JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

AN EXPERIMENTAL STUDY COMPARING INTRATHECAL DEXMEDETOMIDINE WITH INTRATHECAL MAGNESIUM SULPHATE AS BUPIVACAINE ADJUVANTS FOR SPINAL ANAESTHESIA IN LOWER LIMB SURGERIES.

Dr Sarmistha, Dr Sandhya peethani

ABSTRACT

Background: No drug, used as adjuvant to spinal bupivacaine, has yet been identified that specifically inhibits nociception without its associated side-effects.

Aim: A Prospective randomized double-blind study was conducted to evaluate the onset and duration of sensory and motor block as well as perioperative analgesia and adverse effects of dexmedetomidine and magnesium sulphate given intrathecally with 0.5% hyperbaric bupivacaine for spinal anaesthesia.

Methods: Study was conducted in the department of anaesthesiology, Tirumala Hospitals, Vizianagaram. A total of 90 patients classified as American Society of Anesthesiologists status I and II scheduled for lower limb procedures were prospectively studied. Patients were randomly allocated to receive intrathecally either 3.2ml of 0.5% heavy Bupivacaine + 0.1ml (10 μg) dexmedetomidine (group D, n =30) or 3.2ml of 0.5% heavy Bupivacaine + 0.1ml (50mg) magnesium sulphate (group M, n =30) or 3.2ml of 0.5% heavy Bupivacaine + 0.1cc of Normal Saline (group C, n =30) as control. The onset time to reach peak sensory and motor level, the regression time for sensory and motor block, hemodynamic changes and side-effects were recorded.

Result: All the three groups were comparable demographically. Mean onset time of T10 sensory block in groups D, M and C were 2.77±0.68, 10.77±1.28 and 5.60±1.03 mins respectively (p=<0.001). Mean peak motor block in groups D, M and C were 4.97±0.999, 12.27±1.36 and 6.77±1.10 respectively (p=<0.001). The mean time for rescue analgesics in groups D, M and C were 312.6±39.7, 233±27.24 and 141.3±28.3 mins (p=<0.001). Though there was a significant reduction in blood pressure in group D, none of the cases in all groups showed MAP of <60 mm Hg and no cases had bradycardia.

Conclusion: Onset of anaesthesia was rapid and of prolonged duration in the dexmedetomidine group (D). However, in the magnesium sulphate group (M), although onset of block was delayed, the duration was significantly prolonged as compared with the control group (C), but to a lesser degree than in the dexmedetomidine group (D). The groups were similar with respect to hemodynamic variables and there were no significant side-effects in any of the groups.

Key words: Spinal anaesthesia, Dexmedetomidine, Magnesium sulphate, Normal saline.

INTRODUCTION

Spinal anaesthesia remains a popular technique for surgery to abdomen, pelvis and lower limbs. The advantages of spinal anaesthesia are ease of technique, patient remains pain free quiet a long time in the post operative period[14], reduced risk of deep venous thrombosis, avoidance of poly pharmacy in general anaesthesia and post operative complications of general anaesthesia are avoided.

Spinal block still remains the first choice in lower abdominal and lower limb surgeries because of its rapid onset, superior blockade, low risk of infection as from catheter in situ, less failure rates and cost-effectiveness, but has the drawbacks of shorter duration of block and lack of adequate postoperative analgesia. Adjuvants are the drugs added to Local anaesthetics (LA) to improve the analgesic intensity, to increase the duration of blockade, to achieve faster onset and to achieve acceptable analgesia with lower drug doses and reducing the risk of side effects. There are so many drugs tried as adjuvants. Commonly used adjuvants are Opioids like Fentanyl, Morphine, and alpha 2 agonists like Clonidine, Dexmedetomidine, Magnesium Sulphate, and

Neostigmine. Here, is an attempt to study the synergistic effect and safety between Dexmedetomidine and Bupivacaine 0.5% in spinal anaesthesia and comparing this with Magnesium with Bupivacaine 0.5%.

