (THD)
Description	For arterial ligation and anopexy, the THD instrument was introduced to reduce the anal prolapse and to locate the arteries by using the incorporated Doppler probe. Six terminal branches of the superior rectal artery (located at 1, 3, 5, 7, 9, and 11 o'clock (anterior midline representing 12 o´clock)) were identified and ligated with a figure-8 stitch in all cases except 1 (8 ligations). With the same suture, an anopexy was performed by a continuous running suture making 2 to 4 mucosal stitches ending at least 5 mm above the dentate line.
Number (enrolled/analyzed)	20/20
Control	Open hemorrhoidectomy (OH)
Description	Open hemorrhoidectomy was performed without a retractor. The external component was grasped by a forceps, and the hemorrhoids were excised up to the anorectal ring by the use of diathermy for dissection and hemostasis. No ligations were performed, and the wounds were left open. The number of excisions was individualized (2 large excisions in 9 patients and 3 excisions in 10 patients), and adequate mucosal and skin bridges were left between them.
Number (enrolled/analyzed)	20/18
OUTCOMES	Postoperative pain and well-being, complications,
METHODOLOGY/DESIGN	Randomized trial
REMARKS	

STUDY IDENTIFIER	Elmer et al 2013
RANDOMIZATION (Description)	Randomization between THD and OH was done by a research nurse.
ALLOCATION CONCEALMENT (Description)	Sealed envelopes were used and opened in the operating room.
BLINDING (yes/No)	None
WITHDRAWALS	
Yes/No	Yes
How many?	2
Reasons for withdrawal	2 patients in open hemorrhoidectomy arm. One did not receive allocated intervention (1 patient did not want to undergo surgery). One patient did not wish to take part in follow-up
ALL OUTCOMES REPORTED?	Yes
Remarks	

STUDY IDENTIFIER	Elmer et al 2013	
OUTCOME	Transanal hemorrhoidal dearterialization	Open hemorrhoidectomy
Operating time, min, mean (range)	36 (30–45)	20 (10–34)
Secondary hemorrhage	0/20	2/19
Partial reprolapse/Recurrence	3/20	0/19
Reoperation	1/20	0/19
Bleeding after 2 to 4 months	2/20	0/19
Pain after 2 to 4 months	2/20	1/19
Urinary Retention	4/20	3/19

3. De Nardi et al 2011

STUDY IDENTIFIER	Gupta et al 2011
STUDY TITLE	Doppler-guided hemorrhoidal artery ligation does not offer anyvadvantage over suture ligation of grade 3 symptomatichemorrhoids
AUTHORS	P. J. Gupta • S. Kalaskar • S. Taori • P. S. Heda
CITATION	Tech Coloproctol (2011) 15:439–444 DOI 10.1007/s10151-011-0780-7
PARTICIPANTS	
Description	All consecutive patients with symptomatic grade III hemorrhoids, that is, piles that prolapse during defecation but are manually reducible, were enrolled. The following patients were excluded: (1) patients with acute thrombosed hemorrhoids; (2) patients with external hemorrhoids or other concomitant anal diseases (such as fissure, fistula, or abscess); (3) patients with inflammatory bowel disease or hematological disorders; (4)patients on anticoagulants; and (5) patients with a previous history of anorectal surgery, including previous hemorrhoidectomy or fistula surgery.
Total Number enrolled (exp/ctrl)	24/24
INTERVENTION	
Experimental	
Description	Doppler-guided hemorrhoidal artery ligation followed by ligation and mucopexy [DSL]
Number (enrolled/analyzed)	24/22
Control	
Description	ligation and mucopexy [SL]
Number (enrolled/analyzed)	24/23
OUTCOMES	postoperative pain scores, amount of analgesics consumed, and complications encountered. The observer also assessed recurrence of hemorrhoids after 1 year.
METHODOLOGY/DESIGN	double-blind, randomized controlled study
REMARKS	

STUDY IDENTIFIER	Gupta et al 2011
RANDOMIZATION (Description)	A single person performed all randomizations, which were done in blocks so that the number of patients in the two groups was balanced over the course of the trial
ALLOCATION CONCEALMENT (Description)	Recruited patients were randomly allocated, by means of sealed envelopes, to one of the two study arms: (1) ligation and mucopexy [SL group] or (2) DGHAL plus ligation and mucopexy [DSL group]
BLINDING (yes/No)	Yes
WITHDRAWALS	
Yes/No	Yes
How many?	2 in DSL group and 1 in SL group
Reasons for withdrawal	After 1 year, 2 patients from the DSL group and one patient from the SL group were lost to follow up.
ALL OUTCOMES REPORTED?	Yes
Remarks	

STUDY IDENTIFIER	Gupta et al 2011	
OUTCOME	Doppler-guided hemorrhoidal artery ligation followed by ligation and mucopexy [DSL]	ligation and mucopexy [SL]
Operation time (min) (mean(SD))	31 (5.4)	9 (6.3)
Pain VAS score# (0–10) (median)	4.4 (2.9–6.3)	2.2 (1.7–5.9)
Analgesic tablets (n)	17 (8–18)	11 (4–13)
Days analgesic consumed (n)	13 (9–12)	9 (4–9)
Patients with postoperative complications (n)	4/22	4/23
Patients with recurrence at 12-month follow-up (n)	4/22	3/23
Urinary Retention	3/22	1/23
Postoperative Bleeding	1/22	0/23

4. Bursics et al 2004

STUDY IDENTIFIER	Bursics et al 2004
STUDY TITLE	Comparison of early and 1-year follow-up results of conventional hemorrhoidectomy and hemorrhoid artery ligation: a randomized study
AUTHORS	Bursics A, Morvay K, Kupcsulik P, Flautner L.
CITATION	Int J Colorectal Dis 2004;19:176 – 80. DOI 10.1007/s00384-003-0517-9
PARTICIPANTS	
Description	60 consecutive patients (27 men, 33 women; mean age 47.5 ± 3.9 years).
Total Number enrolled (exp/ctrl)	30(18men, 12women)/30 (9 men,21 women)
INTERVENTION	
Experimental	
Description	Doppler-guided-hemorrhoidal artery ligation
Number (enrolled/analyzed)	30/30
Control	
Description	Standardized closed scissors hemorrhoidectomy
Number (enrolled/analyzed)	30/30
OUTCOMES	Length of postoperative inpatient care, negative reactions, complications need for pain killers especially opioids, prolapse, return to normal daily activity, recurrence, late complications (stricture, fistula, impaired defecation, incontinence)
METHODOLOGY/DESIGN	prospective, longitudinal, randomized study
REMARKS	

STUDY IDENTIFIER	Bursics et al 2004
RANDOMIZATION (Description)	Patients were randomized based on the date of the first visit to outpatient department
ALLOCATION CONCEALMENT (Description)	Not mentioned
BLINDING (yes/No)	Not mentioned
WITHDRAWALS	
Yes/No	No
How many?	0
Reasons for withdrawal	none
ALL OUTCOMES REPORTED?	Yes
Remarks	

STUDY IDENTIFIER	Bursics et al 2004	
OUTCOME	Conventional hemorrhoidectomy	Hemorrhoidal Artery Ligation (DG-HAL)
Urinary retention	1/30	0/30
Length of hospital stay (hours)	62.9 ± 29.0	19.8 ± 41.8
Return to normal daily activities (days)	24.9 ± 24.5	3.0 ± 5.5
Needed opioid analgesics	9/30	0/30
Bleeding	3/30	2/30
Pain	4/30	4/30
Prolapse/Recurrence	1/30	0/30

RISK OF BIAS TABLES

Risk of bias table De Nardi et al 2014

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	There was no significant difference of the baseline characteristics among the two groups
Allocation concealment (selection bias)	Low risk	For every consecutively enrolled patient, a sealed envelope, with the randomization arm written on a paper that was folded twice, was prepared by a physician who was not involved in the study. The envelope was assigned after the patient provided this consent, and it was opened before the surgical procedure began
Blinding of participants and personnel (performance bias)	Unclear risk	Blinding was not mentioned but since the two arms are surgical interventions, it would not be possible to blind patients
Blinding of outcome assessment (detection bias)	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias)	Low risk	All outcomes were reported at the end of the study
Selective reporting (reporting bias)	Low risk	There was no bias note on the reporting of outcomes
Other bias	Low risk	No other sources of bias noted

Risk of bias table Elmer et al 2013

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	There was no significant difference among the baseline characteristics of the two groups
Allocation concealment (selection bias)	Low risk	Randomization between THD and OH was done by a research nurse. Sealed envelopes were used and opened in the operating room.
Blinding of participants and personnel (performance bias)	High risk	No blinding was possible because it is a surgical intervention.
Blinding of outcome assessment (detection bias)	High risk	Since there was no blinding in the study, there might be a possible bias in reporting of outcomes
Incomplete outcome data (attrition bias)	Low risk	All outcomes were reported at the end of study
Selective reporting (reporting bias)	Low risk	No bias in the reporting of outcomes in this study
Other bias	Low risk	No other bias noted in the study

Risk of bias table Gupta et al 2011

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A single person performed all randomizations, which were done in blocks so that the number of patients in the two groups was balanced over the course of the trial
Allocation concealment (selection bias)	Low risk	Recruited patients were randomly allocated, by means of sealed envelopes, to one of the two study arms: (1) ligation and mucopexy [SL group] or (2) DGHAL plus ligation and mucopexy [DSL group]
Blinding of participants and personnel (performance bias)	Low risk	This is a double-blinded randomized control study
Blinding of outcome assessment (detection bias)	Low risk	This is a double-blinded randomized control study
Incomplete outcome data (attrition bias)	Low risk	All outcomes were reported at the end of the study
Selective reporting (reporting bias)	Low risk	No reporting bias noted in the study
Other bias	Low risk	No other sources of bias noted in the study

Risk of bias table Burics et al 2004

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized based on the date of the first visit to outpatient department
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias)	Unclear risk	not mentioned
Blinding of outcome assessment (detection bias)	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias)	Low risk	All outcomes were reported
Selective reporting (reporting bias)	Low risk	No bias noted on reporting of outcomes
Other bias	Low risk	No other sources of bias

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A Retrospective Descriptive Study of Frequency of Electroencephalographic Abnormalities and Its Correlation with White Matter Subcortical Lesions in Magnetic Resonance Imaging of the Brain in Acute Migraine Attack in a Tertiary Hospital

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ABSTRACT

The neuropathological processes believed to underlie migraine were still widely debated in the literature. This paper reviewed two ancillary procedures, the scalp electroencephalogram (EEG) and magnetic resonance imaging (MRI) of brain for physiological and anatomical characteristics of the syndrome that may be identified which may aid in the demonstration of the pathogenesis and pathophysiology of migraine. In this study, we determined the frequency of abnormal scalp electroencephalographic findings during acute (within 24 hours) migraine attack, and correlate it with MRI white matter lesions.

This was a retrospective descriptive study among migraine patients admitted at a tertiary hospital over a five-year period was done. Patients included were aged 10 to 70 years, both male and female, diagnosed with migraine according to IHS Criteria who underwent both EEG and MRI. Three hundred twelve patients were included in the study. Patients with both EEG and MRI whose results showed abnormalities in both were collected (n=11). Further analyses of correlation of abnormal EEG and white matter lesion on MRI using SPSS software and phi-coefficient statistical tool was used to provide measures of association in terms of lateralization, lobar distribution. Results showed insufficient evidence to make any correlation between laterality or lesions (pvalue 0.292) and lobar distribution (p-value 0.016). There was a positive but weak relationship among patients with abnormal EEG having an abnormal MRI (Odds Ratio= 2.475).

In conclusion, abnormalities in EEG and MRI findings may be seen during the acute attack (<24 hours EEG, < 3days MRI). Abnormal EEG patterns, specifically focal slowing of background activity and epileptiform discharges in multiple lobes in 37% percent of migraineurs was documented. A trend towards a positive correlation between the presence of abnormalities on MRI and abnormalities on EEG, this was not statistically significant. Evidence was insufficient because of the very limited sample size.

Keywords: *Migraine ☐ Electroencephalography (EEG) Magnetic Resonance Imaging (MRI) ☐ Computerised Tomography (CT) scan ☐ T2WI/FLAIR Hyperintensities*

INTRODUCTION

Migraine is a family of chronic disorders with highly variable clinical features, natural histories, and pattern of treatment response. Although, it is internationally recognized under a classification system of the International Headache Society,9 each classification needs to satisfy criteria (see Appendix 1) for every headache disorder. Diagnosis of the syndrome has traditionally been defined by the clinical characteristics of the acute attack, with no pathognomonic findings on laboratory tests and neuroimaging. This is why electroencephalography and neuroimaging are not considered necessary for the diagnosis of migraine headaches, although they can be helpful in further evaluation of patients with atypical headache presentations. With the advent of increasingly sophisticated diagnostic techniques and technologies, particularly in neuroimaging and neurophysiology, physiological and anatomical characteristics of the syndrome may be identified which may aid in the demonstration of the pathogenesis and pathophysiology of migraine.

Nonspecific T2WI/FLAIR subcortical and periventricular white matter hyperintensities have been found in migraine with aura (13 of 161; 8·1%), occurrence was significantly smaller in patients with migraine without aura (three of 134; 2·2%) and controls (one of 140; 0·7%) in the study of Kruit. 10 Cutrer et al proposed that these might be due to focal cerebral hypoperfusion and oligemia and thus be a risk factor for migraine-associated stroke.4 As these white matter lesions are most commonly subclinical, neurologic function of affected individuals is usually preserved. Because MRI is a test of structure rather than function, this study was conceptualized to determine whether electroencephalography, which is a test of function, would demonstrate any dysfunction among migraine patients, particularly in the presence of MRI white matter hyperintensities.

GENERAL OBJECTIVE

To determine the frequency of abnormal scalp electroencephalographic findings during acute (within 24 hours) migraine attacks, and correlate it with MRI abnormalities.

SPECIFIC OBJECTIVES

1. To describe the abnormal patterns of scalp EEG, including their lobar distribution and laterality, among migraine patients during the acute (within 24 hours) migraine attack.
2. To determine the frequency and describe the abnormalities of MRI findings among migraine patients when taken within 3 days of the acute migraine attack.
3. To correlate abnormal EEG findings with abnormal MRI findings.

METHODOLOGY

Study Design

This was a retrospective, descriptive study of patients admitted in a tertiary hospital because of migraine attacks from January 2007 to June 2013.

The admitting logbook of the Section of Neurology of a tertiary hospital was reviewed. Patients who were admitted due to an acute (within 24 hours) migraine attack were collected. The diagnosis of migraine was made by a neurologist according to International Headache Society (IHS) criteria.[8] When available, EEG recording done within 24 hours of admission and MRI of the brain (plain or with contrast) done within 3 days of admission were retrieved and reviewed.

Inclusion Criteria

Included in the study were patients both male and female diagnosed with migraine between ages of 10 to 70 years old.

Exclusion Criteria

Patients with history of clinical seizure, brain tumor, stroke, CNS infection, demyelinating disease, traumatic brain injury resulting to structural intracranial lesions or skull fractures and recurrent headaches not compatible with HIS criteria for migraine were excluded. Patients who had received antiepileptic

drugs for migraine prophylaxis during the week prior to the EEG recording were excluded. Patients with history of drug abuse were also excluded.

Data Collection

Age, gender, and performance of EEG recording or brain MRI were recorded using data collection forms. Confidentiality was ensured by not reporting patient identifying information (e.g. name, birthday, hospital number).

EEG Recording

Scalp EEG recordings were done using gold electrodes applied in accordance with the international 10-20 system using a Cadwell, Grass or Nihon-Koden electroencephalography machine with thirty-two (32) channels. Recordings were performed within at least 24 hours after the last headache attack. Each recording session lasted for a minimum of 20 minutes, with 3 minutes hyperventilation, and intermittent photic stimulation with a flash frequency ranging from 1-15Hz.

One independent electroencephalographer, blinded to the patient's identity, clinical profile and diagnosis except age, reevaluated the EEG recordings to eliminate interobserver variability. The following specific EEG findings were specifically identified and reported: (a) slow activity (generalized or focal), (b) attenuation/suppression of amplitude of background activity, (c) focal and generalized increase in EEG activity, (d) interhemispheric asymmetry of alpha rhythm; (e) epileptiform discharges (focal spikes, sharp waves, spike-andwave discharges, polyspike complexes, polyspike-and-slow-wave complexes multiple-sharp-wave complexes, multiple-sharp-and-slow -wave complexes, or generalized epileptiform discharges) and (f) response to photic and hyperventilation. Background activity, lobar distribution and laterality of abnormal EEG findings were also determined.

MRI of the brain

The author reviewed all available brain MRIs of subjects included in the study. In addition, when white matter hyperintensities were found, these were rated as follows.

MRI of the brain was reviewed for the presence of T2-weighted/FLAIR hyperintensities on subcortical regions but not present on T1-weighted image. Periventricular hyperintensities were not analyzed. Subcortical white matter lesions are categorized as small (0-3mm), medium (4-10mm), and large (>10mm). The number of subcortical white matter lesions was rated per size category for the frontal, parietal, occipital, temporal lobes and multilobar distribution. Affected cerebral hemisphere corresponding to its laterality was also listed. Distinction between lobes was according to anatomical landmarks. There were no added features recorded from the MRI images.

STATISTICAL ANALYSIS

Descriptive data were presented as frequency tables, cross-tabulations and summary statistics using Excel and/or SPSS for computation of frequencies, means, standard deviations and odds ratio. The researcher utilized the following statistical tools: frequencies and percentages to summarize the characteristics of flair hyperintensity among patients, and SPSS to determine if there exists a significant correlation between the EEG Results and the characteristics of T2WI/FLAIR hyperintensities. All statistical analyses performed were 2-sided at 95% Confidence Level.

RESULTS

During a five-year period of review, three hundred twelve (312) patients diagnosed to have migraine according to the International Headache Society Criteria were admitted in a tertiary hospital due to an acute migraine attack and were included in the study. EEG and MRI were reviewed, whenever available. Out of the total 312 patients listed in the logbook, 74% did not undergo any of the mentioned ancillary procedures, while the rest completed a combination of procedures.

The distribution of patients belonging into each group is presented in Table 1. Note that for the entire group, female patients admitted due to acute migraine greatly outnumbered male patients. Female -to-male ratio is 3:1. These patients have an average age of 38 year with a standard deviation of 12 years.

Table 1. Summary Characteristics of Patients

Group	Count	Percent %	Age (years) Distribution		Sex Distribution	
			Average	Stdev	Male	Female
EEG Only	28	9.0	33.6	12.2	7	21
MRI Only	6	19	33.0	6.7	2	4
EEG+MRI	34	10.9	37.7	13.3	8	26
None	224	78.2	38.5	11.6	60	184
TOTAL	**312**	**100**	**37.9**	**11.8**	**77**	**235**

From the table above, it can be observed that there were 62 (20%) patients who underwent scalp EEG with or without MRI. Of these 62 patients, 23 (37%) had abnormal EEG findings (Table 2). Patients with abnormal EEG findings had an average age of 38 +/- 14 years, and were mostly female.

Table 2. Characteristics of patients with EEGs

Group	Count	Percent %	Age (years) Distribution		Sex Distribution	
			Average	Stdev	Male	Female
Normal EEG	39	63	34.7	12.4	13	26
Abnormal EEG	23	37	37.9	13.7	2	21
TOTAL	**62**	**100**	**35.9**	**12.9**	**15**	**47**

Of the 62 patients who underwent EEG, 34 also underwent MRI (Table 3). Of the 34 subjects, 21 (61.8%) had abnormal MRI findings, among whom 11 subjects also had abnormal EEG findings, whereas 10 subjects had normal EEG findings. Of the 34 subjects, 9 had normal MRI and normal EEG findings while 4 had normal MRI but abnormal EEG findings.

Table 3. Normal and Abnormal EEG and MRI results

		MRI		
		Normal MRI	Abnormal MRI	Total
EEG	Normal EEG	9	10	19
	Abnormal EEG	4	11	15
	TOTAL	**13**	**21**	**34**

To test the relationship between MRI and EEG results (see Table 4), measure of association was done to determine the strength and significance should a relationship exist between the findings of these two tests. The following table provides Phi Coefficient, which was a chi-square-based measure of association that involves dividing the chi-square statistic by the sample size and taking the square root of the result. It measured the level of association between two nominal or categorical data.

The resulting Phi coefficient of 0.212 suggested a positive but weak relationship between MRI and EEG findings. This implied that there was a small chance that findings of normality or abnormality in both tests would coincide with each other. However, this finding is not statistically significant (p-value of 0.217) because of the small sample size.

Table 4. Relationship between MRI and EEG results

Symmetric Measures

		Value	Approx. Sig.
Nominal by Nominal	Phi	.212	.217
	Cramer's V	.212	.217
N of Valid Cases		34	

a. Not assuming the null hypothesis.
b. Using the asymptotic standard error assuming the null

Using the same table, odds ratio was computed to compare the relative odds of the MRI findings, given knowledge of EEG findings (results in Table 5). Given the data, odds ratio was computed to be 2.475. Thus, patients with abnormal EEG findings have a 2.475 times higher probability of having abnormal MRI findings than those with normal EEG findings. This supports the positive Phi coefficient obtained earlier. However, since 1 is included in the 95% confidence interval (0.577, 10.617), the observed relationship was deemed to be not statistically significant.

Table 5. Risk estimate between EEG and MRI findings

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for EEG ABNORMAL/NORMAL)	2.475	.577	10.617
For cohort MRI = ABNORMAL	1.393	.825	2.354
For cohort MRI = NORMAL	.563	.215	1.476
N of Valid Cases	34		

From the 34 patients who had undergone both MRI and EEG, the sample was further narrowed down to those patients with abnormal EEG who underwent MRI of the brain regardless of MRI result (N=23). Of these 23 patients, only 15 patients with abnormal EEG had undergone MRI. This brought down the sample size of our succeeding analyses to only 15 patients as shown in table 6, consisting of 1 male and 14 female patients. Patients were older with an average age of 43 + 13 years.

Table 6. Patients with Abnormal EEG who underwent MRI of the brain according to age and sex distribution

Group	Count	Percent %	Age (years) Distribution		Sex Distribution	
			Average	Stdev	Male	Female
With MRI	15	65	42.9	12.9	1	14
Without MRI	8	35	28.5	9.9	1	7
TOTAL	**23**	**100**	**37.9**	**13.7**	**2**	**21**

Test Results of Abnormal EEG Findings

EEG abnormalities found in the 15 patients with abnormal EEGs who had undergone MRI were studied. Summary of abnormal EEG findings corresponding to lateralization, lobar distribution and number of lobes involved were summarized in Table 7. Out of 15, 60% of abnormal findings were unilateral, with 40% on the left cerebral hemisphere and 20% on the right cerebral hemisphere. In 40% of the patients, abnormal findings were observed over both cerebral hemispheres. Moreover, there was an obvious trend towards higher incidence of abnormality involving multiple lobes in 86%.

Table 7. Characteristics of abnormal EEG findings of patients with abnormal EEG Result

EEG with ABNORMAL FINDINGS				
Lateralization	**Left**	**Right**	**Bilateral**	**Total**
Count	6	3	6	15
%	40	20	40	100
Number of Lobes		**Single Lobe**	**Multilobar**	**Total**
Count		2	13	15
%		13	87	100
Lobar Distribution	**Occipital**	**Temporal**	**Multilobar**	**Total**
Count	1	1	13	15
%	7	7	86	100

Specific EEG abnormalities were enumerated in table 8. The most frequently observed abnormal EEG pattern were focal slowing (46.7%) and epileptiform discharges (46.7%), followed by interhemispheric asymmetry of alpha rhythm (5%). Photic stimulation elicited asymmetric photic driving in 4% and hyperventilation further elicited abnormal response in 5%.

Table 7. Characteristics of abnormal EEG findings

EEG with ABNORMAL FINDINGS			
	Present %	**Absent**	**Total**
Generalized Slow Activity	2 (13.3)	13	15
Focal Slow Activity	7 (46.7)	8	15
Attenuation of Background Activity	1 (6.7)	14	15
Fast Activity	2 (13.3)	13	15
Interhemispheric Asymmetry of Alpha Rhythm	5 (33.3)	10	15
Epileptiform Discharges	7 (46.7)	8	15
Photic Response	4* (26.7)	11	15
Hyperventilation Response	5** (33.3)	10	15
*Asymmetrical photic driving **Abnormal response			

MRI Results

We reviewed the MRIs of patients done within three days of the acute migraine attack. No acute infarctions, hemorrhages or mass lesions were seen. From the 15 patients with abnormal EEG findings who underwent MRI, only 11 had abnormal MRIs. All MRI abnormalities consisted of the subcortical white matter lesions, which appeared isointense on T1-weighted image (T1WI) and hyperintense on T2-weighted image (T2WI) and Fluid Attenuated Inversion Recovery (FLAIR). Table 9 presents characteristic data of subcortical white matter lesions. In terms of number of white matter lesions, results ranged from as low as 1 to a maximum of 16 recorded flair hyperintensities. Right hemisphere was found to have frequent T2WI/FLAIR hyperintensities in 55% and it was the frontal lobe (55%) that was frequently involved. Small hyperintensities (1-3mm) were the most common in 73%.

Table 7. Summary Characteristics of Subcortical White Matter Lesions (T2WI/FLAIR Hyperintensities)

MRI Results: Number of Flair Hyperintensities					
Valid	Mean	Median	Stdev	Maximum	Minimum
11	4.3	2.0	4.9	16	1
MRI Results					
Lateralization		**Left**	**Right**	**Bilateral**	**Total**
Count		2	6	3	11
%		18	55	27	100
Lobar Distribution	**Frontal**	**Temporal**	**Parietal**	**Multilobar**	**Total**
Count	6	1	1	3	11
%	55	9	9	27	100
Size of WML*			**Small**	**Combination**	**Total**
Count			8	3	11
%			73	27	100

**WML - White Matter Lesions*

Correlation / Measures of Association between EEG and MRI findings

To further analyze if there was a relation between the abnormal results of EEG and MRI in the 11 patients who had both abnormal EEG and abnormal MRI results, statistical tests were used to determine their level of association both in terms of lateralization and lobar distribution.

