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RESEARCH ARTICLE

TO EVALUATE THE EFFICACY OF INTRATHECAL BUPIVACAINE AND FENTANYL VERSUS BUPIVACAINE, FENTANYL AND MAGNESIUM SULPHATE IN SPINAL ANAESTHESIA FOR TRANSABDOMINAL HYSTERECTOMY

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ABSTRACT

Context: Intrathecal magnesium sulphate has been found to prolong the duration of analgesia in various surgical procedures like lower limb surgeries and as adjuncts to general anaesthesia for pain management.
Aims: To evaluate the efficacy and safety of bupivacaine. fentanyl and magnesium sulphate and to compare both the groups in terms of onset time for maximum sensory and motor blockage and duration of effective analgesia.
Settings and Design: Randomized double blind trial.
Methods and Material: Hundred patients were randomly allocated to receive intrathecally either 2.5 mL (12.5 mg) of hyperbaric 0.5% bupivacaine + 0.5 mL (25 mcg) of fentanyl 0.2 mL of normal saline (group A) or 2.5 mL (12.5 mg) of hyperbaric 0.5% bupivacaine + 0.5 mL (25 mcg) of fentanyl + 0.2 mL (100 mg) of 50% magnesium sulfate (group B).
Statistical analysis used: SPSS version 16.
Results: The mean onset of sensory and motor block was delayed in group B while duration of motor block was comparable in both groups. Duration of effective analgesia increased in group B however number of rescue analgesics required in both the groups remained statistically insignificant. Side effect profile was similar in both the groups except that shivering incidence decreased in group B.
Conclusion: Addition of 100mg magnesium sulfate intrathecally leads to increased duration of effective analgesia with delayed onset of sensory and motor blockade. It also reduces the incidence of shivering.

INTRODUCTION

The use of adjuvant drugs for regional anaesthesia is intended to prolong local anaesthetic analgesia and avoid their toxic doses. The action of the second drug added to local anaesthetic is directed towards decreasing the sensory input to CNS. Intrathecal magnesium sulphate could potentiate opioid spinal analgesia and avoid the potential side effect of the larger doses of intravenous magnesium sulphate that may be required to observe anti nociception modulation in humans. (2) The present study was designed to evaluate whether or not addition of intrathecal magnesium sulphate would enhance the analgesic efficacy of intrathecal bupivacaine and fentanyl in hysterectomy cases.

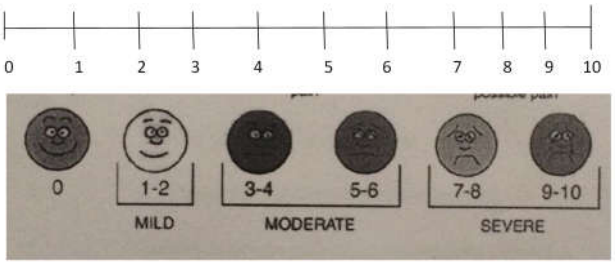
MATERIAL AND METHODS

After approval from the hospital ethical committee, a randomized double blind study was conducted on 100 patients of age group 18 to 60 years of ASA grade I and II undergoing transabdominal hysterectomy. Patients not giving consent or those having any abnormality-of spine, skin infection or local cellulitis, coagulation defect or patients with recent myocardial infarction, neurological disorders or unstable angina, significant aortic stenosis or other established contraindications of spinal anaesthesia were excluded from the study. After obtaining a written informed consent from the patients, they were randomly divided by computer generated numbers into 2 groups of 50 each.

Group A received 2.5 mL (12.5 mg) of hyperbaric 0.5% bupivacaine 4- 0.5 mL (25 mcg) of fentanyl + 0.2 mL of normal saline intrathecally whereas patients in group B received 2.5 mL (12.5 mg) of hyperbaric 0.5% bupivacaine 0.5 mL (25 mcg) of fentanyl -1- 0.2 ml (100 mg) of 50% magnesium sulfate intrathecally.

Patients were explained in detail about the procedure of the study during the pre anaesthetic visit. Patients were familiarized with the visual analogue scale (VAS) (0 — No pain, 10 - Worst pain) one day before surgery.

Visual Analogue Scale (VAS)[3]



Vas Score

0-NO PAIN
1-2 MILD PAIN
3-6 MODERATE PAIN
>7 SEVERE PAIN

They were advised overnight fasting and were given premedication with intramuscular 2mg midazolam and 25mg promethazine in the morning, half hour before surgery.

In the operation room, after attaching routine monitors (electrocardiogram, non invasive blood pressure, pulse oximeter), intravenous access was secured with 18 G cannula. All patients were preloaded with 15 mL/kg of Ringer's lactate solution. The patient was positioned in left lateral position and parts were cleaned and draped under all aseptic precautions.L3-L4 space was identified. The subarachnoid block was administered in the left lateral position at the L3-L4 interspace with a 25G Quincke spinal needle and 3.2 mL of the drug solution was injected intrathecally at rate of 0.2ml/sec as per the group allocation.

