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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

For the Fiscal years 2014-2015 and 2015-2016, this is the 4th PMA Journal to be printed. The PMA has made considerable strides in the associations' search for outstanding researches and studies nationwide. The Committee on Publications recognizes the fact that our colleagues gave all their hard work, time and considerable effort to each article. Reading through them has given us a remarkable uplifting effect and each article published has given us the chance to say well done and also to recognize outstanding achievements.

To the members of the Committee on Publications, I shall be forever grateful for your support, because being officers of an organization comes a two-fold task, first to lead an association to action, and second, to serve one's members by taking into consideration their immediate needs and concerns. For the life span of an organization depends on its leaders. An organization without leaders ceases to exist, while one with inactive leaders dies a natural death. Let us continue to contribute to the betterment of our members and the association we most hold high and dearly love, the PMA.

Our congratulations to all!!

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

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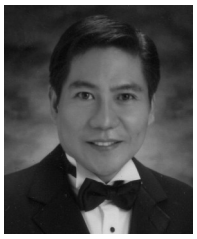

Greetings!

I am deeply pleased to be a part of this worthwhile endeavour. It has been almost two years since we started calling for research papers to come up with two journal issues in a year. The response for submission was exceptionally good. This perfectly proves that our colleagues earnestly desire for an honestly agreeable intellectual cogitation.

It is the Philippine Medical Association's aim to inspire our colleagues with courage to do more research not only to discover competent scientists for the constantly evolving science, but also to provide recently relevant ideas with its scientific advantages.

Allow me to express my sincere gratitude to all those who participated in the past and current issues. I, in behalf of the Committee on Publication and Sub-committee on Journal would like to thank all of you for your interest and cooperation! Thank you very much and God bless!

Sincerely,

Arnel M. Asino, MD, DPBA, FPSA, FPSQua
Chair, Sub-Committee on PMA Journal

Journal of the
Philippine Medical Association

Instruction for Authors

General Information

The Journal of the Philippine Medical Association (JPMA) is the official publication of the Philippine Medical Association (PMA).

The JPMA is published twice in a year at the PMA Office, 2nd Floor, PMA Building, North Avenue, Quezon City 1105, Philippines. It publishes original scientific papers pertinent to medicine and allied fields. It also considers for republications of previously published articles, either in their original or modified forms, provided they are accompanied by written permission from the publisher and principal author.

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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.

All financial or personal relationships that could be viewed as presenting a potential conflict of interest must be disclosed by the author(s) and all participants in the review and publication process.

In experiments involving human subjects, authors must indicate in their reports whatever procedures are complaint with the standards of the responsible institutional and national committee on human experimentation as well as with the Helsinki Declaration of 1975, as revised in 2000. In case of doubts as to the procedures, authors mush show proof of approval of their institutional review body or its equivalent.

In experiments involving animals, authors must indicate in their reports compliance with the institutional and national guide for laboratory animal experimentation.

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.

Abbreviations and nomenclatures: the use of abbreviations should be minimized and preferably confined to tables only; non-standard abbreviations must be accompanied by legends.

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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Subscription and advertisements, including change of address should be sent to the PMA Secretariat at 2nd floor PMA Building, North Avenue, Quezon City, 1105 Philippines.

Management of Plaque Type Psoriasis with Aloe Vera (*Aloe Barbadensis*) Extract in Hydrophilic Ointment versus Clobetasol Propionate Ointment: A Prospective Randomized Double Blind Controlled Trial

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ABSTRACT

BACKGROUND: Psoriasis is considered as a genetically programmed disease of dysregulated inflammation, which is driven and maintained by multiple components of the immune system. Topical medications both evidenced-based medical and herbal, are widely utilized as treatment for psoriasis affecting less than 20% of the total body surface area of involvement.

OBJECTIVE: To compare the efficacy and safety of aloe vera (AV) extract in hydrophilic ointment versus clobetasol propionate in hydrophilic petrolatum in the resolution of lesions of plaque type psoriasis.

METHODS: A randomized, double blind, controlled 4-week study was designed. Forty-six patients randomly received AV ointment and 0.05% clobetasol propionate and their clinical responses were evaluated using Psoriasis Area Severity Index (PASI). The Psoriasis Disability Index (PDI) was also used to evaluate treatment satisfaction from the topical medications.

RESULTS: Intent to treat analysis done at the end of four weeks showed statistical significance in the mean difference between the treatment groups that is 3.4 (CI:0.6-6.1; P:0.0174). Similarly, per protocol analysis elucidated a significant difference of 3.69 (CI:0.89,6.49 P:0.0115) in the means of both the Aloe vera and the clobetasol group.

CONCLUSION: This study showed the efficacy of AV extract in hydrophilic ointment is not inferior to that of Clobetasol propionate ointment in hydrophilic petrolatum for the treatment of plaque type psoriasis. In both groups there were no recorded adverse events and the patients showed marked improvement in the quality of life after treatment.

I. INTRODUCTION

Psoriasis is a clinically well characterized, inflammatory and hyperproliferative skin disorder that results partly from chronic dysregulation of the immune response.[1] Its prevalence varies largely from 0.1 percent to 11.8 percent with the highest reported incidences in Europe specifically in Denmark and Faeroe island (2.9 and 2.8 percent respectively). This incidence is close to 2.2 to 2.6 percent as measured in the United States in contrast to 0.4 percent recorded from Asia.[2]

Efforts on genetic isolation of the multiple genome-wide linkage studies on psoriasis, the Psoriasis susceptibility 1 (PSORS1) locus has been consistently confirmed. This is located on the major histocompatibility complex chromosome 6p21.3. Furthermore, multiple HLA alelles have been associated with psoriasis HLA-B13, HLAB37, HLA-B57, HLA-Cw1, HLA-Cw6, HLA-DR7 and HLA-DQ9.[2] This genetic perturbation can be triggered by environmental stimuli, systemic illness, medication (infections, medications, antigenic stimuli, physical and or emotional stress).[3] Histopathology has provided a useful framework for cause-and-effect relationship between the cellular assault and the development of psoriatic lesion.[2] Initial pinhead sized with marked edema may show spongiosis with focal hypogranulosis confined to one or two papillae with dermal infiltrates are predominantly mononuclear cells. Developing lesions may show suprapapillary thinning, hypogranulosis, psoriasiform dermatitis, in addition to the munro microabscess and Kogoj abscess.[2,4]

Topical therapy is still the fundamental and remains to be the cornerstone of treatment in the management of psoriasis patients with 20% or less body surface area involvement.5 Various treatment techniques such as combination, rotational and sequential therapy using topical agents are in place for psoriasis. 3 Combination therapy is utilized to benefit from the multiple mechanisms of action of the drugs combined at lower individual doses to provide synergistic or additive efficacy with reduced toxicity. Rotational therapy on the other hand aims to minimize the risk of cumulative toxicity by switching from one therapy to another before the initial agent has a chance to build to potential toxic levels. Lastly, a better-studied technique of treatment is the sequential therapy for psoriasis developed to maximize the short term efficacy of topical agent while minimizing the side effects. This entails three phases: (1) Clearance phase usually utilizes rapidly acting topical agents which often has greater side effects (2) Transitional phase, which when once a patient shows improvement, introduction to a maintenance therapy is undertaken; and (3) Maintenance phase, use of maintenance treatment for as long as needed.[5] All of these techniques aim to maximize the short-term efficacy of topical agent while minimizing toxicity.[6]

Topical corticosteroid, one of the most favored topical treatment for psoriasis has proven its versatility and efficacy in resolving lesions of psoriasis. The mechanisms of action include anti inflammatory, immunosuppressive, anti-proliferative and vasoconstrictive properties. Disease severity, areas of affectation, patients preference, age of the patient, choice of the appropriate potency and its vehicle should all be considered in utilizing topical corticosteroids. Recommendation of dosing regimen is from once to twice daily application; and the duration of use and short term efficacy vary greatly on the steroid potency. Possible toxicities of steroid use can be expected to occur either locally or systemically.[7]

Discussion of other frequently used topical therapy for psoriasis such as vitamin D analogues such as Calcipotriene or calcitriol, retinoids like tazarotene, topical calcineurin inhibitors (tacrolimus and pimecrolimus), coal tar, anthralin, salicylic acid and skin moisturizers are all beyond the scope of this study.[8,9,10,11]

Notwithstanding the advances and researches about psoriasis and its treatment, absolute cure remains to be very challenging. As psoriasis is a chronic condition, it is valuable to note that the safety of treatment for long-term use is relevant. Often the duration of the treatment is restricted by the cumulative toxicity of medications. Furthermore, treatment can be complicated by various adverse events and on the patient's end, treatment exhaustion. The increasing popularity of herbal therapy among patients and physicians flood the medical literature due to the numerous claims of its efficacy.

The natural herbal alternatives, aloe vera (AV) is proven to be a well-researched plant with quite a number of proposed health benefits. More than 300 species of Aloe plants are studied up to this date. It is a cactus-like plant that grows readily in hot, dry climates and The peripheral bundle sheath cells of AV produce an intensely bitter, yellow latex, commonly termed aloe juice, or sap, or aloes. AV sap and AV gel are often confused. Unlike aloes, AV gel contains no anthraquinones, which are responsible for its strong laxative effects.[13] The content of polysaccharides in Aloe plants may vary due to differing climatic conditions, different varieties or perhaps most crucially, different gel preparation techniques. For the gel preparation this also encompass the incorporation of other natural polysaccharides which preserve the integrity of AV polysaccharide during storage. At any rate, Aloe products have been shown to contain widely varying levels of polysaccharides.

Several published trials done by Syed et al in 1996 and Paulsen et al in 2005 compared aloe vera and placebo for resolution of psoriatic plaques. These studies illustrated equivocal and unfavorable efficacy respectively.[14,15] In 2009, a published report by Choonhakarn et. al compared the superiority of AV cream versus triamcinolone cream for treatment of psoriasis.[16] Despite varying results in previously conducted researches, this study was undertaken to verify clinical efficacy of aloe vera in terms of resolving plaques of psoriasis without the adverse events expected from using topical agents such as corticosteroids.

II. MATERIALS AND METHODS

Study design and patient selection

This is a randomized, double blind controlled clinical trial consisting of safety and efficacy testing conducted at East Avenue Medical Center (Quezon City, Philippines) conducted between October 2012 to August 2013. A non-inferiority framework was used to evaluate the comparability of the therapeutic modalities in terms of efficacy.

Inclusion criteria included male or female patients with plaque type psoriasis with less than 25% body surface area of involvement or Psoriasis Area Severity Index (PASI) less than 32, aged 18-65 years old without any systemic disease, no intake of any oral maintenance medication and did not undergo phototherapy. A washout period of one week is necessary for patients applying other topical medications.

This study was approved by the ethics committee under the supervision of the Chair of the Institutional Ethics and Review Board of the East Avenue Medical Center and was conducted in accordance with the ethical standards set by the Helsinki

Materials

The standard drug clobetasol propionate 0.05% ointment was obtained from licensed pharmaceutical company. Authenticated leaves of Aloe barbadensis was soaked in 70% ethyl alcohol, distilled to extract varying concentrations (15%, 20%, 25% and 50%) and were finally incorporated in the final ointment base. The aloe vera extract and standard drug were compounded to attain the same odor, color, texture and consistency. and was packaged into uniform 50-gram white plastic tubes.

Study Procedure

Part I: Safety Evaluation

Subjects ages 18-65 years of age, male or female, with an essentially normal physical and cutaneous findings were recruited for irritancy patch testing. Those with history of atopy and other dermatologic diseases, with previous use of oral and topical steroids, oral antihistamines or immunosuppressive drugs for the past 2 weeks were excluded. Written informed consent from all volunteers was obtained

The varying concentrations of aloe vera extract were placed onto individual IQ Ultra Square chambers and were placed at the upper back of volunteers, secured and left on for 2 days. The patients were assessed on the 48th and the 72nd hour. The reactions were recorded in accordance to the International Contact Dermatitis Research Group Scoring. Homogenous erythema on the 48th hour, which did not persist on the 72nd hour was read as Irritant Contact Dermatitis (ICD).

Part II: Clinical Trial

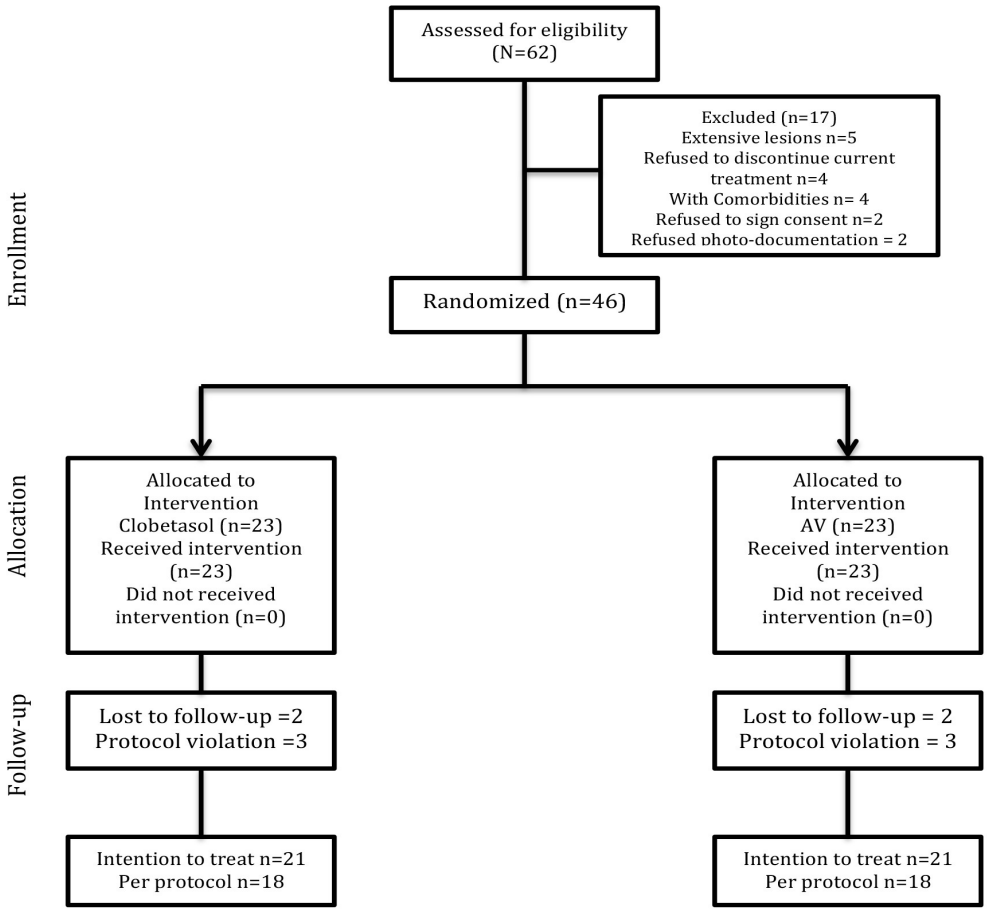
On initial consult, patient underwent extensive history taking of baseline characteristics, detailed physical examination including PASI score determination, photo-documentation and patients were instructed to answer the Psoriasis Disability Index (PDI) at the beginning and end of treatment. Another party guaranteed randomization of clinical trial materials using simple table of random numbers. Patients were instructed to apply the medication over affected areas, twice daily after bathing for 4 consecutive weeks with bimonthly follow-up with strict avoidance of normal skin. On every follow-up PASI determination and photo-documentation were performed.

Outcome Measures

The primary outcome measure was the mean change in PASI score from baseline, week 2 and week 4 of treatment and the change in the Psoriasis disability (PDI) score of patients from baseline to the week 4 of treatment. The secondary outcome was the presence or absence of adverse events.

Statistical analysis

Descriptive analysis was done to illustrate the results of the safety evaluation as well as the reporting of adverse events. For the clinical trial, the improvement differences in PASI and PDI score assessments between groups were analyzed using an independent T-test both for the intent-to-treat (ITT) and per protocol (PP) analysis. The difference between treatment groups were estimated at 95% confidence interval. Furthermore, an intent-to-treat analysis was performed to account for protocol violations and carried forward the recorded data accordingly.



III. RESULTS

Safety Evaluation

Ten healthy volunteers (5 male, 5 female) ages 25-60 years old, were included in the safety evaluation. Results showed that there were three volunteers, one male and two females, who showed doubtful reaction on the 48th hour with the 50% AV extract which when further monitored on the 72nd hour returned negative; this is labeled as ICD. The rest of the other concentrations returned negative results. The concentration utilized for the clinical trial was the next lower dose that is 25% AV extract.

Clinical Trial

Study Patients

Sixty-two patients were assessed for eligibility to join the trial of which only 43 qualified for enrollment (See Figure 2). Twenty-three patients enrollment (See Figure 2). Twenty-three patients (19 males, 17 females) were randomized between the two treatment groups. Four patients were lost to follow-up (50% from AV group, 50% from Clobetasol group), 6 had protocol violations (50% from AV group, 50% from Clobetasol group) see figure 1. Protocol violations consisted of undergoing elective surgery, taking systemic medication, application of other concomitant topical medication, abrupt cessation of topical application.

Intent to treat population showed 21 patients per treatment arm (n=42) while the per protocol population analysis showed 18 patients per treatment arm (n=36). Baseline demographics and disease parameters are presented in Table 1. Both groups had similar baseline characteristics with the exception of a higher PASI and PDI scores in the AV group. In addition, patients from both groups utilized mainly topical treatment, while some utilized combination of all three regimen.

Table 1. Baseline demographics and disease parameters

	AV n=21	**Clobetasol n=21**
Age (years)		
Mean±SD	40.8 ± 14.6	37.9 ± 11.0
Range	18-63	18-60
Gender, n (%)		
Male	9 (43%)	11 (52%)
Female	12 (57%)	10 (48%)
Previous		
Topical only	21	21
Phototherapy	2	1
Systemic	4	5
Baseline Scores		
PASI	15.6 ± 6.8	10.8 ± 5.2
PDI	16.0 ± 8.3	11.8 ± 10.4

Per protocol analysis of the psoriasis disability index showed that the AV group had a mean PDI score of 16.0 + 8.3 at baseline that decreased to 8.9 + 6.38 at week 4. On the other hand, the clobetasol group showed a mean of 11.8 + 10.44 at baseline, which showed an absolute mean decrease to 6.6 + 5.73 at the end of treatment. The between group difference in adjusted means was 6.18 + 8.84 (CI: 3.25-9.10, P:0.5136) showing no statistical difference at the end of treatment. See table 2.

The results further showed that marked (PASI 75) and moderate responses (PASI 50) were attained by both treatment groups, while the slight response (PASI<50) was dominated by the clobetasol group. It is noteworthy to mention that one patient

7. Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, et. al. Guidelines of care for the management of psoriasis and psoriatic arthritis Section 3. Guideline of care for the management and treatment of psoriasis with topical therapies. J of Am Ac Dermatol. 2009 Apr;60(4):643-59.
8. Morimoto S, Kumahara Y. A patient with psoriasis cured by 1-alpha-hydroxyvitamin D3. Med J Osaka Univ 1985 Mar;35(3-4):51-4.
9. Weinstein GD, Koo JY, Krueger GG, Lebwohl MG, Lowe NJ, Menter MA, et al. Tazarotene cream in the treatment of psoriasis: two multi-center, double blind, randomized, vehicle-controlled studies of the safety and efficacy of tazarotene cream 0.05% and 0.1% applied once daily for 12 weeks. J Am Acad Dermatol 2003 May;48(5):760-7.
10. Ring J., Baker J., Behrendt L et. al. Review of the photo-carcinogenicity of topical calcineurin inhibitors: position statement of the European Dermatology Forum. J Eur Acad Dermatol Venereol. 2005 Nov;19 (6):663-71.
11. McGill A., Frank A., Emmet N., et. al. The antipsoriatic drug anthralin accumulates in keratinocyte mitochondria, dissipates mitochondrial membrane potential and induces apoptosis through a pathway dependent on respiratory component mitochondria. FASEB J. 2005 Jun;19(8):1012-4
12. Klein AD, Penneys NS. Aloe vera. J Am Acad Dermatol. 1988 Apr;18(4 PT1):714-20.
13. Vogler BK, Ernst E. Aloe vera: a systematic review of its clinical effectiveness. Br J Gen Pract. 1999 Oct;49 (447):823-8.
14. Syed TA, Ahmad SA, Holt AH, Ahmad SA, Ahmad SH and Afzal M. Management of psoriasis with AV extract in a hydrophilic cream: A placebo-controlled, double blind study. Tropical Med and Intl Health. 1996 Aug;1(4):505-509.
15. Paulsen E, Korsholm L, Brandrup F. A double-blind, placebo-controlled study of a commercial Aloe vera gel in the treatment of slight to moderate psoriasis vulgaris. J Eur Acad Dermatol Venereol. 2005 May;19 (3):326-31.
16. Choonhakarn C., Busaracome P., Sripanidkulchai B., Sarakarn P. A prospective randomized clinical trial comparing topical AV with 0.1% triamcinolone acetonide in mild to moderate plaque psoriasis. J Eur Aca Dermatol Venereol 2010;24,168-172.
17. Langmead L, Makins RJ, Rampton DS. Anti-inflammatory effects of AV gel in human colorectal mucosa in vitro. Aliment. Pharmacol Ther 2004 Mar;19(5):521-7.
18. Vasquez B, Avila G, Segura D, Escalante B. Antiinflammatory activity of extracts from AV gel. J Ethnopharmacol 1996 Dec;55(1):69-75.
19. Yildrim M, Inaloz HS, Baysal , Delibas N. The role of oxidants and antioxidants in psoriasis. J of Eur Ac of Dermatol and Ven. 2003: 17, 34-36.
20. Polkanov VS, Bochkarev IM, Shmeleva LT, Kipper SN. Lipid peroxidation and the blood antioxidant activity in psoriasis. Vestn Dermatol Venereol. 1987;7: 42-46.
21. Therond P, Gerbaud P, Dimon S. Antioxidant enzymes in psoriatic fibroblasts and erythrocytes. J Invest Dermatol.1996;106: 1325–1328.
22. Dal 'Belo SE, Gaspar LR, Maia Campos PM. Moisturizing effect of cosmetic formulations containing AV extract in difference concentrations assessed by skin bioengineering technique. Skin Res. Technol 2006 Nov;12(4):241-6.

Knowledge, Attitude and Practices on Smoking Cessation Among Physicians in Makati Medical Center

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ABSTRACT

BACKGROUND: Despite major efforts through ordinances and government policies against tobacco use, cessation promotion remain to be a challenge and risk of relapse remain high. The World Health Organization (WHO) has recommended that tobacco-smoking surveys be conducted among health professionals to determine how their smoking knowledge and attitude affect their role as models and educators for patient smokers.

OBJECTIVE: To describe and correlate the knowledge, attitudes, and practices on smoking cessation of physicians at the Makati Medical Center

Study Design: Descriptive; cross-sectional study

Methods: A single center, hospital based, survey was conducted among randomly selected 339 physician in Makati Medical Center for the year 2014.All selected participants were sent a copy of a 47- item self-administered modified WHO Global Health Professional Survey (GHPS).

Result: There were 110 respondents out of 339 physicians, giving a response rate of 32.4%. There were more never smokers (70 of 110, 63.6%) than there were ever smokers (40 of 110, 36.4%). 13 out of 40 ever smokers reported to be current smokers while 24 were previous smokers. Less than half of the physician respondents have heard of, read, or are familiar with the smoking cessation guidelines. All physicians agreed that smoking is harmful to health. All physicians have positive attitude regarding smoking cessation. Ever smokers tend to be less active in providing smoking cessation practices compared to never smokers.

Conclusion: The physicians in Makati Medical Center were noted to have good knowledge and attitude regarding smoking cessation, regardless of smoking status; Smokers tend to educate less than nonsmokers. Never smokers tend to have a better practice regarding smoking cessation compared to ever smokers. Majority stated that lack of time and training are the common barriers they encounter in their practice. Majority expressed interest in updating their knowledge.

Keywords: Smoking Cessation Practices, Knowledge, Attitude, Practices, Physicians, tertiary hospital

INTRODUCTION

Smoking has long been proven to be an important modifiable risk factor of numerous diseases such as cancers, vascular and lung diseases. Tobacco kills six million people each year. Of these, more than five million die due to direct tobacco use, while 600,000 die as a result of nonsmokers being exposed to second-hand smoke. Tobacco use is projected to cause approximately 450 million deaths in the next 50 years.[1] According to the estimation of the World Health Organization (WHO), there are about 1.3 billion smokers worldwide including one billion men (47% of the world's male population) and 250 million women (12% of the world's female population). In the US, 3.3% of physicians and 21% of the general population are smokers, while in China it is 23% and 34% respectively. [2,3]The death toll from tobacco consumption is now five million people a year. WHO also estimates that by 2030, if present consumption patterns continue, the number of deaths will nearly double, reaching close to 10 million annually with approximately 70% of the deaths occurring in developing countries.

Its global burden on health and environment led to policies by the WHO and member states. The WHO came up with the Tobacco Free Initiative, joined by 168 countries aiming to control tobacco use. The WHO – Western Pacific Regional Office (WHO-WPRO) and the Southeast Asia Tobacco Control Alliance (SEATCA) called to increase taxes on tobacco products thereby decreasing its demand. The Philippine College of Chest Physicians created the Advocacy Committee on Tobacco Control in 2008 to increase public health literacy on tobacco use as a medical condition and patient empowerment. Different guidelines in smoking cessation/intervention have been made in different countries- National Institute for health and Clinical Excellence Smoking Cessation Services in UK (NICE), The Royal Australian College of General Practitioners, the United states' CDC. In the local setting, the Philippine College of Chest Physicians (PCCP) Council on Tobacco or Health & Air Pollution also recently came up with a Brief Tobacco Intervention Program.

Despite major efforts through ordinances and government policies against tobacco use, cessation promotion remain to be a challenge and risk of relapse remain high. Health professionals, especially physicians play a very important role in reducing this problem. Physicians are in a unique position to spot smokers and initiate smoking cessation counseling because they are able to integrate the various aspects of nicotine dependence and its bad effects. Even healthcare professionals who smoke find it difficult to quit. Nonsmoker physicians identified lack of willpower and interest as barriers to quitting while smoking physicians saw stress as a barrier. Smoking physicians are less likely to initiate cessation interventions.[4]Smoking is a significant threat to health and physicians have an important role to fulfill in its cessation.

Health professionals have a very significant role in helping smokers quit. Although a lot of smokers would quit on their own, some would benefit from physician's advice. Simple advice has small effect on cessation rates. According to a study (Cochrane Tobacco Addiction Group), assuming an unassisted quit rate of 2 to 3%, a brief advice intervention can increase quitting by a further 1 to 3%.

There have been numerous studies on smoking cessation, smoking interventions, as well as epidemiological data stating the harmful effects of smoking, yet it remains to be a tough problem to eradicate. There are similar studies in the region of Southeast Asia, but there is paucity of data in the Philippines regarding smoking cessation practices. The researcher found it relevant to conduct a baseline survey on the knowledge, attitude of physicians in Makati Medical Center. A KAP study measures the knowledge, attitude and practices of a community measuring the extent of smoking as a medical problem of both physicians and patients. This study will be of significant help in evaluating the effectiveness of the intervention and identifying the weakness and limitations encountered in the local setting of physicians regarding smoking cessation practices and why tobacco addiction remains to be a very difficult problem to eradicate. It is in analyzing the situation that we can come up with improvements in our smoking cessation program in the future.

Research Hypothesis

Physicians in Makati Medical Center have good knowledge, attitude and practice on smoking cessation.

OBJECTIVES

General Objective:

To describe and correlate the knowledge, attitudes, and practices on smoking cessation of physicians at the Makati Medical Center

Specific objectives:

1. To evaluate the knowledge and training of physicians on smoking cessation policies and treatment modalities based on WHO, CDC, and Philippine College of Chest Physicians guidelines
2. To measure the proportion of smokers among physicians and correlate the attitudes on smoking cessation practices between smokers and non-smokers
3. To describe the practices and barriers encountered by MMC physicians in providing smoking cessation counseling to patients

Methodology

Study design: Descriptive; cross-sectional study

Study population:

A single center, hospital based, cross-sectional survey was conducted among physician consultants, fellows, and residents working in Makati Medical Center for the year 2014.

Sample size estimation:

Based on the Slovin's formula, the sample size for a population of 945 physicians is 282 respondents. The respondents were 189 consultants, 15 fellows, 78 residents. This sample size is set at a 5% margin of error at a 95% confidence interval. To account for a non-response rate of approximately 20%, 227 consultants, 18 fellows, and 94 residents (339 in total) were recruited to the study.

Plan of randomization and recruitment:

An alphabetical list of consultants, fellows, and residents across the different departments was obtained, and numbered accordingly. Stratified random sampling was employed according to work status (consultant, fellow, resident). A random number generator was used to determine which doctors will be included in the survey.

Once the list of doctors was generated, questionnaires were distributed to doctors' clinics or personally given by the principal investigator to the selected subjects. Informed consent forms were attached to the survey forms. The principal investigator was responsible in obtaining the consent.

Questionnaire:

A 47- item modified self administered questionnaire was used based on the World Health Organization Global Health Professional Survey (GHPS) modified by the Queen's University Family Medicine Development Program in the Balkans Region KAP questionnaire and Deluchi (S-KAP Instrument).[6,7] (See Appendix A)

All valid data from respondents with complete response to the surveys were included in the analysis. Missing values were not replaced or estimated during analysis.

These statistical tests were measured at a 0.05 α-level of significance under a 2-tailed test. Statistical Packages for Social Sciences or SPSS version 20.0 was used for analysis.

Results

General characteristics of 110 physician respondents

There were 110 respondents out of 339 who were given survey forms, giving a response rate of 32.4% after a waiting time of three weeks. The

respondents were compared and divided into 2 groups: Ever Smokers- include the current and occasional smokers as well as those who quit; Never smokers-include those who never smoked.

There were **more never smokers** (70 of 110, 63.6%) than there were ever smokers (40 of 110, 36.4%). Compared to never smokers, the ever smokers had a **higher proportion of females** (p = 0.002) and reported to see more outpatients per week (p = 0.027) compared to the never smokers (Table 1). Age, specialty, level of training were similar in the two groups.

TABLE 1. General characteristics of the 110 physician respondents

	Ever Smokers N = 40	Never Smokers N = 70	P-value
	Frequency (%), Mean ± SD		
Age	40.24 ± 12.20	38.23 ± 12.82	0.425
Gender			
Male	16 (40)	51 (72.9)	**0.002**
Female	23 (60)	19 (27.1)	
Specialty			
Internal Medicine	13 (32.5)	34 (48.6)	0.089
Pediatrics	1 (2.5)	4 (5.7)	
Psychiatry	0 (0)	4 (5.7)	
Surgery	5 (12.5)	3 (4.3)	
Others	20 (50.0)	25 (35.7)	
Current level of training			
Consultant	18 (45)	29 (41.4)	0.588
Fellow	3 (7.5)	10 (14.3)	
Resident	18 (45)	31 (44.3)	
Patients per outpatient basis every week			
Less than 10 patients	1 (2.5)	15 (21)	**0.027**
10-20 patients per week	12 (30)	19 (27.1)	
More than 20	26 (65)	36 (51.4)	

Smoking characteristics of current and previous smokers

Of the 40 ever-smoker physician respondents, **13 reported to be current smokers** while 24 were previous smokers. Three respondents did not specify whether they were currently or previously smoking.Among the physicians who were currently smoking, they started to smoke at a mean age of 19.46 years old, smokes an average of 5.77 cigarettes a day. Only 28.2% of the current smokers had managed to stop smoking for at least one week (Table 2).

When asked about their feelings of quitting, **8 out of 13 current smokers** (61%) are not ready to quit within the next 6 months; **3 out the 13 current smokers** (23%) think of quitting within the next 6 months; and **2 (15%)** are ready to quit during the time of survey.

TABLE 2. Smoking profile of current smokers (n = 13)	
Age initiated smoking on a regular basis	19.46 ± 4.70
Number of cigarettes smoked per day	5.77 ± 3.79
Has stopped smoking for at least one week	11 (84.6)

Previous smokers (n = 24) reported to have begun smoking at **18 years old,** and stopped at a mean age of **31 years old**. There were more respondents who smoked daily (62.5%) rather than occasionally (37.5%).

TABLE 3. Smoking profile of previous smokers (n = 24)	
	Frequency (%), Mean **± SD**
Smoked daily	15 (62.5)
Smoked occasionally	9 (37.5)
Age initiated smoking	18.04 ± 4.32
Age stopped smoking	31.17 ± 8.94

Awareness on smoking cessation guidelines

Less than half of the physician respondents have heard of, read, or are familiar with the smoking cessation guidelines of the Philippine College of Chest Physicians, World Health Organization, or Center for Disease Control. A significantly greater proportion of ever smokers have read the guidelines compared to never smokers (27.5% vs 10% p = 0.017)

TABLE 4. Awareness on smoking cessation guidelines			
	Ever smokers N = 40	**Never smokers N = 70**	**P-value**
	Frequency (%)		
Heard of the guidelines	11 (27.5)	33 (47.1)	**0.047**
Read the guidelines	11 (27.5)	7 (10)	**0.017**
Familiar with the content of the guidelines	3 (7.5)	10 (14.3)	0.368

Attitudes towards smoking and smoking cessation

Both ever and never smokers consistently *strongly* agreed that smoking is harmful to health, that hospitals should be smoke-free, and that smoking should be prohibited in enclosed public places.

TABLE 5a. Attitudes towards smoking in general			
	Ever smokers N = 40	**Never Smokers N = 70**	**P-value**
	Median (Range)		
Smoking is harmful to your health.	1 (1-2)	1 (1-2)	0.324
Hospitals and health care centres should be "smoke-free".	1 (1-4)	1 (1-4)	0.181
Smoking in enclosed public places should be prohibited.	1 (1-3)	1 (1-2)	0.140

Scores range from 1 – Strongly agree to 5 – Strongly disagree

For questions on passive smoking, physicians generally agreed that maternal smoking during pregnancy increased the risk of SIDS. However, the smokers tended to answer *agree* to passive smoking to be associated to neonatal death or lower respiratory tract illnesses, while never smokers replied *strongly agree*.

TABLE 5b. Attitudes towards passive smoking			
	Ever smokers N = 40	**Never smokers N = 70**	**P-value**
	Median (Range)		
Neonatal death is associated with passive smoking.	2 (1-3)	1 (1-4)	0.294
Maternal smoking during pregnancy increases the risk of Sudden Infant Death Syndrome	1 (1-4)	1 (1-4)	0.184
Paternal smoking increases the risk of lower respiratory tract illnesses such as pneumonia in exposed children.	2 (1-4)	1 (1-3)	0.380

Scores range from 1 – Strongly agree to 5 – Strongly disagree

Compared to never smokers, ever smokers agreed to a lesser degree that smoking health professionals are less likely to advise people to stop smoking, that they should serve as role models or set a good example by not smoking (Table 5c).

TABLE 5c. Attitudes towards the role of health professionals in smoking cessation

	Ever smokers N = 40	Never smokers N = 70	P-value
	Median (Range)		
Health professionals who smoke are less likely to advise people to stop smoking.	2.5 (1-5)	2 (1-5)	**0.018**
Health professionals should get specific training on cessation techniques.	2 (1-4)	2 (1-3)	0.156
Health professionals should speak to community groups about smoking.	2 (1-3)	2 (1-4)	0.180
Health professionals should routinely advise patients who smoke to avoid smoking around children.	1 (1-3)	1 (1-3)	0.214
Health professionals serve as role models for their patients and the public.	1 (1-4)	1 (1-3)	**0.021**
Health professionals should set a good example by not smoking.	1 (1-4)	1 (1-3)	**0.033**
Health professionals should routinely ask about their patients smoking habits.	1 (1-5)	1 (1-2)	0.119
Heath professionals should routinely advise their smoking patients to quit smoking.	1 (1-3)	1 (1-2)	0.378
Patient's chances of quitting smoking are increased if a health professional advises him or her to quit.	2 (1-4)	1 (1-4)	0.054

Scores range from 1 – Strongly agree to 5 – Strongly disagree

Both ever and never smokers strongly agreed on the ban of cigarette smoking promotion, and to impose barriers to access, e.g. increase in prices.

TABLE 5d. Attitudes towards the sales and promotion of tobacco use

	Ever smokers N = 40	Never smokers N = 70	P-value
	Median (Range)		
Health warnings on cigarette packages should be in big print.	1 (1-4)	1 (1-2)	0.524
Tobacco sales to children and adolescents should be banned.	1 (1-2)	1 (1-2)	0.633
Sport sponsorships by tobacco industry should be banned.	1 (1-4)	1 (1-4)	0.461
There should be a complete ban on the advertising of tobacco products.	1 (1-5)	1 (1-4)	0.996
The price of tobacco products should be increased sharply.	1 (1-5)	1 (1-4)	0.389

Scores range from 1 – Strongly agree to 5 – Strongly disagree

Practices relating to smoking cessation of the 110 physician respondents

Most of the respondents practiced in urban settings, where smoke-free policies were implemented. However, about a quarter of the respondents did not know whether any such policy was in place.

Nearly half (44%) of the never smokers reported to provide self-help materials from their workplace for smoking cessation, which was significantly greater than the 30% of ever smokers who did the same. Similarly, 55% of the never smokers reported to provide counseling, versus the 22.5% of ever smokers who reported to do so as well.

Another notable finding was that almost half of the ever smokers did not know of medications available in their work practice locations for smoking cessation (45.6% vs 18%, p = 0.008).

Half of the respondents in both groups perceived themselves to be *somewhat* prepared to counsel patients on smoking cessation. Less than 20% of the respondents had any form of training for smoking cessation counseling.

TABLE 6. Smoking cessation practices by the 110 physician respondents

PRACTICE	Ever smokers N = 40	Never smokers N = 70	P-value
		Frequency (%)	
Workplace/practice located			
Urban	38 (95)	67 (95.7)	
Rural	1 (2.5)	2 (2.9)	0.917
Both	1 (2.5)	1 (1.4)	
A smoke-free policy is in place at workplace			
Yes	29 (72.5)	48 (68.6)	
No	2 (5)	3 (4.3)	0.861
Don't know	9 (22.5)	19 (27.1)	
Interventions available to help patients stop smoking			
Traditional remedies			
Yes	9 (22.5)	20 (28.6)	
No	12 (30)	31 (44.2)	0.094
Don't know	19 (47.5)	19 (27.1)	
Self- help materials			
Yes	12 (30)	31 (44.3)	
No	11 (27.5)	30 (42.9)	**0.002**
Don't know	17 (42.5)	9 (12.9)	
Counselling			
Yes	9 (22.5)	39 (55.7)	
No	12 (30)	19 (27.1)	**0.001**
Don't know	19 (47.5)	12 (17.1)	
Medication			
Yes	12 (30)	24 (34.3)	
No	10 (25)	33 (47.1)	**0.008**
Don't know	18 (45)	13 (18.6)	

Do you give patients advice regarding smoking cessation			
Always	8 (20)	19 (27.1)	
Very often	8 (20)	25 (35.7)	0.169
Often	11 (27.5)	11 (15.7)	
Occasionally	11 (27.5)	14 (20)	
Interventions used to help patients stop smoking			
Traditional remedies			
Yes	17 (42.5)	26 (387.1)	
No	23 (57.5)	44 (62.9)	0.580
Don't know	0 (0)	0 (0)	
Self- help materials	10 (25.5)	25 (35.7)	0.291
Counselling			
Yes	26 (65)	57 (81.4)	
No	14 (35)	13 (18.6)	0.054
Don't know	0 (0)	0 (0)	
Medication	8 (20)	14 (20)	0.805
How well prepared do you feel you are when counselling patients on how to stop cigarette smoking			
Very well prepared	10 (25)	12 (17.2)	
Somewhat prepared	20 (50)	40 (57.1)	0.598
Not at all prepared	10 (25)	18 (25.7)	
Received any formal training in smoking cessation approaches to use with patients			
Formal training during medical or nursing school	3 (7.5)	9 (12.9)	0.530
Formal training during specialization programs	2 (5)	8 (11.4)	0.322
Special conferences, symposia or workshops	8 (20)	13 (18.6)	1.000

Ever and never smokers report to spend approximately two to three minutes on counseling patients on smoking cessation. However, **more never smokers** report to be interested in updating smoking cessation skills compared to ever smokers. **Eighty-five (77%)** of the respondents stated that they are interested to update their smoking cessation counseling skills.

	Ever Smokers N = 40	**Never Smokers N = 70**	**P-value**
Minutes spent on smoking cessation counseling	2 (1-3)	3 (1-4)	0.095
Interested in updating smoking cessation counseling skills	25 (62.5)	60 (85.7)	**0.009**

For the open-response item on barriers to offering smoking cessation counseling to patients, there were nine common replies (Table 7).

Table 7. Most commonly cited barriers to offer smoking cessation counseling

	Frequency (%)
Lack of time	23 (20.9)
Education/training of physician	17 (15.5)
Patient's compliance	15 (13.6)
Competency to counsel	13 (11.8)
Lack of counselling materials/resources	11 (10)
Perceive that it is an invasion of the patient's privacy	4 (3.6)
Doctors' compliance	3 (2.7)
Lack of support (i.e. hospital, community, society)	3 (2.7)
Nicotine dependence	2 (1.8)

Discussion and Conclusion:

Overall, **28.3%** (17.3 million) of the Philippine population aged 15 years old and over in the Philippines currently smoke tobacco; 47.7 %(14.6 million) are men, and 9.0% (2.8 million) are women. In this study, the prevalence of current smokers among our physician respondents (**18%**) is lower than the general population but notably with predominance of females.[16]This study is similar to a local survey among cardiologists and pulmonologists at a local government hospital stating that prevalence of smoking in physicians are less compared to the general population, hence physicians are less likely to smoke.[17]

The physicians in Makati Medical Center undeniably have good knowledge, favorable attitude regarding smoking cessation. Of the 110 physician respondents, all agreed regarding the harmful effects of passive and active smoking. Majority have positive attitude on smoking cessation practices. Some Ever Smokers seem to be defensive and agree at a lesser degree that health professionals who smoke are less likely to initiate advise to stop smoking. More never smokers reported that they initiate counseling compared to ever smokers; therefore, physician smokers seem to educate less compare to nonsmokers.

Half of the respondents feel that they are only somewhat prepared to offer smoking cessation counseling. In fact, only less than 20% claims to have any formal training aside from medical school.

