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A comparative study of intrathecal dexmedetomedine and magnesium sulfate as adjuvants to bupivacaine in total hip replacement

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Abstract
Background & Objectives: Spinal anaesthesia is a popular technique for providing anaesthesia for total hip replacement (THR). Intrathecal adjuvant is given along with local anaesthesia to prolong duration of block. Intrathecal administration of dexmedetomidine and magnesium sulphate is known to enhance duration of block without causing significant side effect.
The purpose of this study was to assess the impact of intrathecal dexmedetomidine and magnesium sulfate on the onset and duration of spinal anaesthesia using bupivacaine.
Methods: After IEC approval, a prospective, randomized, double blinded study was conducted on 120 ASA I and II adult patients undergoing THR under spinal anaesthesia. Patients were randomly divided into three groups: Group D received 0.1 ml (10 µg) Dexmedetomidine, Group M received 0.1 ml (50 mg) Magnesium sulfate and Group C received 0.1 ml normal saline as control. All the patients in this study received 15 mg of hyperbaric bupivacaine. Time for sensory onset, Time for motor onset, Duration of Sensory Block, Duration of Motor Block, Duration of Analgesia and Incidence of Side Effects were recorded.
Results: The haemodynamic parameters like systolic blood pressure, diastolic blood pressure and mean heart rate for the groups were comparable. The onset of sensory and motor block were significantly the fastest for Group D ($p< 0.0001$). The duration of sensory and motor block were significantly longer for Group D as compared to both the groups ($p< 0.0001$). The duration of analgesia was significantly prolonged for Group D as compared to both groups ($p< 0.0001$).
Conclusion: Dexmedetomidine added to spinal Bupivacaine shortens the time of recovery and motor onset. It prolongs the duration of both sensory and motor blockade. It also provides significant post-operative analgesia.

Keywords: Spinal anaesthesia, bupivacaine, dexmedetomidine, magnesium sulfate

Introduction
THR may be performed under local, regional (spinal or epidural) or general anaesthesia [1]. But Spinal block is still the first choice 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 postoperative analgesia [2]. In recent years, use of intrathecal adjuvants has gained popularity with the aim of prolonging the duration of block, better success rate, patient satisfaction, decreased resource utilization compared with general anaesthesia and faster recovery. The quality and duration of the spinal anaesthesia have been reported to be improved by the addition of opioids, dexmedetomidine, clonidine, magnesium sulfate, neostigmine, ketamine and midazolam [3]. Dexmedetomidine, a highly selective a-2 agonist drug, is approved as an intravenous sedative and co-analgesic drug [4]. It binds the α2 receptors of locus ceruleus and spinal cord and causes sedation and analgesia respectively. Highly lipophilic nature of dexmedetomidine allows rapid absorption into the cerebrospinal fluid and binding to α2-AR of spinal cord for its analgesic action [5]. It prolongs the duration of both sensory and motor blockade induced by local anaesthetics irrespective of the route of administration (e.g., epidural, caudal, or spinal). Magnesium is an abundant cation in the body, essential to numerous physiological activities. It is an established i.v. treatment of pre-eclampsia, acute asthma, and tachyarrhythmia [6]. Magnesium is a non-competitive N- methyl-D aspartate (NMDA) receptor antagonist, and inhibits voltage-gated calcium channels. There are contradictory reports about the role of i.v. magnesium sulphate in reducing intra- and postoperative

analgesic requirements. But even high doses of i.v. magnesium sulphate such as those used in preeclampsia undergo minimal transfer across the blood–brain barrier [7]. Since we have seen that no intrathecal adjuvant lacks adverse effects, more studies are needed to compare the safety profile of these drugs. The relative lack of studies comparing the characteristics of blockade, and postoperative residual analgesic effect of both Dexmedetomidine and Magnesium Sulfate as adjuvants in Spinal Anaesthesia paralleling an increasing tendency to prefer adjuvants in Neuraxial Blocks prompted the interest in this topic.

