ORIGINAL RESEARCH PAPER

Anaesthesiology

EFFICACY OF NEOSTIGMINE METHYLSULFATE AND MAGNESIUM SULFATE AS ADDITIVES TO HYPERBARIC BUPIVACAINE FOR SPINAL ANAESTHESIA: A CLINICAL COMPARATIVE STUDY

KEY WORDS:

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ABSTRACT

Background: Intrathecal neostigmine and magnesium sulfate (MgSO4) produce substantial antinociception, potentiate analgesia of bupivacaine without neurotoxicity. **Aims:** The aim of the study was to investigate the effect of neostigmine and MgSO4 on characteristics of spinal anesthesia (SA), hemodynamic stability and postoperative analgesia when added to 0.5% hyperbaric bupivacaine for SA. **Subjects and Methods:** In this prospective, randomized, single-blind study 90 American Society of Anesthesiologist status I and II adult males and females posted for major lower abdominal surgery were assigned to one of the three groups (n = 25). Group N received Neostigmine 50 g, Group M received MgSO4 50 mg, Group C received 0.5 ml saline as an adjuvant to 15 mg hyperbaric bupivacaine. Onset, duration of block, heart rate, mean arterial pressure, postoperative analgesia, analgesic requirement, and adverse effects were recorded. Data expressed as mean (standard deviation) or number (%) with P <0.05 considered statistically significant. **Results:** The three groups were comparable in characteristics of SA. The mean duration of analgesia was significantly longer in Group M (294 ± 11.73 minutes) followed by Group N (265.86 ± 47.606 minutes) and Group C (195.8 ± 9.886 minutes) (P = 0.0001). Analgesic requirement was significantly less in Group N followed by Group M and Group C (P = 0.00232). The pain score was significantly less in Group M (P < 0.05). **Conclusion:** Intrathecal Neostigmine and MgSo4 does not affect characteristics of SA. Duration of analgesia is highest with Magnesium Sulfate. Postoperative analgesia of neostigmine was better than MgSO4 as compared to the control group.

Introduction

Pain comes from a Latin word 'Poena' which means penalty or punishment. Pain has been defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.[1] Anesthesiologists are leaders in the development of pain services in the current era and hence are responsible for management of peri and post operative pain. Neural blockade is one of the answers for control of intra and post operative pain.To enhance bupivacaine-induced analgesia in SA, various adjuvant drugs are used such as adrenaline, morphine, fentanyl, clonidine, and ketamine but are associated with many side effects. Recent research has focused on non-opioid spinal receptors that inhibit transmission of pain signals.[2] Increased understanding of the spinal processing of pain has led to the development of specific drugs that inhibit pain transmission. Acetylcholine of muscarinic cholinergic system was found to be one of the endogenous spinal neurotransmitters to have a role in anti-nociception by direct action on spinal cholinergic muscarinic receptors M1 and M3 and nicotinic receptor subtypes as well as indirectly by stimulating release of second messenger Nitric Oxide in the spinal cord. [3-5] Neostigmine exerts its effect by inhibiting the breakdown of the neurotransmitter acetylcholine. [6] This inhibition of acetylcholine degradation by neostigmine enhances the descending control of afferent nociceptive stimuli and provides a new approach for enhancement of desirable analgesia with few dose-related side effects. [7] MgSO4 produces anti-nociception and potentiation of opioid activity, presumably by its action as a voltage gated N-methyl-D-aspartate (NMDA) receptor agonist. The mechanism of action of MgSO4 in reducing postoperative pain and prolonging the duration of sensory blockade in patients fits in well with the pharmacological mechanisms underlying the anti-nociceptive action of the Mg2+ ion.[8] The Mg2+ ion blocks NMDA receptor-associated channels, which are ligand-gated ion channels that generate slow excitatory post-synaptic currents at glutamatergic synapses, in a voltage-dependent manner.[9,10] Intrathecal neostigmine and magnesium sulfate (MgSO4) both produce substantial antinociception without neurotoxicity, potentiate analgesia of bupivacaine and opioids as is evident from animal and human studies. Since their primary site of action is the spinal cord, direct intrathecal injection is preferable to obtain meaningful and clinically effective analgesia.

