Comparison of Effect of Adding Intrathecal Magnesium Sulfate to Bupivacaine Alone and Bupivacaine-Fentanyl Combination during Lower Limb Orthopedic Surgery

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INTRODUCTION

Post-operative pain relief has two practical aims. The first one is the provision of subjective comfort which is desirable for humanitarian reasons. The second is inhibition of trauma induced nociceptive impulses to blunt autonomic and somatic reflex responses to pain and to enhance subsequent restoration of function by allowing the patient to breath, cough, and move more easily¹. Spinal anesthesia is a simple technique that provides a fast surgical block through the injection of small doses of local anesthesia solution in subarachnoid space. It provides excellent operating conditions for surgery below the umbilicus². Spinal anesthesia using bupivacaine heavy is one of the most frequently used techniques for lower limb and lower abdominal surgeries. In last few decades, many agents have been used along with bupivacaine intrathecally to prolong the intra- and post-operative analgesia, the opioid being the most common. Fentanyl is a synthetic primary mu opioid receptor agonist. It is a lipophilic

Abstract

Background: Spinal anesthesia is a simple technique that provides a fast surgical block. It has certain limitations such as limited duration of the blockade and post-operative analgesia.

Materials and Methods: This randomized study was conducted in 60 patients of the American Society of Anesthesiologists Classes I and II aged between 20 and 50 years scheduled for elective lower limb orthopedic surgery. Patients were randomly divided into three groups of 20 each. Group I patients received bupivacaine (0.5%) 2.5 ml with MgSO₄ (50%) 0.1 ml, Group II patients received bupivacaine (0.5%) 2.5 ml with fentanyl (50 mg/ml) 0.5 ml, whereas Group III patients received bupivacaine (0.5%) 2.5 ml with MgSO₄ (50%) 0.1 ml and fentanyl (50 mg/ml) 0.5 ml, to a total volume of 3.1 ml in each group. The parameters assessed were onset and duration of sensory block, time to reach the maximum height of the sensory block, duration of analgesia, and incidence of side effects.

Results: It was found that in Group I, there was a significant delay in the onset of sensory block and time to reach maximum sensory block level when compared with Groups II and III. While the duration of sensory and motor block was significantly higher in Group III than Groups I and II. The moreover, duration of analgesia was prolonged when compared with Group II. In addition of magnesium sulfate provide, a more stable hemodynamic profile and causes less side effects.

Conclusion: The addition of 50 mg magnesium sulfate as adjuvant to intrathecal bupivacaine significantly prolongs duration of analgesia with a lesser side effect. It is suggested that magnesium may be a useful adjuvant to opioids for spinal anesthesia.

Key words: Anesthesia, Bupivacaine, Fentanyl, Magnesium sulfate, Post-operative analgesia
opioid with rapid onset of action following intrathecal administration which provide better intraoperative analgesia for the management of early post-operative pain and do not cause delayed respiratory depression. The multimodal approach to the management of perioperative pain has become routine both to improve efficacy and to minimize the side effects of opioids. Magnesium (Mg) has been one of the agents investigated for this purpose as it is known to inhibit calcium entry into cells and to exhibit non-competitive blockade of the N-methyl-D-aspartate (NMDA) receptor. It does not appear that magnesium has any primary analgesic effect in its own right, but it does offer secondary analgesic effects that may enhance the action of other analgesic agents. The purpose of this study is to investigate and compare the effect of magnesium sulfate in spinal anesthesia and post-operative pain relief with bupivacaine alone and with the bupivacaine-fentanyl combination in lower limb orthopedic surgeries.