For this kind of analysis, SPSS software was utilized to generate the necessary statistics and significance levels. The following test provides Phi Coefficient, which was a chi-square-based measure of association that involves dividing the chi-square statistic by the sample size and taking the square root of the result. It measured the level of association between to nominal or categorical data.

In each of the tests, p-values were given which aided in determining the significance of each relationship. At 5% level of significance, a p-value of less than 0.05 suggests strong and statistically significant relationship between the variables of interest.

For lateralization (see Tables 10.1 and 10.2), the test resulted in a p-value of 0.292, showing that there was insufficient evidence to make any correlations between laterality of lesions on MRI and laterality of findings on EEG.

Table 10.1 Correlation of abnormal EEG findings vs Laterality of Subcortical White Matter Lesions (T2WI/FLAIR Hyperintensities) on MRI

Contingency Table: Lateralization					
			MRI		
		Bilateral	**Left**	**Right**	**Total**
EEG	**Bilateral**	2	0	2	4
	Left	0	2	3	5
	Right	1	0	1	2
	TOTAL	3	2	6	11

Table 10.2 Correlation of abnormal EEG findings vs Laterality of Subcortical White Matter Lesions (T2WI/FLAIR Hyperintensities) on MRI Symmetric Measures

		Value	**Approx. Sig**
Nominal by Nominal	Phi	.671	.292
	Cramer's V	.474	.292
N of Valid Cases		11	

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis

For lobar distribution (see Tables 11.1 and 11.2), the resulting p-value is 0.016, suggesting that there was insufficient evidence to conclude that lobar distribution of MRI abnormalities are positively correlated with lobar distribution of abnormal EEG findings.

Table 11.1 Correlation of abnormal EEG findings vs Lobar Distribution of Subcortical White Matter Lesions (T2WI/FLAIR Hyperintensities) on MRI

Contingency Table: Lobar Distribution							
					MRI		
		Multilobar	Frontal	Pariental	Temporal	Occipital	Total
EEG	Multilobar	3	4	1	1	-	9
	Frontal	-	-	-	-	-	-
	Pariental	-	-	-	-	-	-
	Temporal	-	1	-	-	-	1
	Occipital	-	1	-	-	-	1
	Total	3	6	1	1	-	11

Table 11.2 Correlation of abnormal EEG findings vs Lobar Distribution of Subcortical White Matter Lesions (T2WI/FLAIR Hyperintensities) on MRI Symmetric Measures

		Value	Approx. Sig
Nominal by Nominal	Phi	.430	.916
	Cramer's V	.304	.916
N of Valid Cases		11	

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis

Correlation/Measures of Association between Age and EEG and MRI findings

In the following analysis, age was associated with the EEG and MRI findings. In Table 12.1, the study tests the hypothesis that as age increases, the higher the chance of abnormal findings on EEG. The second hypothesis tests whether the number of T2WI/FLAIR hyperintensities on MRI increases with age.

In the following test, Kendall's tau-b was use to detect a relationship between the variables and measure its strength if it exists. Kendall's tau-b was a nonparametric measure of correlation for ordinal or ranked variables that take ties into account. The sign of the coefficient indicates the direction of the relationship, and its absolute value indicates the strength, with larger absolute values indicating stronger relationships. Possible values range from -1 to 1, but a value of -1 or +1 can be obtained only from square tables.

Table 12.2 demonstrated a negative value of Kendall's tau-b (-0.124) suggesting that as age increases, abnormal EEG findings were more frequently observed. However, this relationship was not statistically significant (p=0.283).

Table 12.1. Age Distribution of EEG results both normal and abnormal

Contingency Table: Age vs EEG Findings				
	ABNORMAL	NORMAL	N.I	TOTAL
11-25	4	11	3	18
26-40	10	17	13	40
41-55	7	8	3	18
56-70	2	3		5
TOTAL	**23**	**39**	**19**	**81**

Table 12.2 Age Distribution of EEG results both normal and abnormal

Symmetric Measures

		Value	Asymp. Std. Error[a]	Apporx. T[b]	Approx. Sig
Ordinal by Ordinal	Kendall's Tau-b	-.124	.115	-1.074	.283
N of Valid Cases		62			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis

In the second hypothesis, the number of T2WI/FLAIR hyperintensities was correlated against the age of patients with acute migraine attack. Since both of the variables were numeric in nature, Pearson's correlation was used instead to detect linear relationship. Note however that only 21 MRI results indicated the number of T2WI/FLAIR hyperintensities, hence the rest did not demonstrate such findings on MRI and were excluded from the test. The following SPSS result indicated a positive value of the coefficient (0.695) consistent with a strong statistically significant positive relationship between patient's age and number of T2WI/FLAIR hyperintensities (p,0.01). This suggests that as age increases, the number of T2WI/FLAIR hyperintensities on MRI also increases. (see Table 13)

Table 13 Correlation of AGE with abnormal EEG finding and number of T2WI/FLAIR hyperintensities,

		AGE	**Number of T2WI/FLAIR Hyperintensities**
Age	Pearson Correlation	**1**	**.695****
	Sig. (2-Tailed)		**.000**
	N	**40**	**21**
Flair_number	Pearson Correlation	**.695****	**1**
	Sig. (2-tailed)	**.000**	
	N	**21**	**21**

***. Correlation is significant at the 0.01 level (2-tailed)*

DISCUSSION

Most of the published studies using routine EEG were done in children with all types of recurrent headaches including tension-type headache, migraine, sinus headache and so on. Studies of Grosneth[7], Kruit[10], and Bockowski et al[3] reported EEG findings to occur more frequently in headache patients. They described the following patterns: generalized or focal slowing, rhythmic highamplitude slowing during hyperventilation, excessive fast activities, epileptiform activities and prominent photic driving, and differences in the asymmetry, modulation or peak frequencies of the alpha rhythm. Similar EEG findings were also observed in our subjects. However, the percentage of the patients with abnormal EEG varies for different studies from 20.6% to 40.8% that was consistent with our result.[6] Despite the low frequency of abnormal EEG findings, migraineurs are more likely to have an abnormal EEG. These data correlate cardinally with our results. EEG was interpreted as abnormal in 28% with the most frequent abnormalities described as focal slowing and presence of epileptiform discharges in the form of sharps, spikes, and spike-and-slow waves. Our patients with epileptiform discharges did no show any periodic lateralized epileptiform discharges (PLEDS) unlike in study of Brinciotti.[8]

The differentiating factor in our study was the timing of the EEG recording, which was done during the acute migraine attack (within 24 hours) – whereas timing of EEG recording was not mentioned in most of the previous EEG and headache studies. Some studies were done during the interictal period. This study showed a trend towards higher frequency of abnormal EEG patterns among older patients, mean age of 37.9+13.7 years as opposed to subjects with normal EEG tracings with mean age of 34.7+12.4 years. However, this finding was not statistically significant.

Consistent findings in our migraine patients of prominent asymmetrical photic driving at high flash rates during the acute attacks3 are compatible with the findings reported by Grosneth6 in a review of 40 studies and in studies of Golia and Winter.[6] However, asymmetry of photic driving may be considered a normal variant.

Presence of EEG abnormalities, might lead to the request for neuroimaging to rule out a structural pathology particularly when such findings were demonstrated in a focal distribution. However, findings on MRI showed T2WI/FLAIR hyperintensities that were isointense on T1WI was common and majority had small sizes between 1-3mm. Linking the association of abnormal EEG pattern and white matter lesions on MRI based on the laterality and lobar distribution of both findings did not show any correlation statistically. Hence, an abnormal EEG finding may not always necessitate request for MRI.

White matter lesions on MRI were independent findings among our patients with migraine, but most migraineurs will not have them. Increasing age was not correlated with increased frequency of abnormal EEG findings. However, this study showed that increasing age is statistically significantly correlated with increase in the number of white matter lesions on MRI. Hence, MRI may be more useful when done among migraine patients in the older age groups.

Limitations of the Study

This study was only limited to patients with the diagnosis of migraine who were admitted because of an acute attack of migraine. The fact that collection of subjects was a retrospective approach limited the amount of data collected. In particular, our patients were not classified according to the type of migraine because not all admitting diagnoses indicated the type of migraine. Frequency of attacks, duration of migraine, presence of family history and previous history of benign febrile convulsions were not assessed.

CONCLUSION

In conclusion, although EEG and MRI are not recommended in the diagnosis of migraine, abnormalities in EEG and MRI findings may be seen during the acute attack (<24 hours EEG, < 3days MRI). This study showed that abnormal EEG patterns, specifically focal slowing of background activity and epileptiform discharges, may be seen in multiple lobes during acute migraine attacks in 37% percent of migraineurs. It also showed that MRI abnormalities, specifically

RECOMMENDATIONS

Our results were preliminary findings relating to a small number of subjects. A larger population-based blinded study would open up new avenues likely to our further understanding of the complexity of migraine syndrome. By combining electrophysiological data obtained through electroencephalogram with hemodynamic data probably through functional magnetic resonance imaging (fMRI), may be possible to arrive at a more detailed and comprehensive picture of the altered processes present in migraine taking into consideration the epoch of headache (both ictal and interictal), and the type of migraine. A blinded prospective controlled study was recommended before firm conclusions were drawn.

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APPENDIX I

INTERNATIONAL HEADACHE SOCIETY DIAGNOSTIC CRITERIA FOR MIGRAINE (2004)

Diagnostic criteria for migraine without aura:

A. At least five attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 hours [when untreated in adults]
C. Headache has at least two of the following characteristics:
   1. unilateral location
   2. pulsating quality
   3. moderate or severe pain intensity
   4. aggravation by or causing avoidance of routine physical activity
D. During the headache, at least one of the following [is present]:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
E. Not attributable to another disorder

— International Classification of Headache Disorders[6]

Diagnostic criteria for Pure menstrual migraine without aura (A1.1.1)

A. Attacks, in a menstruating woman, fulfilling the criteria for migraine without aura
B. Attacks that occur exclusively from days -2 to +3 of menstruation in at least 2 out of 3 menstrual cycles and at no other times of the cycle.

Note: The first day of menstruation is day +1, and the preceding day is day -1; there is no day 0.

— International Classification of Headache Disorders[6]

Diagnostic Criteria for Migraine with Aura

Description: Recurrent disorder manifesting in attacks of reversible focal neurological symptoms that usually develop gradually over 5–20 minutes and last for less than 60 minutes. Headache with the features of "migraine without aura" usually follows the aura symptoms. Less commonly, headache lacks migrainous feature or is completely absent [i.e., the aura may occur without any subsequent headache].

Diagnostic criteria for Migraine with Aura

A. At least two attacks fulfilling criterion B
B. Migraine aura fulfilling criteria [described below]
C. Not attributed to another disorder.

...[Criteria for "Typical aura":] Aura consisting of at least one of the following, but no motor weakness:

1. Fully reversible visual symptoms including positive features (e.g. flickering lights, spots or lines) and/or negative features (i.e., loss of vision)
2. Fully reversible sensory symptoms including positive features (i.e., pins and needles) and/or negative features (i.e., numbness)
3. Fully reversible dysphasic speech disturbance [Aura also has] at least two of the following:
    1. Homonymous visual symptoms [i.e., affecting just one side of the field of vision] and/or unilateral sensory symptoms [i.e., affecting just one side of the body]
    2. At least one aura symptom develops gradually over [at least] 5 minutes and/or different aura symptoms occur [one after the other] over [at least] 5 minutes 3. Each symptom lasts [from] 5 [to] 60 minutes

...[Other potential aura criteria:]

5. Fully reversible motor weakness...
6. Each aura symptom lasts [from] 5 minutes [to] 24 hours...
   [In the case of a "Basilar-type" migraine], Dysarthria [difficulty speaking], vertigo [dizziness], tinnitus [ringing in the ears], [and other symptoms].

- International Classification of Headache Disorders[6]

Diagnostic Criteria for Abdominal Migraine

Diagnostic criteria:

A. At least 5 attacks fulfilling criteria B-D.
B. Attacks of abdominal pain lasting 1-72 hours (untreated or unsuccessfully treated)
C. Abdominal pain has all of the following characteristics:
    1. midline location, periumbilical or poorly localized
    2. dull or "just sore" quality
    3. moderate or severe intensity
D. During abdominal pain at least 2 of the following:
    1. anorexia
    2. nausea
    3. vomiting
    4. pallor
E. Not attributed to another disorder

- International Classification of Headache Disorders[6]

Airway Management In A Patient With Goldenhar Syndrome Using Classic Laryngeal Mask Airway: A Case Report

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ABSTRACT

Goldenhar Syndrome is an embryonic developmental anomaly involving the first and second arches resulting in a wide spectrum of birth defects including ocular, auricular, facial, cranial, vertebral and cardiac anomalies. Among the various deformities associated with the syndrome, hemifacial microsomia, maxillo-mandibulo-facial hypoplasia, and neck bones fusion are anesthesiologist's concern because these features are precursors to difficult airway management, particularly so that its corrective surgical procedures are to be done under general anesthesia. For the excision of the right ocular dermoid with plastic-reconstructive skin grafting of this 9 years old female patient, we were able to prevail over this dilemma by using a right fitting face mask and classic flexible LMA while she was breathing spontaneously under Sevoflurane general anesthesia. Early recognition and keen knowledge of the disorder and proper preparation for its anticipated anesthetic implications are the foundation of successful peri-operative management of patients with Goldenhar Syndrome.

Keywords: *Goldenhar Syndrome, Oculo-Auriculo-Vertebral Spectrum, Classic LMA general anesthesia*

INTRODUCTION

Oculo-Auriculo-Vertebral Spectrum (OAVS) refers to three rare congenital anomalies that although presenting as poorly understood disorders with diverse manifestations and severity, are inter related to each other. Goldenhar Syndrome being the most severe form has most of the manifestations of Oculo-Auriculo-Vertebral disorder (OAVD): the mildest form of disorder, and of Hemifacial Microsomia (HFM): the intermediate form. Reported occurrence of OAVS is estimated to range from one in 3,000 to 5,000 live births up to one in 25,000 to 40,000 live births; male:female ratio of 3:2.[1]

As first described in 1952 by the Swiss ophthalmologist, Maurice Goldenhar,[2] Goldenhar Syndrome involves complex developmental disorders of the face, ears, eyes, spine, etc., manifesting with varying severity in each patient: as facial asymmetry due to hypoplasias of the facial muscle, of the maxillary and mandibular bones and the zygomatic arches (hemifacial microsomia); micrognathia; external ear malformations and hearing loss; ocular dermoids or lipodermoids. Other oral cavity anomalies may include a high-arch or cleft palate and abnormalities of the tongue.[3]

Children with Goldenhar syndrome are known to present with airway management challenges. Difficult intubation may be expected due to mandibular hypoplasia and fused underdeveloped neck bones, among others.[4]

It is our objective to document a case of Goldenhar syndrome; presenting the airway and other anatomical conundrum that accompanies it, and to propose anesthetic approach to patients with this syndrome.

CASE PRESENTATION

This is a case of a 9 year-old, 20-kg, 123cm female patient who was admitted for excision of an ocular dermoid with membrane graft of the right eye.

She was observed to be hard-of-hearing with difficulty in speaking. Other significant findings were: hemifacial microsomia, hypoplasia of the malar bones and mandible, marked micrognathia, microtia and right ocular dermoid.

Figure 1 Facial assymmetry

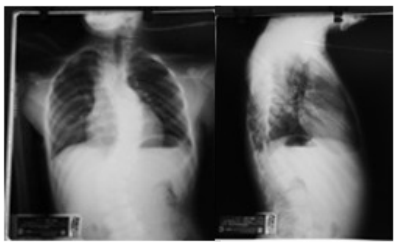

Figure 2 Moderate Levoscoliosis

Her head was tilted to the left, right shoulder higher than the left, the neck had limited movement, the cervical vertebrae are fused, the spine was S shaped with right 'rib hump'; chest XRay: moderate scoliosis.

At the preanesthesia room, she was premedicated with midazolam 0.05mg/kg, ketamine 1mg/kg and atropine 0.01mg/kg intravenously. Once she was sedated, she was brought to the OR suite.

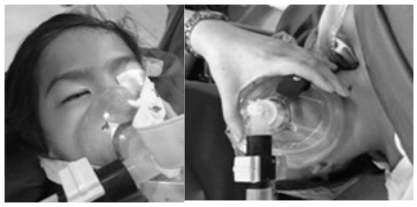

Figure 3 anesthesia face mask fit

We had difficulty fitting the size 2 tear drop shaped standard anesthesia face mask to the right side of her face. The size 2 round shaped flexible anesthesia face mask made a perfect fit without gas leakage and without upper airway obstruction. Induction was carried out with sevoflurane 2vol% then propofol 2mg/kg/IV prior to insertion of size 2.5 classic LMA (undeflated). After inflation of 5 cc of air on the

balloon, no leak was observed; the breath sounds were heard distinctly without air turbulence and the chest moved smoothly while the patient was breathing spontaneously. Capnography was 30 mm Hg.

Anesthesia was maintained with sevoflurane at 2vol% on spontaneous-manually assisted respiration. During emergence, the patient was allowed to self-expel the LMA without coughing or retching.

DISCUSSION

Goldenhar syndrome is a sporadic congenital anomaly of unknown etiology, usually presenting with hypoplasia of the facial muscle, of the maxillary and mandibular bones, of the zygomatic arch and underdeveloped vertebral bones. In majority of cases the deformity is unilateral with 3:2 right-side to left-side prevalence. [1]

Like in 77% of Goldenhar syndrome, this female child had hemifacial microsomia with gross facial asymmetry, severe micrognathia, difficulty in speaking and microtia with deafness. The epibulbar dermoid that was to be removed is also seen in 39% of cases.

Several reports of difficult airway management in pediatric patients with Goldenhar syndrome had been cited in the literature.[3,4,6,8] Compounding the picture was the presence of vertebral anomaly that is exhibited in 70% of this syndrome. Fused neck bones limiting the neck movement can be a major contributor to improper exposure of the laryngeal inlet; this is notwithstanding the possibility that the mandibular bone hypoplasia can alter the anatomy of the hypopharynx. This could have been the underlying cause of unsuccessful intubation reported by Shukry et al[8] and Sugino et al[9] both in 2005: the former resorted to using a laryngeal mask while the latter turned to using a video laryngoscope for intubation. There are even documented reports of patients with Goldenhar syndrome whose operations were deferred because they could not be intubated. [3,4]

The anesthetic technique however, can be adapted to the type and site of the surgical procedure to be done. For the excision of an ocular dermoid with skin grafting, although there is no dire need for endotracheal intubation, this patient still needed adequate depth of general anesthesia. For the same kind of operation Sukhupragarn in 2008 used fexible LMA in a 10-year old patient with Goldenhar syndrome.[11] There were likewise previous reports showing successful use of the LMA in children with severe micrognathia such as that associated with Treacher Collins syndrome and Pierre Robin syndrome.[7]

Even at first glance during inspection, we were able to predict glitches in airway management. True enough we could not even fit the conventional tear shaped anesthesia face mask on the affected side for lack of facial muscle, maxillo-mandibular bones and zygomatic arch to hold and support the soft tissues of the face. We were able to overcome this predicament by shifting to a round shaped face mask; but had the asymmetry and all the above facial disconfigurations been placed on the left side, we could have encountered some challenge in placing her head on the chin lift position because we had nowhere to anchor our fingers on the scenario of left mandibular hypoplasia. The positioning of the head would likewise be more difficult had the cervical vertebra anomaly tilted the head and neck to the right. Although we exercised great caution by not extending her head so as not to compromise the cervical vertebral pathology we could have not guaranteed not doing this maneuver had we opted on intubating this patient.

For the insertion of the LMA, an adequate level of anesthesia must be attained to prevent laryngospasm, and likewise to achieve the best fit on the hypopharynx. In the study of Dr. V. Priya et al in 2002, excellent conditions for LMA insertion were obtained in significantly greater number of patients with Propofol induction than with Sevoflurane gas induction. [19] But 'single breath' Sevoflurane induction as done by these authors is not that feasible in children, while the 2.5 mg/kg Propofol dose may be large enough to precipitate apnea which we have to avoid in patients with probable difficult airway.

To provide depth of anesthesia that could adequately suppress the laryngeal reflexes, we opted on letting this patient breath 2% Sevoflurane; then

once assured that she could be well ventilated, we administered Propofol at 2 mgs/kg.

With this approach, we were also able to circumvent the spasticity that Sevoflurane may invoke on the normal facial muscle and jaw:[19] a situation that may further aggravate the airway's anatomical deformity. Moreover, Propofol has been documented to depress the laryngeal reflexes. [19]

As per recommendation for difficult airway, we did not use a muscle relaxant.

Another point of deliberation we had was that in the presence of right facial muscle and mandibular hypoplasia, the pharyngeal structures might have been pulled to the left; in which case, the LMA cuff might not sit well in the hypopharynx to adequately cover the laryngeal inlet.[20] Ventilation would then become less effective and most importantly the risk of intraoperative aspiration would increase.

Nevertheless, we put emphasis on choosing the right type and optimal size of the LMA and inflating the cuff with the minimum amount of air that can create just enough airtight seal. This way, the Classic LMA we inserted was able to adapt to this patient's distinctive upper airway anatomy. This flexibility of Classic LMA was also demonstrated by Florendo et al. (2014) in their pediatric patient with Hallerman Streiff syndrome.[21] These experiences just confirmed earlier observations that although pediatric Classic LMA is a 'scaled-down version' of the adult model, it was used successfully albeit differences seen between pediatric and adult airways. [12] Additionally, we were able to bend the Classic LMA to give more elbow room for the surgeon and his bulky microscope.

CONCLUSIONS

Hemifacial microsomia, gross facial asymmetry, fused neck bones are just part of the conundrum of anatomic defects in Goldenhar syndrome but these would suffice to push the alarm button for difficult airway management.

Preoperative evaluation therefore of children with Goldenhar syndrome begins with evaluation of the upper airway, with a high suspicion of anticipated difficulty, and formulation of a plan for airway management.

Anaesthetic management has to be tailored to the clinical situation and surgical procedures to be done. With a well fitting round shaped flexible anesthesia facemask and optimal depth of anesthesia with 2 volume % Sevoflurane and Propofol 2mgs/kg, we were able to insert a size 2.5 Classic LMA that sat snugly in this patient's hypopharynx; which stayed well all throughout the 1 ½ hours eye surgery while the patient was breathing spontaneously.

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Epidemiology of Herpes Zoster in Children and Adolescents: A Five-Year Review

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ABSTRACT

Introduction: Reactivation of latent varicella zoster virus results in herpes zoster. It is more common in the elderly. Studies of herpes zoster in children are limited.

Objective: The primary objective of this study is to establish the epidemiological profile of herpes zoster in children (0-9 years old) and adolescents (10-19 years old) diagnosed at the Santo Tomas University Hospital Dermatology department from January 2007-December 2011.

Method: Clinical records of patients aged 0-19 years old, clinically diagnosed as herpes zoster, were retrieved. The incidence, clinical presentation, history of primary varicella infection and/or varicella vaccination, and co-morbidities or possible predisposing factors were reviewed and analyzed.

Result: A total of 75 patients were included in this retrospective study. The incidence among children and adolescents ages 0-19 in this study was computed at 4.82 per 1000. The highest number of cases belonged to the adolescent group (81.33%). There was male predilection (61.33%). The dermatomes of the thoracic ganglia were most commonly affected (64%). No history of varicella vaccination was recorded. Most had a history of varicella infection (62.67%). Possible predisposing factors were respiratory diseases, including asthma, primary complex or pulmonary tuberculosis and respiratory tract infection.

Conclusion: Primary varicella infection is a prerequisite for herpes zoster. Even healthy children were affected and a small percentage did not have any history of varicella infection. The two known risk factors of herpes zoster in children namely: maternal varicella infection and varicella at first year of life were rarely found in this study. Some had underlying diseases, mostly respiratory in nature.

INTRODUCTION

Herpes zoster, commonly known as shingles, results from the reactivation of latent varicella zoster virus (VZV). Primary varicella is a prerequisite for herpes zoster. In general, herpes zoster is more common in the adult population. The incidence increases dramatically, from a low 1.1 and 2.9 per 1000 person-years in people younger than 50 years to 4.6 and 6.9 per 1000 person-years, respectively, in the age groups 50 to 59 and 60 to 69 years. The age groups 70 to 79 and 80 years or older have the highest incidence, with 9.5 and 10.9 per 1000 person-years, respectively.[1] It is associated with a decline in cell-mediated immunity due to aging, immunosuppressive illness or treatment.[1] It is rare in childhood with a reported incidence of 0.74 per 1000 in a group under 9 years of age and 1.1 per 1000 in children younger than 14 years old.[2] It usually occurs in children who are immunocompromised.[1,2] Maternal varicella during pregnancy and varicella occurring in the first year of life are two recognized risk factors for childhood herpes zoster. [1,2,3]

Clinical findings of herpes zoster include a prodrome of pain and paresthesia followed by eruption of vesicles, unilateral in distribution limited to one to three adjacent dermatomes. New vesicles may appear over a period of 3-7 days. These dry and crust in 7-10 days. The eruption is less severe and of shorter duration in children than in adults.[3,4] Zoster associated pain, encompassing prodromal, concomitant, and post-herpetic pain is exceptional in children.[3] Because of its rarity in children, clinical studies of herpes zoster in this age group are limited.

OBJECTIVES

The primary objective of this study is to establish the epidemiological profile of herpes zoster in children (0-9 years old) and adolescents (10-19 years old) diagnosed at Santo Tomas University Hospital Dermatology department from January 2007-December 2011.

The secondary objectives of this study are 1) To determine the incidence of herpes zoster in children and adolescents. 2) To describe the clinical presentation of the disease in this age group. 3) To determine history of primary varicella infection or varicella vaccination if present and 4) To identify possible precipitating factors and/or underlying diseases among those with the disease.

METHOD

The clinical records of patients, aged 0-19 years old, diagnosed and treated as herpes zoster at the Dermatology Department of Santo Tomas University Hospital from January 2007-December 2011 were retrieved and individually analyzed. Data gathered included: sex; age; history of varicella infection; interval between primary varicella and herpes zoster infection; location, particularly laterality and dermatomal distribution; as well as associated illnesses. Results were then tabulated and analyzed.

RESULTS

A total of 99 cases of childhood and adolescent herpes zoster were diagnosed at Santo Tomas University Hospital from January 2007 to December 2011. The incidence was 4.82 per 1000. There were 60 males and 39 females with male to female ratio of 1:1.5.