PATIENTS AND METHODS

A prospective, randomized, double blind controlled study was conducted in the department of anaesthesiology in collaboration with department of orthopaedics at a tertiary care hospital from June 2015 to April 2017 after obtaining the ethical committee clearance of our institution as well as informed written consent taken from the patients.

Inclusion criteria

- ASA I-II adult subjects
- Patients aged 25-75years of either sex
- Patients undergoing Elective lower limb surgery
- Patients who are willing to give informed consent to participate in the study

Exclusion criteria

Patients with-

- Allergy to study drugs
- Uncontrolled Hypertension
- Contraindications to spinal anaesthesia
- Heart disease
- Psychiatric illness

Methodology: Ninety patients, undergoing elective lower limb surgeries under spinal anaesthesia were recruited into the study. Using computer generated random numbers (Microsoft Excel) patients were allocated into three groups and the allocation was concealed. Each group (D, M and C groups) consisted of 30 patients.

Group D-received 3.2 ml of 0.5% heavy Bupivacaine + 0.1cc (10 mcg) of Dexmedetomidine.

Group M-received 3.2 ml of 0.5% heavy Bupivacaine + 0.1cc (50 mg) of preservative free Magnesium sulphate.

Group C- received 3.2 ml of 0.5% heavy Bupivacaine + 0.1cc of Normal saline.

Pre-anaesthetic evaluation was done on the evening before surgery. A detailed history was taken and the cardiovascular, respiratory and central nervous systems were examined in detail with necessary investigations. Pre-operative preparation was done.

The patients were given 3.2 ml of 0.5% heavy Bupivacaine by adding 0.1cc of 10 mcg Dexmedetomidine or 0.1cc (50 mg) of preservative free Magnesium sulphate or 0.1cc of Normal saline by an operator who was unaware of the content of the injected solution and was thus blinded to it.

Assessment of sensory block

Immediately after spinal injection, the level of sensory block was assessed by loss of prick sensation (using a 25G hypodermic needle) every minute till attainment of T10 sensory level and was recoreded as the time for onset of sensory block. Then, the assessment was continued every 2 minutes up to 20 mins and the level at 20 mins was taken as the peak sensory level. After 20 mins, the level was checked every15 mins till there was 2 segment regression. The level of sensory block at the end of surgery was recorded and thereafter observed every 15 minutes for the return of pin prick sensation in S1dermatome. Duration of sensory block was taken as the time from spinal injection to S1regression.

Assessment of motor block

Motor block was assessed using modified BROMAGE SCORE

- Grade 0: no motor block
- Grade 1: inability to flex the hip
- Grade 2: inability to flex the knees
- Grade 3: inability to flex the ankle

Assessment of motor block started immediately after intrathecal injection. It was tested every 2 mins till Bromage score1was reached and the point was taken as the onset of action. The degree of motor block after 20 mins was noted and this was taken as the peak motor block. The recovery and return of motor block to grade 0 was noted in the postoperative period every 15 mins. The time between spinal injection and the recovery to grade 0 was the duration of motor block.

Intra operative monitoring

The secondary outcome measures like the systolic and diastolic BP, Mean arterial pressure, pulse rate, respiratory rate, and oxygen saturation were monitored throughout the procedure. Blood pressure recorded every 5 mins till 30 min after institution of SAB, followed by every 15 mins upto 1 hr and thereafter every 30 mins upto 3 hrs and 2nd hourly upto 16 hours. Hypotension was defined as fall in BP>30% from baseline or MAP <60mm Hg. This was managed with inj. Mephentermine 6 mg i.v. increments. Bradycardia was defined as heart rate <60/min and that could be managed with inj. Atropine 0.6mg i.v. Respiratory depression was defined as RR<8/min, and or Spo2< 85%. All the necessary measures were taken to manage the situation if at all occurs. Level of sedation was assessed using Ramsay sedation scoring:

