Clinical Investigation

Comparison of different doses of magnesium sulphate and fentanyl as adjuvants to bupivacaine for infraumbilical surgeries under subarachnoid block

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ABSTRACT

Background and Aims: Spinal anaesthesia is used for many years for surgeries below the level of umbilicus. It has certain disadvantages such as limited duration of blockade and post-operative analgesia. This study was undertaken to evaluate the effects of additives fentanyl and magnesium sulphate along with bupivacaine during spinal anaesthesia for prolongation of analgesia and motor blockade. **Methods:** This randomised study was conducted in 120 patients of either sex of American Society of Anesthesiologists physical status I and II, posted for infraumbilical surgeries. Patients were randomly allocated to four groups and were given the following drugs intrathecally as per group distribution; group A - bupivacaine 15 mg (0.5% heavy) with fentanyl 25 μg, group B - bupivacaine 15 mg (0.5% heavy) with magnesium 100 mg, group C - bupivacaine 15 mg (0.5% heavy) with magnesium 50 mg and group D - bupivacaine 15 mg (0.5% heavy) with 0.5 ml normal saline. Parameters monitored were duration of analgesia along with haemodynamic parameters and side effects. Data were analysed using the Student's *t*-test for the continuous variables and two-tailed Fisher exact test or Chi-square test for categorical variables. **Results:** There was significant increase in duration of analgesia in group A (374.37 min) and B (328.13 min) as compared to group C (274.87 min) and D (246.03 min). In group A, all haemodynamic parameters decreased by more than 20%, compared to baseline parameters, which was clinically and statistically significant as compared to other groups. There was also increase in duration of motor blockade in groups A and B. **Conclusion:** Addition of magnesium sulphate at 100 mg dose or fentanyl 25 μg as adjuvants to intrathecal bupivacaine significantly prolongs the duration of analgesia, though in the given doses, magnesium provides better haemodynamic stability than fentanyl, with fewer side effects.

Key words: Bupivacaine, intrathecal fentanyl, intrathecal magnesium sulphate, spinal adjuvant

INTRODUCTION

Intrathecal adjuvants have gained popularity for prolonging the duration and quality of block; opioids (morphine, fentanyl and sufentanil) and other drugs such as dexmedetomidine, clonidine, magnesium, neostigmine, ketamine and midazolam are the various drugs used.

Fentanyl being highly lipid soluble diffuses into the spinal cord and binds to dorsal horn receptors rapidly when administered intrathecally. This produces a rapid onset of analgesia with minimal cephalic spread. Magnesium blocks calcium influx and non-competitively antagonises N-methyl-D-aspartate (NMDA) receptor channels. Limitations to parenteral

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route of magnesium for modulation of antinociception via NMDA channel antagonism include insufficient blood brain penetration to achieve effective cerebrospinal fluid (CSF) concentrations.[1,2]

Hence, in our study, we hypothesised that intrathecal magnesium potentiates duration of analgesia like fentanyl and also avoids the side effects posed by intrathecal fentanyl. We compared intrathecal magnesium in two different doses and fentanyl as spinal adjuvants for surgeries below the level of umbilicus.

METHODS

This prospective randomised study was conducted following Ethical Committee Approval of the hospital, from June 2011 to April 2013. A total of 120 patients scheduled for elective surgeries below the level of the umbilicus were selected for the study and randomly allocated into four groups. Patients of either sex of American Society of Anesthesiologists physical status grade I and II, between the ages of 18–60 years with surgery below the level of the umbilicus were included in the study. Anticipated duration of the surgery was <180 min. Patients with hepatorenal and cardiovascular diseases, contraindications to regional anaesthesia such as local infection, bleeding disorders, patients who had received opioid agonist/antagonist in the preceding 6 h were excluded from the study. Patients with allergy to opioid or who had already received magnesium sulphate by other route were also excluded from the study.

Thorough pre-anaesthetic check-up of all patients including all routine investigations were done. Tablet ranitidine 150 mg and alprazolam 0.25 mg were given as pre-medication 1 h before planned surgery. The procedure was explained to the patient and written informed consent was taken. After shifting the patient to operating room, baseline values of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and oxygen saturation were recorded. After securing intravenous (IV) access, all patients received an IV preload of 10 ml/kg lactated Ringers solution before the subarachnoid block. With aseptic technique, a 25 gauge Quincke needle was inserted intrathecally via the L3-L4/L4-L5 interspace by midline approach with the patient in sitting position. After a successful dural puncture, anaesthetic solution was injected. No additional analgesia was administered unless patient complained of pain.