Of the 99 cases, only 75 charts were available for review. There were 46 males and 29 females, again with male to female ratio of 1:1.5. One case (1.33%) was seen in the infantile group, ages 0-1, 14 cases (18.67%) fell in the childhood group ages 2-9 years old and the adolescent group, ages 10-19 years old had the most cases at 60 (80%).

Table 1: Gender and age of patients

	N(%)
Gender:	
Male	46 (61.33%)
Female	29 (38.67%)
Age:	
Infantile (0-1 years old)	1(1.33%)
Childhood (2-9 years old)	14(18.67%)
Adolescent (10-19 years old)	60 (80%)

History of varicella infection was seen in 47 (62.67%) while 12 (16%) had no history of varicella infection. Seven cases (9.33%) had unknown and or unrecalled varicella infection and in nine cases (12%) a history of varicella infection was not recorded in the chart.

Table 2: History of varicella infection

With History of varicella	47 (62.67%)
No history of varicella	12 (16%)
Unrecalled and or unknown	7 (9.33%)
Not in the chart	9 (12%)

No history of varicella vaccination was retrieved. Interval history from varicella infection to development of herpes zoster ranged from 1-16 years with an average interval of 7.3 $\pm$ 1.2 years. Only 1 patient showed a one-year interval and had no predisposing factor.

Right and left involvement occurred with equal frequency. The most common areas involved were the thoracic dermatomes accounting for 48 cases (64%), followed by lumbar 10 cases (13.33%), cervical 9 cases (12%), and sacral 3 cases (4%). Three cases had 2 adjacent areas involved, 2 (2.67%) cervicothoracic and 1 (1.33%) thoracolumbar. The trigeminal nerve was involved in five cases (6.66%), with one case (1.33%) of herpes zoster ophthalmicus and one case (1.33%) of Ramsay Hunt syndrome.

Table 3: Dermatomal distribution

Dermatome Level	N (%)
Cranial (Trigeminal)	5 (6.67%)
Cervical	9 (12%)
Thoracic	48(64%)
Lumbar	10 (13.33%)
Sacral	3 (4%)
Cervicothoracic(dermatome overlap)	2 (2.67%)
Thoracolumbar(dermatome overlap)	1 (1.33%)
Total	75

Of all the patients, only six (8%) had the recognized risk factor for herpes zoster infection in children: a 3-year-old boy whose mother had varicella at eight months age of gestation, three cases (4%) had varicella infection at 1 year of age: a 3-year-old and a 2-year-old boy, and a 14-year-old girl with diffuse non-toxic goiter and two cases (2.67%), an eight-year-old boy and a nine-year-old boy had it at less than 1 year of age.

Twenty-four (32%) patients had respiratory diseases, five (6.67%) had upper respiratory tract infection, eleven (14.67%) had history of asthma (one was in acute exacerbation), seven (9.33%) had history of primary complex (6 treated and 1 on isoniazid therapy) and one (1.33%) had pulmonary tuberculosis on quadruple therapy.

Table 4: Other diseases

Disease	N(%)
Upper Respiratory Tract Infection	5 (6.67%)
Bronchial Asthma	11 (14.67%)
Pulmonary Tuberculosis/ History of primary complex	8 (10.67%)
Diffuse Non-Toxic Goiter	1 (1.33%)
Post-Traumatic Stress Disorder	1 (1.33%)

DISCUSSION

The diagnosis of herpes zoster is often clinical. Childhood herpes zoster accounts for less than 1% of the total zoster cases in the past; recent reports show an increase in the number of cases in apparently healthy children.[5] This study of 75 cases of herpes zoster involved immunocompetent children, aged 1-9 years old, and adolescents 10-19 years old. These findings are consistent with the progressive increase in the incidence of herpes zoster in healthy children over the past decades.[3] Herpes zoster is considered to represent a reactivated infection with varicella virus that has persisted in latent form in sensory nerve ganglia. Typically, varicella occurs in childhood; whereas zoster is most commonly seen in the elderly, a finding attributed to a decline in cell-mediated immune response with advancing age.[6] The shortened length of

time between the primary infection and re-activated infection is influenced by host-dependent factors such as immunosuppression; and, childhood zoster is often due to maternal infection with varicella during pregnancy or varicella during the first year of life.[2,3,5,6] The relative risk of varicella during the first year of life developing into childhood herpes zoster ranges from 2.8% to 20.9%.[3] Out of the 75 cases, 47 (62.67%) had a history of varicella, five patients had a history of varicella in the 1st year of life accounting to 6.67%. The time interval from primary varicella to herpes zoster ranged from 1-16 years with an average interval of 7.3 ± 1.2 years. A study by Takayama et al. of herpes zoster in normal and in those with underlying diseases but were not immunocompromised Japanese children showed that the mean interval between varicella and zoster at 6.2 ± 3.2 years.[4] The shortened time between the primary infection and the reactivation reflects the response of an immature immune system.[6] Although, the medical records of the patients in this study only mentioned 1 case of prenatal exposure to varicella, the possibility of such exposure cannot be excluded because maternal pregnancy records were not reviewed. Conclusion cannot be drawn from this study regarding the relationship between childhood zoster and prenatal exposure to varicella. The absent history of varicella in 12 of the 75 cases is only based on anamnestic recall. Although, it is unlikely that the families did not recognize full-blown varicella in the children, the occurrence of subclinical varicella cannot be totally dismissed. Subclinical varicella as a risk factor for childhood zoster is further supported by a report of childhood herpes zoster following unnoticed varicella.[3]

Among the 75 cases, herpes zoster lesions was most commonly observed in the thoracic nerve regions (64%) as described by other studies.[1,2,3,6,7,8] Historically, childhood herpes zoster was thought to be an indicator for an underlying malignancy, especially a hematologic malignancy like acute lymphocytic leukemia and other immunocompromised states.[5] Patients with chronic obstructive pulmonary disease are also at increased risk for herpes zoster compared with the general population due to chronic inflammation and immune dysregulation, and risk is greater among patients who use inhaled or oral corticosteroids.[9] Although some patients in the study had underlying diseases most especially respiratory in nature, they were not immunocompromised. The most frequent disease recorded was bronchial asthma. Only one was in acute exacerbation receiving oral steroids. The rest were not on oral or inhalational steroids. In a study of herpes zoster by Takayama et al. in immunocompetent and immunocompromised children, bronchial asthma ranked second in frequency to acute lymphocytic leukemia.[4] Other underlying diseases recorded were: pulmonary tuberculosis/primary complex which ranked second in frequency, upper respiratory tract infection, diffuse non-toxic goiter and post-traumatic stress disorder. Two local retrospective studies on herpes zoster also found pulmonary tuberculosis as an underlying disease.[7,8]

LIMITATIONS OF THE STUDY

Of the total 99 cases diagnosed with childhood herpes zoster, only 75 charts were available for review, therefore affecting the possible outcome of results. Other limitations include possible inadequacies in information gathering and documentation as seen in most retrospective studies such as: 1) analysis of data being based solely on the registration of complaints of the patient and not including pertinent negatives; 2) different clinicians diagnosing and describing the disease; and 3) incomplete charts with no data records of pertinent information regarding presence nor absence of history of previous varicella infection, maternal history of varicella and other diseases present.

CONCLUSION

This is the first retrospective study done locally that attempted to describe the epidemiology of childhood and adolescent herpes zoster. It was found to be more common in the adolescent age group although a number was also seen in childhood. There was a male predilection. Most did not present with the two known risk factors of herpes zoster namely: maternal varicella infection and varicella at first year of life. Apparently healthy children were affected and a small percentage did not have any history of varicella infection. Some had underlying diseases, which were mostly respiratory in nature.

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A pilot study to compare the effects of Salicylic Acid 16.5% + Lactic Acid 16.5% Solution and *Melaleuca Alternifolia* (Tea Tree) oil on the Resolution Rates of Verruca Vulgaris

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Background: Verruca vulgaris is common in people of all ages and there is no gold standard of treatment at this time. Present treatment options are costly, painful or worse ineffective.

Objective: To establish if *Melaleuca alternifolia* oil has a value, or not, as a treatment for verruca vulgaris.

Methods: This was a randomized, single-blind, clinical trial wherein twenty patients with verruca vulgaris were included. Ten patients applied salicylic acid 16.5& + lactic acid 16.5% solution and another ten applied *Melaleuca alternifolia* (tea tree) oil on each lesion nightly. Patients were followed-up weekly for four weeks for assessment of resolution rates and adverse effects.

Results: A mean change in the size of the lesion of 2.90 + 1.97 and 3.70 + 5.33 in mm2 for the *Melaleuca alternifolia* oil and salicylic acid + lactic acid solution group, respectively, was observed. These results show that there is no statistically significant difference (p=0.661, t-test) between using *Melaleuca alternifolia* oil or salicylic acid + lactic acid solution for the treatment of verruca vulgaris. On the aspect of adverse reactions to the test substances, there was a statistically significant difference in both groups (p=0.0230, Fisher's test).

Conclusion: *Melaleuca alternifolia* may have a role as an alternative treatment for verruca vulgaris.

INTRODUCTION

The human papilloma virus (HPV) is the virus responsible for verruca vulgaris, or verrucae (singular: verruca verruca).[1] There are approximately 100 strains of human papilloma viruses wherein type 1, 2, and 3 causes most of the common verruca vulgaris.[2] Verrucae are benign growths on the skin that cause cosmetic problems, as well as pain and discomfort, seen on people of all ages but most commonly appear in children and teenagers.[3] The incubation period of a verruca vulgaris is 2 to 9 months following infection with the human papilloma virus, during which, an excessive proliferation of skin growth slowly develops.[4,5]

Verrucae commonly occur on hands and fingers of children and young adults with an incidence rate up to 12.9% in some countries and has been found to be more prevalent in 4-6 and 16-18 year olds with the girls outnumbering the boys.[6-9] It The virus is spread by contact, either directly from person to person, or indirectly via fomites left on surfaces.[10] Diagnosis is mainly made clinically, a skin biopsy is rarely needed nor warranted.[11] It is a common problem seen by the dermatologist everyday.

Verruca vulgaris (common warts) are hyperkeratotic, exophytic and dome-shaped papules or nodules especially located on the fingers, hands, knees, elbows or any other sites of trauma.[11] Lesions may be studded with black dots which represent thrombosed dermal capillary vessels.[11] On close inspection, normal skin lines over the surface of the lesion are typically disrupted, the surface hyperkeratotic with many small filamentous projections.[12]

Studies show that more than 50 percent may undergo spontaneous resolution within two years[13] most are bothered by its presence and opt to have it treated. Treatment of verruca vary from homemade topical concoctions to surgical procedures, each with its own reports of cure,[13-14] as no single therapy has been proven effective at achieving complete remission.[10] Several over-the-counter preparations are available for the self-treatment of verruca. One of these clinically employed treatments is the use of salicylic acid (SA) which, if correctly applied, will result to a cure of 70-80% of common verruca vulgaris.[13] However, the application of SA can have adverse effects such as local irritation.[13] Another common method of treatment is by electrocautery with curettage with pain being the most common complaint amongst the patients, even with the application of anesthesia.[15]

There are a lot of natural, herbal and home remedies available for the treatment of verruca, *Melaleuca alternifolia* oil being one of them. *Melaleuca alternifolia* oil has both antibacterial and antifungal properties.[16-18] It is recommended as a non-poisonous, nonirritant antiseptic of unusual strength even to sensitive tissues.[19] Although using Melaleuca alternifolia oil is not a new concept as treatment for common verruca, much of the evidence appears to be anecdotal as opposed to salicylic acid + lactic acid.

This study aims to assess the effectiveness of the topical application of Salicylic Acid 16.7% + Lactic Acid 16.7% (SA+LA) compared to that of *Melaleuca alternifolia* oil for the treatment of verruca vulgaris using a recommended course of treatment. It is of significance to investigate home treatments in an attempt to provide information for the profession and patients on possible alternative treatment options compared to mainstay treatments. This study aims to see if there is a role or not for *Melaleuca alternifolia* oil in the treatment of verruca, if there is, to compare the resolution rates with SA+LA solution and to compare the frequency of adverse effects between *Melaleuca alternifolia oil* and SA+LA solution.

METHODOLOGY

Study Design and Subject Selection

This is a 4-week, randomized, single-blind, clinical trial conducted at the Dermatology Department – Out Patient of East Avenue Medical Center from February to April 2010 after being approved by the hospital's institutional review board committee. Patients included were a) aged 8 to 45 years old, b) male and female, c) able to follow simple instructions in English and d) diagnosed clinically by a dermatology resident to have verruca vulgaris, characterized by the presence of a hyperkeratotic papule with/

without visible thrombosed vessels, located on the trunk or extremities. Patients excluded from the study were a) those who have previously treated their verruca vulgaris, either with topical or oral medications within the past 4 weeks, b) those who have an inflammatory or infectious skin condition in the location of the verruca vulgaris, c) those who are immunocompromised (i.e. with known systemic illnesses such as diabetes mellitus and malignancy) and d) those who suffer from known allergies, especially to salicylic acid, lactic acid and/or *Melaleuca alternifolia* oil, or other skin conditions. Once eligibility criteria were met, the nature of the study was explained to the subject and an informed written consent was obtained.

Preparation of Test Substances

Test substances used in this study were obtained from Chemworld Philippines and Stiefel Philippines for the *Melaleuca alternifolia* oil and SA+LA solution respectively. The medications were placed in identical 10ml amber-colored glass bottles and labeled as A (Melaleuca alternifolia oil) and B (SA+LA) by a primary investigator, with codes assigned only known to the primary investigator. Computer-generated randomization was done using www.randomizer.org for the assignment of patients to the medications. The randomization codes were placed in sealed, opaque envelopes, opened as each patient was deemed eligible for the study.

Application of Test Substances and Follow-up

If the patient had more than one lesion, only one lesion was selected for the study. Baseline measurements of the lesion was taken using an acetate grid with a measurement of 1 mm2/square on weeks 0, 1, 2, 3 and 4 and recorded by a secondary investigator, who was blinded as to the allocation of the medications. Baseline photographs of the lesion under standardized setting (no flash, ISO400, macro mode) were taken using a Canon G9, 12.1 megapixel camera was taken.

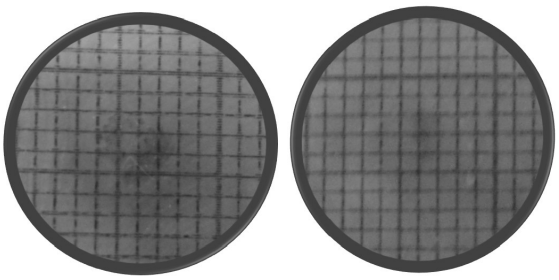


Fig. 1. Measurement of verruca using an acetate grid in mm2 were done on weeks 0, 1, 2, 3 and 4.

On entry, each patient, and guardian if the patient was a minor, was/were given the following materials: a 10ml amber glass bottle with the test substance labeled either A or B, wooden stick applicators, cotton balls and an emery board and an instruction sheet, explained at the start of the study. Method of application will direct participants to perform the following nightly: 1) clean the verruca with soap and water, 2) apply a piece of cotton dipped in tap water over the verruca and left on for 3 minutes, 3) remove cotton over the verruca and dry the area thoroughly with a paper towel, 4) use the emery board given and slide it over the verruca 4 times, as instructed on week 0, 5) apply the just enough amount of the test substance to cover the verruca using a wooden stick applicator which is to be discarded after each use, 6) let the test substance dry for ten minutes and 7) to check the corresponding box on the chart in the instruction sheet given. Patients were advised to adhere to the guidelines as shown in the enclosed instruction sheet, explained to the patient or guardian at the start of the study. If skin irritation does occur, patients were advised to discontinue use and follow-up at the soonest time possible.

Patients were asked to follow-up every week for 4 weeks, during which, measurements and photographs of the lesion were taken, supply of materials replenished and patients asked for any adverse reactions upon application of the test substance. Patients who failed to keep their weekly appointments were given an extra 72 hours in which to be seen by the secondary investigator.

At the end of the study period, patients were given the option to either continue with their corresponding test substance or to undergo

electrodessication and curettage, done by the primary investigator, free of cost.

Outcome Measures

The primary outcome measured in this study is the resolution rate (reduction in size) of the verruca after 4 weeks of treatment with either SA+LA solution or *Melaleuca alternifolia* oil. The secondary outcome measured is the type and frequency of adverse reactions to either SA+LA solution or *Melaleuca alternifolia* oil.

Statistical Analyses

Previous studies showed a cure rate of 75% with salicylic acid with or without lactic acid and no study were found as to the use of *Melaleuca alternifolia* oil for verruca vulgaris. In the absence of any preliminary quantitative data on the efficacy of *Melaleuca alternifolia* for verruca, no sample size calculations were possible. Any information gained from this pilot study may be used to plan a larger study.

Demographic and baseline characteristics of the study population were summarized and described by descriptive statistics. Paired t test was used to compare means and fisher test used to compare counts.

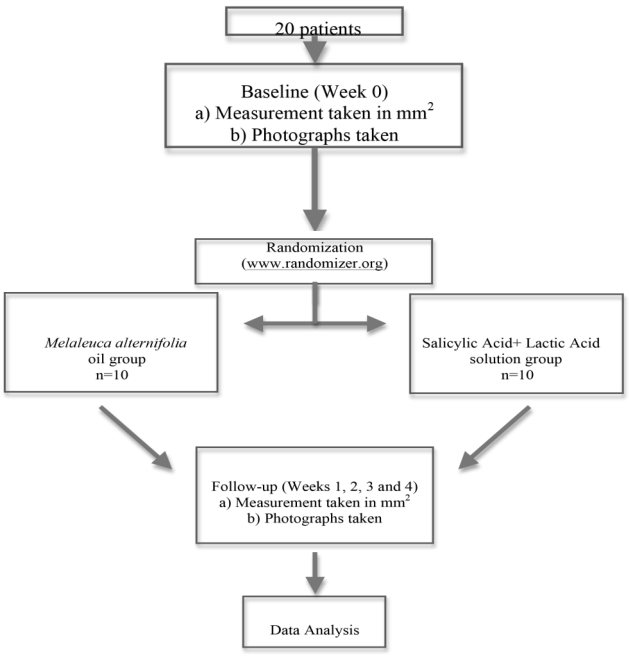


Fig.2. Methodology flow chart

RESULTS

Patient Demographics

The study assessed 20 subjects, 8-44 years of age, (mean of 24.6 + standard deviation 11.98) were included in the study. Test for homogeneity of the study population in all categories, using the paired t-test for means and fisher test for counts showed that there is no significant difference between the two groups in terms of their baseline characteristics (Table 1)

Table 1. Patient demographics and characteristics of lesion at baseline

	Melaleuca alternifolia oil N (Mean ± SD)	Salicylic Acid 16.5% + Lactic Acid 16.5% solution N (mean ± SD)	p value
Age (years)	8-44 (24.4±13.15	8-40 (24.8±11.39)	0.937*
Gender			1.00**
Male	5	6	
Female	5	5	
Location			1.00**
Upper Extremity	6	7	
Lower Extremity	4	3	
Duration of Lesion (Weeks)	1-10 (4.7±3.02)	4-10 (6.6±2.84)	0.201*
Size of Lesion (mm^2)	2-1 (8.60±5.34)	5-28 (12.00±8.25)	0.315*

**** paired t-test; ** Fisher's test***

Resolution Rates

In the TTO group, all of the lesions decreased in size wherein one had complete resolution of the lesion. In the SA+LA group, 7 decreased in size with two of these having complete resolution of the lesion and the other two increased in size while one remained the same size. There is no significant differences between the two groups in the resolution rates of verruca vulgaris. (Table 2)

Table 2. Change in size of lesion

	Week 0 Size in mm2 (mean + SD)	Week 4 Size in mm2 (mean + SD)	Change in Size Size in mm2 (mean + SD)
Melaleuca alternifolia oil	2-18 (8.60±5.34)	0-10 (5.70±3.86)	1-8 (2.90±1.97)
SA+LA Solution	5-28 (12.00±8.25)	0-30 (8.30±9.92)	-2-15 (3.70±5.33)
p value*	0.315	0.450	0.662

paired t-test

On a weekly basis, the mean size of change with the *Melaleuca alternifolia* group decreased continuously as compared to that of the SA+LA group wherein the lesions increased in size in the first week of application of the solution before decreasing in size. (Figure 1)

Figure 1. Change in size of the lesion of both treatment groups from baseline to week 4.

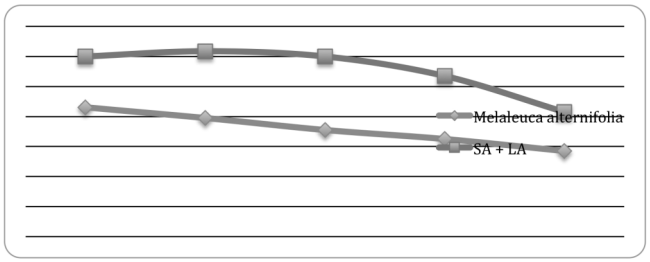
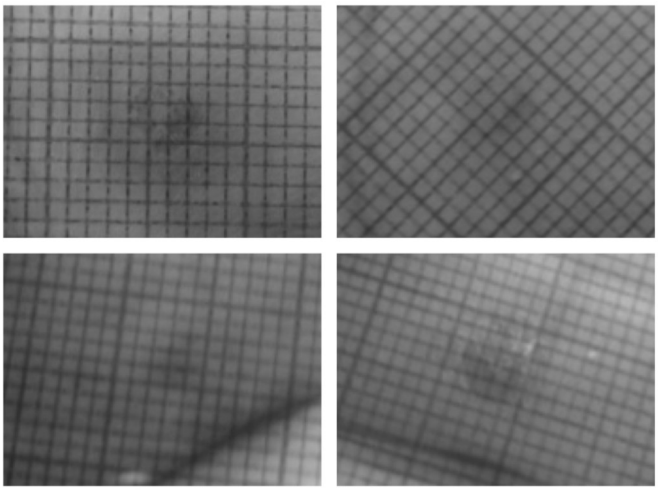


Table 3. Frequency of adverse effects

	Adverse Effects	No Adverse Effects	Total
Melaleuca alternifolia oil	2 (20%)	8 (80%)	10
Salicylic acid + Lactic Acid solution	8 (80%)	2 (20%)	10

p=0.0230, Fishers test

Figure 2. Images on top are before and after application of Melaleuca alternifolia oil. Images on the bottom are before and after application of Salicylic acid + Lactic acid



Safety and Tolerability

Adverse reactions to both test substances were recorded on each follow-up and were localized to the area around the verruca. Patients complained of erythema, pruritus, and stinging over and around the lesion. A total of 10 patients reported adverse reactions to the test substance, 8 from salicylic acid + lactic acid group and 2 from the *Melaleuca alternifolia* oil group. In the salicylic acid + lactic acid group, 2 (20%) complained of erythema, 2 (20%) experienced pruritus and 4 (40%) had a stinging sensation upon application of the solution. In the *Melaleuca alternifolia* oil group, 1 (10%) noticed erythema around the verruca vulgaris and 1 (10%) complained of pruritus upon application of the oil. There is a statistical difference between the ocurrence of adverse effects between the two groups.

DISCUSSION

Verruca vulgaris is a common, relatively benign skin lesion that plague people of all ages all around the world. But just like the common cold, there is no standard treatment for this infection. Lesions may be self-limited but may take up to two years for its spontaneous resolution 15 making the patient want to have the verruca removed as soon as possible due to its increase in size and number, associated pain, pruritus and social stigma brought about by its presence.

Numerous treatments are available for the treatment of verruca vulgaris, both as over the counter medications or those with the help of physicians yet no single therapy has been proven effective at achieving complete remission in every patient.[10] Amongst the over the counter medications available is salicylic acid.

Salicylic acid in concentrations from 15-60 % with or without the addition of lactic acid have shown a cure rate of 75%.[13] Common side effects observed in salicylic acid is contact dermatitis and a potential risk of systemic toxicity in children. [11]

Melaleuca alternifolia oil has been studied well for its antibacterial and antifungal properties, however much has yet to be investigated on its antiviral properties. 19 Reports on its efficacy as treatment for verruca are lacking and mostly anecdotal. It is more cost effective than SA+LA solution and even if it may cause allergic reactions, it has less side effects.

The spontaneous regression of verruca should not be forgotten in assessing the efficacy of any treatment modality used.[14] This regression has been attributed to the induced T-cell mediated tumor cell destruction.[20] The mechanism by which SA+LA solution works is that of being a keratolytic. It slowly destructs the virus-infected epidermis resulting in a mild irritation that may stimulate an immune response.[10] As for the proposed mechanism for *Melaleuca alternifolia* oil, it may be due to a direct effect on the extracellular virus particle, prior to penetration into a host cell by its proposed active components,terpinen-4-ol, alpha-terpineol and 1,8-cineole.[19]

This pilot study was done to provide preliminary data on the use of *Melaleuca alternifolia* oil in the treatment of verruca vulgaris. The outcome of the study showed no statistical difference in the resolution rates of verruca vulgaris in both groups and a statistical difference in the frequency of adverse reactions. Though these results are favorable to the *Melaleuca alternifolia* group, these may be due to the small sample size, hence a larger study group is recommended in the future. Another factor that is of importance is that of the time amount given in the study for follow-ups. Four weeks is a relatively short period of time given for the complete cure of verruca vulgaris with the use of topical agents. The reason for this is to decrease the amount of drop-outs from the study, hence the computation for the resolution rates instead of cure rate.

Melaleuca alternifolia oil holds promise on being a useful alternative treatment for verruca vulgaris. It is relatively inexpensive when compared to other treatment available and tolerability, in both pediatric and adult age groups, may be of higher value when considering treatment options.

