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Effect of intrathecal dexmedetomidine and magnesium sulphate as an adjuvant to bupivacaine for infraumbilical surgeries

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Abstract:

Background: Spinal anaesthesia is the most commonly used regional technique which gives a rapid and effective block on injection of small doses of local anaesthetics in subarachnoid space. In last few decades, adjuvant like magnesium and dexmedetomidine have been administered with bupivacaine intrathecally to prolong the intra and post-operative analgesia. This study was done to evaluate the effects of intrathecal administration of dexmedetomidine and magnesium sulphate as an adjuvant to bupivacaine in infraumblical surgeries.

Material and Methods: *Total of 40 patients aged 18-60 years, of ASA grade I & II scheduled for infraumblical surgeries under subarachnoid block were administered either hyperbaric bupivacaine 15 mg and dexmedetomidine 10 µg (Group BD) or hyperbaric bupivacaine 15 mg and magnesium sulphate 50 mg (Group BM). Onset and duration of sensory and motor block, duration of analgesia, haemodynamic parameters, side effects and complications were compared between both the groups.*

Results*: Demographic profile of patients, duration of surgery, HR, SBP, DBP, MBP, RR and SpO_2were comparable between the groups (p>0.05). Mean onset of sensory block and motor block was rapid in group BD as compared to group BM, the mean duration of sensory block and motor block was significantly prolonged in group BD than BM (p<0.05). Mean duration of analgesia was also prolonged in group BD as compared to group BM but it was not statistically significant (p=0.08). Incidence of nausea and vomiting was 3 and 2 in group BD and 1 and 1 in group BM respectively.*

Conclusion: *As an adjuvant to bupivacaine in subarachnoid block for infraumbilical surgeries dexmedetomidine significantly prolongs the duration of sensory and motor block and duration of analgesia as compared to magnesium sulphate. Although the onset of sensory and motor block was significantly delayed with magnesium sulphate as compared to dexmedetomidine, both the drugs provide good postoperative analgesia with minimal side effects.*

Keyword: *Bupivacaine; Dexmedetomidine; Magnesium sulphate; Postoperative analgesia; Spinal anaesthesia.*

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I. Introduction

Spinal anaesthesia is the most preferred regional anaesthesia technique as it is safe, inexpensive, delivers outstanding operating conditions and postoperative pain relief for infraumbilical surgeries[1]. Local anaesthetics like bupivacaine when used for spinal anaesthesia have a limited duration of analgesia. Combinations of other classes of drugs with local anaesthetics have been used to improve the quality of anaesthesia and prolong postoperative analgesia, facilitating early ambulation and reducing the hospital stay of the patients[2,3]. Magnesium sulphate and dexmedetomidine are one of the adjuvants used for this purpose.

Dexmedetomidine, an α-2 agonist is developing as a useful adjunct to regional anaesthesia and analgesia. The prolongation of motor block is due to the binding of α-2 adrenoceptor agonists to motor neurons in the dorsal horn and prolongation of analgesia is by depressing the C fibre transmission by hyperpolarization of post synaptic dorsal horn neurons. Various animal and human studies have demonstrated that intrathecally administered dexmedetomidine prolonged spinal analgesia[4-7]. Based on previous studies it has been hypothesized that intrathecal dexmedetomidine (5 to 15µg) with hyperbaric bupivacaine would produce more postoperative analgesia with minimal side effect[8,9].

Magnesium is a non-competitive antagonist to N-methyl-D-aspartate (NMDA) receptor and also inhibits calcium entry into cells. It has the ability to avert central sensitization from peripheral nociceptive stimulation[10]. Central sensitization is an activity-dependent increase in the excitability of spinal neurons and is

considered as one of the mechanisms implicated in the persistence of post-operative pain[11]. In previous studies, it was demonstrated that intrathecally administered Mg prolonged spinal opioid analgesia both in rats and humans[12-14].

Based on this context, we decided to observe the efficacy of dexmedetomidine and magnesium sulphate as adjuvant to bupivacaine in subarachnoid block for infraumbilical surgeries. Primary objective was duration of sensory block and secondary objectives were onset of sensory and motor block, duration of motor block, duration of analgesia, hemodynamic stability and adverse effects.

II. Material and Methods

After obtaining approval from the Institutional Ethics and Scientific committees, this study was conducted in the Department of Anaesthesiology and Critical Care, Pt. J.N.M. Medical College & Dr. Bhim Rao Ambedkar Memorial Hospital, Raipur (C.G.) from April 2018 to July 2019. Forty adult patients aged 18-60 years of ASA physical status I and II who underwent infraumblical surgeries under spinal anaesthesia were enrolled in a prospective, observational study. We excluded patients with uncontrolled labile hypertension, allergy to any drugs, cardiac, respiratory and neurological dysfunction, sedative drug consumption, any contraindication to neuraxial blockade or patients who refused to enroll. The patients were divided into two equal groups; group BD (n=20) received bupivacaine 15 mg with dexmedetomidine 10 µg and group BM (n=20) received bupivacaine 15mg with magnesium sulphate 50 mg intrathecally.

