

Prophylactic Paracetamol for Intraoperative Shivering Prevention for Patients Undergoing Gynecological Procedures under Spinal Anesthesia: A Randomized Clinical Trial*

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Abstract

Introduction: Shivering is defined as an involuntary, repetitive activity of skeletal muscles. Mechanisms of shivering for patients undergoing surgical operation include intraoperative heat loss, increase sympathetic tone, pain, and systemic release of pyrogens. Regional anesthesia, particularly spinal anesthesia causes redistribution of core heat to the peripheral tissues this in turn predisposes patient to shivering and hypothermia. The median incidence of shivering related to regional anesthesia observed in a review of 21 studies is 55%. Paracetamol is one of the most commonly used analgesic and antipyretic drugs around the world, available without a prescription, it has analgesic and antipyretic property similar to NSAIDs it also affects core body temperature through the hypothalamus. Though different modalities have been established for shivering prevention, the search for a cost-effective drug with lesser side effects and improvement of patient satisfaction still continues.

Objective: The aim of this study was to evaluate the effect of prophylactic dose of Paracetamol on postanesthesia shivering on patients undergoing gynecological procedures under spinal anesthesia as compared to patients not given Paracetamol.

Methodology: This is a Double blind, Randomized, Placebo Controlled conducted in patients scheduled for benign gynecological procedures such as Hysterectomy with or without adnexectomy. Using simple random sampling through fishbowl method and a sample size of 42, all patients who consented to participate in the study was randomly assigned to

receive Paracetamol 900 mg IV or Placebo 0.9% Saline intravenously 30 minutes prior to induction of spinal anesthesia. Incidence and severity of Shivering was documented using shivering five point scale outlined by Crossley and Mahajan, while patient satisfaction was also evaluated using the Likert Scale, possible side effects was also assessed.

Keywords: Shivering, paracetamol, prophylaxis, spinal anesthesia

INTRODUCTION

Shivering is a common postanesthetic complication, it creates an uncomfortable experience for patients affecting them psychologically and physically¹. Shivering is also believed to increase oxygen consumption, lactic acidosis, carbon dioxide production, metabolic rate up to 400%, risk of hypoxemia, and to some extent postoperative complications². In addition to anxiety for patients undergoing surgical procedure, shivering may also increase patient's discomfort and lower patient's satisfaction post operatively. The patient's perception of pain postoperatively may also increase due to shivering. Shivering is usually triggered by hypothermia but it can also occur even in normothermic patients during the perioperative period, the etiology of shivering has not been fully understood but even if cold induced thermoregulatory shivering remains an obvious etiology, it has also been attributed to numerous other causes such as pain, disinhibited spine reflexes, decreased sympathetic activity and as well respiratory alkalosis.² According to the American Society of Anesthesiologists (ASA) guideline forced-air

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warming devices and meperidine are recommended in the control of shivering.² In our Institution, Since Meperidine is not available, we used Tramadol as an alternative, however has also undesirable effects such as nausea and vomiting. We only have two (2) units of forced air warmer available in the operating room, however it's use for pediatric patients are prioritized and there is an additional charge for the patient when used. We therefore look for solutions to address shivering by using an affordable medication with lesser side effects and may also aid as an additional Pain reliever, also for patient's comfort and satisfaction improving overall well-being of the patient.

Neuraxial anesthesia is one of the most common surgical procedure done in our institution and prompt treatment and prevention of shivering should be part of overall perioperative management. Neuraxial anesthesia induces shivering due to redistribution of core body heat to the peripheral tissues. Neuraxial block results in impairment of autonomic thermoregulation below the level of the block. The vasodilatation is responsible for this redistribution of heat.¹⁸ Antipyretic agents like paracetamol block endogenous pyrogens by inhibiting cyclooxygenase-mediated prostaglandin synthesis in the brain, the substances responsible for elevating the hypothalamic set point leading to peripheral vasodilation and sweating. Paracetamol has been used in some studies for shivering but has not been established as a standard treatment. Current use of Intravenous Paracetamol for post-operative analgesia and reduction in opioid consumption is also increasing.²⁸ While several published studies has been made regarding the use of Paracetamol for shivering, only four studies done internationally was done while none was published locally, two of the studies done used prophylactic paracetamol for shivering for patients under general anesthesia, one study of paracetamol for shivering using logistic regression and only one study of paracetamol for prophylactic shivering under regional(spinal) anesthesia. Results of these studies revealed that Paracetamol is an effective anti-shivering medication though none emphasized patient's satisfaction post-operatively.

The aim of this study was to evaluate the effect of Prophylactic Paracetamol on intraoperative

shivering on patients undergoing gynecological procedures under spinal anesthesia. Also to demonstrate that there would be a significant difference between the effect of prophylactic paracetamol on shivering compared to Placebo.