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Appendix

Appendix A - Informed Consent Information

PATIENT INFORMATION SHEET (KAALAMAN PARA SA PASYENTE)

Verruca vulgaris or warts are caused by the human papilloma virus and is a very common problem which we, dermatologists see and treat regularly. No gold standard has been set for the treatment of warts hence the many different treatments available, both over the counter and those offered by dermatologists. *(Ang kulugo ay sanhi ng isang virus na ang pangalan ay human papilloma. Ito ay isang pangkaraniwang sakit na nakikita at ginagamot naming mga dermatologist sa araw-araw naming trabaho. Maraming paraan para magamot ito ngunit walang makakapagsabi na ito ay makakapagbigay ng lunas ng lubusan. Dahil dito, maraming gamot ang mabibili sa tindahan at paraan ginagamit ng mga dermatologist para maalis ang kulugo.)*

A study is being carried out at the Department of Dermatology of East Avenue Medical Center to investigate the effectiveness of the use two home treatments for warts. The study will involve applying a treatment of Melaleuca alternifolia (tea tree) oil and a mixture of Salicylic Acid and Lactic Acid solution directly onto the wart. *(Isang pag-aaral ang ginagawa sa Department of Dermatology ng East Avenue Medical Center para matukoy ang epektibo ng dalawang gamot na pangkaraniwang nabibili sa mga tindahan para sa paggaling ng kulugo. Ang isa ay Melaleuca alternifolia (tea tree) oil at ang isa ay halo ng Salicylic Acid at Lactic Acid na ipapahid sa kulugo.)*

An investigator will measure your wart and record any pain or discomfort it may be causing. The first treatment will be done in the clinic to teach you how to put the medicine properly onto the wart. You will receive a bottle of one of the medicines to use daily at home for the next 3 weeks, together with written instructions on how to use the them properly. It will also be necessary for you to return to the clinic after 7, 14 and 21 days for the assessment and monitoring of the wart. *(Isang imbestigador ang magsusukat ng laki ng iyong kulugo at ikaw ay tatanungin tungkol sa sakit na nararamdaman dahil dito. Ang unang gamutan ay gagawin sa OPD upang maituro ang wastong paglagay ng gamot sa kulugo. Pagkatapos nito at bibigyan ka ng isang bote na naglalaman ng gamot na iyong gagamitin sa bahay kasama ang instruksyon sa wastong paggamit ng gamot na naayon sa pag-aaral. Ikaw ay inaasahang bumalik sa klinik pagkatapos ng 7, 14, 21 at 28 na araw ng gamutan para masubaybayan ang gamutan.)*

It is unlikely that you will have any adverse reactions to the medications used as there are minimal adverse side effects reported to both treatments used in the study. However, if there are any adverse reactions such as the area becoming red and swollen or undue pain or discomfort is felt, please discontinue use of the medications and go back to the clinic to notify the investigators. Please keep the medication given to you in a place where it may be used in any other means. In case the medication given to you gets to the eyes or skin other than the wart, please wash the area as soon as possible. *(Kakaunti ang nagkakaroon ng "allergy" sa mga gamot na gamit sa pag-aaral na ito. Subalit kung ikaw ay nakaramdam ng hindi pangkaraniwang sakit, namula o namaga ang iyong kulugo, itigil agad ang paggamit nito at pumunta sa klinik sa lalong madaling panahon. Kung maari, itago ang gamot ni binigay sa iyo upang maiwasan na gamitin ito sa maling paraan. Ang gamot na ito ay pinapahid at hindi dapat kailanman inumin ng isang tao. Kung sakaling malagyan ang ibang parte ng katawan ng gamot, hugasan itong maigi lalo na kung ito ay mapunta sa mga mata.)*

All personal information gained is strictly confidential and will only be used for the purposes of this study. At any time you may withdraw from the study and this will not prejudice further treatment.

(Lahat ng impormasyon na makukuha sa pag-aaral na ito ay confidential at ang mga imbestigador lang ang makakaalam nito. Kung may pagkakataon na gusto mong tumigil ng gamutan, bumalik lamang sa klinik para ipaalam sa mga imbestigador.)

Thank you for agreeing to participate in this study. *(Salamat ng marami sa paglahok sa pag-aaral na ito.)*

Maria Rhea B. Lombos-Serondo, MD
Dermatology Resident

Appendix B – Informed Consent Form

Patient Identification Number: _____

CONSENT FORM

Title of Study:
"A Pilot Study to Compare the Effects of Salicylic Acid 16.5% + Lactic Acid 16.5% solution vs *Melaleuca alternifolia* (tea tree) oil on the Resolution rates of Verruca vulgaris"

Name of Researcher: Maria Rhea B. Lombos-Serondo, MD

Please check each box to confirm.
Markahan ng check ang box kung ikaw ay sumasang-ayon sa sinasaad nito.

❑I confirm that I have read and understand the information sheet dated January 25,2010:version 1 for the above study and have had the opportunity to ask questions.
Nabasa at naintindihan ko ang papeles tungkol sa kaalaman para sa pasyente (January 25, 2010:version 1) para sa pag-aaral na ito at binigyan ako ng pagkakaton na magtanong tungkol dito.

❑I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
Naiintindihan ko na ang paglahok ko sa pag-aaral na ito ay boluntaryo at maari akong tumigil kung gusto ko, ng walang paglabag sa ano mang kasulatan.

❑I understand that any record from the study may be looked at by responsible individuals from the Department of Dermatology of East Avenue Medical Center or from regulatory authorities where it is relevant to my taking part in research and give them access to the said records.
Naiintindihan ko na ang mga dokyumento na gagamitin sa pag-aaral na ito ay maaring tingnan o basahin ng mga taong bumubuo ng Department of Dermatology ng East Avenue Medical Center o ng sino man na mangangailangan nito. Dahil dito, binibigyan ko sila ng permiso para gawin ito.

❑I agree to have pictures of my warts to be taken.
Ako ay sumasang-ayon sa pagkuha ng litrato sa aking mga kulugo.

❑I agree to take part in the above study.
Ako ay sumasang-ayon sa paglahok sa pag-aaral na ito.

Name and Signature of Patient: _____
Name and Signature of Person taking consent: _____
Date: _____

Total of 3 copies: 1 for the patient; 1 for the researcher; 1 to be kept with clinical trial

Appendix C – Patient Data Sheet

PATIENT DATA SHEET

STRICTLY CONFIDENTIAL

MEDICAL HISTORY:

Pangalan: _____ Edad: _____ Kasarian: _____

1. Gaano na katagal ang iyong kulugo? _____
   Ilan ang iyong kulugo?_____
   Ito ba ay dumadami o kumukonti ng bilang?_____

2. Nagamot na ba ang iyong kulugo? _____
   Kung oo ang sagot, sagutan ang mga sumusunod na tanong, kung hindi ay lumaktaw na sa pangatlong tanong.
   Sino ang gumamot nito? _____
   Gaano katagal ito ginamot? _____
   Ito ba ay gumaling ng lubusan? _____

3. Mayroon ka bang mga allergy sa ano mang bagay, gamot o pagkain?_____
   Kung oo, saan ka nag-allergy? _____ at kailan nangyari ito? _____

4. Mayroon bang sakit, kati o iba pang hindi magandang karamdaman na idinudulot sa iyo ang iyong kulugo? _____
   Ito ba ay nagiging sagabal sa iyong pang-arawaraw na gawain o trabaho?_____
   Kung oo ang sagot, katulad ng ano ang mga ito?_____
   _____

RECORD OF LESION:

Day 0:
Size: _____ VAS: _____
Description of wart: (presence of hyperkeratosis, black dots, bleeding, etc)
_____

Day 7:
Size: _____ VAS: _____
Description of wart: (presence of hyperkeratosis, black dots, bleeding, etc)
_____

Day 14:
Size: _____ VAS: _____
Description of wart: (presence of hyperkeratosis, black dots, bleeding, etc)
_____

Day 21:
Size: _____ VAS: _____
Description of wart: (presence of hyperkeratosis, black dots, bleeding, etc)
_____

Day 28:
Size: _____ VAS: _____
Description of wart: (presence of hyperkeratosis, black dots, bleeding, etc)
_____

Appendix D – Study Treatment Guidelines

STUDY TREATMENT GUIDELINES

The medication should be applied on the wart on a daily basis, preferably at night.
Nararapat na pahiran ng gamot ang iyong kulugo araw-araw, kung maari ay sa gabi ito gawin.

No other medications for the wart may and should be used at the time of the study other than the one supplied by the investigator. If there is more than one wart, please put the medication on the one indicated by the investigator.
Walang ibang gamot para sa kulugo ang maaring gamitin habang ikaw ay kalahok sa pag-aaral na ito. Kung sakaling lagpas sa isa ang iyong kulugo, ipahid lamang ang gamot na binigay sa kulugo na sinaad ng imbestigador.

1. Clean the wart with soap and water.
   Linisin ang kulugo gamit ang tubig at sabon.
2. Apply a piece of cotton dipped in tap water over the wart and leave for 3 minutes.
   Maglagay ng bulak na binasa ng tubig sa ibabaw ng kulugo at iwanan ito ng 3 minuto.
3 Remove cotton over the wart and dry the area thoroughly with a paper towel.
   Tanggalin ang bulak at tuyuin ng mabuti ang kulugo gamit ang "paper towel".
4. Using the emery board provided, slide it over the wart 4 times as instructed.
   Gamit ang nail file na binigay, ikaskas ito sa ibabaw ng kulugo ng 4 na beses gaya ng itinuro.
5. Using the applicator supplied, carefully apply two drops over the wart. Avoid getting the medication to the surrounding normal skin.
   Gamit ang stick na binigay, maglagay ng 2 patak ng gamot sa ibabaw ng kulugo. Ingatan na hindi malagyan ng gamot ang nakapalibot na balat.
7. Let the solution dry for around ten minutes.
   Hayaang matuyo ang gamot sa balat ng mga sampung minuto.
8. Check the corresponding box on the chart below after doing the steps above.
   Markahan ng check ang box sa ilalim pagkatapos maglagay ng gamot.

	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY	SUNDAY
WEEK 1							
WEEK 2							
WEEK 3							
WEEK 4							

A slight tingling sensation, mild tenderness or redness may be felt during the treatment period and this is normal temporary. However, if any undue pain or irritation occurs, discontinue use of the medication and wash the area immediately. Notify the investigator as soon as possible. Please use the medication given only as prescribed by the investigator.
Maaring makaramdam na kaunting kirot o pamumula sa bahagi ng kulugo sa panahon ng gamutan, ito ay normal lamang at hindi magtatagal. Subalit kung labis na sakit o pamumula ang mararamdaman, itigil kaagad ang pagpahid ng gamot at hugasan ito ng tubig. Ipaalam ito sa imbestigador sa lalong madaling panahon. Pakiusap lamang na gamitin lang ang gamot na binigay sa paraan na sinabi ng imbestigador.

Appendix E – Certificate of Analysis of *Melaleuca alternifolia*

CERTIFICATE OF ANALYSIS

PRODUCT NAME……. TEA TREE OIL WATER SOLUBLE
TYPE OF EXTRACT…… WATER-SOLUBLE
PRODUCT CODE……. TTH-10
BATCH NO……. 186 FF 9 030
MANUFACTURING DATE…… December 11, 2009
EXPIRY DATE……. December 11, 2010
CERTIFICATE NUMBER…… 270609-254

ORGANOLEPTIC & PHYSICAL PROPERTIES:
COLOR…….. COLORLESS
ODOR…… characteristic smell
APPEARANCE……. CLEAR LQUID
SPECIFIC GRAVITY……. 0.9675
INDEX OF REFRACTION……: 1.3840
pH Value…… 5.8
SOLUBILITY…….. Soluble in water.
STORAGE:

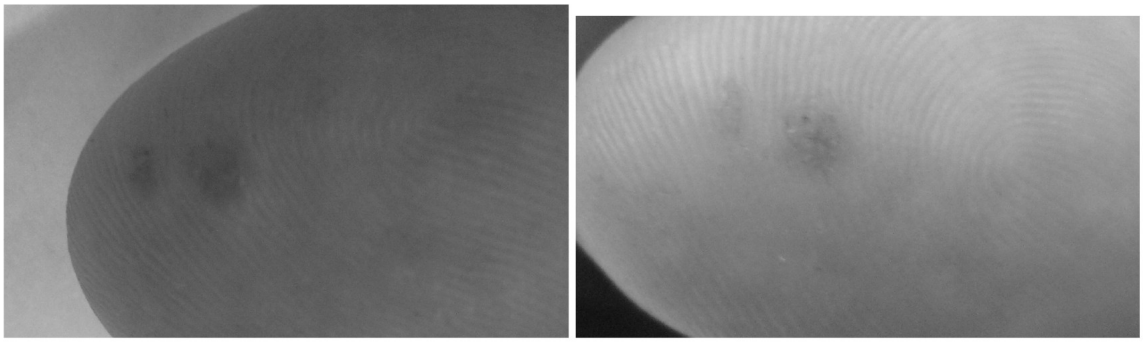
This product will last for at least 12 months at room temperature when stored in a full tightly sealed container.

This computerized document is not signed

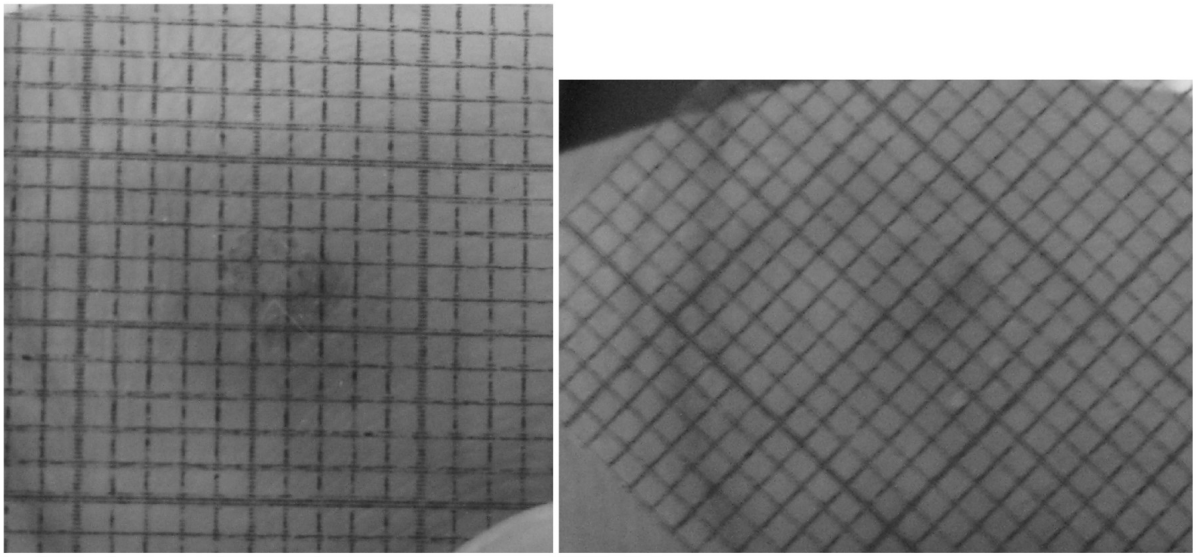
Appendix F

Melaleuca alternifolia

Baseline Week 4

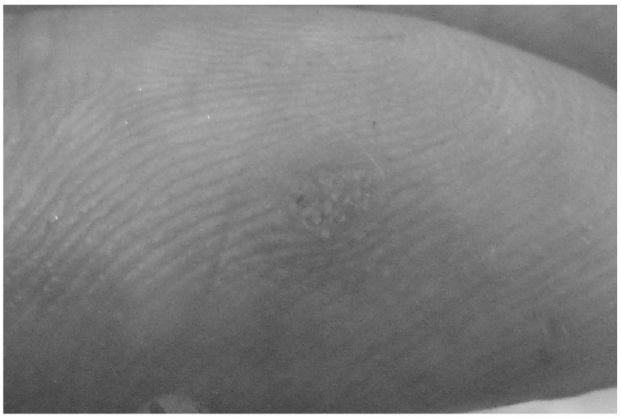


Baseline Week 4

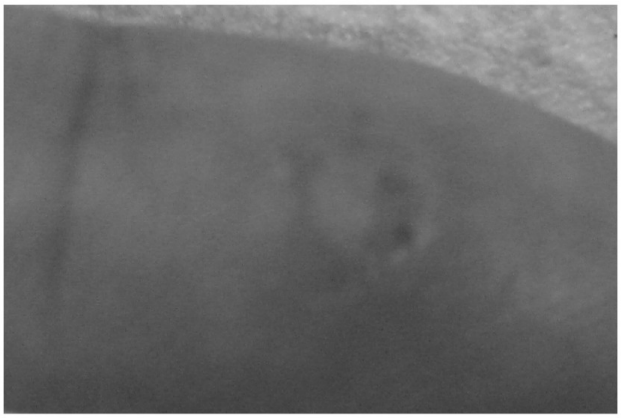


Salicylic Acid 16.5% + Lactic Acid 16.5% solution

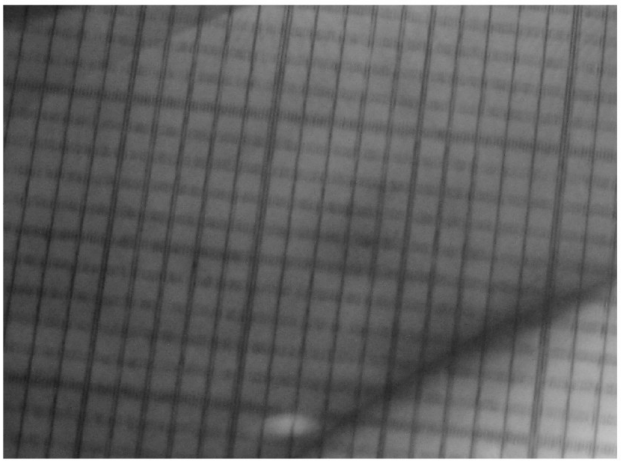
Baseline



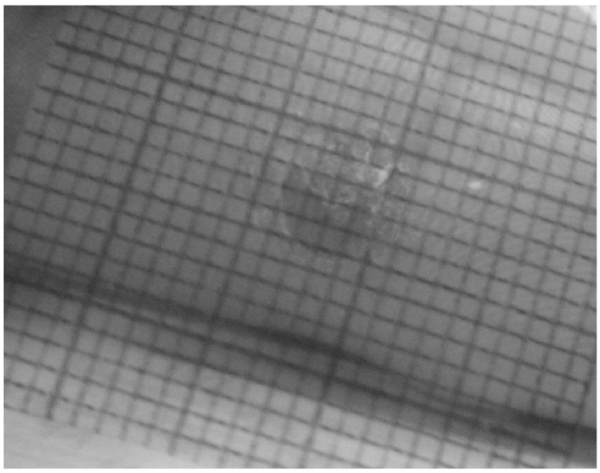
Week 4



Baseline



Week 4



Appendix G - *Melaleuca alternifolia* oil group

Patient Number	Age (yr)/ Sex	Duration of lesion (weeks)	Location of Lesion	Week 0 AR	Week 1 AR	Week 2 AR	Week 3 AR	Week 4 AR
1	14 M	8	UE	12 n	11 Slight pruritus	11 n	10 n	9 n
4	20 F	2	UE	4 n	3 n	3 n	2 n	2 n
5	24 F	4	LE	13 n	13 n	11 n	11 n	9 n
7	16 M	3	UE	6 4 n	5 slight erythema	5 n	4 n	4 n
9	9 M	2	LE	3 2 n	3 n	2 n	2 n	2 n
11	8 M	5	LE	5 n	4 n	4 n	3 n	3 n
12	36 F	8	LE	10 n	8 n	8 n	8 n	8 n
15	41 F	1	UE	2 n	1 n	1 n	1 n	0 n
18	32 M	4	UE	13 n	13 n	12 n	11 n	10 n
19	44 F	10	UE	18 n n	18 n	14 n	13 n	10 n

Appendix H - Salicylic Acid 16.5% + Lactic Acid 16.5% Solution Group

Patient Number	Age (yr)/ Sex	Duration of lesion (weeks)	Location of Lesion	Week 0 AR	Week 1 AR	Week 2 AR	Week 3 AR	Week 4 AR
2	21 M	10	UE	18 n	17 n	17 n	14 n	3 n
3	10 F	8	UE	7 n	11 slight stinging	11 n	7 n	4 n
6	17 M	8	LE	10 n	9.5 pruritus	9 n	7 n	0 n
8	8 M	4	UE	5 n	3 slight stinging	0 n	0 n	0 n
10	31 F	12	UE	12 n	14 stinging	14 stinging	14 slight erythema	14 slight erythema
13	40 F	16	LE	28 n	30 erythema	30 slight erythema	30 slight erythema	30 n
14	39 M	16	LE	23 n	21 pruritus	20 n	20 n	20 n
16	26 M	4	UE	5 n	5 slight stinging	5 pruritus	5 n	5 n
17	21 F	4	UE	6 n	8 erythema	9 pruritus	5 n	2 n
20	35 M	4	UE	6 n	5 n	5 n	5 n	5 n

Appendix I – Cost Analysis/Comparison

For the *Melaleuca alternifolia* oil

Melaleuca alternifoloia	P 38.40
Container	P 15.00
Wooden stick	P 0.40
Sticker Label	P 0.30
Cotton Balls	P 8.40
Forms	P 3.00
TOTAL	**P 65.50**

For the Salicylic Acid 16.5% + Lactic Acid 16.5% solution

SA + LA	P 205.87
Container	P 15.00
Wooden stick	P 0.40
Sticker Label	P 0.30
Cotton Balls	P 8.40
Forms	P 3.00
TOTAL	**P 232.97**

Association, Incidence and Clinical Profile of Patients with Obstructive Sleep Apnea and First-Onset Stroke in a Tertiary Hospital: A Prospective Descriptive Study

Cynthia B. Anacay, MD
Rosalina E. Picar, MD

Makati Medical Center
Section of Neurology

ABSTRACT

Objective: To determine the association, incidence, and clinical profile of patients with Obstructive Sleep Apnea (OSA) and first-onset stroke admitted and managed in a tertiary hospital using the STOP-BANG and Berlin questionnaire.

Design: This is a prospective descriptive study.

Participants: Patients 18 years old and above diagnosed with first-onset cerebrovascular disease by their neurologist were qualified for this study. This study included patients presenting as hemiparesis or hemiplegia, sensory or cranial nerve deficits; with hemispheric or brainstem lesions and with evidence of cerebral infarction or hemorrhage on either CT scan or MRI of the head.

Results: 172 first-onset stroke patients were identified from July to September 2014. 52 patients fulfilled the inclusion criteria. Using the Stop-Bang questionnaire, 71.1% of the 52 patients were identified to be of high risk of having OSA. Older male patients with neck circumferences greater than 40 cms, a BMI greater than 35kg/m^2 and those observed to stop breathing during their sleep are of high risk of having OSA. Of those patients with high-risk of OSA, 91.9% have hypertension. More than half (54.1%) had thrombotic stroke, while 27% and 18.9% had hemorrhagic and cardioembolic strokes, respectively. For the Berlin questionnaire, 69.2% of the same set of patients were diagnosed to have a likelihood of Sleep Apnea. Just like the results obtained using the Stop-Bang questionnaire, patients with likelihood of Sleep apnea using the Berlin questionnaire were found to be older, mostly males, with higher BMI, and with greater neck circumferences. 88.9% of patients with likelihood of sleep apnea have hypertension. Of the subject population, 42.3% were smokers, and 40.4% consume alcohol. 54.1% of those with high risk of OSA had thrombotic stroke, versus 27% and 18.9% of hemorrhagic and cardioembolic strokes, respectively.

Conclusion: There is a direct association and increased incidence of OSA in first-onset stroke based on the risk factors involved and the number of patients who tested positive for the Stop-Bang and Berlin questionnaire. Those who have OSA in Stop-Bang are likely also to have OSA in Berlin. Older age, male gender, a higher BMI, greater neck circumferences, smoking, hypertension and those observed to stop breathing during sleep have an increased risk or likelihood of OSA. Thrombotic stroke is the most common type of stroke seen, with 38.5% located at the subcortical area. Half of the lesions were noted at the right side of the brain, with patients initially presenting with left-sided hemiparesis and/ or dysarthria.

INTRODUCTION

Among known risk factors for stroke are age, sex, hypertension, diabetes mellitus, smoking, and a history of cardiovascular disease. Obstructive sleep apnea (OSA), however, is not widely considered as a risk factor for stroke. In the local setting, this has been commonly overlooked and not included in the investigations of a stroke patient.

The most effective means of diminishing stroke-related burden is by reducing the incidence of first-time and recurrent stroke. Therefore, recognizing and treating modifiable risk factors are of particular importance.[1] As mentioned earlier, besides the well-known modifiable risk factors, such as hypertension, diabetes mellitus, heart disease, smoking, excessive alcohol use, and hypercholesterolemia—obstructive sleep apnea (OSA) is emerging as an important risk factor.[1] It is crucial for stroke patients to be screened for sleep apnea because untreated sleep apnea increases the chances of a second stroke and small studies have found that stroke patients with sleep apnea tended to have worse rehabilitation outcomes.[2]

Obstructive Sleep Apnea (OSA) is associated with significant morbidity, including excessive daytime sleepiness, loud snoring during sleep, refractory hypertension, and impaired quality of life.[3] Obstructive sleep apnea syndrome (OSAS), characterized by repeated episodes of upper airway obstruction during sleep that lead to significant hypoxemia, is a prevalent disorder particularly among middle-aged men, though its existence in women is increasingly recognized.[1]

Polysomnography (PSG) is the gold standard in the diagnosis of Obstructive Sleep Apnea. One of the barriers to study the prevalence of OSA in patients is the difficulty with recruiting patients to undergo polysomnography.[3] It is a time-consuming and costly procedure.

Further, the growing awareness of sleep apnea has exacerbated the long waiting list in many sleep laboratories. Thus, screening questionnaires and clinical screening models have been developed to help identify patients with OSA.[4]

According to the Egyptian Journal of Tuberculosis and Chest diseases in 2012, the occurrence of OSA is far more prevalent than can be handled by the available sleep laboratories.[5] Therefore, as mentioned earlier, a screening tool is necessary to stratify patients based on their clinical symptoms, their physical examinations, and their risk factors, in order to ascertain patients at high risk and in urgent need of PSG and/or further treatment and patients at low risk who may not need PSG.[5]

There are many screening tools that can be used in detecting OSA. A study done in 2011 by Silva et al compared the use of variable screening tools in identifying patients with Sleep-Disordered Breathing (SDB).[6] According to the study, STOP-Bang questionnaire had the highest sensitivity in predicting moderate-to-severe (87.0%) and severe (70.4%) SDB.[6] When in terms of specificity, a recent systematic review done by Abrashami et al showed the Berlin questionnaire to have the highest specificity overall in determining Sleep-Disordered Breathing (SDB), of which OSA is the most common such disorder.[7]

The aim of this study is to identify the association, incidence and clinical profile of patients with Obstructive Sleep Apnea and first-onset stroke in a tertiary hospital using the STOP-BANG and Berlin questionnaires.

