DOI: 10.7860/JCDR/2023/66623.18797

Original Article

Anaesthesia Section

Comparison of Intrathecal Nalbuphine and Magnesium Sulphate for Prevention of Shivering in Caesarean Section: A Randomised Clinical Study

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ABSTRACT

Introduction: Nalbuphine and magnesium sulfate are commonly used drugs for the treatment of Perioperative Shivering (POS), but there is a paucity of comparative studies on their intrathecal use in Lower Segment Caesarean Section (LSCS) patients. LSCS is the most commonly performed obstetric surgery, and Spinal Anaesthesia (SA) is advantageous in LSCS. However, shivering has been found to be the most common side-effect of SA.

Aim: To compare the effect of intrathecal injection of nalbuphine and magnesium sulfate on the prevention of postspinal anaesthesia shivering during LSCS.

Materials and Methods: This randomised clinical study was conducted at the Department of Anaesthesiology, Government Medical College, Kathua, Jammu and Kashmir, India on 60 parturients between the ages of 20-40 years from September 2021 to January 2023. The participants had full-term gestation and an American Society of Anaesthesiologists (ASA) status of I or II, and were scheduled for LSCS under SA. The total sample was divided into two groups of 30 patients each. Group N (n=30) received 0.7 mg nalbuphine intrathecally, while Group M (n=30) received 25 mg of magnesium sulfate intrathecally, both with 0.5% bupivacaine (10 mg). Characteristics of spinal blockade, time to onset of shivering, severity of shivering, and side-effects such as nausea, vomiting, sedation, and hypotension were noted. Student's t-test, Chi-square test, and Fisher's exact test were used for data analysis. A p-value of <0.05 was considered statistically significant.

Results: Both study groups were comparable in terms of age (p-value=0.081), height, weight (p-value=0.079), ASA grade (p-value=0.072), and duration of surgery (p-value=0.077). In group N, 5 patients (16.67%) had POS, while in Group M, 6 patients (20%) had POS, but the difference was not statistically significant. In Group N, 3 patients (10%) had a shivering score of 3 and 2 patients (6.67%) had a shivering score of 4, while in group M, 3 patients (10%) had a shivering score of 3 and 3 patients (10%) had a shivering score of 4. The difference was statistically insignificant. Perioperative complications (sedation, hypotension, nausea, and vomiting) were comparable in both groups with no statistically significant difference.

Conclusion: Intrathecal injection of preservative-free 0.7 mg nalbuphine and 25 mg magnesium sulfate were both effective in reducing the incidence of postspinal shivering. Both drugs had comparable minimum perioperative complications. The intrathecal use of nalbuphine and magnesium sulfate for the prevention of postspinal shivering is encouraged, as both drugs are less expensive and readily available in the operation theaters.

Keywords: Adjuvant, Bupivacaine, Perioperative, Pregnant, Regional anaesthesia

INTRODUCTION

The choice of anaesthesia for LSCS depends on the reason for the operation, degree of urgency, the desires of the patient, and the judgment of the anaesthesiologist [1]. SA is widely preferred as it has several advantages over General Anaesthesia (GA), such as rapid onset, superior blockade, minimal physiological alterations, minimum stress response, cost-effectiveness, and a lower chance of postoperative morbidity [1,2]. However, hypothermia and shivering are common complications after SA, as it impairs thermoregulation, inhibits tonic vasoconstriction, and causes the redistribution of core heat from the trunk to peripheral tissues [3]. Shivering associated with SA in patients undergoing LSCS is a common problem. Shivering is observed in about 55% of patients with neuraxial anaesthesia [4]. It is very uncomfortable for patients and may interfere with the monitoring of Electrocardiogram (ECG), Blood Pressure (BP), and oxygen saturation (SpO_2). Shivering also increases oxygen consumption, lactic acidosis, and carbon dioxide production, causing distress to parturients who have a low cardiopulmonary reserve and high metabolism [5].

