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**ORIGINAL RESEARCH** **REGIONAL ANESTHESIA**

# A randomized, comparative study of prophylactic intravenous acetaminophen, dexamethasone and pethidine regarding the incidence of post spinal anesthesia shivering in lower limb orthopedic surgeries

**Mohamed Medhat Moustafa Kamal Nouh, Galal Adel Mohamed Abd Elrehiem Elkadi, Eman Mohamed Kamal Aboseif, Faisal Said Abd El Hamid, Marwa Mostafa Mohamed Ali Mowafi**

**Author affiliations:**

1. Mohamed Medhat Moustafa Kamal Nouh, Assistant Lecturer of Anesthesia, Intensive Care & Pain Management, Faculty of Medicine, Ain Shams University, Nasr City, Cairo, Egypt; ORCID: {0000-0002-0719-3189}; E-mail: mohamed.medhat.nouh@med.asu.edu.eg
2. Galal Adel Mohamed Abd Elrehiem Elkadi, Professor of Anesthesia, Intensive Care & Pain Management, Faculty of Medicine, Ain Shams University, Nasr City, Cairo, Egypt; E-mail: drgalal_abdelreheam@med.asu.edu.eg
3. Eman Mohamed Kamal Aboseif, Professor of Anesthesia, Intensive Care & Pain Management, Faculty of Medicine, Ain Shams University, Nasr City, Cairo, Egypt; E-mail: dreman_abousaif@med.asu.edu.eg
4. Faisal Said Abd El Hamid, MD, Lecturer of Anesthesia, Intensive Care & Pain Management, Faculty of Medicine, Ain Shams University, Nasr City, Cairo, Egypt; E-mail: faisal.said@med.asu.edu.eg
5. Marwa Mostafa Mohamed Ali Mowafi, MD, Lecturer of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Ain Shams University, Nasr City, Cairo, Egypt; E-mail: dr.marwa.mostafa@med.asu.edu.eg

**Correspondence:** Mohamed Medhat Moustafa Kamal Nouh, Email: mohamed.medhat.nouh@med.asu.edu.eg; Tel: 0201091018880

## ABSTRACT

**Background:** Currently, there is a lack of an established standard or protocol for the management of post-spinal anesthesia shivering (PSAS). We compared the efficacy of intravenous use of three drugs, e.g., acetaminophen, dexamethasone, and pethidine in prevention of PSAS.

**Methodology:** We included 108 patients who were randomly assigned to three equal groups of 36 patients each. Group A patients received pethidine infusion at 0.5 mg/kg; Group B patients were infused with acetaminophen 15 mg/kg and Group C was given dexamethasone infusion at 0.1 mg/kg. The degree of shivering at its onset was determined using the Bedside Shivering Assessment Scale (BSAS). Data was analyzed using Statistical Package for Social Science (SPSS) version 22.

**Results:** PSAS was observed in 10 (27.7 %) patients in Group A vs. 14 (38.8 %) patients in Group B (P = 0.32), and 21 (58.3 %) patients of Group C (P = 0.01). The P-value between B vs C was 0.10, and between all the groups was 0.03. The BSAS score was 26 in Group A (75% patients out of 36 did not develop shivering), 22 in Group B, and 15 in Group C. The P-value between A vs. B was 0.01, A vs. C = 0.01, B vs. C = 0.12, and between all groups was 0.02.

**Conclusion:** Aacetaminophen was more effective than dexamethasone, while pethidine was more effective than both, acetaminophen as well as dexamethasone, in decreasing the incidence of post-spinal anesthesia shivering.

**Trial Registry:** ClinicalTrials.gov ID: NCT05284409

**Abbreviations:** ASA - American Society of Anesthesiologists; BSAS - Bedside Shivering Assessment Scale; PSAS - Post-spinal anesthesia shivering

 

**Key words:** Post spinal, Shivering; Pethidine; Dexamethasone; Acetaminophen

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# 1. INTRODUCTION

The precise etiology of post-spinal anesthesia shivering (PSAS) is not fully understood.[1] The incidence ranges between 20 to 80%.[2] Heat loss, reduced sympathetic tone and pyrogen release are termed as the main causes of intra/postoperative shivering.[3] The redistribution of heat from the core to the periphery of the body is facilitated by the vasodilatation associated with neuraxial anesthesia.[3] Shivering causes lactic acidosis, releases catecholamines, increases oxygen demand, and increases the risk of hypoxemia.