Blinding was achieved through the use of equal amount of drugs (3.5 ml), while syringes used were labelled as A, B, C and D according to their content. Identical coded syringes, prepared by persons not involved in the study, were randomly handed over to the anaesthetists, who were unaware of the identities of the drug. Randomisation was done using closed envelope method. Four groups were labelled as follows: Group A - 15 mg bupivacaine (heavy) with 25 μg fentanyl, group B - 15 mg bupivacaine (heavy) with 100 mg magnesium (total volume - 3.5 ml. magnesium was taken in insulin syringe in both groups as per requirement and then diluted to 0.5 ml with sterile water) (magnesium sulphate used was preservative free), group C - 15 mg bupivacaine (0.5% heavy) with 50 mg magnesium and group D - 15 mg bupivacaine (0.5% heavy) with 0.5 ml of normal saline. Patients in whom more than two attempts and an approach other than midline was used, were excluded from the study. Patients were placed in supine position once the drug was administered. No tilt of the table was allowed till 20 min after the administration of the drug at which time the level of the blockade was noted as the "highest level of block achieved" (sensory level). Sensations were tested by pin prick method with 23 gauge needle and the quality of motor block was assessed using Bromage score, which was measured till 20 min of subarachnoid block after which surgery was started. Visual analogue pain scale (VAS) scores were explained to the patient pre-operatively and were recorded before the intrathecal injection and post-operatively up to 24 h. Rescue analgesia was given when VAS score was >3. Pruritus and somnolence were assessed before the intrathecal injection and at 5, 10, 15 and 30 min intervals till the end of the surgery. Duration of analgesia was recorded as the time from intrathecal injection to the time of first complain of pain, first request for analgesia, or a reported VAS >3.

The onset of motor blockade was assessed at 5 min interval till 20 min (M5, M10, M15 and M20). Somnolence was assessed as per sedation scale: 1 = fully awake, 2 = somnolent and responds to call, 3 = somnolent and responds to verbal stimulation and 4 = asleep and responds to only painful stimulation.

Systolic and diastolic blood pressures were recorded 5 min before (i.e., baseline parameters) and every 5 min for the first 20 min after the administration of subarachnoid block and thereafter every 5 min till the end of the surgery. Systolic blood pressure 20% below the baseline or <90 mmHg was treated

with IV bolus of lactated Ringer's solution or ephedrine 6 mg if required. Duration of analgesia was recorded as the time from intrathecal injection to the time of first complaint of pain, first request for analgesia, or VAS >3. Rescue analgesia consisted of injection tramadol 50 mg IV. Sample size was calculated using statistical software Epi Info 2000 (CDC Atlanta, USA). Considering the significant level of probability at 5% ($P < 0.05$) and assuming 35% difference in the duration of analgesia with intrathecal magnesium (100 mg) or intrathecal fentanyl as being clinically important, we calculated that 30 patients would be required in each group to achieve 80% power at the 5% significance level to detect a true difference among the two groups.

The data were analysed using SPSS version 20 (Neon Laboratories) and all means are expressed as mean ± standard deviation (SD). The comparisons among the groups were done using ANOVA followed by Bonferroni test for multiple comparisons. Appropriate univariate and bivariate analysis were carried out using the Student's *t*-test for the continuous variable (age) and two-tailed Fisher exact test or Chi-square test for categorical variables. The critical levels of significance of the results were considered at 0.05 levels that is, $P < 0.05$ was considered as statistically significant.

RESULTS

A total of 120 patients were included in the study with 30 in each group. Demographic parameters were comparable in all the groups.

All the patients in group D achieved a Bromage score of 3 in 10 min. All the patients in group B achieved the same score in 15 min. In group A and C, Bromage score 3 was achieved by all the patients in 20 min. In group A, all the haemodynamic parameters (HR, SBP, DBP) decreased by more than 20% when compared to baseline parameters. [Table 1]. In the other three groups (groups B,C and D), changes in all the parameters were within the clinically acceptable range of ± 20% from baseline [Table 1]. One patient in Group A and two in Group D had sensory blockade below T10 whereas 9 and 8 patients respectively in Groups B and C had block below T10 [Table 2].