1- Anxious and agitated or restless, or both
2- Co-operative ,oriented, and calm
3- Responsive to commands only
4- Exhibiting brisk response to light glabellar tap or loud auditory stimulus
5- Exhibiting a sluggish response to light glabellar tap or loud auditory stimulus
6- Unresponsive

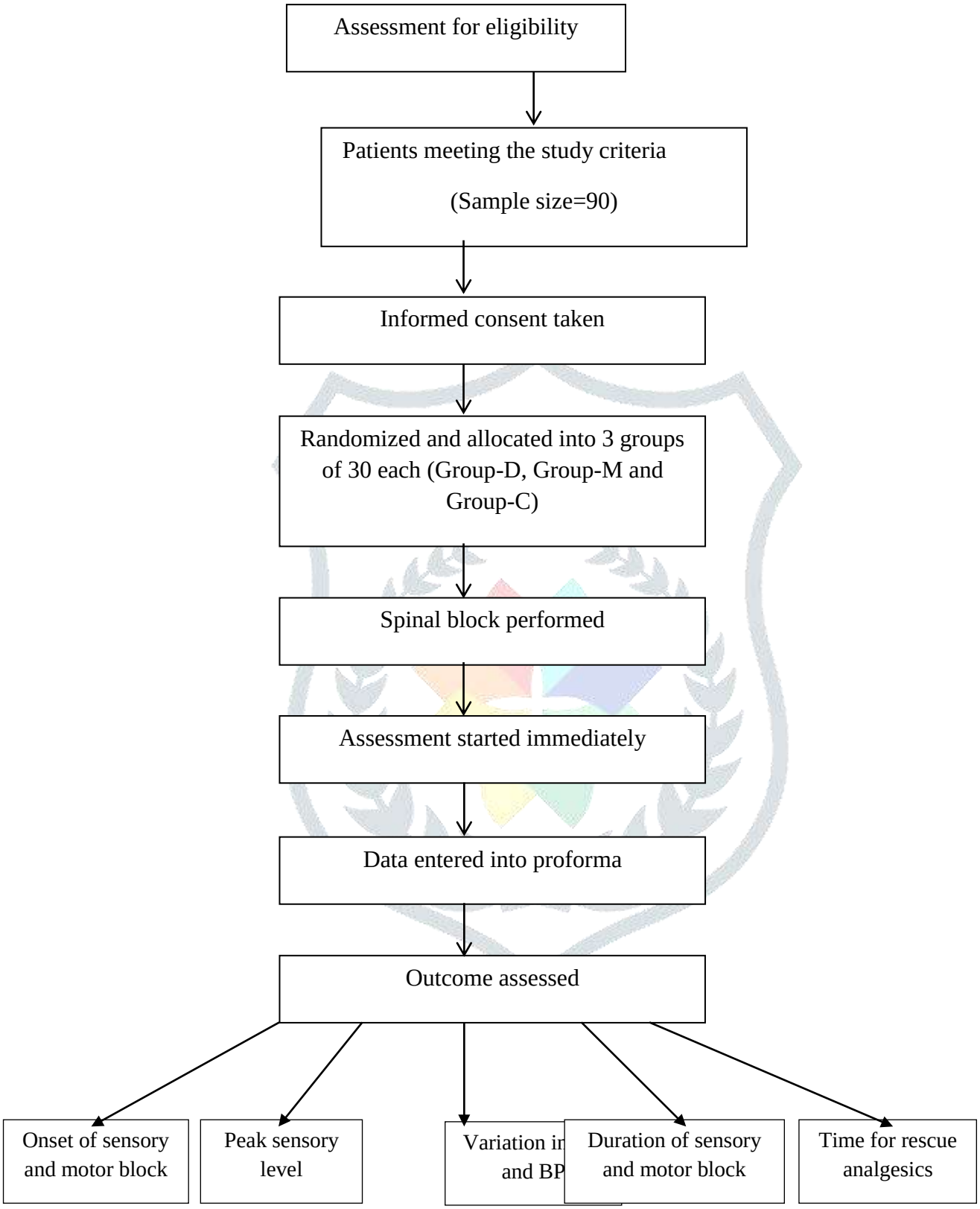
Post operative monitoring

The verbal rating score (0-No Pain; 1-Mild Pain; 2-Moderate Pain; 3-Severe Pain) was used to denote the time for rescue analgesics. Rescue analgesic (inj.Tramadol 2mg/kg i.v.) was given when patient was complaining of moderate pain. Adverse effects like hypotension, bradycardia, pruritus, vomiting, shivering and respiratory depression were noted for 16 hrs.