Post-spinal shivering is one of the main sources of discomfort for patients recovering from surgery.[4] Furthermore, it worsens wound pain and impedes electrocardiographic monitoring.[2] Prophylactic intravenous administration of acetaminophen has been currently used for controlling intra-operative and post spinal anesthesia shivering.[5] It acts centrally through prostaglandin inhibition decreasing the hypothalamic temperature set point.[6] The induction of the inflammatory response during surgery results in the release of cytokines, which causes vasodilatation and heat loss, which is the non-thermoregulatory cause of post-anesthesia shivering.[7] Dexamethasone's anti-inflammatory effects may thereby lessen post-anesthesia shivering by reducing the gradient between skin and core body temperatures. It may also lessen shivering through controlling immunological responses.[8] Pethidine is used frequently to prevent postoperative shivering. It's anti-shivering action is mediated through activating kappa receptors and lowering the threshold for shivering.[9]

We compared the efficacy of intravenous acetaminophen, dexamethasone, and pethidine to prevent PSAS in patients undergoing lower limb orthopedic surgeries under spinal anesthesia.

# 2. METHODOLOGY

This double-blind randomized prospective clinical trial took place at Ain Shams University Hospitals from January 2021 to August 2022. The study was authorized by the Ain Shams University Faculty of Medicine's research ethics committee (FMASU MD 262a/ 2020/2021/2022) and registered with ClinicalTrials.gov under the clinical trial identification number NCT05284409. All the patients signed a written informed consent. The study included 108 patients, ASA physical status I and II, aged between 21 to 55 y, BMI less than 35 kg/m2, and of both sexes, undergoing orthopedic surgeries of the lower limbs. Exclusion criteria were; obesity (BMI > 35 kg/m2), pregnancy, sensory blockade levels of T4 or higher, patient refusal, history of allergic response to local anesthetics or any of the medications used in the study, patients with cognitive impairment, surgeries exceeding 120 min, basal body temperatures of more than 38° or less than 36° C, and on drugs that might affect thermoregulation. A computer-generated table of random numbers, which were kept secret in sealed, opaque envelopes and only revealed at the moment of drug administration, was used to randomly divide the patients into three equal groups each with 36 patients. Patients in Group A received pethidine 0.5 mg/kg IV, Group B received acetaminophen 15 mg/kg IV and Group C patients were given dexamethasone 0.1 mg/kg IV as PSAS prophylaxis as shown in Figure 1. A color-coded polypropylene bottle of normal saline was used to mix the drugs, and a total of 200 ml was infused.

After the level of sensory blockade had stabilized over a period of 15 min, the allocated infusion was administered by a resident who was not participating in the study, and the anesthesia residents who were not involved in any other aspect of the study monitored the patients. All participants in the study—patients, residents, and the anesthesiologist who administered the spinal anesthesia were blind to the study.

All the patients were assessed preoperatively, and were fasting for 6 h. Each patient received a peripheral 18 G cannula for IV access when they entered the operating room. Lactated Ringer's solution 10 ml/kg, warmed up to room temperature, was infused. Later, the infusion rate was adjusted in accordance with the fluid balance during surgery. Traditional monitoring techniques were used, including electrocardiograms (ECG), non-invasive blood pressure (NIBP) and Pulse oximetry (SpO2).

Before spinal anesthesia was administered, peripheral and room temperatures, mean arterial blood pressure (MAP), heart rate (HR), and SpO2 values were recorded. The operating room and PACU were kept at a fixed temperature of 25°C, with a relative humidity of roughly 60%. Using a percutaneous thermometer, body temperature (axillary

 

temperature) was measured. Single shot spinal anesthesia was initiated aseptically at L3/4 or L4/5 interspace. While the patient was seated, 2.5 to 3.5 mL of 0.5% hyperbaric bupivacaine were injected at a rate of 0.2 ml/sec using a 25-gauge Quincke spinal needle. The patient was then positioned in the supine posture. During the procedure, oxygen (6 L/min) was given via a facemask. Pinprick testing was used to measure sensory level in order to calculate the two-segment regression time in minutes and the peak sensory level. To assess motor block, the modified Bromage scale was employed. Bromage scale 3 and T6 were the ideal motor and sensory blocks, respectively. General anesthesia was used if the spinal blockade was unsuccessful, and the patient was excluded of the study. The intraoperative management of fluid was done in accordance with the patient's body weight and intraoperative losses. Patients were admitted to the PACU postoperatively.