Barriers Encountered

The most common reason that limit intervention encountered by the respondents was lack of time, formal training and materials.

Thirteen percent of physician respondents feel that they lack competency to initiate counseling. For the patient part, 13% believe that patient compliance is a factor. Others mentioned nicotine dependence and lack of support from the community regarding smoking. In a local study done in a government hospital, they have identified principal reasons for difficulty quitting in the general population are social and environmental goads, particularly in the workplace, and associative processes. [18]

Only half of all smokers seeing a primary care physician report being asked about their smoking (Robinson et al, 1995), and only minority of smokers are being advised to quit (CDC, 1993).

In the US, the National Cancer Institute projects that if physicians assisted even 10% of their patient smokers, tobacco users in the US would drop by an additional 2 million people annually (Fiore et al, 1990). Physicians do make a difference in the battle against smoking.

Smoking cessation involves multiple specialties and includes a behavioral approach.Structured counseling is effective in smoking cessation rates according to a local study. The effectiveness of counseling may be influenced by the subject's intention to quit and the number of sticks consumed per day at baseline.[19]

In conclusion, physicians in Makati Medical Center have good knowledge and attitude regarding smoking cessation; however, there is problem translating these into practice due to the mentioned barriers and smoking status of physicians.

Limitation of the Study and Recommendations

The study is limited by the poor response rate; therefore, it may not represent accurately the population being studied. More than half of survey forms distributed was not returned. Ten consultants declined to participate, the others were either on leave or busy at the time the survey was conducted. A higher response rate would give more accurate results. A personal interview would probably yield a more favorable result compared to self-administered survey; however, this will need more time, investigators and manpower. On the other hand, a longer survey period and more careful form retrieval should be done for future studies. New surveys are also being followed in other institutions-to compare different populations of physicians.

This study identifies the need for additional training of doctors. The Philippine College of Chest Physicians have come up with the Brief Tobacco Intervention Skills Certification Program to train health professionals, educators and lay community members interested in offering basic services to help tobacco user quit.[18]

REFERENCES

1. Peto et al. Future worldwide health effects of current smoking patterns. In: Koop CD, Pearson C, Schwarz MR, eds. Critical issues in global health. New York, NY: Jossey-Bass; 2001.
2. Nelson et al. Trends in Cigarette Smoking Among US Physicians and Nurses., JAMA 1994
3. Beyond the Cloud: Chinese smoking doctors: Lee, S.; J Thorac Dis 2011;3:211-212
4. Pipe A. Minto. Physician smoking status, attitudes toward smoking and cessation advice to patients: An International Survey. Prevention and Rehabilitation Center, University of Ottawa Heart Institute; Ontario, Canada; December 5, 2007
5. Tan et al, Smoking behavior and practices and smoking cessation in the general population and among Health-care Professionals in Metro Manila- MD.* *Phil. J. Internal Medicine, 47: 129-135, May-June, 2009*
6. Hodgetts et al Smoking behavior, knowledge and attitudes among Family Medicine Physicians and nurses in Bosnia and Herzegovina. BMC Family Practice 2004
7. Deluchi et al. Smoking Knowledge, Attitudes and Practices (S-KAP) Survey for Staff. Development of the Smoking Knowledge, Attitudes and Practices (S-KAP) Instrument. Journal of Drug Issues. 39; 347-364.
8. Stead et al. Behavioural Interventions as Adjuncts to Pharmacotherapy for Smoking Cessation
9. DOH Smoking Cessation Program
10. The Role of Health Professionals in Tobacco Control, WHO, 2005
11. The Royal Australian College of General Practitioners, Supporting Smoking Cessation-a guide to healthcare professionals
12. NICE smoking cessation services (UK)
13. Saleh et al. Investigation of Hong Kong Doctors' Current Knowledge, Beliefs, Attitudes, Confidence and Practices: Implications for the Treatment of Tobacco Dependency. Department of International Health, Boston University School of Public Health. Journal of Chinese Medicine Association 2006;69(10):461–471
14. Jiang et al. Chinese Physicians and Their Smoking Knowledge, Attitudes, and Practices. American Journal of Preventive Medicine 2007; 33(1):15–22)
15. Asid, Elham, The effect of physicians' smoking-related knowledge, attitude, and practices on their smoking-cessation counseling (in Zamboanga). April 2010
16. WHO 2009 Philippines Global Adult Tobacco Survey
17. Anonuevo et al. Knowledge, Attitude and Practices of Cardiologists and Pulmonologists on Smoking Cessation
18. Barbaza et al, Effectiveness of structured counseling in improving smoking cessation rate among regular employees of UP-PGH: A randomized controlled trial. Jan 2002
19. Philippine College of Chest Physicians (PCCP) Council on Tobacco or Health & Air Pollution- Brief Tobacco Intervention Module
20. Stead LF,Physician advice for smoking cessation (Review). The Cochrane Collaboration. 2008

APPENDIX A

Modified WHO Global Health Professional Survey
(Questions from Queen's University Family Medicine Development Program in the Balkans Region KAP questionnaire and Deluchi's S-KAP Instrument)

Date: _____ Hospital:_____
Form number: _____ 1. Private 2. Government

	Section 1: Demographics (Please encircle you answer)					
1	What is your gender? 1. Female 2. Male					
2	What is your age? Age _____					
3	What is your specialty? 1. Internal Medicine 2. Pediatrics 3 Psychiatry 4. Others (pls. specify)_____					
4	What is your current level of training? 1. Consultant 2. Fellow 3. Resident					
5	How many patients do you see per outpatient basis every week? 1. Less than 10 patients 2. 10-20 patients per week 3. More than 20					
	Section 2: Cigarette use					
6	Which of the following best describes your smoking behaviour? (Please circle your answer) 1. I have never smoked cigarettes Go to question 14 2. I have quit smoking Go to question 11 3. I currently smoke occasionally (Some days) Go to question 7 4. I currently smoke every day Go to question 7					
	If you CURRENTLY smoke					
7	How old were you when you first started to smoke on a regular basis ? Age ____					
8	On the days that you smoke, how many cigarettes do you smoke per day? (Give average number) # _____					
9	Have you ever stopped smoking for at least one week? 1. Yes 2. No					
10	Which of the following best describes how you feel about your smoking? 1. Not ready to quit within the next 6 months Go to 14 2. Thinking about quitting within 6 months Go to 14 3. Ready to quit NOW Go to 14					
	If you smoked in the PAST					
11	When you smoked in the past, how often did you smoke? 1. Daily (Every day) 2. Occasionally (Some days)					
12	How old were you when you first started to smoke on a regular basis? Age ____					
13	How old were you when you stopped smoking completely? Age ____					
	Section 3: Knowledge and attitudes					
14	Different Centers, both international and local, such as the **CDC, WHO, Philippine College of Chest Physicians** have issued guidelines for healthcare professionals for treating nicotine dependence. a) Have you heard of these guidelines? 1. Yes 2. No b) Have you read these guidelines? 1. Yes 2. No c) Are you familiar with the content of these guidelines? 1. Yes 2. No					
	Check appropriate box	*1. Stronglyagree*	*2. Agree*	*3. Unsure*	*4. Disagree*	*5. Strongly Disagree*
15	Smoking is harmful to your health.					
16	Neonatal death is associated with passive smoking.					
17	Maternal smoking during pregnancy increases the risk of Sudden Infant Death Syndrome.					
18	Passive smoking increases the risk of lung disease in non-smoking adults.					
19	Passive smoking increases the risk of heart disease in non-smoking adults.					
20	Paternal smoking increases the risk of lower respiratory tract illnesses such as pneumonia in exposed children.					
21	Health professionals who smoke are less likely to advise people to stop smoking.					

	Check appropriate box	*1. Stronglyagree*	*2. Agree*	*3. Unsure*	*4. Disagree*	*5. Strongly Disagree*
22	Health professionals should get specific training on cessation techniques.					
23	Health professionals should speak to community groups about smoking.					
24	Health professionals should routinely advise patients who smoke to avoid smoking around children.					
25	Health warnings on cigarette packages should be in big print.					
26	Tobacco sales to children and adolescents should be banned.					
27	Sport sponsorships by tobacco industry should be banned.					
28	There should be a complete ban on the advertising of tobacco products.					
29	Hospitals and health care centres should be "smoke-free".					
30	The price of tobacco products should be increased sharply.					
31	Health professionals serve as role models for their patients and the public.					
32	Health professionals should set a good example by not smoking.					
33	Patient's chances of quitting smoking are increased if a health professional advises him or her to quit.					
34	Health professionals should routinely ask about their patients smoking habits.					
35	Heath professionals should routinely advise their smoking patients to quit smoking.					
36	Smoking in enclosed public places should be prohibited.					
	Section 4: Worksite practice					
37	Where is your workplace/practice located? 1. Urban 2. Rural 3. Both					
38	What sort of smoke-free policy is in place at your workplace? 1. No smoking policy in place GO TO 39 2. Smoking rooms available GO TO 39 3. No smoking allowed at all on the premises GO TO 38					
39	Is the smoke-free policy enforced? 1. Yes: always 2. Yes: sometimes 3.No 4. Don't Know					
40	Are the following interventions AVAILABLE to YOU to help your patients stop smoking? a Traditional remedies? 1. Yes 2. No 3. Don't know b Self- help materials 1. Yes 2. No 3. Don't know c Counselling 1. Yes 2. No 3. Don't know d Medication (Nicotine gum, patch, buproprion) 1. Yes 2. No 3. Don't know e Other (specify) _____					
41	Do you give patients advice regarding smoking cessation? 1. Always 2. Very often 3. Often 4. Occasionally 5. Never (Why not? Eg. Lack of time) _____					
42	Which of the following interventions do you USE to help your patients stop smoking? a Traditional remedies? (cold turkey) 1. Yes 2. No b Self- help materials 1. Yes 2. No c Counselling 1. Yes 2. No d Medication (Nicotine gum, patch, buproprion) 1. Yes 2. No e Other (specify) _____					
43	How well prepared do you feel you are when counselling patients on how to stop cigarette smoking? 1. Very well prepared. 2. Somewhat prepared 3. Not at all prepared.					
44	Have you ever received any formal training in smoking cessation approaches to use with your patients ? a Formal training during medical or nursing school 1. Yes 2. No b Formal training during specialization programs 1. Yes 2. No c Special conferences, symposia or workshops 1. Yes 2. No d Other explain _____					
45	What do you think is the most common reason/barrier that limit capacity to offer smoking counselling? _____					
46	How many minutes do you spend discussing tobacco use, with patients who smoke, during a typical patient visit? 1. no time 2. 3 to 10 minutes 3. 1 - 3 minutes 4. more than 10 minutes					
47	Would you be interested in updating your smoking cessation counseling skills? 1. Yes 2. No					

Late-Onset Myasthenia Gravis in an Elderly Female After Thymectomy: A Case Report

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ABSTRACT

Late-onset myasthenia gravis is characterized with onset after 60 years of age and has a male predominance. Myasthenia gravis may develop after surgery on any thymic mass hence questions as to the role of thymectomy in individuals without myasthenia gravis symptoms have been raised and is still controversial. We now present a rare case of a 75 year old female who was initially asymptomatic but had incidental finding of a thymic mass on routine chest x-ray and subsequently had thymectomy done when she was 65 years old. Two months after thymectomy, she developed fluctuating generalized muscle weakness, diplopia and ptosis more pronounced in the afternoon. She was diagnosed to have myasthenia gravis confirmed by positive results on both repetitive nerve stimulation and Tensilon tests. She was maintained on Pyridostigmine and Prednisone as well which provided improvement of her symptoms. She remained stable until 7 years and 9 months after thymectomy when she again had fluctuating muscle weakness as well as ptosis and diplopia.

***Key Words**: Myasthenia gravis; Late-onset myasthenia gravis; Thymectomy; Post-thymectomy myasthenia gravis; elderly female*

INTRODUCTION

Myasthenia gravis (MG) is the most common primary disorder of neuromuscular transmission. It is an autoimmune disease characterized by autoantibodies against different components of the neuromuscular junction (NMJ), thereby eliciting muscle fatigability and weakness.[1,2] It is characterised clinically by fluctuating painless muscle weakness, which worsens with exercise and towards the end of the day, and improves with rest. Its clinical hallmark is the fluctuating pronounced weakness limited to the voluntary muscles. It is usually caused by antibodies to postsynaptic proteins, of which three have been identified: nicotinic acetylcholine receptor (AChR), muscle-specific tyrosine kinase (MuSK), and the low density lipoprotein receptor- related protein 4 (LRP4). Myasthenia gravis includes heterogeneous autoimmune diseases, with a postsynaptic defect of neuromuscular transmission as the common feature.

The annual incidence of MG is reported to range between 3 and 30 per million population, with the rates at the upper end of the range reported by prospective studies probably providing the most accurate estimates.[3] Prevalence of MG is reported to be approximately 200 per million population now,[4] compared with about 5 per million population between 1915 and 1934.

Myasthenia gravis can be classified as to onset of symptoms. Early-onset MG appears before the age of 50 and is characterized by female predominance (60-70%) whereas between the age of 50 and 60, there is no gender difference.[5] Late-onset MG appears after the age of 60 and this form is characterized by a clear male predominance.[6]

The thymus is thought to play an important pathogenic role in anti-AChR antibody positive MG, with thymic hyperplasia present on 65 percent of cases and thymoma in 10 percent of cases.[7] Furthermore, MG occurs in 30 percent of patients with a thymoma as a paraneoplastic phenomenon.[8] Studies have shown evidences implicating the thymus as the main site of autosensitisation with acetylcholine receptor in the presence of an inflammatory environment leading to induction and maintenance of the anti-acetylcholine receptor auto-immune response in MG.

Concerns regarding the need to perform thymectomy on patients noted to have a thymic mass whether a thymoma or thymus hyperplasia had been raised in recent years. Thymoma occurs in approximately 10% of patients with MG and, in turn, MG occurs in approximately one-third of patients with thymoma.[9] Few thymoma patients without myasthenia gravis (MG) have been observed to develop MG after total removal of the thymoma (postoperative MG). However, the cause of this is not yet known because of the rarity of postoperative MG patients. There has been little information regarding postoperative MG in the literature. It has been said in previous reports that the onset of MG after total thymoma removal occurs only in 1.5–28% of cases without MG.[10] Thymectomy is generally recommended for patients with thymoma. However, myasthenia gravis occasionally develops postoperatively in patients who have had thymoma despite no signs of myasthenia gravis before the surgery. Some studies have reported post-thymectomy myasthenia gravis (PTMG); however, its mechanism and risk factors remain unclear.

We now report a rare case of a late-onset myasthenia gravis in an elderly female after thymectomy admitted at our institution.

CASE PRESENTATION

This is a case of EDR, a 75 year old female who was admitted at our institution last March 23, 2014 due to drooping of eyelids. Patient was asymptomatic until 10 years prior to admission (at 65 years of age) she had routine chest x-ray done for screening for pulmonary tuberculosis which later revealed a suspicious mediastinal mass. Chest CT scan was subsequently done which revealed right mediastinal mass. Patient was asymptomatic, had regular surveillance of chest CT scan which did not show any changes until 8 years prior to admission, on regular follow up chest CT, there was an increased in size of the mediastinal mass. She then had thymectomy done (March 2006) and was discharged with no complications with biopsy results showing a benign thymic hyperplasia. Seven years 10 months prior to admission (May 2006), 2 months post-thymectomy, she noted to have fluctuating generalized muscle weakness, more in the afternoon, associated with

diplopia and ptosis. Consult was done due to persistence of symptoms. Tensilon test as well as repetitive nerve stimulation test both showed positive results. She was managed as Myasthenia Gravis and given Pyridostigmine and Prednisone of unrecalled dosage. Patient noted improvement of symptoms, medications subsequently tapered off and Prednisone discontinued 6 years after onset of myasthenia gravis. Seven years and 6 months post-thymectomy, patient then noted saliva to be thick and had difficulty in swallowing it. She was then advised to discontinue Pyridostigmine by her attending physician. She remained stable with no symptoms until 7 years and 9 months after thymectomy, she again had recurrence of fluctuating weakness in the afternoon as well as ptosis and diplopia. Patient again took Pyridostigmine 60mg four times a day. There was still progression of symptoms despite intake of Pyridostigmine hence consult at our institution and subsequent admission. Pertinent neurologic examination during admission showed (+) ptosis of both eyes, right more than left; (+) lid lag after one minute and (+) fatigable muscles on repetitive movements as well as weakness of proximal muscles of both upper and lower extremities. Patient was admitted at a regular room and observed for difficulty of breathing and motor weakness. She was started on Mycophenolate Mofetil 500mg twice a day, Prednisone 60mg once a day, Pyridostigmine 60mg every 4 hours. She then had difficulty of breathing, dysphagia and increased motor weakness on the 5th hospital day hence intubated and transferred to the ICU due to myasthenic crisis. She had 3 cycles of plasmapheresis done wherein improvement of symptoms were noted after each cycle. She was worked up on a possible recurrence of mediastinal mass wherein a high resolution chest CT scan (Figures 1 and 2) done showed patchy pneumonia, bilateral anterior and posterior upper lobes, no evidence of recurrent anterior or superior mediastinal mass; no mediastinal, hilar or axillary lymphadenopathy; no sign of pulmonary mass or metastasis. No improvement of motor strength was noted. Patient was subsequently transferred out of the ICU after 9 days. Prednisone was then tapered down to 50mg once a day, Pyridostigmine decreased to 60mg three times a day, Mycophenolate Mofetil maintained on 500mg twice a day. She continued to improved, was weaned off the mechanical ventilator and extubated subsequently. Motor strength also improved, and was noted to be able to stand and walk with assistance. She was discharged improved on the 19th hospital day with Mycophenolate Mofetil 500mg twice a day, Pyridostigmine 60mg three times a day and tapering dose of Prednisone starting at 45mg once a day. Subsequent follow-ups were done 2 months after discharge, noted to have slight weakness of the quadriceps and deltoid muscles with lid lag after prolonged upward gaze. Prednisone was tapered off, Pyridostigmine three times a day. Recent follow up showed less fatigable muscle strength, no lid lag and was able to do squats. Pyridostigmine was now discontinued and was maintained only on Mycophenolate 500mg three times a day.

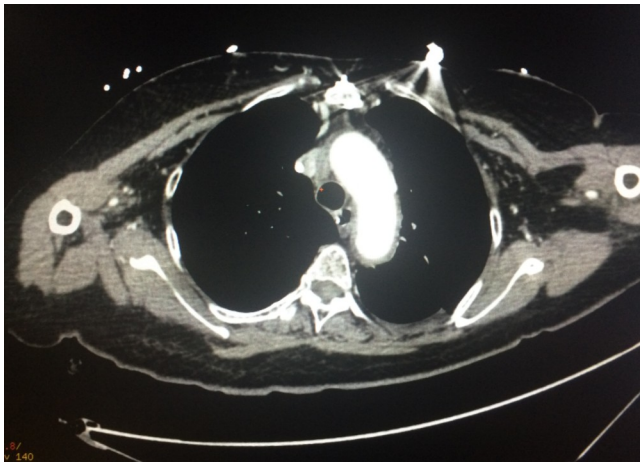

Figure 1. High resolution chest CT showing no evidence of recurrent anterior or superior mediastinal mass

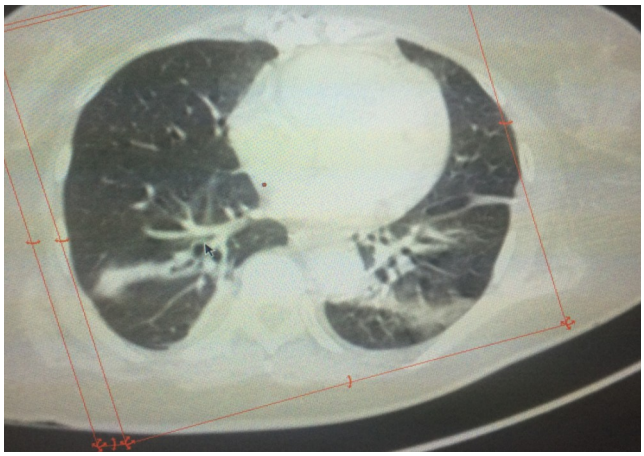

Figure 2. High resolution chest CT showing patchy pneumonia, bilateral anterior and posterior upper lobes

DISCUSSION

Myasthenia gravis (MG) is caused by antibodies against proteins in the neuromuscular junction postsynaptic membrane. Late-onset myasthenia gravis occurs after the age of 60 and is characterized by a clear male predominance. Three postsynaptic neuromuscular junction antigenic target proteins have been identified in myasthenia gravis, namely: nicotinic acetylcholine receptor (AChR), muscle-specific tyrosine kinase (MuSK) and low density lipoprotein receptor-related protein 4 (LRP4). The thymus gland plays a role in myasthenia gravis and is the main site of autosensitisation in anti-AChR MG. Thymic hyperplasia (65%) and thymoma (10%) as a paraneoplastic phenomenon is seen in anti- AChR antibody positive MG.

According to the Philippine Neurological Association (PNA) Consensus Guidelines report of the Neuromuscular Council issued last last March 2012 on treatment for myasthenia gravis, thymectomy is one option for MG patients. The inclusion criteria for patients given the option of thymectomy are: 1. presence of thymoma in all ages; and 2. non-thymomatous MG that is generalized at the onset with a high level of antibodies to AchR, rapid progression of disease, aged 18-55 years and within 3-5 years of MG duration. Based from the study of Berrih-Aknin, etal, thymectomy is frequently used treatment for myasthenia gravis. It is always indicated in MG patients who have a thymoma. Evidence for thymectomy in non-thymomatous MG remains less certain-no randomised controlled trials have been published to date, although one is currently underway (results expected to be available in 2016).[11] A study reviewed the management and clinical outcome of patients with MG who underwent thymectomy over a 12 year period wherein 89 patients who underwent transsternal thymectomy were identified. A thymoma was subsequently identified on histology in 24 %, whereas 48, 9 and 19 % had hyperplastic, atrophic and normal thymic histology, respectively. One patient developed postoperative myasthenic crisis but generally the procedure was well tolerated. Outcome was favourable for the majority of patients, with 34 % achieving complete stable remission (CSR) and an additional 33 % achieving pharmacological remission. Moreover, steroid requirements fell progressively during follow-up. Patients with a hyperplastic gland had a significantly greater chance of achieving CSR compared to other histological subtypes and the incidence of CSR increased with a longer duration of follow-up. Thymectomy for MG is generally safe and well tolerated and is associated with a sustained improvement of symptoms in the majority of patients.[12] Imaging of the mediastinum should be repeated using high resolution chest CT in the context of a MG relapse after a period of stable disease to exclude the development of a thymoma, which can occur later in the disease course.[7]

Late-onset myasthenia gravis is characterized by a clear male predominance. It is frequently associated with the presence of a thymoma, a tumor of the thymic epithelial cells and most patients would present generalized and severe symptoms such as bulbar involvement. A recent article of Aarli defined myasthenia gravis (MG) in the elderly as onset after the age of 50 years. MG is diagnosed more often today than previously. The increase is mainly found in patients over the age of 50 years. Neurologists therefore see more old patients with MG now than before. Prevalence of the early-onset form of MG seems to be unchanged. Recent data indicate that MG may still be substantially underdiagnosed in very old people.[13] This study also stated that thymomatous MG is more common among older patients than it is in younger onset. Approximately 30% of patients with late-onset, nonthymoma MG have antibodies to titin, while such antibodies are extremely scarce in early-onset MG. Titin antibodies in MG patients seem to be associated with a higher frequency of DR7 antigen and a decrease of DR3 antigen. They also noted that the age peak for late-onset MG (onset after age 50) is now the same for both sexes, between 70 and 80 years, mainly because of a relative increase in the onset of MG among older women. Late -onset MG is seen only slightly more often in men than in women. The female-to-male ratio, which is near 3:1 in the early-onset form, is 1:1.1 in late-onset MG. An important cause for the increase is the demographic change. The age group from which late-onset MG is recruited, has expanded during the last 30 years.

Thymoma is usually seen in late-onset myasthenia gravis (LOMG), however, a study showed some "LOMG" thymuses show lymphoid follicles like most in

early onset myasthenia gravis (EOMG) even in patients over 60, particularly in females.[14] Lympho-epithelial tissue of the aging thymus is gradually replaced with fat, but residual parenchyma may continue exporting some T-cells at least into middle age. Remnants may rarely show signs of expansion and even infiltration, however morphometric analysis did not reveal significant difference between LOMG and normal thymuses.[14] Thymectomy appears to be of benefit in elderly patients with EOMG-like immunological features but not in those with striational antibodies.

A few thymoma patients without myasthenia gravis (MG) have been observed to develop MG after total removal of the thymoma (postoperative MG). However, the cause of this is not yet known because of the rarity of postoperative MG patients. A study conducted by Kazuya Kondo, etal[10] evaluated the clinical characteristics of the 8 postoperative MG patients. They compiled 1089 thymoma patients treated between 1990 and 1994 in 115 institutes in Japan, and found 8 cases of postoperative MG. This study showed postoperative MG was found in 8 (0.97%) of 827 thymoma patients without preoperative MG. The postoperative MG patients included 1 male and 7 females, with a mean age of 50.5 +/-15.0 years. The thymoma was completely resected in all cases. The surgical method used was extended thymectomy in 2 cases and thymothymectomy in 6 cases. There were 2 cases (0.7%) of postoperative MG in the extended thymectomy group (n=275), 6 (1.9%) in the thymothymectomy group (n=321), and none in the tumor resection group (n=137).[10] The interval between thymectomy and the onset of postoperative MG varied (6 days–45 months). The type of MG was ocular in 2 cases and general in 5 cases, according to the modified Osserman classification. The postoperative MG was responsive to anti-cholinesterase compounds and/or steroids. The improvement rate was 86%.[10] The study concluded that the onset of MG after total thymoma removal occurred in 1–3% of thymoma patients without MG. Although the resection of the thymus gland does not prevent the onset of postoperative MG, the patients who underwent thymectomy showed a good prognosis. They recommend thymothymectomy or extended thymectomy as a surgical procedure for thymoma patients without MG.[10]

Myasthenia gravis symptoms appearing post-thymectomy is a rare occurrence. On literature review, one case report entitled Post-thymectomy myasthenia gravis with an episode of Osserman stage III by Kuwata, etal[15] published last 2012 was seen . They reported a case of an 81 year old female admitted for an abnormal shadow seen in a chest radiograph with no symptoms of myasthenia gravis. Chest CT showed a bulky anterior mediastinal tumor (thymoma on biopsy) and subsequently had thymothymectomy, left upper lobectomy, pericardial resection, and phrenicectomy. Pathological examination of the tumor identified it as a thymoma (type B2, Masaoka stage II). Two months after the surgery, she experienced the onset of post-thymectomy myasthenia gravis with Osserman stage III and started steroid pulse therapy (prednisolone 1g/day for 3 days). Additionally, the patient was treated with immunoadsorption to shorten the duration of the steroid therapy. At three months after the admission, she was removed from the ventilator with a drug regimen of 60 mg/day prednisolone.

The current hypothesis of the pathogenic mechanism of post- thymectomy myasthenia gravis (PTMG) includes: thymoma recurrence; surgical exposure to larval MG; and activation of peripheral lymphocytes from thymoma after surgery. Hoffacker et al.[16] demonstrated that thymoma releases mature autoantigen- specific T-cells into the periphery, using T-cell proliferation assays for a fragment of the acetylcholine receptor, the midsize neurofilament protein, and tetanus toxoid. Buckley etal on the other hand states that T-cells in the thymoma are exported to the peripheral blood, and that these T-cells can persist in the periphery for many years.[17] These studies suggest that thymoma actively exports large numbers of mature T-cells into the peripheral blood and that, following export, the cells persist in the periphery, potentially stimulating autoantibody production and subsequent autoimmune disease.

CONCLUSION

Late-onset myasthenia gravis in an elderly female was once a rare neurologic occurrence but is now becoming more common due to the increasing number of elderly population. Asymptomatic

individuals with thymic mass who have undergone thymectomy may develop myasthenia gravis. Signs and symptoms of myasthenia is easily detected thus an increase in the index of suspicion should be made even if it is seen in an elderly female. Since there are still no evidence as to whether thymectomy is warranted for asymptomatic patients and for non-thymomatous MG, careful considerations and further research should be done as to whether thymectomy should be recommended as a standard of care. A thorough and detailed pre- and postoperative work up for myasthenia gravis to screen for likelihood of a post-thymectomy myathenia gravis should be done for all patients who would have surgery of any thymic mass.

REFERENCES

1. Farrugia ME, Vincent A. Autoimmune mediated neuromuscular junction defects. Curr Opin Neurol 2010;23:489–95.
2. Vincent A. Autoimmune channelopathies: well-established and emerging immunotherapy-responsive diseases of the peripheral and central nervous systems. J Clin Immunol 2010;30(Suppl. 1):S97–S102.
3. McGrogan A, Sneddon S, de Vries CS. The incidence of myasthenia gravis: a systematic literature review. Neuroepidemiology 2010;34:171-83.
4. Phillips LH 2nd. The epidemiology of myasthenia gravis. Ann NY Acad Sci 2003;998:407-12
5. Carr AS, Cardwell CR, McCarron PO, McConville J. A systematic review of population based epidemiological studies in myasthenia gravis. BMC Neurol 2010;10:46
6. Alkhawajah NM, Oger J. Late onset myasthenia gravis: a review when incidence in the older adults keeps increasing. Muscle Nerve 2013;48:705e10.
7. Sivakumar Sathasivam. Diagnosis and management of myasthenia gravis. Progress in Neurology and Psychiatry January/February 2014
8. Marx A, Willcox N, Leite MI, et al. Thymoma and paraneoplastic myasthenia gravis. Autoimmunity2010;43:413-27.
9. Thomas CR, Wright CD, Loehrer PJ. Thymoma: state of the art. J Clin Oncol 1999;17:2280–9.
10. Kazuya Kondo, Yasumasa Monden. Myasthenia gravis appearing after thymectomy for thymoma. European Journal of Cardio-thoracic Surgery 28 (2005) 22–25
11. S. Berrih-Aknin, R. Le Panse. Myasthenia gravis: A comprehensive review of immune dysregulation and etiological mechanisms Journal of Autoimmunity xxx (2013) 1e11
12. Spillane J, Hayward M, Hirsch NP, Taylor C, Kullmann DM, Howard RS. Thymectomy: role in the treatment of myasthenia gravis. J Neurol. 2013 Jul;260 (7):1798-801. doi: 10.1007/s00415-013-6880-8. Epub 2013 Mar 19.
13. Aarli, J. Myasthenia Gravis in the Elderly: Is It Different? Ann. N.Y. Acad. Sci. 1132: 238–243 (2008). C. 2008 New York Academy of Sciences.
14. Marx, A et al The different roles of the thymus in the pathogenesis of the various myasthenia gravis subtypes. Autoimmunity Reviews 12 (2013) 875–884
15. Kuwata T, Iwata T, Iwanami T. Post-thymectomy myasthenia gravis with an episode of Osserman stage III. JSCR 2012 5:3; Journal of Surgical Case Reports
16. Hoffacker V, Schultz, etal. Thymomas alter the T-cell subset composition in the blood: a potential mechanism for thymoma associated autoimmune disease. Blood 2000;96:3872–9
17. Buckley C, Douek D, Newsom-Davis J, Vincent A, Willcox N. Mature, long lived CD4C and CD8C T cells are generated by the thymoma in myasthenia gravis. Ann Neurol 2001;50:64–72

The Effectiveness of Harmonic Scalpel compared to Metal Clips in Ligating the Cystic Duct during Laparoscopic Cholecystectomy: A Meta-Analysis

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James Angelo Illescas, MD

Background

During the course of laparoscopic cholecystectomy, ligation of the cystic duct is a necessary step in performing the procedure. Traditionally, the ligation of the cystic duct is carried out using metal clips. Even though this has been the standard tool for ligation, there are still reports of post-operative bile leaks leading to peritonitis.[1,2] One of the reasons noted is laceration of cystic duct by the metal clips, which was attributed to necrosis of the clamped tissue and the ability of the metal clips to conduct electricity when electrocuatery was used.[3] Another reason is the occlusion and eventual necrosis of the cystic duct and erosion of the metal clips into the common bile duct.[4] With the recent invention of ultrasonically activated scalpel or harmonic scalpel, this device was also used as an alternative to the traditional way of ligating the cystic duct. However, the efficacy of this alternative has not been proven. For this reason, the authors aim to present the best current evidence on the effectiveness of harmonic scalpel compared to metal clips in ligating the cystic duct during laparoscopic cholecystectomy.

Objectives

The authors aimed to determine the effectiveness of ultrasonically activated scalpel compared to metal clips during ligation of the cystic duct during laparoscopic cholecystectomy.

The specific objectives of this study includes:

1. To compare the operative time when either of the tools was used
2. To compare the duration of hospital stay when either of the tools was used
3. To compare the rate of post-operative complications of both methods

Methodology

A computer assisted literature search was done on electronic databases online such as Pubmed and Cochrane Central Register of Controlled Trials (CENTRAL). The electronic databases were identically searched using the following key words: "clipless cholecystectomy", "harmonic scalpel", "ultrasonically activated scalpel", "laparoscopic cholecystectomy." The search strategy used for both PUBMED and Cochrane CENTRAL are as follow: (((((((((clipless) OR harmonic scalpel) OR ultrasonically activated scalpel) OR ligature) OR suture) OR intracoporeal ligation) OR absorabable clip) OR absorbable lock) AND cystic duct) AND laparoscopic cholecystectomy. The inclusion criteria used in this review were primarily randomized controlled trials that were written in the English language and published on 2014 or earlier.

Criteria for Considering Studies for this Review

Type of studies included were limited to randomized controlled trial, with patients who underwent laparoscopic cholecystectomy for symptomatic gallstones and were written in English. The interventions compared are use of harmonic scalpel and metal clips in ligation of cystic duct during laparoscopic cholecystectomy. The primary outcome measure was the rate of post-operative complications. Secondarily, the operative time when either of the tools were used.

Results

A total of 73 studies were collected after a computer assisted literature search using the above mentioned key words. After review and evaluation of the studies searched, 3 studies met the set criteria for this study. A total of 492 patients were included in this review. Out of the 492 patients, 246 patients underwent laparoscopic cholecystectomy using Harmonic scalpel while 492 underwent conventional laparoscopic cholecystectomy. The age range of patients in the 3 trials was 18-66 (Kandil 2009), 18-83 (Kandil 2011) and less than 20 to more than 60 years old (Redwan 2010). The percentage of male in the 3 trials was 42% (Kandil 2009), 37.5% (Redwan 2010), and 9% (Jain 2011).

Different complications were reported in the 3 studies. However, there was no complication noted that was similar for all 3 studies. Two studies (Redwan 2010, Kandil 2009) reported a total of 3 postoperative bile leak in patients who underwent conventional laparoscopic cholecystectomy. In the study by Kandil (2009), 3 patients who underwent conventional laparoscopic cholecystectomy experienced postoperative pulmonary complications while there was 1 patient who experienced the same complication who underwent laparoscopic cholecystectomy using harmonic scalpel. Also in the same study, 4 patients in the conventional group were noted to have experienced port site infection while there was 1 in the harmonic scalpel group.

In the conventional laparoscopic cholecystectomy, the duration of surgery are 64.7 (Jain 2011), 44.01 (Redwan 2010), and 51.7 minutes (Kandil 2009) while in the laparoscopic cholecystectomy using harmonic scalpel, the duration of surgery are 50 (Jain 2001), 16.8 (Redwan 2010), and 33.2 minutes (Kandil 2009).

The length of hospital stay in the conventional group are 2.52 (Jain 2011), 1.53 (Redwan 2010), and 1.12 days (Kandil 2009), while in the harmonic scalpel group are 1.89 (Jain 2009), 1 (Redwan 2010), and 0.98 days (Kandil 2009).

The risk of bias is summarized in Figure 1 and Figure 2. Three of the trials (100%) had adequate random sequence generation and all outcome data were reported. None of the trials discussed allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and selective reporting of data.

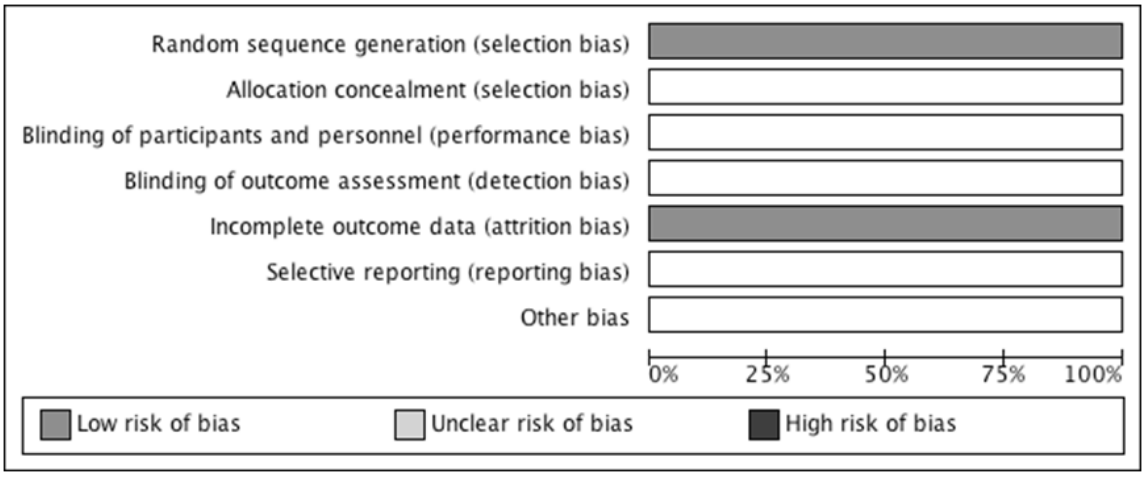


Figure 1. Risk of bias graph: review author's judgments about each risk of bias item presented as percentages across all included studies

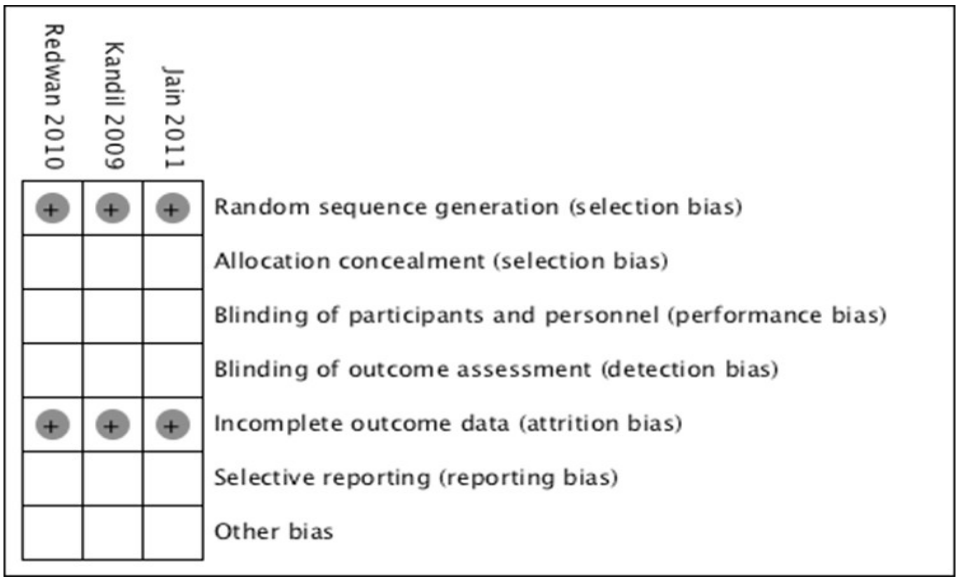


Figure 2. Risk of bias summary: review author's judgments about each risk of bias item for each included study

DISCUSSION

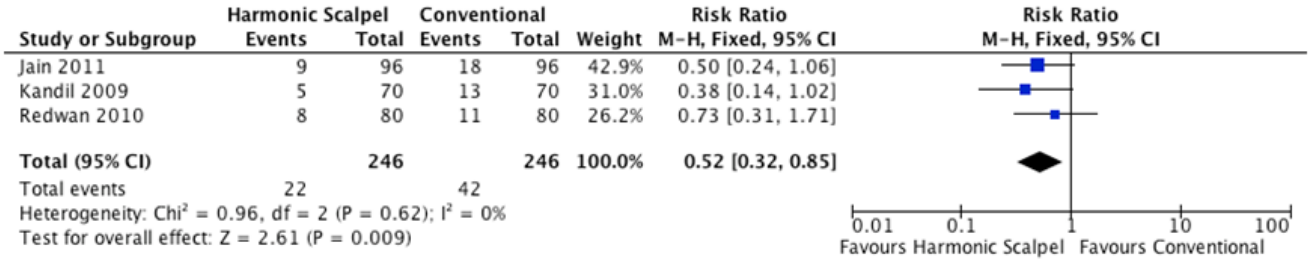


Figure 3. Gallbladder perforation

The three trials consistently showed a tendency towards a higher risk of gallbladder perforation with conventional cholecystectomy. However, metaanalysis of the results showed that there is a significantly higher risk of gallbladder perforation with conventional cholecystectomy. The risk of the complication with the use of harmonic scalpel is only half that with the use of conventional technique (RR=0.52, 95%CI 0.32, 0.85)

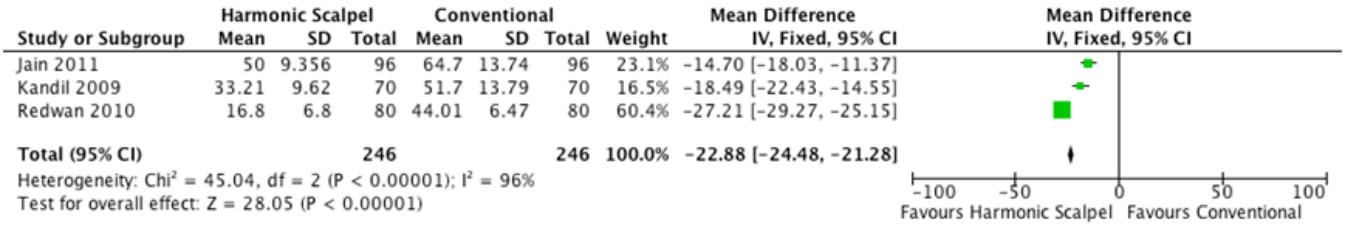


Figure 4. Duration of Surgery (minutes)

All three studies consistently showed significantly shorter duration of surgery with the use of harmonic scalpel. Combined results showed that the use of harmonic scalpel shortened the surgery by 23 minutes compared to conventional cholecystectomy (95% CI -24.5, -21.3)

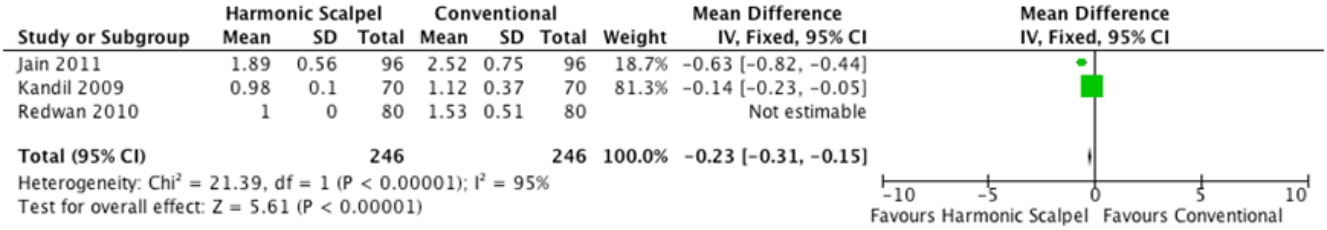


Figure 5. Duration of hospital stay

This review which consisted of 3 trials with a total of 492 patients compared the effectiveness of harmonic scalpel compared to metal clips in ligating the cystic duct during laparoscopic cholecystectomy.