Patients were then placed in the supine position. Oxygen was provided via venturi mask at the rate of 4 L/min. All local anaesthetic solutions and adjuvant drugs were prepared by an anaesthesiologist not involved in the performance of spinal anaesthesia, patient care or data collection.

Sensory block was assessed by pinprick method. The level of sensory blockade was assessed every minute till blockade at T8 level was achieved. The onset of sensory blockade (defined as the time from the injection of intrathecal drugs to the absence of pain at the TS dermatome) was recorded. Onset of motor blockade was assessed at 5-minute intervals till 15 mins (i.e B5, BIO and B15) according to the Modified Bromage Scale[4]:

0---------- no motor block
1 ----------inability to flex the hip [hip blocked]
2---------- inability to flex the knee [hip and knee blocked]
3---------- inability to flex the ankle [hip, knee and ankle blocked].

Onset of motor block was assumed when Modified Bromage Score was 3. Grades of sedation during surgery were assessed by the Modified Ramsay's Sedation Scale:

1----------anxious and agitated or restless, or Both
2--------Cooperative, oriented, tranquil
3--------responding to commands only
4--------brisk response to light glabellar tap or loud noise
5---------sluggish response to light glabellar tap or loud noise
6--------no response

Blood pressure (systolic, diastolic and mean), heart rate, respiratory rate and peripheral oxygen saturation (sp02) were recorded 5 minutes before the intrathecal injection (baseline) and at 5, 10, 15, 20, 25 and 30 minutes after the injection, and subsequently every 15 minutes. Hypotension (defined as systolic blood pressure of less than 90 mmHg or less than 20% of baseline blood pressure) was treated with intravenous fluid initially (250 mL boluses repeated twice) and intravenous mephentermine 5 mg, if required. Bradycardia (defined as heart rate of less than 60) was treated with intravenous 0.6 mg atropine sulphate. At the completion of surgery all haemodynamic parameters (HR, SBP, DBP, RR and Sp02), sensory, motor block and VAS score were recorded and then the patient was shifted to recovery room. Motor block recovery (Modified Bromage Score of 0) was assessed every 15 mins after completion of surgery till Bromage Score 0 was achieved. Quality of post-operative analgesia was assessed using VAS and recording was done every 10 mins till 50 mins post-operatively after which rescue analgesic intramuscular diclofenac 75 mg was given whenever the patient complained pain (VAS score > 4) in the postoperative period. The duration of spinal anaesthesia was defined as the period from spinal injection to the first occasion when the patient complained of pain (VAS score >4) in the post-operative period. Patients were assessed for side-effects like nausea, vomiting, shivering, hypotension and bradycardia. All data was analysed statistically.

RESULTS

Descriptive statistics was done for all data and were reported in terms of mean values and percentages. Continuous variables were analysed with the unpaired t test. Categorical variables were analysed with the Chi-Square Test and Fisher Exact Test. Statistical significance was taken as $p < 0.05$. The data was analysed using SPSS version 16 and Microsoft Excel 2007.
Demographic characteristics of the patients were similar in the two groups (Table 1).

Table 1

	Group A	Group B	P Value
AGE(YRS)	43.08±6.57	43.26±7.17	0.8962
WEIGHT(KG)	65.84± 5.6	66.12± 9.86	0.86
ASA 1:2	37:13	38:12	0.82
DURATION OF SURGERY	117.84±11.18	120.38± 12.08	0.2778

However it was found that most common indication for hysterectomy in both the groups was fibroid uterus. The time of onset of sensory block in group A was 4.84 = 0.37 minutes and in group B was 7.88 ± 0.69 minutes (Table 2).

Table 2

Time of onset of sensory block	Group A	Group B
N	50	50
Mean	4.84	7.88
SD	0.37	0.69
P VALUE Unpaired T Test		0.0000

The number of patients having Modified Bromage Score of 3 was comparable in both the groups at 5 and 15 minutes. However, at 10 minutes, all patients in group A had Modified Bromage Score of 3 whereas only 56% patients in group B had similar score, thereby showing significantly delayed onset of

sensory and motor blockade after addition of magnesium sulphate to bupivacaine and fentanyl (Table 3)

Table 3

Modified Bromage Scale	Group A N=50	%	Group B N-50	%	P value chi squared test
5 min	18	36	17	34	0.8339
10 min	50	100	28	56	0.0017
15 min	50	100	50	100	>0.9999

The mean time to recovery of motor blockade was comparable in both the groups (Table 4).

