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Original Article

Anaesthesia Section

Comparative Efficacy of Two Different Dosages of Intrathecal Magnesium Sulphate Supplementation in Subarachnoid Block

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ABSTRACT

Background: Spinal anaesthesia is the primary anaesthetic technique for many types of surgeries. Adjuncts to the local anaesthetics (LA) used in spinal anaesthesia can exhibit undesirable side-effects like respiratory depression, urinary retention, pruritis, haemodynamic instability and nausea and vomiting, limiting their use. Magnesium when used in therapeutic doses avoids all of these side-effects.

Materials and Methods: We conducted a randomized double blind study on 90 patients, 30 in each group, scheduled for orthopaedic lower limb surgery under subarachnoid block. Group I: received bupivacaine (0.5%), 12.5 mg + 0.5 ml of preservative free 0.9% normal saline, Group II received bupivacaine (0.5%), 12.5 mg + 0.2 ml (50 mg) of preservative free 25 % magnesium sulphate + 0.3 ml of preservative free 0.9% normal saline Group III: received bupivacaine (0.5%) 12.5 mg + 0.3 ml (75 mg) of 25 % magnesium sulphate + 0.2 ml of preservative free 0.9% normal saline for subarachnoid block. The onset and duration of sensory block, the highest dermatomal level of sensory block, motor block, time to complete motor block recovery and duration of spinal anaesthesia were recorded.

Statistical Analysis: ANOVA was applied to determine the significance of difference between different groups. If p-value was significant then Turkey's Post Hoc Multicomparison test was applied. Values of $p<0.05$ were considered to be statistically significant.

Results: The time of maximum sensory block, time of onset of motor block, duration of sensory block, duration of motor block and time of analgesia request were prolonged in patients given magnesium 50mg and 75mg along with local anaesthetic intrathecally.

Conclusion: N-methyl-D-aspartate (NMDA) receptor antagonist, magnesium when administered intrathecally along with local anaesthetics prolongs the duration of spinal analgesia without adverse effects.

Keywords: Anaesthesia duration, Local anaesthetic, Magnesium, Opioid, Spinal

INTRODUCTION

Regional anaesthesia is a safe, inexpensive technique, widely used for lower limb orthopaedic surgery due to the advantage of prolonged post-operative pain relief. Combination with adjuncts [1-5] like epinephrine, clonidine, neostigmine, opioids, midazolam and magnesium [6-19] have been used to prolong analgesia and reduce the incidence of adverse events. These spinal adjuvants allow the use of lower dose of local anaesthetic agents, prolong and intensify the subarachnoid block and offer hemodynamic stability. Opioids such as fentanyl are commonly used as additive to local anaesthetics to prolong the duration and intensify the effects of subarachnoid block. However significant side effects of opioids such as pruritis, urinary retention, respiratory depression, hemodynamic instability and occasionally severe nausea and vomiting may limit their use. Newer methods of prolonging the duration of subarachnoid block and reducing post- operative analgesic requirements are of special interest in major surgical procedures.

One of the mechanisms implicated in the persistence of post-operative pain is central sensitization, which is an activity-dependent increase in the excitability of spinal neurons . Central sensitization has been shown to depend on the activation of dorsal horn*N*-methyl-D aspartate (NMDA) receptors by excitatory amino acid transmitters such as aspartate and glutamate. NMDA receptor antagonists prevent central sensitization induced by peripheral nociceptive stimuli by blocking dorsal horn NMDA receptor activation. Magnesium (Mg^{2+}) is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist that blocks ion channels in a voltage dependent fashion. Koining reported that intravenous magnesium administration led to significant reduction in fentanyl consumption in peri and post-operative periods. Studies have evaluated use of magnesium intrathecally and shown to prolong the action of subarachnoid anaesthesia [6-19]. However, most of these studies used an opioid along with magnesium, which could have contributed to the prolongation of blockade after subarachnoid block [6-13], Magnesium alone with LA in a dose of 50 mg and maximum upto 100 mg has been used in a few studies [14-19]. Although the results of adding $MgSO_4$ 50 mg to IT bupivacaine are conflicting, the effect of increasing the dose of additional $MgSO_4$ has not been fully investigated. We used a dose of about 0.7mg/kg (50 mg) to ≤ 1mg/kg (75 mg) of intrathecal magnesium and found similar results. The primary outcome was the duration of spinal anaesthesia, beginning of sensory and motor block, time to maximal sensory block, and duration of sensory and motor block. The secondary outcomes included hemodynamic variations and post-operative analgesic requirements .