Various agents such as meperidine, doxapram, nalbuphine, dexamethasone, tramadol, nefopam, ketanserin, clonidine, propofol, physostigmine, magnesium sulfate ($MgSO_4$), and fentanyl have been used to eliminate postoperative shivering [6-8]. $MgSO_4$ is a non competitive antagonist of N-methyl-D-aspartate (NMDA) receptors and by blocking these receptors, it leads to a decrease in both epinephrine and 5-HT, which play a role in thermoregulation. $MgSO_4$ is a naturally occurring calcium antagonist and has a known central and peripheral muscle relaxation effect, which may reduce the intensity of shivering by peripheral vasodilation, increasing cutaneous circulation and leading to a decrease in the incidence of shivering [9,10]. Nalbuphine is a mixed agonist-antagonist opioid that exerts postanaesthetic antishivering action through its high affinity for κ opioid receptors in the central nervous system [11,12]. Intravenous (IV) nalbuphine and $MgSO_4$ have proven effectiveness in controlling shivering after regional anaesthesia [7,12]. There are few studies comparing intrathecal nalbuphine and magnesium sulfate for lower abdominal surgeries, and to the best of authors knowledge, there is hardly any study comparing the effects of intrathecal injection of nalbuphine and $MgSO_4$ on the prevention of post-SA shivering during LSCS [9,10,13].

The present study aimed to compare the effects of adding intrathecal nalbuphine and $MgSO_4$ to bupivacaine on the prevention

of postspinal shivering in parturients undergoing LSCS under SA. The primary aim of the study was to determine the incidence of shivering in both groups, and the secondary aims were to assess the severity of shivering, characteristics of spinal block, evaluation of intraoperative vitals, and any side-effects or complications.

MATERIALS AND METHODS

The present study was a randomised, double-blinded clinical study conducted in the Department of Anaesthesiology and Critical Care at Government Medical College and Hospital, Kathua, Jammu and Kashmir, India. The study duration was one and a half years, from September 2021 to January 2023. The study commenced after approval from the Institutional Ethical Committee (IEC) (IEC/GMCK/88/Pharma dated 25-08-2021). Written consent was obtained from the participants during the preanaesthetic evaluation, after explaining the study in their local language.

Inclusion criteria: A total of 60 parturients aged 20-40 years, belonging to ASA Grade I and II, with full-term gestation scheduled for LSCS under SA, were enrolled in the study after obtaining informed consent.

Exclusion criteria: Pregnant women below 20 or above 40 years of age, those with uncontrolled co-morbidities, failure of spinal blockade, and any contraindication to SA such as patient refusal, cardiorespiratory problems, coagulopathy, neurological disease, and allergy to the drugs used, were excluded from the study.

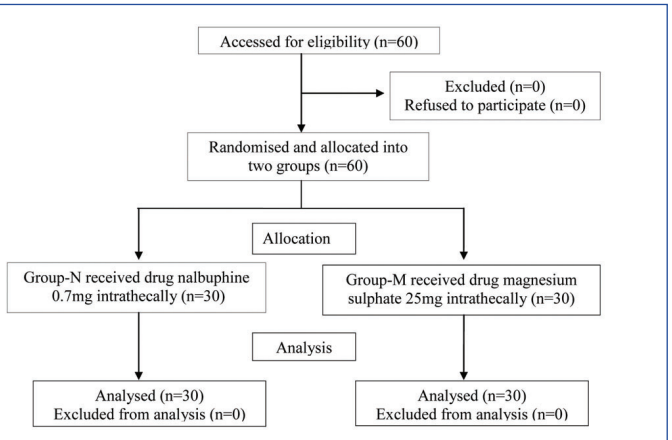
Sample size calculation: The sample size was calculated based on previous studies. The incidence of postspinal shivering ranged from 40-70% [4,14]. A sample size of approximately 30 patients in each group was required to demonstrate the effectiveness of nalbuphine and $MgSO_4$ in reducing shivering by 50% with 95% confidence (α=0.05) and a study power of 80% [15,16].

All patients who met the inclusion criteria were enrolled and randomly allocated in a 1:1 ratio to either of the two groups using computer-generated randomisation.

Group N (n=30) received 2.5 mL of (10 mg bupivacaine+0.7 mg nalbuphine) intrathecally [17].