Therefore, in the present study, we intend to compare intrathecal neostigmine at dose of 50 µg and intrathecal MgSO4 at a dose of 50 mg as an adjuvant to Bupivacaine Heavy at a dose of 15 mg for intra and postoperative analgesia after surgery under spinal anesthesia. In developing countries where affordability of health care is a major concern, neostigmine and MgSO4 are cost effective, easily available nonopioid alternatives to ameliorate mostly undertreated postoperative pain.

SUBJECTS AND METHODS

The aim of present study was to evaluate the effect of smaller doses of neostigmine (50 g) and MgSO4 (50 mg) on characteristics of SA, hemodynamic stability, and postoperative analgesia when added to hyperbaric bupivacaine for SA. It is a randomized, single-blind, prospective study conducted at Department of Anaesthesiology, Silchar Medical College, Silchar during 1st June 2020 to 31st May 2021. The study was approved by Institutional Ethics Committee. Keeping the power of study as 80% and confidence limit at 95% to detect a 25% change in duration of analgesia between neostigmine methylsulphate and MgSO4 groups, the minimum sample size was 21 in each group. We have included 30 patients in each group. Patients classified as per American Society of Anesthesiologists (ASA) classes I and II scheduled for elective surgery under spinal anesthesia were studied. Patients were divided into three groups, each containing 30 patients.

After obtaining informed written consent from patients, they were randomly divided into three groups

Group C (n=30): Control group
Group N (n=30): Neostigmine group
Group M (n=30): MgSO4 group

All the patients who are in the inclusion criteria were assessed by pre-anaesthetic examination. Preparation of patients included a period of overnight fasting > 8 hours, anxiolysis with single dose of oral Alprazolam 0.25 mg and Ranitidine 150 mg on the night before. In the pre-operative room, an intra-venous line was secured with a 16G cannula on an arm. Baseline pulse rate, NIBP (Noninvasive Blood Pressure), SP02 (Oxygen saturation) and E.C.G (Electrocardiogram) will be recorded.

The patients were premedicated with injection Ranitidine 50 mg i.v. stat and injection Ondansetron 4 mg i.v. stat. 30 minutes before the commencement of anaesthesia. Using all aseptic precautions, L3–L4 or L4–L5 intervertebral space was located, and 2% lignocaine was infiltrated. The 25-gauge Quincke's spinal needle was used to access subarachnoid space. Successful dural puncture was confirmed by withdrawing the stylet to verify free flow of cerebrospinal fluid (CSF). Syringe loaded with injection bupivacaine alone or in combination with neostigmine or MgSO4, depending on the group was attached to the hub of the needle and whole of the drug injected slowly into subarachnoid space. Patients were immediately turned supine after administration of subarachnoid block. All patients were given oxygen at 5 L/min by mask throughout the surgical procedure.

Duration of the sensory and motor block were assessed every hour till the recovery of sensation. Injection Diclofenac Sodium was given intramuscularly as a rescue analgesic when requested by patient. During the procedure, the vital parameters like pulse, BP, SpO2 and ECG were monitored till the procedure is completed.

The patient was shifted to the post-operative ward and the pulse rate, SBP, DBP, post-operative nausea, vomiting and any other post-operative side effects were recorded at every 30 minutes interval till 120 minutes and thereafter at 2-hour interval till 12 hours duration after surgery.

The duration of analgesia was calculated from onset of block to the first complaint of pain. The incidence of side effects such as bradycardia, hypotension and sedation were noted and managed accordingly. Data was expressed in mean ± SD and p-value of <0.05 was considered statistically significant.

Parameters observed:

1. Duration of analgesia, Onset of sensory block, total duration of sensory block, onset of motor block, total duration of motor block. Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean Arterial Pressure (MAP), Heart Rate, SPO2, were recorded intra-operatively at baseline before neuraxial block, after the block and thereafter until the surgery was over.

2. Time to request for analgesia.
3. Sensory block by Pinprick Method Modified Bromage Scale, VAS Score

C. Statistical Analysis:

Statistical analysis was done using Graphpad Instat® V.306. Data was expressed as means and standard deviation (SD). For qualitative data ANOVA test and quantitative data unpaired t test was used with P value reported at the 95% confidence interval (CI). Microsoft Word and Microsoft Excel was used to generate graphs, tables etc.