The mean duration of analgesia in groups A, B, C and D was 374.30 min (SD ± 128.058), 328.13 min (SD ± 115.302), 274.87 min (SD ± 91.573), 246.03 min (SD ± 67.273), respectively which was statistically significant in group A and B [Table 3].

The mean duration for complete motor recovery was maximum in group A (291.93 min) followed by group B (228.10 min) and was least in

Table 1: Comparison of HR, SBP, DBP in the three groups

Timing	Groups	HR (beats/min)		SBP (mm of Hg)		DBP (mm of Hg)	
		Mean±SD	*P*	Mean±SD	*P*	Mean±SD	*P*
Baseline	Group A	88.67±17.83		128.93±16.84		81.40±12.28	
	Group B	87.40±9.16		132.60±17.95		84.93±8.25	
	Group C	96.27±13.70		130.87±11.52		80.97±9.92	
	Group D	88.97±14.56		133.80±13.09		85.33±7.57	
At 5 min	Group A	63.60±16.97	<0.001	97.17±12.42	<0.001	57.33±10.99	<0.001
	Group B	81.10±12.21	<0.05	121.30±10.86	<0.001	74.70±9.19	<0.001
	Group C	89.27±12.77	<0.05	118.70±14.71	<0.001	70.47±7.40	<0.001
	Group D	82.17±13.55	>0.05	122.03±10.17	<0.001	77.07±6.79	<0.001
At 10 min	Group A	62.20±16.02	<0.001	94.83±11.24	<0.001	56.77±10.42	<0.001
	Group B	78.77±10.71	<0.001	116.30±11.62	<0.001	73.30±8.55	<0.001
	Group C	85.20±11.54	<0.001	114.70±9.81	<0.001	73.03±7.05	<0.001
	Group D	81.33±15.65	>0.05	117.63±9.18	<0.001	76.87±8.17	<0.001
At 15 min	Group A	61.13±14.87	<0.001	93.20±10.03	<0.001	55.00±10.82	<0.001
	Group B	77.57±11.01	<0.001	115.17±12.13	<0.001	75.47±7.95	<0.001
	Group C	82.67±9.48	<0.001	114.07±9.96	<0.001	72.77±6.64	<0.001
	Group D	78.97±14.46	<0.01	117.20±8.67	<0.001	76.10±7.54	<0.001
At 20 min	Group A	60.17±14.32	<0.001	90.90±10.04	<0.001	54.37±9.82	<0.001
	Group B	76.70±11.71	<0.001	113.43±10.88	<0.001	73.93±7.63	<0.001
	Group C	81.80±10.77	<0.001	112.57±10.75	<0.001	72.00±7.15	<0.001
	Group D	77.90±13.62	<0.001	118.13±9.55	<0.001	74.77±6.42	<0.001

HR – Heart rate; SBP – Systolic blood pressure; DBP – Diastolic blood pressure

group D (211.93 min). The mean duration for complete motor recovery was more in group B (228.10 min) compared to group C (212.50 min) although it was statistically insignificant [Table 3].

Rescue analgesia was administered when VAS score was >3. Ten patients needed rescue analgesia in group A,11 in group B,15 in group C and 18 in group D. None of the patients had somnolence or pruritus in any group.

DISCUSSION

In the present study, it was observed that the motor conditions favourable for surgery (Bromage score 3) was achieved earliest in group D, in 10 min. With addition of magnesium, in groups B and C, the onset of motor blockade was delayed. Ozalevli *et al*. observed a similar delay when adding intrathecal magnesium to fentanyl and isobaric bupivacaine (we used hyperbaric bupivacaine in our study).[3] It could be because of difference in pH and baricity of the solution containing magnesium that contributed to the delayed onset. This was also reported in the study by Malleswaran *et al*.[4] and Arora *et al*.[5] in mild pre-eclampsia patients. Buvanendran *et al*.[6] measured the baricity of magnesium sulphate mixed with fentanyl using refractometry and found it to be slightly hypobaric with respect to CSF which is contradictory to their previous study in which they reported 100 mg of magnesium as hyperbaric in relation to CSF. Khezri *et al*.[7] also demonstrated delayed onset of analgesia. Also, the increase in metabolism of bupivacaine due to activation of cytochrome p450 by magnesium may be responsible for the delayed onset of spinal anaesthesia.[8,9] This may be the reason for lesser duration of analgesia compared to fentanyl as reported in other studies. Unlugenc *et al*. in their study on intrathecal magnesium showed that it does not affect the onset or maximal level of sensory blockade, implying that it has an effect solely at the spinal level.[10] In our study, maximum number of patients achieved the block up to T10 level. With magnesium, in group B, there was slower ascent of the drug, probably due to change in baricity of the drug.