METHODS OF RESEARCH

Research Design

This is a Double Blind, Randomized Control trial. Included participants was randomly assigned to two groups by fishbowl method where Group A received Paracetamol 900 mg IV (experimental) and Group B received PLACEBO (control).

POPULATION

Patients scheduled for benign gynecological procedures such as Hysterectomy with or without adnexectomy was recruited to participate in the study and included once surgical, anesthetic and consent for the study has been secured.

Inclusion criteria

- Neuraxial Anesthesia
- Female
- Ages 19 to 65 years old
- ASA Physical status Class I and II
- Benign Gynecological procedures such as hysterectomy with or without adnexectomy

Exclusion criteria

- Contraindications to neuraxial anesthesia
 - Patients refusal
 - Spinal Injuries
 - Localized infection
 - Hypovolemia
 - Coagulopathies
- History of stroke or myocardial infarction
- Known Liver and renal diseases
- Hypersensitivity reaction with previous Paracetamol administration

SAMPLE SIZE

Using OPEN-EPI v 3.01 software, the sample size was computed using the confidence level of 95%. The computed sample size using Fleiss formula with continuity correction is 42. The sample size for each group would be 21 with a computed power at 80%. Sixty four percent (64%) of unexposed with outcome and

eighteen percent (18%) of exposed with outcome was based on the study of Gholami, et al (2016).¹³ According to the Anesthesia operating room monthly census and Management information system, for the last 6 months we had a total of 585 Hysterectomy cases and 1021 exploratory laparotomy involving uterus and fallopian tube, thus the number of target population of the study would be feasible.

Sample Size: X-Sectional, Cohort, & Randomized Clinical Trials			
Two-sided significance level(1-alpha):			95
Power(1-beta, % chance of detecting):			80
Ratio of sample size, Unexposed/Exposed:			1
Percent of Unexposed with Outcome:			64
Percent of Exposed with Outcome:			18
Odds Ratio:			0.12
Risk/Prevalence Ratio:			0.28
Risk/Prevalence difference:			-46
	Kelsey	Fleiss	Fleiss with CC
Sample Size - Exposed	18	17	21
Sample Size-Nonexposed	18	17	21
Total sample size:	36	34	42

SAMPLING DESIGN

The sampling design used was simple random sampling. Using the fish bowl method, 42 small rolled piece of paper was equally divided into two groups, each was written with either "Group A" or "Group B" and placed in an opaque envelope. Group A received Prophylactic Paracetamol while Group B received placebo. All eligible participants were asked to pick from the opaque envelope and was allocated to either group A or group B accordingly. A third person, not involved in the study was able to see the result and administer the medications. The results of randomization was concealed from the patient and researcher until all participants have completed the study.

MATERIALS AND METHODS

Participants included in this study are patients who had Elective benign Gynecological Procedures under neuraxial anesthesia either with single shot spinal anesthesia or combined spinal and epidural anesthesia. After eligibility, preoperative evaluation was done by the

anesthesia resident-in-charge and researcher, including a detailed history and physical examination. Procedure and medication was explained to the patient. After fulfillment of the inclusion criteria, 42 participants was recruited into study. Eligible participants was recruited during the pre-operative evaluation and Informed consent was secured by the researcher at the patient's room or ward a day before the procedure. For the randomization, before the procedure, the participants was randomly assigned to receive Prophylactic Paracetamol 900 mg IV (Group A) or Placebo (Group B) using fishbowl method. A senior anesthesia resident not involved in the study prepared the medications, labelled and randomized. There was 42 small rolled piece of paper that was labeled and equally divided into two groups; "Group A" or "Group B" placed in an opaque envelope. Group A received Prophylactic Paracetamol while Group B received the placebo. A 900 mg Iv (6 ml) Paracetamol was aspirated in a 10 ml sterile syringe and was labeled as "A" and another 6 ml of Saline 0.9% was aspirated in a 10 cc sterile syringe and was labeled as "B". A nurse not involved in the study asked the patient to pick from the prepared opaque envelope with labels of either group A or group B. Depending on the result, to ensure blinding of the patient and anesthesiologist the

nurse saw the result of randomization and administered the medication as labelled accordingly. The Paracetamol is a clear solution so it is impossible to distinguish from a 0.9% saline which is the placebo. Intraoperatively, the anesthesiology resident-in-charge of the patient after administering neuraxial anesthesia observed the patient using the shivering scale. For Group A, Paracetamol 900 mg IV was administered to the patient 30 minutes prior to induction of anesthesia. Group B received 6ml of 0.9% saline intravenously and has also received standard anesthesia care and a similar data collection form was used to document both Group A and Group B. Data Collection form indicated patient's Age and weight and variables to be measured such as shivering scale, side effects, and patients satisfaction rating.