### 2.1. Outcome assessments

The incidence and onset of PSAS were recorded, and Bedside Shivering Assessment Scale (BSAS) was used to grade the severity: Grade 1 (zero points): No shivering; Grade 2 (1 point) - mild shivering that is limited to the neck and thorax and may only be detected by palpation or as an artefact on ECG; Grade 3 (2 points) - Moderate: Intermittent upper extremity involvement plus/minus thorax; and Grade 4 (3 points) - Severe: prolonged trembling of the upper or lower extremities or widespread shivering.[10] The intensity of the shivering was measured in each group at the time it started, either intraoperatively or postoperatively, and for an hour in the PACU. A rescue dose of 25 mg of pethidine was delivered intravenously and the overall dose of rescue pethidine was recorded when the shivering score reached a grade of 3 or 4. Before the intrathecal injection, at 5, 10, 15, and 20 min, and then every 10 min for the following 90 min following the intrathecal injection, the following measurements were recorded using conventional non-invasive monitors: HR, MAP, $SpO_2$ and temperature. A crystalloid infusion was used to treat hypotension, and ephedrine 5 mg IV was given if necessary.

If the heart rate was < 50 beats/min, atropine 0.01 mg/kg was administered. A four-point ordinal scale was used to grade pruritus, with zero representing no itching, one representing minor itching, two representing moderate itching but no desire for treatment, and three representing severe itching and a request for treatment. Pheniramine hydrogen maleate (45.5 mg IM) was administered in the event of pruritus. Metoclopramide 10 mg IV was given if two or more episodes of emesis occurred or nausea lasted for longer than 10 min with normal BP or HR. Over a 90-min period, sedation was monitored every 15 min and graded using the Modified Ramsay Sedation Scale.

The primary outcome was the incidence of PSAS. The secondary outcome measurements were the onset and severity of PSAS, the need to administer pethidine as a rescue anti-shivering medication, and the total dose given, and the effect of the study medications on hemodynamics and the level of sedation, and the side effects of the studied drugs. The end point of the study was one hour postoperatively.

### 2.2. Statistical Analysis

Based on the previous studies from (Gholami AS and Hadavi M, 2016) and (Entezariasl M and Isazadehfar K, 2012), a sample size of 108 cases was distributed equally among three groups (36 cases per group), and it was sufficient to detect a medium effect size (0.3) using chi square test with level of significance of 0.05 and power of 0.80. To analyze the data, Statistical program for Social Science (SPSS) version 22.0 was used. Quantitative data was shown as mean, median (IQR), or standard deviation (SD). Qualitative data was represented by frequency and percentage.

## 3. RESULTS

The comparisons of demographic information (age, sex, and ASA) as shown in Table 1 did not reveal any statistically significant differences.

In Table 2, There was a statistically significant difference regarding the groups in terms of the incidence of shivering. The p-value between A vs B: 0.32, A vs C: 0.01, B vs C: 0.10, and between all the groups was 0.03. Shivering was witnessed in 10 patients in Group A (27.7%), 14 patients in Group B (38.8%), and 21 patients (58.3%) in Group C. There was a statistically significant difference regarding the groups in terms of the onset of shivering. The p-value was

**Table 1: Comparison of the demographic information**

| Demographic data | | Group A (n = 36) | Group B (n = 36) | Group C (n = 36) | f/X2 | p-value |
|---|---|---|---|---|---|---|
| **Age (y)** | | 32.69 ± 8.0 | 34.28 ± 8.6 | 35.67 ± 9.8 | 1.0 f | 0.36 |
| **Sex** | **Male** | 15 (41.6) | 19 (52.7) | 14 (38.8) | 1.575 $^{x2}$ | 0.455 |
| | **Female** | 21 (58.4) | 17 (47.3) | 22 (61.2) | | |
| **ASA** | **I** | 20 (55.5) | 13 (36.1) | 17 (47.2) | 2.756 $^{x2}$ | 0.2521 |
| | **II** | 16 (44.5) | 23 (63.9) | 19 (52.8) | | |

Data is expressed as mean ± SD or n (%); f = ANOVA test, $X^2$ = chi square

 

**Table 2: explains the comparison of the groups in the incidence, onset, and grade of shivering, and the need for the administration of the rescue medication**

| Parameter | Group A (n = 36) | Group B (n = 36) | Group C (n = 36) | f/X2 | P-value |
|---|---|---|---|---|---|
| **Incidence of shivering** | 10 (27.7) | 14 (38.8) | 21(58.3) | 7.1 x2 | **0.03** |
| **Onset of shivering (min)** | 95.00 ± 5.7 | 70.00 ± 4.2 | 35.83 ± 4.1 | 332 f | **< 0.01** |
| **BSAS (Bedside Shivering Assessment Scale)** | | | | | |
| **0** | 26 (75) | 22 (61.1) | 15 (41.7) | 14.9x2 | **0.02** |
| **1** | 7 (19.4) | 2 (5.6) | 9(25) | | |
| **2** | 3 (8.3) | 5(13.9) | 5 (13.9) | | |
| **3** | 0 (0.0) | 7 (19.4) | 7 (19.4) | | |
| **Received rescue pethidine** | 3 (8.3) | 12 (33.3) | 12 (33.3) | 8.0 x2 | **0.02** |
| **Total pethidine dose (mg)** | 25.00 ± 0.0 (n = 3) | 33.33 ± 12.3 (n = 12) | 32.91 ± 12.6 (n = 12) | 0.62f | 0.55 |