RESULTS

The present study was carried out under the Department of Anaesthesiology and Critical Care, Silchar Medical College and Hospital, Silchar for a period of 1st June 2020 to 31st May 2021. The study was undertaken after getting approval from the hospital ethical committee to evaluate the effect of neostigmine and MgSO4 added to 0.5% hyperbaric bupivacaine with plain 0.5% hyperbaric bupivacaine as control. It comprised of 90 patients of ASA I and ASA II, aged 18-60 years, weighing between 50-80 kg undergoing elective lower abdominal and lower limb surgeries. All patients were randomly assigned to one of the three groups of 90 patients each.

Group C – comprised of 14 males and 16 females of mean age 40.6 ± 15.736 years and mean weight of 60.5 ± 8.266 kg who received 3ml of 0.5% hyperbaric bupivacaine plus 0.5 ml normal saline intrathecally (a total of 3.5 ml).

Group N - comprised of 19 males and 11 females of mean age 33.166 ± 13.799 years and mean weight of 62.4 ± 7.968 kg who received 3.0ml of 0.5% heavy bupivacaine and 0.5ml (50 mcg) of Neostigmine Methylsulphate, a total of 3.5ml.

Group M - comprised of 15 males and 15 females of mean age 40.8 ± 17.133 years and mean weight of 60.733 ±8.246 kg who received 3.0ml of 0.5% heavy bupivacaine and 0.5ml (50 mg) of MgSO4, a total of 3.5ml.

In our study, we selected patients between the age group of 18 to 60 years and randomly distributed them in Group C, Group N and Group M. The mean weight in all groups were identical and comparable. Also, the mean age and the ASA physical status in all the groups were similar and comparable, with no statistically significant difference. On comparing, the mean duration of surgery in all the groups, it was found to be not different significantly and were comparable. These parameters were kept identical in all the groups to avoid variations in the intra operative and postoperative outcome of patients.

Table 1: Subarachnoid Block Characteristics

	Group C	Group N	Group M	P value
	Mean+ SD	Mean + SD	Mean + SD	
Onset of sensory block	7.2566 ± 0.5132	7.0466 ± 0.6535	7.43 ± 0.5977	0.1063
Onset of motor Block	3.78667 ± 0.4718 mins	3.97 ± 0.6535 mins	3.72 ± 0.431 mins	0.0798
Two segment regression Time of sensory block (min)	97.72 ± 1.958 mins	95.46 ± 2.432 mins	98.32 ± 1.27 mins	0.0001
Duration of Sensory block	166.43 ± 27.027 mins	238.86 ± 49.7 mins	267.14 ± 0.095 mins	0.001
Duration of motor block	149.26 ± 18.554 mins	198.53 ± 34.926 mins	224.2 ± 15.99 mins	0.0001
Duration of Analgesia	195.8 ± 9.886 mins	265.86 ± 47.606 mins	294 ± 11.73 mins	0.0001

In the present study the mean onset of sensory blockade in Group C was 7.2566 ± 0.5132 minutes, Group N was 7.0466 ± 0.6535 minutes and in Group M was 7.43 ± 0.5977, statistically not significant in between the three groups (P= 0.1063 i.e P >0.05). The mean onset of motor blockade in Group C was 3.78667 ± 0.4718 minutes, Group N was 3.97 ± 0.4137 minutes and in Group M was 3.72 ± 0.431 (P=0.0798).

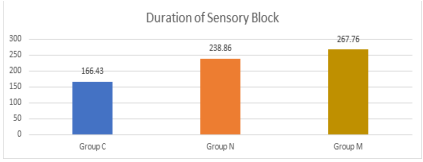

Fig. 1 Graphical representations of duration of sensory block (min) in three groups

The mean time for onset of motor bock was found to be s In the present study no patients required additional analgesic intra-operatively. The mean value of duration of Analgesia in Group C was 195.8 ± 9.886 minutes, in Group N it was 265.86 ± 47.606 minutes and in Group M it was 294 ± 11.73 minutes, On statistical comparison of the P value using ANOVA test, was found 0.0001 which is nonsignificant in all three groups i.e. P value <0.05. tatistically insignificant in all the groups.