Statistical analysis:

Data was analysed using SPSS Software (Version 20). Continuous variables were compared among the three groups using ANOVA test. Categorical variables were compared among three groups using chi-square test. Alpha level for all inferential statistics was set at 5% i.e. $p \leq 0.05$ was considered as significant.

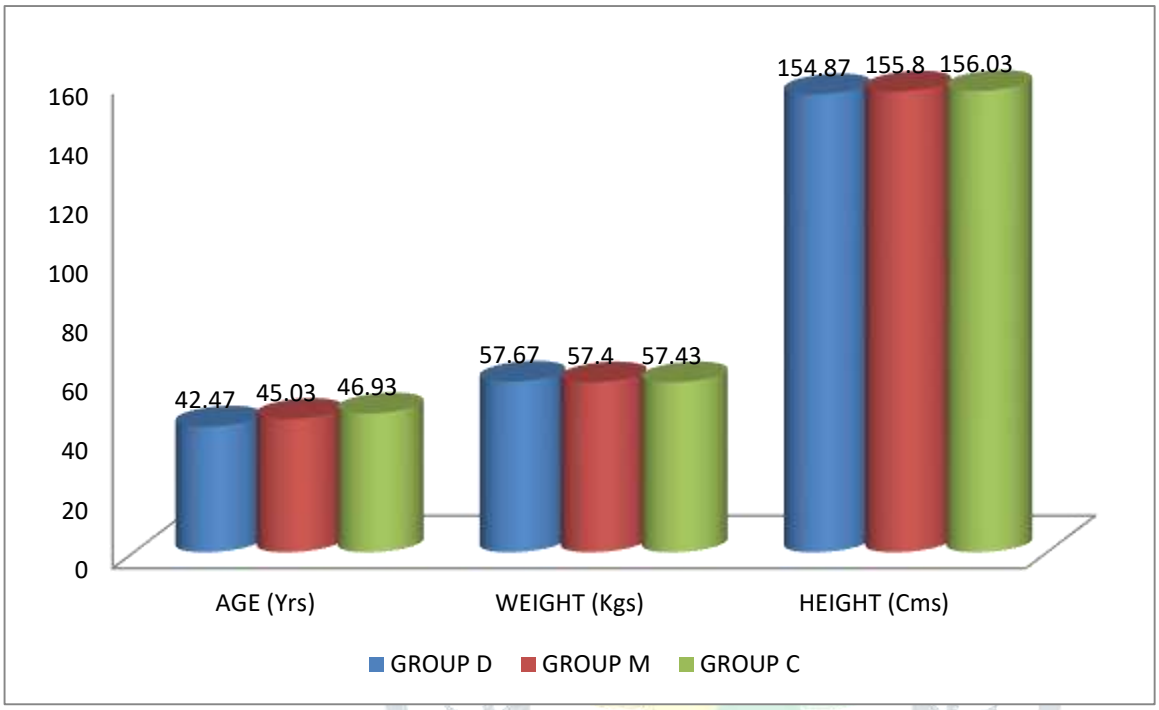
Study flow chart



RESULTS:

The demographic profile of the three groups was comparable and there was no significant difference between the groups with respect to age, height, weight ($p < 0.05$) (Figure 1).