Materials and Methods

This study was conducted at Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India after taking approval from Institutional ethics committee. The duration was study was 6 months and was done between June 2018 to November 2018. It was prospective, randomized controlled double blind study by Computer generated randomization. Blinding was performed by another investigator. Sample size was calculated using Open Epi 5.0. Keeping the power of study as 80% and confidence limit at 95% of the minimal sample size required was 38 rounded off to 40 in each group. Inclusion criteria: The patients who give informed written consent, Age group 18-45 years of any sex, ASA grade I and II, Height more than 140 cms, Weight less than 90 kgs, and BMI less than 38. Exclusion criteria: Patients who refuse to provide informed consent., Patient with contraindication to Spinal Anaesthesia, Known Cardiovascular Disease, Haematocrit less than 30 %, Hepatic/ Renal failure, Any degree of heart block, Beta blocker use. After obtaining informed written consent the patients were assigned to one of the three groups by means of randomization tables. Group D received 15 mg hyperbaric bupivacaine and 0.1 ml (10 µg) Dexmedetomidine. Group M received 15 mg hyperbaric bupivacaine and 0.1 ml (50 mg) MgSo4 Group C received 15 mg hyperbaric bupivacaine and 0.1 ml normal saline as control. Upon arrival of patients into the operating room, ECG, pulse oximetry (SpO_2) and non -invasive blood pressure (NIBP) were monitored. Following infusion of 500 mL lactated Ringer's solution and with the patient in the sitting position, lumbar puncture was performed at the L3-L4 level through a midline approach using a 25G Quincke spinal needle. The study solutions were prepared in a 5 ml syringe by an anesthesiologist who then handed them over in a coded form to the attending anesthesiologist blinded to the nature of drug given to him/her. The three groups were monitored preoperatively, intra-operatively and during shifting for heart rate, NIBP and SpO_2. Hypotension was defined as systolic blood pressure <90 mmHg or >30% decrease in baseline values. Tachycardia was defined as heart rate >100/min and bradycardia is defined as heart rate <60/min. Intraoperative side-effects were recorded. After intrathecal injection, patients were positioned in supine position and oxygen 2 L/min was given through a face mask. The anesthesiologist performing the block was blinded to the study drug and recorded the intraoperative data. Sensory block was assessed bilaterally by using analgesia to pin prick with a short hypodermic needle in the midclavicular line. Motor blockade was assessed by using the modified Bromage scale. The time to reach T10 dermatome level was taken as time of sensory onset. Time to taken to achieve Bromage 3 motor block was also recorded before surgery. All durations were calculated considering the time of spinal injection as time zero. Duration of sensory block was considered as interval from time of intrathecal injection to regression of sensory level of block to S1 dermatome. Duration of motor block was considered as interval from time of intrathecal injection to regression of motor block to Bromage 0. Visual analogue pain scale (VAS) scores were explained to the patient pre-operatively and were recorded before the intrathecal injection, and assessed every 1 hour upto 24 hrs. 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.Vitals were recorded 5 min before intrathecal injection; 1, 3, 5, 10, 15, 20, 25, 30 minutes after and subsequently every 15 minutes upto 2 hrs. Patients were discharged from the PACU after sensory regression to S1 dermatome and Bromage 0.

Results

Table 1: Distribution of patients in the three groups

Group	Number	%
Group-C	40	33.3%
Group-D	40	33.3%
Group-M	40	33.4%
Total	120	100.0%

There were 40 patients in each group.

Table 2: Demographic Parameters

Parameters (Mean ± S.D.)	**Group-C**	**Group-D**	**Group-M**	**F-value**	**p-value**
Age (in years)	31.75±7.36	31.43±7.22	31.80±7.29	0.031	0.969
Height (in cm)	167.05±8.11	166.80±8.47	167.53±8.05	0.080	0.923
Weight (in kg)	76.83±8.94	76.15±8.22	75.40±8.68	0.274	0.761
BMI (in kg/m^2)	27.46±1.87	27.42±2.83	26.85±2.39	0.817	0.444

One ANOVA way showed that there was no significant difference in the mean of all the demographic parameters of the three groups ($p > 0.05$). Thus the patients of the three groups were matched for all the demographic parameters.