Table 2: Level of block achieved after 20 min

Dermatomal level	Group A (%)	Group B (%)	Group C (%)	Group D (%)
T4	1 (3.3)	1 (3.3)	0 (0.0)	0 (0)
T6	2 (6.7)	0 (0.0)	0 (0.0)	4 (13.3)
T8	5 (16.7)	4 (13.3)	6 (20.0)	8 (26.7)
T9	2 (6.7)	2 (6.7)	2 (6.7)	2 (6.7)
T10	19 (63.3)	14 (46.7)	14 (46.7)	14 (46.7)
T11	1 (3.3)	7 (23.3)	7 (23.3)	0 (0)
T12	0 (0)	2 (6.7)	1 (3.3)	2 (6.7)
Total	30	30	30	30

Table 3: Comparison of mean duration of analgesia, complete recovery and rescue analgesic requirement

Group	Duration of analgesia (min)	Complete recovery (min)	Rescue analgesics (number)
Group A	374.30±128.058	291.93±89.011	10
Group B	328.13±115.302	228.10±96.180	11
Group C	274.87±91.573	212.50±49.505	15
Group D	246.03±67.273	211.93±43.924	18

With 100 mg of intrathecal magnesium (group B), we observed increased duration of analgesia (328.13 min) without increase in adverse effects as observed with intrathecal fentanyl group. This prolongation of analgesia is consistent with the experimental synergistic interaction between spinal local anaesthetic and NMDA antagonists, like magnesium, which causesantinociceptive effects via different mechanisms, hence the rationale for combining the two.[10] Group B patients had a reduced total consumption of tramadol in the first 24 h after surgery. Taken together, these results indicate that in order for total analgesic consumption to be reduced, higher doses of magnesium sulphate are required, similar to the dose used in the study by Arcioni *et al*.[11] Dayioglu *et al*. observed that with 50 mg of magnesium sulphate, the time to first analgesic requirement was prolonged but post-operative analgesic consumption was not reduced, which is in contrast to our study.[12] Duration of analgesia was prolonged in group B as well as in group A as compared to groups C and D. Duration of analgesia in group B was prolonged as compared to group C which is highly significant.

Although 100 mg magnesium sulphate reduced the post-operative analgesic requirement, there was no substantial difference between the magnesium sulphate groups (B and C) in the frequency and pattern of side effects. This study also explored the possibility that the addition of higher doses of magnesium sulphate could replace fentanyl, thereby avoiding opioid side effects, such as sedation, pruritus and respiratory depression. Analysis of intra-operative haemodynamics showed that the incidence of hypotension and bradycardia was more in fentanyl group as compared to magnesium groups. The haemodynamic variables were comparable between groups B and C, similar to the study by Nath *et al*.[2] This may be attributable to supraspinal action of fentanyl by intrathecal cephalic spread.[13]

The intrathecal dose of 100 mg magnesium sulphate that we used was comparable to that of the study by Arcioni *et al*.[11] and Khalili *et al*.[14] who found that larger doses decreased post-operative analgesic requirement without inducing adverse reactions.

The clinical trials performed to date have not reported any evidence of neurological sequel or other deleterious effects in humans. Further studies are needed to prove safety profile of larger doses of intrathecal magnesium because ours and other studies only investigated patients during their hospital stay and there was no long-term follow-up. Deleterious effects have been reported only in animal studies.[15-17] None of our patients had pruritus. None of the patients had somnolence >2 points in any group.

CONCLUSION

Addition of magnesium sulphate at 100 mg dose or fentanyl 25 μg as adjuvants to intrathecal bupivacaine significantly prolongs the duration of analgesia. At these doses, magnesium provides better haemodynamic stability than fentanyl, with fewer side effects.

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Conflicts of interest
There are no conflict of interest.

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