All 3 trials were consistent in their results showing the advantages of using harmonic scalpel during laparoscopic cholecystectomy. Pooled analysis of the trials showed that utilization of harmonic scalpel is significantly associated with less risk of gallbladder perforation during dissection, lesser duration of operation, and lesser duration of hospital stay. As for the duration of duration hospital stay, although it was deemed significant, the difference between the two interventions is only a few hours.

Two studies were able to report post-operative bile leakage (Kandil 2009, Redwan 2010). In the conventional laparoscopic cholecystectomy, 2 out of 70 patients (Kandil 2009) and 1 out of 80 patients (Redwan 2010) experienced post-operative bile leakage while there was none in the harmonic scalpel group.

Conclusion

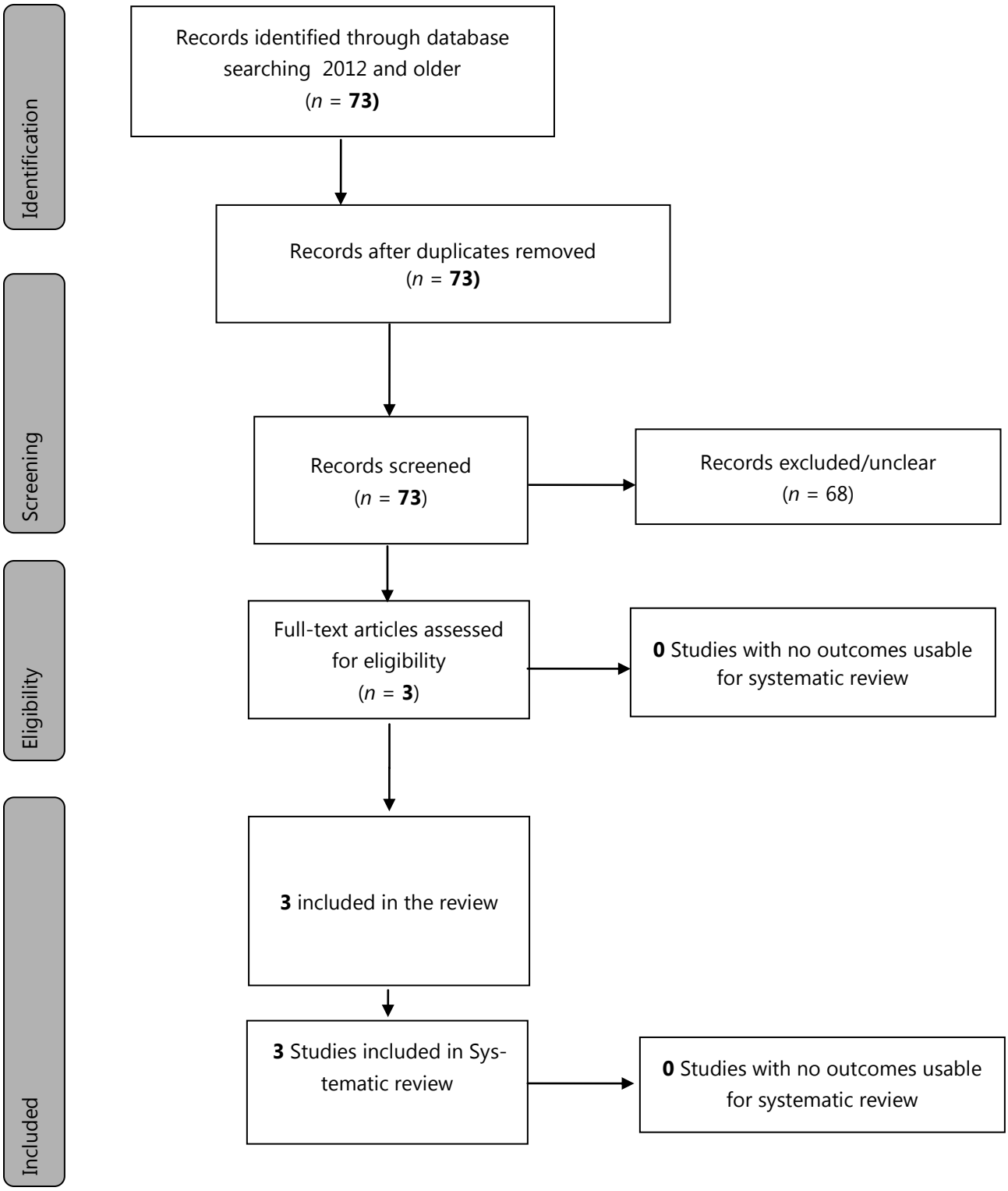
There is a lesser risk of gallbladder perforation and, shorter operative time when harmonic scalpel is used during laparoscopic cholecystectomy. The use of harmonic scalpel during laparoscopic cholecystectomy may be recommended. However, due to the lack of evidence of the advantages of harmonic scalpel in preventing post-operative complications, more trials with similar design and longer follow up should be done and reviewed to assess its advantage over conventional cholecystectomy in this respect.

REFERENCES

1. Kavlakoglu B, Pekcici R, Oral S. Verification of clipless closure of cystic duct by harmonic scalpel. Laparoendosc Adv Surg Tech A. 2010 Sep;20(7):591-5. Ministry of Health Ankara Oncology Training and Research Hospital , Ankara, Turkey.
2. Gelmini R, Franzoni C, Zona S, Andreotti A, Saviano M. Laparoscopic cholecystectomy with Harmonic scalpel. JSLS. 2010 Jan-Mar;14(1):14-9. Department of Surgery, Policlinico of Modena, University of Modena and Reggio Emilia, Italy.
3. I. M. C. Janssen, D. J. Swank, O. Boonstra, B. C. Knipscheer, J. H. G. Klinkenbijl and H. van Goor. Randomized clinical trial of ultrasonic versus electrocautery dissection of the gallbladder in laparoscopic cholecystectomy. Departments of Surgery, Rijnstate Hospital Arnhem, Groene Hart Hospital Gouda and University Medical Centre Nijmegen, The Netherlands.
4. Gurusamy KS, Bong JJ, Fusai G, Davidson BR. Methods of cystic duct occlusion during laparoscopic cholecystectomy. Cochrane Database of Systematic Reviews 2010, Issue 10. Art. No.: CD006807. DOI: 10.1002/14651858.CD006807.pub2
5. Jain SK, Tanwar R, Kaza RC, Agarwal PN. A prospective, randomized study of comparison of clipless cholecystectomy with conventional laparoscopic cholecystectomy. Laparoendosc Adv Surg Tech A. 2011 Apr;21(3):203-8. Epub 2011 Mar 5. Department of Surgery, Maulana Azad Medical College, New Delhi, India.
6. Redwan AA. Single-working-instrument, double-trocar, clipless cholecystectomy using harmonic scalpel: a feasible, safe, and less invasive technique. Laparoendosc Adv Surg Tech A. 2010 Sep;20(7):597-603. General Surgery Department, Assuit University Hospitals, Faculty of Medicine, Assuit University , Assuit, Egypt.
7. Kandil T, El Nakeeb A, El Hefnawy E. Comparative study between clipless laparoscopic cholecystectomy by harmonic scalpel versus conventional method: a prospective randomized study. Gastrointest Surg. 2010 Feb;14(2):323-8. Epub 2009 Oct 31. Gastroenterology Surgical Center, Faculty of Medicine, Mansoura University, Jihan St., Mansoura, Egypt.
8. Westervelt J. Clipless cholecystectomy: broadening the role of the harmonic scalpel. JSLS. 2004 Jul-Sep;8(3):283-5. Clark Memorial Hospital, Jeffersonville, Indiana, USA.

APPENDICES

APPENDIX 1. PRISMA Flow Diagram



APPENDIX 2. CHARACTERISTICS OF INCLUDED STUDIES

STUDY IDENTIFIER	Jain 2011
STUDY TITLE	A Prospective, Randomized Study of Comparison of Clipless Cholecystectomy with Conventional Laparoscopic Cholecystectomy
AUTHORS	Sudhir Kumar Jain, MS, FRCS, Raman Tanwar, MBBS, Ram Chandra Murti Kaza, MS, and Prem Narayan Agarwal, MS
CITATION	JOURNAL OF LAPAROENDOSCOPIC & ADVANCED SURGICAL TECHNIQUES Volume 21, Number 3, 2011
PARTICIPANTS	
Description	Laparoscopic cholecystectomy has become a gold standard in the treatment of symptomatic gallstone disease. Amalgamation with upcoming technology makes the present-day procedure faster and safer. Ultrasonic shears, which perform dissection and ligation by cavitation and coaptation of vessels, are the latest addition to the armamentarium of laparoscopic surgeons. Acceptance of its safety and efficacy awaits its use as the sole instrument in the widely accepted procedure.
Total number enrolled (exp/ctrl)	200 patients with symptomatic gallstone disease, who were randomly divided into two comparable groups, one undergoing cholecystectomy using ultrasonically activated shears and the other using conventional clip and electrocautery One hundred patients were included in each group
Total number analyzed	200 patients
INTERVENTION	Harmonic scalpel vs Conventional
Experimental	Harmonic scalpel
Description	Ultrasonically activated shears
Number	100
Control	Conventional
Description	Surgical clips and Cautery
Number	100
OUTCOMES (list all outcomes)	Duration of stay (in days) Stay range (in days) Fall in Hemoglobin (in g%) Fall in Hematocrit (in %) Duration of Surgery (in minutes) Duration range (in minutes) Time taken to remove gallbladder from bed (in minutes) VAS day 0 VAS day 1 Analgesic requirement – day 1 (number of 50 mg diclofenac tablets consumed) Gallbladder perforation Number of patients requiring drains

METHODOLOGY/ DESIGN	A prospective, randomized, control study was undertaken in the Department of Surgery, Maulana Azad Medical College, and associated Lok Nayak Hospital, wherein 200 patients with symptomatic gallstone disease undergoing laparoscopic cholecystectomy between 18 and 70 years of age were included if they did not fall in the exclusion criteria. These patients were randomly divided into two groups using a computer-generated software, one undergoing surgery with electrocautery (group A) and the other with ultrasonic shears (group B). Exclusion criteria included the following: (a) Patients who had impaired liver function tests; (b) History of jaundice or pancreatitis; (c) Suspicion of gallbladder carcinoma; (d) Patients having concomitant common bile duct (CBD) calculi; (e) Acute cholecystitis, cholangitis, and empyema of gallbladder; (f) Pregnant patient; (g) CBD size more than 5mm on ultrasonography. Appropriate clearance from the scientific and ethical committee of the institution was obtained before starting the study. A detailed informed consent was obtained from all patients. All patients were given the option to opt out of the study at any stage without compromising their right for treatment. Laparoscopic cholecystectomy was performed using the four-port American technique. In group B patients, after dissecting the Calots triangle with ultrasonic shears, ligation of the cystic artery and duct was done by ultrasonic shears at the power setting of 2, and shears were not removed till the two ligated ends gave way on their own. Before ligation of cystic duct with ultrasonic shears, the size of the cystic duct was judged by comparing it with the size of CBD. To do this, first the width of CBD was judged by opening the jaws of harmonic shear and then compared with the width of cystic duct. In none of our patients, the width of cystic was found to be more than the width of CBD and we did not include any patient with CBD size >5 mm. The surgeons assessed the cystic duct for any calculi before cutting by moving the jaws of ultrasonic scalpel up and down the duct. The jaws were placed at a safe distance from the CBD to avoid injury to it. The instrument was then activated after fixing the jaws and keeping the instrument still till the two ends got separated at their own without applying traction. Dissection of the gallbladder liver bed was also done using ultrasonic shears at a setting of 5, with minimal bleed. The gallbladder was extracted from the epigastric port and drains were inserted whenever there was significant bleed, ooze from the gallbladder fossa, or bile spillage due to gallbladder perforation. Patients undergoing conventional cholecystectomy in group A underwent dissection with Maryland's dissector and cystic duct and artery were ligated using clips. The gallbladder was extracted from the gallbladder bed using hook and electrocautery. Intraoperatively the time of surgery (starting from skin incision to closure) and the time taken to remove the gallbladder from the gallbladder bed were noted. Postoperative pain scores using visual analog score and analgesic requirement were noted at 6 hours following surgery and at days 1 and 2 by an observer who was unaware of the procedure performed, to eliminate observation bias. Postoperative complications if any and duration of stay were noted. Gallbladder perforation and need for placement of drains were also noted. The amount of blood loss was adjudged by the fall in hemoglobin and hematocrit on postoperative day 1. Patients were followed up at 1 and 3 weeks and at end of 6 months following surgery for completion of data regarding pain score, consumption of analgesics, and complications of surgery if any. Statistical analysis The data collected was analyzed using SPSS software. For quantitative variables such as duration of hospital stay, severity of pain as per visual analog scale, and time taken for surgery, difference between means was analyzed using t-test or Mann–Whitney test. For qualitative data such as requirement of analgesics, difference between proportions was analyzed using chi-square test or Fisher's exact test. P value of less than or equal to .05 was taken as the cutoff point for statistical significance.
CONCLUSIONS	Ultrasonically activated scalpel can be used safely in laparoscopic cholecystectomy without risk of major injuries or leaks. It fairs better than electrocautery in terms of not just a faster and safer surgery but also a surgery with decreased associated morbidity and pain and early return back home.
LIMITATIONS	None

Study Quality Assessment

STUDY IDENTIFIER	Jain 2011
RANDOMIZATION (Description)	Patients were retrospectively divided into 2 groups according to the instruments used for division of the cystic artery and duct as well as for dissection of the liver bed. On the one hand, group 1 consisted of 95 patients who were all treated with the ultrasonically activated scalpel as the sole instrument used in the whole procedure (an additional ligature with clips was performed in 17 patients (17.89%) with a cystic duct of more than 4mm in diameter). On the other hand, group 2 comprised 90 patients in whom dissection and coagulation were performed using monopolar coagulation, and section of the artery and duct with clips.
ALLOCATION CONCEALMENT (Description)	Not applicable
BLINDING (yes/no)	No
WITHDRAWALS	
Yes/No?	No
How many?	Not applicable
Reasons for withdrawal	Not applicable
ALL OUTCOMES REPORTED?	Yes
REMARKS	

Study Data

Study identifier	Jain 2011		
	Harmonic scalpel	Conventional	P value
Duration of stay (in days)	1.89 ± 0.86	2.52 ± 0.75	.001
Stay range (in days)	1 - 3	2 - 7	.001
Fall in Hemoglobin (in g%)	0.53 ± 0.52	1.33 ± 0.85	.001
Fall in Hematocrit (in %)	1.59 ± 2.50	2.60 ± 1.295	.001
Duration of Surgery (in minutes)	50.00 ± 9.356	64.70 ± 13.74	.001
Duration range (in minutes)	31 - 72	42 - 102	.001
Time taken to remove gallbladder from bed (in minutes)	3.94 ± 2.07	7.36 ± 3.43	.001
VAS day 0	2.65 ± 1.04	4.58 ± 1.00	.001
VAS day 1	1.86 ± 0.76	3.01 ± 0.86	.001
Analgesic requirement – day 1 (number of 50 mg diclofenac tablets consumed)	1.86 ± 0.59	2.66 ± 0.66	.001
Gallbladder perforation	9	18	.002
Number of patients requiring drains	12	31	.002

STUDY IDENTIFIER	Kandil 2009
STUDY TITLE	Comparative Study between Clipless Laparoscopic Cholecystectomy by Harmonic Scalpel Versus Conventional Method: A Prospective Randomized Study
AUTHORS	Tharwat Kandil & Ayman El Nakeeb & Emad El Hefnawy
CITATION	J Gastrointest Surg (2010) 14:323–328
PARTICIPANTS	
Description	The advantages of laparoscopic cholecystectomy (LC) have been published extensively, and LC has become the gold standard in treating benign gallbladder diseases. LC has largely replaced conventional open cholecystectomy. The traditional LC is commonly performed by means of dissector, the electrosurgical hook, spatula, and/or scissors, and this method has been used in most centers. Simple metal clips are frequently used to achieve cystic duct and artery closure. Alternative technique using sutures for cystic duct closure is infrequently used. Various energy sources are routinely used as cutting and coagulating aids in laparoscopic surgery. Risks involved with the use of monopolar electrosurgery are significantly greater. Nonetheless, monopolar electrosurgery is the preferred method in more than 85% of surgeons. Bipolar electrosurgery, being as effective as monopolar electrosurgery, has not been widely used in the LC procedure. The majority of electrosurgical injuries manifests late or goes unrecognized. The incidence of accidental burns caused by unintentional energy transmission during a LC ranges between 0.06% and 0.3%. However, only one or two patients in 1,000 are recognized. Several studies have described the use of ultrasound dissection technology in the LC, which concluded that ultrasonic dissection was safe and easy to use. Few studies reported the harmonic scalpel, though superior, is not immune from causing undesirable biological effects on the body. However, current available studies on LC using harmonic ultrasonic dissector are too small to determine any statistically significant difference in outcomes between traditional LC and LC with harmonic. This study planned to compare traditional method of LC versus LC using harmonic as regard the safety and efficacy.
Total number enrolled (exp/ctrl)	140 laparoscopic cholecystectomies were performed in the Gastroenterology Surgical Center and Mansoura University General Hospital 70 were all treated with ultrasonically activated scalpel 70 were all treated with dissection and coagulation using monopolar coagulation and clips
Total number analyzed	140 patients
INTERVENTION	Harmonic scalpel vs Conventional
Experimental	Harmonic scalpel
Description	Ultrasonically activated scalpel
Number	70
Control	Conventional
Description	Surgical clips and Cautery
Number	70
OUTCOMES (list all outcomes)	Intraoperative blood bloss Bile spillage Duration of operation Conversion rate Amount of drainage Hospital stay Postoperative pulmonary complication Port site infection Postoperative collection Postoperative bile leakage Body temperature Postoperative nausea Postoperative vomiting

METHODOLOGY/ DESIGN	This study was carried out from January 2008 to December 2008. Patients with gallbladder stone were treated by LC at the Gastroententerology Surgical Center and Mansoura University General Hospital and were included in this prospective randomized trial. The exclusion criteria included patients above 80 years old, patients with history of upper laparotomy, patients with common bile duct stones, and pregnant women. All patients were subjected to thorough history and clinical examination focused on manifestation of gallstone disease and chronic liver disease. The following investigations were performed [whole blood picture, liver function tests (serum albumin, ALT, AST, and prothrombine time "INR"), HCV and HBV markers, and abdominal ultrasound] to show the state of the liver, portal vein, gallbladder, and CBD. Informed consent was obtained from all patients to be included in the study, after explaining the nature of the disease and operative steps and possible complications. This study was approved by the local ethical committee. The patients were randomized into two groups using enclosed envelope. The envelopes were drawn and opened by a nurse not otherwise engaged in the study before operation. Group A LC was done using traditional method, which included 70 patients, and group (B) LC was done using harmonic scalpel, which included 70 patients. Under general anesthesia and the same antibiotics (third generation cephalosporin), surgery was performed using conventional four ports umbilical port, port below xiphoid, and two ports below right costal margin. Pneumoperitoneum at pressure 12 mmHg was used. In group A, LC was done using traditional method by dissection of Calot's triangle and clipping of both cystic duct and artery by metal clips. After that, dissecting the gallbladder from its bed by hook using electrocautery technique was performed. Finally, we insert abdominal drain in Morrison pouch. In group B, LC was done using harmonic ACE (Ethicon Endo-Surgery) by dissection of Calot's and then occlusion of both cystic duct and artery using harmonic ACE. For closure and division of cystic pedicle, we set the instrument at power 2, i.e., more coagulation, and do it at two levels and separate the duct at the proximal level toward the gallbladder. When dissecting the gallbladder from its bed, we set it to level 5, i.e., more cutting power, and control of any bleeding from the bed using the active blade of harmonic ACE. Finally, we insert abdominal drain in Morrison pouch. The intraoperative parameter observed included duration of the operation, amount of CO2 used in the operation, bile escape, saline irrigation during operation, and volume of blood loss were all recorded. The patients started oral feeding 8 h postoperatively; abdominal ultrasound was done for all patients in both groups on day of discharge to show any collection or free fluid in the abdomen. The patients were usually discharged after removal of drain and when the patient is surgically free. Postoperative pain (PP) was evaluated at 12 h, 24 h, 48 h, and 1 week after operation using a visual analog scale (VAS)18 (with which each patients noted the severity of pain at each evaluated time using a linear between 0 (no pain) and 10 (severe pain). Postoperative analgesia in the form of nonsteroidal anti-inflammatory drug was administered intramuscularly when required. If the patients still complained of pain, strong analgesic (1 mg/kg pethidine intramuscularly) was administered. The total dose of these medications was recorded. Postoperative maximum body temperatures were recorded at (24 and 48 h) for all patients. Postoperative nausea and vomiting "PONV" were assessed after 24 and 48 h. Metoclopramide was given if the patients required reduction of nausea, and the total doses of this medication were recorded. The frequency of vomiting was recorded. At the end of the first postoperative week, first month, and sixth postoperative month, patients underwent a clinical examination and an abdominal ultrasonography. In addition, blood sample was taken to show follow up of liver function. The statistical analysis of the data in this study was preferred using the SPSS version 10. Analysis of data was by intension to treat. For continuous variables, descriptive statistics were calculated and reported as mean+SD.
CONCLUSIONS	The harmonic scalpel provides complete hemobiliary stasis for all patients and is a safe alternative to stander clip of cystic duct and artery. It provides a shorter operative duration, less incidence of gallbladder perforation, less PP, and less rate of conversion to open cholecystectomy.
LIMITATIONS	None

Study Quality Assessment

STUDY IDENTIFIER	Kandil 2009
RANDOMIZATION (Description)	The patients were randomized into two groups using enclosed envelope. The envelopes were drawn and opened by a nurse not otherwise engaged in the study before operation. Group A LC was done using traditional method, which included 70 patients, and group (B) LC was done using harmonic scalpel, which included 70 patients.
ALLOCATION CONCEALMENT (Description)	Not applicable
BLINDING (yes/no)	Not applicable
WITHDRAWALS	
Yes/No?	Not applicable
How many?	Not applicable
Reasons for withdrawal	Not applicable
ALL OUTCOMES REPORTED?	Yes
REMARKS	

Study Data

Study identifier	Kandil 2009		
	Conventional	Harmonic scalpel	P value
Intraoperative blood loss (mL)	83.31 +46.23	43.28 +31.27	0.0001
Bile spillage	13 (18.6%)	5 (7.1%)	0.04
Duration of operation (min)	51.7 +13.79	33.21 +9.62	0.0001
Conversion rate	2 (2.9%)	0	0.156
Amount of drainage	47.78 +31.54	29 +30.79	0.001
Hospital stay (hours)	26.95 +8.94	23.44 +2.29	0.002
Postoperative pulmonary complication	3 (4.3%)	1 (1.4%)	0.312
Port site infection	4 (5.7%)	1 (1.4%)	0.173
Postoperative collection	2 (2.9%)	1 (1.4%)	0.561
Postoperative bile leakage	2 (2.9%)	0	0.156
Body temperature			
Before operation	36.6 +0.5	36.74 +0.4	0.310
24 h	37.6 +0.6	37.29 +0.4	0.01
48 h	37.6 +0.6	37.36 +0.4	0.01
Presence of postoperative nausea			
24 h	24 (34.3%)	16 (229.%)	0.462
48 h	5 (7.1%)	3 (4.3%)	0.136
Presence of postoperative vomiting			
24 h	4 (5.7%)	2 (2.9%)	0.4
48 h	2 (2.9%)	1 (1.4%)	0.56

STUDY IDENTIFIER	Redwan 2010
STUDY TITLE	Single-Working-Instrument, Double-Trocae, Clipless Cholecystectomy using Harmonic Scalpel: A Feasible, Safe, and Less Invasive Technique
AUTHORS	Alaa A. Redwan, MD
CITATION	JOURNAL OF LAPAROENDOSCOPIC & ADVANCED SURGICAL TECHNIQUES Volume 20, Number 7, 2010
PARTICIPANTS	
Description	Laparoscopic cholecystectomy is a commonly performed operation for patients diagnosed with gallstones. Usually, the procedure involves electrosurgery and sealing of the gallbladder duct and arteries with titanium clips. Dissection with concomitant hemostasis can be performed with the use of ultrasonic instruments, such as the Harmonic scalpel, (Ethicon Endo-Surgery, Cincinnati, OH), and can radically simplify the whole operation and offer good hemostasis, so ultrasonically activated devices have been used for dissection with encouraging results. The ultrasonically activated (Harmonic) scalpel has proven to be an effective, efficient, and safe instrument for dissection and hemostasis. It works on the tissue's cutting and coagulating very effectively with the replacement of the high-frequency current, which can be connected with diverse complications. The primary use of the Harmonic scalpel in laparoscopic cholecystectomy has been for the division of the cystic artery and liver-bed dissection. Recently, ultrasonic energy has been used to seal the cystic duct during successful clipless cholecystectomy. So, total Harmonic scalpel dissection, in the performance of a laparoscopic cholecystectomy, is described in this article. The resulting decrease in temperature, smoke, and lateral tissue damage has placed the Harmonic scalpel in contrast to the effects seen with more traditional electrocautery. In addition, the elimination of inadvertent, sometimes unrecognized, electrical arcing injuries, with their potentially hazardous sequelae, has supported the role of the Harmonic scalpel as a potentially safer instrument for tissue dissection. It tackles the concerns regarding smoke production, and inadvertent injuries to the abdominal organs and structures.
Total number enrolled (exp/ctrl)	160 patients underwent laparoscopic cholecystectomy 80 were all treated with ultrasonically activated scalpel (Harmonic scalpel) 80 were all treated with dissection and coagulation using monopolar coagulation and clips
Total number analyzed	160 patients
INTERVENTION	Harmonic scalpel vs Conventional
Experimental	Harmonic scalpel
Description	Ultrasonically activated scalpel
Number	80
Control	Conventional
Description	Surgical clips and Cautery
Number	80
OUTCOMES (list all outcomes)	Duration of stay Duration of surgery Intraoperative complications Postoperative complications

METHODOLOGY/ DESIGN	All patients were subjected to 1) full history taking, 2) clinical examination, and 3) investigations that included routine lab tests (i.e., blood count, random sugar, and serum creatinine), routine chest X-ray, electrocardiography, etc., liver function tests, prothrombine time, and abdominal ultrasonography. Additional investigations were needed sometimes, in some doubtful cases, such as computed tomography and magnetic resonance cholangiopancreatography. All patients were randomly assigned for laparoscopic cholecystectomy. Group 1 (the clipless Harmonic group) included 80 cases. The Harmonic scalpel was used as a single working instrument, with only two working trocars. Patients were positioned in an anti-Trendelenburg position, with some rotation to the left side to help in good visualization and manipulation of the gallbladder, if difficulty was still encountered. Thereafter, a curved Kirschner wire (1mm) was introduced in the subcostal area and hooked the gallbladder fundus, with gentile retraction upward, or by the direct introduction of the laparoscopic trocar wound-closure forceps through the subcostal region, with gentle retraction of the gallbladder upward. However, these maneuvers were rarely resoled to during the work. An ultrasonic shear (Olympus Keymed Sono surg version G2 220–240V 3A, 50/60 Hz; Tokyo, Japan) was used as the only working instrument during the procedure, through a 10-mm epigastric port, for the dissection and cutting of the cystic artery and duct. Then, gallbladder dissection from the liver bed was helped by a grasper, through the right midclavicular 5-mm port, to attain complete hemobiliary stasis. Last, the gall bladder was retrieved from the epigastric 10-mm trocar site. Group 2 (the clip/cautery group) included 80 cases. The conventional instruments were used with the application of clips and the use of cautery in a three-working-trocar laparoscopic cholecystectomy technique. One small catheter drain was inserted in all cases, which was removed a few hours later. All patients were followed up in the General Surgery Department at Assuit University Hospitals, with the appropriate postoperative treatment in the form of broad-spectrum antibiotic prophylaxis, and analgesics, according to the amplitude of pain, using a ''pain scoring system,'' where a single shot of narcotics was sufficient to kill pain of a moderate type, but more doses were needed (double) with severe types of pain, until being discharged from the hospital. The recording of all patient data was done and categorized as follows: intraoperative difficulty, intraoperative perforation of the bladder and biliary spillage, intraoperative injuries or complications, operative time, as well as postoperative complications, postoperative pain and the need for analgesics, and hospital stay. Patients were followed up in the outpatient clinic for the detection of any complications, with an assessment of the cosmetic results and, also, patient satisfaction of the surgery.
CONCLUSIONS	The Harmonic scalpel is a safe, efficient, and practical instrument to use during laparoscopic cholecystectomy, especially if used as a sole working instrument, with complete hemobiliary stasis. Its application shortens operative time and decreases accidental bile spillage; consequently, it decreases postoperative complications and may shortens length of hospitalization. Downsizing the number or size of laparoscopy trocars improved the results of minimal invasiveness that may lead to better recovery, less pain, improved cosmesis, and better patient satisfaction.
LIMITATIONS	None

Study Quality Assessment

STUDY IDENTIFIER	Redwan 2010
RANDOMIZATION (Description)	Patients were divided into SC and HS groups (n=160)
ALLOCATION CONCEALMENT (Description)	All patients were randomly assigned
BLINDING (yes/no)	Not mentioned
WITHDRAWALS	
Yes/No?	No
How many?	Not applicable
Reasons for withdrawal	Not applicable
ALL OUTCOMES REPORTED?	Yes
REMARKS	

Study Data

Study identifier		
	Harmonic scalpel	Conventional
Duration of stay (in days)		
Range	1	1-2
Mean ± SD	1 ± 0	1.53 ± 0.51
Duration of surgery (in minutes)		
Range	9-30	35-55
Mean ± SD	16.8± 6.8	44.01 ± 6.47
Gallbladder Perforation	8	11
Biliary soaking	1	0

The Profile of Acute Encephalitis Cases Admitted at the Philippine Children's Medical Center from 2008-2012: A 5 Year Retrospective Study

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Supervising investigators*:* **Lillian V. Lee, MD, Marilyn H. Ortiz, MD**

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Endorsed by: **Teresita N. Rabanal, MD**
Head, Neuroscience Center, PCMC

ABSTRACT

BACKGROUND: The common etiologies of encephalitis are Japanese B encephalitis and Herpes simplex virus encephalitis and also autoimmune mediated causes like the anti-N-Methyl D-Aspartate receptor (NMDAR) encephalitis. These are known for their propensity to cause severe neurologic complications.

OBJECTIVES: 1.To determine the incidence of acute encephalitis among pediatric patients admitted in a tertiary hospital from 2008-2012 based on: demographic, socio-economic and clinical profile; 2. To determine other variables related with the incidence of encephalitis such as presence of non-specific signs and symptoms, presence of Neurologic signs and symptoms and the diagnostics used like Cerebrospinal fluid, Electroencephalogram and neuroimaging; 3.To determine the different hospital epidemiological indices of encephalitis among pediatric patients.

METHODOLOGY: We reviewed the medical records of all encephalitis cases admitted in a tertiary hospital from January 2008 to December 2012. Viral studies on the serum and CSF were obtained from the Philippine Research Institute of Tropical Medicine while specimen for Anti-NMDAR were sent to Dalmau Laboratory in Barcelona, Spain and to Oxford Radcliffe Hospitals, Pathology Laboratory in UK.

RESULTS: Among the 109 cases reviewed, only 19 (18%) cases were subsequently verified as to etiology. Most of the cases were Japanese B encephalitis (68%). Majority belongs to 5-9 age group with male preponderance.

CONCLUSION: Most of the cases (66%) had no neurologic deficit upon discharge with only 4.5% mortality rate

KEY WORDS: Viral Encephalitis; Anti N-Methyl D Aspartate receptor encephalitis; Japanese B encephalitis; Herpes Simplex virus encephalitis; choreoathetoid; orofacial dyskinesias

INTRODUCTION

The clinical involvement of the central nervous system (CNS) is an unusual manifestation of human viral infection. The spectrum of brain involvement and the outcome of the disease are dependent on the specific pathogen, the immunological state of the host and a range of environmental factors. Although specific therapy is limited to only several viral agents, correct diagnosis, and supportive and symptomatic treatment (when no specific therapy is available) are mandatory to ensure the best prognosis.

Acute encephalitis syndrome (AES) is a constellation of clinical signs and/or symptoms, i.e. acute fever, with an acute change in mental status and/or new onset of seizures. These clinical signs suggest the patient has acute inflammation of the brain and are used by clinicians to identify patients with acute encephalitis. Viruses are regarded as the most important cause of the acute encephalitis syndrome worldwide. However, the syndrome can be associated with a range of pathogens, including acute bacterial, parasitic infections or can be autoimmune. Where population based studies have been undertaken, the incidence ranges between 3.5 and 7.4 cases per 100,000 patient-years.[1]

Acute encephalitis can be associated with severe complications, including impaired consciousness, seizures, limb paresis or death. In Asia, the major identified cause of acute encephalitis is Japanese B encephalitis (JE) virus. It affects over 50,000 people annually, leading to 8-30% mortality and 50-60% disability, with the children bearing the brunt of the disease burden.[1]

A severe form of encephalitis associated with antibodies against NR1-NR2 heteromeres of the NMDA receptor was recently identified. NMDA receptors are ligand-gated cation channels with crucial roles in synaptic transmission and plasticity. The receptors are heteromeres of NR1 subunits that bind glycine and NR2 subunits that bind glutamate. This test is a cell based indirect immunofluorescence antibody (IFA) assay for anti-NR1, which is strongly associated with treatment-responsive limbic encephalitis. Anti-N-methyl-D- aspartate receptor (NMDAR) encephalitis is an inflammatory encephalopathic autoimmune disease frequently affecting young women with teratomas of the ovary. It is also observed in men, children and females without tumors. [2]

Clinical distinction between viral encephalitis and nonviral infective meningoencephalitis is difficult, often impossible. Epidemiological and demographic features, such as prevalent or emergent infections in the community, occupation, a history of travel and animal contacts may provide helpful clues. In acute bacterialmeningitis, meningeal symptoms of intense headache, photophobia and vomiting appear early and are usually more severe than the encephalopathic features. Presence of multiple cranial neuropathies is also suggestive of a primary meningeal process. History of continued fever and a subacute onset of symptoms with progressive obtundation and/or features of raised intracranial pressure are more typical of suppurative intracranial infections such as brain abscess. Tuberculous meningitis (TBM) also presents similarly, and in children, symptoms of TBM are often subacute in onset. In a nonepidemic setting, the most common cause of focalencephalopathic findings is HSE; however, among cases with biopsy-proven herpes encephalitis, there were no distinguishing clinical characteristics between patientspositive for HSV and those who were negative (Whitley and Gnann, 2002).

Locally, there is still no available data regarding the incidence and burden of all the causes of encephalitis syndrome in the Philippines whether it be infectious or autoimmune in origin.

REVIEW OF RELATED LITERATURE

Encephalitis is the presence of an inflammatory process in the brain parenchyma associated with clinical evidence of brain dysfunction. It can be due to a non infective condition such as in acute disseminated encephalomyelitis (ADEM) or to an infective process, which is diffuse and usually viral. Herpes simplex virus type 1 (HSV-1), varicella-zoster virus (VZV), Epstein–Barr virus (EBV), mumps, measles and enteroviruses are responsible for most cases of viral encephalitis in immune-competent individual (Koskiniemi et al.,2001).

In the most robust, prospective studies conducted in Western industrialised countries, a minimum incidence of 10.5 per 100,000 acute encephalitic syndrome cases were reported for children and 2.2 per 100,000 for adults. The minimum incidence for all ages was 6.34 per 100,000 from a tropical setting. On this basis, for ease of use in protocols and for future WHO surveillance standards, a minimum incidence of 10 per 100,000 AES cases is suggested as an appropriate target for studies of children alone and 2 per 100,000 for adults and 6 per 100,000 for all age groups.

Japanese encephalitis (JE) has been documented to be endemic in the Philippines but only few studies document the incidence by using laboratory diagnostics.The Philippine Department of Health (DOH) is particularly concerned with Region 3 since several encephalitis cases were noted to occur but still remained insufficiently characterized. JE cases were reported from Region 3 provinces such as Tarlac, Bulacan, Nueva Ecija and Pampanga as well as in other areas such as Laguna, Quezon Province and Cavite. Nationwide syndromic surveillance for meningitis and encephalitis, complemented by sentinel sites with case-based surveillance and collection of specimens for laboratory confirmation is the model used in other countries (e.g. Thailand) and recommended by WHO for estimating the disease burden due to different pathogens causing meningoencephalitis. The assumption here is that children with JE and bacterial meningitis are typically very sick and would normally be treated in a hospital; therefore, sentinel surveillance focuses on tertiary level hospitals rather than lower-level health facilities.[4]

Encephalitis with antibodies against N-methyl -D-aspartate (NMDA)-type glutamate receptors was recently recognized as a defined clinical entity. The initial reports concerned exclusively young women with ovarian germinal tumor and encephalitis. All had a number of clinical signs in common: cognitive deterioration and abnormal movements of the orofacial region and limbs. The outcome after tumor resection was favorable and the patients displayed slow clinical recovery. These patients also had antibodies against NMDA receptors, consistent with a paraneoplastic syndrome. However, the spectrum of the disease is probably wider. The diagnosis of viral encephalitis is suspected in the context of a febrile disease accompanied by headache, altered level of consciousness, and symptoms and signs of cerebral dysfunction. These may consist of abnormalities that can be categorized into four: cognitive dysfunction (acute memory disturbances), behavioural changes (disorientation, hallucinations, psychosis, personality changes, agitation), focal neurological abnormalities (such as anomia, dysphasia, hemiparesis, hemianopia etc.) and seizures. After the diagnosis is suspected, the approach should consist of obtaining a meticulous history and a careful general and neurological examination.

SIGNIFICANCE OF THE STUDY

Thus, the result of this descriptive type of study would increase the index of suspicion for encephalitis cases in the absence of readily available diagnostic tests. This study can also be utilized to generate evidence which can be presented to health policy makers in the National Capital Region and in the Philippines in general. This study can also be used by a future researcher as a basis for another research that will verify some important findings from this study.

SCOPE AND DELIMITATION OF THE STUDY

This study involves a review and analysis of case records of all acute pediatric encephalitis patients from 2008 to 2012. In as much as this is a hospital based study, it is limited to the use of secondary data which is vulnerable to selection bias arising from the selective factors that guide affected individuals to a particular medical facility. Furthermore, hospital records are sometimes incomplete and inaccurate.

OPERATIONAL DEFINITION OF TERMS

1. **Encephalitis**- is the presence of an inflammatory process in the brain parenchyma associated with clinical evidence of brain dysfunction. It can be due to a non-infective condition such as in acute disseminated encephalomyelitis (ADEM) and Anti N-methyl-

D- aspartate receptor encephalitis or to an infective process, which is diffuse and usually viral like Japanese B encephalitis and Herpes Simplex Virus encephalitis.

2. **Encephalopathy-** is defined as a disruption of brain function that is not because of a direct structural or inflammatory process. It is mediated via metabolic processes and can be caused by intoxications, drugs, systemic organ dysfunction (e.g. liver, pancreas) or systemic infection that spares the brain.

3. **Japanese B encephalitis** - is among the most important viral encephalitides in Asia, especially in rural and suburban areas where rice culture and pig farming coexist. It has also occurred rarely and sporadically in northern Australia and parts of the Western Pacific. JE is due to infection with the JE virus (JEV), a mosquito-borne flavivirus. The main JEV transmission cycle involves *Culex tritaeniorhynchus* mosquitoes and similar species that lay eggs in rice paddies and other open water sources, with pigs and aquatic birds as principal vertebrate amplifying hosts. Humans are generally thought to be dead-end JEV hosts, i.e. they seldom develop enough viremia to infect feeding mosquitoes. Fewer than 1% of human JEV infections result in JE. Approximately 20–30% of JE cases are fatal and 30–50% of survivors have significant neurologic sequelae.

4. **Herpes Simplex Virus encephalitis** - Herpes simplex encephalitis (HSE) is an acute or subacute illness that causes both general and focal signs of cerebral dysfunction. Brain infection is thought to occur by means of direct neuronal transmission of the virus from a peripheral site to the brain via the trigeminal or olfactory nerve. The exact pathogenesis is unclear, and factors that precipitate HSE are unknown.

5. **Anti-N-Methyl-D-aspartate receptor encephalitis** - is an inflammatory encephalopathic autoimmune disease frequently affecting young women with teratomas of the ovary. It is also observed in men, children, and females without tumors. The N-methyl-D-aspartate receptor (NMDAR) is an ion channel located in the post-synaptic membrane that plays a key role in synaptic transmission and plasticity. The receptor is made up of two subunits, NR1 and NR2, that contain extracellular epitopes. Anti-NMDAR antibodies are directed against the extracellularepitope of the NR1 subunit. This test is a cell-based indirect immunofluorescence antibody (IFA) assay for anti-NR1, which is strongly associated with treatment-responsive limbic encephalitis.