Upon entering the Operating room, monitors was hooked to the patient such as Cardiac monitor, blood pressure and pulse oximeter. Patient was given oxygenation at 2-3lpm via nasal cannula. After recording of basic vital signs, preloading of 10 mL/kg Ringer's solution was infused and then Paracetamol 900 mg IV was given. After 30 minutes, patient was placed in a left lateral decubitus position and aseptic technique was done, spinal anesthesia was performed at L3 -L4 or L4 - L5 intervertebral space with Quincke needle - 25 gauge or with a combined spinal and epidural anesthesia using touhy needle gauge 18, proper placement was ensured and Bupivacaine heavy was administered. Adequate blockade of anesthesia was assessed using Pin prick and Bromage scoring. Patients who experienced failure of SAB or low block level was excluded in the study since the anesthesia may be converted into a general anesthesia for the procedure to continue and is already not in the scope of the study.

During surgery, vital signs was measured every 5 minutes until the end of the surgery. In case of the incidence of hypotension (reduction in systolic pressure below 100 mmHg or 25% decrease in systolic pressure to base pressure of patient), it was treated by 10 cc/kg Lactate Ringer and 5 mg intravenous ephedrine and if PR reduced below 55 beats, 0.01 mg/kg intravenous Atropine was injected to the patient and if it was necessary, it is repeated with the maximum of 0.04 mg/kg.¹⁰

For the severity of shivering, the anesthesia resident-in-charge recorded and observed severity of

shivering using Mahjon and Crossely Shivering Scale (0 = without shivering; 1 = presence of one or more symptoms including vasoconstriction, cold extremities, hair sting, peripheral cyanosis without specific reason; 2= movements in one muscle group; 3= movements in more than one muscles group; 4= severe movements in whole body). For Grades 3-4, Tramadol 50mg IV slow IV push was administered. The anesthesia resident-in-charge also documented possible side effects such as bradycardia, hypotension, headache, nausea and vomiting intraoperatively. At the Post Anesthesia care Unit (PACU), patient's satisfaction was done by asking the patient to answer the question, "How would you rate your experience after the surgery?" using a 7-point Likert verbal rating scale and acceptable satisfaction score of the patient being 5-7.

After the proper documentation and observation and the patient transferred to the ward from PACU, the anesthesia resident-in-charge relayed all the results to the researcher. The researcher was not allowed to collect data directly from the patient, instead relied on the data collected by the anesthesia resident-in-charge.

Prior to Induction of the anesthesia, ASA recommended standard monitors such as cardiac monitor, non-invasive blood pressure monitor and pulse oximeter was used to measure patient's heart rate, electrocardiogram tracing, blood pressure and oxygen saturation. Patient was monitored for changes in vital signs. Sudden incidence of desaturations, hypotension, difficulty of breathing, extreme bradycardia and tachycardia was promptly dealt with.

Patient's safety and comfort was considered at all times. Adequate analgesia, oxygenation, and hydration was ensured. Any unwanted incidences has been reflected in the report.

SAFETY CONSIDERATIONS

Prior to Induction of the anesthesia, ASA recommended standard monitors such as cardiac monitor, non- invasive blood pressure monitor and pulse oximeter was used to measure patient's heart rate, electrocardiogram tracing, blood pressure and oxygen saturation. Patient was monitored for changes in vital signs. Sudden incidence of desaturations,