FIGURE 1: COMARISON OF DEMOGRAPHIC PROFILE AMONG GROUPS



PRIMARY PARAMETERS:

The time of onset of sensory block at T10 was 2 to 4 minutes for all the patients in Dexmedetomidine (D) group; 11-13 minutes for majority (56.7%) in Magnesium sulphate (M) group; and 5-7 minutes for 83.3% in the Control group. The difference among the groups was highly significant (Table 1).

TABLE 1: TIME OF ONSET OF SENSORY BLOCK

TIME (Min.)	GROUP D	%	GROUP M	%	GROUP C	%	P
2-4	30	100	0	0	5	16.7	
5-7	0	0	0	0	25	83.3	
8-10	0	0	13	43.3	0	0	<0.001**

11-13	0	0	17	56.7	0	0	
TOTAL	30	100	30	100	30	100	

Chi-Square Test used

TABLE 2: PEAK SENSORY LEVEL

PEAK SENSORY LEVEL	GROUP D	%	GROUP M	%	GROUP C	%	P
T4	22	73.3	17	56.7	13	43.3	
T5	2	6.7	1	3.3	5	16.7	0.092
T6	6	20.0	12	40.0	12	40.0	
Total	30	100	30	100	30	100	

Chi-Square Test used

The range of peak sensory level was T4-T6 in all the three groups. There was no significant difference in the peak sensory level among the groups (Table 2).

TABLE 3: COMPARISON OF DIFFERENT ANAESTHESIA PARAMETERS AMONG THE STUDY AND CONTROL GROUPS

Parameters	GROUP D	GROUP M	GROUP C	p
	Mean ± SD	Mean ± SD	Mean ± SD	
Time to achieve T10 sensory level	2.77 ± 0.679	10.77 ± 1.278	5.6 ± 1.037	<0.001**
Onset of motor block	4.97 ± 0.999	12.27 ± 1.363	6.77 ± 1.104	<0.001**
Two segment regression	134.13 ± 10.425	86.50 ± 9.694	72.07 ± 7.852	<0.001**
One segment regression	319.83 ± 30.463	188.10 ±10.519	141.53 ± 14.134	<0.001**
Recovery of motor block	298.03 ± 27.872	173.6 ± 9.615	133.23 ± 14.102	<0.001**
Time for rescue analgesia	312.27± 40.371	223.73± 25.771	141.27± 28.822	<0.001**
Mean arterial pressure	76.8 ± 4.164	82.67 ±5.397	81.37 ±3.135	<0.001**

Heart rate (Intra operative)	72.42 ± 3.407	85.41 ±2.953	83.77 ± 3.178	<0.001**

ANOVA test was used; ** Highly Significant.

Time to achieve T10 sensory level:

The time to achieve T10 sensory level in Dexmedetomidine group (D) was significantly less than in control group (C) and magnesium sulphate group (M) indicating rapid onset of sensory block in the former group.

Onset of motor blockade:

The mean time to reach Grade 1 motor blockade was 4.97±1.0 mins in Group D, 12.3±1.36 mins in Group M and 6.77±1.1 mins in Group C. The onset was significantly shorter in Dexmedetomidine group than in controls and it was significantly prolonged in Group M.

Duration of sensory blockade:

Time to two segment regression: The mean time to two segment regression of sensory block was 134.13±10.42 mins in Group D, 86.5±9.69 mins in Group M and 72.1±7.85 mins in Group C. This illustrated statistical significant difference between the control and the study groups.

Time to one segment regression: The duration of sensory blockade (from the time of spinal injection to S1 regression) was 319.8±30.46 mins in Group D, 188±10.52 mins in Group M and 141.53±14.13 mins in Group C. S1 regression was significantly prolonged in both the study groups.

Duration of motor blockade:

The duration of motor blockade was taken from the time of institution of spinal anaesthesia and the time taken to return to Bromage score 0. It was 298±27.11 mins, 173.6±9.61 mins and 133±14.11 mins in the groups D, M and C respectively. These differences were statistically significant.