6. **Probable cases** - is a suspected case that occurs in close geographic and temporal relationship to a laboratory-confirmed case, in the context of an outbreak.

7. **Confirmed cases** - is a suspected case that has been laboratory-confirmed.

8. **Annual Hospital Incidence Rate** - this refers to the computed total number of encephalitis cases admitted in the hospital in a year divided by the total number of Pediatric Admissions in the same year multiplied by a factor (ie. I000 or 10,000 or 100,000 population).

9. **Annual Hospital Encephalitis Case Fatality Rate** - this refers to the computed total number of encephalitis cases admitted but died in the hospital in a year divided by the total number of encephalitis cases admitted in that hospital in the same year multiplied by 100.

10. **Annual Pediatric Encephalitis Survival Rate** - this refers to the computed total number of encephalitis cases admitted and survived in the ward of the hospital in a year divided by the total number of encephalitis cases admitted in the same year multiplied by 100.

OBJECTIVES

General Objective:

To determine the incidence of acute encephalitis among pediatric patients admitted in a tertiary hospital from 2008-2012 based on:

1. demographic
2. socio-economic and
3. clinical profile

Specific Objective:

1. To determine the incidence of encephalitis based on the following variables.
   - 1.1 Age Groups
   - 1.2 Sex
   - 1.3 Etiology
     - 1.3.1 Probable
     - 1.3.2 Confirmed
       - 1.3.2.1 Japanese B
       - 1.3.2.2 Anti NMDAR
       - 1.3.2.3 Herpes Simplex Virus
   - 1.4 Place of Residence
2. To determine other variables related with the incidence of encephalitis such as:
   - 2.1 Presence of non-specific signs and symptoms
   - 2.2 Presence of Neurologic signs and symptoms
   - 2.3 Diagnostics
     - 2.2.1 Cerebrospinal fluid CSF)
     - 2.2.2 Electroencephalogram (EEG)
     - 2.2.3 Neuroimaging (Cranial Ultrasound, Cranial Computed Tomography scan, Cranial Magnetic Resonance Imaging)
   - 2.4 Outcome upon discharge
3. To determine the following hospital epidemiological indices of encephalitis among Pediatric patients from 2008 to 2012:
   - 3.1 Annual Hospital Incidence Rates
   - 3.2 Annual Hospital Case Fatality Rates
   - 3.3 Annual Hospital Survival Rates

METHODOLOGY

This study utilized a descriptive type of study in which a retrospective analysis of medical records of pediatric encephalitis cases admitted in a tertiary hospital from 2008 to 2012 was done.

Sample size consisted of one hundred nine (109) pediatric patients diagnosed with encephalitis. No sample size estimation was done since total enumeration of cases within the five year period was adopted.

The variables being considered in this profile of encephalitis cases are age groups, sex, place of residence, etiology, nutritional status, presenting signs and symptoms, diagnostics used, response to treatment and outcome upon discharge.

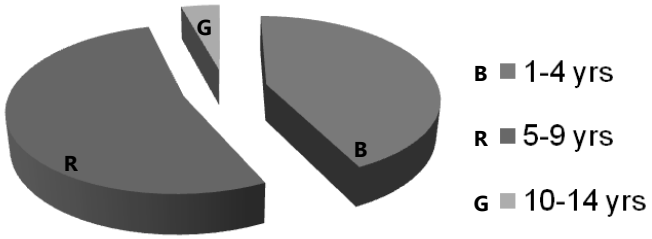
Descriptive statistics was used in this study. Graphical and tabular presentations were utilized as tools in presenting the demographic, clinical and socio-economic profile of the subjects.

PRESENTATION OF RESULTS

I. DEMOGRAPHIC PROFILE

A. Age Groups

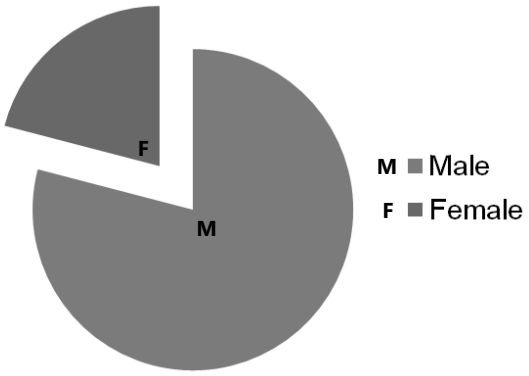
Figure. 1. Percentage Distribution of Encephalitis Cases According to Age, n = 109, 2008-2012



The highest percentage of encephalitis cases belong to age groups 5-9 years old (37%) followed by the 1-4 years old (30%) and lastly by the age group 10-14 years old (3%).

B. Gender

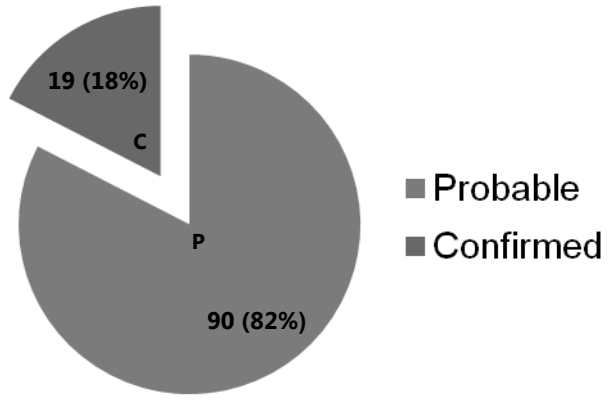
Figure. 2. Percentage Distribution of Encephalitis Cases According to Gender, n = 109, 2008-2012



The proportion of male subjects (80%) is higher than the female subjects (20%).

C. Etiology

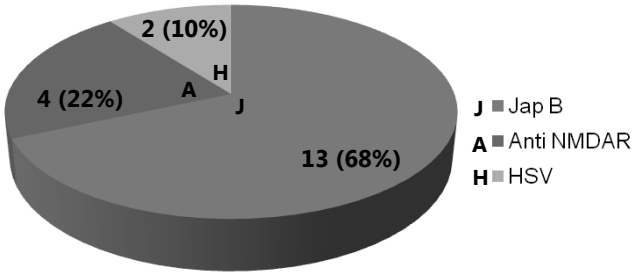
Figure. 3. Percentage Distribution of Encephalitis Cases According to Etiology, n=109, 2008-2012



Among the 109 encephalitis cases that were reviewed, only 19 (18%) were subsequently verified as to their etiology. The 90 (82%) cases manifested signs and symptoms of encephalitis but tested negative in the diagnostic tests.

D. Etiology

Figure. 4. Percentage Distribution of Confirmed encephalitis cases according to Etiology, n=19, 2008-2012



Among the 19 confirmed cases, majority were Japanese B encephaltis (68%) followed by Anti-NMDAR encephalitis (22%).

E. Place of Residence

Table 1. Percentage Distribution of encephalitis cases according to Place of Residence, n=109, 2008-2012

Region	N=109
NCR	61 (55%)
III	16 (15%)
IV	13 (12%)
II	11 (10%)
V	8 (8%)

Most of the encephalitis cases came from the National Capital Region (55%) followed by Region III (15%) and Region IV (12%).

F. Place of Residence

Table 2.1 Percentage Distribution of confirmed Japanese B encephalitis cases according to Place of Residence, n=13, 2008-2012

Region	N=13
IV	6 (46%)
III	3 (23%)
V	2 (15%)
NCR	1 (8%)
II	1 (8%)

Majority of the Japanese B encephalitis cases came from Region IV (46%) followed by Region III (23%) and Region V (15%).

Table 2.2 Percentage Distribution of confirmed Anti- NMDAR encephalitis cases according to Place of Residence, n=4, 2008-2012

Region	N=4
II	1 (25%)
III	1 (25%)
NCR	1 (25%)
IV	1 (25%)

The 4 cases of Anti NMDAR encephalitis came from Region II (25%), Region III (25%), National Capital Region (25%) and Region IV (25%).

Table 2.3 Percentage Distribution of confirmed Herpes Simplex Virus encephalitis cases according to Place of Residence n=2, 2008-2012

Region	N=2
III	1 (50%)
NCR	1 (50%)

The 2 cases of Herpes Simplex virus encephalitis came from Region III and National Capital Region.

II.CLINICAL FINDINGS

G. Presenting Signs and Symptoms

Table 3. Non specific Signs and Symptoms elicited from the history of encephalitis, N=109, 2008-2012

Symptoms	No. of Cases	Percent (%)
Fever	109	100%
Headache	88	80%
Vomiting	82	75%
Chills	30	28%
Nausea	25	23%
Decrease appetite	25	23%
Dizziness	24	22%

All (100%) of the patients had fever during the first 4-5 days of their illness. Almost 75-80% of cases experienced headache and vomiting. Thirty (28%) of patients had chills. Only 22% 23% of cases had nausea, decreased appetite and dizziness.

III. NEUROLOGIC FINDINGS

A. Presence of Neurologic Findings

Table 4. Presence of Neurologic findings elicited from the history of encephalitis, N= 109, 2008-2012

Neurologic	No. of Cases	Percent (%)
Altered sensorium	93	85%
Neck Rigidity	89	82%
Seizures	72	66%
Involuntary movements	70	64%
choreoathetoid	21	19%
catatonia	15	14%
Rigidity	13	12%
Orofacial dyskinesia	12	11%
Dystonic posturing	9	8%
Abulia	65	60%
Abnormal muscle tone	56	51%
Abnormal motor function	50	45%
Abnormal reflexes	50	45%

Majority of the patients manifested encephalopathic symptoms such as altered sensorium (85%), neck rigidity (82%), seizures (72%) and abulia (60%). Involuntary movements were also noted in 64% of cases. The 5 movement disorders noted were choreoathetoid (19%), catatonia (14%), rigidity (12%), orofacial dyskinesias (11%) and dystonic posturing (8%).

B. Neurologic Findings of Japanese B encephalitis cases on the time they were first seen. They were arbitrarily grouped as acute (< 7 days), subacute (7-12 days), and chronic (>14 days).

Table 4. Neurologic findings of Japanese B encephalitis, N= 13, 2008-2012

	< 7days	days	>14days
Altered sensorium	8	5	-
Abulia/Masked like facies	8	5	-
Involuntary movements	3	9	1
Catatonia	1	4	-
Choreoathetoid	-	1	1
Orofacial dyskinesia	2	4	-
Hypertonia	7	6	-
Hyperreflexia	7	6	-
Presence of Babinski	7	6	-
Seizures	9	4	-
Behavioral changes	1	1	-
Neck Rigidity	3	10	-

Most of the neurological signs and symptoms occurred within 3-5 days from the onset offever except for the involuntary movements which were noted mostly during the second week of illness.Abulia or mutism which were seen mostly during the first week of illness were described with an expressionless face even when the patient cried or grimaced. Seizures also appeared more frequent during first week of illness.

C. Neurologic Findings of Anti-NMDA receptor encephalitis cases on the time they were first seen. They were arbitrarily grouped as acute (< 7 days), subacute (7-12 days), and chronic (>14 days).

Table 5. Neurologic findings of Anti-NMDAR encephalitis, N= 4,2008-2012

	< 7days	7-14days	>14days
Altered sensorium	1	3	-
Involuntary movements			
Catatonia	1	3	-
	1	-	-
Choreoathetoid	-	1	-
Orofacial dyskinesia	-	1	-
Dystonic posturing	-	1	-
Behavioral Changes	3	1	-
Seizures	2	2	-
Hypertonia	2	2	-
Hyperreflexia	1	3	-
Presence of Babinski	-	4	-

Most of the Anti-NMDAR cases manifested behavioral changes, seizures and hypertonia during the first week of illness whereas the altered sensorium, involuntary movements, hyperreflexia and presence of Babinski sign were observed during the second week of illness.

D. Neurologic Findings of Herpes simplex virus encephalitis cases on the time they were first seen. They were arbitrarily grouped as acute (< 7 days), subacute (7-12 days), and chronic (>14 days).

Table 6. Neurologic findings of Herpes Simplex virus encephalitis, N= 2, 2008-2012

	< 7days	7-14days	>14days
Altered sensorium	-	1	1
Involuntary movements			
Orofacial dyskinesia	-	1	-
Hyperreflexia	-	2	-
Neck rigidity	-	2	-
Presence of Babinski	-	2	-

Of the only 2 cases of Herpes Simplex virus encephalitis, the neurologic signs and symptoms were mostly noted during the second week of illness.

IV. BLOOD AND CEREBROSPINAL FLUID (CSF) FINDINGS

Viral studies on the serum and CSF were obtained and sent to Philippine Research Institute of Tropical Medicine, Manila while specimen for Anti-NMDAR were sent to Dalmau Laboratory in Barcelona, and to Dr. Angela Davis in Oxford Radcliffe Hospitals, Pathology Laboratory in United Kingdom.

Opening pressure on lumbar tap were taken in all patients. The highest pressure was 28mm water. Among the confirmed cases, the succeeding tables will show the results of the cerebrospinal fluid based on the time of extraction.

Table 7. Peripheral Count of Japanese B encephalitis cases, N=13, 2008-2012

WBC (/cu L)	< 7days (N=7)	7-14days (N=5)	>14days (N=1)
<5	-	-	-
5-10,000	-	2	-
10,001-15,000	1	3	-
15,001-20,000	2	-	-
20,001-25,000	2	-	-
25,001-30,000	2	-	-
30,001-35,000	-	-	-

Table 7 shows that mild leukocytosis was seen in 54% of cases during the first week of illness. The highest was 32,000/cu L initially. By the second week, most counts were already within the normal limits.

Table 8. Cerebrospinal fluid result of Japanese B encephalitis cases, N=13, 2008-2012

A.WBC (10^6/cu mm)	< 7days (N=7)	7-14days (N=5)	>14days (N=1)
<10	-	-	-
11-100	-	-	-
101-200	2	3	-
201-300	3	2	-
301-400	1	-	1
401-500	1	-	-
>500	-	-	-

Table 9. Cerebrospinal fluid result of Japanese B encephalitis cases, N=13, 2008-2012

A. WBC Differential count	< 7days (N=7)	7-14days (N=5)	>14days (N=1)
L>N	5	2	1
N>L	2	3	-
B. Sugar (mg%)			
>45%	4	4	1
<45%	3	1	-
C. Protein (gm/L)			
15-45	5	2	-
46-100	1	3	1
101-150	1	-	-
151-200	-	-	-

L- lymphocytic; N- Neutrophilic

Table 8 showed pleocytosis in the first week ranged from 101-470cells/cu mm. The counts gradually reversed so that by the third week, almost 90% were normal. Lymphocytosis was predominant in the first week of the disease, Table 9-A. Occasionally polymorphonuclear cells predominated in the first week. The sugar levels were mostly normal (58%) except in three, Table 9-B. The protein levels were commonly normal (71%), and when elevated, mild increased levels were seen even in the late period, Table 9-C. However, levels higher than 100 mg% were not seen after the first week.

Table 10. Peripheral Count of Anti-NMDAR encephalitis cases, N=4, 2008-2012

WBC (/cu L)	< 7days (N=1)	7-14days (N=3)	>14days (N=0)
<5	-	-	-
5-10,000	-	2	-
10,001-15,000	1	1	-
15,001-20,000	-	-	-
20,001-25,000	-	-	-
25,001-30,000	-	-	-
30,001-35,000	-	-	-

Table 10 showed that mild leukocytosis was seen in only 25% during the first two weeks of illness.

Table 11. Cerebrospinal fluid result of Anti NMDAR encephalitis cases, N=4, 2008-2012

WBC (10^6/cu mm)	< 7days (N=1)	7-14days (N=3)	>14days (N=0)
<10	-	-	-
11-100	-	1	-
101-200	1	2	-
201-300	-	-	-
301-400	-	-	-
401-500	-	-	-
>500	-	-	-

Table 12. Cerebrospinal fluid result of Anti NMDAR encephalitis cases, N=4, 2008-2012

A. WBC Differential count	< 7days (N=1)	7-14days (N=3)	>14days (N=0)
L>N			-
N>L	1	1	-
	-	2	
B. Sugar (mg%)			
>45%	1	4	-
<45%	-	1	-
C. Protein (gm/L)			
15-45	-	2	-
46-100	1	1	-
101-150	-	1	-
151-200	-	-	-

L- lymphocytic; N- Neutrophilic

Tables 11 and 12 showed that mild pleocytosis ranged from 11-200 cells/cu mm during the first and second week of illness. Differential count was noted with equal proportion. Sugar and protein levels were within normal limits.

Table 13. Peripheral Count of Herpes Simplex virus encephalitis cases, N=2, 2008-2012

WBC (/cu L)	< 7days (N=0)	7-14days (N=1)	>14days (N=1)
<5	-	-	-
5-10,000	-	1	1
10,001-15,000	-	-	-
15,001-20,000	-	-	-
20,001-25,000	-	-	-
25,001-30,000	-	-	-
30,001-35,000	-	-	-

Tables 13 showed that the two cases had normal peripheral counts by the second and third week.

Table 14. Cerebrospinal fluid result of Herpes Simplex virus encephalitis cases, N=2, 2008-2012

WBC (10^6/cu mm)	< 7days (N=0)	7-14days (N=1)	>14days (N=1)
<10	-	-	-
11-100	-	-	-
101-200	-	1	-
201-300	-	-	1

Table 15. Cerebrospinal fluid result of Herpes Simplex virus encephalitis cases, N=2, 2008-2012

	< 7days (N=0)	7-14days (N=1)	>14days (N=1)
A. WBC Differential count			
L>N	-	1	1
N>L	-	-	-
B. Sugar (mg%)			
>45%	-	1	1
<45%	-	-	-
C. Protein (gm/L)			
15-45	-	-	-
46-100	-	-	1
101-150	-	1	-
151-200	-	-	-

L- lymphocytic; N- Neutrophilic

The CSF leukocyte count, different count, sugar and protein levels of the two HSV encephalitis cases were within normal limits when they were examined by the second and third week of illness.

V. ELECTROENCEPHALOGRAM(EEG) FINDINGS

All encephalitis cases underwent electroencephalogramupon admission. They were arbitrarily grouped as acute (< 7 days), subacute (7-12 days), and chronic (>14 days) based on the days of their illness when they were admitted.

Table 16. EEG findings of all the confirmed encephalitis cases, N=19, 2008-2012

I. Japanese B (N=13)	< 7days (N=5)	7-14days (N=6)	>14days (N=2)
Abnormal			
Generalized slowing	5	4	-
Focal slowing	-	2	-
Normal	-	-	2
II. Anti-NMDAR (N=4)	< 7days (N=1)	7-14days (N=3)	>14days (N=0)
Abnormal			
Generalized slowing	1	2	-
Focal slowing	-	1	-
Normal	-	-	-
III. HSV (N=2)	< 7days (N=0)	7-14days (N=2)	>14days (N=0)
Abnormal			
Generalized slowing	-	1	-
Focal slowing with Left temporal discharges	-	1	-
Normal	-	-	-

Most of the Japanese B encephalitis cases (38%) showed generalized slowing of the background activity during the first week of illness and decreased to 30% by the second week of illness. 15% of the cases also showed focal slowing on the fronto-temporal regions by the second week. During the third week, 15% of the Japanese B encephalitis cases had normal EEG results.

Of the four Anti-NMDAR encephalitis cases, 3 (75%) showed generalized slowing of the background activity during their first two weeks of illness while only 1 (25%) showed intermittent slowing over the left fronto-temporal regions during the second week of illness.

Of the two cases of HSV, 1 (50%) showed generalized slowing of the background activity and the other case showed focal slowing with epileptiform discharges over the left temporal region. Both cases however were seen during their second week of illness.

VI. NEUROIMAGING FINDINGS

Table 14. Neuroimaging findings of all the confirmed cases (Japanese B (N=13), Anti-NMDAR (N=4), Herpes simplex virus (N=2)) encephalitis cases, N=19, 2008-2012

I. Japanese B (N=13)	< 7days (n=2)	7-14days (N=7)	>14days (N=4)
Abnormal	2	7	-
Normal	-	-	4
II. Anti-NMDAR (N=4)	< 7days (N=1)	7-14days (N=4)	>14days (N=0)
Abnormal	1	3	-
Normal	-	-	-
III.HSV (N=2)	< 7days (N=0)	7-14days (N=2)	>14days (N=0)
Abnormal	-	2	-
Normal	-	-	-

Abnormal findings in the neuroimaging of most of the Japanese B encephalitis cases (54%) were seen during their second week of illness while 15% were seen during the first week of illness. Cranial magnetic resonance imaging, computed topography and ultrasound were done. All showed cerebral edema with hyperintense signal abnormalities over the basal ganglia, brainstem and bilateral thalamic regions. Four (30%) of the Japanese B encephalitis cases showed normal results taken during their 3rd to 4th week of illness.

Of the four Anti-NMDAR cases, 3 (75%) showed cerebral edema and areas of hyperintensity in the medial temporal lobes and hippocampus taken during the second week of illness. One case (25%) showed meningeal enhancement on cranial CT done during the first week of illness.

Cerebral edema and hemorrhage seen as hypointense and hyperintense in the Left fronto-temporal areas on T2 and T1 weighted images respectively were seen in the two HSV patients during the 10th-12th week of illness.

VII. OUTCOME

Table 15. Outcome of all the encephalitis cases upon discharge (Japanese B (N=13), Anti-NMDAR (N=4), Herpes simplex virus (N=2)) encephalitis cases, N=109, 2008-2012.

Category	**N=109**
No deficit	61 (66%)
Mild deficit	25 (23%)
Moderate to severe deficit	18 (16.5%)
Died	5 (4.5%)

Majority of the encephalitis cases (66%) did not show any neurologic deficit upon discharge. Mild deficit was seen in 23% while 16.5% manifested moderate to severe deficit. Five cases (4.5%) died during their confinement. Two of the mortalities had severe pneumonia and 3 patients had disseminated intravascular coagulopathy.

Table 16. Outcome of the Japanese B encephalitis cases upon discharge, N=13, 2008-2012.

Category	**N=13**
No deficit	1
Mild deficit	8
Moderate to severe deficit	2
Died	2

Majority of the Japanese B encephalitis (62%) showed mild neurologic deficit, 2 (15%) had moderate to severe deficit and two patients died. Only 1 (8%) patient was discharged with no neurologic deficit.

Table 17. Outcome of the Anti-NMDAR encephalitis cases upon discharge, N=4, 2008-2012.

Category	**N=4**
No deficit	-
Mild deficit	3
Moderate to severe deficit	1
Died	-

Most of the Anti-NMDAR encephalitis (75%) showed mild deficit upon discharge while 1 (25%) had moderate to severe neurologic deficit.

Table 18. Outcome of the Herpes Simplex virus encephalitis cases upon discharge, N=2, 2008-2012.

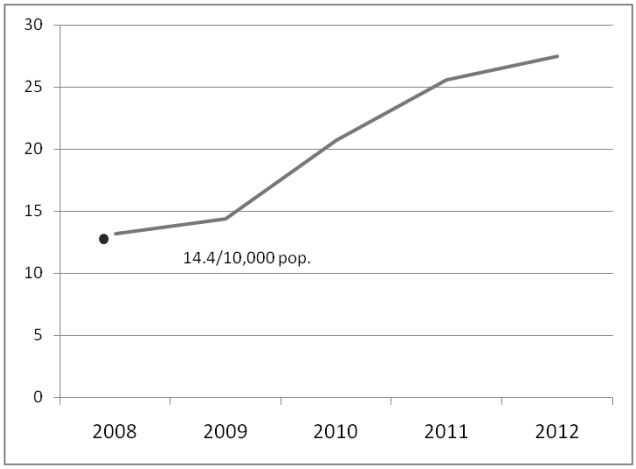
Category	N=2
I-No deficit	-
II-Mild deficit	1
III-Moderate to severe deficit	-
IV-Died	1

Mild deficit was manifested by one (50%) of the two HSV patients while the other died of severe systemic infection.

VIII. HOSPITAL EPIDEMIOLOGIC INDICES

A. Annual Hospital Incidence Rates of Encephalitis

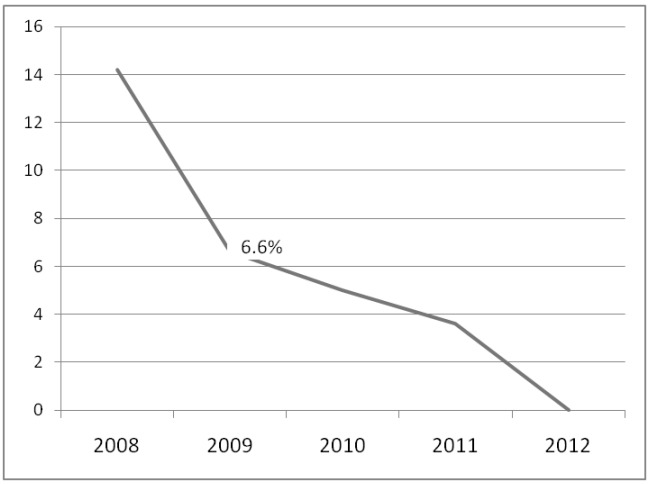
Figure 5. Annual Hospital Incidence Rates of Encephalitis from 2008 to 2012



The line graph above shows an increasing trend of Annual Hospital Incidence Rates of Encephalitis from 2008 to 2012 in a tertiary hospital. Most encephalitis cases occurred in 2012.

B. Annual Hospital Case Fatality Rates of Encephalitis

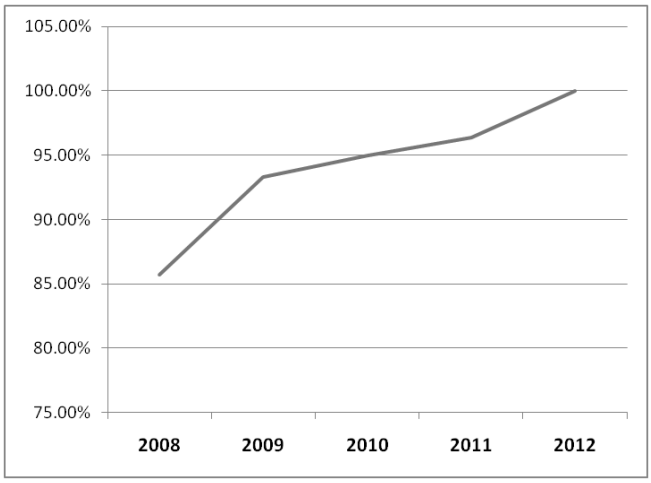
Figure 6. Annual Hospital Case Fatality Rates of Encephalitis from 2008 to 2012



The line graph above shows a decreasing trend of Annual Hospital Case Fatality Rates of Encephalitis from 2008 to 2012in a tertiary hospital

C. Annual Pediatric Encephalitis Survival Rate

Figure 7. Annual PediatricEncephalitisSurvival Rate from 2008 to 2012



The line graph above shows an increasing trend of Annual Hospital Survival Rates of Encephalitis from 2008 to 2012in a tertiary hospital.

DISCUSSION

The diagnosis of viral encephalitis is suspected in the context of a febrile disease accompanied by headache, altered level of consciousness, and symptoms and signs of cerebral dysfunction. These may consist of abnormalities that can be categorized into four: cognitive dysfunction (acute memory disturbances), behavioural changes (disorientation, hallucinations, psychosis, personality changes, agitation), focal neurological abnormalities (such as anomia, dysphasia, hemiparesis, hemianopia etc.) and seizures. After the diagnosis is suspected, the approach should consist of obtaining a meticulous history and a careful general and neurological examination. The neurological manifestations gathered from the history of our patients were generally similar to the observations of other authors. In Japanese B encephalitis cases, abulia or mutism accompanied by masked facies were more common and prominent in our study and presented as the initial neurological deficit in 8 cases. Previous studies have described masked facial expressions to be a characteristic feature of JEV encephalitis although other viral or nonspecific encephalitis can produce a similar feature. Seizures have been observed to be more common in younger age group. Most of the Anti -NMDAR cases manifested behavioral changes, seizures and hypertonia.

Demographic Profile

The history is mandatory in the assessment of the patient with suspected viral encephalitis.The geographical location as well as the recent travel history could be of relevance to identify causative pathogens that are endemic or prevalent in certain geographical regions. The mode of disease course up to the appearance of the neurological signs may provide clues to the aetiology. Likewise, the evolution of the clinical signs and their severity depend on host and other factors such as immune state and age and cannot serve as guidelines to identify the pathogen. In general, the very young and the very old have the most extensive and serious signs of encephalitis.

Clinical Profile

Clinical distinction between viral encephalitis and non viral infective meningoencephalitis is difficult, often impossible. The neck rigidity in the subacute and chronic periods was mostly due to increased muscular tone rather than meningeal irritation. The choreoathetosis seen in the 2nd week of illness probably surface when the level of consciousness improved because choreic patients are known to lose these abnormal movements during sleep. Choreoathetosis may also be chronic sequelae of the disease. These involuntary movements can be attributed to thalamic -subthalamic lesions and basal ganglia. The pathological reflexes correlate well with motor or tone abnormalities.

Laboratory Profile

Peripheral blood count and cellular morphology, arehelpful in separating viral from non-viral infections. Lymphocytosis in the peripheral blood is common in viral encephalitis. The auxiliary studies that examine viral infections of the nervous system include studies that characterize the extent and nature of CNS involvement (EEG and neuroimaging), microbiological attempts to identify the pathogen and histopathology. EEG is generally regarded as a non-specific investigation, although it is still sometimes a useful tool in certain situations. Thus, leucoencephalitides shows more diffuse slow activity in the EEG. Likewise, the EEG findings in post-infectious encephalitides differ from infectious encephalitis only in the time schedule of the abnormalities. The main benefit of EEG is to demonstrate cerebral involvement during the early state of the disease.

CONCLUSION

The geographical location of encephalitis cases were observed mostly in the rural areas and were correlated on the different practices of the people. The characteristic neurological features in our cases that could be considered as Japanese B encephalitis are abulia with masked facies, variable changes in mentation, and asymmetric and irregular distributionof motor and tone abnormality. For the anti-NMDAR cases, they manifested behavioural

changes, seizures and hypertonia during the first week of illness whereas the altered sensorium, involuntary movements, hyperreflexia and presence of Babinski sign during the second week of illness. The first week of the disease prominently showed neutrophilic pleocytosis in theperipheral smear while the cerebrospinal fluid showed leucocytic lymphocytosis, mild to normalprotein level and normal sugar values. Most of the Japanese B encephalitis cases and anti-NMDAR encephalitis showed generalized slowing of the background activity during the 10^{th}-14^{th} day of illness while herpes simplex virus encephalitis showed focal background slowing and there is a temporal focus showing lateralized epileptiform discharges. However, this is usually temporary.

Magnetic resonance imaging (MRI) is more sensitiveand specific than CT for the evaluation of encephalitis. Neuroimaging findings in Japanese B encephalitis showed cerebral edema with hyperintense signal abnormalities over the basal ganglia, brainstem and bilateral thalamic regions. Cranial MRI findings for anti-NMDAR encephalitis cases are cerebral edema and areas of hyperintensity in the medial temporal lobes and hippocampus while areas of hemorrhage were seen as hypointense and hyperintense in the Left fronto-temporal areas on T2 and T1 weighted images respectively in HSV patients. Most of the encephalitis cases only manifested mild deficit upon discharge.

Based on the hospital data for the past 5 years, there is an increasing trend of incidence and survival rates and a decreasing case fatality rates.

REFERENCES

1. Ajit Rayamajhi, Imran Ansani, et al. Clinical and Prognostic features among children with acute encephalitis syndrome in Nepal: a retrospective study. BMC Infectious Diseases 2011.
2. Anti-NMDA Receptor (NR1) IgG antibodies for diagnosis of Limbic Encephalitis. November 2010.
3. Lebas Axel, MD et al., Expanding Spectrum of Encephalitis with NMDA Receptor Antibodies in young Chlidren, Journal of Child Neurology. June 13, 2009.
4. Dalmau J, et al. Anti-NMDA-receptor encephalitis: Case series and analysis of the effects of antibodies. *Lancet Neurology* 2008;7(12):1091–8.
5. Granerod J, Crowcroft NS: The epidemiology of acute encephalitis.Neuropsychol Rehabil 2007, 17(4-5):406-428.
6. San Luis, Amado, Curtis G. Hayes, et al. The Neurologic features of Japanese Encephalitis in the Philippines. Philippine Journal of Microbiology Infectious Disease, 1990.
7. WHO- Recommended standards for Surveillance of Selected vaccines- preventable diseases WHO/V & B/03.01, January 2006. Available from: http:// www.who.int/vaccines-documents/ DocsPDF06/843.pdf
8. Grant L. Campbell, Susan L. Hills, et al. Estimated Global incidence of Japanese encephalitis: A systemic review. Bulletin World Health Organization, 2011; 89:766-774E doi:10.2471.
9. Ances BM, Vitaliani R, Taylor RA, et al. Treatment-responsive limbic encephalitis identified by neurophil antibodies: MRI and PET correlates. Brain. 2005;128 (pt 8):1764-1777.

A COMMUNITY-BASED, COMPARATIVE STUDY OF EXECUTIVE FUNCTIONING OF MUSICIANS AND NON-MUSICIANS

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INTRODUCTION

It is estimated that the proportion of people over 60 years old will increase from 10% in 2000 to 21.8% in 2050 in all regions.[1] A critical consequence of this rise will be the exponential increase in the prevalence of neurodegenerative diseases and other pathologies common in latter stages of life.[2] With this in mind, strategies to prevent cognitive decline and promote a healthy physical and psychological lifestyle are keystones for the future.

Reports of non-pharmaceutical interventions for the prevention of cognitive decline in dementia patients were use of music therapy. By listening to music, patients with Alzheimer's disease (AD) showed improvement in categorical word fluency[5], autobiographical memory[6], and the memory of lyrics[7].

Executive functions (EF) encompass a number of cognitive processes that allow for independent and self-regulated behavior.[25] These cognitive constructs include inhibition, problem solving, goal-directed behavior, and maintenance of information in working memory. Another component of EF is cognitive flexibility, the ability to adjust to novel or changing task demands which is often captured through a task-switch design.[26]

This study aims to evaluate how musical participation throughout the life span may influence cognitive functioning, specifically executive functioning.

RELATED LITERATURE

Musical participation is easily quantified in terms of number of years of training or participation, and there is data supporting differential brain organization for amateur musicians.[9,10,11] Therefore, investigation of amateur musicians and non-musicians offers an excellent model for how deliberate long-term practice and engagement in cognitively stimulating activities may alter brain development and influence cognition.[12] Parbery-Clark[8], reported that older musicians showed greater auditory working memory relative to non- musicians, and suggested that musical training might reduce the impact of age-related decline. Results from these studies suggest that music therapy might be useful for maintaining cognitive function in normal elderly adults and dementia patients.

Musical leisure activities, including playing an instrument, listening to music, and creating music, stimulate a variety of cognitive functions and may be informative regarding training induced brain plasticity that may be recruited in advanced age to compensate for age-related cognitive decline.[13-14] Successfully acquiring musical expertise requires at least a decade of training, which typically begins at an early age and includes intensive repetitive practice that may result in plastic brain reorganization. Evidence suggests that musical activity may be associated with cortical reorganization including enhanced

sensorimotor functions in young instrumental musicians.[15-21] However, there are there are limited studies examining how the extent of musical experience throughout the life span may influence maintenance of cognitive functioning in advanced age.

Various extra and intra-curricular activities have been shown to improve EF skills in children. Extracurricular activities shown to enhance EF development in school-age children include martial arts, mindfulness training, and physical exercise. [27] While these findings support the potential for extracurricular activities to boost EF skills, interpretations are limited due to methodological weaknesses in these studies. Limitations include, for instance, a lack of control groups and/or the potential influence of other factors leading to improved performance, such as motivation or social engagement.

One extracurricular activity of recent interest to researchers is music, and its link to EF skills has been debated. Playing a musical instrument (especially within an ensemble setting) requires many sub-skills associated with EF such as sustained attention, goal-directed behavior and in particular the task -switching demands of cognitive flexibility. Individuals with musical training have demonstrated enhanced general cognitive, academic and language abilities when compared to those without musical training, and this connection may be mediated by EF. [28, 29] For example, higher intellectual functioning has been reported in children and adults with as compared to those without musical training through both cross-sectional and longitudinal study designs, though this connection remains debated.[30] Musicians have shown enhanced language skills compared to non-musicians across several domains, namely vocabulary knowledge, pitch processing in speech, selective attention for speech in noise, and prosody perception. [31]

Enhanced processing in adult musicians has been reported for components of EF, demonstrated through a nonverbal spatial task and both auditory and visual Stroop tasks.[32, 33] One study reported significant associations between musical training and numerous EF constructs in children [34], whereas in another study no superior performance was found on any measures of EF in musically trained children compared to those without training.[35] The discrepant findings may be due to no comparisons to a control group that was not carefully screened to have no musical experience; unknown variation in the intensity and longevity of training of the musicians; or the inconsistent implementation of standardized EF measures. Differences in socioeconomic status between musicians and non-musicians may also be the source of inconsistent findings.

It is evident that musical training relates to cognitive abilities, but it remains somewhat unclear which constructs of EF, if any, may mediate this connection.

GENERAL OBJECTIVE

- To compare the executive functioning (EF) skills between musicians and non-musicians

SPECIFIC OBJECTIVES

- To correlate the relationship of executive functioning (EF) skills of musicians and the number of musical activities participated in
- To correlate the relationship of executive functioning (EF) skills of musicians and the number of years of formal musical training

METHODOLOGY

Study Design

This is a prospective cross-sectional descriptive clinical study that was conducted in different organizations (convents, church organizations, church choirs) in at least 60 musically inclined subjects. All participants are 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

Included in the study are healthy, independent, musicians, 40 years old and above. High activity musicians were defined as performing artists, singers, full-time music teachers, vocal coaches, choirmaster, choir members with an average daily practice time of singing or playing musical instruments, or listens to music at least 1 hour or more each day, with or without formal musical training. Low activity musicians were defined as that who plays a musical instrument regularly, sings regularly or listens to music with no regular daily practice for less than hour each day. They were recruited from church choir members, seminaries or convents. Non-musicians are defined as that who had never played a musical instrument, not a member of any choir or who does not listen to music. Participants included in this study have a Mini-Mental State Exam (MMSE) score of more than 26, Hamilton-Depression Scale (HAM-D) score of less than 7 and with controlled existing medical conditions.

Exclusion Criteria

Participants with history of neurological diseases (like cerebrovascular accidents, epilepsy, parkinsonism etc.), uncontrolled diabetes, uncontrolled hypertension, alcohol and other drug abuses like narcotics, sedatives and hypnotics were excluded from the study.

Outcome Variables

Demographic information were collected for all patients (age, gender, educational status, socioeconomic status, occupation, handedness; and for the professional musicians, the number of years of formal training, age of acquisition of musical expertise, years of actively playing the instrument/s and number of instruments played. Results of cognitive tests measuring executive function skills were performed.

Data Collection

1. Clinical Characteristics

Demographic information was collected for all patients as stated above.

2. Cognitive assessment test

The examiner administered these tests:

a. Montreal Cognitive Assessment Test (MoCA)

The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

b. Verbal Fluency (Phonemic and Semantic)

Verbal Fluency subtest contains three conditions that measure phonemic fluency, semantic fluency, and category switching fluency. Our output of interest compared achievement on phonemic fluency with semantic fluency. In phonemic fluency, participants were prompted with a single letter and asked to state as many words as possible, starting with that letter within 60 seconds; excluding names of people, places, or numbers. In semantic fluency, participants will be prompted with a category (e.g. animals) and were asked to name as many objects as possible, within the category of interest within 60 seconds. Normal Score is 11 words and above, less than 11 is considered abnormal.

c. Design Fluency Test (DFT)

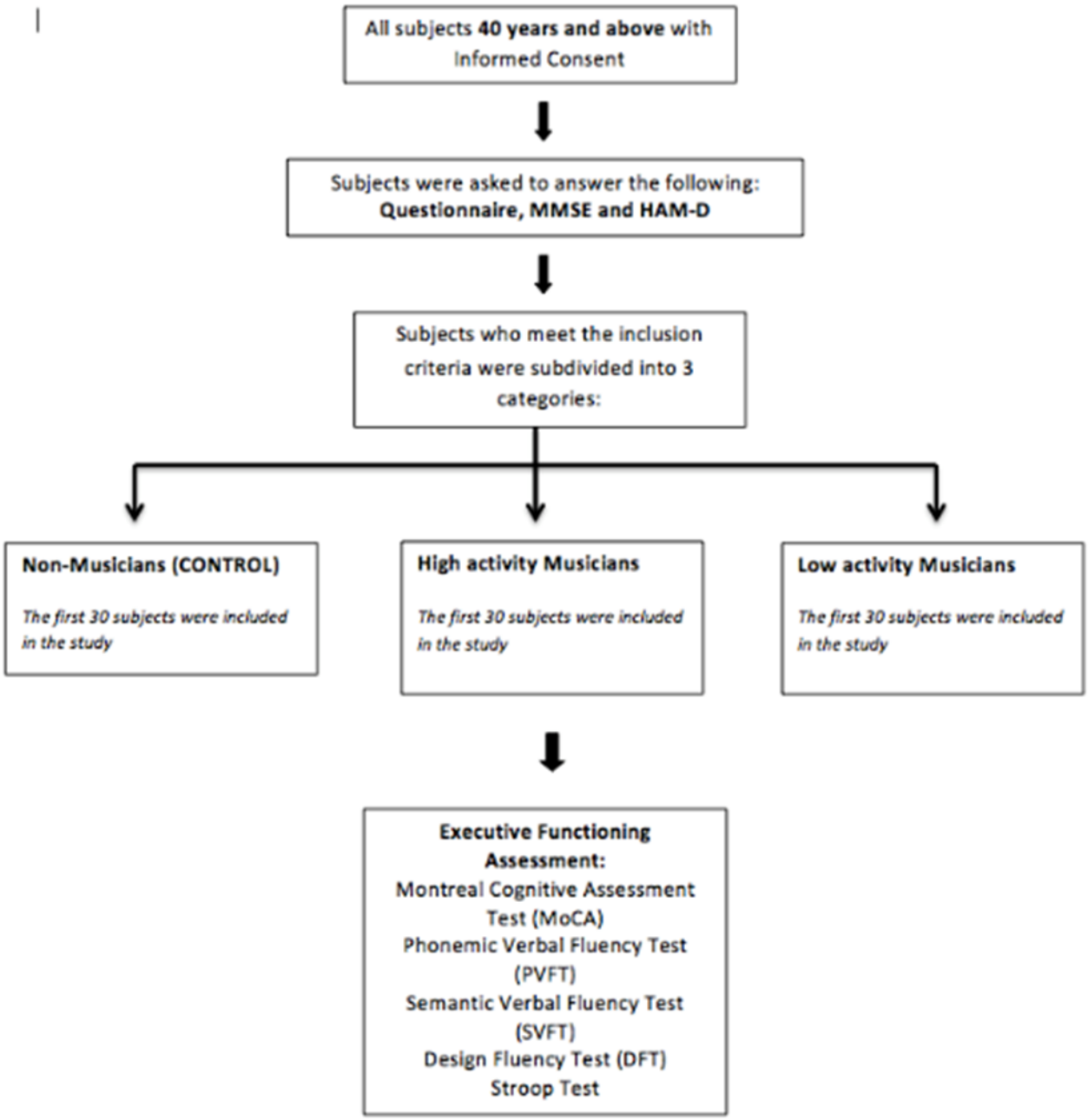
For the design fluency task, participants will be instructed to make a different design using only four straight lines such that, each line had to touch at least one other line. The task was limited to 60 seconds to draw as many different designs as they could. Normal score is 10 figures in one minute, and figures less than 8 were considered abnormal.

d. Stroop Test

The Stroop test used in this study has three conditions: one requires reading black colored names of colors (Stoop Word; SW); the second condition

implies naming of the colors in which four consecutive colors are printed (Stroop Color; SC); and in the latter condition, the subject must name in each item, the color of ink used for printing a color name, which has been printed in a color different to the one written (Stroop Color-Word; SCW). This test is based on the finding that it takes longer to name colored symbols than to name words that refer to colors, and even longer to name the color of ink in which incongruent color names are written[22]. The final score for each condition is obtained by counting the number of colors correctly named or read (depending on condition) in a 45 second time interval, with higher scores indicating better performance.