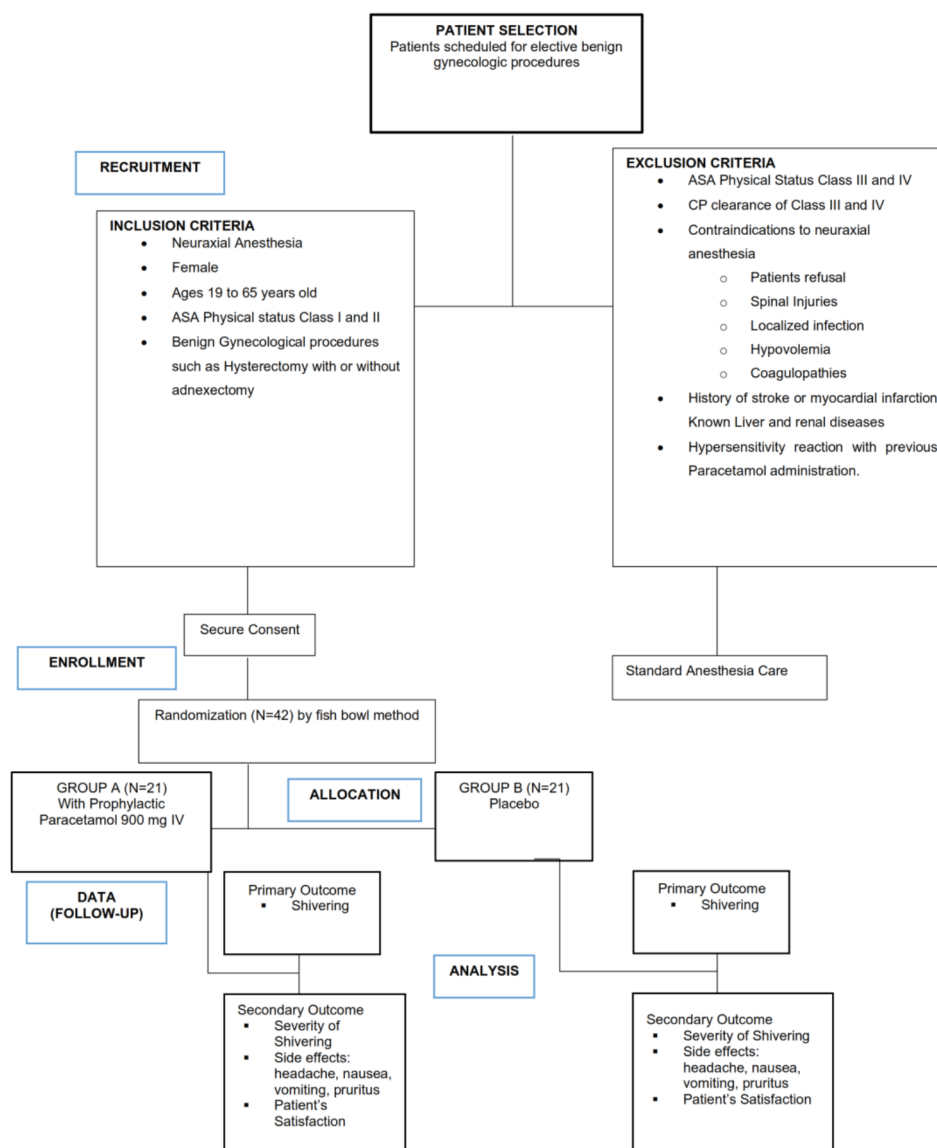
hypotension, difficulty of breathing, extreme bradycardia and tachycardia was promptly dealt with. To avoid toxicity, therapeutic doses of Paracetamol was administered and has not exceeded the recommended daily dose. Although in therapeutic doses there were no reported adverse reactions in humans, possible adverse reactions would be watched out for such as nausea, vomiting, pruritus and headache. Patient's safety and comfort will be considered at all times. Adequate analgesia, oxygenation, and hydration will be ensured. Any unwanted incidences will be reflected in the report.

For patients who had hypothermia, warm blankets was provided, cold fluid infusion was avoided and aircon was turned off during the procedure.

Participation in this study was voluntary and participant was allowed to withdraw at any given time during the study without any penalty for whatever reason the participant may have and was not questioned.

EFFICACY

Several studies on Paracetamol claimed its effectiveness in reducing the incidence on post anesthesia shivering. The study aims to evaluate the effect of Prophylactic Paracetamol in shivering (primary outcome) and as well as it's severity of shivering, possible side effects side effects: headache, nausea, vomiting, pruritus and Patient's Satisfaction (secondary outcome).^{9,10,13,14}



STATISTICAL ANALYSIS

All data was recorded using a workbook and encoded to Microsoft Excel worksheet. Statistical Data was analyzed using Statistical Package for Social Sciences Software V.25 (SPSS). The main statistical analysis used was frequency, percentages, mean and odds ratio. Chi-square test of homogeneity to compare between Group A and Group B. Median Test for the statistical analysis of occurrence of Shivering, severity, side effects and patient satisfaction. P value of less than .05 was considered statistically significant. Odds ratio was also used for odds of exposure for shivering and patient satisfaction between Group A and Group B, odds ratio that are greater than 1 indicate that the event (belonging to experimental group) is more likely to occur as the predictor increases. Odds ratios that are less than 1 indicate that the event (belonging to experimental group) is less likely to occur as the predictor increases.

STATEMENT OF HYPOTHESIS

Null Hypothesis

There is no significant difference between the effectiveness of Prophylactic Paracetamol compared to Placebo in the incidence of Shivering among patients undergoing benign gynecological procedures under neuraxial anesthesia.

Alternative Hypothesis

There is a significant difference between the effectiveness of Prophylactic Paracetamol compared to Placebo in the incidence of Shivering among patients undergoing benign gynecological procedures under neuraxial anesthesia.

ETHICAL CONSIDERATIONS

Prior to enrolment from this study, an informed consent was obtained. Confidentiality of information was maintained. All patients scheduled for elective gynecologic surgery and met the inclusion criteria was asked and subjected to informed consent prior to

enrollment of the study. The anesthesia resident-in-charge explained and fully disclosed the procedure and its possible risks and complications in their native language if necessary to make sure that the participant have fully understood the procedure. The participant was free to ask questions and clarifications. The identifying data included was the age and weight. Only the researchers have access to the data collected.

After data summary and analysis, the data acquired was stored in a password protected USB drive and was kept in the Department of Anesthesiology for future purposes. Results and findings was disseminated to the Department of Anesthesiology and other care providers involved in anesthetic management.

Participation in this study was voluntary and participants were free to withdraw from the study anytime without penalty. Participants did not receive any form of payment. No participant was forced or coerced to join this research.