Table 4

Recovery of motor blockade	Group A	Group B
N	50	50
Mean	221.34	221.18
SD	4.70	4.44
P VALUE Unpaired T Test		0.8615

The duration of effective analgesia was significantly longer in group B being 276.94 ± 4.48 minutes as compared to group A, 247.22 ± 1.99 minutes. (Table 5)

Table 5

Duration of Effective Analgesia	Group A	Group B
N	50	50
Mean	247.22	276.94
SD	1.99	4.48
P VALUE Unpaired T Test		0.0000

There was no difference between the groups in terms of mean postoperative rescue analgesic requirement. (Table 6)

Table 6

Duration of Rescue Analgesics Required	Group A	Group B
N	50	50
Mean	3.74	3.7
SD	0.443087	0.46291
P VALUE Unpaired T Test		0.659279

Intraoperatively, the mean VAS Score in group B at 5 minutes is higher than the score in group A. The mean VAS scores after 5 minutes till 150 minutes were comparable in the two groups. However, mean VAS scores at 165 and 180 minutes were lower in the magnesium sulfate containing group. Figure 1(a)

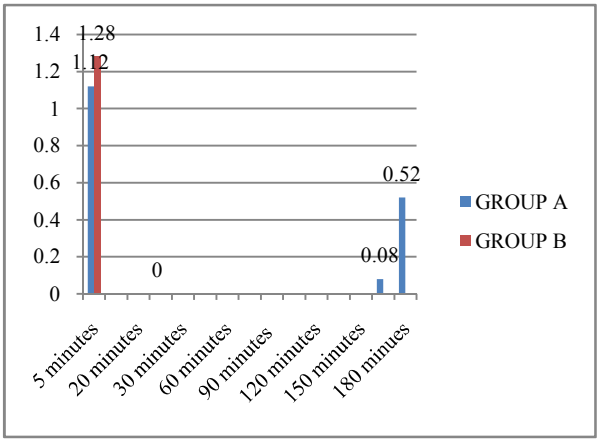
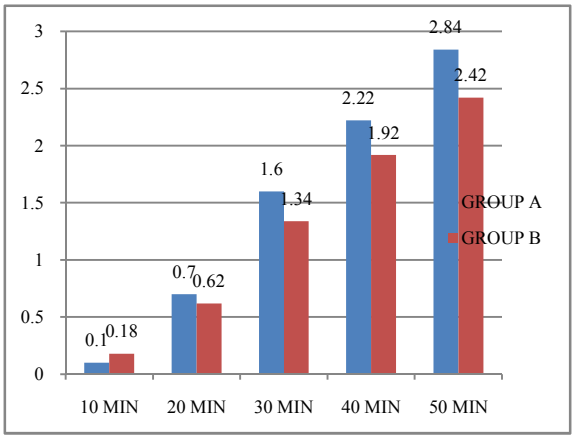


Figure 1A

Postoperative VAS scores after 20 minutes post operatively were lower in group B as compared to group A (Figure 2).

FIGURE 2

Postoperative Vas Score



groups intraoperatively. Regarding hemodynamic parameters, the intraoperative pulse rate 3), the systolic, diastolic and mean arterial blood pressures of both groups all times were comparable intraoperatively.

Side effects like pruritus, dry mouth. nausea. respiratory depression, bradycardia and hypotension were comparable in both the groups. However, the only statistically significant difference in the two groups was in the incidence of shivering which was recorded significantly lower in the magnesium sulfate containing group (p value being 0.0177). (Table 7)

Table 7

Side effects	Group A	%	Group B	%	P value Fischer Exact Test
Pruritis	12	24	7	14	0.2164
Dry mouth	2	4	2	4	0.9999
Nausea	8	16	6	12	0.5811
Vomiting	2	4	2	4	0.9999
Respiratory depression	0	0	0	0	NA
Shivering	16	32	6	12	0.0177
Bradycardia	0	0	0	0	NA
Hypotension	10	20	7	14	0.4412

DISCUSSION

The safety of intrathecal magnesium sulfate administration has been evaluated in animal studies. In a randomized, controlled canine study, intrathecal magnesium sulfate at a dose of 3 mg/kg was administered before aortic cross-clamping. The dogs were assessed after surgery for neurological deficits followed by histopathological examination of the spinal cord. None of the dogs that received intrathecal magnesium sulfate (45-60 mg) had neurological deficits (assessed by Tarlov's scale) or changes in cord histopathology. If the 45-60 mg intrathecal magnesium sulfate dose that is protective of the spinal cord in dogs were extrapolated by comparing the relative CSF volumes (approximately 12 mL versus 120 mL), this would represent a 450-650 mg dose in humans. Comparatively, the 100 mg intrathecal magnesium sulfate dose used in this study represents 20% of a dose shown to be nontoxic in dogs.