*Data presented as mean ± SD or n (%)*

less than 0.01. The onset was at (95.00 ± 5.7), (70.00 ± 4.2), and (35.83 ± 4.1) in Groups A, B, and C respectively.

Regarding the BSAS score, in Group A that received prophylactic pethidine infusion, 26 (75%) patients out of 36 did not develop shivering, while 7 patients (19.4%) developed mild shivering (Grade 1), 3 patients (8.3%) developed moderate shivering (Grade 2), and no patients developed severe shivering (Grade 3). In Group B that received prophylactic acetaminophen infusion, 22 patients (61.1%) did not complain of shivering, while 2 patients (5.6%) developed mild shivering, and 5 patients (13.9%) developed moderate shivering as well as 7 patients (19.4%) developed severe shivering. In Group C that received prophylactic dexamethasone infusion, 15 patients (41.7%) did not develop shivering, while 9 patients (25%) developed mild shivering, and 5 patients (13.9%) manifested moderate shivering, as well as 7 patients (19.4%) suffered from severe shivering. There was a statistically significant difference regarding the groups. The p-value between A vs B: 0.01, A vs C: 0.01, B vs C: 0.12, and between all the groups was 0.02. These results showed that, the prophylactic pethidine infusion was more effective than the prophylactic acetaminophen, and dexamethasone infusions

**Table 3: clarifies the comparison of the groups in the complications and the modified Ramsay sedation score. Data presented as n (%)**

| Parameter | | Group A (n = 36) | Group B (n = 36) | Group C (n = 36) | $X^2$ | p-value |
|---|---|---|---|---|---|---|
| **Hypotension** | | 4 (11.1) | 5 (13.9) | 2 (5.5) | 1.42 | 0.49 |
| **Brady cardia** | | 5 (13.9) | 4 (11.1) | 5 (13.9) | 0.16 | 0.92 |
| **Pruritus score** | **0** | 30 (83.3) | 30 (83.3) | 29 (80.6) | 0.81 | 0.94 |
| | **1** | 4 (11.1) | 3 (8.3) | 5 (13.9) | | |
| | **2** | 2 (5.6) | 3 (8.3) | 2 (5.6) | | |
| **Nausea & Vomiting score** | **0** | 24 (66.7) | 26 (72.2) | 30 (83.3) | 6.63 | 0.36 |
| | **1** | 4 (11.1) | 5 (13.9) | 3 (8.3) | | |
| | **2** | 3 (8.3) | 3 (8.3) | 0 | | |
| | **3** | 5 (13.9) | 2 (5.6) | | | |
| **Modified Ramsay sedation score** | **1** | 27 (75) | 29 (80.6) | 29 (80.6) | 0.44 | 0.8 |
| | **2** | 9 (25) | 7 (19.4) | 7 (19.4) | | |

 

respectively in preventing post spinal anesthesia shivering (PSAS). Also, acetaminophen was more effective than dexamethasone in decreasing the incidence of PSAS.

As regards the need to administer rescue pethidine, there was a statistically significant difference regarding the groups of p-value 0.02. 3 patients (8.3%), 12 patients (33.3%) and 12 patients (33.3%) received rescue pethidine dosage in Groups A, B and C respectively.

Regarding the total dose of pethidine in mg given as rescue medication, none of the groups' differences were statistically significant. It was (25.00 ± 0.0), (|33.33 ± 12.3), and (32.91 ± 12.6) in Groups A, B and C respectively.

In Table 3, regarding the developed complications, none of the groups' differences were statistically significant. 4 (11.1%), 5 (13.9%), and 2 (5.5%) patients developed hypotension in Groups A, B, and C respectively. 5 (13.9%), 4 (11.1%), 5 (13.9%) patients developed bradycardia in Groups A, B, and C respectively. 2 (5.6%), 3 (8.3%), 2 (5.6%) patients developed moderate degree of pruritis in Groups A, B, and C respectively. 5 (13.9%), 2 (5.6%), and 0 patients developed more than two episodes of Nausea and/or vomiting. in Groups A, B, and C respectively. There wasn't a statistically significant difference between the groups regarding the modified Ramsay sedation score.