Rescue analgesics time:

The mean time for rescue analgesics in Group D, M and C was 312.6±39.7 mins, 233±27.24 and 141.3±28.3 mins respectively. It was significantly prolonged in Group D and Group M when compared to control group.

HEMODYNAMIC PARAMETERS:

Mean arterial blood pressure:

The mean arterial blood pressure was monitored throughout the procedure and for about 16 hrs in the post operative period. In the first hour, there was significant fall in MAP in the Dexmedetomidine group when compared to Magnesium and Control group. Not much variation noted after first hour.

Changes in heart rate:

Heart rate was monitored through out the procedure and in the post operative period. There was a significant difference in the pulse rate between Group D and Group C in the first hour but no marked difference after that. There was no difference found between Group M and Group C.

TABLE 4: TIME OF PEAK MOTOR BLOCK

	GROUP D	%	GROUP M	%	GROUP C	%	P value
4-7	30	100	0	0	18	60	
8-11	0	0	5	16.7	12	40	
12-15	0	0	25	83.3	0	0	<0.001**
TOTAL	30	100	30	100	30	100	

Chi-Square Test used

SIDE EFFECTS AND COMPLICATIONS:

After injection of spinal anaesthesia, in the first 120 minutes, the sedation effect as assessed by Ramsay sedation scoring showed a significant variation between Group D and Group C. The median values were 3±0.2, 2±0.1, 2±0.4 in group D, group M and group C respectively. In 150 minutes, the median values were 3±0.3,

2±0.4, 1±0.6 in group D, M and C respectively. After that Ramsay sedation scoring could not be compared due to provision of rescue analgesics.

Though there was a significant reduction in blood pressure in Group D, none of the cases in all groups showed a MAP of < 60 mm Hg. Similarly no cases had bradycardia or rate < 50. Only 2 patients one in Group D and one in Group C complained of nausea. None of the patient had vomiting, respiratory depression or pruritus.

DISCUSSION

Spinal anaesthesia is the most widely employed technique for surgical procedures involving lower limb and lower abdomen. From the date of invention, the technique has experienced so many renovations leading to refinement. One of those modifications is the addition of adjuvants to local anaestheticsto make the patient and the surgeon more comfortable for longer period.

Sensory block characteristics:

We observed a faster onset of sensory blockade (T10 dermatome level) in the Dexmedetomidine group. This was similar to the results observed by **Kanazi et al**[2] who found that the addition of 3µg DXM to 12mg spinal Bupivacaine produced a significant short onset of sensory and motor block.

The onset of block in Magnesium group was significantly delayed when compared to the Dexmedetomidine and control groups. **Ozlaveli et al.,**[14] in Turkey, observed that in patients undergoing lower extremity surgery, the addition of Magnesium sulphate to Bupivacaine significantly delayed the onset of both sensory and motor blockade. **Khalili et al,**[24] observed in patients undergoing lower limb orthopedic surgery that the addition of 100 mg (0.2ml) MgSO4 (50%) to 15mg 0.5% Bupivacaine delayed the onset of sensory block MgSO4 group than control group. In our study, we observed no significant difference between the groups in attaining the peak sensory level though the time required toachieve that level may vary.

Two segment regression and S1 regression:

In our study, the mean time for two segment regression was significantly prolonged in Group D when compared to Group M and Group C. Similar results were obtained in a study done by **Rajni Gupta et al[3]** when they compared local anaesthetic with DXM and local anaesthetic alone. Block regression was significantly slower with the addition of intrathecal Dexmedetomidine as compared to Ropivacaine alone, as both time to two segment regressions and time to S2 regression were significantly more with intrathecal Dexmedetomidine. Similarly **Dayioglu et al,[19]** found that the addition of intrathecal Magnesium sulphate (50mg) to spinal anaesthesia prolonged the time for regression of two segments in the maximum block height and time to L2 regression, but did not affect maximum sensory level.