MATERIALS AND METHODS

We conducted a randomized double blind study on 90 patients of either sex, belonging to ASA physical status I and II scheduled for orthopaedic lower limb surgery under subarachnoid block. A written informed consent was taken from all the patients. The patients were allotted to either of the three study groups of 30 patients each as per random number list. The patients with history of significant co-existing diseases, morbid obesity, contraindication or refusal for

subarachnoid block, allergy to any of the drugs and neuropathies were excluded from the study. A thorough pre-anaesthetic check up was conducted a day prior to surgery. The pre-operative anaesthesia check up, included instructions about visual analogue scale (VAS) [20] (mark 0 = no pain, 10 = worst pain imaginable). All routine investigations were done prior to surgery.

All the patients were kept nil per oral for at least six hours prior to surgery and given pre-medication with Tab Diazepam 10 mg and Tab Ranitidine 150 mg a night prior and on the morning of surgery. After shifting the patient to the operation theatre, baseline parameters like Electrocardiography (ECG), Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Respiratory rate (RR), Peripheral Oxygen Saturation (SpO_2) were recorded by the candidate who was blinded to the adjuvant drug used. The drug code to be given was sealed in envelopes numbered 1-90 which were opened by the designated consultant of the area just before the administration of anaesthesia. These solutions were prepared in a 5 ml syringe by an anaesthesiologist and handed over to the candidate for administration. The various treatment groups were as under:

Group I: Received bupivacaine (0.5%), 12.5 mg + 0.5 ml of preser vative free 0.9% normal saline.

Group II: Received bupivacaine (0.5%), 12.5 mg + 0.2 ml (50 mg) of preservative free 25% magnesium sulphate + 0.3 ml of preservative free 0.9% normal saline.

Group III: Received bupivacaine (0.5%) 12.5 mg + 0.3 ml (75 mg) of 25% magnesium sulphate + 0.2 ml of preservative free 0.9% normal saline for subarachnoid block.

After achieving an intravenous access and preloading with 10ml/kg of lactated ringer's solution, all patients were administered subarachnoid block under all aseptic precautions in the sitting position using a 26-guage Quincke's spinal needle at the L_{2-3} or L_{3-4} vertebral level. With the needle orifice cephalad and after confirmation of free flow of CSF, the pre mixed coded solution was injected through the spinal needle.

The onset and duration of sensory block, highest dermatomal level of sensory block, motor block, time to complete motor block recovery and duration of spinal anaesthesia were recorded.

The onset of sensory block was defined as time between injection of the anaesthetic and the absence of pain at (T_{8-9}) dermatome, assessed by pinprick. The highest level of sensory block was evaluated by pinprick at midclavicular line anteriorly every 5 minutes (mins) for 20 mins after injection, thereafter every 15 mins. The duration of sensory block was defined as time of regression of two segments in the maximum block height, evaluated by pinprick. Motor block onset was assessed by modified Bromage score [21]. Time for motor block onset was assumed when modified Bromage score became three. Complete motor block recovery was assumed when modified Bromage score was zero. The duration of spinal anaesthesia was defined as the period from spinal injection to the first occasion when the patient complained of pain in the post-operative period.

Surgery was allowed to commence on achieving adequate sensory block height (T_{8-9}). Sensory block was recorded 5 mins before injection, 5, 10, 15 and 20 mins after injection and subsequently every 15 mins. Motor block was recorded till the modified Bromage score was three. SBP, DBP, HR, RR and SpO_2 were recorded 5 mins before injection, 5, 10, 15, 20 and 25 mins after injection and subsequently every 15 mins. Pain scores using VAS were recorded 5 mins before injection, after the start of surgery and subsequently every 15 mins till the surgery was commenced and thereafter VAS was assessed in the post-operative period.