MATERIALS AND METHODS

A total of 60 patients were enrolled for the study after the approval from Institutional Ethics Committee. The design of the study was randomized, double-blinded in patients who have undergone lower limb orthopedic procedures and fulfilling the criteria for regional anesthesia. A detailed history, thorough physical examination, routine investigation like complete blood count, blood sugar, renal profile, serum electrolytes, and any special investigation if required was done for the study. An informed written consent was taken from all the patients. Obviously, the patients who had coagulopathy, sepsis at the site of intrathecal injection, major organ pathology like heart disorder, hepatic, and renal disorder were excluded from the study. The patients were randomly divided into three groups of 20 each. The three groups were named as Groups I, II, and III. Group I patients received injection bupivacaine (0.5%) 2.5 ml with injection MgSO₄ (50%) 0.1 ml, Group II patients received injection bupivacaine (0.5%) 2.5 ml with injection fentanyl (50 mcg/ml) 0.5 ml, whereas Group III patients received injection bupivacaine (0.5%) 2.5 ml with injection MgSO₄ (50%) 0.1 ml and injection fentanyl (50 mcg/ml) 0.5 ml. The appropriate volume of normal saline was added to each study solution so as to make the injectate volume comparable. Material required for this is spinal trolley with 25 G spinal needle, 5 ml disposable syringe, injection bupivacaine (0.5%), injection magnesium sulfate (50%), injection fentanyl (50 mcg/ml), tuberculin syringe, normal saline, emergency drugs/intubation kit and resuscitation kit. After we received the patients in the operation room, a careful pre-operative examination was done and monitors were attached including non-invasive blood pressure, pulse oximetry and electrocardiogram. An intravenous line was secured using an 18 G cannula on the right forearm vein. The patients were preloaded with ringer lactate solution 15 ml/kg over 20 min. The patient received a spinal injection in sitting position using the study solution. Intraoperative episodes of hypotension (define as ≥30% fall in mean blood pressure [MBP]) were treated with intravenous 6 mg ephedrine injection. Intraoperative episodes of bradycardia (defined as pulse rate <60 bpm) were treated with intravenous injection of 0.3 mg atropine. Various parameters were then assessed and recorded on a prescribed proforma like onset of sensory block (time elapsed from the end of study solution to absence of pinprick sensation at T10 dermatome), maximum height achieved of sensory block, time to reach the maximum height of sensory block (time elapsed from the end of injection to attain maximum height [level] of sensory block), duration of sensory block (time elapsed from the end of injection to regression of sensory block by two dermatomes), and duration of analgesia. Onset, height and duration of sensory block were assessed by pinprick method. The duration of analgesia was recorded as the time from intrathecal injection until the patients request for additional analgesia in post-operative period which was assessed by a visual analogue score of ≥4. The intensity of post-operative pain was evaluated using a visual analogue scale, one end (“0” point of VAS) of which shows no pain and other end (“10” point of VAS) shows worst possible pain. Demographic parameters, such as age and sex, were also recorded on a prescribed proforma. Intraoperative hemodynamic variables like pulse rate per min, systolic blood pressure, diastolic blood pressure, MBP were recorded preoperatively and at 10th min, 30th min, and 150th min. Though the mean surgery was around 115 min, which means that 150th min recording of hemodynamic variable was recorded in the post anesthesia recovery unit. Our study also entailed recording of various side effects like the incidence of nausea-vomiting, pruritus and shivering. Randomization of the subjects was done using standard random number table. The study was double-blinded in which both the patients and assessor of parameters were blinded for the type of injection used in the spinal anesthesia. All case report forms were checked for completeness and inappropriate or illogical responses. All the data pertaining to the demographic characteristic, sensory block, hemodynamic analysis. The forms were filled using Microsoft 2007 Excel worksheets. The databases were validated, and all inconsistencies and differences were resolved. Statistical analyses were performed using STATA 12 for Windows (StataCorp LP, Texas, USA). Categorical data are presented as frequency counts (percentage) and compared using the Chi-square or Fisher’s exact statistic as appropriate. Odds ratio and 95% confidence intervals were also presented for 2 × 2 contingency tables. Continuous data are presented as means (± standard deviation) and
compared using the $t$-test or analysis of variance as appropriate.

**RESULTS**

Table 1 shows age and sex distribution of the three groups. Among the three groups, the most patients were of male gender. However, there was no statistically difference the demographic parameters of age and sex.

Table 2 depicts the maximum level of sensory block achieve among the three groups. Maximum patient of Group II had the maximum sensory level block until $T_4$ dermatome. There was statistically difference observed among the groups especially between Groups I and II for the maximum level of sensory block observed at $T_4$ dermatomes.