The researcher only used Paracetamol that is available in the institution and did not use any other brands. There was no conflict of interest and the researcher does not intend to promote the use, sale of Paracetamol of any brand. The researcher also shouldered all expenses not shouldered by PhilHealth and did not promote or patronize the drug used nor company or distributor involved.

RESULTS & DISCUSSION

A total of 42 adult patients were enrolled in this study: 21 patients in the prophylactic paracetamol group and 21 in the placebo group. Patient characteristics are shown in Table 1.

Table 1: Clinico-Demographic Characteristics of Subjects between Prophylactic Paracetamol group and with no Prophylactic Paracetamol group who underwent benign gynecologic procedures under Neuraxial anesthesia

Table 1: Clinico-Demographic Characteristics of Subjects between Prophylactic Paracetamol group and with no Prophylactic Paracetamol group who underwent benign gynecologic procedures under Neuraxial anesthesia

Clinico-Demographic Characteristics		Prophylactic Paracetamol Group n (%)	Placebo Group n (%)	Total
A. Age (years)	19-27	4 (19.05%)	6 (28.57%)	10 (23.81%)
	28-36	3 (14.29%)	4 (19.05%)	7 (16.67%)
	37-45	4 (19.05%)	5 (23.81%)	9 (21.43%)
	46-54	4 (19.05%)	3 (14.29%)	7 (16.67%)
	55-65	6 (28.57%)	3 (14.29%)	9 (21.43%)
B. Weight (kg)	41-50	4 (19.05%)	7 (33.33%)	11 (26.19%)
	51-60	11 (52.38%)	8 (38.10%)	19 (45.24%)
	61-70	4 (19.05%)	4 (19.05%)	8 (19.05%)
	71-80	1 (4.76%)	2 (9.52%)	3 (7.14%)

The age group with the greatest number of participants (n =10; total of 23.81%) is 19 -27 years old, with 4 people receiving Paracetamol and 6 persons receiving Placebo. Majority of the participants (45.24%) weighed 51-60 kilograms. Both age and weight were analyzed using frequency and percentages.

Table 2: Incidence and Severity of Shivering who underwent benign gynecologic procedures under Neuraxial anesthesia

Severity of Shivering	Prophylactic Paracetamol Group n (%)	Placebo Group n (%)	p-value	Odds Ratio	90% CI for Odds Ratio
Grade 0	15 (71.43%)	6 (28.57%)	0.062*	0.561	(0.337, 0.936)
Grade 1	2 (9.52%)	5 (23.81%)			
Grade 2	0	2 (9.52%)			
Grade 3	4 (19.05%)	7 (33.33%)			
Grade 4	0	1 (4.76%)			

*Significant at 0.10 level of significance but not significant at 0.05 level

Following benign gynecologic procedures under neuraxial anesthesia, the incidence and severity of shivering among the participants were determined in Table 2. Majority of the patients who used Paracetamol (71%) had a Grade 0 or did not experience shivering. The placebo group, on the other hand, had a variety of outcomes: most of the participants in the placebo group

(33%) had a grade of 3, 28% are Grade 0, 23% were Grade 1, 9% were Grade 2 while there was 1 patient who has Grade 4 shivering using frequency and proportions.

The Chi square test was used to determine whether there was a relationship between Paracetamol and the severity of shivering. Based on the computed p-value of 0.062, there is no statistically significant

difference in the proportions of patients between the two groups in terms of the severity of shivering at the 0.05 level of significance. At the 0.10 level of significance, however, there is a borderline statistical difference in the percentage of patients in the two groups, supporting the evidence of Rasoli in 2019. Despite having weak evidence, the Paracetamol group has a significantly larger number of patients with Grade 0. The placebo group had a significantly larger number of patients who have at least Grade 1 shivering compared to the control group.

Among the total number of patients, 19% had a grading of ≥ 3 in paracetamol (4 out of 21) while 38% with a grade of ≥ 3 was noted (8 out of 21 participants) in the placebo group.

In the context of the study, the odds ratio of 0.561 indicates that being part of the experimental group (Prophylactic Paracetamol Group), it is less likely that the patients will experience higher degree of severity of shivering.

Table 3: Possible Adverse Reaction between Prophylactic Paracetamol group and with no Prophylactic Paracetamol group

Side effects	Prophylactic Paracetamol Group n (%)	Placebo Group n (%)
Hypotension	0	2 (9.52%)
Headache	3 (14.29%)	1 (4.76%)
Nausea	0	4 (19.05%)
Vomiting	0	1 (4.76%)

In the following table, we present the differences in Adverse Reaction between the groups receiving prophylactic paracetamol and those who did not (placebo group). Only 3 patients in the paracetamol group (14%) suffered from side effects (headache), whereas 8 patients in the placebo group suffered from nausea (19%), hypotension (9%), vomiting (4%), and headache (4%). In this study, the cause of postoperative headache among the participants is difficult to rule out

since it can be a side effect of administering spinal anesthesia in both groups. This is evidenced in Table 3 where there are more participants in the Paracetamol group who experienced headaches (n =3) versus the placebo group (n=1) despite Paracetamol being a common drug to treat headaches. The “medication overuse headache” due to excessive use of Paracetamol for chronic pain, including tension-type headache and migraine was not assessed in the study.