Figure 1. Research Process



ANALYSIS OF DATA

Data were encoded and tallied in SPSS version 10 for windows. Descriptive statistics were generated for all variables. For nominal data frequencies and percentages were computed. For numerical data, mean ± SD were generated. Analysis of the different variables was done using the following test statistics: Chi-square test was used to compare/associate nominal (categorical) data.

RESULTS

A total of 90 subjects were included in the study equally divided into three groups. Table 1 shows the comparison of the demographic characteristics between the three groups. The results showed that there was no significant difference noted as proven by all p values >0.05. This shows that both the control group and the study group are homogenous.

Table 1. ***Comparison of the Demographic Characteristics Between the Three Groups***

	Groups			p-value*
	Control (n=30)	**High Activity** (n=30)	**Low Activity** (n=30)	
Age (year)				
Mean ± SD	53.33 ± 7.54	53.53 ± 7.71	53.50 ± 9.55	0.99 (NS)
Sex				
Female	20 (66.7%)	15 (50.0%)	18 (60.0%)	0.42 (NS)
Male	10 (33.3%)	15 (50.0%)	12 (40.0%)	
Educational Attainment				
Tertiary	27 (90.0%)	20 (66.7%)	24 (80.0%)	0.08 (NS)
Post-graduate	3 (10.0%)	10 (33.3%)	6 (20.0%)	
Handedness				
Both	0	1 (3.3%)	0	
Left	0	3 (10.0%)	0	0.07 (NS)
Right	30 (100%)	26 (86.7%)	30 (100%)	

** p-values >0.05- Not significant; p-values ≤0.05-Significant*

Table 2 shows the comparison of the executive functioning subtest and total MOCA scores between the three groups. The results showed that there was no significant difference as proven by all p values >0.05. On the other hand, there was a significant difference noted in the total MoCA scores between the three groups as proven by the p values 0.04.

Table 2. ***Comparison of the Executive Functioning Subtest and Total MoCA Scores Between the Three Groups***

	Groups			p-value*
	Control (n=30)	**High Activity** (n=30)	**Low Activity** (n=30)	
Executive Functioning Subtest				
Mean ± SD	4.63 ± 0.56	4.83 ± 0.38	4.83 ± 0.38	0.14 (NS)
Total MOCA Score				
Mean ± SD	27.60 ± 1.45	28.43 ± 2.04	28.63 ± 1.38	*0.04 (S)*

** p-values >0.05- Not significant; p-values ≤0.05-Significant*

Table 3 shows the comparison of phonemic verbal fluency test (PVFT) for letter F, A and S, semantic verbal fluency test (SVFT) for the category animal and design fluency test (DFT) scores between the three groups. The results showed that there was a significant difference noted in the PVFT, SVFT and DFT scores between the three groups as proven by all p values <0.05.

Table 3. ***Comparison of the Phonemic, Semantic and Design Verbal Fluency Test scores Between the Three Groups***

	Groups			p-value*
	Control (n=30)	**High Activity** (n=30)	**Low Activity** (n=30)	
PVFT (F) Mean ± SD	13.06 ± 3.57	15.03 ± 4.26	12.00 ± 3.18	*0.007 (S)*
PVFT (A) Mean ± SD	11.40 ± 2.88	14.53 ± 3.95	11.67 ± 3.70	*<0.001 (S)*
PVFT (S) Mean ± SD	13.43 ± 4.74	14.67 ± 4.70	10.97 ± 3.75	*0.006 (S)*
SVFT Mean ± SD	13.97 ± 2.74	18.57 ± 5.32	13.27 ± 3.06	*<0.001 (S)*
DFT Mean ± SD	5.73 ± 2.42	7.63 ± 2.46	5.23 ± 2.47	*<0.001 (S)*

** p-values >0.05- Not significant; p-values ≤0.05-Significant*

Since there was a significant difference noted in the PVFT, SVFT and DFT scores between the three groups, a pairwise comparison was done between two groups as shown in Table 4. For F and S, there was no significant difference between the control and the high activity group (p>0.05) and between control and the low activity group (p>0.05) but a significant difference was noted between the high and the low activity group (p<0.05). For A, semantic and design fluency, a significant difference was noted when the high activity group was compared with either the control or the low activity group as shown by all p values <0.05 but no significant difference between the

Table 4. ***P Values for the Pairwise Comparison of PVFT, SVFT and DFT Between the Three Groups***

	Control vs High Activity	**Control vs Low Activity**	**High Activity vs Low Activity**
PVFT (F)	0.12 (NS)	0.80 (NS)	0.006 (S)
PVFT (A)	0.001 (S)	1.00 (NS)	0.004 (S)
PVFT (S)	0.84 (NS)	0.10 (NS)	0.005 (S)
SVFT	<0.0001 (S)	1.00 (NS)	<0.0001 (S)
DFT	0.01 (S)	1.00 (NS)	0.001 (S)

** p-values >0.05- Not significant; p-values ≤0.05-Significant*

Table 5 shows the comparison of Stroop word (SW), Stroop color (SC) and Stoop color-word (SCW) scores between the three groups. The results showed that there was a significant difference noted in the SW and SCW scores between the three groups as proven by all p values <0.05. On the other hand, there was no significant difference noted in the SC between the three groups as proven by the p values >0.05.

Table 5. ***Comparison of the Stroop Word (SW), Stroop Color (SC) and Stroop Color-Word (SCW) Scores Between the Three Groups***

	Groups			p-value*
	Control (n=30)	**High Activity** (n=30)	**Low Activity** (n=30)	
SW				
Mean ± SD	53.26 ± 4.86	61.80 ± 8.52	56.33 ± 6.10	<0.0001 (S)
SC				
Mean ± SD	41.86 ± 6.80	39.40 ± 8.99	41.16 ± 9.45	0.51 (NS)
SCW				
Mean ± SD	41.40 ± 11.12	52.60 ± 8.84	51.93 ± 13.68	<0.001 (S)

** p-values >0.05- Not significant; p-values ≤0.05-Significant*

Since there was a significant difference noted in SW and SCW score between the three groups, a pairwise comparison was done between two groups as shown in Table 6. For SW, there was no significant difference between the control and the low activity group as shown by the p values 0.24. For SCW score, there is a significant difference noted when the control group was compared with either the high or the low activity group as shown by all p values <0.05 but no significant difference between the high and the low activity group (p>0.05).

Table 6. ***P Values for the Pairwise Comparison of SW and SCW Between the Three Groups***

	Control vs High Activity	**Control vs Low Activity**	**High Activity vs Low Activity**
SW	<0.0001 (S)	0.24 (NS)	0.006 (S)
SCW	0.001 (S)	0.002 (S)	1.00 (NS)

** p-values >0.05- Not significant; p-values ≤0.05-Significant*

Table 7 shows the comparison of the musical participation between the high and the low activity groups. The results showed that there was a significant difference between the two groups with their musical participation specifically with the low activity group participating on vocals or singing and listening to music (p 0.02) and the high activity group participating with vocals, listening and playing musical instruments (p 0.01) and this is proven by p values <0.05. This table also shows the number of formal music training between high and low activity groups. The results showed that there was a significant difference between the two groups as proven by p value of 0.04 (<p 0.05) with the high activity group, having more participants with more than 5 years of formal musical training (36.7%).

Table 7. ***Musical Activity Participated In and Number of years of Formal Musical Training Between the High and the Low Activity Groups***

Musical Activity Participated In	Groups		p-value*
	High Activity (n=30)	**Low Activity** (n=30)	
Listen (L)	1 (3.3%)	0	1.00 (NS)
Vocals (V)	1 (3.3%)	0	1.00 (NS)
Vocals, Listen (V, L)	11 (36.7%)	20 (66.7%)	*0.02 (S)*
Vocals, Plays Instrument (V, P)	3 (10.0%)	5 (16.7%)	0.70 (NS)
Vocals, Plays Instrument, Listen (V, P, L)	14 (46.7%)	5 (16.7%)	*0.01 (S)*
Number of years of Formal Musical Training			
<5 years	9 (30.0%)	3 (10.0%)	
>5 years	11 (36.7%)	8 (26.7%)	0.04 (S)
None	10 (33.3%)	19 (63.3%)	

** p-values >0.05- Not significant; p-values ≤0.05-Significant*

Table 8 shows the correlation of musical activity participated in with executive functioning subtest, total MoCA, PVFT, SVFT, DFT, SW, SC, and SCW scores. The results showed that there was no significant associations noted as proven by all p values >0.05 except for SCW (p=0.05).

Table 8. ***Correlation of Musical Activity Participated In and the Test Scores of Executive Functioning subtest (EF), MoCA, Phonemic Verbal Fluency Test (PVFT), Semantic Verbal Fluency Test (SVFT), Design Fluency Test (DFT), Stroop Word Test (SW), Stroop Color Test (SC) and Stroop Color-Word Test (SCW)***

	Musical Activity Participated In					*p value
	Listen (L) (n=1)	**Vocals (V)** (n=1)	**Vocals, Listen (VL)** (n=31)	**Vocals, Plays Music (VP)** (n=8)	**VPL** (n=19)	
EF						
4/5	0	0	3 (9.7%)	1 (12.5%)	6 (31.6%)	0.33 (NS)
5/5	1 (100%)	1 (100%)	28 (90.3%)	7 (87.5%)	13 (68.4%)	
MOCA						
Mean ± SD	30 ± 0	30 ± 0	28.77 ± 1.28	28.38 ± 1.50	27.90 ± 2.33	0.34 (NS)
Median	30	30	29	28	28	
PVFT						
0	0	0	8 (25.8%)	0	3 (15.8%)	0.48 (NS)
1	1 (100%)	1 (100%)	23 (74.2%)	8 (100%)	16 (84.2%)	
SVFT						
0	0	0	0	2 (25%)	1 (5.3%)	0.08 (NS)
1	1 (100%)	1 (100%)	31 (100%)	6 (75%)	18 (94.7%)	
DFT						
0	1 (100%)	0	28 (90.3%)	7 (87.5%)	14 (73.7%)	0.10 (NS)
1	0	1 (100%)	3 (9.7%)	1 (12.5%)	5 (26.3%)	
SCW						
Mean ± SD	**80 ± 0**	**72 ± 0**	**57.42 ± 7.38**	**56.75 ± 5.01**	**60.95 ± 7.55**	**0.05 (S)**
Median	**80**	**72**	**54**	**55**	**58**	
SC						
Mean ± SD	34 ± 0	40 ± 0	39.71 ± 8.91	37.25 ± 11.71	42.84 ± 8.80	0.56 (NS)
Median	34	40	40	35	46	
SW						
Mean ± SD	40 ± 0	44 ± 0	52.52 ± 11.88	53.50 ± 9.06	52.42 ± 12.12	0.68 (NS)
Median	40	44	50	58	56	

** p-values >0.05- Not significant; p-values ≤0.05-Significant*

Table 9 shows the correlation of formal musical training with executive functioning subtest, MoCA, PVFT, SVFT, DFT, SW, SC, and SCW scores. The results showed that there was no significant associations noted as proven by all p values >0.05 except for SCW (p=0.05).

Table 9. ***Correlation of Formal Musical Training and the Test Scores of Executive Functioning subtest (EF), MoCA, Phonemic Verbal Fluency Test (PVFT), Semantic Verbal Fluency Test (SVFT), Design Fluency Test (DFT), Stroop Word Test (SW), Stroop Color Test (SC) and Stroop Color-Word Test (SCW)***

	Formal Musical Training			*p value
	<5 (n=12)	**>5** (n=19)	**None** (n=29)	
EF				
4/5	1 (8.3%)	5 (26.3%)	4 (13.8%)	0.36 (NS)
5/5	11 (91.7%)	14 (73.7%)	25 (86.2%)	
MOCA				
Mean ± SD	27.83 ± 2.79	28.78 ± 1.27	28.55 ± 1.40	0.67 (NS)
Median	28	28	28	
PVFT				
0	2 (16.7%)	3 (15.8%)	6 (20.7%)	0.90 (NS)
1	10 (83.3%)	16 (84.2%)	23 (79.3%)	
SVFT				
0	1 (8.3%)	2 (10.5%)	0	0.22 (NS)
1	11 (91.7%)	17 (89.5%)	29 (100%)	
DFT				
0	9 (75.0%)	16 (84.2%)	25 (86.2%)	0.68 (NS)
1	3 (25.0%)	3 (15.8%)	4 (13.8%)	
SCW				
Mean ± SD	**62.50 ± 10.20**	**60.63 ± 7.72**	**56.62 ± 6.14**	**0.05 (S)**
SC				
Mean ± SD	42.50 ± 9.84	39.78 ± 9.70	39.69 ± 8.76	0.65 (NS)
SW				
Mean ± SD	53.16 ± 9.70	50.21 ± 11.98	53.24 ± 11.88	0.64 (NS)

** p-values >0.05- Not significant; p-values ≤0.05-Significant*

DISCUSSION

This study examined the executive functioning skills of healthy, musically inclined subjects and correlate them with the number of activities of musical participation and the number of years of formal musical training. The results of the study revealed significant differences between musicians and non-musicians on measures of verbal and design fluency tests and color-word interference test.

Tests of verbal fluency assess cognitive functioning and involve associative exploration and retrieval of words based on phonemic or semantic criteria (phonemic and semantic fluency, respectively), usually conducted in the setting of a time constraint (60 seconds). These measures are considered to impose comparable demands upon executive or supervisory processes because both require efficient organization of verbal retrieval and recall, as well as self-monitoring aspects of cognition (the participant must keep track of responses already given), effortful self-initiation, and inhibition of responses when appropriate. In this study, there was a noted significant difference in the performance in the verbal fluency tests among the three groups however, the results were not significant when correlated with musical participation and years of formal training.

Another type of fluency that has been studied is design fluency, which is measured by a patient's ability to generate a series of novel (i.e., nonrepeating), abstract designs. Impairment on the design fluency test or DFT was specific to patients with excisions involving the right frontal lobes, and further suggested that the right central region was particularly important in design fluency. The unstructured nature of the DFT, while complicating scoring, may increase sensitivity to frontal lobe mediated executive functions by increasing the initiation and organization required of the patient. In this study, there was a noted significant difference in the performance in the design fluency tests among the three groups however, when correlated with musical participation and years of formal training, the result was not significant. It is important to note though that in pairwise comparison, there was a significant difference between the DFT scores of the control and high activity group. The right brain, often considered the more subjective and creative hemisphere, focuses on the melody in music. The left hemisphere, considered the analytical part of the brain, is responsible for the understanding of musical structure and motor skills, such as playing the violin [37]. Since the DFT tests the right frontal lobe specifically, high activity participants were able to perform better.

Stroop test is a reliable measure of executive function that requires cognitive flexibility, selective attention, cognitive inhibition, and information processing speed. There was a noted significant difference between the scores of the three groups that was also evident when pairwise comparison was done. It was significant specifically when measuring color word interference or stroop color-word (SCW). This difference was also evident when correlated with years of formal musical training and musical participation. Interestingly, a previous study showed that professional musicians had significantly smaller color-word interference effects in the Stroop task [33]. This reflects an enhanced selective processing, automaticity, and inhibitory control of the study group.

The results of this study reveal that the years of engagement in musical activities is associated with better performance on tests of executive functioning, specifically cognitive flexibility. Furthermore, it is also conceivable that sustained musical activity in advanced age may maintain cognitive flexibility. Also, this study may suggest that musicians have cognitive advantages that may potentially provide cognitive reserve in advanced age. However, future investigations are needed to explore the mediating factors and neural mechanisms. There is growing evidence that lifestyle factors, including stimulating cognitive and leisure activities, may impact "cognitive reserve" and postpone the onset of Alzheimer's disease and other dementias. The reasons why musicians outperform non-musicians are unclear from our findings, although it may be considered that musical training serves as additional education. Educational attainment has been reported to retard cognitive decline in advanced age and has demonstrated differences in recruitment of networks during memory tasks providing greater compensation [37].

CONCLUSION

Executive function skills of musicians, specifically cognitive flexibility, cognitive inhibition, selective attention and information processing speed are enhanced when compared with non-musicians and this is influenced by the number of years of formal musical training and the number of musical activities participated in.

REFERENCES

1. Lutz, W., Sanderson, W., and Scherbov, S. (2008). The coming acceleration of global population ageing. *Nature* 451, 716–719. doi: 10.1038/nature06516

2. Norton, S., Matthews, F. E., and Brayne, C. (2013). A commentary on studies presenting projections of the future prevalence of dementia. *BMC Public Health* 13:1. doi: 10.1186/1471-2458-13-1

3. Societas Neurologica Japonica (2010). Guideline for dementing disorder. IgakuShoin Ltd. Tokyo.

4. Abbott RD, White LR, Ross GW, Masaki KH, Curb JD, et al. (2004) Walking and dementia in physically capable elderly men. JAMA 292: 1447–1453.

5. Thompson RG, Moulin CJA, Hayre S, Jones RW. (2005) Music enhances category fluency in healthy older adults and Alzheimer's disease patients. Exp Aging Res 31: 91–99.

6. Irish M, Cunningham CJ, Walsh JB, Coakley D, Lawlor BA, et al. (2006) Investigating the enhancing effect of music on auatobiographical memory in mild Alzheimer's disease. Dement Geriatr Cogn Disord 22: 108–120.

7. Simmons-Stern NR, Budsopn AE, Ally BA. (2010) Music as a memory enhancer in patients with Alzheimer's disease. Neuropsychologia 48: 3164–3167.

8. Parbery-Clark A, Strait DL, Anderson S, Hittner E, Kraus N. (2011) Musical experience and the aging auditory system: implications for cognitive abilities and hearing speech in noise. PLoS One, May 11 2011, volume 6, issue 5, DOI: 10.1371/journal.pone.0018082.

9. Gaser, C., & Schlaug, G. (2003). Brain structures differ between musicians and non-musicians. *Journal of Neuroscience, 23*(27), 9240–9245.

10. Koelsch, S., Fritz, T., Schulze, K., Alsop, D., & Schlaug, G. (2005). Adults and children processing music: An fMRI study. *Neuroimage, 25*(4), 1068 – 1076.

11. Tervaniemi, M., Castaneda, A., Knoll, M., & Uther, M. (2006). Sound processing in amateur musicians and nonmusicians: Event-related potential and behavioral indices. *Neuroreport, 17*(11), 1225–1228.

12. Bangert, M., Peschel, T., Schlaug, G., Rotte, M., Drescher, D., Hinrichs, H., Altenmuller, E. (2006). Shared networks for auditory and motor processing in professional pianists: Evidence from fMRI conjunction. *Neuroimage, 30*(3), 917–926.

13. Monaghan, P., Metcalfe, N. B., & Ruxton, G. D. (1998). Does practice shape the brain? *Nature, 394* (6692), 434.

14. Zatorre, R. J., & McGill, J. (2005). Music, the food of neuroscience? *Nature, 434*(7031), 312–315.

15. Elbert, T., Pantev, C., Wienbruch, C., Rockstroh, B., & Taub, E. (1995). Increased cortical representation of the fingers of the left hand in string players. *Science, 270* (5234), 305–307.

16. Fujioka, T., Ross, B., Kakigi, R., Pantev, C., & Trainor, L. J. (2006). One year of musical training affects development of auditory cortical-evoked fields in young children. *Brain, 129*(Pt 10), 2593–2608.

17. Lotze, M., Scheler, G., Tan, H. R., Braun, C., & Birbaumer, N. (2003). The musician's brain: Functional imaging of amateurs and professionals during performance and imagery. *Neuroimage, 20*(3), 1817–1829.

18. Meister, I., Krings, T., Foltys, H., Boroojerdi, B., Muller, M., Topper, R., & Thron, A. (2005). Effects of long-term practice and task complexity in musicians and nonmusicians performing simple and complex motor tasks: Implications for cortical motor organization. *Human Brain Map- ping, 25*(3), 345–352.

19. Schmithorst, V. J., & Wilke, M. (2002). Differences in white matter architecture between musicians and non-musicians: A diffusion tensor imaging study. *Neuroscience Letters, 321*(1–2):57–60.

20. Zatorre, R. J., Belin, P., & Penhune, V. B. (2002). Structure and function of auditory cortex: Music and speech. *Trends in Cognitive Sciences, 6*(1), 37–46.

21. Zatorre, R. J., Chen, J. L., & Penhune, V. B. (2007). When the brain play music: Auditory-motor interactions in music perception and production. *Nature Reviews Neuroscience, 8*(7), 547–558.

22. Schlaug, Norton, A., Overy, K., & Winner, E. (2005). Effects of music training on the child's brain and cognitive development. *Annals of the New York Academy of Sciences, 1060,* 219–230.

23. Chan, A. S., Ho, Y. C., & Cheung, M. C. (1998). Music training improves verbal memory. *Nature, 396* (6707), 128.

24. Barwick, J., Valentine, E., West, R., & Wilding, J. (1989). Relations between reading and musical abilities. *British Journal of Educational Psychology, 59* (Pt 2), 253–257.

25. Lezak MD (2004) Neuropsychological Assessment. New York: Oxford University Press.

26. Blair C, Zelazo PD, Greenberg MT (2005) The measurement of executive function in early childhood. Dev Neuropsychol 28: 561-571.

27. Davis CL, Tomporowski PD, McDowell JE, Austin BP, Miller PH, et al. (2011) Exercise improves executive function and achievement and alters brain activation in overweight children: a randomized, controlled trial. Health Psychol 30: 91–98.

28. Hannon EE, Trainor LJ (2007) Music acquisition: effects of enculturation and formal training on development. Trends Cogn Sci 11: 466–472.

29. Schellenberg EG, Peretz I (2008) Music, language and cognition: unresolved issues. Trends Cogn Sci 12: 45 –46.

30. Stoesz BM, Jakobson LS, Kilgour AR, Lewycky ST (2007) Local processing advantage in musicians: Evidence from disembedding and constructional tasks. Music Percept 25: 153–165.

31. Thompson WF, Schellenberg EG, Husain G (2003) Perceiving prosody in speech. Effects of music lessons. Ann N Y Acad Sci 999: 530–532.

32. Bialystok E, Depape AM (2009) Musical expertise, bilingualism, and executive functioning. J Exp Psychol Hum Percept Perform 35: 565–574.

33. Travis F, Harung HS, Lagrosen Y (2011) Moral development, executive functioning, peak experiences and brain patterns in professional and amateur classical musicians: Interpreted in light of a Unified Theory of Performance. Conscious Cogn 20: 1256–1264.

34. Dege´ F, Kubicek C, Schwarzer G (2011) Music lessons and intelligence: a relation mediated by executive functions. Music Percept 29: 195–201.

35. Schellenberg EG (2011) Examining the association between music lessons and intelligence. Br J Psychol 102: 283–302.

36. Yoon, J. (2000, January 1). Music in the Classroom: Its Influence on Children's Brain Development, Academic Performance, and Practical Life Skills.

37. Springer, M. V., McIntosh, A. R., Winocur, G., & Grady, C. L. (2005). The relation between brain activity during memory tasks and years of education in young and older adults. *Neuropsychology, 19*(2), 181–192.

Kaposi Sarcoma in an HIV-Negative Filipino with Myasthenia Gravis and Anterior Mediastinal Mass*

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ABSTRACT

Kaposi sarcoma (KS) is a rare vascular tumor derived from endothelial cell lineage with four clinical variants: classic, endemic, HIV-associated and immunosuppression-associated Kaposi sarcoma. Immunosuppression-associated Kaposi sarcoma has been reported among organ transplant recipients and those who are receiving immunosuppressive therapy for a variety of medical conditions that include myasthenia gravis.

A 44-year-old HIV-negative Filipino male, diagnosed with myasthenia gravis and an anterior mediastinal mass who was maintained on pyridostigmine and prednisone presented with a two-month history of non-tender, non-pruritic, bluish to violaceous papules, nodules and plaques over both feet. The patient mechanically manipulated the lesion over the right plantar foot, which resulted in right leg swelling that was eventually managed as cellulitis. Skin punch biopsy done over the violaceous plaque on the right medial foot revealed histopathologic findings consistent with Kaposi sarcoma, patch stage. This was confirmed by CD34 immunostaining. A final diagnosis of immunosuppresion-associated Kaposi sarcoma was made. The consensus was to perform excision of the anterior mediastinal mass before initiating treatment of Kaposi sarcoma. The patient expired before the plan could be carried out.

Immunosuppression-associated Kaposi sarcoma responds well to cessation of immunosuppressive therapy however management decisions should be made based on the presentation and coexistent systemic problems of each patient.

Keywords: *Kaposi sarcoma, immunosuppression-associated Kaposi sarcoma, HHV-8, myasthenia gravis, anterior mediastinal mass*

INTRODUCTION

Kaposi sarcoma (KS) is a rare neoplasm of lymphatic endothelial cells frequently evident as multiple vascular cutaneous and mucosal nodules.[1] It has been linked to Kaposi Sarcoma associated herpesvirus also known as human herpesvirus 8 (HHV-8).[2,3]

Before the AIDS epidemic, Kaposi sarcoma was regarded as extremely rare in all areas of world, with exceptionally elevated rates observed in certain population of Mediterranean, middle Eastern, or Eastern European descent, and more notably in sub-Saharan Africa populations.[4]

There are four clinical variants of Kaposi sarcoma, the classic, African-endemic, AIDS-associated and the iatrogenic or immunosuppression-associated type. The classic KS, most often seen in middle-aged and elderly men tends to run an indolent course.[3] AIDS-associated KS is one of the most common neoplasms among homosexual and bisexual men with AIDS and runs a rapidly progressive course.[3] African endemic KS has been implicated in 10% of malignancies in Central Africa.[3] Iatrogenic KS or immunosuppression-associated KS is seen among transplant recipients and in those taking corticosteroids or other immunosuppressants.[3]

Lesions initially develop on the distal lower extremities as unilateral or bilateral bluish red or purplish macules which later progress into firm plaques and nodules. Aside from the skin, it may also arise and may be confined to the oral cavity, genitals, lymph nodes and visceral organs. [2]

CASE REPORT

The patient is a 44-year old Filipino male, single, Roman Catholic, from Tabuk, Kalinga Apayao, Philippines who was referred to our institution due to papules and nodules over the distal upper and lower extremities. The patient was diagnosed with myasthenia gravis in 2012 when he was admitted in another government institution due to progressive dysphagia and dyspnea. He was subsequently managed as myasthenic crisis. Results of work-up included a plain chest CT scan which, revealed a 2.0x1.0 cm ovoid soft tissue density in the anterior superior mediastinum at the level of the aortic arch for which a consideration of thymoma was made. He was discharged with home medications of pyridostigmine and prednisone at 60 mg/day (1 mg/kg/day), with plans for biopsy of the mass once medical condition further improved. Prednisone was gradually tapered to 50 mg/day. However, he failed to follow-up for four months during which time he continued taking prednisone at the same dose.

During these four months, the patient noted a solitary, non-tender, non-pruritic, round, violaceous "hematoma-like" patch over the plantar aspect of the right foot. There were also few violaceous papules over the toes and medial aspect of the right foot. There was no history of trauma or manipulation prior to appearance of the lesions. No consultation was done. No medications were taken or applied. One month prior to consultation, there was noted increase in the size of the lesions. The patient manipulated the lesion on the plantar right foot. A few days later, there was erythema and inflammation with swelling of the right leg. This was accompanied by undocumented febrile episodes and occasional throbbing pain on the right foot. This prompted consultation and subsequent admission at another government hospital where a working impression of cellulitis on top of chronic venous insufficiency and myasthenia gravis, in stable remission was made. Acid-fast bacilli stain and 10% potassium hydroxide examination were negative. Arterio-venous duplex ultrasound of the lower extremities revealed deep venous insufficiency. Skin punch biopsy over the plaque on the medial right foot was done. Repeat chest CT scan showed an anterior superior mediastinal mass measuring 1.8 x 3.8 x 3.6 cm suggestive of thymoma *(figure 1)*. A chest radiograph was done and showed subsegmental atelectasis versus fibrosis of both lower lung fields. The patient was started on ampicillin-sulbactam 750 mg/tab once day, cotrimoxazole 160mg/180mg tablet twice a day, and enonaxaparin 0.4 cc subcutaneously once a day. Prednisone for the myasthenia gravis was gradually tapered off. Patient discharged with stable and improved condition. The histopathology result revealed a vascular tumor. Hence referral to our institution for further evaluation and management was done.

The review of systems was unremarkable. The past medical history was negative for thyroid disease and diabetes. However, he developed steroid-induced Type II diabetes mellitus subsequently. The family medical history was non-contributory. The patient previously worked as a helper in a rice meal and laboratory aide in an organic fertilizer production factory. He is single, non-promiscuous with only one heterosexual partner in the past. He denied a history of sexually transmitted infections or recent sexual contact.

The physical examination including neurological examination was unremarkable except for cutaneous examination which revealed several, ill-defined, irregularly shaped, erythematous to violaceous slightly raised plaques and nodules over the 2nd to 5th proximal toes extending to the dorsum of the feet *(figure 2)*. There were well-defined round violaceous and hyperpigmented plaques topped with crusts and scales over the medial and plantar aspect of the right foot *(figures 3)* and few well-defined, oval-shaped hyperpigmented nodules over the right forearm and left hand *(figure 4)*.

The initial working impression was vascular tumor probably Kaposi sarcoma. The differential diagnoses were acroangiodermatitis of Mali or pseudokaposi sarcoma, bacillary angiomatosis and angiosarcoma *(Table 1)*.

Recent laboratories showed mild anemia. Urinalysis and blood chemistries were normal. HIV Elisa was requested and showed a negative result. Histopathology slide review revealed an increase in the number of blood vessels throughout the dermis, and foci of extravasated erythrocytes. Spindle-shaped cells were disposed around the blood vessels, adnexal structures and interstitial dermis *(figure 5)*. Immunohistochemistry studies showed positive CD31 and CD34 expression in the perivascular spindle shaped cells confirming the diagnosis of Kaposi sarcoma *(figure 6 and 7)*.

Prednisone, which had been tapered down to 25 mg/day was continued as prescribed by the attending neurologist. Proper foot care and leg elevation was advised.

After the diagnosis was established, the patient was presented in a multidisciplinary conference where the consensus was to perform resection of the anterior mediastinal mass once the patient achieved optimal medical condition before initiating treatment of Kaposi sarcoma lesions with localized vinblastine. Prednisone was decreased to 20 mg/day.

Two months later, the patient again failed to follow-up. At this time, new papules and nodules appeared on the back, groin and posterior thigh with further increase in size of the plaques over both feet. Patient was admitted at a government tertiary hospital for resection of the mass.

During his hospital stay, new lesions continued to appear on both feet *(figure 8)*. Laboratory tests revealed persistent thrombocytopenia. The patient was referred to a hematologist. Bone marrow aspiration biopsy was done and findings were consistent with a reactive marrow, possibly immunologic in etiology, for which reason biopsy of the anterior mediastinal mass was deferred. While work-up was being done, he developed generalized body weakness, fever, chest heaviness, and tachypnea, which was diagnosed and managed as pneumonia. On the 17th hospital day, he developed severe respiratory difficulty and his condition rapidly deteriorated. He eventually expired. There was no consent for autopsy.

Final impressions were Kaposi sarcoma, immunosuppression-associated type, myasthenia gravis, with acute respiratory failure probably secondary to pulmonary embolism versus acute myocardial infarction as the cause of death.

DISCUSSION

Kaposi sarcoma (KS) is a lymphoangioproliferative disease often caused by human herpesvirus 8 (HHV-8). Although HHV-8 determination was not done in this patient, the diagnosis of Kaposi sarcoma in this patient was based on the clinical, histopathologic findings and confirmed by CD34 immunostaining. The patient having an anterior mediastinal mass, myasthenia gravis maintained on immunosuppressive therapy, and the HIV-negative status are features consistent with immunosuppression associated Kaposi sarcoma.

The pathogenesis of KS begins with HHV-8 infection. HHV-8 expresses viral oncogenes that, through the action of endothelial growth factors, promote inflammation and angiogenesis.[3,5,6] HHV-8 infection has been an essential factor in the pathogenesis of Kaposi sarcoma. Not all HHV-8 infected individuals develop the disease and co-factors in the development of KS have been postulated.[3]

Significant risk factors in the development of Kaposi sarcoma in this patient are the presence of a possible neoplasm (anterior mediastinal mass probably thymoma), autoimmune disorder (myasthenia gravis) and immunosuppressive therapy (prednisone).

Several studies have been published supporting the relationship of Kaposi sarcoma and corticosteroid therapy.[7,8,9] In the study of Guo et al[3], Kaposi sarcoma tumor cells and have shown that exogenous glucocorticoids stimulate their proliferation. They demonstrated that the glucocorticoid receptors are present at high levels on Kaposi sarcoma lesions and these receptors can be upregulated by exogenous glucocorticoid and inflammatory cytokines.

Likewise, Hudnall et al[8] have reported increased viral replication and activation of lytic cycle of HHV-8 after glucocorticoid administration in infected cells. Thus the effects of glucocorticoids are two-fold, the upregulation of Kaposi cell proliferation and the activation of HHV-8.

A study by Perez et al[10] found that Kaposi sarcoma has been reported in association with a second neoplasm in 37% of cases. The most frequently observed are lymphoproliferative disorders such as thymoma. The imbalance between CD34 and CD8 T lymphocytes has been considered responsible for the immunosuppression in the patients with thymoma. Coexisting Kaposi sarcoma and thymoma have been related to myasthenia gravis.[10]

Mantero et al[11] reported a case of myasthenia gravis developing in an HIV-negative patient with Kaposi sarcoma. The potential correlation between Kaposi sarcoma and myasthenia gravis is through immunological mechanism: Myasthenia gravis as paraneoplastic manifestation of Kaposi sarcoma and the role of antitumoral agent as treatment for both conditions.

The study of Ulbright et al[12] concludes that either a naturally occurring (thymic neoplasia or autoimmune disorder) or iatrogenically induced immunodeficiency (long term corticosteroid therapy) gives a background of a deranged immune status and likely predisposes patients to Kaposi sarcoma. [12]

Evaluation of Kaposi sarcoma should include a complete history and physical examination. Laboratory studies tend to be within normal limits. Occasionally eosinophilia has been noted in African-endemic and homosexual patients whom parasitosis may be common. Serum glucose levels may reflect an increased incidence of diabetes mellitus with classic Kaposi sarcoma.

The diagnosis of Kaposi sarcoma rests on the biopsy findings and identification of HHV-8 infection.[3] However assays for HHV-8 have been challenging and no universally accepted method exists.[13] Hence immune-histochemical stains are more reliable methods for confirming the diagnosis.

Histopathologically, Kaposi sarcoma lesions typically show proliferation of spindle cells and vascular structures in a network of collagen and reticular fibers. The epidermis is usually normal. Identification of endothelial cell markers CD31 and CD34, allow differentiation of Kaposi sarcoma from non-spindle cell vascular proliferations such as acroangiodermatitis.[3] In this patient, CD34 immunostaining is positive.

Unlike other malignancies, Kaposi sarcoma does not lend itself to the conventional TNM classification. Schwartz et al[2] proposed the currently preferred staging in 2008 *(Table 2)*.

Treatment for Kaposi sarcoma depends on the disease stage, the pattern and distribution of the lesions, the KS variant, and the patient's immune status.[3] Management modalities for Kaposi sarcoma include non-intervention, surgical excision, intralesional chemotherapy, laser therapy, cryotherapy, immunotherapy, antiviral drugs or cessation of immunosuppressive therapy.

In patients with only limited disease confined to the skin, local therapies aimed at eliminating

individual lesions are frequently used as initial treatment. Chemotherapy including doxorubicin, bleomycin, vincristine, etoposide, dacarbazine alone or in combination has been given to patients with progressive or widespread classic Kaposi sarcoma especially if internal organs are involved.[2]

Studies in HIV-infected patients and transplantation recipients have shown that immune restoration is the best treatment for Kaposi sarcoma in these patients. For patients with AIDS, highly active anti-retroviral therapy should be initiated to decrease incidence of AIDS-associated Kaposi sarcoma. However, HAART alone is not sufficient to control Kaposi sarcoma that has already advanced. Thus, addition of chemotherapy is required. In immunosuppression-associated Kaposi sarcoma, the goal of treatment is discontinuation or reduction of immunosuppressive therapy.[14] In this patient, the goal of treatment is discontinuation of immunosuppressive therapy. The initial plan is resection of the anterior mediastinal mass, negating the need for the corticosteroids as treatment for myasthenia gravis, thus controlling progression of Kaposi sarcoma. This will be followed by intralesional chemotherapy for the localized lesions.

The best prognosticator is the clinical classification of Kaposi sarcoma. Immunosuppression associated Kaposi sarcoma with regression of lesions after discontinuation of the immunosuppressive therapy gives an excellent prognosis. Cases of Kaposi sarcoma remission have been reported after a decrease in the use of corticosteroid medication. Mortality is most often secondary to other unrelated causes. [2,3]

CONCLUSION

A rare case of immunosuppression-associated Kaposi sarcoma in an HIV-negative Filipino male with myasthenia gravis and anterior mediastinal mass is presented. Immunosuppressive therapy such as corticosteroids may trigger the development of Kaposi sarcoma in patients who possess several other pathogenic factors such as the presence of deranged immune status and presence of human herpesvirus 8. Naturally occurring or iatrogenic immune-deficiency likely predisposes patients to Kaposi sarcoma. Immunosuppression associated Kaposi sarcoma responds well to cessation of immunosuppressive therapy however management decisions should be made astutely based on the presentation and coexistent systemic problems of each patient.

REFERENCES

1. Jakob L, Metzler G, Chen K-M, Garbe C. Non-AIDS Associated Kaposi's Sarcoma: Clinical Features and Treatment Outcome. 2011. PLoS ONE 6(4): e18397. doi:10.1371/journal.pone.0018397
2. Schwartz R, Micali G, Nasca M, Scuderi L. Kaposi sarcoma: a continuing conundrum. J Am Acad Dermatol 2008; 59 (2): 179-206
3. Pardo I, Pastorfide G, Canal J. Kaposi sarcoma in an HIV-negative Filipino man. J Phil Dermatol Soc 2012; 21 (2): 41-44
4. Jemal A, Freddie B, Center M,Ferlay J, Ward E, Forman D. Global Cancer Statistics. CA Cancer J Clin 2011; 61 (2):69-90.
5. Pyakurel P, Pak F, Mwakigonja A, Kaaya E, Biberfield P. KSHV/HHV-8 and HIV infection in Kaposi's sarcoma development. Infect Agent Cancer 2007;2:2-4
6. Martinelli PT, Tyring SK. Human herpesvirus 8. Dermatol Clin 2002; 20 (2):307-14, vii-viii.
7. Guo WX, Antakly T. AIDS-related Kaposi's sarcoma: evidence for direct stimulatory effect of glucocorticoid on cell proliferation. Am J of Pathol. 1995; 146(3): 727-733.
8. Hudnall S, Rady P, Trying S, Fish J. Hydrocortisone activation of human herpesvirus8 viral DNA replication and gene expression in vitro. Transplantation. 1999; 67(5): 648-52
9. Bruet A, Mahe A, Sei J, Mathe C, Felsenheld C, Lechevalier L, Fendler J. Kaposi's sarcoma complicating long-term corticotherapy for severe asthma. Rev Med Interne. 1990; 11(4):322-4.
10. Perez E, Barnadas A, Garcia-Patos V, Pedro C, Curell R, Sander C, Kind P, de Morgas J, Alomar A. Kaposi's sarcoma in a Patient with Erythroblastopenia and thymoma: reactivation after topical corticosteroids. Dermatology 1998;197(3):264-267
11. Mantero V, Mascolo M, Bandettini di Poggio M, Caponnetto C, Pardini M. Myasthenia Gravis developing in an HIV-negative patient with Kaposi Sarcoma. Neurol Sci. 2013;34 (7):1249-50

12. Ulbright T, Cruz D. Kaposi's sarcoma: Relationship with hematologic, lymphoid, and thymic neoplasia. Cancer 1981; 47: 963-973

13. Schwartz R, Lambert C, Wells M, Mowad C, Elston D, Van Voorhees A. Medscape [internet]. [Place unknown]: [publisher unknown]; 1994 [updated 2015 April 27; cited 2015 Sept 20]. Available from: http://emedicine.medscape.com/article/1083998-workup

14. Tappero J, Conant M, Wolfe SF. Kaposi's sarcoma. J Am Acad Dermatol. 1993; 28: 371-395.

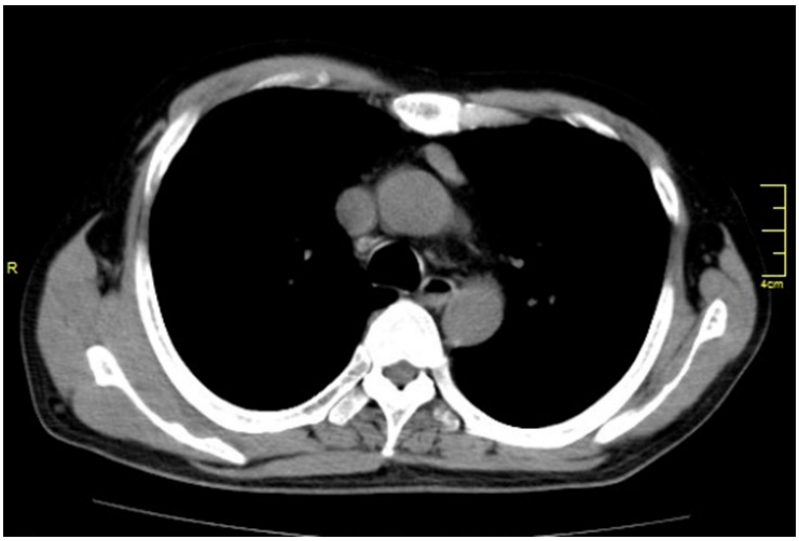

Figure 1. Chest CT scan showing the anterior mediastinal mass

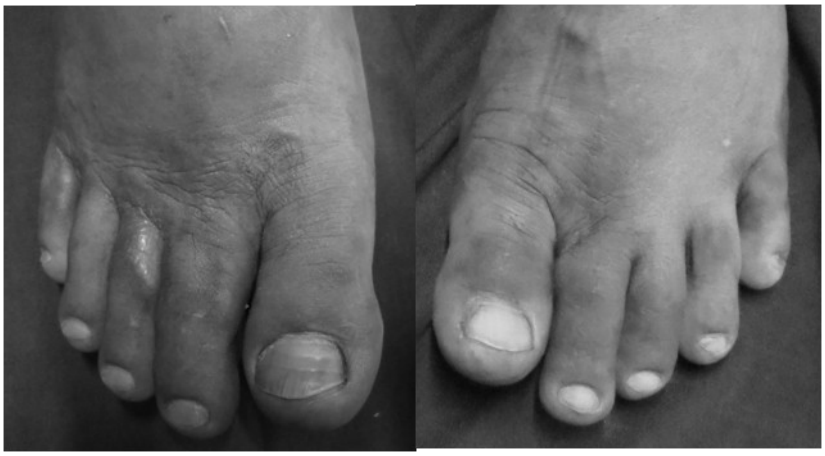

Figure 2. Several, ill-defined, irregularly shaped, erythematous to violaceous papules, slightly raised plaques and nodules over the 2nd to 5th proximal toes extending to the dorsum of the feet.