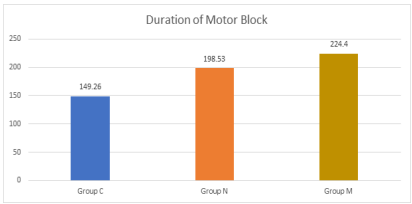

Fig 2. Graphical representations of duration of motor block (min) in three groups

In the present study VAS score at rest for pain was measured at 1st, 2nd, 3rd, 4th, 5th, 6th, 8th and 12th hrs. It was observed that VAS score for MgSO4 group was more than neostigmine Group and control Group and the difference was found to be statistically significant.

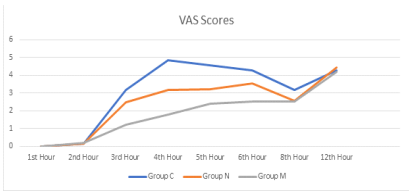

Fig 3. Graph Showing VAS Scores in all 3 Groups

In the present study, there were no any incidences of hypotension or bradycardia. There was initial decrease in SBP, DBP and MAP but was not statistically significant between the three groups and the fall in SBP, DBP and MAP is more for neostigmine in comparison to MgSO4 Group was not significant.

The incidences of complications after operations in 90 patients are shown in the following table.

Table 2: Complications in the three groups

Complications	Group C	Group N	Group M
Nausea	5 (16.67%)	3 (10%)	4(13.33%)
Vomiting	4 (13.33%)	3 (10%)	0 (0%)
Pruritus	0 (0%)	3 (10%)	1 (3.33%)
Bradycardia	0 (0%)	0 (0%)	0 (0%)
Hypotension	0 (0%)	0 (0%)	0 (0%)
Shivering	0 (0%)	3 (10%)	2 (6.66%)
Urinary Retention	2 (6.66%)	1 (3.33%)	0 (0%)
Resp. Depression	0 (0%)	0 (0%)	0 (0%)

DISCUSSION

Spinal anesthesia is most commonly used for patients who require surgical anaesthesia for procedure of known duration that involves the lower extremities, perineum, pelvic girdle, or lower abdomen. Spinal anaesthesia offers many advantages as it is easier to perform, has rapid onset of action, and profound motor blockade. It is also indicated when patients wish to remain conscious or when some comorbid condition is present such as severe respiratory disease, an airway that maybe difficult to manage or if there is increased risk in using of general anaesthesia.

Spinal anaesthesia with local anesthetic may not be sufficient in producing ideal operating condition. In recent years supplementation of local anesthetic with adjuvants is widely in practice, to reduce the dose of local anaesthetic, minimize the side effects and prolong the duration of anaesthesia., Local anaesthetic with combination of adjuvants intrathecally has a synergistic effect in control of postoperative pain. Intrathecal local anaesthetic in combination with other adjuvants like neostigmine or MgSO4 provides excellent quality of block, long lasting intra and post operative analgesia in labour and delivery, during and after hip or knee replacement and in laparotomy. They are also used in management of chronic pain. However, side effects are also reported such as nausea, vomiting, respiratory depression, pruritus, urinary retention.

Effective treatment of pain represents an important component of postoperative recovery. It serves to blunt autonomic, somatic, and endocrine reflexes with a resultant potential decrease in perioperative morbidity.[11] Despite advances in treatment of postoperative pain, many patients still suffer from pain after surgery, probably due to difficulties in balancing postoperative analgesia with acceptable side effects.

In this prospective randomized controlled trial, evidence was provided that patients who received intrathecal neostigmine 50 g or MgSO4 50 mg with spinal bupivacaine had reduced postoperative pain score and analgesic requirement after major lower abdominal surgery.

In the present study the mean onset of sensory blockade in Group C was 7.2566 ± 0.5132 minutes, Group N was 7.0466 ± 0.6535 minutes and in Group M was 7.43 ± 0.5977, statistically not significant in between the three groups (P= 0.1063 i.e P >0.05). The mean onset of motor blockade in Group C was 3.78667 ± 0.4718 minutes, Group N was 3.97 ± 0.4137 minutes and in Group M was 3.72 ± 0.431 (P=0.0798). The mean time for onset of motor bock was found to be statistically insignificant in all the groups.

The study done by Joshi-Khadke,[12] et al, Khalili et al[13], Saini-Sethi, et al.[14] found no significant difference in duration of sensory block and motor block between the neostigmine and MgSO4 as adjuvants with bupivacaine heavy which is similar to the present study.