The time taken for the loss of sensation to pin prick at T8 level after intrathecal injection was considered as time of onset of sensory block. On comparing both the groups onset of sensory block was delayed in magnesium group. The delayed onset could be due to the solution of magnesium sulfate having a different pH and baricity which might explain our findings[6] Also, increase in metabolism of bupivacaine due to the activation of cytochrome P450 (CYP) by magnesium may be responsible for the delayed onset[1,8]. Our results are in

concordance with Nath MP *et al*[8], Jaiswal R *et al*[9] and Kathuria B *et al*[10] also reported similar delay in the onset of sensory blockade.

Both groups were comparable with regard to blood pressure (mean, systolic and diastolic), heart rate, respiratory rate, Sp02. Though i.v. magnesium is known to cause hypotension when used to treat eclampsia [12], the present study found no significant hemodynamic effect following the addition magnesium to our spinal solution. This may be attributed to the absence of systemic vasodilator effects of spinal magnesium.[11,12]',Our results were in accordance with studies conducted by Nath MP *et al* and Jaiswal R et at who also observed stable hemodynamics with addition of magnesium sulfate[8,9]., Katiyar *et al* observed magnesium provides better hemodynamic stability than fentanyl, with fewer side effects.[13]

The duration of effective analgesia was defined as the period from spinal injection to the first occasion when the patient complained of pain (VAS score >4) in the postoperative period. Increase in the duration of spinal anaesthesia was statistically significant thereby indicating addition of magnesium sulfate intrathecally prolongs the duration of spinal anaesthesia. Dayioglu *et al* recorded a significant prolongation in the time to first analgesic requirement following addition of intrathecal magnesium sulfate[14]. Malleeswaran *et al* recorded statistically significant increase in the duration of anaesthesia (229.3 mins in magnesium sulfate group vs 187.7 mins in control group) in the magnesium sulfate containing group[15], Nath MP *et al* and Jaiswal R *et al*so reported similar results. Our findings reinforce the role of magnesium sulfate, an NMDA antagonist, as an effective spinal adjuvant. However the results of present study are in contrast to the study by Unlugenc *et al* who reported a decrease in the duration of analgesic with the addition of magnesium sulfate.[16]

Rescue analgesic intramuscular diclofenac 75 mg was given whenever the patient complained pain. i.e VAS > 4. We observed that the mean post operative analgesic consumption was comparable between the two groups. This is in accordance with the study conducted by Dayioglu *et al*.[14], Malleeswaran *et al* however reported that diclofenac requirement for 24 h following surgery was significantly lower in the magnesium group 047.5 vs.I 82.5 mg. P=0.02)[15]

In our study there, was no statistical difference in the mean time to recovery of motor blockade in the two groups (221.34 min vs 221.18 min). Dayioglu *et al*[14], Nath MP *et al*[8], Jaiswal R *et al* [9] also reported similar results. Malleeswaran *et al*, however, reported a significantly prolonged recovery of motor blockade after addition of magnesium sulfate (200 vs. 175.3 min).[15] Similar results were obtained by Kathuria B et at[10], Arora B *et al*[17] who found significantly increased duration of motor blockade after addition of magnesium sulfate.

Both groups were comparable with regard to sedation throughout the intraoperative period. Although an increased incidence of drowsiness and confusion was reported in eclamptic parturients treated with magnesium[16]. Our study did not find an increase in sedation following addition of intrathecal magnesium. Nath MP et at and Arora B *et al* observed similar results.[8,17]

The various side effects following administration of spinal anaesthesia like pruritus, dry mouth, nausea, vomiting, respiratory depression, bradycardia and hypotension were comparable in both the groups. However, the incidence of shivering was significantly lower after addition of magnesium sulfate intrathecally. Yousef AA and Amr YM [18],Jaiswal R *et al*[9] also recorded significantly lower incidence of shivering. Also, the incidence of other side effects following administration of spinal anaesthesia was comparable in the all the groups.

This is in contrast to Nath *et al* [8]who didn't observe any decrease in shivering following intrathecal administration of magnesium sulfate to hyperbaric bupivacaine in hysterectomy cases. The drug not only exerts central effect but is also a mild muscle relaxant. Many postoperative patients have their core temperatures only slightly below the normal shivering threshold. General or neuraxial anaesthesia impairs thermoregulatory control consequently treatments that reduce the shivering threshold by a few tenths of a degree celsius may be sufficient to attenuate postoperative shivering. Thus magnesium can be an effective antishivering agent and yet reduce the shivering threshold by only a few tenths of degree celsius.[19]

CONCLUSION

Addition of 100mg magnesium sulfate to bupivacaine and fentanul for spinal anaesthesia leads to increased duration of effective analgesia with delayed onset of sensory and motor blockade. It also reduces the incidence of shivering following administration of subarachnoid block

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