REVIEW OF RELATED LITERATURE

Obstructive sleep apnea (OSA) is frequent in acute stroke patients and is associated with increased mortality and poor functional outcome.

In a study done by Camilo et al, OSA is detected in ischemic stroke patients who underwent full -night polysomnography at the first night after symptom onset.[8] Palomake and colleagues studied 167 men with stroke and found that 35.5% experienced their strokes during sleep.[9] Using stepwise multiple logistic regression analysis, they showed that among possible risk factors for stroke (snoring, age, body mass index, smoking, alcohol consumption, and diabetes mellitus), only snoring was significantly related to stroke in sleep.[9] They also reported that the odds ratio of snoring as a risk factor for stroke was strongly

increased if snoring was accompanied by excessive daytime sleepiness and obesity. These findings suggest that obstructive sleep apnea syndrome is a risk factor for stroke.[9]

The Canadian Stroke Congress in 2012 considered Obstructive Sleep Apnea as both a risk factor for stroke and a complication following stroke. Researchers said that among the general population, sleep apnea increases the likelihood of having a stroke, even after controlling for other stroke risk factors, such as high blood pressure and diabetes.[2]

According to Durgan et al, the incidence of OSA in patients who have had a stroke or transient ischemic attack is greater than that of the general population.[10] Patients presenting with stroke or transient ischemic attack were 3 to 4 times more likely to have OSA than were matched control subjects.[10] Their study points to strong evidence indicating that: OSA is an independent risk factor for stroke, it exacerbates damage produced by a stroke, it increases the risk for a subsequent stroke, and it contributes to brain atrophy and dementia in the elderly.[10] OSA interferes with the basic control mechanisms for regulating cerebral blood flow (CBF) by decreasing resting CBF, impairing autoregulation, and reducing cerebrovascular reserve.[10] These alterations to normal cerebrovascular control interfere with brain function and render the brain more vulnerable to ischemic events, leading to a cerebrovascular event.[10]

A study done by Silva et al in 2011: Identification of Patients with Sleep Disordered Breathing: Comparing the Four-Variable Screening Tool, STOP, STOP-Bang, and Epworth Sleepiness Scales, in terms of sensitivity, the STOP-Bang tool identified more subjects with moderate-to-severe SDB and severe SDB. The STOP-Bang performed better than the STOP questionnaire.[6] A local study done by Jorge et al in 2012 at Philippine General Hospital showed the use of the Berlin questionnaire in identifying populations at risk for sleep apnea syndrome.[11] They concluded that the Berlin Questionnaire (BQ) showed high construct validity and can be used as a research tool to conduct studies on risk assessment and disease correlation with OSA in the local community.[11] It may also be used as a screening tool in order to identify patients who may need further workup for OSA.[11]

Other questionnaires have been proposed for screening SDB. In their meta-analysis, Ramachandran and Joseph evaluated several clinical screening tests for obstructive sleep apnea, including the American Society of Anesthesiologists (ASA) checklist, the Berlin questionnaire, the Sleep Questionnaire, the sleep disorders questionnaire (SDQ) and the STOP and STOP-Bang questionnaires.[12] The authors concluded that the Berlin questionnaire and the SDQ were the most accurate questionnaires overall to screen for SDB.[12] They also concluded that the ESS was the least accurate, and that the STOP questionnaire, although the simplest tool, was a poor predictor of SDB, as was the ASA screening tool.[12] The authors, however, identified the STOP-Bang questionnaire as an excellent method for predicting severe SDB due to its simplicity and relatively ease of use rather than incorporating tools with more complex scoring methods into standard preoperative evaluations.[12]

OBJECTIVES

General Objective

To determine the association, incidence, and clinical profile of patients with Obstructive Sleep Apnea (OSA) and first-onset stroke admitted and managed in a tertiary hospital using the STOP-BANG and Berlin questionnaire.

Specific Objectives:

a. To determine the demographic profile as to age, gender, anthropometric measurements, pertinent medical and social history of OSA patients that contribute to the development of stroke.
b. To determine the association of Obstructive Sleep Apnea among first-onset stroke patients using the "STOP BANG" and Berlin Questionnaire.

METHODOLOGY

Study Design

This is a prospective descriptive study conducted among at least 30 patients with first-onset stroke, admitted and managed by the Section of

Neurology in a tertiary hospital during the period of July 1, 2014 to September 30, 2014. All participants were required to sign an informed consent. This study was done in accordance to the ethical principles of the Declaration of Helsinki and the National Ethics Guidelines for Health Research.

Inclusion criteria

Patients 18 years old and above diagnosed with first-onset cerebrovascular disease by their neurologist are qualified for this study. The diagnosis of stroke is according to The Stroke Data Bank, and National Institute of Neurological and Communicative Disorders. This study include patients presenting as hemiparesis or hemiplegia, sensory or cranial nerve deficits; with hemispheric or brainstem lesions and with evidence of cerebral infarction or hemorrhage on either CT scan or MRI of the head.

Exclusion criteria

Exclusion criterion disqualified patients with aphasia, with previous diagnoses of sleep disordered-breathing, those who have restless leg syndrome, narcolepsy, on current CPAP treatment, with unstable comorbidities (cardiac or respiratory failure), and on ventilatory dependence.

Data Collection Procedure

A total of 172 first-onset stroke patients were identified from July 2014 to September 2014. Fifty-two (52) patients fulfilled the inclusion criteria. Exclusion criterion disqualified one hundred twenty (120) patients due to a variety of factors: forty (40) patients have previous histories of stroke at the time of admission, thirty-five (35) patients have transient ischemic attacks on admission with no evidence of neurologic deficits and infarcts or hemorrhages on neuroimaging, twenty-nine (29) have unstable co-morbidities and were unable to give an informed consent (ie, active Upper Gastrointestinal Bleeding , septic shock, Alzheimer's disease, Parkinson's Dementia, congestive heart failure, on hemodialysis treatment, and myocardial infarction), seven (7) patients were on ventilatory dependence due to Pneumonia, six (6) have concomitant Subarachnoid hemorrhages and head trauma, two (2) presented with global aphasia and had difficulty in comprehension, and one (1) patient was previously diagnosed with OSA and was on CPAP treatment. All subjects signed an informed consent. Their respective sleep partners were also asked for verification of patients' answers.

1. Clinical Characteristics:

The following information were collected for each patient during the interview:

a. Baseline demographic data: (patient's name, age, gender, handedness, marital status, occupation)

b. Anthropometric measurements: (height (in centimeters), weight (in kilograms), neck size or collar size (in centimeters), and body mass index (BMI) (calculated in $kg/m^{2)}$)

c. Pertinent medical histories: (such as previous transient ischemic attacks (TIA) or strokes, and concomitant diseases that are among modifiable risk factors of stroke such as hypertension, diabetes, cardiovascular disease and hypercholesterolemia)

d. Social history: (former or current smoking history, and alcohol consumption)

e. Stroke ictus and stroke data (lateralization, location and type of lesion) was also documented.

2. Obstructive Sleep Apnea screening tool: Complaints of habitual snoring, excessive daytime sleepiness, and witnessed apneas before stroke were assessed through screening tools. Participants and their sleep partners were asked to answer questionnaires through interview conducted by the primary investigator. These were administered within 24-48 hours of admission

Research Instrument

The data sheet contained the demographic profile containing the patient's personal information, as well as pertinent past medical and social history and current medications. The type, location and lateralization of stroke during admission were also documented.

For this study, the "STOP – BANG" and the Berlin questionnaires were used on all participants as well as their respective sleep partners. Studies have showed that these have the highest sensitivity and specificity, respectively, in identifying patients with OSA.

The "STOP-BANG" questionnaire is a concise and easy-to-use screening tool for OSA. It has been developed and validated mainly in surgical patients at preoperative clinics. Combined with body mass index, age, neck size, and gender, it has a high sensitivity, especially for patients with moderate to severe OSA. It was formed after the consensus from a group of anesthesiologists and sleep specialists, and a literature review.[5] The STOP-BANG questionnaire (Appendix II) consists of the following eight questions: S—"Do you **S**nore loudly (louder than talking or loud enough to be heard through closed doors)?" T—"Do you often feel **T**ired, fatigued, or sleepy during daytime?" O—"Has anyone **O**bserved you stop breathing during your sleep?" P—"Do you have or are you being treated for high blood **P**ressure?", B---**B**MI (BMI >35 kg/m^2), A---**A**ge (>50 years old), N---**N**eck circumference (NC >40 cm), and G---**G**ender (male). The answers to all questions were designed in a simple yes/no format and the scores range from a value of 0 to 8. It scores subjects as either "high risk" or "low risk" for OSA. Answering yes to 3 or more questions is considered "high risk", whereas answering yes to less than 3 questions is considered "low risk". [5]

The Berlin questionnaire (Appendix III) consists of ten questions divided into three categories. The first category consists of five questions that deal with snoring. The second category consists of three questions that deal with waketime sleepiness. The third category asks questions on the presence of hypertension and self-reported height and weight for computation of the body mass index. Risk stratification for obstructive OSA is divided into high and low risk categories based on the responses to the questions in the three categories. [13] A Filipino Version of the Berlin Questionnaire (Appendix IV) was provided for those patients who had difficulty understanding the English language. [11]

Data Processing and Statistical Analysis

The subjects' characteristics were summarized as means ± SD for continuous variables, and counts and percentages for categorical variables. Association between categorical variables was determined using the Chi-square test for independence. Wilk-shapiro test was performed to determine whether the continuous variables are normally distributed; variables which are normally distributed will be compared using Students's t-test while those which were tested instead using the nonparametric test Mann-Whitney U-test.

Incidence proportion of having likelihood of OSA was computed by getting the number of patients which are identified to be likely to have onset OSA using Stop- Bang and Berlin questionnaires and divide it by the total number of patients initially at risk.

Cross tabulation of the result of Stop Bang and Berlin questionnaires was determined to check whether their results were in agreement. The association between the result of Stop-Bang and Berlin questionnaire was computed using the Chi-square test of independence.

Descriptive statistics of age, gender, weight, height, BMI and neck circumference were determined for each grouping produced by both Stop- Bang and Berlin questionnaires to determine the profiles of patients. Cross tabulations of the distribution of answers to items under the two questionnaires with the resulting grouping were also determined to observe which items conduce in the result.

Association of the result of Stop- Bang and Berlin questionnaires with variables under the pertinent medical history, social history and stroke data were determined to further characterize the patients with likelihood of OSA.

Cross tabulation of those variables which are significantly associated with likelihood of having OSA were constructed to observe the direction of these relationships.

RESULTS

a. Demographic Profile and Anthropometric Measurements

Baseline Demographic Data	
Handedness	*no. of patients*
Right	51 (98.1%)
Left	1 (1.9%)
Total	52
Age in years	
Mean ± SD	58.38 ± 16.11
	no of patients
45 and below	12 (23.1%)
46 to 60	19 (36.5%)
61 to 75	13 (25%)
76 and above	8 (15.4%)
Total	52
Sex	*no of patients*
Male	28 (53.95%)
Female	24 (46.1%)
Total	52
Civil Status	*no of Patients*
Single	8 (15.4%)
Married	36 (69.2%)
Widowed/Widower	8 (15.4%)
Total	52
Address	*no of patients*
Batangas	4 (7.7%)
Laguna	2 (3.9%)
Las Piñas City	1 (1.9%)
Lebanon	1 (1.9%)
Makati City	25 (48.1%)
Mandaluyong City	1 (1.92%)
Manila City	4 (7.7%)
Marikina City	1 (1.9%)
Paranaque City	4 (7.7%)
Pasay City	5 (9.6%)
Pasig City	1 (1.9%)
Quezon City	1 (1.9%)
Rizal	1 (1.9%)
South Cotabato	1 (1.9%)
Total	52

	no. of patients
Elementary Undergraduate	1 (1.9%)
High School Graduate	10 (19.2%)
College Graduate	40 (77%)
With Post-Grad Degree	1 (1.9%)
Total	52
Employment Status	*no. of patients*
Employed	22 (42.3%)
Self-employed/With own business	3 (5.8%)
Homemaker	7 (13.4%)
Retired	17 (32.7%)
Cannot/Not allowed to work	3 (5.8%)
Total	52
Month Admitted	no. of patients
July	17 (32.7%)
August	20 (38.4%)
September	15 (28.9%)
Total	52
Anthropomentric Measurements	
Height in cm (n=52)	
(mean ± SD	164.24 ± 8.72
Weight in kg (n=52)	
(mean ± SD	73.37 ± 22.17
BMI in kg/sq.m. (n=52)	
(mean ± SD	38.18 ± 4.59
	no. of patients
Underweight	1 (1.9%)
Normal	20 (38.5%)
Overweight	20 (38.5%)
Obese	11 (21.1%)
Total	52

b. Pertinent Medical and Social History

Pertinent Medical Histories	
Hypertension	*no. of patients*
No	10 (19.2)
Yes	42 (80.8%)
Total	52
Diabetes	*no. of patients*
No	39 (75%)
Yes	13 (25%)
Total	52
Dyslipidemia	*no. of patients*
No	47 (90.4%)
Yes	5 (9.6%)
Total	52
Social History	
Smoking	*no. of patients*
No	30 (57.7%)
Yes	22 (42.3%)
Total	52
Smoking Frequency	*no. of patients*
Everyday	15 (68.1%)
2 to 4 times	7 (31.9%)
Total	22
Alcohol drinking	*no. of patients*
No	31 (59.6%)
Yes	21 (40.4%)
Total	52
Alcohol Consumption	*no. of patients*
Everyday	2 (9.5%)
Once a week	3 (14.3%)
2 to 4 times a week	14 (66.7%)
1 to 2 times a month	2 (9.5%)
Total	21

c. Stroke Data

Stroke Data	
Stroke Ictus in hours	
mean ± SD	45.36 ± 103.94
	no. of patients
6 hours and below	19 (36.5%)
7 to 12 hours	11 (21.2%)
1 to 2 days	12 (23.1%)
3 days and above	10 (19.2%)
Total	52
Stroke Type	*no. of patients*
Cardioembolic	14 (26.9%)
Hemorrhagic	14 (26.9%)
Thrombotic	24 (46.2%)
Total	52
Stroke Location	*no. of patients*
Brainstem	8 (15.4%)
Corticak	5 (9.6%)
Subcortical	20 (38.5%)
Mixed	19 (36.5%)
Total	52
Stroke Lateralization	*no. of patients*
Right	26 (50%)
Left	21 (40.4%)
Bilateral	5 (9.6%)
Total	52

d. Sleep Apnea

Using the Stop-Bang questionnaire, 37 (71.1%) out of the 52 first-onset stroke patients were identified to be of high risk of having OSA. On the other hand, 36 (69.2%) of the same set of patients were diagnosed to have a likelihood of Sleep Apnea in the Berlin questionnaire.

Sleep Apnea	
STOP BANG Questionaire	*no. of patients*
Low Risk of OSA	15 (28.9%)
High Risk of OSA	**37 (71.1%)**
Total	52
Berlin Questionnare	*no. of patients*
Without likelihood of Sleep Apnea	16 (30.8%)
With likelihood of Sleep Apnea	**36 (69.2%)**
Total	52

The table below shows the comparison between results of the Berlin and Stop- Bang Questionnaire. Out of 52 patients, 11 were identified by both Stop-Bang and Berlin to have low/non-existent risk of OSA, while 32 were determined by both to have high risk of OSA. However, there are 9 patients that were differently classified by the two screening tools. Four patients which were identified by Berlin questionnaire to be with likelihood of sleep apnea are with low risk OSA in Stop-Bang questionnaire. On the other hand, five patients without likelihood of sleep apnea in Berlin questionnaire were identified by Stop-Bang questionnaire to be with high risk of OSA. With χ^2 =17.9293 and p-value=0.000, there is enough evidence to say that the results of Stop Bang and Berlin questionnaires were dependent. This shows that the results of Stop-Bang and Berlin questionnaires are associated with each other, hence those who have OSA in Stop-Bang are likely also to have OSA in Berlin.

Berlin Questionnaire	Stop Bang Questionnaire		
	Low risk of OSA	High Risk of OSA	Total
Without likelihood of Sleep Apnea	11	5	**16**
With likelihood of Sleep Apnea	4	32	**36**
Total	**15**	**37**	**52**

1. STOP-BANG QUESTIONNAIRE--

Table below shows the distribution of answers between low-risk and high-risk patients among the items under the Stop Bang questionnaire. All male patients with neck circumferences greater than 40 cms, a BMI greater than 35kg/m^2 and observed to stop breathing during their sleep are of high risk of having OSA. T-test was conducted for age and BMI to determine if the age and BMI of high-risk patients are significantly higher than that of low-risk patients. Chi-square test for independence was used to determine which among the remaining questions under Stop Bang are significantly associated with the result.

Stop Bang	Low risk of OSA (n=15)	High Risk of OSA (n=37)	Overall
Snore loudly (louder than talking or loud enough to be heard through closed doors)	5 (12.5%)	35 (87.5%)	40
Often feel tired, fatigued, or sleepy during daytime	4 (4.2%)	23 (95.8%)	24
Observed to stop breathing during sleep	0 (0%)	13 (100%)	13
Have been or being treated for high blood pressure?	7 (16.7%)	35 (83.3%)	42
BMI more than 35 kg/m^2	0 (0%)	5 (100%)	5
Age over 50 yr old	9 (25%)	27 (75%)	36
Neck circumference greater than 40 cm	0 (0%)	13 (100%)	13
Male	0 (0%)	24 (100%)	24

Table below shows the comparison of the mean age, height, weight, neck circumference and BMI of patients with low risk of OSA and high risk of OSA, and also the distribution of patients according to their age group, gender and BMI classification.

As expected, patients with high risk of OSA are those who are older, mostly males, a higher BMI, and with greater neck circumferences.

Factors		Low Risk of OSA (n=15)	High Risk of OSA (n=37)
Age	mean ± S.D.	51.8 ± 17.01	61.05 ± 15.15
		no. of patients	
	45 and below	5 (33.3%)	7 (18.9%)
	46 to 60	7 (46.7%)	12 (32.4%)
	61 to 75	1 (6.7%)	12 (32.4%)
	76 and above	2 (13.3%)	6 (16.2%)
Gender		*no. of patients*	
	Female	12 (80 %)	12 (32.4%)
	Male	3 (20%)	25 (67.9%)
Height in cm	mean ± S.D.	160.41 ± 6.20	165.8 ± 9.18
Weight in kg	mean ± S.D.	62.01 ± 9.43	78.0 ± 24.21
Neck Circumference in cm	mean ± S.D.	34.93 ± 2.19	39.5 ± 4.67
BMI	mean ± S.D.	24.07 ± 3.15	28.0 ± 6.73
		no. of patients	
	Underweight	1 (6.7%)	0 (0%)
	Normal	8 (53.3%)	12 (32.4%)
	Overweight	6 (40.0%)	14 (37.8%)
	Obese	0 (0%)	11 (29.7%)

Table at the right shows the results of the Chi -square test for independence between having risk of OSA and the following variables and also the result of the Mann-Whitney U test on determining whether the median stroke ictus of patients with high risk of OSA and those with low risk are statistically different.

At α=0.10, the civil status, employment status, and stroke type were found to be associated with having risk of OSA using the Stop Bang questionnaire. While at α=0. 05, having hypertension and other medical conditions were identified to be associated with having risk of OSA using the Stop-Bang questionnaire.

Variables	Test Statistic	p-value
Civil Status	5.04	0.081*
Educational Attainment	0.38	0.535
Employment Status	8.07	0.089*
Hypertension	10.22	0.001**
Diabetes	0.28	0.596
Dyslipidemia	0.21	0.646
Other medical condition	6.66	0.01**
Smoking	0.05	0.830
Smoking frequency	0.01	0.926
Alcohol	0.00	0.971
Alcohol Consumption	4.20	0.241
Stroke Ictus~	-0.10	0.919
Stroke Ictus Group	0.20	0.978
Stroke Type	4.79	0.091*
Stroke Location	0.68	0.879
Stroke Lateralization	0.44	0.801

~ Mann-Whitney U test used

** Significant at α=10%*

*** Significant at α=5%*

Cross tabulations of variables which are found to be associated with having risk of OSA using Stop Bang questionnaire were constructed to observe the direction of association between these variables and risk of OSA.

Patients with low and high risk of OSA were mostly married; with equal number of patients being singles and widowed/widowers. Although, the number of married patients with high risk of OSA are significantly higher than those with low risk of OSA. This could be due to the fact that age is an indicator of OSA, since older patients are more likely to be married.

Civil Status	Low risk of OSA	High Risk of OSA
Single	4 (26.7%)	4 (10.8%)
Married	7 (46.7%)	29 (78.4%)
Widowed/Widower	4 (26.7%)	4 (10.8%)
Total	**15**	**37**

Majority of both the low-risk and high-risk patients had a college degree, with very few elementary undergraduates and post-grad degree holders, which is expected since 40 of the 52 patients were college graduates. Interestingly, 29 out of the 40 patients are of high risk of OSA while only 11 were considered as low-risk.

Educational Attainment	Low risk of OSA	High Risk of OSA
Elementary Graduate	0 (0%)	1 (2.7%)
High School Graduate	4 (26.7%)	6 (16.2%)
College Graduate	11 (73.3%)	29 (78.4%)
With Post-Grad Degree	0 (0%)	1 (2.7%)
Total	**15**	**37**

Those patients with low risk of OSA are almost equally distributed between those with and those without hypertension. However, of those patients with high-risk of OSA, 91.9% have hypertension.

Hypertension	Low risk of OSA	High Risk of OSA
Without	7 (46.7%)	3 (8.1%)
With	8 (53.3%)	34 (91.9%)
Total	**15**	**37**

More than half (59.5%) of high-risk patients have other medical conditions while 80% of low-risk patients are without other medical conditions. NOTE: It may be good to explore on the other actual medical conditions of low-risk versus high-risk patients. See the list below the table.

Other Medical Conditions	Low risk of OSA	High Risk of OSA
Without	12 (80.0%)	15 (40.5%)
With	3 (20.0%)	22 (59.5%)
Total	**15**	**37**

Other Medical Conditions of Low Risk Patients
Seizure
Unstable Angina
s/p Thyroidectomy

Other Medical Conditions of High Risk Patients
Atrial fibrillation and Bronchial Asthma
Pancreatitis
s/p Bell's Palsy, Left and Polycythemia Vera
Atrial fibrillation; s/p Hip Replacement and s/p Lap Cholecystectomy
Rheumatic Heart Disease and Atrial Fibrillation
s/p Colonic Surgery
s/p Cholecystectomy
s/p Spine fracture secondary to fall; s/p Thyroidectomy with Hypothyroidism
s/p Coronary Artery Bypass Graft and Coronary Artery Disease
s/p Cholelithiases
Abdominal Aortic Aneurysm; s/p Gortex Graft
s/p Carotid Tumor Resection
Paroxysmal Atrial Fibrillation
s/p TAHBSO and s/p Appendectomy

Of the 37 high-risk patients, more than half (54.1%) had thrombotic stroke, while 27% and 18.9% had hemorrhagic and cardioembolic strokes, respectively. Distribution of low-risk patients among stroke type is different, with majority (46.7%) having experienced hemorrhagic stroke and the remaining patients evenly went through thrombotic and cardiembolic stroke.

Stroke type	Low risk of OSA	High Risk of OSA
Cardioembolic	4 (26.7%)	10 (27.0%)
Hemorrhagic	7 (46.7%)	7 (18.9%)
Thrombotic	4 (26.7%)	20 (54.1%)
Total	**15**	**37**

2. BERLIN QUESTIONNAIRE--

All patients who obtained positive results in Category 2 are with likelihood of sleep apnea, while few patients with positive responses on Categories 1 and 3 were classified to be not unlikely to have sleep apnea. Chi-square test for independence was used to determine which among the questions under Berlin are significantly associated with the result.

Berlin	Without likelihood of Sleep Apnea (n=16)	With likelihood of Sleep Apnea (n=36)	Overall
Category 1 Positive	3 (7.9%)	35 (92.1%)	38
Category 2 Positive	0 (0%)	19 (100%)	19
Category 3 Positive	6 (14.6%)	35 (85.4%)	41

Just like the results obtained using the Stop-Bang questionnaire, patients with likelihood of Sleep apnea using the Berlin questionnaire were found to be older, mostly males, with higher BMI, and with greater neck circumferences.

Factors		Without likelihood of Sleep Apnea (n=16)	With likelihood of Sleep Apnea (n=36)
Age	mean ± S.D.	53.94 ± 15.97	60.36 ± 15.99
		no. of patients	
	45 and below	5 (31.3%)	7 (19.4%)
	46 to 60	7 (43.8%)	12 (33.3%)
	61 to 75	2 (12.5%)	11 (30.6%)
	76 and above	2 (12.5%)	6 (16.7%)
Gender		*no. of patients*	
	Female	9 (56.3%)	15 (41.7%)
	Male	7 (43.8%)	21(58.3%)
Height in cm	mean ± S.D.	163.61 ± 7.18	164.53 ± 9.41
Weight in kg	mean ± S.D.	66.57 ± 17.25	76.39 ± 23.63
Neck Circumference in cm	mean ± S.D.	35.38 ± 2.63	39.43 ± 4.74
BMI	mean ± S.D.	24.64 ± 4.92	27.85 ± 6.46
		no. of patients	
	Underweight	1 (6.3%)	0 (0%)
	Normal	9 (56.3%)	11 (30.6%)
	Overweight	5 (31.3%)	15 (41.7%)
	Obese	1 (6.3%)	10 (27.8%)

There were only two variables found to be associated with having likelihood of Sleep Apnea using Berlin Questionnaire. Interestingly, these two variables, which are having hypertension and other medical conditions, were consistent in the sense that these two were also found to be associated with risk of OSA using the Stop-Bang questionnaire.