Group M (n=30) received 2.5 mL of (10 mg bupivacaine+25 mg of $MgSO_4$) intrathecally [15].

The Consolidated Standards of Reporting Trials (CONSORT) diagram is shown in [Table/Fig-1].



[Table/Fig-1]: CONSORT diagram.

Patients' age (in years), weight (in kg), height (in meters), and baseline body temperature (in °C) as well as ASA grade were recorded. All patients underwent history taking, assessment of present symptoms, and past medical/surgical history. They were evaluated for routine investigations and scheduled for surgery after anaesthesia fitness was confirmed. In the preanaesthesia room, an IV line was inserted, and IV preloading was done with isotonic saline solution (2 mL/kg). In the operating room, ECG, SpO_2, and Non Invasive Blood Pressure (NIBP) monitors were attached. The operating room temperature was maintained at 22-24°C.

The anaesthesia procedure was standardised for all patients. Under strict aseptic precautions, a subarachnoid block was performed using a 27 G spinal needle at the L3-L4 or L4-L5 intervertebral spaces. Body temperature was recorded upon entry to the operating room and then measured at 15-minute intervals. All IV and irrigation fluids were warmed to 37°C in warming cabinets. During the operation, all patients were covered with one layer of surgical drapes over the chest, thighs, and calves.

This study was a randomised, double-blinded study, as both the patients and the anaesthesiologist assessing the shivering were blinded to the study drug used. The attending anaesthesiologist recorded the time in minutes at which shivering started after the subarachnoid block (onset of shivering) and the severity of the shivering, graded using a scoring system validated by Crossley AW and Mahajan RP [Table/Fig-2] [18].

Shivering score	Characteristic
0	No shivering
1	Piloerection or peripheral vasoconstriction, but no visible shivering
2	Muscular activity in only one muscle group
3	Muscular activity in more than one muscle group, but not generalised
4	Shivering involving the whole body.

[Table/Fig-2]: Shivering Score (Crossley AW and Mahajan RP) [18].

If shivering was noted with a shivering score ≥3, patients were treated with an intravenous injection of tramadol at a dosage of 0.5 mg/kg. After surgery, patients were shifted to the Postanaesthesia Care Unit (PACU), where the ambient temperature was maintained at 25-26°C. All patients were covered with one layer of drapes and one cotton blanket. The onset and duration of motor and sensory block were assessed using the Modified Bromage Scale (MBS) and pinprick test, respectively. Recorded parameters included haemodynamic parameters, characteristics of spinal blockade (such as time to achieve maximum dermatomal block height), onset of complete motor blockade, duration of spinal blockade, incidence and severity of shivering, and side-effects like nausea, vomiting, pruritus, hypotension, and bradycardia.

STATISTICAL ANALYSIS

The recorded data were compiled and entered into a Microsoft Excel spreadsheet and then exported to the data editor of Statistical Package for Social Sciences (SPSS) version 23.0. Quantitative data were expressed as mean and standard deviation, while qualitative data were expressed as number (N) and percentage (%). Student's t-test was employed to compare continuous variables, while the Chi-square test or Fisher's exact test, whichever was applicable, was used to compare categorical variables. A p-value >0.05 was considered non-significant. A p-value <0.05 was considered significant, and a p-value <0.001 was considered highly significant.

RESULTS

In both groups, age, height, weight, ASA grade, and duration of surgery were comparable, with no statistically significant difference among them [Table/Fig-3].

The onset of sensory block was significantly faster in group N. However, the time to reach the sensory level of T5, time to achieve maximum motor blockade measured by MBS-3, time to regress motor blockade to MBS-1, and duration of sensory block were comparable in both groups and statistically insignificant [Table/Fig-4].

In group N, five patients (16.67%) had POS, while in group M, six patients (20%) had POS. The difference was not statistically significant [Table/Fig-5].

Demographic characteristics	Group N (mean±SD)	Group M (mean±SD)	p-value (Student's t-test)
Age (years)	25.9±3.5	24.2±4.1	0.081
Weight (kg)	64.1±13.1	66.4±11.9	0.079
Height (meter)	1.49±13.1	146.4±12.9	0.083
Duration of surgery (mins)	52.2±23.7	54.1±24.2	0.077
ASA I/II	20/10	21/9	0.072

[Table/Fig-3]: Demographic profile of patients of both groups.