Table 3: Onset of Sensory block (in minutes)

Onset of Sensory block (in minutes)	Group-C	Group-D	Group-M	F-value	p-value
Mean ± S.D.	4.35±0.66	3.44±0.87	6.05±0.68	127.37	<0.0001*

Time required for onset of sensory block of Group-D was the lowest of all the groups.

Table 4: Onset of Motor block (in minutes)

Onset of Motor block (in minutes)	Group-C	Group-D	Group-M	F-value	p-value
Mean ± S.D.	5.38±1.07	4.93±0.67	7.83±0.75	127.12	<0.0001*

Time required for onset of motor block of Group-C was the lowest of all the groups.

Table 5: Overall mean (±S.D.) of the haemodymanic parameters

Haemodynamic parameters (Mean ± s.d.)	Group-C	Group-D	Group-M	F-value	p-value
HR	63.91±8.50	63.86±8.11	63.84±8.14	1.91	0.14
SBP (mmHg)	110.00±6.34	107.70±9.72	110.20±6.16	2.32	0.09
DBP (mmHg)	65.26±8.07	62.91±10.58	65.09±10.45	2.08	0.12
MAP (mmHg)	80.17±7.04	77.84±9.40	80.09±8.17	2.16	0.11

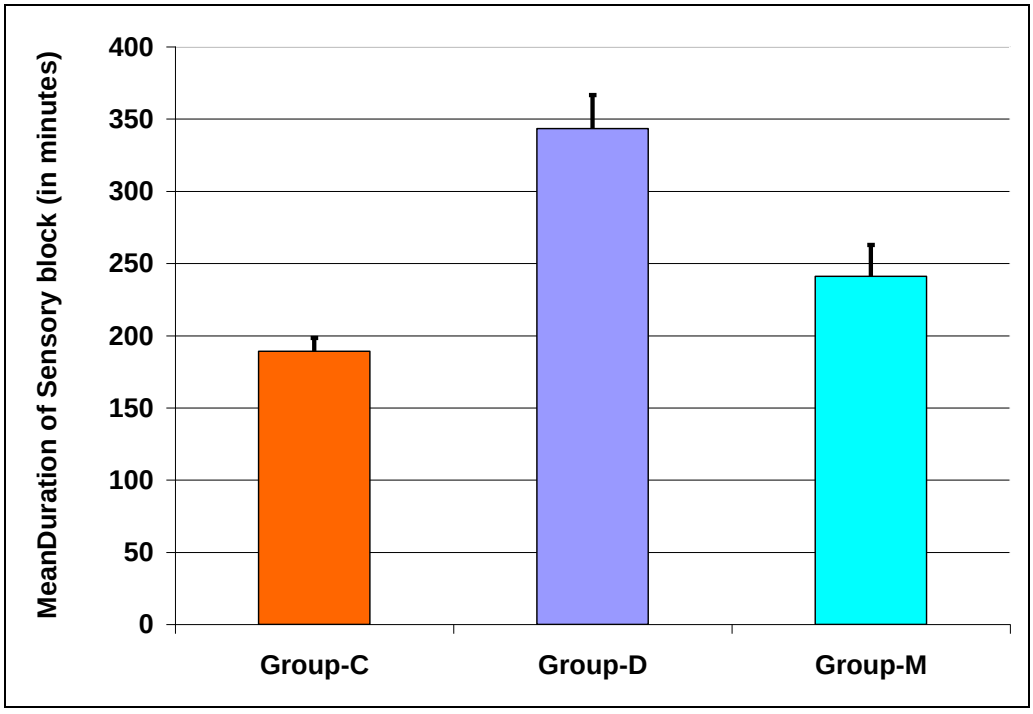
One way ANOVA way showed that there was no significant difference in the overall mean of all the haemodynamics parameters of the three groups ($p > 0.05$).

Table 6: Duration of Sensory block (in minutes)

Duration of Sensory block (in minutes)	Group-C	Group-D	Group-M	F-value	p-value
Mean ± S.D.	189.10±9.37	343.30±23.19	241.10±21.64	920.56	<0.0001*

Duration of sensory block of Group-C was the lowest of all the groups.