Table 4: Patient Satisfaction between Prophylactic Paracetamol group and with no Prophylactic Paracetamol group

Patient Satisfaction	Prophylactic Paracetamol Group n (%)	Placebo Group n (%)	p-value	Odds Ratio	95% CI for Odds Ratio
Extremely Dissatisfied	0	0	0.501	1.408	(0.922, 2.152)
Dissatisfied	0	0			
Somewhat Dissatisfied	2 (9.52%)	2 (9.52%)			
Undecided	1 (4.76%)	4 (19.05%)			
Somewhat satisfied	5 (23.81%)	7 (33.33%)			
Satisfied	7 (33.33%)	4 (19.05%)			
Satisfied Extremely	6 (28.57%)	4 (19.05%)	0.186	-	-
Mean	5.71	5.19			

Table 4 shows Patient Satisfaction between Prophylactic Paracetamol group and with no Prophylactic Paracetamol group. It is highlighted in this table that there are more patients satisfied in the paracetamol group compared to the placebo group, as demonstrated by higher mean ratings (Paracetamol = 5.71 vs Placebo = 5.19) and that majority of patients in the paracetamol group (33%) are satisfied. In the placebo group, on the other hand, 7 participants (33%) are somewhat satisfied; 4 participants are undecided and 2 are somewhat dissatisfied.

Using independent-samples t-test to compare the mean ratings of patient satisfaction and chi square test to compare proportions and percentages between both groups, results have found that the distribution was statistically the same in both groups, indicating that there was no statistically significant association between satisfaction and use of prophylactic paracetamol for shivering at 0.05 level of significance.

In the context of the study, the odds ratio of 1.408 indicates that being part of the experimental group (Prophylactic Paracetamol Group), it is more likely that the patients will have a higher degree of patient satisfaction.

DISCUSSION

Shivering is a common complication among patients who have undergone anesthesia. Physical modalities such as intravenous infusion of warm fluids and forced air warmers can help control hypothermia, but they are not always readily available. Forced air warmers are typically administered postoperatively, whereas infusing prewarmed fluids to prevent shivering is not routinely performed in our institution. The mainstay treatment for shivering remains pharmacological due to inadequate control of central hypothermia caused by anesthesia. As a result, it makes sense to prevent shivering rather than treat it once it occurs. The findings of our study indicate that Paracetamol has the potential to reduce the incidence of shivering, as 71% of those in the paracetamol group did not experience shivering. Esmat published a study in 2021 that found Paracetamol and Dexamethasone to be effective in preventing shivering in patients

undergoing lower abdominal and limb surgeries under neuraxial anesthesia.³² Given the role of Paracetamol in inhibiting prostaglandin synthesis as well as its effect on the descending serotonergic pathways in the central nervous system, the fact that it is both an anti-shivering and analgesic agent is a strong point to consider. Furthermore, the second point to consider is its wide safety profile, as Paracetamol is safe to use in pregnant patients and children. Third, in addition to the benefits mentioned previously, it was also evident in the study that, while not statistically significant, Paracetamol leads to greater satisfaction as evidenced by higher satisfaction mean scores among participants due to fewer side effects experienced. Finally, Paracetamol is easily accessible in the operating room, making it more convenient to use. This drug makes it a cost-effective shivering management protocol that could be easily implemented in our institution as well as in resource-limited areas.

LIMITATIONS

There were several limitations to this study. The present study was conducted in a very short period and was carried out at one institution; hence it lacks representation of the general population. The investigators, on the other hand, believed that the randomized, double-blind design and effect size estimation reduced the possibility of bias. Another limitation was the absence of meperidine as a control group due to its unavailability. Lastly, there was a failure to identify the sources of dissatisfaction, both from Paracetamol and placebo groups.³⁹

REFERENCES

1. Botros, J. M., Mahmoud, A., Ragab, S. G., Ahmed, M., Roushdy, H., Yassin, H. M., Bolus, M. L., & Goda, A. S. (2018). Comparative study between Dexmedetomidine and Ondansetron for prevention of post spinal shivering. A randomized controlled trial. *BMC anesthesiology*, 18(1), 179.
2. Lopez M. B. (2018). Postanaesthetic shivering - from pathophysiology to prevention. *Romanian journal of anaesthesia and intensive care*, 25(1), 73-81.
3. Smith C, Coleman A, Al-Baghdadi Y & Orlewicz M. (2011). Therapeutic hypothermia in PEA cardiac arrest