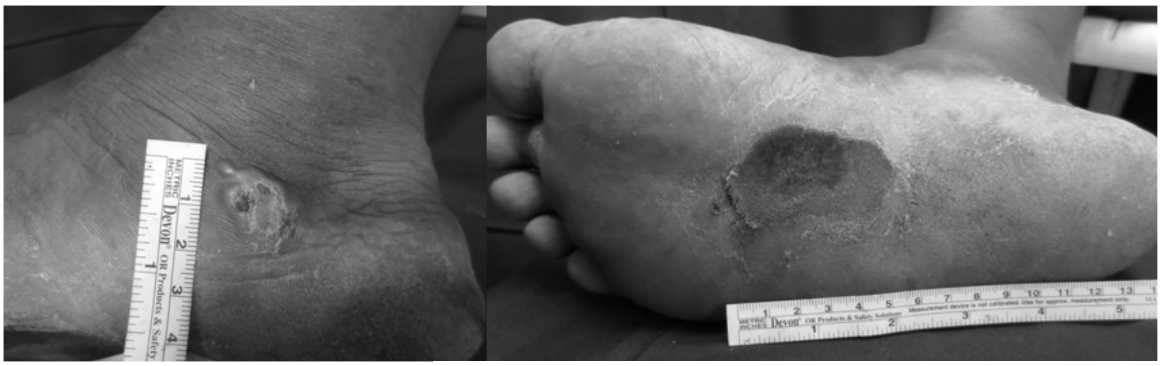

Figure 3. Round to oval, violaceous and hyperpigmented plaques topped with crusts and scales over the (a) medial and (b) plantar aspect of the right foot

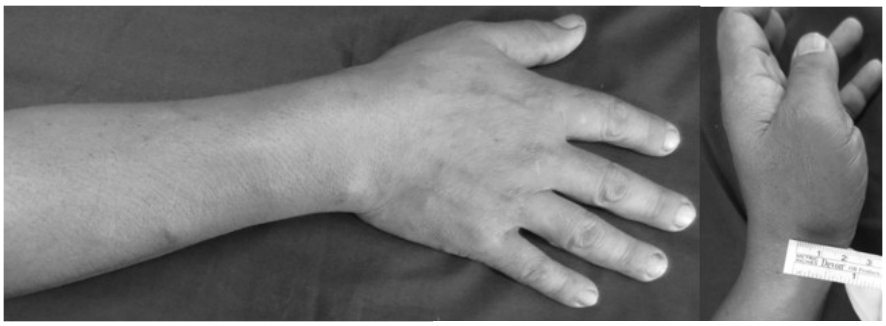

Figure 4. Few well-defined, oval-shaped, violaceous to hyperpigmented nodules over the (a) right forearm and (b) left hand.

Table 1. Differential diagnoses

CRITERIA	INDEX PATIENT	KAPOSI SARCOMA	ACROANGIODER-MATITIS OF MALI (PSEUDO-KAPOSI)	BACILLARY ANGIO-MATOSIS	ANGIOSARCOMA
Age and Gender	44 year old ; Male	Adult ; Male	Elderly ; Male	Any Age ; No gender predilection	>40 years old ; Highest incidence among the elderly
Clinical findings	Red to violaceous or bluish papules, nod-ules and plaque; Initially unilateral	Red-violet to bluish macules or papules that may form large plaques or develop into nodules; Initially unilateral	Brown or violaceous nodules and plaques which become verru-cous or ulcerates; Bilateral	Violaceous papules, nodules and plaques; Pedunculated with collarettte scaling and central umbilication	Single or multifocal bluish or violaceous papules nodules and lichenoid plaques
Associated signs and symptoms	Asymptomatic	Asymptomatic	Pain and edema	Lesions are tender and bleed easily	Lesions bleed easily; facial swelling and edema
Location	Distal extremities	Distal lower extremities	Extensor surface of the lower extremities	Any body part (rare on palms, soles or mouth)	Head, scalp, face and neck
Associated factors	Known case of myasthenia gravis maintained on corti-costeroid therapy	May be immunosuppres-sion associated	Associated with chronic venous insuffi-ciency	Exposure to flea-infested cats; responds to antibiotics	Increase incidence in skin with chronic lym-phedema
Association with HIV infection	HIV-negative	With or without associ-ated HIV infection	Not associated with HIV	With or without associ-ated HIV infection	Not associated with HIV

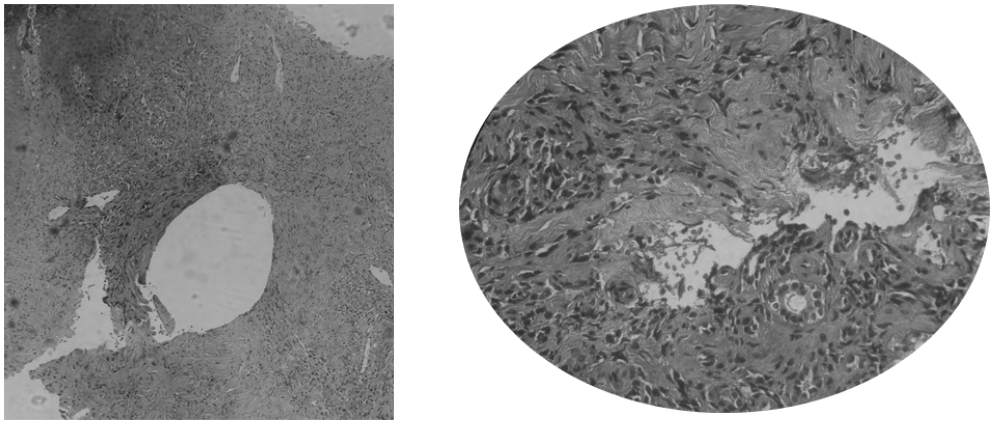

Figure 5. Hematoxylin and eosin staning revealed (a) an increase in number of blood vessels throughout the dermis, and (b) foci of extravasated erythrocytes and spindle-shaped cells are disposed around the blood vessels, adnexal structures and interstitial dermis

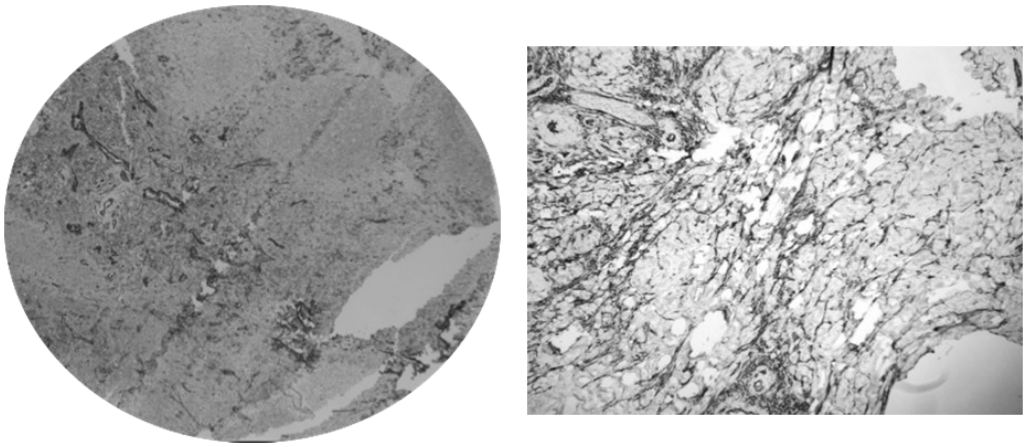

Figure 6. CD31 immunostaining shows a strong positive staining of the spindle cells insinuated between the collagen bundles throughout the dermis.

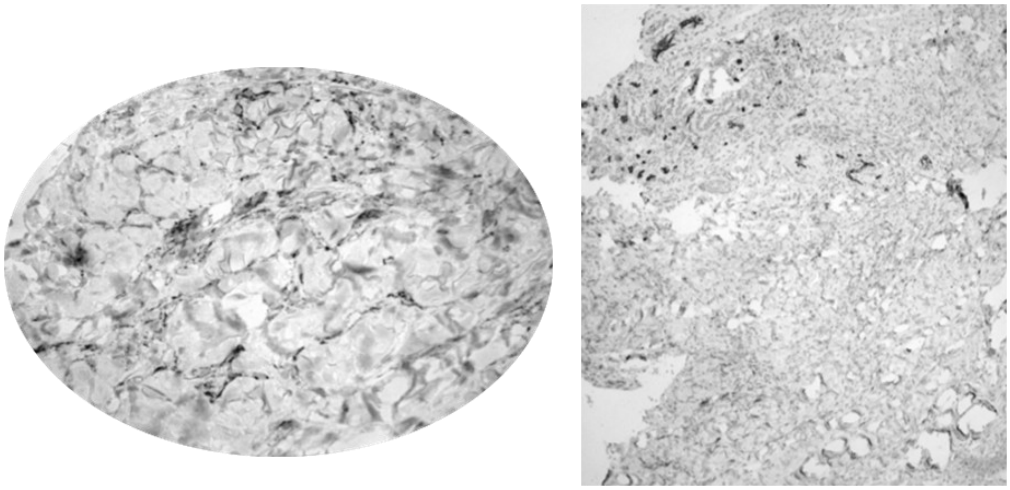

Figure 7. CD 34 shows strong positive staining of the spindle cells mainly located in the lower half of the dermis

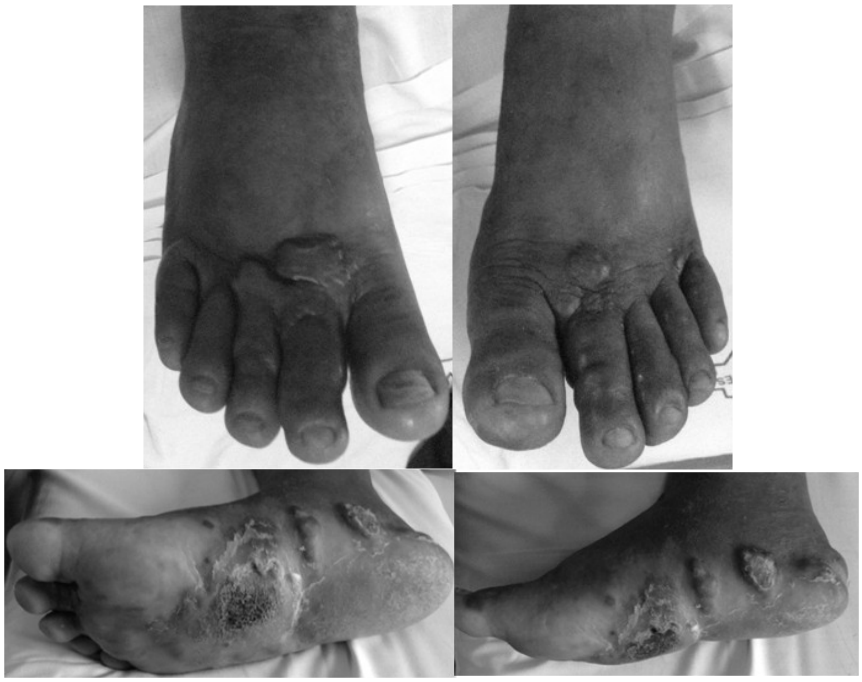

Figure 8. Progression of multiple, well defined, round to irregularly shaped bluish to violaceous nodules and plaques some topped with scales over both feet. Figure 8. Progression of multiple, well defined, round to irregularly shaped bluish to violaceous nodules and plaques some topped with scales over both feet.

Table 2. Kaposi sarcoma staging based on Schwartz et al in 2008

STAGE	DESCRIPTION
Stage I	Localized nodules Kaposi sarcoma (KS) <15 cutaneous lesions or involvement restricted to one bilateral anatomic site, and few, if any, gut nodules
Stage II	Includes both exophytic destructive KS and locally infiltrative cutaneous lesions and locally aggressive KS or nodular KS, or > 15 cutaneous lesions or involvement of more than one bilateral anatomic site and few or many gut nodules
Stage III	Generalized lymphadenopathic KS Widespread lymph node involvement, with or without cutaneous KS but with limited if any visceral involvement
Stage IV	Disseminated visceral KS Widespread KS usually progressing from stages II or III, with involvement of multiple visceral organs with or without cutaneous KS

A Double-Blind, Randomized Controlled Trial on the Efficacy, Safety, and Tolerability of Argan Oil Cream in the Treatment of Mild to Moderate Acne Vulgaris

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Background: Acne vulgaris is one of the most common skin disorders for which patients seek consultation with a dermatologist. One of the pathogenetic mechanisms is sebaceous gland hyperplasia. Argan oil has been proposed to have anti-sebum effects as a topical 5a-reductase inhibitor.

Objective: This study aimed to evaluate the efficacy and safety of argan oil cream in the treatment of mild to moderate acne vulgaris.

Method: 64 subjects, aged 13 to 39 years, were randomized into 4 groups (1%, 2%, 5% argan oil cream, and placebo group). They applied the test medications twice a day for 4 weeks. Every 2 weeks, six parameters were assessed: inflammatory lesion count (ILC), non-inflammatory lesion count (NILC) total lesion count (TLC), casual sebum levels (CSL), investigator global assessment (IGA) and participant global assessment (PGA). Adverse events were recorded.

Results: 2% and 5% argan oil cream were effective in lowering all lesion counts 2 weeks after treatment. Although there was no significant differences in CSL among the groups, CSL and TLC for the 2% and 5% group exhibited a statistically significant direct relationship suggesting that when argan oil lowers sebum levels, lesion counts also decrease, and vise versa. Majority of subjects reported a significant improvement in their skin after treatment, albeit not statistically significant. Adverse events, most commonly dryness of the skin, were generally mild and temporary.

Conclusion: Although all concentrations of argan oil cream were effective in reducing lesion counts, 2% argan oil cream showed the best profile – aside from decreasing all lesion counts, it also prevented the recurrence or appearance of new acne, had the highest self-perceived clearing at 2 weeks, and had the least number of side effects among the 3 concentrations studied.

Keywords: argan oil, acne vulgaris, sebum

INTRODUCTION

Acne vulgaris is one of the most common disorders for which patients consult with a dermatologist. Approximately 80-85% of adolescents have acne, where 15-30% require medical treatment[1]. There are currently four main pathogenetic factors in acne formation: sebaceous gland hyperplasia with seborrhea, pilosebaceous unit obstruction by abnormal keratinization, *Propionobacterium acnes* colonization of the hair follicle, and inflammation mediated by chemotactic factors and various enzymes[2].

Sebum is produced and exclusively secreted by the sebaceous glands. It consists of a complex mixture of fatty acids and triglycerides (57%), wax esters (25%), squalene (15%), and cholesterol esters (3%). The density of sebaceous glands varies with body site, age, and sex. In humans, the highest rate of sebum secretion can be found on the face. Men tend to have a higher rate of sebum secretion as compared to women, which is more notable with aging, when hormonal changes (i.e. menopause) cause a strong decrease in sebaceous gland activity in women[3].

Sebaceous lipids are said to provide skin protection and some photoprotection, to exert pro- and anti-inflammatory actions, and to have antibacterial properties. However, *excess* sebum secretion may lead to acne and an undesired cosmetic appearance manifested as oily skin. Different studies have pointed out that 66-75% of adolescents have increased sebum production, which may lead to reduced self-confidence and impairment in an individual's quality of life[4].

Studies in the past have proven that an increased CSL of facial skin is directly correlated with ILC, suggesting that a higher sebum level has a strong influence on the development of acne. A Medline search conducted by Dolphin et al reviewed a total of 6 studies on acne and sebum level, which included subjects who had mild, mild-moderate, and moderate-severe acne who followed up for 3-4 months. They concluded that a sebum reduction of at least 35% is probably needed to produce a concomitant decrease in acne. In addition, they noted that "acne outcome appears to be highly dependent on sebum reduction not only within individual studies but also across studies and multiple drug classes"[5]. Studies have also shown that aside from the number of lesions, the proportion and location of lesions are influenced by the patient's sebum level[5]. The present study aims to determine if an argan oil containing cream is effective in reducing the oiliness of the skin, thereby decreasing inflammatory lesions (papules and pustules) and non-inflammatory acne (comedones) in subjects.

The argan tree (*Argania spinosa*) is a slow-growing tree exclusively endemic to the barren lands of southwest Morocco. Oil extraction involves a multistep process that begins with careful fruit drying and the use of electric screw-presses. Argan oil is industrially prepared, mostly in Europe, by solvent extraction of imported kernels, then used as an ingredient for the preparation of shampoos, moisturizers, and industrial cosmetic products. For the skin, it has traditionally been used in Morocco as a topical oil to treat dryness, acne, psoriasis, eczema, wrinkles, and other inflammatory processes. Recently, argan oil containing creams have gained popularity and are frequently marketed in cosmetology as moisturizing, anti-aging, and repair creams[6]. However, these cosmetic properties are based only on traditional claims and have minimal scientific research.

Argan oil has been found to have a high content of natural fatty acids. It contains up to 80% unsaturated fatty acids, mainly oleic acid (45%) and linoleic acid (35%). It also contains saturated fatty acids such as palmitic and stearic acids, phytosterols, and tocopherols or vitamin E, which is considered to be the major antioxidant of sebum. It has been proposed that these act as natural 5a-reductase inhibitors, which ultimately decrease dihydrotesterone levels, thereby reducing sebum levels[7]. This anti-sebum activity was demonstrated in a study done by Dobrev, where 20 patients applied on their faces an argan oil containing cream twice daily for four weeks. Results revealed significant reduction in sebum levels, leading to reduced greasiness and improved appearance of oily facial skin[8]. The present study aims to determine any relationship between casual sebum levels and the use of an argan oil containing cream, and if

argan oil can effect a decrease in acne lesions. To the best of the author's knowledge, no published clinical trials of this nature have been conducted locally.

OBJECTIVES

General Objectives

1. To evaluate the efficacy of argan oil cream in the treatment of mild to moderate acne.
2. To assess the safety of argan oil cream in the treatment of mild to moderate acne.
3. To determine the tolerability of argan oil cream in subjects with mild to moderate acne in relation to its adverse event profile.

Specific Objectives

1. To establish the concentration of argan oil cream that will result in decreased lesion counts.
2. To determine any relationship between sebum levels and acne.
3. To assess subjective increase or decrease of lesions using the PGA and IGA

METHODOLOGY

Study Design

This was a 4-week, experimental study designed as a double blind, randomized controlled trial on patients with mild to moderate acne vulgaris and IGA

Definition of Terms

Mild acne is defined as predominance of comedones with ≤ 15 inflammatory papules, while *moderate* acne is defined as predominance of inflammatory papules and pustules (≥15), with comedones and few nodules (≤3). This definition is adapted from the Acne Severity Score of the Acne Board of the Philippines.

Inflammatory lesions are divided into papules, pustules, and nodules. Papules and pustules have surrounding halos of erythema. Nodules are typically erythematous and often tender and/or painful, and are deep-seated in the skin. Non-inflammatory lesions are open or closed comedones. Total lesion counts are defined as the sum of inflammatory and non-inflammatory lesions.

Patient Selection and Randomization

A total of 64 subjects (44 females and 20 males), aged 13 to 39 years, with mild to moderate acne were recruited from the outpatient department of the Department of Dermatology, Jose R. Reyes Memorial Medical Center, Sta. Cruz, Manila, Philippines from May to July 2012.

Subjects not eligible for inclusion into the study were those who used topical anti-acne medications in the past 2 weeks, systemic antibiotic treatments and any form of light treatment for acne in the past month, and systemic retinoids and hormonal contraceptives in the past 6 months. Also excluded were pregnant and lactating women, those who have a known history of sensitivity to the oil or any of the study components, those with comorbid illnesses, and those who were unwilling or unable to give a written informed consent. For minors, suitable guardians were asked to sign the consent in their behalf.

All eligible participants were enrolled into 1 of the 4 treatments arms via computer-generated randomization.

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

The study had 4 treatment arms. Group A (n = 15) was given 1% argan oil in cream formulation; Group B (n = 18) was given 2% argan oil in cream; Group C (n = 12) received 5% argan oil in cream; and Group D (n = 18) received vehicle only. All test

medications had identical texture, color, and odor, and were provided in identical containers. The components used were: pure argan oil, distilled water, sodium lauryl sulfate, propylene glycol, stearyl alcohol, methyl paraben, propyl paraben, and white petrolatum.

At the first visit, subjects and/or their guardians were asked to sign a written informed consent. Baseline standardized photographs were taken with a digital camera (Panasonix Lumix LX-3, 12.1 mp) of their central, right lateral, and left lateral face using standardized lighting and distance. CSL on the face were evaluated using a sebumeter (SM 815, Courage & Khazak, Cologne, Germany). Sebumetry was done on the 4 test areas of the face: forehead (mid-glabella), left cheek (most prominent area of the left zygomata), right cheek (most prominent area of the right zygomata), and chin (mental prominence). They were instructed not to apply any cosmetics on their face and not to wash their face within 2 hours of sebum measurement.

Participants were given a mild facial wash (lipid free cleansing wash from ARM Essentials), which they applied morning and evening on damp skin using light circular strokes for 1 minute on all areas of the face. After washing the cleanser off and patting the face dry, they were instructed to apply the test medication using one fingertip's amount each to the 4 test areas of the face. They were asked not to use any other topical medications, cosmetics, or to have any facial treatments during the study period. They were also advised to avoid prolonged sun exposure. Subjects were asked to follow up every 2 weeks.

At each visit, baseline photographs and sebumetry were done. Adverse events were recorded on standardized case report forms. Each adverse event was graded on a 4-point ordinal scale scored as follows: 0 = none; 1 = mild; 2 = moderate; 3 = severe. A blinded evaluator assessed ILC, NILC, and TLC based on the digital photographs.

At the end of 4 weeks, a global assessment of treatment outcome in comparison with the baseline was performed by both the subject and the investigator, using a 5-point ordinal scale scored as follows: 0 = no appreciable improvement (less than 25% of lesions cleared); 1 = mild (25-49% clear); 2 = moderate (50-74% clear); 3 = marked (75-89% clear); 4 = almost clear (90-99% clear); 5 = clear (100% clear).

Out of the 64 subjects randomized, 6 withdrew consent (4 from 1% argan oil group and 2 from the placebo group). Reasons for withdrawing consent in the 1% argan oil group were: perceived increase in papules and pustules (n=3) and angular cheilitis (n=1). Reasons for withdrawing consent in the placebo group were: perceived increase in papules and pustules (n=1) and emigrated to another country (n=1). A total of seventeen subjects were lost to follow up (5 from 1% argan oil group, 6 from 2% argan oil group, 2 from 5% argan oil group, and 4 from placebo group).

Statistical Methods

Data were encoded and tallied in SPSS version 10 for Windows. Descriptive statistics were generated for all variables. For nominal data, frequencies and percentages were computed. For numerical data, mean ± SD were generated. Analyses of the different variables were done using ANOVA, the Kruskal Wallis test, Spearman correlation coefficient, and the Chi-square test.

RESULTS

Patient Disposition and Baseline Characteristics

No significant differences were seen in the baseline characteristics and demographics among the groups ($p>0.05$). This is summarized in Table 1.

Table 1. Demographics and baseline characteristics

	1% Argan Oil (n = 15)	**2% Argan Oil** (n = 18)	**5% Argan Oil** (n = 12)	**Vehicle** (n = 18)	**p-Value**
Age in Years					
Mean ± SD	21.26 ± 5.30	26.11 ± 8.23	21.25 ± 3.62	23.78 ± 6.43	0.06
Median	20	24	20.5	23	
Sex n (%)					
Female	7 (46.7%)	15 (83.3%)	10 (83.3%)	12 (66.7%)	0.08
Male	8 (53.3%)	3 (16.7%)	2 (16.7%)	6 (33.3%)	
ILC	Mean ± SD				
F	2.93±2.76	2.22 ± 4.38	3.58±4.83	1.33 ± 2.64	0.06
RC	1.60±2.47	3.94±3.33	3.67±3.17	1.78±3.20	0.07
LC	1.86±3.11	4.00±3.60	4.33±2.74	2.39±3.86	0.15
C	0.40±1.06	1.50±2.04	1.50±2.15	1.11±3.08	0.19
NILC					
F	6.20 ± 6.48	6.67 ± 4.27	6.08 ± 3.50	5.17 ± 3.58	0.61
RC	2.93 ± 2.98	4.22 ± 2.88	4.42 ± 3.58	3.33 ± 2.22	0.45
LC	3.40 ± 3.08	5.50 ± 3.86	4.58 ± 3.90	3.94 ± 2.64	0.32
C	0.93±1.79	2.33±2.50	2.00±2.92	0.88±1.71	0.15
CSL					
F	157.60 ± 108.55	254.06 ± 167.15	219.17± 115.97	220.67± 157.24	0.29
RC	253.23 ± 127.61	243.11 ± 118.07	221.67± 155.17	271.44± 157.78	0.29
LC	190.13 ± 160.27	216.06 ± 127.48	242.92± 125.01	244.72± 146.88	0.68
C	198.73 ± 152.77	301.17 ± 158.21	273.25± 128.33	309.94± 106.36	0.12

SD, standard deviation; ILC, inflammatory lesion count; NILC, non-inflammatory lesion count; CSL, casual sebum level F, forehead; RC, right cheek; LC, left cheek; C, chin

Comparing ILC, NILC, and TLC across the Groups over Time

Table 2 compares the means of TLC, ILC, and NILC and the mean differences from baseline to week 2 (first follow up visit) and from week 2 to week 4 (final follow up visit). No significant differences were seen in any of the parameters in the 1% argan oil group ($p>0.05$). However, when comparing the means of lesion counts, a decreasing trend was noted.

The 2% and 5% argan oil cream groups both showed statistically significant decreases in all lesion counts after 2 weeks of treatment, but *not* after 4 weeks of treatment. Lastly, the vehicle group showed statistically significant differences only in the TLC ($p=0.043$) and NILC ($p=0.000$), but not in the ILC.

Table 2 Lesion count means and mean differences during the trial period

	1% Argan Oil Group			2% Argan Oil Group			5% Argan Oil Group			Vehicle Group		
	Mean	Mean Diff	p-value	Mean	Mean Diff	p-value	Mean	Mean Diff	p-value	Mean	Mean Diff	p-value
TLC												
B W2	22.833 13.000	9.833	0.061	32.333 23.500	8.833	**0.002**	34.444 19.000	15.444	**0.014**	22.909 16.545	6.364	**0.043**
W2 W4	13.000 9.667	3.333	0.257	23.500 19.167	4.333	0.059	19.000 19.889	-0.889	0.823	16.545 13.727	2.818	0.060
ILC												
B W2	1.833 1.000	0.833	0.073	3.083 2.292	0.792	**0.016**	3.417 1.889	1.528	**0.034**	2.091 1.455	0.636	0.290
W2 W4	1.000 0.917	0.083	0.793	2.292 1.792	0.500	0.102	1.889 2.000	-0.111	0.841	1.455 1.000	0.455	0.074
NILC												
B W2	3.917 2.250	1.667	0.093	5.000 3.583	1.417	**0.023**	5.167 2.889	2.278	**0.022**	3.636 2.523	1.114	**0.000**
W2 W4	2.250 1.500	0.750	0.328	3.583 2.979	0.604	0.148	2.889 3.500	-0.611	0.309	2.523 2.432	0.091	0.742

TLC, total lesion count; ILC, inflammatory lesion count; NILC, non-inflammatory lesion count
B, baseline; W2, week 2; W4, week 4

Effect of Argan Oil Cream on CSL

Table 3 shows the total CSL (sum of CSL on all parts of the face) among the different groups during the treatment period. There were no significant differences in the total CSL.

Table 3. Comparison of CSL among groups

Group	TCSL at baseline	TCSL at 2 weeks	TCSL at 4 weeks	P-value
1% argan oil	7.33 ± 7.84	4.00 ± 4.47	3.67 ± 3.72	0.478
2% argan oil	12.33 ± 10.24	9.17 ± 7.65	7.17 ± 5.17	0.290
5% argan oil	13.67 ± 11.80	7.56 ± 7.76	8.00 ± 4.39	0.258
Vehicle	8.36 ± 12.15	5.82 ± 5.69	4.00 ± 4.29	0.459

TCSL, total casual sebum level

Establishing the Relationship Between Casual Sebum Levels and Total Lesion Counts

Table 4 presents the correlation of CSL and TLC. Positive correlation coefficients indicate that there is a direct association between CSL and TLC that is statistically significant at week 2 and week 4 for both the 2% and 5% argan oil cream group, and only at week 2 for the vehicle group.

Table 2 Lesion count means and mean differences during the trial period

	Correlation Coefficient	P-value
1% Argan Oil		
Week 2	0.794	0.059
Week 4	0.638	0.173
2% Argan Oil		
Week 2	0.598	**0.040**
Week 4	0.637	**0.026**
5% Argan Oil		
Week 2	0.731	**0.025**
Week 4	0.688	**0.041**
Vehicle		
Week 2	0.760	**0.007**
Week 4	0.533	0.092

Participant Global Assessment

Table 5 shows the comparison of the participant global assessment after 2 weeks and after 4 weeks among the four groups. At week 2, the 2% argan oil cream group reported the most clearing, while at week 4, the 5% argan oil cream group noted the most improvement. In all groups, PGA mean scores increased, meaning most patients reported clearing or improvement of the skin, although these were not statistically significant.

Table 5. Comparison of the participant global assessment among groups

Score	1% Argan Oil (n=14)	2% Argan Oil (n=18)	5% Argan Oil (n=12)	Placebo (n=15)	P value
Week 2					
No improvement	4	1	1	3	
Mild improvement	6	5	6	5	
Moderate improvement	1	7	5	5	
Marked improvement	2	4	0	2	
Almost clear	1	1	0	0	
100% clear	0	0	0	0	
Mean ± SD	1.28 ± 1.26	**1.94 ± 0.99**	1.33 ± 0.65	1.40 ± 0.98	0.21
Week 4					
No improvement	1	1	1	1	
Mild improvement	0	2	0	4	
Moderate improvement	3	5	4	4	
Marked improvement	2	3	3	2	
Almost clear	1	2	1	0	
100% clear	0	0	0	0	
Mean ± SD	2.28 ± 1.25	2.23 ± 1.17	**2.33 ± 1.12**	1.64 ± 0.92	0.45

Investigator Global Assessment

Table 6 summarizes IGA scores after 2 weeks and after 4 weeks of treatment. IGA was highest for the vehicle group at both week 2 and week 4 determinations. However, no statistically significant improvement or worsening of acne was perceived among the groups.

Table 6. Comparison of the investigator global assessment among groups

	1% Argan Oil (n=15)	2% Argan Oil (n=18)	5% Argan Oil (n=12)	Vehicle (n=18)	P value
Week 2					
No improvement	5	9	4	2	
Mild improvement	3	5	1	5	
Moderate improvement	3	3	3	2	
Marked improvement	1	1	3	5	
Almost clear	2	0	1	1	
100% clear	0	0	0	0	
Mean ± SD	1.43 ± 1.45	0.78 ± 0.94	1.45 ± 1.29	1.87 ± 1.25	0.352
Week 4					
No improvement	3	5	4	2	
Mild improvement	2	4	1	1	
Moderate improvement	0	1	2	1	
Marked improvement	1	1	1	4	
Almost clear	1	2	1	4	
100% clear	0	0	0	0	
Mean ± SD	1.29 ± 1.60	1.31 ± 1.49	1.00 ± 1.20	2.58 ± 1.51	0.997

Adverse Events

Adverse events noted in this study include the following: erythema, dryness, peeling, stinging, itching, increased perceived oiliness of the face, and hyperpigmentation (summarized in Table 6). The incidences of adverse reactions were not statistically significant among the groups.

Table 7. Comparison adverse events among the groups

Adverse Event	1% Argan Oil	2% Argan Oil	5% Argan Oil	Vehicle	p value
Erythema					
Absent	2	4	4	5	
Mild	5	7	1	6	
Moderate	5	5	5	1	
Severe	2	2	2	3	
Mean ± SD	1.50 ± 0.94	1.28 ± 0.96	1.42 ± 1.16	1.13 ± 1.12	0.79
Dryness					
Absent	1	0	0	0	
Mild	6	10	5	7	
Moderate	5	7	6	4	
Severe	2	1	1	4	
Mean ± SD	1.57 ± 0.85	1.50 ± 0.62	1.67 ± 0.65	1.80 ± 0.86	0.70
Peeling					
Absent	1	1	1	1	
Mild	4	6	4	5	
Moderate	8	6	6	7	
Severe	1	5	1	2	
Mean ± SD	1.64 ± 0.75	1.83 ± 0.92	1.58 ± 0.80	1.67 ± 0.82	0.85

Adverse Event	1% Argan Oil	2% Argan Oil	5% Argan Oil	Vehicle	p value
Stinging					
Absent	1	6	1	2	
Mild	7	6	5	3	
Moderate	5	2	4	7	
Severe	1	4	2	3	
Mean ± SD	1.42 ± 0.76	1.22 ± 1.16	1.58 ± 0.90	1.73 ± 0.96	0.49
Itching					
Absent	5	14	7	6	
Mild	5	2	2	5	
Moderate	3	1	1	3	
Severe	1	1	2	1	
Mean ± SD	1.00 ± 0.96	0.39 ± 0.85	0.83 ± 1.19	0.93 ± 0.96	0.28
Oily sensation					
Absent	12	9	9	11	
Mild	0	4	1	2	
Moderate	1	4	2	1	
Severe	1	1	0	1	
Mean ± SD	0.36 ± 0.92	0.83 ± 0.99	0.42 ± 0.79	0.46 ± 0.92	0.44
Hyperpigmenta-					
tion	9	13	6	9	
Absent	1	2	0	2	
Mild	3	1	3	3	
Moderate	1	2	3	1	
Severe	0.71 ± 1.06	0.56 ± 1.04	1.25 ± 1.36	0.73 ± 1.03	0.41 (NS)
Mean ± SD					

DISCUSSION

Effect of Argan Oil Cream on ILC, NILC, and TLC

It appears that in all groups receiving argan oil cream, reductions in lesion counts were evident after application of the creams. For the 1% argan oil group, since there is a decreasing trend in the lesion counts, it can be postulated that a larger sample size and longer study duration may produce significant differences among the groups. The 2% and 5% argan oil group showed significant lessening of *all* types of lesions 2 weeks after the start of treatment. Although these numbers remained the same during the duration of the study (no increase in lesions were seen) suggesting that argan oil cream may also be effective in the prevention of new lesions.

Effect of Argan Oil Cream on CSL

The total CSL takes into account sebum level in all areas of the face. Data shows that there was no statistical difference among the groups during the treatment period. This could be due to a high standard deviation, which means that the values of CSL are scattered across respondents for each group.

Relationship between the Casual Sebum Level and Total Lesion Counts

Although were no significant differences in the CSL among the groups, data from this study does show positive correlation coefficients or a direct relationship between sebum levels and lesion counts in the 2% and 5% argan oil group. It can be postulated then that both 2% and 5% argan oil may possess an anti-sebum property wherein applying argan oil can decrease sebum levels, thereby lessening acne lesions.

PGA and IGA

Although the data was not statistically significant, majority of the subjects rated their skin as more improved at the end of the treatment period as compared to baseline. This could be due to an expectant improvement secondary to application of medication. Improvement in skin tone and texture (e.g. tightening and brightening), possibly secondary to the exfoliative effects of the cream, may have also contributed to the subjects reporting improvement in their skin. Self-assessed clearing of the skin as measured by the PGA, mirrors the improvement in lesion counts, especially for the 2% and 5% argan oil cream groups. Again, it remains to be seen whether increasing the sample size or lengthening the study duration will make these values statistically significant.

The IGA also did not show any statistical differences throughout the duration of the study. This could be due to difficulty in accurately assessing the exact percentage of clearing of the skin since some lesions that may not be visible through digital photography may be palpated and/or visualized only during an actual examination.

Adverse Events

The most common adverse reaction seen across all groups was drying of the skin, which most of the subjects reported to be of mild intensity except for the vehicle group, which reported severe dryness. Erythema was also mostly mild, except again for the vehicle group, which had the most number of subjects reporting it to be severe. Majority of subjects reported peeling of the skin to be moderate. The 2% argan oil group had the highest incidence of peeling and it was also this group with the highest number of severe peeling. Stinging was also mild, most commonly observed by the 1% argan oil group while severe stinging was mostly seen in the 2% argan oil group. Itching was most commonly observed by the 1% argan oil group, which was graded severe by the 5% argan oil group. The 5% argan oil group also had the most incidence of hyperpigmentation and majority of the severe reactions also came from this group.

Most of the side effects mentioned above are similar to the known side effects of topical retinoids, currently one of the well-established first line treatments for acne vulgaris. The main therapeutic utility of tretinoin lies in its comedolytic action: it alters the microclimate of the comedone by inhibition of tonofilaments and the detachment of desmosomes – this prevents the corneocytes from sticking and causing impactions. It also increases mitotic activity in the epithelium, thus helping in the resolution of existing open comedones and prevention of new lesions. Closed comedones are rapidly converted into open comedones and extruded, accounting for the flare of acne during the first few weeks of treatment[9].

Patients on tretinoin typically complain of erythema, itching, dryness, and a pustular flare after 1 to 2 weeks of therapy. This skin irritation occurs in the early stage of therapy, but gradually, the skin becomes hardened and treatment can be maintained with virtually no irritation. Because it causes thinning of the skin, tretinoin can cause a stinging sensation due to increased sensitivity to infrared radiation on exposure to sunlight. This is another transient phenomenon and is known to disappear as tolerance develops[10]. Knowing all these, the researchers then wonder if these adverse effects of argan oil are the keys to its mechanism of action for acne. It is possible that argan oil cream possesses a comedolytic action just like tretinoin, causing erythema, itching, dryness, stinging, and a pustular flare (which caused some subjects to drop out).

Adverse reactions similar to the control groups were also observed in the placebo group. There is a possibility then that some of the adverse events experienced in the argan oil group *may* be attributed to the vehicle's components and not to argan oil itself. The researcher recommends that future researches may first conduct a preliminary patch testing to rule out irritation or allergy to any of the components of the vehicle.

CONCLUSION

Based on the findings of this study, all groups receiving argan oil cream had a decrease in the number of lesions, although the figures were statistically significant only for the 2% and 5% argan oil cream after 2 weeks of treatment. Patients receiving these concentrations did not have any increase in lesions

during the duration of the study, showing that with a concentration of 2% and 5%, argan oil cream may have prevented new lesions. No significant differences in CSL was found among groups, but the CSL of both the 2% and 5% argan oil cream group were directly correlated with lesion counts, suggesting that argan oil may have an anti-sebum property that caused a concomitant decrease in lesion counts. Majority of patients noted a significant improvement in their skin after application of argan oil cream. Adverse events, most commonly dryness of the skin, were generally mild and temporary, and may point to a comedolytic property of argan oil. Based on the side effect profile, the 2% argan oil showed the least number of reported events.

Taking into consideration data gathered from this research, it appears that 2% argan oil showed the best profile – it was effective in decreasing all lesion counts, it prevented the recurrence or appearance of new acne, had the highest self-perceived clearing at 2 weeks, and had the least number of side effects among the 3 concentrations studied.