Variables	Group N (mean±SD)	Group M (mean±SD)	p-value (Chi-square)
Onset of sensory block (mins)	1.75±0.35	4.38±0.53	0.001
Time to reach sensory level of T5 (mins)	6.33±3.01	6.92±2.14	0.051
Motor block onset (time to reach MBS-3) (mins)	5.81±0.8	7.12±0.7	0.751
Time to regress motor blockade to MBS-1 (mins)	221.52±45.64	219.64±51.16	0.062
Duration of sensory block (mins)	231.52±40.59	229.64±46.11	0.062

[Table/Fig-4]: Characteristics of spinal blockade in both the groups. Modified Bromage Scale (MBS).

Time since Spinal Anaesthesia (SA)	Group N n (%)	Group M n (%)	p-value (Fisher's test)
0-15 min	0	0	0.056
15-30 min	0	0	
30-45 min	1 (3)	2 (6.67)	
45-60 min	2 (6.67)	2 (6.67)	
Postoperatively	2 (6.67)	2 (6.67)	
Total	5 (16.67)	6 (20)	

[Table/Fig-5]: Incidence of shivering in both the groups.

The severity of shivering in group N and group M is shown in [Table/Fig-6] and the difference were statistically insignificant.

Intraoperative vital signs such as HR, MAP, and temperature were comparable in both groups and statistically insignificant [Table/Fig-7].

Grades of shivering	Group N n (%)	Group M n (%)	p-value (Fisher's-exact test)
0	0	0	0.051
1	0	0	
2	0	0	
3	3 (10)	3 (10)	
4	2 (6.67)	3 (10)	

[Table/Fig-6]: Severity of shivering in both the groups.

Heart rate	Group N (mean±SD)	Group M (mean±SD)	p-value (Student' t-test)
0 min	94.52±7.07	92.76±5.83	0.178
5 mins	91.58±7.10	90.58±6.08	0.450
10 mins	86.78±7.21	85.26±6.37	0.267
15 mins	84.84±6.69	84.34±3.68	0.644
20 mins	82.68±4.00	81.30±3.53	0.070
30 mins	81.48±3.74	82.18±3.51	0.337
40 mins	81.00±4.34	82.04±4.77	0.209
50 mins	80.20±4.22	80.14±4.46	0.945
60 mins	83.34±3.65	82.04±4.77	0.129
MAP	**Group N (mean±SD)**	**Group M (mean±SD)**	**p-value (Student's t-test)**
0 min	97.18±4.66	96.50±5.30	0.497
5 mins	91.74±6.75	91.96±6.11	0.864
10 mins	91.06±3.65	90.28±3.72	0.293
15 mins	91.48±3.14	91.92±3.49	0.401
20 mins	92.70±6.42	94.72±3.99	0.062
30 mins	93.50±6.62	92.04±6.32	0.262
40 mins	95.06±4.65	94.44±4.79	0.513
50 mins	96.64±6.75	95.46±5.22	0.331
60 mins	97.62±4.17	97.50±5.30	0.497
Body temperature	**Group N (mean±SD)**	**Group M (mean±SD)**	**p-value (Student's t-test)**
0 min	98.80±0.79	98.64±0.56	0.336
10 mins	98.60±0.70	98.12±0.79	0.097
20 mins	97.27±0.96	97.82±0.67	0.143
30 mins	97.50±0.66	97.57±0.99	0.317
45 mins	97.65±0.80	97.95±0.75	0.580
60 mins	97.93±0.83	97.93±0.68	0.707

[Table/Fig-7]: Evaluation of the intraoperative vitals among the study groups. (a) Heart rate; (b) MAP (Mean Arterial Pressure); (c) Temperature; p-value <0.05 to be considered significant

Perioperative complications (sedation, hypotension, nausea, and vomiting) were comparable in both groups and statistically insignificant [Table/Fig-8].