Table 3 demonstrate the onset of sensory block in the study population. The mean onset time for the sensory block was observed to be 4.45, 1.62 and 3.30 min for Groups I, II and III, respectively, ($F = 70.60; P < 0.0001$).

Mean time to reach maximum sensory block level was 10.40, 5.65, and 9.55 min, respectively, for Groups I, II, and III. It was found that the mean difference between Groups I and II and Groups II and III were statistically highly significant ($P < 0.0001$), whereas the result was statistically significant ($P < 0.05$) between Groups I and III.

The duration of sensory block was 136, 180 and 232 min in Groups I, II and III, respectively. Which was statistically significant ($F = 160.53; P < 0.0001$).

The duration of analgesia was significantly higher in Group III. It was 164, 238 and 368 min in Groups I, II and III ($F = 786.0; P < 0.0001$).

The mean surgical time duration was 111.5, 113.1 and 117.9 min in the three groups, respectively. The data were comparable.

Table 4 shows the incidence of side effects among all the groups.

**DISCUSSION**

The intrathecal route is attractive, as it obviates the problems of systemic administration and it solves the problem of transport of the agent across the blood brain barrier. Various intrathecal adjuvants such as NMDA antagonists, clonidine, and neostigmine have been assessed as possibilities for improved pain relief without side effects.

Magnesium exerts its analgesic action as a non-competitive NMDA receptor antagonist, blocking ion channels in a voltage-dependent manner. In the dose range necessary for the effective enhancement of opiate-based analgesia, there is no evidence that magnesium is harmful to neuronal tissue. Indeed, it may offer some degree of protection against hypoxia and ischemia through

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$p < 0.05$ in significant

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<th>Table 3: Sensory block parameters</th>
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<td>Onset of sensory block (min)</td>
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<td>Duration of sensory block (min)</td>
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<td>Duration of analgesia (min)</td>
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<th>Table 4: Incidence of side effect</th>
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a combination of spinal cord vasodilatation, calcium antagonism and blockade of the NMDA channel. However, magnesium is ineffective as a primary analgesic and must be used in conjunction with opiates to provide a useful analgesic extension. The combination of magnesium and opiates appears to offer enhanced opioid analgesia, a reduction in the risk of secondary hyperalgesia and possibly a reduction in the risk of the development of post-operative chronic pain syndromes.

Previous studies have used the dose of 50 mg neuraxial magnesium sulfate either as intrathecal or epidural dose and reported an increase in duration of analgesia and found to be safe and effective. In contrast, very high doses of magnesium sulfate produce a transient toxic effect. Khalili et al., also demonstrated that the application of a larger dose (100 mg) could not produce any further desirable effects compared to 50 mg magnesium sulfate except prolonging the duration of sensory block with no effect on duration of spinal analgesia.

Since all the groups were demographically similar (P > 0.05 in all the comparisons), it can be presumed that the groups are comparable for the purpose of the study. No premedication was used in the study population, it can, therefore, be presumed that recording of parameters pertaining to sensory analgesia was consistently accurate. All the patients were preloaded to offset the effect of relative hypovolemia or hypotension.

In this study, we showed that magnesium 50 mg when added to bupivacaine-fentanyl combination for spinal anesthesia could provide prolonged post-operative analgesia without additional side effects in patients undergoing lower limb orthopedic surgery. Furthermore, it significantly delays the onset of the sensory block as well as time to reach maximum sensory block and also prolongs the duration of sensory blockade. Magnesium 50 mg alone when added to bupivacaine too leads to delay in onset of sensory block and prolongation of time to reach maximum sensory block but without prolongation of sensory block duration and duration of post-operative analgesia.

Onset of sensory block in the present study was defined as time taken for loss of pinprick sensation at T10. Mean time for onset of sensory block and time to reach maximum sensory level was significantly higher in Group I as compared to Groups II and III.