REFERENCES

1. Thielitz A, Abdel-Naser M, Fluhr J, Zouboulls C, Gollnick H. Topical retinoids in acne – an evidence-based overview. JDDG 2008; 6: 1023-1031.
2. Babayeva L, Akarsu S, Fetil E, Gunes AT. Comparison of tretinoin 0.05% cream and 3% alcohol-based salicylic acid preparation in the treatment of acne vulgaris. J Eur Acad Dermatol Venereol 2010; 25 (3): 328-33.
3. Peirano R, Hamann T, Dusing H, Akhiani M, Koop U, Schmidt-Rose T, Wenck H. Topically applied L-carnitine effectively reduces sebum secretion in human skin. J Cosmet Dermatol 2011; 11: 30-36.
4. Ibid.
5. Janiczek-Dolphin N, Cook J, Thiboutot D, Harness J, Clucas A. Can sebum reduction predict acne outcome? British Journal of Dermatology 2010; 163: 683-688.
6. Choi CW, Choi JW, Park KC, Youn SW. Facial sebum affects the development of acne, especially the distribution of inflammatory acne. J Eur Acad Dermatol Venereol 2011;1-6.
7. Makrantonaki E, Ganceviciene R, Zouboulis C. An update on the role of the sebaceous gland in the pathogenesis of acne. 2011; 3(1): 41-49.
8. Dobrev H. Clinical and instrumental study of the efficacy of a new sebum control cream. J Cosmet Dermatol 2007; 6(2): 113-8.
9. Serdana K, Sehgal V. Retinoids: Fascinating up-and-coming scenario. 2003; 30:355-380.
10. Ibid

The Effectiveness and Safety of Midazolam and Diazepam via the Buccal and Rectal Route for the Emergency Treatment of Seizures among Children at the Philippine Children's Medical Center: A Randomized Controlled Trial

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The Effectiveness and Safety of Midazolam and Diazepam via the Buccal and Rectal Route for the Emergency Treatment of Seizures among Children at the Philippine Children's Medical Center:

ABSTRACT

BACKGROUND: Prolonged seizures are one of the most distressing pediatric emergencies. Prompt management with anticonvulsants is necessary to prevent significant morbidity and mortality. However, the transport from the home to hospital has numerous factors that can be problematic, especially in remote regions, which could further delay treatment initiation. Alternative modes of administration of benzodiazepines as first line anti-epileptic medications, would be lifesaving. OBJECTIVES: *General Objective:* To compare the effectiveness & safety of buccal midazolam and buccal diazepam against rectal diazepam and rectal midazolam for the treatment of children 1 month to 18 years presenting with an acute seizure at Philippine Children's Medical Center. *Specific Objectives:1)*To determine the time duration of seizure cessation among children 1 month to 18 years of age when midazolam or diazepam via the buccal route against the rectal route in PCMC; 2) To determine the side-effects of midazolam and diazepam when given via the buccal route against the rectal route when given for acute seizures among children 1 month to 18 years of age in PCMC.

METHODOLOGY: This is a randomized single-blinded open label controlled trial. Data collection was done from April to September 2013 at the PCMC. Eligible patients were aged 1 month to 18 years who were admitted in the emergency room, service wards or intensive care unit; and patients seen in the out-patient department and diagnostic center (under going EEG or prolonged video EEG monitoring) with continuous, either afebrile or febrile, seizures and children with or without established intravenous access.

RESULTS: All the treatment groups were similar based on the age, weight, sex, seizure types and admission temperature. However, those patients on buccal midazolam group who were receiving anti-epileptic drugs prior to the occurrence of seizure showed significant difference among the treatment groups with p value of 0.039. The seizure cessation has a trend favoring buccal diazepam however difference among the groups were not statistically significant because of small sample size. No adverse effects were noted.

CONCLUSION: The study showed that there is no statistical difference among the four treatment groups as to their effectiveness and safety in the treatment of acute seizures.

KEYWORDS: Seizures, Epilepsy, Therapeutic Success, Status Epilepticus, Buccal, Rectal, Treatment failure

INTRODUCTION

Prolonged seizures are one of the most distressing reasons among pediatric emergencies. This condition requires immediate management to prevent convulsive status epilepticus which causes significant morbidity and mortality. Immediate management of a continuing seizure follows the basic principles of emergency care with the role of anti-seizure medications to terminate the seizure promptly and effectively. Ideally, the medications should be easy to administer, effective, safe, and would have a long anti-seizure effect. However, transfer of a child from home to the hospital can delay treatment substantially. If treatment is delayed, the chances of a successful response to a single medication are diminished.

For the immediate management of prolonged seizures, benzodiazepines are often used as first-line drugs; and the intravenous route is the most suitable in an emergency room setting. In other countries, intravenous lorazepam has been used widely utilized for the treatment of status epilepticus both in the emergency room (for children) and out of the hospital (for adults). Unfortunately, this medication is not available in our country. Locally, diazepam and midazolam are available as first line medications for prolonged seizures. However, intravenous access can be a problem when the seizure event occurs out of the hospital or in small children. In these situations, alternate routes of administration should be employed.

SIGNIFICANCE OF THE STUDY

Buccal midazolam was more effective than rectal diazepam for treating children with acute seizures. (McIntyre, et. al. 2005) Presently, only one prospective study used rectal midazolam for treatment of seizures in children is available.

Anecdotal reports from India (Sridharan, 2005) claimed that buccal diazepam may also be as effective treatment for serial seizures. This was applied at a primary care level in tribal and rural areas of Karnataka, India. They have been running a community based epilepsy control program for the last 15 years, and have used buccal diazepam to control serial or cluster attacks of both convulsive and non convulsive seizures, and claimed the results have been very good.

However, there are currently no local data which could demonstrate the applicability of these different alternative treatment approaches in our present local setting particularly in remote areas and non-hospital setting.

REVIEW OF RELATED LITERATURE

Diazepam is very efficacious for all seizure types because of its rapid onset. However, modes of administration are limited to the intravenous and rectal routes. Intramuscular administration leads to variable absorption. Repeated doses of diazepam accumulate in the serum, which can lead to respiratory depression.

Midazolam, the first water soluble benzodiazepine, is widely accepted as a parenteral anxiolytic and premedicant. It is the only anti-seizure medication which could be given by intramuscular, intranasal or buccal routes. Intranasal midazolam has been shown to be safe and effective in children undergoing various diagnostic studies and minor surgical procedures. Intranasal midazolam has shown to suppress epileptic activity and improves the background of electroencephalograms in epileptic children. However, seizures were controlled more quickly by intravenous diazepam compared to intranasal midazolam (Lahat, 2000).

Intravenous access for benzodiazepines is very difficult during an active seizure. Rectal diazepam has been shown to be as effective as intravenous diazepam. Buccal midazolam may offer a suitable alternative to rectal diazepam. The mouth and the rectum have similar surface areas and pH, have rich blood supplies, and absorption is directly into the systemic circulation, which avoids high first-pass metabolism. Midazolam is effective in the treatment of acute repetitive seizures, with 80% of the episodes ending within 10 minutes of buccal administration. (Scott et. Al.,1999) However, rectal administration may prove problematic in the adolescent and adult population. Oral and sublingual drug administration during a

seizure is not recommended for risk of aspiration and injury. The buccal route has been shown to be an effective alternate route among patients in active convulsions. (Sridharan, 2005)

The overall frequency of response within the first 5 minutes after drug administration in the buccal midazolam group was significantly greater than that in the rectal diazepam group, and all the patients were controlled in less than 5 minutes after drug administration in the buccal midazolam group, although the drug effect time after 5 minutes and less than 10 minutes was similar in both groups. The drug was administered faster in the buccal midazolam group than in the rectal diazepam group. (Mpimbaza, 2012)

Treatment failure for buccal midazolam may reach approximately 40%, in contrast to rectal diazepam which averages 30%. Respiratory depression occurred uncommonly in both of the treatment arms. They concluded that buccal midazolam was as safe as and more effective than rectal diazepam for the treatment of seizures in Ugandan children, although benefits were limited to children without malaria. (Mpimbaza, 2012)

This difference could be explained by possible delays resulting from the need to remove clothing and to position the patient appropriately for the administration of rectal diazepam. Similar considerations do not apply for the administration of buccal midazolam. The majority of the parents (94%) were satisfied with drug administration in the buccal midazolam group. This is probably because of the greater social acceptance of the oral route of drug administration in our country as against the rectal route. Buccal diazepam was utilized in one rural community to treat serial seizures. (Sridharan, 2005)

Midazolam introduced into the buccal cavity is as effective as rectal diazepam in aborting prolonged seizures (roughly 8–10 min). The study was done at a residential centre for children and young people with severe epilepsy. All the patients included in the study had received rectal diazepam previously for acute seizures. The investigators found the buccal cavity easy and safe to reach, and there were no significant adverse cardio-respiratory events. Because of the small volume of liquid given and the rapid absorption of midazolam, aspiration was not an issue in the study. The buccal administration of midazolam seems to have some distinct advantages over rectal administration of diazepam. Although no difference in efficacy between buccal midazolam and rectal diazepam was noted in this study, further work was recommended before this mode of therapy is totally adopted. The patients ranged in age from 5–18 years, but a single dose of each treatment was used for every patient. Whether differences in response rate would have emerged if the dose was based on weight (as is usual for children) was not clear. (Scott et. Al.,1999)

The efficacy of buccal midazolam in children aged 1 month to 15 years with seizures of more than 5 minutes duration showed that the drug efficacy for status epilepticus was 50%. The children were given buccal midazolam at a dose of 0.3mg/k/dose. However, all patients with seizures less than 30 minutes showed a 100% response, wherein the seizures stopped within 3.89 ± 2.22 min (median 3 minutes). No clinically important side effects were reported in this study. (Kutlu, et. al. 2003)

A multi-center randomized controlled trial was done to compare buccal midazolam with rectal diazepam for emergency treatment of children aged 6 months and older presenting with active seizures without intravenous access. The dose utilized for both medications was 0.5 mg/k/dose (ranging from 2.5 mg to 10 mg). The therapeutic success was defined as cessation of seizures within 10 minutes and for at least 1 hour, without respiratory depression. They reported a therapeutic success rate of 56% for buccal midazolam and 27% for rectal diazepam. Thus, they stated that buccal midazolam was more effective than rectal diazepam. (McIntyre et. Al, 2005)

Currently, there is only one study which utilized rectal midazolam for the treatment of acute seizures. A study conducted in Nigeria, comparing the efficacy of rectal midazolam against intramuscular paraldehyde in the control of seizures in 55 children with febrile convulsion. Children aged 5 months to 6 years presenting with febrile convulsion were assigned to either of two treatment groups - rectal midazolam or intramuscular paraldehyde. Rectal

midazolam had an onset of action of 4.9±0.5 minutes. as against 5.2±0.4 minutes in the intramuscular paraldehyde group, though the difference is insignificant ($p>0.10$). The effect of paraldehyde lasted 85±16 minutes compared to 22±5 minutes in those who received rectal midazolam ($p<0.001$). The temperature, pulse and respiration were insignificantly different in the two groups after the administration of the drugs ($p>0.10$), but midazolam significantly lowered the mean arterial blood pressure compared to paraldehyde ($p<0.05$). They concluded that rectal midazolam is as effective and efficacious as intramuscular paraldehyde in the control of seizures in children with febrile convulsion. The ease of administration made it suitable for use in their primary health care setting. (Ojuawo et al. 2001)

RESEARCH OBJECTIVES

General Objective

1. To compare the effectiveness & safety of buccal midazolam and buccal diazepam against rectal diazepam and rectal midazolam for the treatment of children 1 month to 18 years presenting with an acute seizure at the Philippine Children's Medical Center.

Specific Objectives

1. To determine the time duration of seizure cessation among children 1 month to 18 years of age when midazolam or diazepam via the buccal route against the rectal route at the Philippine Children's Medical Center.
2. To determine the side-effects of midazolam and diazepam when given via the buccal route against the rectal route when given for acute seizures among children 1 month to 18 years of age at the Philippine Children's Medical Center.

OPERATIONAL DEFINITION OF TERMS:

1. **Non-invasive administration of medications** – the utilization of the alternative routes of administration of either midazolam or diazepam other than the intravenous or intramuscular route, i.e. buccal, intranasal, sublingual or via rectal routes.
2. **Seizure or convulsion** – episodes of excessive, abnormal muscle contractions, either focal or generalized, which may be sustained or interrupted which are manifestation of excessive or hyper-synchronous (usually self-limited) activity of neurons in the brain.
3. **Status epilepticus** – seizure or a recurrence of seizures that lasts for 30 minutes or more during which the patient does not regain consciousness. However, for management purposes, the operational definition of status epilepticus proposed by Lowenstein & Alldredge (1998) will be utilized in this study. Lowenstein et. al. proposed that institution of treatment for status epilepticus should start for continuous lasting for at least 5 minutes, or there are two or more discrete seizures in between which there is incomplete recovery of consciousness.
4. **Serial seizures** – occurrence of two or more seizures occurring for a relatively brief period (i.e. minutes to hours), but the patient regains consciousness between seizures.
5. **Seizure Recurrence-** recurrence of motor seizure activity from the end of the IV drug infusion after enrollment in the study.

METHODOLOGY

Research Design

This research is a randomized single-blinded open label controlled trial. The data collection was done from April to September 2013 at the Philippine Children's Medical Center. The trial design allowed for entry of a patient more than once because of the potential delay in the treatment if the clinician will still check for prior enrollment into the study.

Population:

Inclusion Criteria:

Eligible patients were aged 1 month to 18 years who were admitted in the emergency room, service wards or intensive care unit; and patients seen in the out-patient department and diagnostic center

(under going EEG or prolonged video EEG monitoring) with:

1. continuous, either afebrile or febrile, seizures
2. children with or without established intravenous access

Children with epilepsy were not excluded in this study (Scott 1999, Kutlu, 2003 and McIntyre, 2005)

Exclusion Criteria:

The following patient were excluded in the study:

1. Patients with proven impaired hepatic, renal and cardiac dysfunction.
2. Patients with seizures who received prior emergency anti-seizure medications from another hospital.

Sample Size Calculation:

By use of two-tailed tests, the estimated sample size is twenty five (25) for each group to detect a difference of at least 2.5 minutes in seizure cessation between groups with 80% power, 5% level of significance, based from previous data.[9]

Calculation:

$$\frac{4C}{(\Delta/\sigma)^2}$$

Where: $C = 7.85$ *(at 80% power)*
$\Delta = 2.5$ *minutes*
$\sigma = 2.22$ *mins*

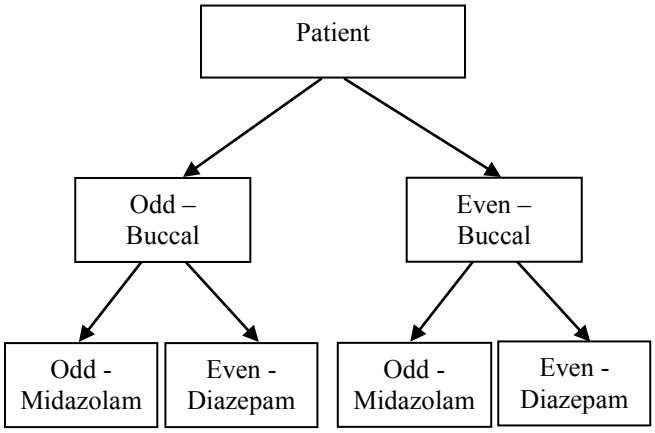
$$N = \frac{4\,(7.85)}{(2.5/\,2.22)^2}$$

$$= \mathbf{24.9 \sim 25}$$

PROCEDURE

Randomization:

Randomization sequence were generated using the random generation tool of Microsoft Excel Program. Generated odd numbers utilized the buccal route, while even numbers were assigned to rectal route. These two groups were further subdivided to either use midazolam or diazepam. For the subgroups, even numbers were assigned to use midazolam, while the odd numbered group used diazepam. The treatment regimen were placed with preassigned schedule and were directly communicated with the senior residents on duty on their respective posts.



Informed Consent:

Patients who arrived at the emergency room in active seizures were verbally given an option to utilize the alternative non-invasive routes of midazolam or diazepam while trying to put an intravenous access. Written consent from the parents or guardians were obtained as soon as practicably possible after treatment and seek consent to use their data in the study.

For those patients with risk factors for recurrent seizures in the service wards, diagnostic center, ICU, an informed consent were obtained from the parents or guardians prior to enrollment into the study.

Drug Preparation and Administration:

A. Preparation:

For the study, the following drug preparations were utilized in the study: 1) Midazolam 15mg/3ml IV ampule and 2) Diazepam 10 mg/2 ml. To avoid confusion, a prepared kit containing either diazepam or midazolam were provided for each target area, with the mode of administration clearly indicated outside the kit.

B. Buccal Routes of Administration:

Based on the study by McIntyre (2005), the dose of midazolam or diazepam were based on the child's age and were designed to give about 0.5mg/kg of midazolam or diazepam (maximum of 10mg/kg/dose). Based on the age, the following projected doses for buccal midazolam and diazepam were followed:

AGE GROUP	DOSE	Buccal/ Rectal **Midazolam** 15 mg/3 ml Volume	Buccal/ Rectal **Diazepam** 10 mg/2 ml Volume
1 month to 5.9 mos old	2 mg	0.4 ml	0.4 ml
6 mos to 12 mos	2.5 mg	0.5 ml	0.5 ml
1 to 4 yrs old	5 mg	1 ml	1 ml
5 to 9 yrs old	7.5 mg	1.5 ml	1.5 ml
10 years and older	10 mgs	2 ml	2 ml

The intravenous preparation of midazolam hydrochloride or diazepam was filtered through a needle. And after removing the needle, the medicine was squirted into the buccal cavity between the gum and cheek mucosa.

C. Rectal Routes of Administration

Even though, the gel form of diazepam or midazolam is not available in the country, diazepam given as a solution rectally has been shown to be as effective (Knudsen, 1977), and the intravenous solution of Midazolam has been utilized for rectal administration (Ojuawo, 2001). The therapeutic dose was similar to the buccal route, i.e. 0.5mg/kg/dose. Thus, the desired dose of diazepam or midazolam was obtained and mixed with distilled water to make 1 to 2 ml solution, and the tip of the tuberculin syringe was inserted per rectum. After giving diazepam or midazolam per rectum, the buttocks were pressed together to prevent escape of the medication.

The investigator was the one who administered the medications in either route after proper coordination with the parents and to the patient.

Outcome Measure:

The primary outcome measure or therapeutic success is defined as cessation of visible signs of seizure activity within 10 minutes of administration of the randomized drug without respiratory depression and without another seizure within 1 hour. Respiratory depression is defined as a fall in oxygen saturation or decrease in respiratory effort sufficient to require assisted breathing either via face mask inflation or intubation after the administration of the drug. This effect however is rare, and is usually managed by transient bag-mask ventilation.

The time of administration of all medications and the start and termination of the seizures were recorded. Observations of oxygen saturation, respiratory rate and supportive interventions were recorded at every 5, 15, 30 and 45 min by the investigator. The total number of seizures within the first 6 hours and first 24 hours were recorded. Seizure duration before treatment were obtained from the report of the child's parents or care-givers.

Intention-to-treat analysis was done and those who left treatment against medical advice was included in the study.

Treatment Failure

If the child had a seizure for 10 minutes after giving buccal midazolam, buccal diazepam, rectal diazepam or rectal midazolam, and intravenous access has been established, then IV diazepam was

was administered, and the status epilepticus protocol of the hospital was followed. The requirement of another anti-convulsant at this stage is classified as treatment failure.

ETHICAL CONSIDERATION

This study was performed in accordance with the current version of the Declaration of Helsinki for medical research involving humans and according to the principles of the European Union and the International Conference of Harmonization Guidelines for Good Clinical Practice and regulations application in our country.

The study protocol, the subject information and the informed consent and assent forms were submitted to and were approved by the Institutional Review Board- Ethics Committee (IRB-EC) of the Philippine Children's Medical Center.

Informed consent was taken by the primary and/or co- investigator from the parents of patients under 18 years of age who fulfilled the criteria of enrolling the patients to the study after thorough explanation of the clinical trial. Likewise, informed assent was taken by the primary and/or co- investigator as soon as possible if feasible from patients 7 – 18 years of age.

The patients and their parents or caregivers were informed that the data gathered in this study were part of the hospital medical records and will be kept confidential to the extent imposed by law.

They were informed that the risks associated with this study are related to the administration of both drugs, midazolam and diazepam. These would include hypotension, respiratory depression, hepatotoxicity and hypersensitivity reactions as noted by rash, hives, itching, difficulty of breathing, tightness in the chest, swelling of the mouth, face, lips, or tongue. Strict measures were employed to prevent the incidence of such adverse events, however they were also informed that there is no guarantee that these will not occur. They were also informed that adverse events during the study period were addressed by the clinical investigators.

Statistical Analysis

For the analysis of data, ANOVA test was utilized to compare the means of seizure cessation of the four test groups.

RESULTS

Table 1. Comparison of the Treatment Groups according to Baseline Characteristics

Characteristics		Treatments				P value
		Midazolam rectal (N=8)	Midazolam buccal (N=9)	Diazepam rectal (N=8)	Diazepam buccal (N=9)	
Age (mean)		4.4	5.9	3.1	3.1	.062
Weight (mean)		14.6	15.2	13.1	12.9	.921
Sex	Male	50.0%	22.2%	25.0%	44.4%	0.545
	Female	50.0%	77.8%	75.0%	55.6%	
Seizure type	Generalized tonic-clonic	62.5%	55.6%	62.5%	66.7%	0.738
	Focal	37.5%	44.4%	37.5%	22.2%	
	Myoclonic	.0%	.0%	.0%	11.1%	
Previous seizures	Yes	37.5%	55.6%	25.0%	66.7%	0.320
	No	62.5%	44.4%	75.0%	33.3%	
Admission Temperature	Febrile	62.5%	33.3%	12.5%	33.3%	0.217
	Afebrile	37.5%	66.7%	87.5%	66.7%	
Receiving Anti-epileptic drugs	Yes	.0%	55.6%	12.5%	44.4%	0.039
	No	100.0%	44.4%	87.5%	55.6%	
Episode with pre-hospital treatment	None	37.5%	44.4%	25.0%	33.3%	0.783
	Once	.0%	22.2%	12.5%	11.1%	
	Twice	62.5%	33.3%	62.5%	55.6%	

Table 1 showed that when the treatments were compared based of age, weight, sex, seizure types, presence or absence of seizures, admission temperature and the number of episode with pre-hospital treatment, they were not statistically significant to each other. However, those patients who were receiving anti-epileptic drugs prior to the occurrence of seizure showed significant difference among the treatment groups with p value of 0.039. The group with the highest number of received anti-epileptic drugs are the midazolam buccal group.

Table 2. A. Comparison of the Treatment Groups according to the Duration of Seizure Before Drug

Treatment Groups	N	Mean (Minutes)	Std. Deviation
Midazolam rectal	8	3.6250	.91613
Midazolam buccal	9	3.1111	1.29368
Diazepam rectal	8	2.1875	.65124
Diazepam buccal	9	3.3333	1.19896

Table 2.A showed that the group with the shortest duration of seizure before drug administration is the rectal diazepam followed by buccal midazolam and buccal diazepam with mean duration of 2.1, 3.1 and 3.3 minutes respectively. The group with the longest duration is the rectal midazolam with 3.6 minutes.

Table 2.B Multiple Comparison of the Treatment Groups according to the Duration of Seizure Before Drug Administration

(I) Treatments	(J) Randomization	Mean Difference (I-J)	P value	95% Confidence Interval	
Midazolam rectal	Midazolam buccal	.51389	1.000	-.9416	1.9693
	Diazepam rectal	1.43750	.066	-.0601	2.9351
	Diazepam buccal	.29167	1.000	-1.1638	1.7471
Midazolam buccal	Midazolam rectal	-.51389	1.000	-1.9693	.9416
	Diazepam rectal	.92361	.499	-.5318	2.3791
	Diazepam buccal	-.22222	1.000	-1.6342	1.1898
Diazepam rectal	Midazolam rectal	-1.43750	.066	-2.9351	.0601
	Midazolam buccal	-.92361	.499	-2.3791	.5318
	Diazepam buccal	-1.14583	.203	-2.6013	.3096
Diazepam buccal	Midazolam rectal	-.29167	1.000	-1.7471	1.1638
	Midazolam buccal	.22222	1.000	-1.1898	1.6342
	Diazepam rectal	1.14583	.203	-.3096	2.6013

Table 2.B. showed that the duration of seizure prior to the institution of treatment was not statistically significant when compared to all the treatment groups.

Table 3. Comparison of the groups according to the Effectiveness of Treatment

Characteristics		Treatments								P value
		Midazolam rectal		Midazolam buccal		Diazepam rectal		Diazepam buccal		
		N	%	N	%	n	%	n	%	
Therapeutic success	Yes	6	75.0%	8	88.9%	8	100.0%	9	100.0%	0.230
	No	2	25.0%	1	11.1%	0	.0%	0	.0%	
Stopped seizure within 10mins	Yes	6	75.0%	7	77.8%	8	100.0%	9	100.0%	0.207
	No	2	25.0%	2	22.2%	0	.0%	0	.0%	
Given benzodiazepines to stop seizure	Yes	3	37.5%	2	22.2%	2	25.0%	2	22.2%	0.879
	No	5	62.5%	7	77.8%	6	75.0%	7	77.8%	
Seizure recurrence within 6hrs	Yes	1	12.5%	0	.0%	0	.0%	1	11.1%	0.544
	No	7	87.5%	9	100.0%	8	100.0%	8	88.9%	
Seizure recurrence within 24hrs	Yes	1	12.5%	0	.0%	0	.0%	3	33.3%	0.098
	No	7	87.5%	9	100.0%	8	100.0%	6	66.7%	
Respiratory distress	Yes	1	12.5%	1	11.1%	0	.0%	0	.0%	0.544
	No	7	87.5%	8	88.9%	8	100.0%	9	100.0%	

Table 3 showed that the cessation of visible signs of seizure activity within 10 minutes of administration of the randomized drugs without respiratory depression and without another seizure within one hour were not statistically significant. Likewise, the patients enrolled in the treatment groups were not statistically significant whether they were given long acting benzodiazepines after the seizure and the recurrence of seizures within six hours. However, the recurrence of seizures within 24 hours was found to be borderline significant with a p value of 0.098.

Table 4. A. Comparison of the Treatment Groups according to the duration to stop seizure after treatment

	N	Mean (Miniutes)	Std. Deviation
Midazolam rectal	8	5.9187	5.05401
Midazolam buccal	9	3.4648	3.27190
Diazepam rectal	8	3.1500	.95115
Diazepam buccal	9	2.3722	1.22636

Table 4.A. showed that the group with the shortest duration of seizure after administration of the drug is the buccal diazepam followed by rectal diazepam and buccal midazolam group with mean duration of 2.3, 3.1 and 3.4 minutes respectively. The rectal diazepam having a 5.9 minutes has the longest duration.

Table 4.B. Multiple comparison of the Treatment Groups according to the duration to stop seizure after treatment

(I) Randomization	(J) Randomization	Mean Difference (I-J)	Sig.	95% Confidence Interval
Midazolam rectal	Midazolam buccal	2.45394	.663	(-1.7603-6.6681)
	Diazepam rectal	2.76875	.488	(-1.5676-7.1051)
	Diazepam buccal	3.54653	.144	(-.6677-7.7607)
Midazolam buccal	Midazolam rectal	-2.45394	.663	(-6.6681-1.7603)
	Diazepam rectal	.31481	1.000	(-3.8994-4.5290)
	Diazepam buccal	1.09259	1.000	(-2.9958-5.1810)
Diazepam rectal	Midazolam rectal	-2.76875	.488	(-7.1051-1.5676)
	Midazolam buccal	-.31481	1.000	(-4.5290-3.8994)
	Diazepam buccal	.77778	1.000	(-3.4364-4.9920)
Diazepam buccal	Midazolam rectal	-3.54653	.144	(-7.7607-.6677)
	Midazolam buccal	-1.09259	1.000	(-5.1810-2.9958)
	Diazepam rectal	-.77778	1.000	(-4.9920-3.4364)

The table 4.B. showed that the multiple comparisons of all the treatment groups based on the time duration to stop the seizure after giving the drug were not statistically significant with each other.

DISCUSSION

Previous studies have shown that the first and foremost aim in treating an acute episode of convulsion is controlling it as quickly as possible. Every effort should be made to prevent prolonged seizures from developing into status epilepticus.

This is a randomized single-blinded open label controlled trial research conducted from April to September 2013 at the Philippine Children's Medical Center. This study aimed to compare the effectiveness and safety of buccal midazolam and buccal diazepam against rectal midazolam and rectal diazepam for the treatment of children 1 month to 18 years presenting with an acute seizures. There were only 34 subjects enrolled in this study instead of 100 subjects based on the 5% level of confidence with 80% power.

As to the baseline characteristics of the patients such as age, weight, sex, seizure type, presence and absence of previous seizures, temperature on admission and the number of seizure episodes prior to hospitalizations were found to be not statistically significant. However, patients who received anti-epileptic drugs prior to the occurrence of seizure among the treatment groups showed significant difference with a p value of 0.039.

As to the seizure type, majority of the subjects presented with generalized tonic-clonic seizure but were not statistically significant between the groups. Majority of the patients were afebrile at the time of admission but was not statistically significant when compared to the treatment groups. The results of the comparison of the treatment groups to the baseline characteristics are comparable to the study of Scott et al in 1999.

The number of subjects who were maintained on or receiving anti- epileptic drugs were statistically significant between the treatment groups.

The therapeutic success or the cessation of visible signs of seizure activity within 10 minutes of administration of the drugs without signs of respiratory depression and without another seizure within 1 hour was found to be highest among the diazepam buccal and rectal groups. However, when compared to other treatment groups, it is not statistically significant.

All the subjects under the diazepam buccal and rectal groups showed cessation of seizure within 10 minutes however some of the patients were given long acting benzodiazepines after 1-2 hours of giving the medication.

The duration of seizure prior to the institution of treatment and the time duration to give the drug after arrival to hospital were not statistically significant among the treatment groups.

The time to stop the seizure after giving the drug among the treatment groups were found to be not statistically significant. The group with the shortest duration to stop the seizure activity was buccal diazepam group (mean= 2.3 minutes) and the longest was rectal midazolam (mean= 5.9 minutes). Among the route, the buccal group particularly that of Diazepam group has the shortest duration of seizure after giving the medication.

Overall, the author found out that there is a trend of not having significant differences between the drugs according to its efficacy, time from arrival at the patient to drug administration, time from administration to end of seizure, or total seizure length. No subjects had adverse cardiorespiratory events, which suggests drug safety.

Safety, efficacy, and long-lasting anti-seizure activity are said to be important characteristics of any drug for emergency treatment of seizures. The result of this study showed that buccal diazepam has been proved superior to the other drugs in the treatment of acute repetitive seizures which was justified in this report. Since there were no differences between the efficacy of the drugs, buccal diazepam is also likely to be superior to the other drugs. Use of buccal diazepam has clear practical and social advantages over rectal diazepam, buccal midazolam and rectal midazolam.

CONCLUSION

The results of this study showed that there is no statistical difference among the four treatment groups as to their effectiveness and safety in the treatment of acute seizures.

Based also on this preliminary report, the author can conclude that both drugs (diazepam and midazolam) of either routes (rectal and buccal) can be used as alternative treatment in patients with acute seizures in a setting with no intravenous access. There were no cardio-respiratory events noted in all the treatment groups, which suggests drug safety.

RECOMMENDATION

In this study, samples recruited were not enough. Thus, it should be continued by the co-authors to have a larger population for a better reflection of the results.

Likewise, it is to be recommended for future research to include sub-analysis of the anti-epileptic drugs given prior to giving the medications.

REFERENCES

1. Knudsen, FU. Plasma diazepam in infants after rectal administration in solution and by suppository. Acta Paediatr Scand. 1997 Sep; 66(5): 563-7. (Abstract)
2. Vengudi Swaminathan Sridharan, Electronic Letter to the Editor re article on Status epilepticus: an evidence based guide. BMJ 2005; 331. Sept 23, 2005.
3. Lowenstein DH, Alldredge BK. Status epilepticus. N Engl J Med. 1998; 338; 970-76.
4. Scott, RC, Besag FM, Boyd SG, Berry D, Neville BG. Buccal absorption of midazolam: Pharmacokinetics and EEG pharmacodynamics. Epilepsia. 1998 Mar; 39 (3): 290-4.
5. Scott, RC et. al. Buccal Midazolam and Rectal Diazepam for treatment of prolonged seizures in childhood and adolescence: A Randomized Trial. The Lancet. Feb 1999.
6. A. Ojuawo, O. Owolabiolabi , Comparison of Rectal Midazolam and Intramuscular Paraldehyde in the Control of Seizures in Children with Febrile Convulsion. The Nigerian Medical Journal, 2001, Vol. 40(3): 67-70. (Abstract)
7. Lahat E, Goldman M, Barr J, Eshel G, Berkovitch M. Comparison of Intranasal Midazolam with intravenous diazepam for treating febrile seizures in children: prospective randomized study. BMJ, 2000 Jul; 321: 83-86.

8. Kutlu, NO, Dogrul M, Yakinci C, Soylu H. Buccal Midazolam for treatment of prolonged seizures in children. Brain Dev. 2003 Jun; 25(4): 275-8.

9. McIntyre J. Roberson S, Norris E, Appleton R, Whitehouse WP, Phillips B, Martland T, Berry, K, Collier j., Smith S, Choonara I. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomized controlled trial. Lancet. 2005 Jul; 366(9481): 205-10.

10. Ashrafi, Mahmoud, et al. Efficacy and usability of buccal midazolam in controlling acute prolonged convulsive seizures in children. Journal of the European Pediatric Neurology Society, April 2010.

11. Mpimbaza, Arthur, Ndeezl Grace, et al. Comparison of Buccal Midazolam with rectal Diazepam in the treatment of Prolonged seizures in Ugadan Children: A randomized clinical trial.American Academy of Pediatrics, September 2012.

12. Levy, et.al., Anti-epileptic Drugs, Fifth edition, 2002.

13. Engel, et.al, Epilepsy: A comprehensive textbook, 1997.

A Rare Case of Pemphigus Vulgaris, Mucocutaneous Type in a 26-year Old Female

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Pemphigus is an autoimmune blistering disease of the skin, mucous membrane, or both. There are two main categories: pemphigus foliaceus (PF) and pemphigus vilgaris (PV) based on clinical, histopathologic and serologic features. PV The mean age of onset of the disease is approximately 40 to 60 years of age. We report a case that clinically showed blisters and erosions in the skin and mucous membrane in a 26 years old female patient. Histologic examination of the cutaneous lesions demonstrated suprabasilar acantholysis. Direct immunofluorescence showed intercellular deposition of IgG (+2) and C3 (+2). Prednisone and a steroid sparing agent- Azathioprine were given and significant improvement was observed after just three weeks.

Abbreviation used.
PV: Pemphigus vulgaris
PF: Pemphigus foliaceus
Dsg: Desmogleins

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Pemphigus is an autoimmune blistering disease of the skin, mucous membrane, or both. There are two main categories: pemphigus foliaceus (PF) and pemphigus vulgaris (PV) based on clinical, histopathologic and serologic features. PF is characterized clinically by the presence of shallow erosions, with evident scaling and crusts on the skin, without mucosal involvement. PV is characterized clinically by mucosal erosions mainly on the oral cavity with minimal skin involvement. PV is further subdivided into mucosal and mucocutaneous type, according to the extent of cutaneous lesions.[7] The mean age of onset of the disease is approximately 40 to 60 years of age, with equal men and women involvement. It has a worldwide incidence of 0.5-3.2 cases per 100,000.[10] In our institution, there were only 11 cases of PV seen since 2001 up to present and the patients were mostly female in their 40's to 60's. This is the first case of PV reported in a 26 years old female.

CASE REPORT

We report a case of 26 year old female, with a 1 ½ year history of recurrent painful erosions on the lower lip. No fever nor lymphadenopathy was noted. Over time patient noted fluid-filled lesions that would easily rupture on the abdominal area. No history of trauma prior to appearance of lesions. Blisters spontaneously rupture forming erythematous plaques with erosions which healed with hyperpigmentation. New lesions appeared on her face, back, neck, breasts and lower extremities. Patien self-medicated with Amoxicillin 500mg three times a day for 1 week and applied topical fluocinonide ointment irregularly on the lesions but only afforded temporary relief. Hence, she decided to consult in our institution.

Past medical history was unremarkable. Patient is single, unemployed, with no history of illicit drug use, no intake and topical application of herbal medications nor any other medications and no history of chronic sun exposure. She is non-alcoholic beverage drinker and non-smoker.

On physical examination, there was a solitary, erythematous erosion on right side of soft palate. Lesions on the genitalia. Dermatologic examination revealed multiple erythematous plaques, some with erosions on the scalp, forehead, neck, chest, back and few on the lower extremities. Few flaccid bullae containing clear fluid also noted on the trunk. Positive for Nikolsky and Asboe-Hansen signs.

Basing on the clinical findings, the initial impression was Pemphigus vulgaris. Punch biopsy of a bulla revealed an intraepidermal vesicle filled with red blood cells and few acantholytic cells. Focal areas of the base of the vesicle show a suprabasal tombstoning acantholytic pattern. The dermis shows moderately severe inflammatory infiltration consisting of lymphocytes (predominantly) and histiocytes. Few melanophages are also seen in the upper dermis (*Fig 1*). Punch biopsy of the normal skin adjacent a bulla was done and was sent for direct immunofluorescence which showed intercellular deposition of IgG (+2) and C3 (+2) (*Fig 2*). Other laboratory work up were normal, which included complete blood count, erythrocyte sedimentation rate, urinalysis, stool examination with occult blood, chest xray, SGPT, SGOT, BUN, serum creatinine, sodium, potassium, calcium, random blood sugar and lipid panel. Final clinicohistopathologic diagnosis is Pemphigus Vulgaris.

Patient was started on Prednisone 1 mg/kg/day decreasing the dose by 10 mg weekly. On the second week of treatment, Azathioprine 50mg/day was added. Both medications continued up to 3 months. Dramatic improvement was observed starting at the third week of treatment (*Fig 4*). No new lesions appeared and the old lesions healed with hyperpigmentation.

DISCUSSION

PV occurs worldwide, but is more common in Jews and in people of Mediterranean descent.[1] It affects men and women equally and is considered an organ-specific autoimmune disease.[2] The mean age of onset of disease is approximately 40 to 60 years of age; however, the range is broad, and disease may start in the elderly and in children. There was no report of PV occurring in young adults.