- for global and local cerebral protection: A case report and mini -review. *Romanian J Anaesth Intensive Care*;18:153-5.
4. Choi, H. A., Ko, S. B., Presciutti, M., Fernandez, L., Carpenter, A. M., Lesch, C., Gilmore, E., Malhotra, R., Mayer, S. A., Lee, K., Claassen, J., Schmidt, J. M., & Badjatia, N. (2011). Prevention of shivering during therapeutic temperature modulation: the Columbia anti- shivering protocol. *Neurocritical care*, 14(3), 389–394.
5. Honasoge, A., Parker, B., Wesselhoff, K., Lyons, N., & Kulstad, E. (2016). First Use of a New Device for Administration of Buspirone and Acetaminophen to Suppress Shivering During Therapeutic Hypothermia. *Therapeutic hypothermia and temperature management*, 6(1), 48–51.
6. Kasner, S. E., Wein, T., Piriyaawat, P., Villar-Cordova, C. E., Chalela, J. A., Krieger, D. W., Morgenstern, L. B., Kimmel, S. E., & Grotta, J. C. (2002). Acetaminophen for altering body temperature in acute stroke: a randomized clinical trial. *Stroke*, 33(1), 130–134.
7. Ayoub, S. S., Botting, R. M., Goorha, S., Colville-Nash, P. R., Willoughby, D. A., & Ballou, L. R. (2004). Acetaminophen-induced hypothermia in mice is mediated by a prostaglandin endoperoxide synthase 1 gene-derived protein. *Proceedings of the National Academy of Sciences of the United States of America*, 101(30), 11165–11169.
8. Park, S. M., Mangat, H. S., Berger, K., & Rosengart, A. J. (2012). Efficacy spectrum of antishivering medications: meta-analysis of randomized controlled trials. *Critical care medicine*, 40(11), 3070–3082.
9. Rasoli, S., Ansari, E., Moslemi, F., & Ghajazadeh, M. (2019). The Prophylactic Administration of Intravenous Paracetamol for Control of Shivering During and After Cesarean Section Under Spinal Anesthesia. *Archives of Anesthesiology and Critical Care*, 5(2), 38–40.
10. Khalili, G., Sajedi, P., & Alinaghian, A. (2014). The effect of intravenous infusion of paracetamol before anesthesia induction on the core and peripheral temperature changes and post-operative shivering in patients undergoing general anesthesia. *Advanced biomedical research*, 3, 89.
11. Dippel, D. W., van Breda, E. J., van Gemert, H. M., van der Worp, H. B., Meijer, R. J., Kappelle, L. J., & Koudstaal, P. J. (2001). Effect of paracetamol (acetaminophen) on body temperature in acute ischemic stroke: a double-blind, randomized phase II clinical trial. *Stroke*, 32(7), 1607–1612.
12. De Witte, J., & Sessler, D. I. (2002). Perioperative shivering: physiology and pharmacology. *Anesthesiology*, 96(2), 467–484.
13. Gholami, A., & Hadavi, M. (2016). Prophylactic intravenous paracetamol for prevention of shivering after general anesthesia in elective cesarean section. *Journal of Obstetric Anaesthesia and Critical Care*, 6(2), 81.
14. Rabi'u M., & Chabiya B. (2019) Prophylactic Ketamine for Prevention of Post-Spinal Shivering: Randomised Control Trial. *Anesthesia and Critical Care* 1 (2019): 39-47.
15. Jóźwiak-Bebenista, M., & Nowak, J. Z. (2014). Paracetamol: mechanism of action, applications and safety concern. *Acta poloniae pharmaceutica*, 71(1), 11–23.
16. Park, B., Lee, T., Berger, K., Park, S. M., Choi, K. E., Goodsell, T. M., & Rosengart, A. (2015). Efficacy of Nonpharmacological Antishivering Interventions: A Systematic Analysis. *Critical care medicine*, 43(8), 1757–1766.
17. Jain, A., Gray, M., Slisz, S., Haymore, J., Badjatia, N., & Kulstad, E. (2018). Shivering Treatments for Targeted Temperature Management: A Review. *The Journal of neuroscience nursing: journal of the American Association of Neuroscience Nurses*, 50(2), 63–67.
18. Crowley, L. J., & Buggy, D. J. (2008). Shivering and neuraxial anesthesia. *Regional anesthesia and pain medicine*, 33(3), 241–252.
19. Kurz, A., Plattner, O., Sessler, D. I., Huemer, G., Redl, G., & Lackner, F. (1993). The threshold for thermoregulatory vasoconstriction during nitrous oxide/isoflurane anesthesia is lower in elderly than in young patients. *Anesthesiology*, 79(3), 465–469.
20. Dal, D., Kose, A., Honca, M., Akinci, S. B., Basgul, E., & Aypar, U. (2005). Efficacy of prophylactic ketamine in preventing postoperative shivering. *British journal of anaesthesia*, 95(2), 189–192.
21. Alfonsi P. (2003). Postanaesthetic shivering. Epidemiology, pathophysiology and approaches to prevention and management. *Minerva anesthesiologica*, 69(5), 438–442.