These results are consistent with studies of Ozalevli et al., who too observed a similar delay in onset of spinal anesthesia when magnesium is added to fentanyl and isobaric bupivacaine. Malleeswaran et al., also observe similar results in their study when they used a mixture of bupivacaine-fentanyl and magnesium intrathecally in patients with mild preeclampsia undergoing caesarean section. Arcioni et al., also observed that intrathecal and epidural magnesium sulfate potentiated and prolonged motor block. These findings are in agreement with various studies. The authors suggested that the difference in pH and baricity of the solution by addition of magnesium contributed to the delayed onset, which may also be the case in our study.

The mean duration of sensory was significantly higher in Group III than Groups I and II. These results are in corroboration with Malleeswaran et al., Unlugenc et al., who showed prolongation of the duration of sensory block in magnesium group.

Jabalameli and Pakzadmohadami used different doses of magnesium, i.e., 50, 75 and 100 mg with 0.5% bupivacaine in caesarean section and observed maximum duration of sensory block with 100 mg group. Khalili et al., observed prolongation of the duration of the sensory block with 100 mg intrathecal magnesium. Sayed and Fathy, showed the prolongation of onset as well as time to regression of sensory block was more with 100 mg of magnesium as compared to 50 mg.

The combination of fentanyl and magnesium sulfate is hyperbaric as compared with CSF and would limit cephalic spread. This explained the delay by the difference in pH and baricity of the solution containing magnesium.

The mean duration of analgesia was significantly higher in III than Groups I and II (P < 0.0001). In our study, duration of analgesia was taken as the period from spinal injection to the time of administration of first rescue analgesia for pain postoperatively when requested by the patient. Malleeswaran et al., found that the addition of intrathecal magnesium increased the duration of spinal anesthesia by 42 min. Dayioglu et al., also conclude that addition of magnesium sulfate to spinal anesthesia prolonged the time to first analgesic requirement. Khezier et al., demonstrated that the addition of MgSO₄ (50 mg) to 15 mg of spinal bupivacaine (0.5%) failed to prolong the time to first analgesic requirement, as seen with fentanyl and bupivacaine combination.

In Group I, where only magnesium is added to bupivacaine show minimum duration of analgesia in comparison to other groups. There are a few possible reasons why magnesium failed to prolong the time to the first analgesic requirement. First of all, it has been claimed that the effects of magnesium sulfate on the NMDA receptor complex are weaker than those of some other NMDA receptor antagonists. The second possible cause is that...
magnesium sulfate which most likely vasodilator around the injection site will eventually accelerate the systemic uptake of local anesthetic, thereby prolonging the onset time of block. Third, magnesium sulfate might activate bupivacaine hydroxylation by the cytochrome P450. Therefore, the addition of intrathecal magnesium sulfate to spinal bupivacaine may alter bupivacaine pharmacokinetics and cause a more rapid elimination of bupivacaine. Furthermore, magnesium sulfate is reported to have been successfully used to attenuate the bupivacaine-induced toxicity in the central nervous system and heart.

In the present study, there were no clinically significant changes in vital parameters. There was initial fall in MBP and heart rate from pre-operative value in patients of all three groups which was statistically but not clinically significant and easily corrected with administration of mephentermine, additional fluids or atropine for hypotension and bradycardia. This may be attributed to the absence of systemic vasodilator effects of spinal magnesium. Higher dose of magnesium (100 mg) might result in increasing some of the side effects (hypotension, nausea and vomiting).

In our study, the incidence of nausea and vomiting showed no significant difference among groups and this may be related to similar hemodynamic and absence of significant hypotension among groups.

Pruritus and shivering were observed only in patients of Group II. The incidence of post-anesthetic shivering in Group II was 15% as against none in rest of the two groups. Magnesium causes peripheral vasodilatation which probably improves the cutaneous circulation, thus decreasing the incidence of shivering.

CONCLUSION

To summarize, our results shows that addition of 50 mg magnesium sulfate in patients undergoing lower limb orthopedic surgery lead to prolonged duration of analgesia significantly without increasing the incidence of side effects. Furthermore, there was a significant delay in the onset of sensory block and prolongation of sensory block duration.

REFERENCES