The major histologic feature is acantholysis.[3] Direct immunofluorescence of perilesional skin

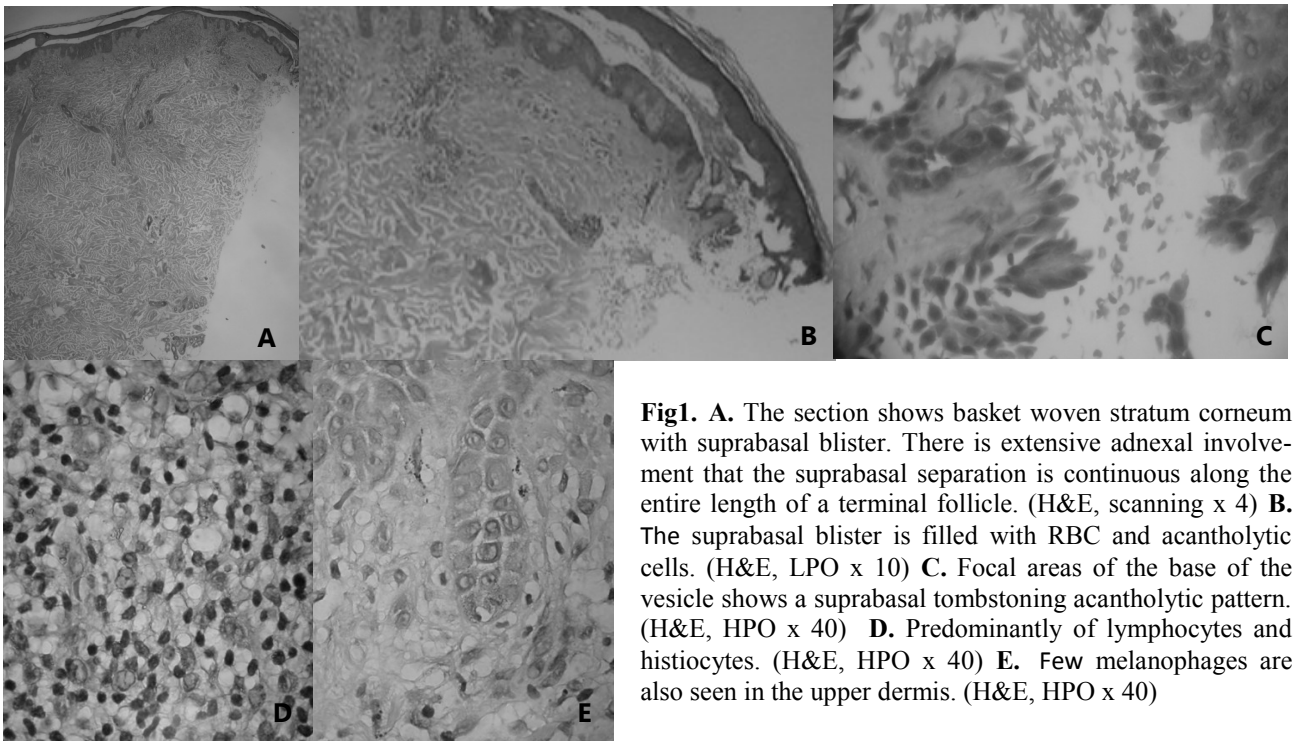

Fig1. A. The section shows basket woven stratum corneum with suprabasal blister. There is extensive adnexal involvement that the suprabasal separation is continuous along the entire length of a terminal follicle. (H&E, scanning x 4) **B.** The suprabasal blister is filled with RBC and acantholytic cells. (H&E, LPO x 10) **C.** Focal areas of the base of the vesicle shows a suprabasal tombstoning acantholytic pattern. (H&E, HPO x 40) **D.** Predominantly of lymphocytes and histiocytes. (H&E, HPO x 40) **E.** Few melanophages are also seen in the upper dermis. (H&E, HPO x 40)

binding of IgG antibodies to the epidermis in an intercellular pattern.[4] Pemphigus antibody is pathogenic and is present in the serum of patients with PV.[5] It is directed against a normal component of the intercellular substance known desmoglein 3.[6] The clinical and histologic sites of blister formation in pemphigus are now logically explained by desmoglein compensation theory. Dsg1 and Dsg3 have distinct intraepithelial expression patterns in the skin and mucous membranes. In the superficial layers. Dsg3 is expressed in the lower part of the epidermis, mainly in the basal and parabasal layers. In contrast, in the mucous membranes, Dsg1 and Dsg3 are expressed throughout the squamous mucosal epithelia, but the expression level of Dsg1 is much lower than that of Dsg3.[7]

Pemphigus vulgaris, once a fatal disease, now has a mortality rate below 10% with the introduction of corticosteroids and adjuvant therapy with immunosuppressive drugs. Currently, the mainstay of treatment is corticosteroids. Before the availability of corticosteroids, approximately 75% of patients died of pemphigus, usually within 1 year. The use of corticosteroids in the 1950s reduced the mortality to approximately 25% to 45%. However, the use of long-term glucocorticosteroids is linked to severe and life-threatening complications. Side effects from corticosteroids can be the major cause of death in patients with pemphigus.[8]

The addition of adjuvant therapy with a "steroid sparing" effect has reduced the mortality of pemphigus to less than 10%.[7] Adjuvant therapies for pemphigus can be divided according to the mechanism of action. Immunosuppressive drugs include cyclophosphamide, azathioprine, chlorambucil, cyclosporine, methotrexate, and mycophenolate mofetil. Antiinflammatory drugs include antimalarials, dapsone, and gold. Immunomodulatory procedures include plasmapheresis and photopheresis.[9] dapsone, and gold. Immunomodulatory procedures include plasmapheresis and photopheresis.[9]

The most efficacious cytotoxic drug to reduce steroid was found to be azathioprine, followed by cyclophosphamide (pulse therapy), and mycophenolate mofetil.[11] Azathioprine (1-2 mg/kg/day) and corticosteroid treatment of pemphigus is highly effective and safe; it leads to long-term remissions in most patients and possibly to a cure in some.[12]

It is possible to eventually induce complete and durable remissions in most patients with pemphigus that permit systemic therapy to be safely discontinued without a flare in disease activity. The induction of complete remission was related to the initial severity and extent of disease and to early response to treatment.[13]

REFERENCES

1. Pisanti S,et al, Pemphigus vulgaris: incidence in Jews of different ethnic groups, according to age, sex, and initial lesion. Oral Surg Oral Med Oral Pathol. Sep 1974; 38 (3):382-7.
2. Ahmed AR, Graham J, Jordon RE, et al. Pemphigus: current concepts. Ann Intern Med 1980;92:396-405.
3. Schiltz JR, Michel B. Production of epidermal acantholysis in normal human skin in vitro by the IgG fraction from pemphigus serum. J Invest Dermatol 1976;67:254-60.
4. Beutner EH, Jordon RE, Chorzelski TP. The immunopathology of pemphigus and bullous pemphigoid. J Invest Dermatol 1968;51:63-80.
5. Beutner EH, Jordon RE. Demonstration of skin antibodies in serum of pemphigus vulgaris patients by indirect immunofluorescence staining. Proc Soc Exp Biol Med 1964;117:505-10.3.
6. Eyre RE, Stanley JR. Identification of pemphigus vulgaris antigen extracted from normal human epidermis and comparison with pemphigus foliaceous antigen. J Clin Invest 1988;81:807-12.
7. Kazue Yoshida, MD, Yujiro Takae, MD, Hitoshi Saito, MD, Hiroshi Oka, MD, PhD, Akiko Tanikawa, MD, PhD, Masayuki Amagai, MD, PhD, and Takeji Nishikawa, MD, PhD Tokyo, Japan Cutaneous type pemphigus vulgaris: A rare clinical phenotype of pemphigus J Am Acad Dermatol 2005;52:839-45
8. Rosenberg FR, Sanders S, Nelson CT. Pemphigus: a 20-year review of 107 patients treated with corticosteroids. Arch Dermatol 1976;112:962-70.
9. Marie V. Hayag, MD,a Jonathan A. Cohen, MD,b and Francisco A. Kerdel, BSc, MBBSa Miami, Florida. Immunoablative high-dose cyclophosphamide without stem cell rescue in a patient with pemphigus vulgaris J Am Acad Dermatol 2000;43:1065-9.
10. Klaus Wolff et al. Fitzpatrick in General Medicine 7th ed.
11. Cheyda Chams-Davatchi, J Am Acad Dermatol. Volume 57, Issue 4, Pages 622-628 (October 2007)
12. Aberer W, et al. Azathioprine in the treatment of pemphigus vulgaris: A long term follow-up. J Am Acad Dermatol . 1987; 16: 527.
13. Herbst A, et al. J Am Acad Dermatol. 2000;42:422-7

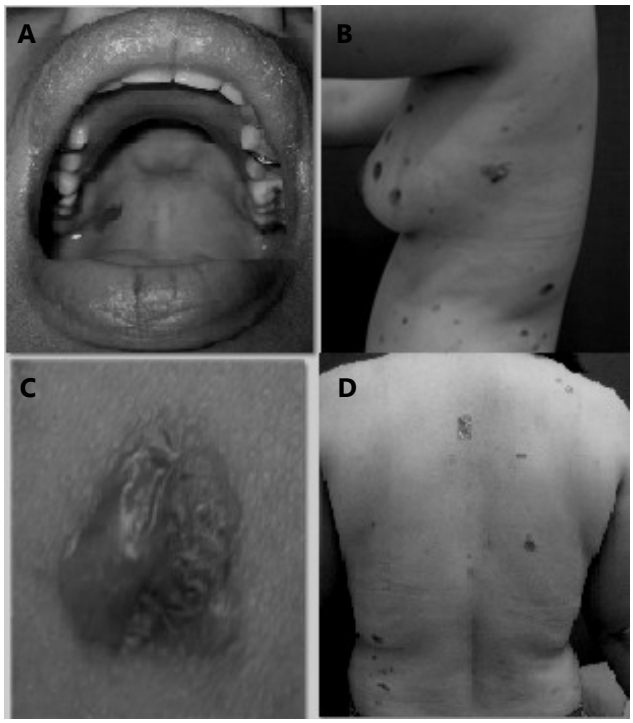

Fig 3. Patient before treatment . **A,** solitary erosion on right side of soft palate. **B and D,** multiple hyperpigmented plaques some with erosions on trunk. **C,** few bullae with clear fluid

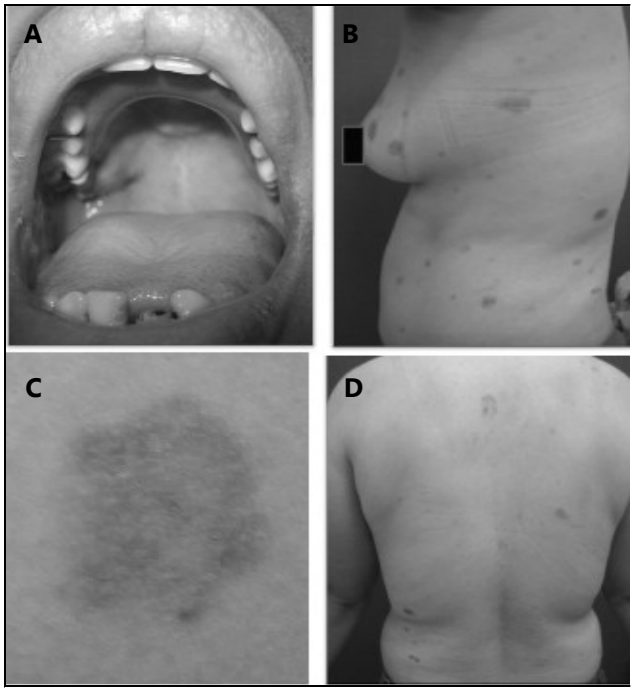

Fig 4. Patient after 7 weeks of treatment with Prednisone and Azathioprine. **A**, smaller erosion on the soft palate. **B and D**, multiple hyperpigmented patches on trunk. **C**, resolution of

A Randomized, Double-Blind, Controlled Study on the Safety and Efficacy of 10% Bee Propolis Ointment versus 2% Mupirocin Ointment on Superficial Pyodermas caused by *Staphylococcus Aureus*

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BACKGROUND: Superficial pyoderma is a skin condition commonly seen in a dermatology primary care setting. This infection is caused by invasion of the skin with pathogenic bacteria, most commonly *Staphylococcus aureus*. The current drug of choice for this condition is 2% mupirocin ointment. Unfortunately, the high cost of this drug may significantly affect compliance and overall cure. There is also the risk of developing drug resistance to mupirocin with prolonged treatment. Hence, there is a need to explore alternative treatments for superficial pyodermas caused by *S. aureus* that are low-cost, safe and effective. Bee propolis, a resinous substance from beehive, is a potential alternative treatment for *S. aureus* superficial pyodermas considering its anti-inflammatory effects and strong antibacterial properties against staphylococci. Its safety and efficacy in the treatment of such dermatoses however, need to be investigated.

OBJECTIVES

The general objective is to determine the safety and efficacy of 10% bee propolis ointment versus 2% mupirocin ointment in the treatment of superficial pyodermas caused by *S. aureus*. The specific objectives are: 1) to compare the bactericidal activity of 10% bee propolis ointment and 2% mupirocin ointment based on the percentage of patients bacteriologically cured (negative for *S. aureus*) at Day 14 of treatment; 2) to compare the efficacy of 10% bee propolis ointment and 2% mupirocin ointment in treating superficial pyodermas caused by *S. aureus* based on the clinical efficacy grading of erythema, edema, induration and size of lesions at baseline, Day 3, Day 7 and Day 14 of treatment; 3) to compare the Participant's Global Assessment score in the 10% bee propolis and 2% mupirocin treatment groups at Day 3, Day 7 and Day 14 of treatment; and, 4) to compare the occurrence and severity of adverse cutaneous reactions in the 10% bee propolis and 2% mupirocin treatment groups at Day 3, Day 7 and Day 14 of treatment.

METHOD

The study involved two phases. Phase I was a 72-hour I.Q. Chamber Irritancy patch test of the test medication, 10% bee propolis ointment on thirty (30) healthy volunteers. Reading and interpretation of results were done after 48- and 72 hours. The irritancy potential was computed and from this, the test medication was classified as non-irritant, mild irritant or too irritant. Classification of 10% bee propolis as non-irritant and safe (non-allergenic) prompted continuation of the study to the next phase.

The second phase was a clinical trial involving 60 patients aged 18 to 60 years old, clinically diagnosed to have superficial pyoderma defined as a lesion that measures less than 5 cm with absence of co-morbid diseases and constitutional signs and symptoms, according to Eron et al. and confirmed to have lesions infected by *S. aureus* as detected by Gram stain and culture of wound discharge. These patients were randomly assigned into one of two treatment groups: 10% bee propolis ointment or 2% mupirocin ointment. There were 30 patients in each treatment arm. Patients were instructed to apply the assigned ointment twice daily for two weeks. Bactericidal activity of the assigned ointment was determined based on the percentage of patients cured at the end of the treatment period (Day 14). The efficacy of the assigned ointment was also evaluated based on clinical efficacy grading of erythema, edema, induration and size of lesions at baseline, Day 3, Day 7 and Day 14 of treatment. Erythema, edema and induration of lesions were scored or graded based on a 5-point scale while lesion size was determined by measuring the widest diameter of the lesion in centimeters. Patients were also asked to rate the improvement of their condition using a Participant's Global Assessment scale. The presence of adverse cutaneous reactions (if any) was also noted on each visit. All data were subjected to statistical analyses to compare the effects of the medications in the two treatment groups.

RESULT

In Phase I of the study, all 30 healthy adult volunteers who were subjected to patch testing did not exhibit a positive reaction to 10% bee propolis ointment after 48- and 72 hours. The computed primary irritancy index score for this test product was zero. Hence, 10% bee propolis ointment was classified as non-irritant and safe, prompting continuation of the study into the next phase: the clinical trial. In Phase II, data were recorded for 53 subjects (88.33%) who completed the trial. Twenty-two out of thirty patients (73.33%) in the bee propolis group were bacteriologically cured (negative for *S. aureus*) while 24 out of 30 patients (80%) in the mupirocin group were bacteriologically cured after two weeks of treatment. Nevertheless, results of the chi-square test showed that the proportion of patients with positive bacterial activity (*S. aureus* still present in wound discharge) did not vary significantly between the two treatment groups ($p=0.542$). Figure a.1 shows the percentage of patients cured and not cured in each treatment group.

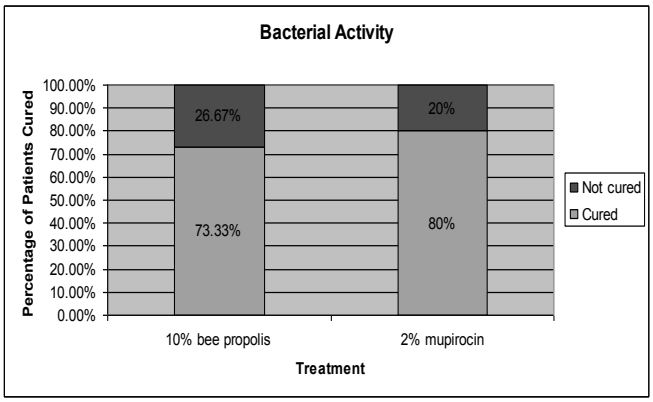

Figure a.1. *Percentage of patients bacteriologically cured and not cured in the 10% bee propolis and 2% mupirocin group after two weeks of treatment*

Erythema of patients was also reduced in both treatment groups from moderate to severe at baseline to less than mild at Day 14 of treatment. Results of the Mann-Whitney test showed that the mean severity score of erythema did not vary significantly between the two treatment groups at baseline (p=0.5351), Day 3 (p=0.4804), Day 7 (p=0.6975), and Day 14 (p=0.2385) of treatment. Figure a.2 shows the mean severity score of erythema in each treatment group over time.

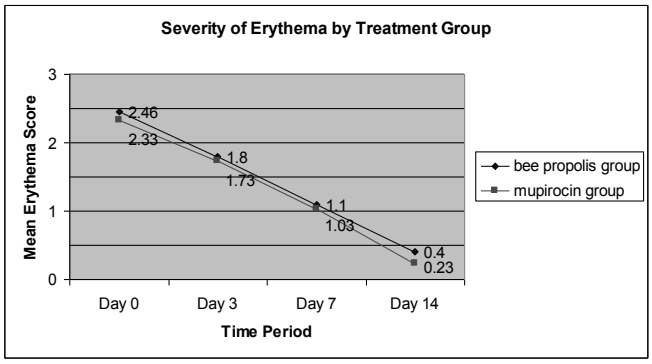

Figure a.2. *Mean severity score of erythema in the 10% bee propolis and 2% mupirocin group over time*

Edema of patients was also reduced in both treatment groups from moderate to severe at baseline to less than mild at Day 14 of treatment. Results of the Mann-Whitney test showed that the mean severity score of edema did not vary significantly between the two treatment groups at baseline (p=0.8427), Day 3 (p=0.5903), Day 7 (p=0.4759), and Day 14 (p=0.3751) of treatment. Figure a.3 shows the mean severity score of edema in each treatment group over time.

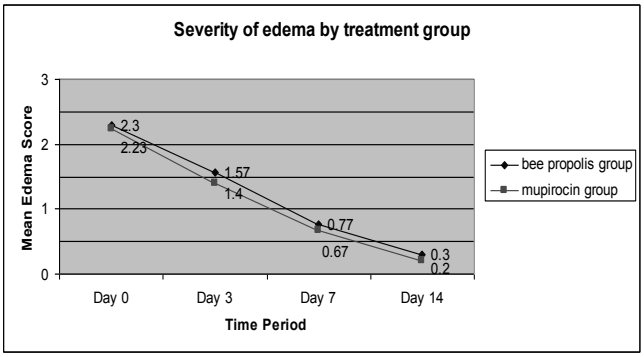

Figure a.3. *Mean severity score of edema in the 10% bee propolis and 2% mupirocin group over time*

Induration of patients was also reduced in both treatment groups from moderate to severe at baseline to less than mild at Day 14 of treatment. Results of the Mann-Whitney test showed that the mean severity score of induration did not vary significantly between the two treatment groups at baseline (p=0.8101), Day 3 (p=0.8830), Day 7 (p=0.5259), and Day 14 (p=0.2638) of treatment. Figure a.4 shows the mean severity score of induration in each treatment group over time.

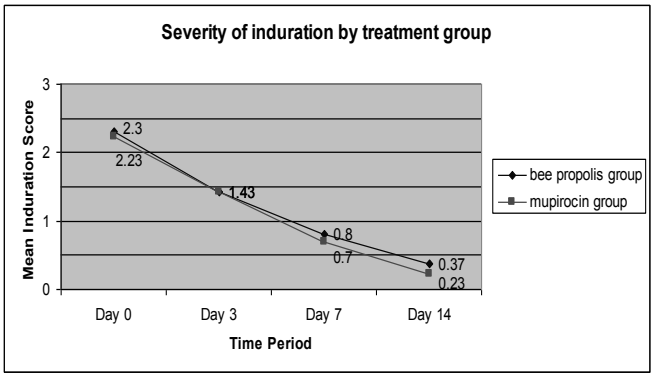

Figure a.4. *Mean severity score of induration in the 10% bee propolis and 2% mupirocin group over time*

The size of lesions also decreased in both treatment groups. Results of the Mann-Whitney test showed that the mean lesion size did not vary significantly between the two treatment groups at baseline (p=0.7211), Day 3 (p=0.5638), Day 7 (p=0.3489), and Day 14 (p=0.3606) of treatment. Figure a.5 shows the lesion size in each treatment group over time.

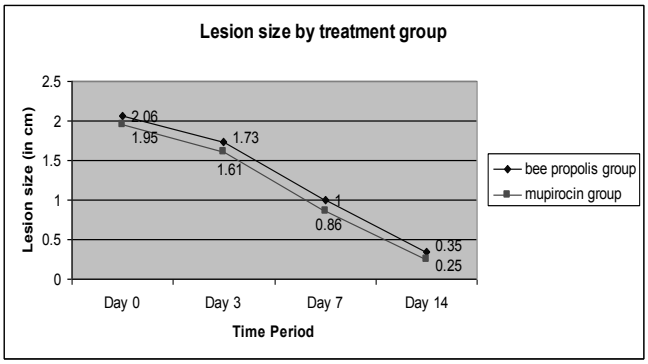

Figure a.5. *Lesion size in the 10% bee propolis and 2% mupirocin group over time*

The Participant's Global Assessment (PGA) score given by patients at Day 3, Day 7 and Day 14 of treatment was also reduced from slight to moderate response at baseline to almost cleared at Day 14 of treatment in both the 10% bee propolis and 2% mupirocin treatment groups. Results of the Mann-Whitney test showed that the PGA score did not vary significantly between the two treatment groups at Day 3 (p=0.5706) and Day 14 (p=0.6536) but it did vary significantly at Day 7. The PGA score in the bee propolis group was significantly higher than that of the mupirocin group at Day 7 (p=0.0175). This is attributed to the subjectivity of the test and the fact that patient perception of improvement can vary significantly. Figure a.6 shows the PGA score given by patients in both treatment groups at Day 3, Day 7 and Day 14 of treatment.

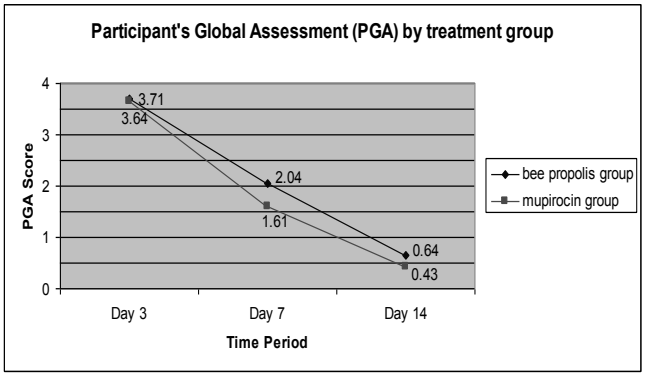

Figure a.6. *Participant's Global Assessment (PGA) scores in the 10% bee propolis and 2% mupirocin group over time*

There was only one adverse event of mild stinging sensation and pruritus noted for 10% bee propolis ointment after 3 days of treatment. There were no adverse events reported in the mupirocin group. Nevertheless, results of the Fisher's exact test showed that the proportion of patients with AE did not vary significantly (p=0.50) in the two treatment groups.

In summary, there were no statistically significant differences in bactericidal activity (p=0.542), efficacy based on clinical efficacy grading of erythema (p=0.4513), edema (p=0.4324), induration (p=0.4324) and size of lesions (p=0.5775), PGA score (p=0.0627), and adverse events (p=0.509) between the two treatment groups after holding the effects of time constant.

CONCLUSION

1) Ten percent bee propolis ointment is comparable in bactericidal activity to 2% mupirocin ointment against *S. aureus* in superficial pyodermas; 2) ten percent bee propolis ointment is comparable in efficacy to 2% mupirocin ointment based on clinical efficacy grading of erythema, edema, induration and size of lesions; 3) ten percent bee propolis ointment is comparable to 2% mupirocin ointment in terms of Participant's Global Assessment (PGA) score at Day 3 and Day 14 except on Day 7, where a significant difference was noted between the two treatments but nevertheless attributed to the subjectivity of the test and how patient perception of improvement can vary signficantly; and 4) both 10% bee propolis ointment and 2% mupirocin ointment were well-tolerated, producing no significant adverse reactions in *S. aureus* superficial pyoderma patients within two weeks of treatment.

Therefore, 10% bee propolis ointment is equally safe and effective as 2% mupirocin ointment in the treatment of superficial pyodermas caused by *Staphylococcus aureus*. Ten percent bee propolis ointment can therefore be considered a good cost-effective alternative to 2% mupirocin ointment in the treatment of *S. aureus* superficial pyoderma.

REFERENCES

1. Hay R, Bendeck S, Chen S, Estada R, Haddix A, McLeod T, Mahe A. Skin Diseases. 2010; 37: 1-8.
2. Matts PJ, Ryan TJ. Water and the skin: Skin carers collaborate with industry in a new initiative and humanitarian drive. Community dermatology (unpublished paper). 2010.
3. Mahe A, Faye O, Fanello S. Public health and dermatology in developing countries. *Bull Soc Pathol Exot* 2003; 96(5): 351-6.
4. Disease Control Priorities Project. The Scourge of Skin Diseases: Most Can Be Resolved With Cost-Effective Treatments. 2008. Accessed from: http:// www.dcp2.org.
5. Ki V, Rostein C. Bacterial skin and soft tissue infections in adults: A review of their epidemiology, pathogenesis, diagnosis, treatment and site of care. *CJIDMM* 2008; 19(2): 173-184.
6. Phillips LM, Yogev R, Esterly NB. The efficacy of mupirocin (pseudomonic acid) in the treatment of pyoderma in children. *Pediatric Emergency Care* 1985; 1 (4): 180-3.
7. Scheinfeld N. Infections in the elderly. *Dermatology Online Journal* 2005*;* 11 (3): 8.
8. Beam TR, Gilbert DN, Kunin CM. General guidelines for the clinical evaluation of Anti-infective drug products. *FDAJ* 1992; 1:1-35.
9. Gisby J, Bryant J. Efficacy of a New Cream Formulation of Mupirocin: Comparison with Oral and Topical Agents in Experimental Skin Infections. *Antimicrobial Agents and Chemotherapy* 2000; 44(2): 255-260.
10. Wolverton S. Comprehensive dermatologic drug therapy. 2nd ed. Pennsylvania: Saunders Elsevier, Inc. 2007.
11. Eells LD, Mertz PM, Piovanetti Y, Pekoe GM, Eaglstein WH. Topical antibiotic treatment for impetigo with mupirocin. *Arch Dermatol* 1986; 122: 1273-6.
12. Breneman DL. Use of mupirocin ointment in the treatment of secondarily infected dermatoses. *J AM Acad Dermatol* 1990; 22: 886-92.
13. Conly JM, Johnston L. Mupirocin – Are we in danger of losing it? *Can J Infect Dis* 2002; 13(3): 157-159.
14. Bankova V, de Castro S, Marcucci M. Propolis: recent advances in chemistry and plant origin. *Apidologie* 2000; 31: 3-15.
15. Bankova V. Chemical diversity of propolis and the problem of standardization. *J of Ethno Pharmacology* 2005; 100: 114-117.
16. Castaldo S, Capasso F. Propolis, an old remedy used in modern medicine. *Fitoterapia 73* 2002; Suppl. 1: S1-S6.
17. Temiz A, Sener A, Ozkok Tuylu A, Sorkun K and Salih B. Antibacterial activity of bee propolis samples from different geographical regions of Turkey against two foodborne pathogens, *Salmonella Enteritidis* and *Listeria monocytogenes. Turk J Biol* 2011; 35: 503-511.
18. Yaghoubi SMJ, Ghorbani GR, Soleimanian Zad S., Satari R. Antimicrobial activity of Iranian propolis and its chemical composition. *DARU* 2007; 15 (1): 45-48.
19. Rahman MM, Richardson A, Sofian-Azirun M. Antibacterial activity of propolis and honey against *Staphylococcus aureus* and *Escherichia coli*. *African Journal of Microbiology Research* 2010; 4(16): 1872-1878.
20. Grange JM, Davey RW. Antibacterial properties of propolis (bee glue). *Journal of the Royal Society of Medicine* 1990; 83: 159-160.
21. Gonsales GZ, Orsi RO, Fernandes Junior A, Rodrigues P, Funari SRC. Antibacterial activity of propolis collected in different regions in Brazil. *J Venom Anim Toxins incl. Trop Dis* 2006; 12(2): 276-284.
22. Lotfy M. Review: Biological Activity of Bee Propolis in Health and Disease. *Asian Pac J Cancer Prev* 2006; 7: 22-31.
23. Miorin PL, Levy Junior NC, Custodia AR, Bretz WA, Marcucci MC. Antibacterial activity of honey and propolis from *Apis mellifera* and *Tetragonisca angustula* against *Staphylococcus aureus*. *Journal of Applied Microbiology* 2003; 95: 913-920.
24. Grange JM, Davey RW. Antibacterial properties of propolis (bee glue). Journal of the Royal Society of Medicine 1990; 83: 159-160.
25. Temiz A, Sener A. Antibacterial activity of bee propolis samples from different geographical regions of Turkey against two foodborne pathogens, Salmonella Enteritidis and Listeria monocytogenes. Turk J Biol 2011; 35:503-511.
26. Paulino D, Dantas A, Bankova V, Longhi D, Scremin A, de Castro S, Calixto J. Bulgarian propolis induces analgesic and anti-inflammatory effects in mice and inhibits in vitro contraction of airway smooth muscle. *J Pharmacol Sci* 2003; 93: 307-313.

27. Kosalec I, Bakmaz M, Pepeljnjak S, Vladimir-Knezevic S. Quantitative analysis of the flavonoids in raw propolis from northern Croatia. *Acta Pharm* 2004; 54: 65-72.

28. Farnesi AP, Aquino-Ferreira R, De Jong D, Bastos JK, Soares AEE. Effects of stingless bee and honey bee propolis on four species of bacteria. *Genetics and Molecular Research* 2009; 8 (2): 635-640.

29. Ivancajic S, Mileusnic I, Cenic-Milosevic D. *In Vitro* Antibacterial Activity of Propolis Extracts on 12 Different Bacteria in Conditions of 3 Various pH Values. *Arch Biol Sci* 2010; 62(4): 915-934.

30. Fernandes Junior A, Balestrin EC, Betoni JEC, Orsi RO, Cunha MLR, Montelli AC. Propolis: anti-*Staphylococcus aureus* activity and synergism with antimicrobial drugs. *Mem Inst Oswaldo Cruz* 2005; 100 (5): 563-566.

31. Park YK, Ikegaki M. Note: Preparation of Water and Ethanolic Extracts of Propolis and Evaluation of the Preparations. *Biosci Biotechnol Biochem* 1998; 62 (11): 2230-2232.

32. Lu LC, Chen YW, Chou CC. Antibacterial and DPPH Free Radical-scavenging Activities of the Ethanol Extract of Propolis Collected in Taiwan. *Journal of Food and Drug Analysis* 2003; 11 (4): 277-282.

33. Marcucci M. Propolis: chemical composition, biological properties and therapeutic activity. *Apidologie* 1995; 26: 83-99.

34. Stepanovic S, Antic N, Dakic I, Svabicvlahovic M. In vitro antimicrobial activity of propilis and antimicrobial drugs. *Microbiol Res* 2003;158: 353-357.

35. Park YK, Ikegaki M. Preparation of Water and Ethanolic Extracts of Propolis and Evaluation of the Preparations. Biosci. Biotechnol, Biochem 1998; 62 (11) 2230-2232.

36. GlaxoSmithKline NZ Ltd. New Zealand Data Sheet. Bactroban (Mupirocin 2%). 20 May 2013. Accessed from: www.medsafe.govt.nz

37. EBSCO Information Services. Bee Propolis. July 2012. Accessed from: health.cvs.com

APPENDIX A

DOCUMENTATION

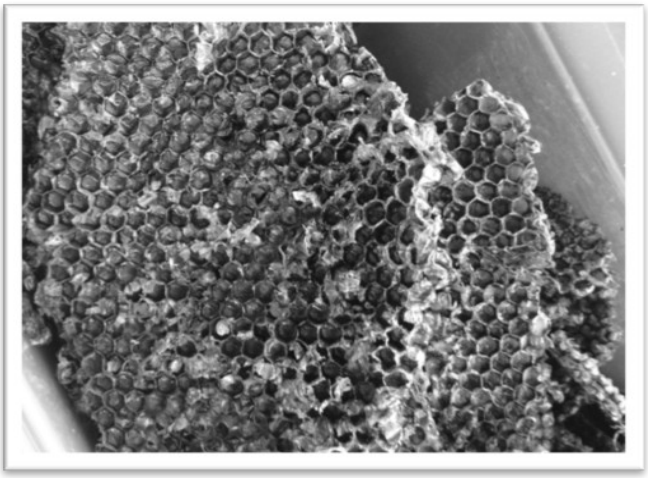

Figure A.1. *Source of bee propolis*

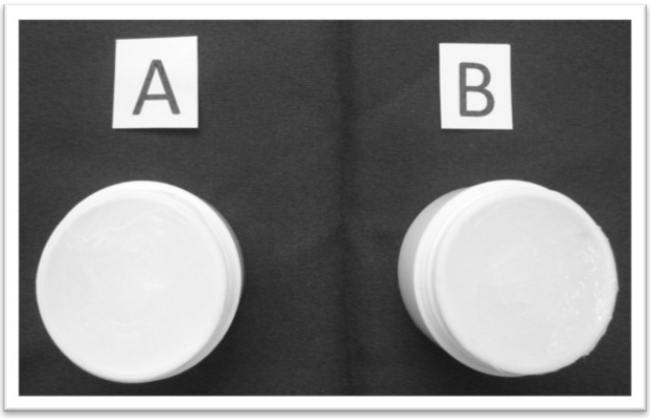

Figure A.2. *Test materials in 10-gram jars*

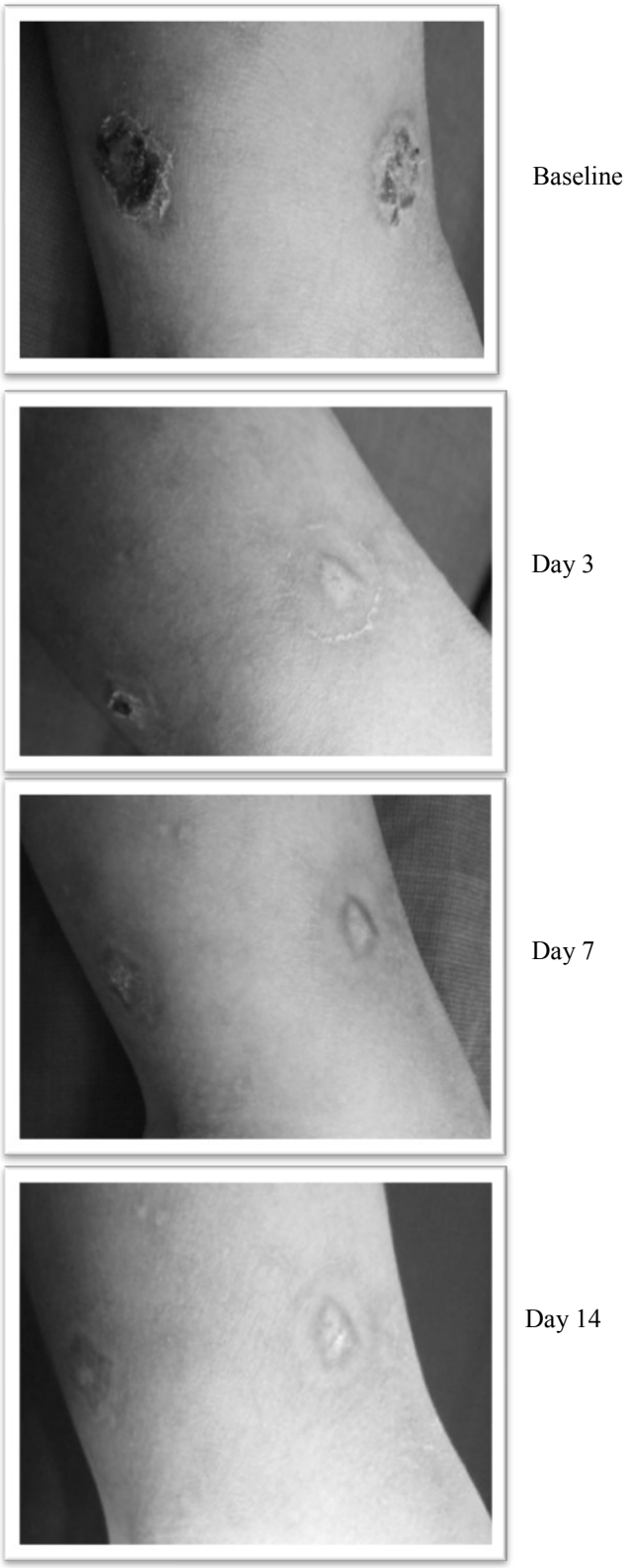

Figure A.4. *Superficial pyoderma lesions of representative subject no. 1 in the 10% bee propolis group at baseline, Day 3, Day 7 and Day 14 of treatment*

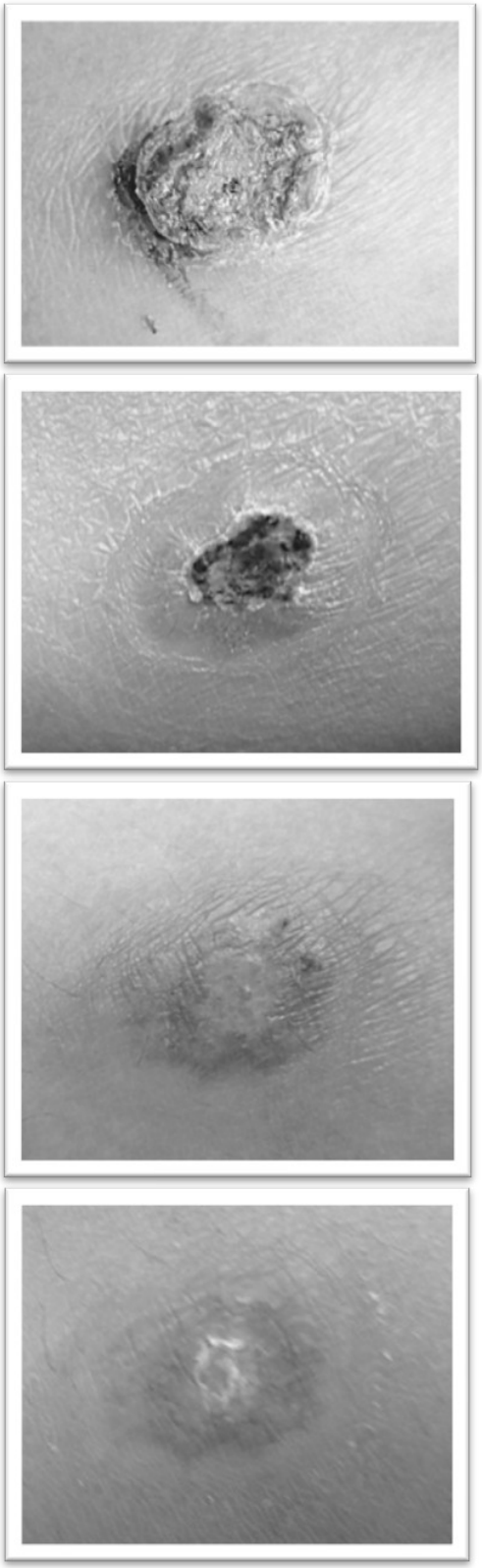

Figure A.5. *Superficial pyoderma lesion of representative subject no. 2 in the 10% bee propolis group at baseline, Day 3, Day 7 and Day 14 of treatment*

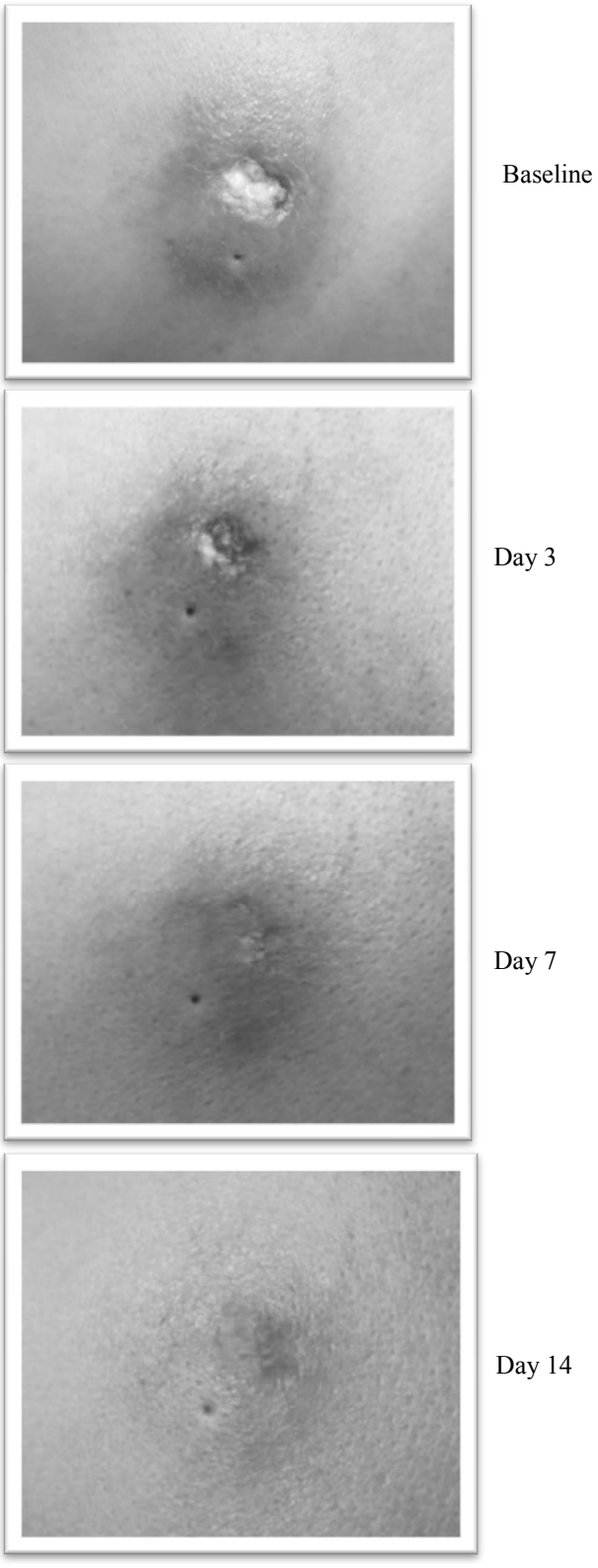

Figure A.6. *Superficial pyoderma lesion of representative subject no. 1 in the 2% mupirocin group at baseline, Day 3, Day 7 and Day 14 of treatment*

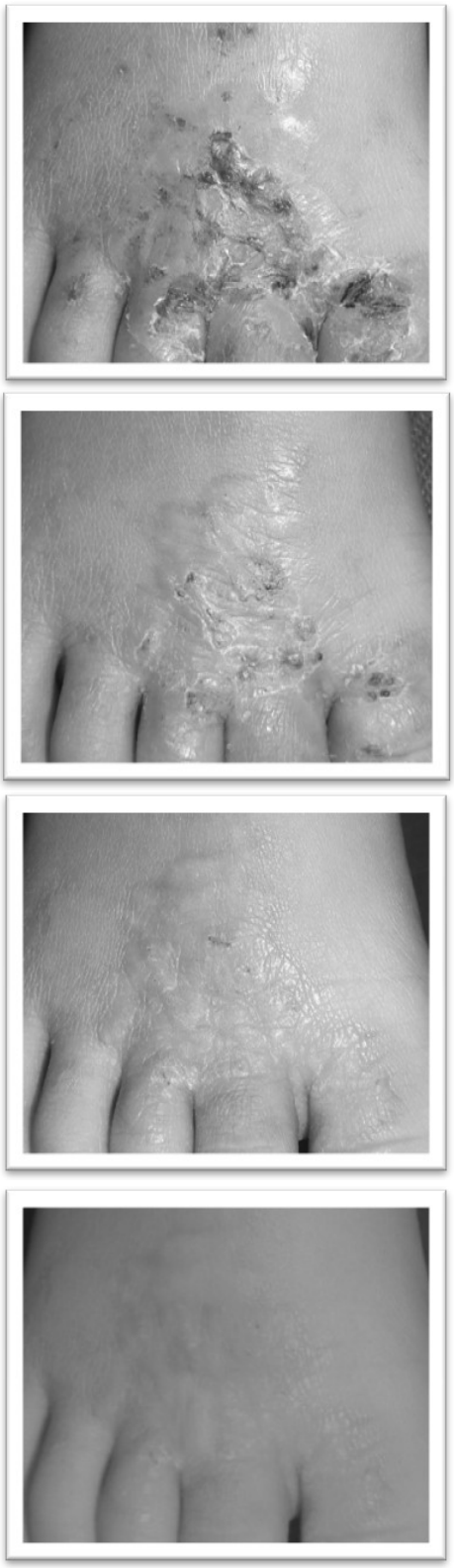

Figure A.7. *Superficial pyoderma lesion of representative subject no. 2 in the 2% mupirocin group at baseline, Day 3, Day 7 and Day 14 of treatment*