In the present study no patients required additional analgesic intra-operatively. The mean value of duration of Analgesia in Group C was 195.8 ± 9.886 minutes, in Group N it was 265.86 ± 47.606 minutes and in Group M it was 294 ± 11.73 minutes, On statistical comparison of the P value using ANOVA test, was found 0.0001 which is nonsignificant in all three groups i.e. P value <0.05.
The study done by Joshi-Khadke, et al[12] found that duration of analgesia was more prolonged in the neostigmine group than in MgSO4 group when compared to saline group which does not correspond with our study. In our study, we found that MgSO4 group has the longest duration of analgesia followed by neostigmine, though the results are non significant.

Difference in pH, baricity of the solution and dose of the drug might have contributed to this variable response.

The mean value of two segment regression time of sensory block in Group C was 97.72 ± 1.958 minutes, in Group N it was 95.46 ± 2.432 minutes and in Group M it was 98.32 ± 1.27 minutes. On statistical comparison the P value using ANOVA was found 0.001 which was significant in all groups i.e. P value <0.05.

The study done by Joshi-Khadke,[12] et al, Khalili et al[13], Saini-Sethi, et al.[14] found a similar observation in their studies.

In the present study, the mean value of duration of Sensory block in Group C was 166.43 ± 27.027 minutes, in Group N, it was 238.86 ± 49.7 minutes and in Group M, it was 267.14 ± 10.095 minutes. The difference was statistically significant in between the three groups (P=0.001). The mean value of duration of motor block in Group C was 149.26 ± 18.554 minutes, in Group N, it was 198.53 ± 34.926 minutes and in Group M, it was 224.2 ± 15.99 minutes. The difference was statistically significant in between the three groups (P=0.0001). The duration of sensory and motor block was longer for MgSO4 group in comparison to neostigmine and control groups.

The study done by Joshi-Khadke,[12] et al, Khalili et al[13], Saini-Sethi, et al.[14] found a similar observation in their studies.

In the present study VAS score at rest for pain was measured at 1st, 2nd, 3rd, 4th, 5th, 6th, 8th and 12th hrs. It was observed that VAS score for MgSO4 group was more than neostigmine Group Cnd control Group and the difference was found to be statistically significant.

Joshi-Khadke, et al[12] in their study found that patients receiving intrathecal MgSO4 requested rescue analgesia post operatively earlier than neostigmine group even though the duration of analgesia was extended in all three groups. The time to first analgesic demand was longest with neostigmine (5.1 h) followed by MgSO4 (4.2 h) and saline control (3.8 h). The results are consistent with our study.

Hypotension may occur due to the decrease in systemic efferent's activity after spinal anesthesia. Initially after spinal anaesthesia there decrease in blood pressure but neither of them caused hypotension, the decrease in blood pressure is maximum at around 25 to 30 minutes.

In the present study, there were no any incidences of hypotension or bradycardia. There was initial decrease in SBP, DBP and MAP but was not statistically significant between the three groups and the fall in SBP, DBP and MAP is more for neostigmine in comparison to MgSO4 Group Nut was not significant.

Joshi-Khadke, et al[12] found that there is no significant changes in haemodynamic parameters and intrathecal neostigmine in given dose provides some protection against SA-induced hypotension whereas MgSO4 protects against bradycardia of SA which is consistent with our study.

CONCLUSION

Based on our clinical comparative study, we can conclude that upon the addition of 50 g neostigmine methylsulfate and 50 mg MgSO4 with 0.5% hyperbaric bupivacaine intrathecally for spinal anaesthesia in patients undergoing lower abdominal and lower limb surgeries, there was no significant difference in onset of sensory block and motor block in all the groups. The duration of sensory block, motor block and duration of post operative analgesia was best in MgSO4 group in comparison to neostigmine group and control group. Both the drugs prolong the duration of analgesia on giving intrathecally along with bupivacaine heavy. So, these drugs can be used to prolong duration of analgesia in lower abdomen and lower limb surgeries without having any significant side effect. But further study is necessary to find out the optimum dose of the drugs which can be used for intra operative as well as post operative analgesia without any significant side effect.

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Nil.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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