ANOVA showed there was significant difference in duration of sensory block ($F_{2,117} = 920.56; p < 0.0001$).



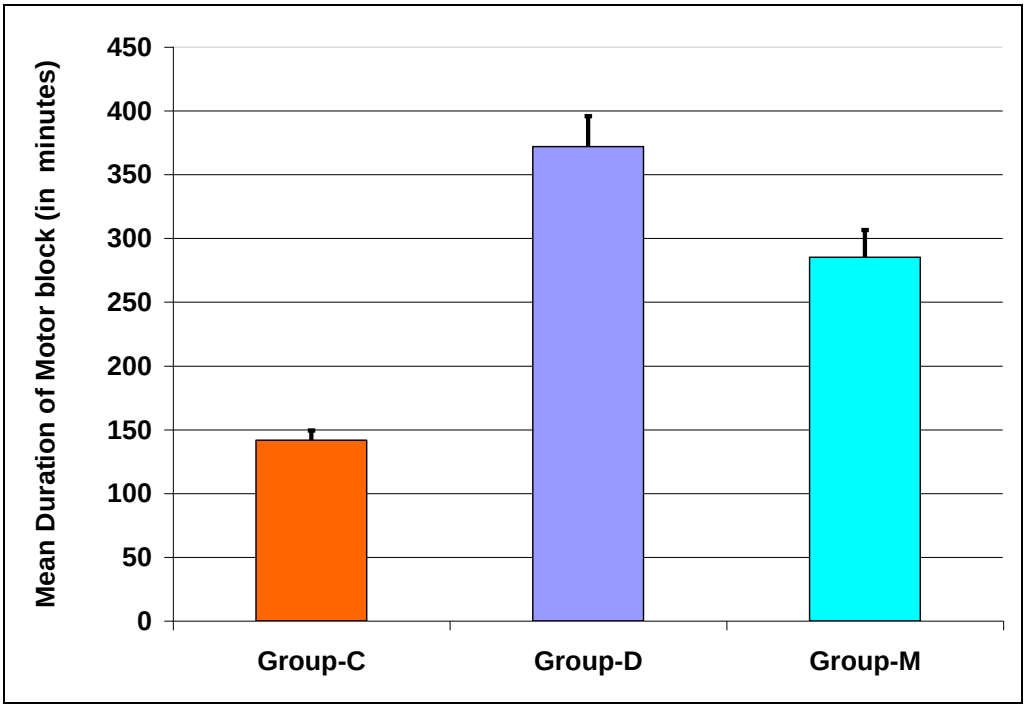
Graph 1: Mean Duration of Sensory Block for the Groups

Table 8: Duration of Motor block (in minutes)

Duration of Motor block (in minutes)	Group-C	Group-D	Group-M	F-value and p-value	p-value
Mean ± S.D.	141.65±7.79	371.85±23.87	258.25±21.27	1143.40	<0.0001*

Duration of motor block of Group-C was the lowest of all the groups.

ANOVA showed there was significant difference in duration of motor block ($F_{2,117} = 1143.40; p < 0.0001$).