If SBP was > 20% below baseline or 90 mmHg, intravenous (i.v.) ephedrine, 10 mg, was given repeatedly [22]. If HR was < 50 beats/min, 0.6 mg of atropine sulphate was administered intravenously. The incidence of hypotension (mean arterial pressure, < 20% of baseline), bradycardia (HR < 50 beats/min), hypoxemia and excessive sedation, pruritis, dizziness, nausea and vomiting were recorded. At the completion of surgery all haemodynamic parameters (HR, SBP, DBP, RR and SpO_2), sensory, motor block and VAS score were recorded and then the patient was shifted to recovery room. Immediately after shifting the patient to post-operative recovery room HR, SBP, DBP, RR and SpO_2 were recorded every 5 mins for first 30 mins and then half hourly till fourth hour and then every four hours till completion of 24 hours. Motor block recovery (modified Bromage score of zero) and sensory block regression were assessed till 3 hours every 15 mins after completion of surgery. All observations were recorded by an anaesthesiologist who was blinded to the group allocation of the patient.

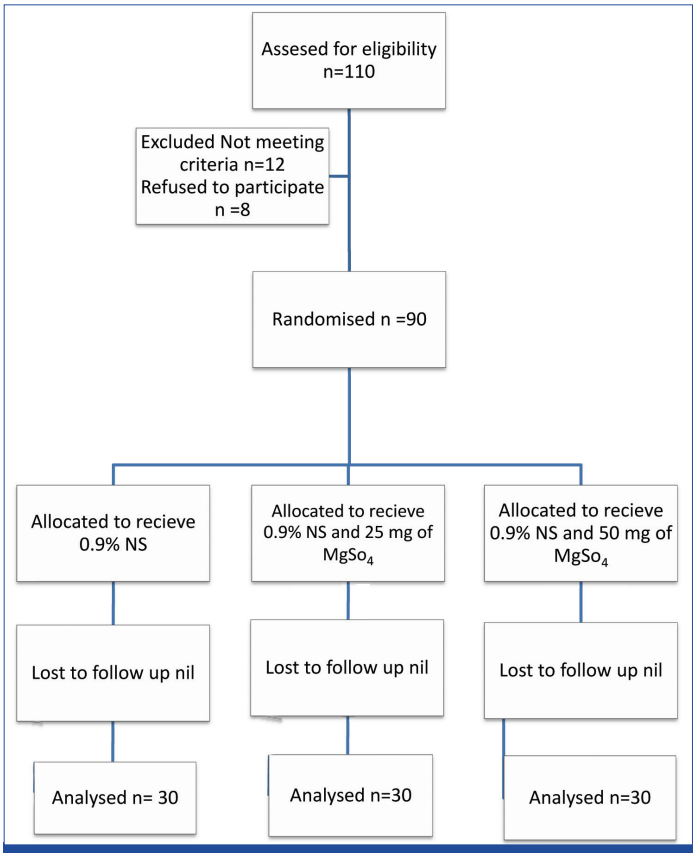
Quality of post-operative analgesia was assessed using VAS and recording was done at 0, ½, 1, 1½, 2, 3, 4, 8, 12, 18 and 24 hours post-operatively. Any patient showing VAS more than or equal to 3 was administered a supplemental dose of an analgesic with Inj. Tramadol 1mg/kg intravenously and was quantified and documented in all the groups. Patients were discharged from the recovery room when the motor block had completely resolved.

STATISTICAL ANALYSIS

After completion of the study, observations obtained were tabulated and analyzed. To evaluate the clinical efficacy of the treatment given the blind was opened at the end of the study. Student's t-test was used to compare different groups amongst themselves and ANOVA for repetitive observations. For determining the significance of difference between different groups, ANOVA was applied. Turkey's Post-Hoc Multicomparison test was applied if p-value was significant to see the significance between each pair of groups. Chi-square test was applied for sex comparison. Values of $p<0.05$ were considered to be statistically significant.