Variables Associated With likelihood of Sleep Apnea	Test Statistic	p-value
Civil Status	4.01	0.135
Educational Attainment	0.08	0.777
Employment Status	0.06	1.000
Hypertension	4.97	0.026**
Diabetes	0.48	0.448
Dyslipidemia	0.30	0.583
Other medical condition	2.62	0.105*
Smoking	0.56	0.454
Smoking frequency	0.27	0.604
Alcohol	0.08	0.777
Alcohol Consumption	2.80	0.423
Stroke Ictus	-0.44	0.661
Stroke Ictus Group	1.48	0.687
Stroke Type	1.37	0.505
Stroke Location	0.57	0.903
Stroke Lateralization	0.98	0.612

~ Mann-Whitney U test used

** Considerably significant at α=10%*

*** Significant at α=5%*

Of the 42 patients noted to have hypertension, 32 have a likelihood of sleep apnea while only 10 have without.

Hypertension	Without likelihood of Sleep Apnea	With likelihood of Sleep Apnea
Without	6 (37.5%)	4 (11.1%)
With	10 (62.5%)	32 (88.9%)
Total	**16**	**36**

Out of the 36 patients with likelihood of sleep apnea using the Berlin questionnaire, a little over half (55.6%) have other medical conditions while 68.8% of those without likelihood of Sleep Apnea did not have other medical conditions.

Other medical conditions	Without likelihood of Sleep Apnea	With likelihood of Sleep Apnea
Without	11 (68.8%)	16 (44.4%)
With	5 (31.2%)	20 (55.6%)
Total	**16**	**36**

Other Medical Conditions of those Without Likelihood of Sleep Apnea
Pancreatitis
Seizure
Unstable Angina
s/p Thyroidectomy

Other Medical Conditions of those with Likelihood of Sleep Apnea
Abdominal Aortic Aneurysm with s/p Gortex Graft
Atrial fibrillation and Bronchial Asthma
Atrial fibrillation; s/p Hip Replacement; s/p Lap Cholecystectomy
Bronchial Asthma and Chronic Atrial Fibrillation
Paroxysmal Atrial Fibrillation
Rheumatic Heart Disease and Atrial Fibrillation
s/p Appendectomy
s/p Bell's Palsy, Left; with Polycythemia Vera
s/p Coronary Artery Bypass Graft and Coronary Artery Disease
s/p Carotid Tumor Resection
s/p Cholecystectomy
s/p Cholelithiases
s/p Colonic Surgery
s/p Spine fracture secondary to fall; s/p Thyroidectomy with Hypothyroidism
s/p TAHBSO and s/p Appendectomy

DISCUSSION

Several screening tools for obstructive sleep apnea have been proposed. However, validation studies were conducted on different populations, which limit comparisons on the predictive capabilities of these tools. In 2012, El-Sayed and colleagues compared four sleep questionnaires with regards to their predictive probabilities for OSA.[5] Of the four questionnaires (STOP, STOP-BANG, Berlin and Epworth Sleepiness Scale [ESS]), the STOP-Bang, Berlin and STOP questionnaires had the highest sensitivity to predict OSA (97.55%, 95.07% and 91.67%, respectively), moderate-to-severe OSA (97.74%, 95.48% and 94.35%, respectively) and severe OSA (98.65%, 97.3% and 95.95%, respectively), but with a very low specificity for OSA patients (26.32%, 25% and 25%, respectively), moderate-to-severe OSA patients (3.7%, 7.41% and 25.93%, respectively) and severe OSA patients (5.36%, 10.71% and 19.64%, respectively).[5] According to Silva et al in 2011, the STOP-Bang had the highest sensitivity in identifying persons with moderate-to-severe and severe OSA.[6] On the other hand, Kang et al used the Berlin questionnaire in evaluating its use and validity in OSA in Korean population.[18] Results showed that the Berlin questionnaire has a 72.1% sensitivity and 42.1% specificity at the apnea-hypopnea index (AHI) >5 level.[18] There was a moderate association between the severity of OSA and category 1 (p=0.015), and also category 2 (p=0.006).[18] A systematic review by Abrashami et al in 2010 showed the Berlin questionnaire to have a higher specificity in screening OSA.[7] To better identify patients who are at high risk and with high likelihood of OSA among first-onset stroke patients, this study used the Stop-Bang and the Berlin questionnaire.

Using the Stop-Bang questionnaire, thirty-seven (71.1%) of the fifty-two (52) patients with first-onset stroke were identified to have high-risk for OSA. On the other hand, the Berlin questionnaire showed that thirty-six (69.2%) of the same set of patients have a likelihood of sleep apnea. The difference in the results may arise from review of related literature showing that the Stop-Bang questionnaire has high sensitivity and the Berlin questionnaire has high specificity in screening patients with OSA. These questionnaires were able to identify high-risk patients for OSA but without accurately excluding those at low risk.[5]

As for the clinical profile, majority of the patients identified were right-handed. The individual's handedness was determined because distribution of the hemispheric language dominance varies with the degree of handedness. If the language area (left dominant hemisphere in most patients) is greatly affected, patients presenting with aphasia were excluded due to limitation of information that can be gathered from these individuals. Of the right-handed patients included, none were aphasic, while some presented with mild to moderate dysarthria with intact comprehension.

Most of the stroke patients were documented to have a mean age of 58.38 (± 16.11 years), males,

married, college graduates, employed, and residing within the metropolitan area. When comparing the distribution of answers between the Stop-Bang and Berlin questionnaires, those who are older, mostly males, a BMI of greater than 35 kg/m^2, those with neck circumferences of greater than 40 centimeters, are noted to be at high risk/ likelihood of OSA. This is comparable to a systematic review of literature by Mirrakhimov et al in 2013: Prevalence of obstructive sleep apnea in Asian adults. Their results showed that male gender, older age, a higher BMI and waist to hip ratio, and greater neck circumference, arterial hypertension, smoking, snoring and daytime sleepiness were associated with OSA.[16]

Using the Stop-Bang questionnaire, 91.9% percent of those with high risk of OSA have hypertension. The Berlin questionnaire also showed almost the same results; majority of those with likelihood of OSA (88.9%) have hypertension. Aside from hypertension, those with high risk/ with likelihood of OSA have other medical conditions, of which atrial fibrillation is the most common. According to a study by Dyken et al, obstructive sleep apnea has been associated with hypertension and cardiovascular disease.[15] Obstructive respiratory events can elicit excessive sympathetic and parasympathetic activation, with consequent surges in blood pressure (up to 220/130 mm Hg) and bradyarrhythmias (including complete heart block and sinus pause).[15] Hypoxia and hypoperfusion may predispose patients with obstructive sleep apnea to stroke, especially during sleep.[15] Tilkian et al hypothesized that repetitive hypertensive events associated with nocturnal apneas might lead to sustained hemodynamic abnormalities.[17]

A great number of the patients also presented with significant smoking history and frequent alcohol intake. Since the RIFASAF study has declared that smoking and alcohol intake are independent risk factors for stroke,[19] it is not unlikely that they may be associated with OSA as well. According to the Sleep Apnea In-Depth Report of the New York Times, smokers have a higher risk of sleep apnea.[14] Those who smoke more than two packs a day have a risk of 40 times greater than nonsmokers. Alcohol use may also be associated with apnea. Patients diagnosed with sleep apnea are recommended not to drink alcohol before bedtime.[14] In this study, majority (68.1%) smoke every day, while 40.4 % of alcohol drinkers consume alcohol about 2-4 times a week.

Most of the patients were admitted in less than 6 hours of symptom onset. This may be due to the increasing awareness of patients to stroke symptoms and due to their accessible location within the vicinities of hospitals. Thrombotic stroke is the most common type of stroke seen, with 38.5% located at the subcortical area while 36.5% were mixed. A journal by Dyken et al noted that brain stem strokes and other disorders causing injury to the medullary respiratory centers have been reported to produce primarily central sleep apnea.[15] However, in this study, this only ranked third (15.4%) in the most common location of stroke. Half of the strokes documented were located on the right side of the brain, with patients initially presenting with left-sided hemiparesis and/or dysarthria.

Given that OSA can continue for years without recognition and most individuals with OSA go undiagnosed because these are not commonly explored in the investigations of a first-onset stroke, it is logical that the damage to the cerebral circulation occurs over a long period of time, creating an environment that predisposes an individual to stroke and transient ischemic attacks. Because our population is aging and becoming more obese (risk factors for OSA), with contributory factors from hypertension, cardiac disease, smoking and alcoholism, the incidence of cerebrovascular disease associated with OSA should be expected to increase, and cerebrovascular disease should occur at an earlier age. It is imperative that primary care physicians and specialists be vigilant in the screening of these patients who are at high risk of OSA so as to prevent first-onset stroke.

CONCLUSION

This study shows the direct association and increased incidence of OSA in first-onset stroke based on the risk factors involved and the number of patients who tested positive for the screening tools used in this study (Stop-Bang and Berlin questionnaire). Those who have OSA in Stop-Bang are likely also to have OSA in Berlin. Older age, male gender,

a higher BMI, greater neck circumferences, smoking, hypertension and those observed to stop breathing during sleep have an increased risk or likelihood of OSA. Thrombotic stroke is the most common type of stroke seen, with 38.5% located at the subcortical area. Half of the lesions were noted at the right side of the brain, with patients initially presenting with left-sided hemiparesis and/ or dysarthria. Durgan et al cited that repeated exposures to hypoxia in individuals with OSA could lead to hypoxic/ischemic brain injury, especially if cerebrovascular control is impaired. [11] This situation predisposes an individual's brain to be vulnerable to an ischemic event, leading to stroke.

RECOMMENDATIONS

The prevalence of OSA is fairly high in international research studies. Since the diagnosis and treatment of OSA is of particular importance in stroke prevention, it is recommended in the local setting that the use of screening tool such as the STOP-BANG and Berlin questionnaire be utilized in all patients presenting with stroke. It is ideal to use screening tools with high sensitivities, like the Stop-Bang, to screen populations with high risk for OSA in order to avoid missing cases that may lead to adverse health consequences; whereas, screening tools with high specificities and the percentages of correctly classifying persons into low- and high-risk groups for OSA may take precedence in low-risk populations who demonstrate no overt signs of OSA or associated comorbidities and lack easy access to polysomnography.

All patients whose results showed high risk for developing OSA are encouraged to undergo an overnight, technician-supervised polysomnographic study (sleep study) upon the advice of the patient's attending physician. Increasing the awareness and aggressive treatment of OSA may prevent the growing number of stroke patients, both in the young and the elderly who are at risk.

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APPENDIX I

A. General Data:

Name: Handedness:
Age/Sex: Civil Status:
Address:
Contact #:
Educational attainment:
Work:
Date of admission: Attending Physician:

B. Anthropometric measurements:

Height: Neck size/ Collar size:
Weight:
Body Mass Index (BMI) kg/$m^{2)}$:

C. Medical history and its duration: Medications taken:

( ) Hypertension
( ) Diabetes
( ) Dyslipidemia
( ) Previous strokes:
    ( ) Transient Ischemic Attack:
    ( ) Ischemic Stroke:
        ( ) Thrombotic ( ) Cardioembolic
    ( ) Hemorrhagic:
( ) Others:

D. Social history:

( ) Smoking
( ) Alcohol consumption

E. Stroke Data Upon Admission:

Stroke Ictus:
Stroke Type:
( ) Ischemic: ( ) Thrombotic ( ) Cardioembolic
( ) Hemorrhagic
Stroke Location:
Stroke Lateralization:

APPENDIX II

STOP BANG Questionnaire

Height _____ inches/cm Weight _____ lb/kg
Age _____ Male/ Female ____
BMI _____ Collar size of shirt: S, M, L, XL, or _____ inches/cm
Neck circumference* _____ cm

1. ***S***noring
   Do you *s*nore loudly (louder than talking or loud enough to be heard through closed doors)?
   Yes No
2. ***T***ired
   Do you often feel *t*ired, fatigued, or sleepy during daytime?
   Yes No
3. ***O***bserved
   Has anyone *o*bserved you stop breathing during your sleep?
   Yes No
4. Blood ***P***ressure
   Do you have or are you being treated for high blood *p*ressure?
   Yes No
5. ***B***MI
   *B*MI more than 35 kg/m2?
   Yes No
6. *A*ge
   Age over 50 yr old?
   Yes No
7. ***N***eck circumference
   *N*eck circumference greater than 40 cm?
   Yes No
8. ***G***ender
   *G*ender male?
   Yes No

High risk of OSA: answering yes to three or more items
Low risk of OSA: answering yes to less than three items

Adapted from:
STOP Questionnaire: *A Tool to Screen Patients for Obstructive Sleep Apnea*. *Frances Chung, F.R.C.P.C.,* Balaji Yegneswaran, M.B.B.S.,† Pu Liao, M.D.,‡ Sharon A. Chung, Ph.D.,§Santhira Vairavanathan, M.B.B.S.,_ Sazzadul Islam, M.Sc.,_ Ali Khajehdehi, M.D.,† Colin M. Shapiro, F.R.C.P.C.#* Anesthesiology 2008; 108:812–21 Copyright © 2008, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

APPENDIX III

Berlin Questionnaire

Sleep Evaluation in Primary Care

Please Complete the following:

height _____ age _____

weight _____ male/female _____

Category 1

1. Do you snore?

- ☐ yes
- ☐ no
- ☐ don't know

If you snore:

2. Your snoring is?

- ☐ slightly louder than breathing
- ☐ as loud as talking
- ☐ louder than talking
- ☐ very loud. Can be heard in adjacent rooms.

3. How often do you snore?

- ☐ nearly every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ never or nearly never

4. Has your snoring ever bothered other people?

- ☐ yes
- ☐ no

5. Has anyone noticed that you quit breathing during your sleep?

- ☐ nearly every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ never or nearly never

Category 2

6. How often do you feel tired or fatigued after your sleep?

- ☐ nearly every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ never or nearly never

7. During your waketime, do you feel tired, fatigued or not up to par?

- ☐ nearly every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ never or nearly never

8. Have you ever nodded off or fallen asleep while driving a vehicle?

- ☐ yes
- ☐ no

if yes, how often does it occur?

- ☐ nearly every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ never or nearly never

Category 3

9. Do you have high blood pressure?

- ☐ yes
- ☐ no
- ☐ don't know

10. BMI > 30 (*See Chart*)

- ☐ yes
- ☐ no

Scoring Questions: Any answer within box outline is a positive response.

Scoring categories:

- ☐ Category 1 is positive with 2 or more positive responses to questions 1-5
- ☐ Category 2 is positive with 2 or more positive responses to questions 6-8
- ☐ Category 3 is positive with 1 positive responses to questions 9-10

Final Result: If 2 or more possible categories are positive, you have a high likelihood of sleep apnea.

Name _____

Address _____

_____

APPENDIX III

FILIPINO VERSION OF BERLIN QUESTIONNAIRE

PANGKAT 1

1. **Humihilik ka ba?**
   a. Oo
   b. Hindi
   c. Di ko alam

Kung humihilik ka, sagutan ang tanong 2-5 sa pangkat na ito. Kung hindi o hindi mo alam, pumunta sa tanong 5.

2. **Ang iyong paghilik ay:**
   a. Mas malakas sa paghinga
   b. Kasing lakas ng pagsasalita
   c. Mas malakas sa pagsasalita
   d. Napakalakas – maririnig sa kalapit silid

3. **Gaano kadalasa kang humilik?**
   a. Halos araw-araw
   b. 3-4 beses sa bawat linggo
   c. 1-2 beses sa bawat lingo
   d. 1-2 beses sa bawat buwan
   e. Hindi kahit kalian o halos hindi

4. **Ang hilik mo ba ay nakakabagabag sa iba?**
   a. Oo
   b. Hindi
   c. Di ko alam

5. **May nakapansin bang tumigil ka na sa paghinga sa pagtulog?**
   a. Halos araw-araw
   b. 3-4 beses sa bawat linggo
   c. 1-2 beses sa bawat lingo
   d. 1-2 beses sa bawat buwan
   e. Hindi kahit kalian o halos hindi

PANGKAT 2

6. **Gaano kadalas kang makaramdam ng pagod tapos matulog?**
   a. Halos araw-araw
   b. 3-4 beses sa bawat linggo
   c. 1-2 beses sa bawat lingo
   d. 1-2 beses sa bawat buwan
   e. Hindi kahit kalian o halos hindi

7. **Sa oras na ikaw ay gising, nakaramdam ka ba ng pagod?**
   a. Halos araw-araw
   b. 3-4 beses sa bawat linggo
   c. 1-2 beses sa bawat lingo
   d. 1-2 beses sa bawat buwan
   e. Hindi kahit kalian o halos hindi

8. **Naidlip ka na ba o nakatulog habang nagmamaneho ng sasakyan, habang naghinintay sa doktor, habang nanonood ng telebisyon sa bahay o habang nakapila sa pagbayad ng kuryente o telepono?**
   a. Oo
   b. Hindi

Kung oo, sagutan ang tanong 9. Kung hindi, pumunta sa tanong 10.

9. **Gaano kadalas ito mangyari?**
   a. Halos araw-araw
   b. 3-4 beses sa bawat linggo
   c. 1-2 beses sa bawat lingo
   d. 1-2 beses sa bawat buwan
   e. Hindi kahit kalian o halos hindi

PANGKAT 3

10. **Meron ka bang alta presyon?**
    a. Oo
    b. Hindi
    c. Di ko alam

Jorge et al. Validation of the Filipino Version of the Blin Questionnaire to Identify Population at Risk for Sleep Apnea Syndrome. Vol 46 No 3. 2012.

Informed Consent to Participate in a Research Study

Research Information	
Research Title: **Association, Incidence and Clinical Profile of Patients with Obstructive Sleep Apnea and First-Onset Stroke in a Tertiary Hospital: A Prospective Descriptive Study**	
Principal Investigator:	Department of Neuroscience- Section of Neurology
Location:	Phone:

You are being invited to take part in a research study. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully.

1. **PURPOSE OF THIS RESEARCH STUDY**
   - Among known risk factors for stroke are age, sex, hypertension, diabetes mellitus, smoking, and a history of cardiovascular disease. Obstructive sleep apnea (OSA), however, is not widely considered as a risk factor for stroke. In the local setting, this has been commonly overlooked and not included in the investigations of a stroke patient. The aim of this study is to identify the association and incidence of Obstructive Sleep Apnea among first-onset stroke patients admitted and managed in a tertiary hospital using the STOP-BANG and Berlin questionnaire

2. **PROCEDURES**
   - This research will involve the use of a data collection sheet and questionnaires used for the screening of OSA. The data sheet contains the demographic profile containing the patient's personal information such as name, age, sex, occupation, athropometric measurements, as well as pertinent past medical and social history and current medications. The type, location and lateralization of stroke during admission will also be documented. The "STOP – BANG" and the Berlin questionnaire will be used on all participants as well as their respective sleep partners. Studies have shown that these have the highest sensitivity and specificity, respectively, in identifying patients with OSA. All patients whose results showed high risk for developing OSA will be encouraged to undergo an overnight, technician-supervised polysomnographic study upon the advice of the patient's attending physician.

3. **FINANCIAL CONSIDERATIONS**
   - There is no financial compensation for your participation in this research.

4. **CONFIDENTIALITY**
   - Your identity in this study will be treated as confidential. The results of the study, including laboratory or any other data, may be published for scientific purposes but will not give your name or include any identifiable references to you.

5. **TERMINATION OF THE STUDY**
   - You are free to choose whether or not to participate in this study. There will be no penalty or loss of benefits to which you are otherwise entitled if you choose not to participate.

AVAILABLE SOURCES OF INFORMATION
Any further questions you have about this study will be answered by the Principal Investigator:
Name: Phone Number:

6. **AUTHORIZATION**
   I have read and understood this consent form, and I volunteer to participate in this research study.

   Participant Name (Printed or Typed): Participant Signature:
   Date: Date:

   Principal Investigator Signature/ Signature of Person Obtaining the Consent: Date:

Effect of Duty Schedule on Emergency Medicine and Internal Medicine Residents in Training with Early, Intermediate and Late Chronotypes on Attention, Alertness and Reaction Time

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ABSTRACT

Physicians have been practicing in a shift-work environment since the early days of medicine. What has changed is the recognition of how much shift work can affect the physical and mental performance of physicians. The recent mandatory reduction in the work hours in residency was a first attempt to mitigate the effects of shift work and sleep deprivation on residents' performance and education[1]

The objective of this study is to compare the changes in the level of attention, alertness, reaction time of Emergency and Internal Medicine undergoing 12 hours and 33 hours duty shift respectively in relation to their chronotype. This is a prospective-cross sectional study conducted in a private training hospital from July to September 2014 consisting of 58 residents in training under the Emergency Medicine and Internal Medicine departments. Their attention, alertness and reaction time were evaluated and compared using the following tests: Morningness- Eveningness Questionnaire; Standford Sleepiness Scale; Stroop test or the Color and Word Test; Digit Span Performance; and Symbol Search Performance. Participants were tested at the start of their duty, in the middle and at the end of their duty period.

Results showed that chronotypes correlated with the degree of constraints on sleep experienced on the morning, or evening shifts. As a result of such constraints, late types showed significantly higher social jetlag than early types on the morning shift and vice versa.

When tested across the duty period, chronotype did no longer associate with the degree of social jetlag, indicating that, overall, the different chronotypes experience the same degree of constraints as do rotating worker, meaning that lack of sleep, stress and hectic schedule would take a toll on the resident by midshift as shown by decreasing attention, alertness, reaction time by the different tests.

Augmentation of workforce is recommended at midshift to counteract the decreasing level of attention, alertness and reaction time experienced by the residents to minimize medical errors.

Lastly, for the ER group, it is recommended that those morning chronotypes would be assigned to an AM shift and those late chronotypes to the PM shift. Also workforce should be added during morning shift, since results showed a declining pattern of measures.

KEY WORDS: Alertness, attention, reaction time, work schedule, residency training

INTRODUCTION

Physicians have been practicing in a shift-work environment since the early days of medicine. What has changed is the recognition of how much shift work can affect the physical and mental performance of physicians. The recent mandatory reduction in the work hours in residency was a first attempt to mitigate the effects of shift work and sleep deprivation on residents' performance and education[(1)].

The search for the "perfect" work schedule for physicians continues, and the challenges are abundant. The optimal balance between work hours on one hand and training and education on the other is unknown. The new regulations have raised concerns about the fragmentation of patient care and a breakdown in communication during shift changes[(1)].

Since the introduction of the ACGME (Accreditation Council for Graduate Medical Education) resident work hours, numerous studies have been made comparing the effect of those physicians on the new work hour regulations versus those on the traditional duty schedule of more than 80 hours per week in terms of performance, cognition, safety of physicians and patient complications and mortality.

In 1990, Residency Review Committees (RRCs) that accredited resident education in the individual specialties established a limit for Emergency Medicine of 72 hours. This was to allow flexibility in terms of the different requirements that would accommodate patient care, safety, education needs within the specialty.

Ideally, studies about the effects of such limits would have been gathered and show positive trends toward patient care as well as physician well being. However, this information does not exist. Studies predominantly consisted of opinion surveys without the power to demonstrate effect[(2)].

Thus this study aims to explore the effect of the work schedule of ER and Internal Medicine residents in terms of level of attention, alertness and reaction time during the course of their duty.

OBJECTIVES OF THE STUDY

General Objectives

To investigate the changes in the level of attention, alertness and reaction time of Emergency Medicine(ER) residents with early, intermediate and late chronotype undergoing 12 hours duty shift

To investigate the changes in the level of attention alertness and reaction time of Internal Medicine residents (IM) residents with early, intermediate and late chronotype undergoing 33 hours duty shift

Specific Objectives

To determine the degree of sleepiness using the Stanford Sleepiness Scale and compare among the different follow up points within a shift (baseline, 6^{th} and 12^{th} hour for the ER residents and; baseline, 16.5^{th} and 33^{rd} hour for the IM residents).

To determine the level of reaction time using the "On line reaction time test" and compare among the different follow up points within a shift (baseline, 6th and 12th hour for the ER residents and baseline, 16.5^{th} and 33th hour for the IM residents).

To determine the degree of attention, concentration and mental control using the "Digit Span" Working Memory subtest of WAIS IV and compare among the different follow up points within a shift (baseline, 6th and 12th hour for the ER resident; baseline, 16.5^{th} and 33^{rd} hour for the IM residents).

To determine the degree of visual perception/analysis and scanning speed using the "Symbol Search" Processing Speed subtest of WAIS IV and compare among the different follow up points within a shift (baseline, 6th and 12th hour for the ER residents and; baseline, 16.5^{th} and 33^{rd}hour for the IM residents)

To determine the degree of attention, processing speed and response inhibition using the Stroop test and compare among the different follow up points within a shift (baseline, 6th and 12th hour

for the ER residents and; baseline, 16.5th and 33rdhour for the IM residents)

A prospective cross-sectional study was conducted in a private training hospital from July to September 2014 which consisted of 18 Emergency Medicine and 40 Internal Medicine residents.

Approval was obtained from the Institutional Review Board (IRB). An IRB approved informed consent was administered by the researcher or research assistant to the residents and written informed consent was obtained. This study was done in accordance with the ethical principles of the Declaration of Helsinki and the National Ethics Guidelines for Health Research.

ER residents were chosen because of their particular schedule of undergoing 12 hour duty schedule for 3 days followed by a 24 hour rest period. ER residents in this tertiary hospital undergo 2 shifting schedule, the AM (0700-1900H) and PM shift (1900-0700 the next day). ER residents usually have a random shifting of schedule in order to meet the needed number of residents to go on duty. The most hectic schedule is for a resident to have 3 consecutive AM or PM shift with 12 hours rest period in between. After the 3 consecutive duty period, Emergency Medicine residents would usually have a 24 hour rest period and then they would undergo random change in shifting schedule or be on a 3 consecutive am or pm shift again.

For the procedure, the examiner asked for the monthly schedule from the chief resident of the ER department and from there, determined the resident who has a 3 consecutive am or pm duty shift. The resident was then informed ahead of time that he/she would be tested on the 3rd day of his/her duty shift.

For the procedure, the examiner visited the Emergency Department and the available resident that consented and met the criteria was tested (whether AM or PM shift). For the AM shift, tests were done before or at start of their duty (0600-0800H), at the 6th hour (1300H-1400H) and at the end of duty period (1900H-2000H). For the PM shift, tests were done before or at the start of their duty (1800H-2000H), at the 6th hour (0100H-0200H) and at the end of their duty period (0700H-0800H).