Parameter	Group N n (%)	Group M n (%)	p-value (Chi-square)
Sedation	2 (6.67)	1 (3)	0.063
Hypotension	1 (3)	1 (3)	--
Nausea	2 (6.67)	1 (3)	0.063
Vomiting	2 (6.67)	1 (3)	0.063

[Table/Fig-8]: Comparison of side-effects and complications in both the groups.

DISCUSSION

Postoperative Shivering (POS) is a common complication in patients undergoing SA. While shivering serves as a protective reflex to increase core temperature through involuntary muscle contractions, it can also have adverse effects. These effects include increased oxygen consumption, which can impact wound healing [19]. Moreover, shivering interferes with intraoperative and postoperative monitoring due to the involuntary oscillatory muscular activity. It elevates circulating catecholamines, resulting in increased heart rate and cardiac output, which can be detrimental for patients with limited cardiac reserve. Shivering also raises oxygen consumption, carbon dioxide production, lactic acid levels, and postoperative pain due to the stretching of surgical incisions, infection, and bleeding [20].

Management of intraoperative and postoperative shivering involves both pharmacological and non pharmacological approaches. Non pharmacological methods, such as active cutaneous warming, radiant heat to the body surface, electric heating pads, active forced air-warming, warm intravenous fluids, warming blankets, and gowns, have proven effectiveness but are often impractical in resource-limited settings due to their cost. Therefore, pharmacological techniques for preventing or treating shivering remain the preferred choice [21].

Mostafa M et al., also noted a statistically significant difference in shivering scores between the study groups during intraoperative and postoperative periods, with a lower incidence of shivering in the $MgSO_4$ group. They concluded that intrathecal administration of 25 mg of $MgSO_4$ is safe and reduces the incidence and intensity of shivering during LSCS under SA, without serious side-effects, as observed in the present study [9]. Similarly, Faiz SHR et al., concluded in their study that the addition of 25 mg of $MgSO_4$ intrathecally improved the perioperative incidence and severity of shivering in females undergoing LSCS under SA, without significant side-effects, which was consistent with the present study [15].

Kapdi MS et al., compared 1 mg of nalbuphine and 100 mg of $MgSO_4$ as adjuvants to intrathecal hyperbaric bupivacaine for

infraumbilical surgeries. They observed shivering in 3.33% of patients in the nalbuphine group and none of the patients in the $MgSO_4$ group. However, in the present study, 16.67% of patients in the nalbuphine group and 20% of patients in the $MgSO_4$ group experienced shivering. The lower incidence of shivering in their study may be attributed to the higher doses of intrathecal nalbuphine and $MgSO_4$ used [13].

Eskandr AM and Ebeid AM, also concluded that adding a small dose of nalbuphine (400 µg) to intrathecal bupivacaine during SA for knee arthroscopy reduces the incidence and severity of shivering. However, the incidence of shivering in their study was 23.3% compared to 16.67% in the present study, possibly due to the use of 400 µg of intrathecal nalbuphine compared to 0.7 mg used in the present study [16].

In this study, 20% of the patients who received 25 mg of $MgSO_4$ intrathecally experienced shivering, which contrasts with the findings by Jain K et al., who observed shivering in 6.6% of patients. This discrepancy could be due to the fact that they used 75 mg of $MgSO_4$ intrathecally [22]. Mohamed MAR et al., concluded that the addition of 400 µg of nalbuphine intrathecally to bupivacaine for prophylaxis of postspinal shivering in patients undergoing lower limb surgeries was more effective than intrathecal midazolam. However, the incidence of shivering was 23.3% in the nalbuphine group in their study, slightly higher than the 16.67% observed in the present study, which may be due to the lower dose (400 µg) of intrathecal nalbuphine used [23].

Kapdi M and Desai S, compared intrathecal midazolam 1 mg with intrathecal nalbuphine 0.75 mg and noted shivering in 10% of patients in both groups. However, in the present study, 16.67% of patients in the nalbuphine group experienced shivering, as a slightly higher dose of intrathecal nalbuphine (0.75 mg) was used. They concluded that both intrathecal nalbuphine and midazolam are effective adjuvants to hyperbaric bupivacaine for LSCS in terms of haemodynamic stability and good Apgar scores at 1 and 5 minutes [24].