RESULTS

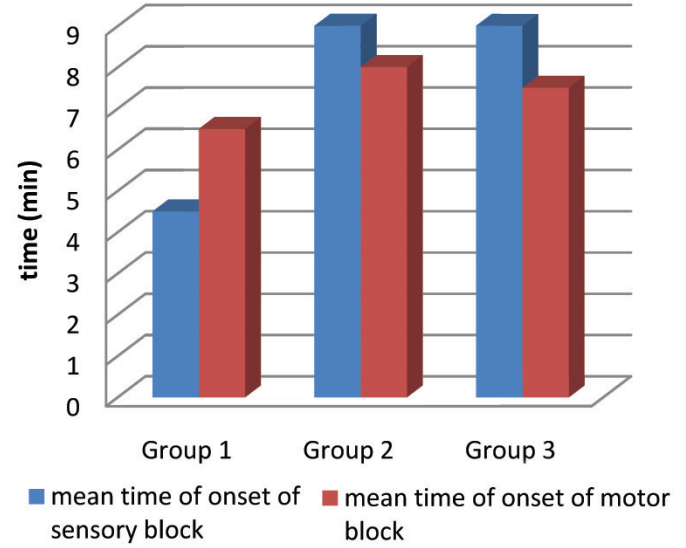
The demographic data of the three groups were comparable [Table/Fig-1,2]. There was no significant difference in the duration of



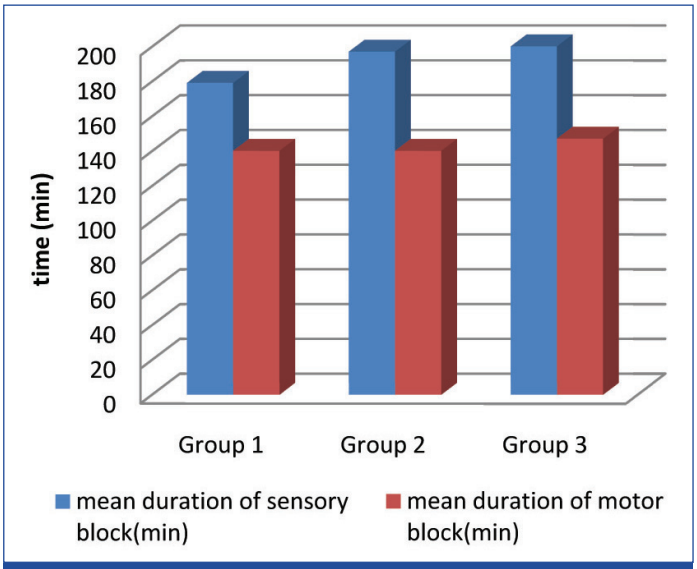
[Table/Fig-1]: Consort diagram

Group	Age	Gender M/F (%)	Height	Weight	ASA I/II (%)	Mean duration of surgery
I	43.20	73.33/26.67	165.67	63.67	60/40	65.83
II	36.40	70.0/30.0	166.00	64.30	54/46	76.00
III	43.10	90.0/10.0	166.75	64.77	50/50	75.67
p-value	0.37841	0.08521	0.773	0.918	>0.05	

[Table/Fig-2]: Demographic data



[Table/Fig-3]: Comparison of mean time of onset of motor and sensory blockade



[Table/Fig-4]: Comparison of mean time of duration of motor and sensory blockade

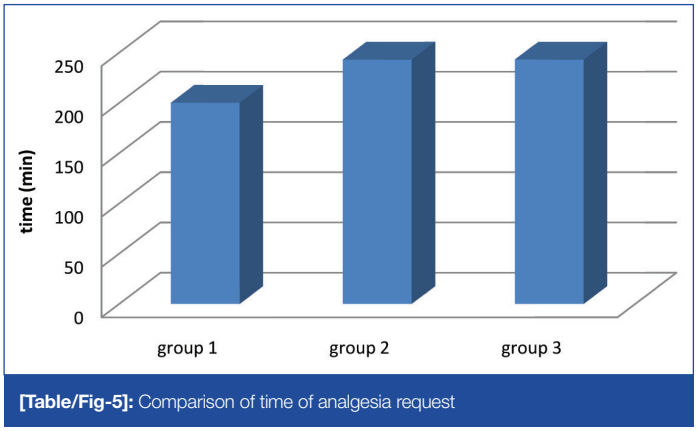
surgery between the groups. The time of onset of sensory Block (TOSB) was significantly ($p<0.05$) and the time of onset of motor block (TOMB)was delayed in Group II and Group III as compared to Group I as shown in [Table/Fig-3].