22. Pausawasdi, S., Jirasirithum, S., & Phanarai, C. (1990). The use of tramadol hydrochloride in the treatment of post-anesthetic shivering. *Journal of the Medical Association of Thailand = Chotmai het thangphaet*, 73(1), 16–20
23. Tobi, K., Imarengiaye, C., & Edomwonyi, N. (2012). Tramadol effects on perioperative shivering in lower limb orthopaedic surgeries under spinal anaesthesia. *Journal of the West African College of Surgeons*, 2(2), 63–79.
24. Graham, G. G., & Scott, K. F. (2005). Mechanism of action of paracetamol. *American journal of therapeutics*, 12(1), 46–55.
25. Toes, M. J., Jones, A. L., & Prescott, L. (2005). Drug interactions with paracetamol. *American journal of therapeutics*, 12(1), 56–66.
26. Ye, H., Nelson, L. J., Gómez Del Moral, M., Martínez-Naves, E., & Cubero, F. J. (2018). Dissecting the molecular pathophysiology of drug-induced liver injury. *World journal of gastroenterology*, 24(13), 1373–1385.
27. Sagir, O., Gulhas, N., Toprak, H., Yucel, A., Begec, Z., & Ersoy, O. (2007). Control of shivering during regional anaesthesia: prophylactic ketamine and granisetron. *Acta anaesthesiologica Scandinavica*, 51(1), 44–49.
28. Gozdemir, M., Usta, B., Demircioglu, R. I., Muslu, B., Sert, H., & Karatas, O. F. (2010). Magnesium sulfate infusion prevents shivering during transurethral prostatectomy with spinal anesthesia: a randomized, double-blinded, controlled study. *Journal of clinical anesthesia*, 22(3), 184–189.
29. Tie, H. T., Su, G. Z., He, K., Liang, S. R., Yuan, H. W., & Mou, J. H. (2014). Efficacy and safety of ondansetron in preventing postanesthesia shivering: a meta-analysis of randomized controlled trials. *BMC anesthesia*, 14, 12.
30. Kinjo, T., Tadokoro, T., Tokushige, A., Zamami, T., Taira, S., Ikehara, Y., Tsuhako, C., Ohtsu, H., Ueda, S., & Kakinohana, M. (2020). Effects of Perioperative Administration of Acetaminophen on Postoperative Shivering: A Randomized, Triple-Blind, Placebo-Controlled Trial. *Anesthesia and analgesia*, 130(4), 983–990.
31. Shirozu, K., Umehara, K., Ikeda, M., Kammura, Y., & Yamaura, K. (2020). Incidence of postoperative shivering decreased with the use of acetaminophen: a propensity score matching analysis. *Journal of anesthesia*, 34(3), 383–389
32. Esmat. (2018). Prophylactic Paracetamol or Dexamethasone for Post-spinal Anesthesia Shivering in Patients Undergoing Non-obstetric Surgeries: a Randomized Controlled Trial. Prophylactic Paracetamol or Dexamethasone for Post-spinal Anesthesia Shivering in Patients Undergoing Non-obstetric Surgeries: A Randomized Controlled Trial, 1(1), 1. <https://clinicaltrials.gov/ct2/show/NCT03679065>
33. Kanabar D. J. (2017). A clinical and safety review of paracetamol and ibuprofen in children. *Inflammopharmacology*, 25(1), 1–9. <https://doi.org/10.1007/s10787-016-0302-3>
34. Gerreits V., Anderson J., & Nappe TM. (2020). Acetaminophen. *Acetaminophen, StatPearls Publishing*(2020), 1–5. https://www.ncbi.nlm.nih.gov/books/NBK482369/#_NBK482369_pubdet_
35. Yousef H., Ahanger E., Varacallo M., (2020, June 19). Physiology, thermal Regulation. *StatPearls NCBI bookshelf*. National Center for Biotechnology Information
36. Printout: fever-thermoregulation. (n.d.). Infectious Disease and Antimicrobial Agents. <https://www.antimicrobe.org/new/printout/e9printout/e9thermoregulation.htm>
37. Sharma, C., & Mehta, V. (2014). Paracetamol: mechanisms and updates. *Continuing Education in Anaesthesia, Critical Care & Pain*, 14, 153–158.
38. Tobi, Kingsley & Osaheni, Osayomwanbo & E, Amadasun. (2018). Comparison of Intravenous Nefopam and Intravenous Tramadol for Shivering Prophylaxis in Patients Undergoing Myomectomy under Spinal Anaesthesia. 10. 171–186.
39. Chen Z, Wei H, Pertovaara A, Wang J, Carlson S. Anxiety- and activity-related effects of paracetamol on healthy and neuropathic rats. *Pharmacol Res Perspect*. 2018;6(1):1–11.