Ahmed FI conducted a study where 800 µg of nalbuphine was added intrathecally to bupivacaine and compared it with intrathecal fentanyl in LSCS. They noted shivering in 27.5% of patients in the fentanyl group and 7.5% of patients in the nalbuphine group, with no effect on neonatal Apgar scores and neurologic and adaptive capacity scores. However, the incidence of shivering in the nalbuphine group was higher in the present study, possibly due to the slightly lower dose of intrathecal nalbuphine used [25].

The characteristics of spinal block in the $MgSO_4$ group are comparable to the study conducted by Jain K et al., [22]. The characteristics of spinal block in the nalbuphine group in the present study are comparable to the studies conducted by Gomma HM et al., and Kapdi M and Desai S, [17,24]. However, the characteristics of spinal block in both groups in the present study were comparable, except for the onset of sensory block, which was faster in the nalbuphine group.

Kapdi MS et al., noted that the haemodynamic parameters remained within normal limits, despite using 1 mg of nalbuphine and 100 mg of $MgSO_4$ intrathecally for infraumbilical surgeries [13]. Gupta KL et al., also used 1 mg of nalbuphine intrathecally for lower limb orthopaedic surgeries and observed a significant difference in Heart Rate (HR) and Mean Arterial Pressure (MAP), but they remained within normal limits and did not require any intervention [26]. Parveen S et al., compared the combination of nalbuphine 1 mg with bupivacaine versus bupivacaine alone intrathecally and observed no major difference in various haemodynamic variables, as observed in the present study [27]. In the present study, there was a fall in HR and MAP after administering intrathecal nalbuphine and $MgSO_4$, but it was not significant and was comparable in both groups.

In the present study, the side-effects were comparable in both study groups, with a slightly higher incidence of nausea, vomiting, and sedation in the nalbuphine group, which was consistent with the study conducted by Kapdi MS et al., [13]. Kapdi M and Desai S, noted nausea and vomiting in 10% of patients who received 0.75 mg of nalbuphine intrathecally, which was slightly higher than the present study as the present study used 0.7 mg of nalbuphine [24]. Ahmed FI, noted nausea and vomiting in 12.5% of patients in the nalbuphine group, which was higher than the present study, as they used 800 µg of nalbuphine intrathecally [25]. Mukherjee A et al., studied different doses of intrathecal nalbuphine in patients undergoing lower limb surgeries and concluded that the duration of sensory block and analgesia prolongs with doses of 400 µg and 800 µg, but side-effects increase with the higher dose of 800 µg [28].

In a review article by Raghuraman MS, he analysed the different doses of intrathecal nalbuphine used in studies and suggested that intrathecal nalbuphine in doses ranging from 0.4 to 0.8 mg would be an acceptable dose as an intrathecal adjuvant to a local anaesthetic agent in adult patients [29]. Since there is no study that has used 0.7 mg of nalbuphine intrathecally in LSCS, authors decided to use this dose of nalbuphine intrathecally.

Limitation(s)

Core temperature was not monitored, and larger studies with a larger sample size may be useful to confirm and validate present study results.

CONCLUSION(S)

Preservative-free 0.7 mg nalbuphine and 25 mg $MgSO_4$ are good adjuvants to intrathecal hyperbaric bupivacaine for women undergoing LSCS under SA. Both of these drugs are safe and decrease the incidence and intensity of shivering in women undergoing LSCS under SA without any serious side-effects. The characteristics of spinal block are the same in both groups, except for the onset of sensory blocks, which was faster in the nalbuphine group. Therefore, it is recommended to use both the drugs intrathecally as they are readily available in most operating theaters and are less expensive.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jul 20, 2023
- Manual Googling: Oct 25, 2023
- iThenticate Software: Nov 03, 2023 (17%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jul 20, 2023**
Date of Peer Review: **Aug 28, 2023**
Date of Acceptance: **Nov 07, 2023**
Date of Publishing: **Dec 01, 2023**