The duration of sensory block (DOSB) and duration of motor block (DOMB) were significantly prolonged in Group II and Group III as shown in [Table/Fig-4].

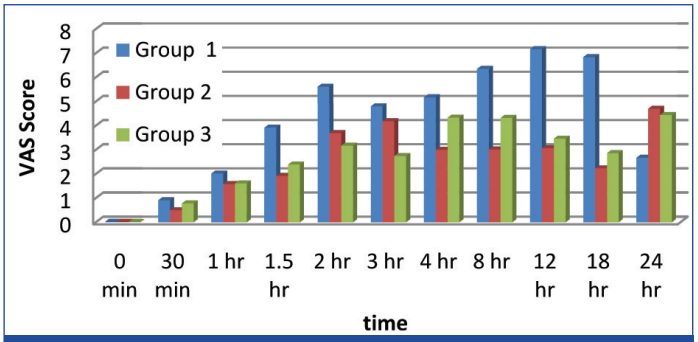
Time of analgesia request (TOAR) was significantly later in Group II and Group III as compared to Group I. The total dose of rescue analgesic was also significantly less in Group II and Group III as shown in [Table/Fig-5].

However there was no difference among Group II and Group III. Visual analogue scale in the pre-operative was comparable in the three groups and was zero in all patients in the intra-operative period. Post-operatively it was significantly different with Group I showing higher VAS at all time intervals compared to Group II and Group III as shown in [Table/Fig-6].

On comparing the intra-operative and post-operative heart rates and mean blood pressure there was no significant difference in the three groups [Table/Fig-7]. No patient showed hypotension or bradycardia. There was no difference in the intra-operative and post-operative respiratory rates and oxygen saturation.



[Table/Fig-5]: Comparison of time of analgesia request



[Table/Fig-6]: Comparison of VAS

DISCUSSION

In our study using two different doses of intrathecal magnesium we found that the time of the of onset of the sensory block and time of onset of the motor block was significantly ($p<0.05$) longer and the duration of sensory and motor block was significantly prolonged in Group II and Group III as compared to Group I. Time of analgesia request was significantly delayed in Group II and Group III. However there was no clinically significant difference in the haemodynamic parameters and adverse effects .

Noxious stimulation leads to the release of glutamate and aspartate neurotransmitters, which bind to various subclasses of excitatory amino acid receptors, including the N-methy l D – aspartate (NMDA) receptor. Activation of NMDA receptors leads to calcium and

Group	HR	Mean NIBP	RR	SpO_2
I	78±8.75	94.69±11.29	18.13±1.48	98.37±1.40
II	82.63±9.66	98.49±7.49	18.00±1.29	98.43±1.59
III	78.07±9.59	94.24±8.63	18.40±1.43	98.57±0.97
p-value	0.090	0.171	0.533	0.843
Significance	NS	NS	NS	NS