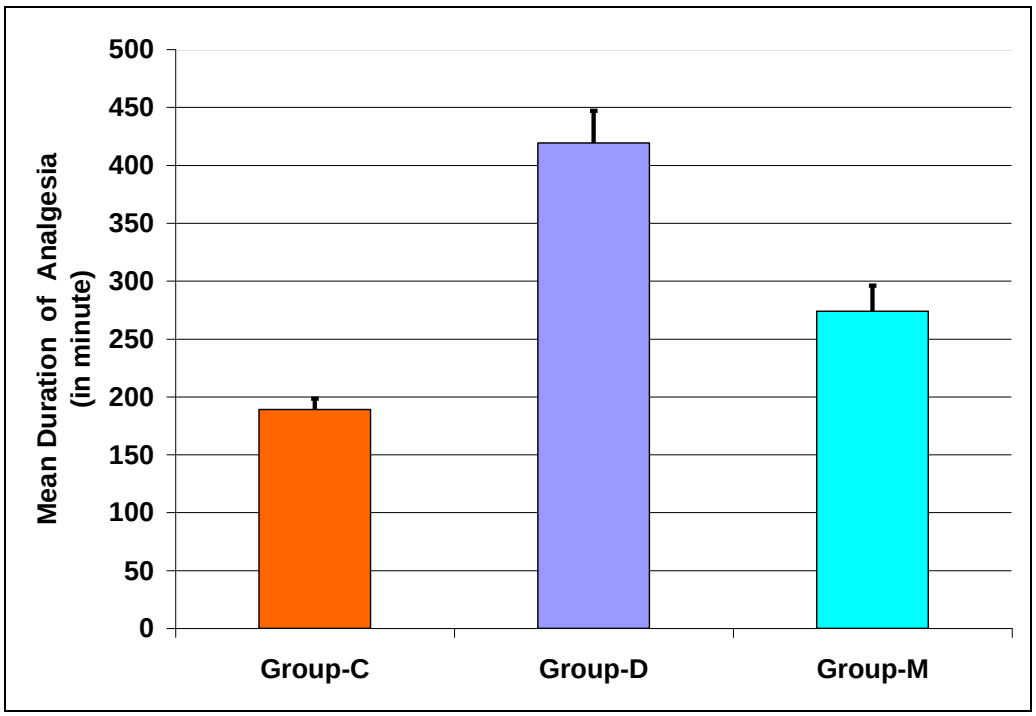
Graph 2: Mean Duration of Motor Block for the Groups

Table 9: Duration of Analgesia (in minute)

Duration of Analgesia (in minute)	Group-C	Group-D	Group-M	F-value	p-value
Mean ± S.D.	189.10±9.37	419.28±27.69	273.85±22.14	1209.56	<0.0001*

Duration of analgesia of Group-C was the lowest of all the groups.

ANOVA showed there was significant difference in duration of motor block ($F_{2,117}$= 1209;*p*< *0*.0001).



Graph 3: Mean Duration of Analgesia for the Group

The only significant side effect observed was Bradycardia, the incidence of which was 5, 13 and 8 in Groups C, D and M respectively. Although the incidence of Bradycardia in Group D was higher, it was not found to be statistically significant.

Discussion

Spinal block is still the first choice 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 postoperative analgesia[3]. In recent years, use of intrathecal

adjuvants has gained popularity with the aim of prolonging the duration of block, better success rate, patient satisfaction, decreased resource utilization compared with general anaesthesia and faster recovery [8]. Adequate pain management is essential to facilitate rehabilitation and accelerate functional recovery, enabling patients to return to their normal activity more quickly [9]. Dexmedetomidine is an established adjuvant in Neuraxial Blocks, and Magnesium Sulfate is also being used for the same [10]. The lack of studies comparing the benefits and advantages Vis-a-vi each other prompted this topic to be chosen, given the rising popularity of the use of adjuvants. In this study, all 120 patients posted for Lower Limb procedures were statistically similar with respect to age, height, weight and sex.

The haemodynamic parameters for the groups were as follows: Mean Heart Rate for the Groups C, D and M were 63.91±8.50, 63.86±8.11 and 63.84±8.14 (p value- 0.14). Thus, there was no significant difference between the Heart Rate for the three groups. Mean Systolic Blood Pressure for the Groups C, D and M were 110.00±6.34, 107.70±9.72 and 110.20±6.16 (p value- 0.09). Thus there was no significant difference between the Systolic Blood Pressures for the three groups. Mean Diastolic Blood Pressures for the Groups C, D and M were 65.26±8.07, 62.91±10.58 and 65.09±10.45 (p-value – 0.12). Thus there was no significant difference between the Diastolic Pressures for the three Groups. Haemodynamic parameters monitored pre-operatively, intra-operatively and post- operatively were comparable and statistically insignificant in all the three groups. The onset time of sensory block was 4.35±0.66 for Group C, as compared to 3.44±0.87 for Group D and 6.05±0.68 for Group M. The onset of sensory block was thus significantly the fastest for Group D, and also significantly faster for Group C compared to Group M ($p<$ 0.0001).