# 4. DISCUSSION

Several studies showed that pethidine provided good prophylaxis against PSAS. Destaw and their team evaluated the effects of prophylactic intravenous dexamethasone against pethidine for prevention of PSAS for patients who underwent transurethral resection of the prostate and received spinal anesthesia, and their findings are consistent with our findings. They reported that 21.9% of the patients in the pethidine group developed PSAS, 12.5% of them were of grade 2 and 9.4% were of grade 3. While in the dexamethasone group, PSAS was witnessed in 43.8% of the patients, 12.5%, 18.8%, and 12.5% of them were of grades 1,2, and 3 respectively.[11] They also reported that the onset of PSAS in was (81 ± 13) and (65 ± 43) in the pethidine and dexamethasone groups respectively.[11]

In their study comparing ketamine, tramadol, and pethidine for the prevention of shivering under spinal anesthesia, Gangopadhyay and colleagues found that the rates of perioperative shivering were 20%, 13%, and 40%, respectively, in the pethidine, ketamine, and tramadol groups.[12]

In contrast to our study, Gholami and their colleagues determined that in a comparison of the effects of dexamethasone and pethidine in avoiding PSAS, 27.3% and 54.5% of the patients in the dexamethasone and pethidine groups, respectively, developed shivering.[13]

Also in contrast to our results, Moeen and their team, discovered that, in patients who underwent prostate surgery under spinal anesthesia, dexamethasone was just as efficient as pethidine in lowering PSAS in comparison to placebo with fewer side effects. PSAS was witnessed in 6.7% of the patients in the dexamethasone group and was of the moderate degree (grade 2), and in 10% of the patients in the pethidine group. 6.7% of the patients in the pethidine group were of grade 2 shivering and 3.3% developed severe shivering (grade 3).[14]

Our findings are supported by a study on the action of acetaminophen on postoperative shivering by Kinjo and his colleagues. In their study, the acetaminophen group had a considerably lower occurrence of postoperative shivering (22.2%) than the placebo group (73.7%).[15]

In similarity to our results, Esmat et al. compared acetaminophen and dexamethasone regarding the incidence of PSAS during procedures of the lower part of the body and reported clinically significant PSAS in 15% of the patients in the acetaminophen group and 40% of the patients in the dexamethasone group.[16] 10% of the patients who developed PSAS in the acetaminophen group was of the moderate degree (grade 2) while 5% were of the severe degree (grade 3). 24% of the patients in the dexamethasone group developed PSAS of the moderate degree (grade 2), and 16% developed severe shivering (grade 3).[16] Moreover, In the acetaminophen and dexamethasone groups, they noted that the mean IV pethidine doses needed to alleviate shivering were (25.0) and (32.5 11.6), respectively.[16]

Supporting our results, Yared and their research team reported in their study results that postoperative shivering was detected in 13.1% of the patients who received dexamethasone after cardiac surgery.[8] Destaw et al. reported that the onset of PSAS in was (81 ± 13) and (65 ± 43) in the pethidine and dexamethasone groups respectively.[11]

Regarding the incidence of complications as mentioned before, it didn't hinder the progress of the study. Antagonizing our study results, Gangopadhyay, Talakoub, Chu and their fellow researchers reported a significant incidence of pruritus in pethidine group.[12,17,18]

Esmat et al. found that, in contrast to our findings, 8.0% of individuals receiving dexamethasone and 28% of patients receiving acetaminophen experienced hypotension. In the acetaminophen and dexamethasone groups, they also noted that pruritis developed in 7% and 9% of the patients, respectively. In addition, they pointed out that nausea developed in 9.0% and 6.0%, and vomiting developed in 5.0% and 3.0% of the patients of the acetaminophen and dexamethasone groups respectively.[16]

 

# 5. LIMITATIONS

This study was conducted in a single hospital and patients' satisfaction was not assessed.

# 6. CONCLUSION

Aacetaminophen was more effective than dexamethasone, while pethidine was the most effective in decreasing the incidence of PSAS.

## 7. Study registration

This study was approved by the research ethics committee at the faculty of medicine, Ain Shams University (FMASU MD 262a/ 2020/2021/2022) and registered with ClinicalTrials.gov PRS, ClinicalTrials.gov ID: NCT05284409. Written informed consent was obtained from all patients.

## 8. Availability of data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## 9. Competing interests

The authors declare that there were no conflicts of interest.

## 10. Authors' contribution

MN: Conduction of the study work.

GE: Manuscript editing

EA: Literature search

FAH: Statistical analysis and review

MM: Literature search.

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