[Table/Fig-7]: Pre-operative Cardiorespiratory variables

sodium influx into the cell, with an efflux of potassium and initiation of central sensitization and wind-up phenomenon [23,24]. NMDA receptor signalling is an important factor in determining the duration of acute pain and NMDA receptor antagonists are used in the prevention and treatment of pain. Ketamine, a better known NMDA antagonist, abolishes peripheral afferent noxious stimulation and also prevents the central sensitization of nociceptors. Magnesium, a non-competitive NMDA receptor antagonist blocks ion channels in a voltage – dependent fashion thereby preventing central sensitization from peripheral nociceptive stimulation leading to enhanced analgesia [25]. However, it has been reported that ketamine and magnesium inhibit the NMDA system differently [23].There are contradictory reports about the role of intravenous magnesium sulphate in reducing intra- and postoperative analgesic requirements [26] and even at high doses, is associated with limited passage across the blood-brain barrier. An inverse relationship has been demonstrated between the severity of pain with different painful medical and surgical conditions and the serum magnesium concentration [25]. Direct intrathecal administration of magnesium has been shown to prolong the action of subarachnoid anaesthesia in animal experiments [27] and in humans [6-19]. However magnesium sulphate is currently unlicensed for intrathecal use in the UK. It is likely that intrathecal magnesium sulphate potentiates spinal anaesthesia by a localized action on spinal nociceptive pathways and so the absence of central side-effects seen after systemic administration [9].

In recent years, administration of magnesium has been reported as an effective analgesic and as an adjunct to intrathecal opioid analgesia. Intrathecal magnesium was first used in humans in 1906 [28]. Lejuste [29] described the inadvertent intrathecal injection of 1000 mg of magnesium sulphate, producing a dense motor block followed by complete resolution within 90 min, with no neurological deficit at long-term follow up. Buvanendran et al., [6] in the first human study trial found that intrathecal magnesium 50 mg and fentanyl 25 µg, significantly prolonged the median duration of analgesia as compared with plain intrathecal fentanyl when given in laboring parturients. On addition of magnesium with opioids and local anaesthetics similar results were found by Ozalevli [13] in patients undergoing surgery of the lower extremeties, Khemakhem [8], Unlugenc [9], Malleeswaran [10] and Bidyut and Kumar [19] in patients undergoing cesarean section.

However studies using magnesium alone with local anaesthetics are limited [14-19]. Addition of 50 mg magnesium sulphate to lignocaine 5% (1.5 ml) showed a significant delay in the onset of both sensory and motor blockade, prolongation of the duration of spinal anesthesia [15]. Other studies using doses of 50 mg and 100 mg magnesium in addition to bupivacaine showed similar results. A comparison of 50, 75, or 100 mg magnesium sulphate with hyperbaric bupivacaine in patients undergoing the caesarean section was done and it was observed that 75 mg of this drug was enough to produce desired effects [17]. Increased frequency of intraoperative complications (hypotension, nausea, and vomiting) in group given 100 mg magnesium were observed. A systematic review of intrathecal magnesium given alone or in combination with LAs and opioids showed that intrathecal magnesium prolongs duration of spinal analgesia and decreases post-operative analgesic requirements, but delays onset and time to maximal sensory block [30].

Our results are comparable to these studies as we observed that the addition of 50 mg and 75 mg intrathecal magnesium without opioid to bupivacaine, prolonged the duration of the sensory block, decreased post-operative analgesic consumption, and significantly prolonged the onset of spinal anaesthesia in patients undergoing surgery of the lower limb.As found previously a dose of 75 mg is adequate to produce the desired effects [17] and reporting of hypotension and bradycardia , we decided to go in for a maximum of 75mg of magnesium.Increased dose may also carry the risk of respiratory depression [30].

The safety of magnesium in the central nervous system has been evaluated. Chanimov [31] showed that repeated intrathecal injections of magnesium sulphate in a rat model indicate a lack of neurotoxicity in histological examination.However, in a study done by Saeki et al., [32] the neurotoxicity of i.t. 0.3, 1, 2, or 3 mg/kg of $MgSO_4$ was examined in rabbits, and significant sensory dysfunction was observed in the 3 mg/kg group 7 days after administration.

CONCLUSION

In conclusion, non-competitive NMDA antagonist , magnesium when administered intrathecally prolongs the duration of spinal analgesia. There is reduction in opioid induced side-effects and decreased demands on post-operative monitoring. However further studies using larger sample size is needed to differentiate between the two doses of intrathecal magnesium with regard to analgesic efficacy.

The only limitation of the study is the reported risk of respiratory depression with increased doses, but none of our patients had any episode of respiratory depression [33]. We recommend that a dose of upto 75 mg can be used safely in the intrathecal space to prolong the sensory and motor blockade.

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