The onset of motor block was 5.38±1.07 for Group C, as compared to 4.93±0.67 for Group D and 7.83±0.75 for Group M. The onset of motor block was significantly faster in Group D compared to the two Groups, and the onset of motor block was significantly longer in Group M compared to the two groups ($p<$ 0.0001).

The duration of sensory block was 189.10±9.37 for Group C, 241.10±21.64 for Group M and 343.30±23.19 for Group D. The duration of sensory block was significantly longer for Group D as compared to both the groups, and the duration of block for Group M was significantly longer as compared to Group C ($p< 0.0001$).

The duration of motor blockade was 141.65±7.79 for Group C, 371.85±23.87 for Group D and 258.25±21.27 for Group M. The duration of motor blockade was significantly longer for Group D as compared to the other groups, and the duration of Group M was significantly prolonged as compared to Group C ($p<$ 0.0001).

The duration of analgesia for Group C was 189.10±9.37, Group D was 419.28±27.69 and Group M was 273.85±22.14. The duration of analgesia was significantly prolonged for Group D as compared to Groups M and C, and for Group M was significantly prolonged compared to Group C. ($P<$ 0.0001)

The onset time of sensory block was 4.35±0.66 for Group C, as compared to 3.44±0.87 for Group D and 6.05±0.68 for Group M. This agrees well with the findings of Shukla *et al.* [11], who used the same dosages of Spinal Local Anaesthetic and adjuvants as this study and found that the onset time of block, both sensory up to T10 dermatome and motor to Bromage 3 scale, was rapid in the DXM group D (2.27 ± 1.09 and 3.96 ± 0.92) and delayed in the Mg group M (6.46 ± 1.33 and 7.18 ± 1.38) in comparison with the control group C (4.14 ± 1.06 and 4.81 ± 1.03). The difference between the groups conducted through one-way ANOVA with post-tests was statistically significant in both sensory (F=97.118, $P< 0.0001$) and motor (F=65.7, $P< 0.0001$) in that study. The findings also concur with those of Kanazi *et al.* [12], Kim *et al.* [13] and Al- Mustafa *et al.* [14] in terms of faster onset of sensory blockade with Dexmedetomidine. This is also consistent with the findings of Bajwa *et al.* [15] who found that addition of 1.5 mcg/ kg Dexmedetomidine to Epidural Ropivacaine as an adjuvant resulted in an earlier onset (8.52 ± 2.36 min) of sensory analgesia at T10 as compared to the addition of clonidine (9.72 ± 3.44 min). Dexmedetomidine not only provided a higher dermatomal spread but also helped in achieving the maximum sensory anaesthetic level in a shorter period (13.14 ± 3.96 min) compared to clonidine (15.80 ± 4.86 min).

In our study, addition of Intrathecal Magnesium Sulfate 50 mg to 3 ml of Heavy Bupivacaine resulted in prolonged time of onset of sensory blockade compared to the Groups C and D. This again agrees well with the findings of Shukla *et al.* [11]. Khalili *et al.* [16] carried out a study to evaluate the effect of additional magnesium sulfate (MgSO (4)) 100 mg to intrathecal isobaric 0.5% bupivacaine 3 ml on spinal anaesthesia in patients undergoing lower extremity orthopedic surgery. They found that the onset of the sensory block was slower in the MgSO (4) group than in the control group (13.3 vs. 11.6 min, P = 0.04). Similar findings were reported by Kathuria *et al.* [17].

The onset of motor block was 5.38±1.07 for Group C, as compared to 4.93±0.67 for Group D and 7.83±0.75 for Group M. The onset of motor block was significantly faster in Group D compared to the two Groups, and the onset of motor block was significantly longer in Group M compared to the two groups ($p<$ 0.0001). This again agrees with the findings of Shukla *et al.* [11] who observed prolonged onset of motor blockade with Magnesium Sulfate and faster onset with Dexmedetomidine. The faster onset of motor blockade with Dexmedetomidine again agrees well with studies by Kanazi *et al.* [78] and Bajwa *et al.* [15]. Delayed onset of motor blockade with Magnesium Sulfate concurs with the finding Kathuria *et al.* [84].