In our study, the regression to S1 dermatome from the time of injection of spinal anaesthesia which was taken as the duration of spinal sensory blockade was prolonged in the study groups which was similar to the previous study[4], where the addition of 5µg of Dexmedetomidine to Bupivacaine compared to fentanyl significantly prolonged the time of sensory regression to S1 (476±23 mins in group D and 187±12 mins in group F) ($P<0.001$). **Kanazi et al[2]** who compared Dexmedetomidine and Clonidine, observed the mean time of sensory regression to the S1 segment was 303±75 min in Dexmedetomidine group, 272±38 min in Clonidine group and 190±48 min in only Bupivacaine without adjuvants ($p<0.001$).

Characteristics of motor blockade:

In our study, the onset of motor blockade was significantly delayed in Magnesium sulphate group compared to control group. This was in accordance with the results obtained by **Malleswaran et al[22],** who studied the effect of adding 50 mg Magnesium sulphate to Bupivacaine for caesarean in mild pre-eclamptic patients. The duration of spinal anaesthesia and motor block were significantly longer in the Magnesium group. In our study the mean time for recovery from motor blockade was prolonged in both the study groups.

Rescue analgesics and postoperative pain:

In the present study, the addition of Dexmedetomidine or Magnesium sulphate to Bupivacaine have prolonged the time of first analgesic requirement. This was supported by **Gupta et al[4]**, where the addition of 5µg of Dexmedetomidine to12.5mg Bupivacaine reduced the demand for rescue analgesics in 24 hrs as compared to Fentanyl. Similar results were also obtained by **Ogan et al[7]** who observed that, the pregnant patients who received spinal Bupivacaine and Dexmedetomidine had a prolonged analgesia than those whose received Bupivacaine and Fentanyl or Bupivacaine alone. The analgesic effect of Dexmedetomidine might be due to synergism with the local anaesthetic. One more study done by **Gupta et al,[4]** who compared Ropivacaine with Dexmedetomidine and Ropivacaine alone concluded that the duration of analgesia (time to requirement of first rescue analgesic) was significantly prolonged in group D (467±21.8 min) as compared to group R (231.67±22.56 min). The maximum visual analogue scale score for pain was less in group D (4.2±0.9) compared to group R (7.2±1.9). **Malleeswaran et al,[22]** found that the addition of Magnesium sulphate 50 mg to the intrathecal combination of Bupivacaine and fentanyl prolonged the duration of analgesia and reduces postoperative analgesic requirements without additional side effects.Similarly **Jongva lee et al,[17]** concluded that intrathecal Magnesium sulphate can be used as a local anaesthetic adjuvant to strengthen the analgesic effect of spinal local anaesthesia and to intensify the analgesic effect of epidural local anaesthesia for postoperative pain control to the extent of 5 mg epidural Morphine.

Hemodynamic parameters:

In our study the mean arterial pressure and the pulse rate recorded in first 60 minutes after the induction of spinal anaesthesia showed significant reduction in group D when compared to group M and group C. There was no difference between group M and group C. Postoperative hemodynamics showed no variation among groups. This was similar to the study by **Asrafamin et al,[5]** who found that the mean intraoperative heart rate was significantly reduced in the Dexmedetomidine group ($p<0.05$) compared with the control group (DXM

combined with fentanyl group). There was a significant reduction in mean intraoperative systolic and diastolic blood pressure in the Dexmedetomidine group ($p<0.05$) compared with the control group, with no significant difference in postoperative hemodynamics or sedation.

CONCLUSION: The onset of anaesthesia was rapid and of prolonged duration in the dexmedetomidine group (D). However, in the magnesium sulphate group (M), although onset of block was delayed, the duration was significantly prolonged as compared withthe control group (C), but to a lesser degree than in the dexmedetomidine group (D). The groups were similar with respect to hemodynamic variables and there were no significant side-effects in either of the groups.

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