ER residents were tested on the 3rd day of their 12th hour duty period, which was the day prior to their 24 hour rest period. This was on the basis that on the 3rd day of their duty, the effect of work, stress, lack of sleep were at its peak.

Internal Medicine residents were chosen because they were the most numerous among the resident population and usually had a greater work load. Tests were also administered three times (at the beginning, middle and at the end of duty period) in a duty shift

Internal Medicine residents would usually be on Duty every 3 days. (Ex: if the resident would be on Duty status on the 1st day, start of day would be at 7:00am and would end 7 am the next day; from 7 am onwards to 4pm on the 2nd day, status would be "From duty". From duty residents are usually still within the vicinity of the hospital doing their respective work. On the 3rd day, the "Pre duty status", residents start at 7 am and would end at 4 pm. Subsequently, on the 4thday, the resident would be "on Duty" status again and the cycle repeats itself.

For the procedure, the examiner conducted the test to the "On Duty "residents before or at the start (600H to 800H), at the 16.5th hour (2330H-0030H) and at the end/dismissal from "From duty" status (1600H-1700H)

IM subjects were brought in a quiet room where the tests were administered by the researcher or research assistant.

These tests were administered only three times per resident because during these procedures, the examiner pulled them out from their respective posts hampering patient care if tests were administered more frequently. In addition to, doing tests more frequently would cause procedural bias.

The examiner did these tests in one ER or one IM resident per duty shift to ensure that the staff would not be depleted. In addition to, only those residents that were available at that particular time of the said examination can be tested.

Demographic data were taken as well as some data that would be of use in the study (which include: amount of coffee taken, hours of sleep, activities prior to duty, medication/drug taken prior).

Consenting residents would complete following questionnaires (please see appendix): Morningness-Eveningness Questionnaire which is a 19 point questionnaire about daily sleep wake habits and time of day preference of certain activities. This would assess the chronotype of each participant. Stanford Sleepiness Scale (SSS) which is a seven point self rating scale that quantifies progressive steps in sleepiness, ranging from a score of 1 denoting high alertness to a score of 7 indicating imminent sleep. The Stroop test or the Color and Word test. (please see appendix for official instructions). This test measures selective attention, cognitive flexibility and brain processing speed. It is used as a tool in the evaluation of executive function and response inhibition. The Digit Span Performance, a part of Working Memory subtest of WAIS IV. This test is used to measure attention, concentration and mental control. It is composed of 3 parts (forward, backward and sequencing), 8 items each. The "Symbol Search Performance", a part of processing Speed Index of WAIS IV is a 60 item test that would measure the level of visual perception/analysis and scanning speed of the individual. Computer based test include: Online reaction time test (recording response to a visual stimulus: red spot turning green in milliseconds). Throughout the procedure, the researcher or her assistant would be present to facilitate the different test procedures. These tests were chosen upon the recommendation of the co-investigators and were freely given for use for this study.

STATISTICAL ANALYSIS

Qualitative and categorical variables were represented using descriptive statistics—mean, standard deviation, median and range

ETHICAL CONSIDERATIONS

The study was conducted after approval was obtained from the Institutional Review Board (IRB). Informed consent was obtained from every participant before conducting the research. The protocol was implemented in accordance with the ethical principles of the Declaration of Helsinki and the National Ethics Guidelines for Health Research.

Participants joined the study voluntarily with clear understanding that there is no obligation to do so and there is no negative consequence for them if they do not assist in the research. Each respondent was assigned codes to protect their identity and given the utmost confidentiality. Results will be revealed only to participants who wanted to know the outcome of their individual participation.

RESULTS

1. General characteristics

There were a total of 58 residents who participated in the study. Forty (40 of 58, 69%)) residents were from the Department of Medicine while 18 (31%) were from Emergency Medicine. Female respondents dominated both the ER group and IM group at 61% and 57.5% respectively. The average ages for the two groups were almost similar—30 years old for the ER group and 28 years old for the IM group.

The ER group had two sets of shifting and 28% of them belonged to the AM Shift, while 72% comprised the PM Shift.

Among the ER residents, 33% were first years, 33% second years, 32% third years and 11% in their fourth year. On the other hand, for the IM residents, most of them were senior residents belonging to the 3rd and 2nd year levels at 40% each while the 1st years were 20%.

For the number of hours slept, the IM group had a longer median sleeping duration of 6 hours (4-9) compared to the 5 hours (3-6) for the ER. Both groups had equal amount of coffee intake.

Most of the residents were not taking any medications at the time of testing- 89% for the ER and 75% for the IM group. While lesser percentages

of them reportedly were taking vitamins—11% of the ER group and 12.5% for the IM group; incidentally 12.5% of the IM group had revealed to be taking other medications.

For the activities done one day prior to testing, 78% of the ER group reported not doing any physical/strenuous activity while 17% did some reading/studying and 6% performed exercises. The IM group reported that 65% also did not do any physical/strenuous activity, while 20% did some reading/studying, 7.5% performed exercises, and 5% doing other activities such as malling/shopping.

Of the five classifications for MEQ, the resident respondents mostly belonged to the Intermediate, Moderate Morning, and Moderate Evening types. Table 1 shows the general characteristics and MEQ classes of the resident respondents

Table 1. Sociodemographic profiles and MEQ classification of ER and IM residents respondents (n=58)

	ER	IM
Age	29.94± 1.85	28.33 ± 1.91
Gender		
Male	7 (39%)	17 (42%)
Female	11(61%)	23 (57.5%)
Shift		
AM Shift	5 (28%)	NA
PM Shift	13 (72%)	NA
Year Level		
1st	6 (33%)	8 (20%)
2nd	6 (33%)	16 (40%)
3rd	4 (32%)	16 (40%)
4th	2(11%)	NA
No of hours slept prior to duty	5 (3-6)	6 (4-9)
Amount of Coffee taken in cups	1 (0-3)	1 (0-2)
Current medications		
None	16 (89%)	30 (75%
Vitamins	2 (11%)	5 (12.5%)
Others	0 (0%)	5 (12.5%)
4th	2(11%)	NA
Activities done the night prior to duty		
None	14(78%)	26 (65%)
Reading/Studying	3 (17%)	8 (20%)
Exercise	1 (6%)	3 (7.5%)
Others	0(0%)	2 (5%)
Morningness or Eveningness Classification (MEQ)		
Definite Evening	0 (0%)	1 (3%)
Moderate Evening	4 (22%)	8 (20%)
Intermediate	7 (39%)	19 (48%)
Moderate Morning	7 (39%)	11 (28%)
Definite Morning	0 (0%)	0 (0%)

1. Stanford Sleepiness Scale (SSS)

Internal Medicine residents (33 hours duty shift)

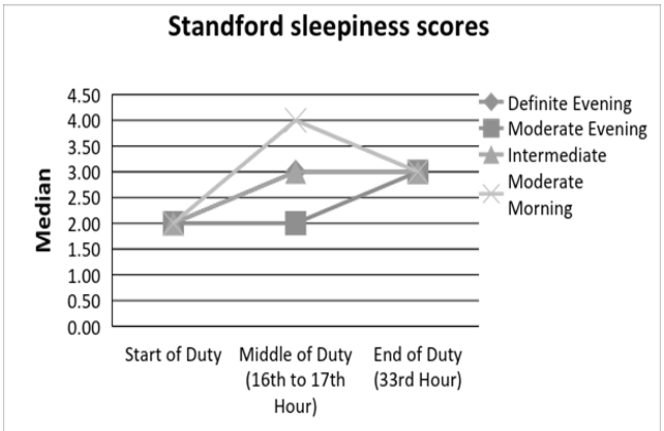
Residents of the moderate morning chronotype had increased median sleepiness scores by two points at the mid-shift then decreased sleepiness at the end of the shift. A similar pattern was presented by both the definite evening and intermediate chronotypes showing an increased degree of sleepiness by one point by mid-shift but remained at the same level by the end of the shift. The moderate evening group showed a different trend by maintaining the same score from baseline to middle of the shift then increasing sleepiness at the end of the shift. Trends in the change of median SSS scores among the four chronotypes of IM residents were determined (Figure 1).

Table 2. Stanford sleepiness Scale of IM residents expressed in median (range)

MEQ results	Start of Duty 7:00 AM	Middle of Duty (16.5 to 17.5 Hour) Approximately 11:00 PM	End of Duty (33rd Hour) 4:00 PM the following day
Definite Evening (n = 1)	2 (2-2)	3 (3-3)	3 (3-3)
Moderate Evening (n = 8)	2 (1-3)	2 (2-6)	3 (2-6)
Intermediate (n = 19)	2 (1-3)	3 (2-6)	3 (1-6)

SSS scores correspond to 1 = feeling active, vital, alert, or wide awake; 2 = functioning at high levels but not peak, able to concentrate; 3 = awake, relaxed, responsive but not fully alert; 4 = somewhat foggy, let down; 5 = foggy, losing interest in remaining awake; slowed down; 6 = sleepy, woozy, fighting sleep, prefer to lie down

Figure 1. Stanford sleepiness scale scores of IM residents during their 33 hours shift



Emergency Medicine residents (AM and PM shift)

The Emergency Medicine residents belonged only to three chronotypes, and were divided according to AM or PM shifts. For the AM shift, which started at 7:00 AM, the intermediate group had the lowest sleepiness scores at the start of duty but increased by 2 points by midhshift and increased another point by the end of the duty shift. The sleepiness scores of the three chronotypes were similar at midshift (1:00 PM). By the end of duty shift, both the moderate evening and intermediate chronotypes increased by one point in the degree of sleepiness

For the PM shift, which started at 7:00 PM, the moderate morning chronotypes had the lowest sleepiness scores at the start until the end of the shift. The moderate evening showed a steady increase in sleepiness scores from baseline, middle to the end of the shift, while the intermediate evening only had an increase in sleepiness at the end of the shift.

Table 1. Sociodemographic profiles and MEQ classification of ER and IM residents respondents (n=58)

			AM Shift		PM Shift	
MEQ	Start of Duty 7:00 AM	Middle of Duty (6th Hour) 1:00 PM	End of Duty (12th Hour) 7:00 PM	Start of Duty 7:00 PM	Middle of Duty (6th Hour) 1:00 AM	End of Duty (12th Hour) 7:00 AM
Moderate Evening (n = 4)	3 (3-3)	3 (3-3)	4 (4-4)	2 (2-2)	3 (1-3)	4 (2-6)
Intermediate (n = 7)	1 (1-1)	3 (3-3)	4 (4-4)	3 (2-3)	3.5 (2-5)	4.5 (3-5)
Moderate Morning (n=7)	2 (1-2)	3 (1-3)	3 (2-3)	2 (1-3)	2 (2-5)	2.5 (2-6)

SSS scores correspond to 1 = feeling active, vital, alert, or wide awake; 2 = functioning at high levels but not peak, able to concentrate; 3 = awake, relaxed, responsive but not fully alert; 4 = somewhat foggy, let down; 5 = foggy, losing interest in remaining awake; slowed down; 6 = sleepy, woozy, fighting sleep, prefer to lie down

Figure2. Stanford Sleepiness Scale of ER residents on AM shift

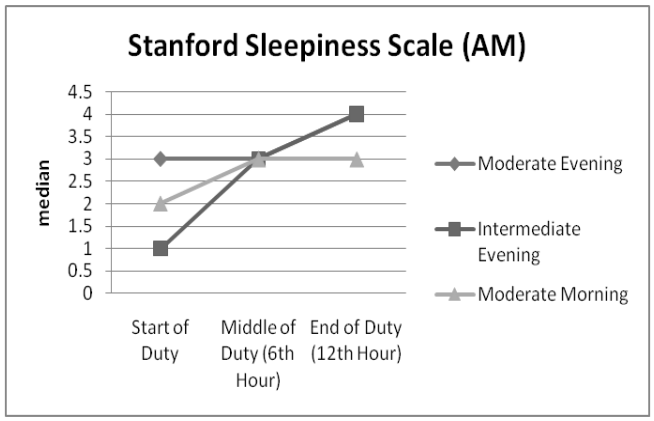
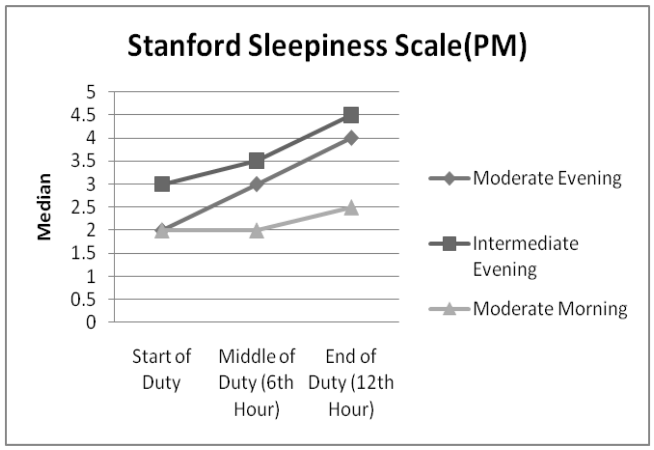


Figure 3. Stanford Sleepiness Scale of ER residents on PM shift



2. Symbol Search Performance of Wechsler Adult Intelligence Scale, 4th edition (WAIS-IV)

Internal Medicine residents (33 hours shift)

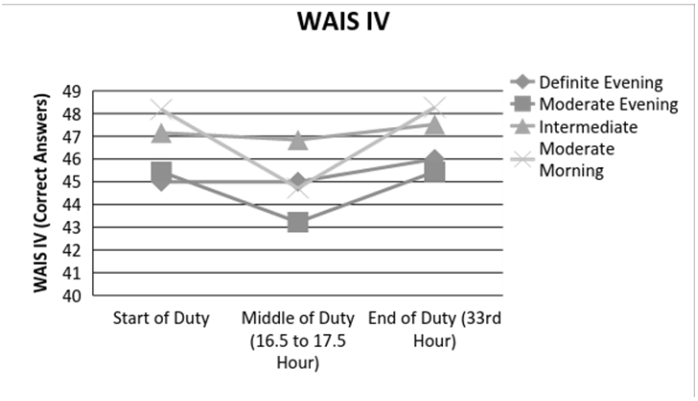
The moderately morning chronotypes had the highest score at the start of duty period while the definitely evening and moderately evening showed the lowest scores.

The moderate evening, intermediate, and moderate morning chronotypes all showed a decrease in WAIS-IV Symbol Search scores at mid-shift, which generally returned to baseline at the end of the tour of duty. The definitely evening chronotype on the other hand showed no change in score by midshift and increased by one point by the end of duty.

Table 4. Symbol Search Performance of Wechsler Adult Intelligence Scale, 4th edition by IM residents

MEQ	Start of Duty 7:00 AM	Middle of Duty (16.5 to 17.5 Hour) Approx 11:00 PM	End of Duty (33rd Hour) 4:00 PM
Definite Evening (n = 1)	45 ± 0	45 ± 0	46 ± 0
Moderate Evening (n = 8)	45.44 ± 6.54	43.22 ± 8.91	45.44 ± 8.63
Intermediate (n = 19)	47.15 ± 7.06	46.84 ± 7.65	47.52 ± 7.72
Moderate Morning (n=11)	48.18 ± 5.58	44.72 ± 7.95	48.27 ± 4.56

Figure 4. Symbol Search Performance of Wechsler Adult Intelligence Scale, 4th edition (WAIS-IV) by IM residents during their 33 hours duty



Emergency medicine residents (AM AND PM shift)

For the AM shift, the moderately evening chronotypes showed the lowest score, while both the intermediate and moderately morning chronotypes had similar score at the start of duty period.

The WAIS IV Symbol Search scores for the 3 chronotypes showed a drop in scores by midshift and further dropped by the end of duty for both the moderately evening and moderately morning chrnonotypes

For the PM shift, the intermediate chronotypes started with the lowest score and the moderately morning chronotypes had the highest score. All of them exhibited an increase in score from midshift to end of duty period.

Table5. WAIS IV items (Symbol Search) answered correctly by ER residents

		AM Shift			PM Shift	
MEQ	Start of Duty	Middle of Duty (6th Hour)	End of Duty (12th Hour)	Start of Duty	Middle of Duty (6th Hour)	End of Duty (12th Hour)
Moderate Evening	50 ± 0	48 ± 0	42 ± 0	45.66 ± 2.3	48 ± 7.54	49.33 ± 4.16
Intermediate	54 ± 0	50 ± 0	50 ± 0	43.33 ± 4.8	44.16 ± 4.87	49.66 ± 5
Moderate Morning	54 ± 9.54	47.33 ± 9.29	46 ± 8.18	47 ± 8.24	47.75 ± 6.65	50.75 ± 4.85

Figure 5. WAIS IV items (Symbol Search) answered correctly by ER residents (AM shift)

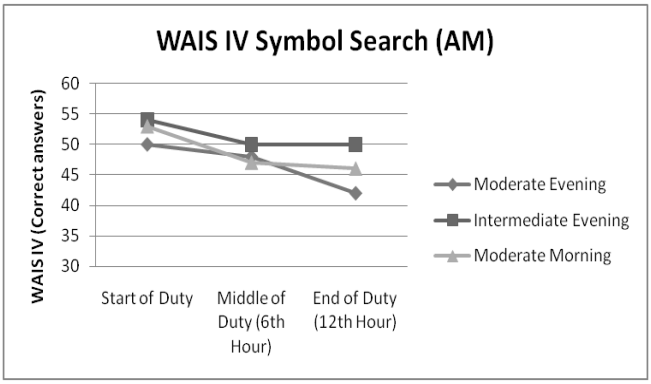
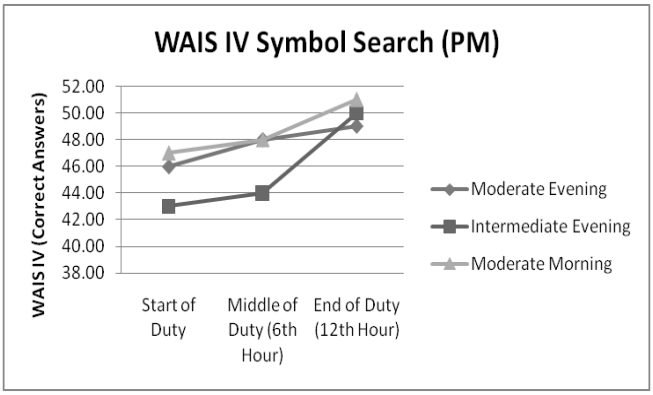


Figure 6. WAIS IV items (Symbol Search) answered correctly by ER residents (PM shift)



3. Digit Span test

Internal Medicine residents (33 hours duty shift)

For the Digit Span Forward scores, the definite evening chronotypes revealed an obvious different pattern from the rest of the types. It started at a high score at 14 then had a steep drop by three points at the middle of the shift. It recovered by one point at the end of the shift. The moderate evening, intermediate and moderate morning chronotypes exhibited a steady pattern of scores from middle of duty until the end of duty period.

For the Digit Span Backward scores, the moderate evening, intermediate, and moderate morning chronotypes had higher scores compared to the definite evening chronotype. Aside from having the lowest scores, definite evening chronotype maintained the same score from the start, middle and by the end of duty shift.

Among the three, the intermediate and moderate morning had similar line graphs. Both maintaining their baseline scores to the middle of the shift, their scores had minimal drop by the end of the shift. Notably, the moderate evening chronotypes showed a steady increase of its scores from the baseline, middle and towards the end of the shift.

For the Digit Span Sequence scores, the definite evening chronotype exhibited the initial low score compared to other chronotypes, this further decreased by 2 points in the middle of the shift and did not recover by the end of the shift. The remaining three chronotypes, namely the moderately evening, intermediate and moderately morning showed a slight decline in their scores by the middle of the shift, with the moderately morning showing the highest decline among the three. However, the moderately morning chronotypes was able to recover by the end of the shift while the remaining two remained the same.

Table 6. Digit Span Test Scores of IM residents (maximum score = 16)

MEQ	Start of Duty 7:00 AM	Middle of Duty (16.5th to 17.5th Hour) Approx 11:00PM	End of Duty (33rd Hour) 4:00 PM
Forward			
Definite Evening (n = 1)	14 ± 0	11 ± 0	12 ± 0
Moderate Evening (n = 8)	12.11 ± 2.52	12.66 ± 2.69	12.33 ± 2.69
Intermediate (n = 19)	11.78 ± 2.14	11.31 ± 1.88	11.57 ± 2.11
Moderate Morning (n = 11)	11.9 ± 1.81	11.9 ± 1.97	11.81 ± 1.94
Backward			
Definite Evening (n = 1)	8 ± 0	8 ± 0	8 ± 0
Moderate Evening (n = 8)	11.44 ± 3.08	11.66 ± 2.95	12 ± 2.06
Intermediate (n = 19)	10.94 ± 2.04	11.05 ± 2.29	10.78 ± 2.14
Moderate Morning (n = 11)	10.63 ± 1.85	10.81 ± 2.04	10.36 ± 2.33
Sequence			
Definite Evening (n = 1)	10 ± 0	8 ± 0	8 ± 0
Moderate Evening (n = 8)	10.11 ± 0.92	9.88 ± 1.83	9.22 ± 1.85
Intermediate (n = 19)	10.26 ± 1.75	9.47 ± 2.45	9.63 ± 1.64
Moderate Morning (n = 11)	11 ± 2.04	9.63 ± 2.24	10.72 ± 1.55

Figure 7. Digit Span Forward scores of IM resident during their 33 hours duty

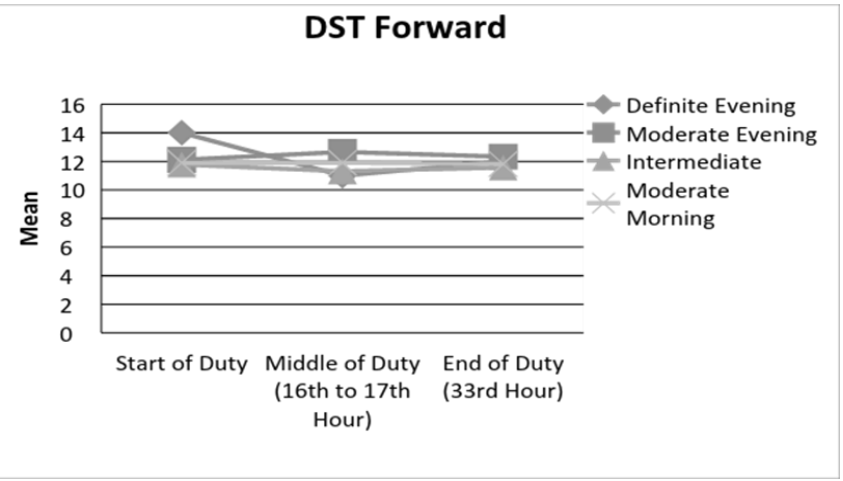


Figure 8. Digit Span Backward scores of IM residents during their 33 hours duty

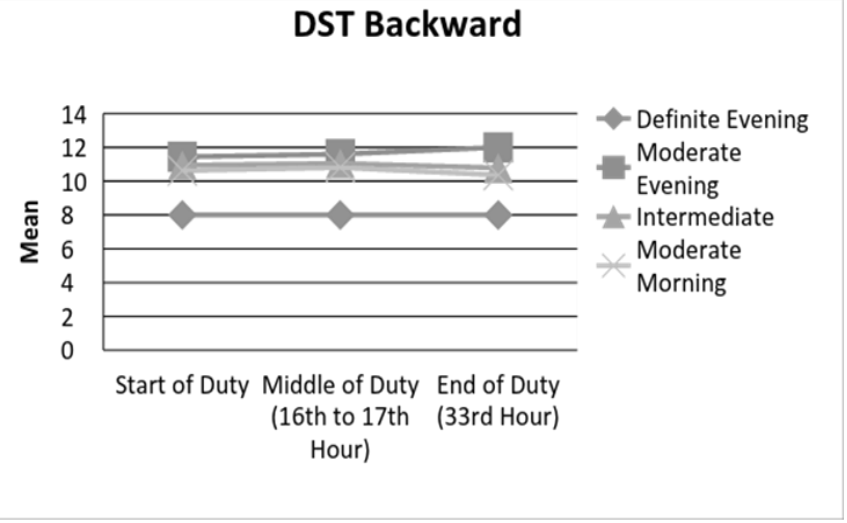
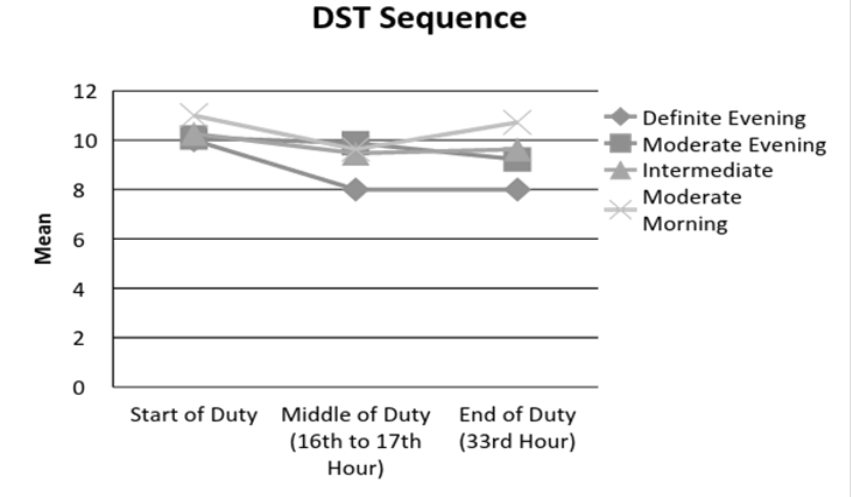


Figure 9. Digit Span Sequence scores of IM residents during their 33 hours duty



Emergency Medicine residents (AM and PM shift)

For the Digit Span Forward test: AM group: the moderately evening chronotypes showed the initial low score at the start of duty period compared to other chronotypes. By the middle of duty period, the moderately evening and intermediate chronotypes showed no change in the score compared to their baseline/1st score however, the scores dropped by the end of duty. The moderately morning chronotypes showed a 1 point drop in scores by the middle of the shift however was able to maintain the same score by the end of the duty shift.