The duration of sensory block was 189.10±9.37 for Group C, 241.10±21.64 for Group M and 343.30±23.19 for Group D. The duration of sensory block was significantly longer for Group D as compared to both the groups, and the duration of block for Group M was significantly longer as compared to Group C ($p< 0.0001$). This again agrees well with the findings of Shukla *et al.* [11] who found the regression time of block, both sensory up to T10 dermatome and motor to Bromage 3 scale, was prolonged in the DXM group D (352 ± 45 and 331 ± 35) and in the Mg group M (265 ± 65 and 251 ± 51) when compared with the control group C (194 ± 55 and 140 ± 34). However, the duration was longest in the DXM group among the three groups. The difference between the groups conducted through one-way ANOVA with post-tests was statistically significant in both sensory (F=60.3, $P< 0.0001$) and motor (F=166.9, $P< 0.0001$). Most other studies such as those by, Al- Mustafa *et al.* [14], Kanazi *et al.* [12] and Bajwa *et al.* [15] confirm

prolongation of sensory blockade duration by Dexmedetomidine and also the dose dependant nature of the duration of blockade

The duration of motor blockade was 141.65±7.79 for Group C, 371.85±23.87 for Group D and 258.25±21.27 for Group M. The duration of motor blockade was significantly longer for Group D as compared to the other groups, and the duration of Group M was significantly prolonged as compared to Group C ($p< 0.0001$).This again concurs with the findings of Shukla *et al.* [11]., Al- Mustafa *et al.* [14], Kanazi *et al.* [12], Bajwa *et al.* [15] confirm prolongation of motor blockade duration by Dexmedetomidine.

The duration of analgesia for Group C was 189.10±9.37, Group D was 419.28±27.69 and Group M was 273.85±22.14. The duration of analgesia was significantly prolonged for Group D as compared to Groups M and C,and for Group M was significantly prolonged compared to Group C ($P< 0.0001$). The prolonged duration of analgesia, as defined by time to first analgesic request or pain > VAS Score 3, found for Dexmedetomidine, correlates well with a dose dependant effect found in other studies. In a study by Gupta *et al.* [18], sixty patients scheduled for lower abdominal surgeries were randomly allocated to receive either 12.5 mg hyperbaric bupivacaine plus 5 µg Dexmedetomidine or 12.5 mg hyperbaric Bupivacaine plus 25 µg Fentanyl intrathecal. The duration of analgesia was found to be 251.7± 30.69, significantly prolonged for the Dexmedetomidine compared to the control. Kim *et al.* [13] randomized fifty-four patients undergoing transurethral prostate surgery were into two groups receiving either Dexmedetomidine 3 µg (n=27) or normal saline (n=27) intrathecally with 6 mg of 0.5% hyperbaric bupivacaine. There was less analgesic request and the time to the first analgesic request was longer in the dexmedetomidine group than in the saline group (each 487, 345 min, $p< 0.05$). Bajwa *et al.* [15], also noted a superior post-operative analgesia for 1.5µg/kg epidural Dexmedetomidine compared to that of 2 µg/kg Clonidine.

The findings and the correlation with available evidence show that more studies are needed on the combination of Magnesium Sulfate alone with Local Anaesthetic in Neuraxial Blocks, as also comparison of the blockade profile with other Neuraxial Adjuvants.

Conclusion

From our study, we conclude that Dexmedetomidine (10 mcg) added to Spinal Bupivacaine (15 mg) shortens the time of sensory and motor onset. It prolongs the duration of both sensory and motor blockade. It also provides significant post-operative analgesia. Magnesium Sulfate (50 mg) added to Spinal Bupivacaine (15 mg) prolongs the onset of sensory and motor blockade. It also prolongs the duration of motor and sensory blockade and provides postoperative analgesia, although a lesser degree compared to 10 mcg Dexmedetomidine.

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