For the PM shift: the intermediate chronotypes showed the initial low score at the start of duty compared to other chronotypes. By the middle of the duty shift, both the moderately evening and intermediate chronotypes showed 2-3 points increase in scores. The moderately morning showed a drop in score by the middle of the duty shift. By the end of the duty shift, both the moderately evening and moderately morning chrnonotypes showed a decrease in score while the intermediate chronotypes showed a slight increase in score.

Table 7. Digit Span Forward scores of ER residents

		AM Shift			PM Shift	
MEQ	Start of Duty	Middle of Duty (6th Hour)	End of Duty (12th Hour)	Start of Duty	Middle of Duty (6th Hour)	End of Duty (12th Hour)
Moderate Evening	10 ± 0	10 ± 0	8 ± 0	11 ± 3	13.33 ± 2.88	10.33 ± 3.21
Intermediate	14 ± 0	14 ± 0	11 ± 0	9.83 ± 1.16	11.33 ± 1.36	11.5 ± 2.34
Moderate Morning	13.33 ± 1.15	12.66 ± 1.15	12.66 ± 1.15	12 ± 1.82	11.25 ± 3.09	10.75 ± 0.95

Figure 10. Digit Span Forward scores of ER residents during AM shift

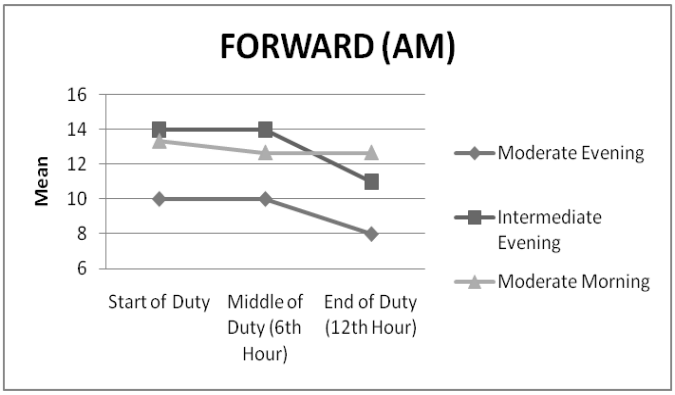
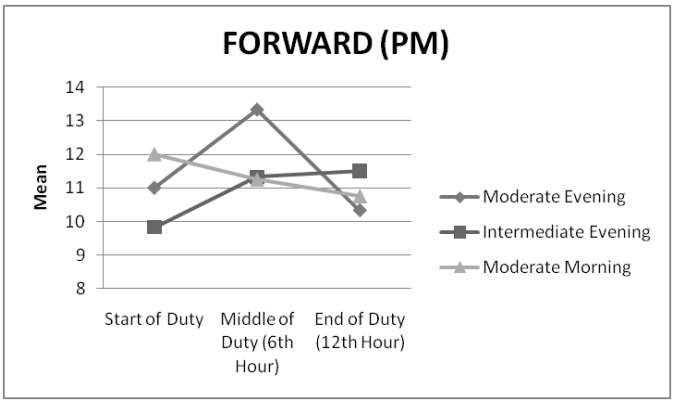


Figure 11. Digit Span Forward scores of ER residents during PM shift



For the Digit Span Backward test: AM shift: The moderately evening chronotypes showed the initial low score at the start of the duty period. The score was maintained throughout the duty period. Both the moderately evening and the moderately morning chronotypes showed no change in score by the middle of the duty shift while the intermediate chronotypes exhibited a 2 point decrease in score. By the end of duty period, the intermediate chronotypes regained the 2 points back. The moderately morning chronotypes showed a slight decline in score.

For the PM shift: The intermediate chronotypes exhibited the initial low score compared to other chronotypes at the beginning of the duty shift. The moderately evening chronotypes showed a slight decline in score by the middle of the shift while the intermediate and moderately morning showed a slight increase in score by the middle of the duty shift. By the end of the duty shift, the moderately evening and the moderately morning exhibited a decline in score while the intermediate chronotypes showed a slight increase in score.

Table 8. Digit Span Backward scores of ER residents

		AM Shift			PM Shift	
MEQ	Start of Duty	Middle of Duty (6th Hour)	End of Duty (12th Hour)	Start of Duty	Middle of Duty (6th Hour)	End of Duty (12th Hour)
Moderate Evening	8 ± 0	8 ± 0	8 ± 0	11.33 ± 1.52	11 ± 3.6	10.66 ± 4.04
Intermediate	12 ± 0	10 ± 0	12 ± 0	9.5 ± 1.87	10.16 ± 3.25	11 ± 3.52
Moderate Morning	13 ± 1	13 ± 0	12.66 ± 0.57	11 ± 2.44	11.25 ± 2.06	10.5 ± 2.64

Figure 12. Digit Span Backward scores of ER residents during AM shift

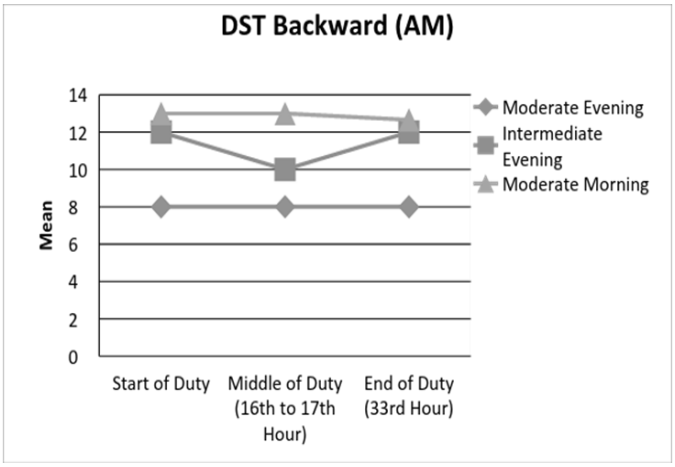
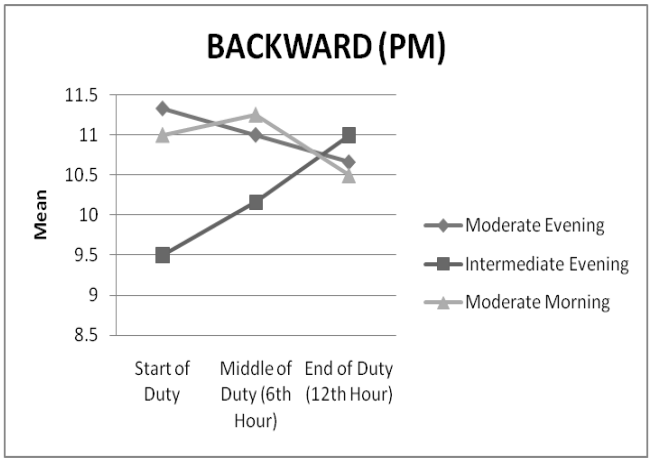


Figure 13. Digit Span Backward scores of ER residents during PM shift



For the Digit Span Sequence Test: AM shift: The moderately evening group had the initial low score at the beginning of the duty shift. The group did not also exhibit any changes in score until the end of duty. The intermediate and moderately morning chronotype showed a decline in scores during the middle and end of duty shift. chronotypes showed a decline in score.

PM shift: The intermediate chronotypes had a low initial score at the start of duty which showed a slight decline by the middle of the duty period and was maintained by the end of duty shift. The moderately evening and moderately morning chronotypes exhibited increased scores by the middle of the duty shift. By the end of duty shift, the moderately morning chronotypes showed a decline in score.

Table 9. Digit Span Sequence scores of ER residents

		AM Shift			PM Shift	
MEQ	Start of Duty	Middle of Duty (6th Hour)	End of Duty (12th Hour)	Start of Duty	Middle of Duty (6th Hour)	End of Duty (12th Hour)
Moderate Evening	8 ± 0	8 ± 0	8 ± 0	9.33 ± 1.52	11 ± 2	11 ± 2.64
Intermediate	14 ± 0	13 ± 0	11 ± 0	8.5 ± 2.81	8.16 ± 2.63	8.5 ± 2.88
Moderate Morning	11.33 ± 3.05	11 ± 2	10.66 ± 1.52	9.75 ± 2.36	11 ± 2.3	10 ± 2.94

Figure 14. Digit Span Sequence scores of ER residents during AM shift

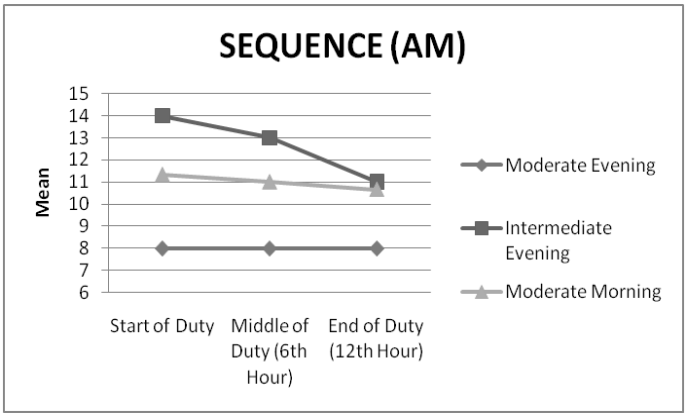
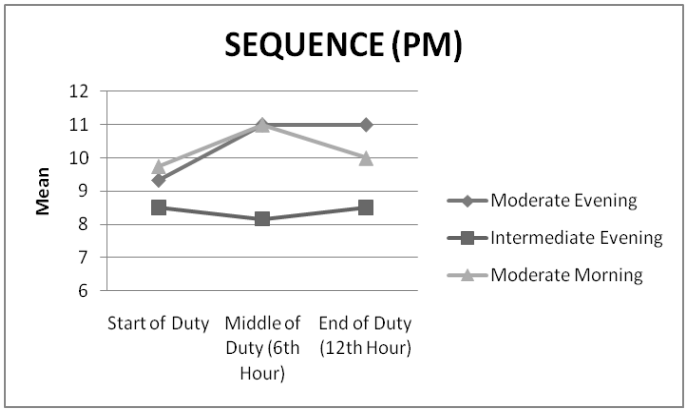


Figure 15. Digit Span Sequence scores of ER residents during PM shift



4. Online Reaction Test

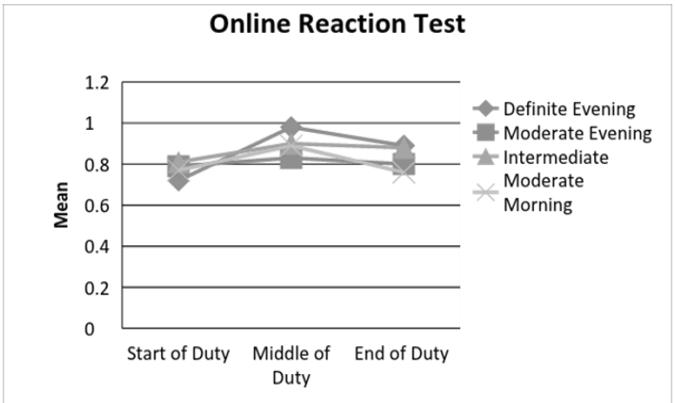
Internal Medicine residents (33 hours duty shift)

For the online reaction test, all four chronotypes of the IM residents consistently registered reaction times less than one second, slightly slowing down during mid-shift, and recovering by the end of duty. The moderate morning chronotypes was able to recover with a faster mean reaction time at 0.76 seconds compared to baseline**.**

Table 10. On line reaction test of IM residents

MEQ	Start of Duty 7:00 AM	Middle of Duty (16.5 to 17.5 Hour) Approx 11:00 PM	End of Duty (33rd Hour) 4:00 PM
Definite Evening (n = 1)	0.72 ± 0	0.98 ± 0	0.89 ± 0
Moderate Evening (n = 8)	0.79 ± 0.11	0.83 ± 0.11	0.8 ± 0.1
Intermediate (n = 19)	0.81 ± 0.11	0.9 ± 0.2	0.88 ± 0.1
Moderate Morning (n = 11)	0.77 ± 0.11	0.89 ± 0.21	0.76 ± 0.11

Figure 16. On line reaction test of IM residents



Emergency Medicine residents (AM and PM shift)

The moderate morning, intermediate, and moderate evening chronotypes all had increasing online reaction times for the AM shift.

In contrast, the moderate evening and intermediate types had shorter average reaction times as the PM shift progressed. The moderate morning chronotypes had a longer reaction time at mid-shift (1:00 AM), compared to baseline and end of duty.

Table11. On line reaction test of ER residents

		AM Shift			PM Shift	
MEQ	Start of Duty 7:00 AM	Middle of Duty (6th Hour) 1:00PM	End of Duty (12th Hour) 7:00 PM	Start of Duty 7:00 PM	Middle of Duty (6th Hour) 1:00 AM	End of Duty (12th Hour) 7:00 AM
Moderate Evening (n = 4)	0.82 ± 0	0.83 ± 0	0.92 ± 0	0.92 ± 0.32	0.86 ± 0.24	0.7 ± 0.15
Intermediate (n = 7)	0.68 ± 0	0.86 ± 0	0.92 ± 0	0.88 ± 0.18	0.79 ± 0.06	0.78 ± 0.09
Moderate Morning (n = 7)	0.69 ± 0.05	0.73 ± 0.1	0.82 ± 0.02	0.81 ± 0.18	0.84 ± 0.16	0.82 ± 0.16

Figure 17. On line reaction test of ER residents during AM shift

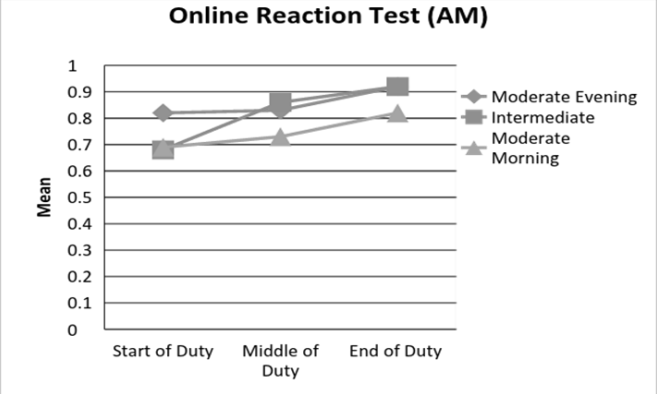
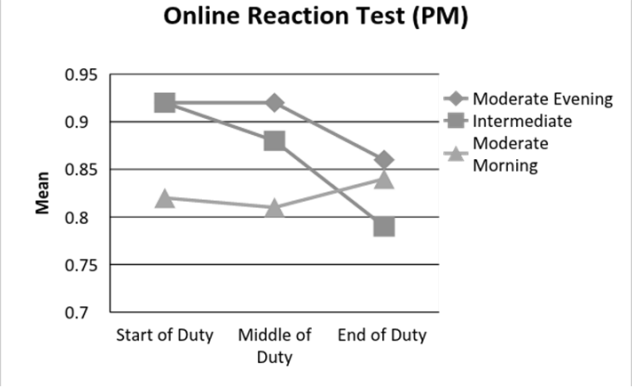


Figure 17. On line reaction test of ER residents during PM shift



5. Stroop test

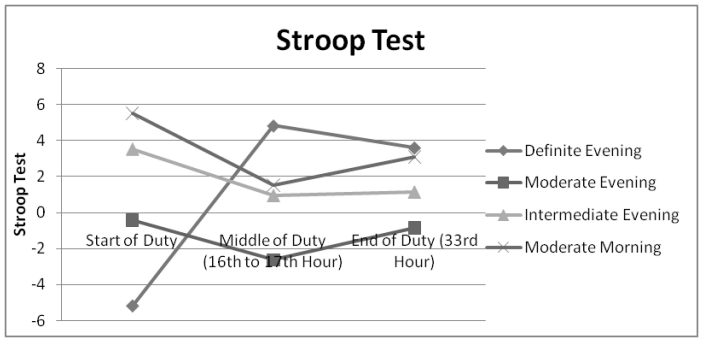
Internal Medicine residents

The three chronotypes—moderate evening, intermediate and moderate morning, although having different initial Stroop test scores- -0.43, 3.52 and 5.51 respectively, they had similar graphs. Their scores dropped during the middle of the shift but recovered by the end of their shift. These mean that their ability to sustain attention, inhibit responses and brain processing speed by recognizing and differentiating colors and words in contained in the test decrease as they approach the middle of the shift but eventually regained to some extent by the end of the shift. Only the definite evening displayed a different pattern that started with the lowest score of – 5.16 then gained a very steep rise by 9 points during the middle with only a minimal decrease in score at the end of his shift.

Table 12 Stroop test of IM residents

MEQ	Start of Duty	Middle of Duty (16.5th to 17.5th Hour)	End of Duty (33rd Hour)
Definite Evening	-5.16 (-5.16 to -5.16)	4.83 (4.83 to 4.83)	3.61 (3.61 to 3.61)
Moderate Evening	-0.43 (-8.74 to 8.81)	-2.63 (-4.64 to 10.48)	-0.84 (-6.43 to 7.88)
Intermediate	3.52 (-8.21 to 12.32)	0.94 (-8.63 to 12.6)	1.14 (-9.44 to 9.47)
Moderate Morning	5.51 (-2.6 to 19.76)	1.53 (-4.78 to 9.79)	3.09 (-4.54 to 14.14)

Figure 17. Stroop test-IM residents



Emergency Medicine Residents (AM and PM shift)

For the morning shift residents, the three chronotypes displayed decreasing scores for the Stroop test during the span of their duty as represented by the line graphs slopping down. However, the moderate morning type had the steepest graph with an average of 5 points from start to the middle of the shift then 6 points by the end of the shift. These showed that their ability to sustain attention, inhibit responses and brain processing speed were decreasing, with the number of correct recognition of colors and words contained in the test of as their tour of duties progressed

For the afternoon shift residents, the three chronotypes had decrease in scores of correct recognition of color and words contained in the test as they approached the middle of the shift with recovery with rise in scores by the end of the shift

Table 13. Stroop test off ER residents (AM and PM shift)

		AM Shift			PM Shift	
MEQ	Start of Duty	Middle of Duty (6th Hour)	End of Duty (12th Hour)	Start of Duty	Middle of Duty (6th Hour)	End of Duty (12th Hour)
Moderate Evening	1.17 (1.17 to 1.17)	-0.17 (-0.17 to -0.17)	-3.43 (-3.43 to -3.43)	7.6 (5.47 to 8.82)	4.56 (3.18 to 5.84)	0.33 (-3.12 to 7.78)
Intermediate	5.37 (5.37 to 5.37)	6 (6 to 6)	-0.31 (-0.31 to -0.31)	-2.475 (-6.33 to 5.63)	-4.12 (-21.11 to 8.81)	-2.635 (-9.38 to 17.29)
Moderate Morning	12.12 (11.33 to 17.81)	7.49 (5.4 to 8.6)	1.53 (-0.47 to 8.28)	4.845 (0.57 to 12.94)	1.25 (-2.59 to 16.27)	3.545 (-7.56 to 14.92)

Figure 18. Stroop test (ER-AM shift)

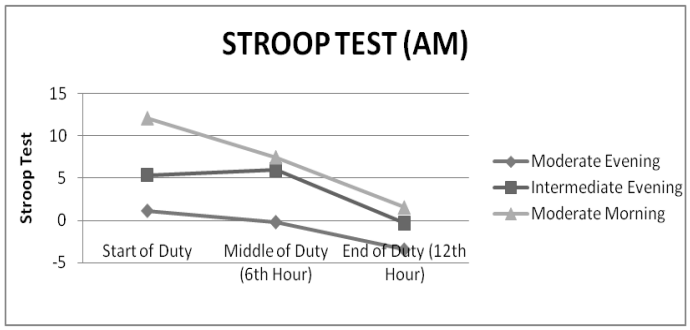
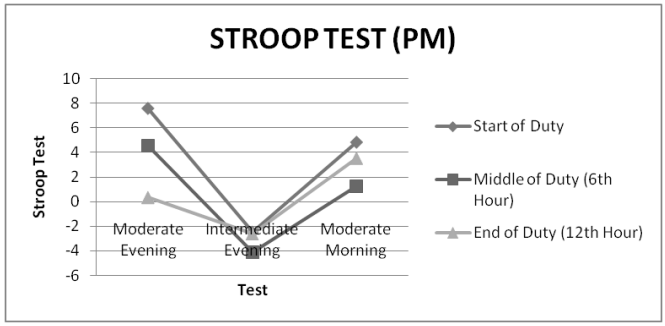


Figure 18. Stroop test (ER-PM shift)



DISCUSSION

Based on the results, the different chronotypes correlated with the degree of sleepiness of the residents. Late chronotypes tend to be sleepier at the start of the duty with little or no variation by the midshift and subsequent maintained the degree of sleepiness or had a slight increase sleepiness by the morning. Early chronotypes was noted to be more active at the start of duty then would lag behind by have an increase in the degree of sleepiness by mid duty followed by a little improvement by the next morning.

The level of visual perception/scanning speed of the IM residents as measured by the Symbol Search subtest of the WAIS IV showed that irrespective of chronotype, most of them would have a decrease speed by the midshift and the residents would regain back their ability by the end of duty shift.

For the ER, AM shift: Results showed that the ability of the residents to visually process information decreased until the end of the duty irrespective of chronotypes. In contrast, for the PM shift, late chronotypes had improved visual perception by midshift and was maintained until the end of duty. The early chronotypes on the other hand showed no change in scores by midshift and subsequent improvement by the end of duty.

The level of attention, concentration and mental control as measured by the Digit Span Working Memory subtest showed that, for the Digit Span Forward and Backward category, scores were almost the same throughout the duty period for the IM group except for the definite evening (very late chronotype) which showed a decline in score by midshift and a one point increase toward the end of duty. However, it should be remembered that the only one IM resident belonged to the definitely evening group, thus a generalized statement cannot be concluded regarding the very late chronotypes. For the Digit Span Sequence category, results showed that the late chronotypes had the lowest scores at the start of duty in the morning while the early chronotypes having the highest scores. By the midshift, regardless of chronotype, all showed a declining pattern. The late chronotypes while the intermediate and the early chronotypes showed slight improvement in scores.

For the ER AM shift, results consistently showed that baseline scores for all Digit Span subcategories, it was lowest for the late chronotypes and was highest either with the intermediate or early chronotypes. Late chronotypes maintained their score by midhshift for all subcategories while the early chronotypes showed a slight decline. By the end of duty period, scores for the backward and sequence test was maintained for the late chronotypes while showing a decline for the forward test. By the end of duty shift, early chronotypes again showed a minimal decrease in scores for the backward and sequence scores while no change was noted for the forward scores. No specific pattern was noted for the PM shift, sometimes late chronotypes would have the initial high score and vice versa with the early chronotypes.

The level of reaction time, as measured by the On line reaction test showed that IM residents reaction time decreased by midhshift and returned to near baseline level by the end of duty shift.

For the ER AM shift, all chronotypes showed decreasing level of reaction throughout the duty period. For the PM shift, late and intermediate chronotypes had improved reaction time during their tour of duty. The early chronotypes was noted to have decreased reaction time by midhshift which gradually improved by the end of duty.

For the Stroop test, results for the IM residents showed that late chronotypes have a lower initial/baseline scores compared to the early chronotypes. Stroop test also revealed that for all 3 chronotypes, namely, the moderate evening, intermediate and moderate morning chronotypes, they all experienced a decreased level of processing speed, sustained attention and response inhibition by midhshift. Exception again would be the very late chronotype (definitely evening) which showed an improved degree of attention and cognitive flexibility by midshift. However, because only one resident belonged to the very late chronotype, a general statement cannot be made regarding very late chronotypes. By the end of the duty period, all 3 chronotypes gradually showed a

slight improvement of their Stroop scores however scores did not return to their baseline levels.

For the ER residents on AM shift, results revealed that similar to the IM residents, late chronotypes had lower baseline scores compared to the early chronotypes. Both early and late chronotypes showed a decline in sustained attention, processing speed and response inhibition by the end of duty. For the ER residents on PM shift, results showed the opposite, late chronotypes had the high baseline score compared to the early chronotypes. All of them showed a declining pattern by midshift however, by the end of duty, the early chronotype was able to show slight improvement.

CONCLUSION

As predicted, chronotypes correlated with the degree of constraints on sleep experienced on the morning, or evening shifts. As a result of such constraints, late types showed significantly higher social jetlag than early types on the morning shift. Early types, on the other hand, revealed significantly higher constraints on the night shift compared to late types on the night shift. This was reflected with the different tests done wherein early chronotypes garnered a higher score at the start of the day, and with the late chronotypes having a lower score. Likewise, chronotype correlated with subjective well-being during night work, with early types feeling significantly less well than late types. Also, early types reported lower well-being on the night shift than on the morning shift, while the opposite could be observed for late types.

However, when tested across the duty period, chronotype did no longer associate with the degree of social jetlag, indicating that, overall, the different chronotypes experience the same degree of constraints as do rotating worker, meaning that lack of sleep, stress and hectic schedule would take a toll on the resident by midshift as shown by decreasing attention, alertness, reaction time by the different tests. Few instances from the results showed that during midshift, late chronotypes had a lesser drop in terms of attention, alertness and reaction time compared to the early chronotypes.

RECOMMENDATION

Not all IM and ER residents were included in the study. Some IM residents were rotating in the ER and thus was excluded, others only have a half day during from duty thus was also excluded. For the ER residents, some of them are rotating with other department, hence was excluded. Some residents were also not in a three day AM or PM shift, thus was not tested. It would be beneficial to the training institution involved if all were included as subjects so that the researcher can conclude appropriately if there would be a significant drop in terms of the different measures tested such that the Department concerned can be alerted to prevent medical errors.

At the middle of the duty period when the level of alertness, reaction time and attention decreased, it would be appropriate if medical workforce would be added to augment the medical team and mimimize medical errors.

For the ER group, it is recommended that those morning chronotypes would be assigned to an AM shift and those late chronotypes to the PM shift. Also workforce should be added during morning shift, since results showed a declining pattern of measures.

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APPENDIX:

Informed consent (English and Tagalog)

Gantt chart

Methodology

Data information sheet

Morningness and Eveningness Questionnaire

Stanford Sleepiness Scale

Stroop test

Online reaction time

Symbol Search" Processing Speed subtest of WAIS IV

"Digit Span" Working Memory subtest of WAIS IV