Pre-anaesthetic evaluation was done and written informed consent was obtained from all the patients after explaining about procedure and associated risk. After the arrival of patient in the operation theatre, multipara monitor (Schillers B1589 model) was attached and baseline vital parameters (ECG, non-invasive blood pressure, heart rate, respiratory rate and SpO_2) were recorded. Intravenous (i.v.) line was secured by inserting 18G i.v. cannula over dorsum of hand and all patients were preloaded with ringer lactate 500 ml. All the patients were premedicated with i.v. ondansetron 4 mg and i.v. ranitidine 50 mg. Under all aseptic precautions and patient in sitting position, lumbar puncture was performed using a 25G Quincke's spinal needle at L3-L4 intervertebral level through a midline approach. After confirming free flow of CSF through the needle, 3 ml of 0.5% hyperbaric bupivacaine along with either dexmedetomidine 0.1 ml (10 µg) or magnesium sulphate 0.1 ml (50 mg) was given.

The time at intrathecal injection was considered as zero (0) and vital parameters were noted as soon as patients were turned supine. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), and arterial oxygen saturation (SpO_2) were recorded every 5 minutes up to 30 minutes and then every 15 minutes till completion of surgery. Sensory block was assessed by cold discrimination test at every 1 min interval till it reached T10 dermatome then every 5 min interval till maximum height was achieved. Motor block was assessed by Modified Bromage scale [Grade 0- Free movement of legs, feet with ability to raise extended legs, Grade 1- Inability to raise extended legs, but able to move knees and feet, Grade 2- Inability to raise extended legs, flex knees but able to move feet, Grade 3- Inability to raise extended legs, flex knees, ankle or move toes] every 1 min till it reached modified Bromage scale 3 then every 5 min until it reached complete recovery.

Onset of sensory block was defined as time interval from the time of injection of drug to loss of cold sensation at T10 dermatome. Onset of motor block was defined as time interval from the time of injection of drug to inability to flex the ankle (modified Bromage scale 3). The time to reach T10 dermatome, peak sensory level and Bromage 3 motor block were recorded before surgery.

Hypotension was defined as decrease in MBP>20% from baseline and was treated using i.v ringer lactate bolus. If there was no response then i.v. mephentermine 6 mg was administered. Heart rate below 50 beats per min was considered as bradycardia and 0.6 mg i.v. atropine was administered. Side effects like nausea, vomiting, hypotension, bradycardia, respiratory depression, pruritus and shivering were observed and recorded.

Duration of sensory block was defined as the time interval between complete sensory block and regression of analgesia by two segments from the maximum height of analgesia achieved. Duration of motor block was defined as time interval from the complete motor block (Modified Bromage Scale 3) to complete recovery (Modified Bromage Scale 0). Time to two segment regression of sensory block and time to return of modified Bromage scale to 0 were recorded.

Postoperatively HR, SBP, DBP, MBP, SpO_2, and RR were recorded initially every 1 hour for 2 hours, then every 2 hour for next 8 hours and then every 4 hour till 24 hours. The duration of analgesia was considered as the time from the injection of the study drug to the first request made by the patient for rescue analgesia. Intramuscular diclofenac 75 mg was given as rescue analgesic, which was repeated after 12 hours.

For the purpose of sample size, we used the study of Shukla D et al (2011)[29], who compared mean duration of sensory blockade of intrathecal dexmedetomidine and magnesium sulphate as an adjuvant to bupivacaine. They found that the mean duration of sensory blockade was 352±45 min in dexmedetomidine group and 265±65 min in magnesium sulphate group. Sample size was calculated considering the difference

between these two mean with confidence level of 95%, α error probability of 0.05 and 80% power by Epitool software. A sample size of minimum 40 patients was required (20 patients in each group).

So, we collected data of 20 patients who had received bupivacaine and dexmedetomidine (group BD) and 20 patients who had received bupivacaine and magnesium sulfate (group BM). Statistical analysis was performed using graph pad in stat software. The results were analyzed by various statistical techniques like percentage, mean and standard deviation. The unpaired student t test was applied to compare the mean of two independent samples. p Value < 0.05 was considered as significant.

III. Results

The demographic data and duration of surgery were statistically comparable between the groups with a p Value of >0.05. (Table 1)

Mean onset of sensory block and motor block was rapid in group BD as compared to group BM, the mean duration of sensory block and motor block was prolonged in group BD than BM and the difference between the groups were statistically significant (p<0.05). Mean duration of analgesia was slightly prolonged in group BD as compared to group BM but it was statistically insignificant (p=0.08). (Table 2)

At various time intervals mean HR, mean SBP, mean DBP, mean MBP, mean RR and mean SpO_2 showed no statistically significant differences. (Graph1, 2 and 3)

Hypotension was observed in 3 (15%) patients of group BD. Nausea and vomiting were found in 3 (15 %) patients and 2 (10%) patients of group BD. In group BM 1 (5 %) and 1 (5 %) patients experienced nausea and vomiting, respectively which was statistically insignificant. Bradycardia, pruritus, respiratory depression and shivering were not found in any patient of either group. (Table 3)

Table 1: Demographic profile, and duration of surgery

Parameters	Group BD (n=20)	Group BM (n=20)	p Value
Age (years)	32.70±7.533	35.85±9.68	0.258
Sex (Male:Female)	11 (55%):9 (45%)	13 (65%):7 (35%)	0.52
Weight (kg)	53.85±6.722	54.75±3.767	0.605
Height (cm)	156.2±4.851	157.25±5.892	0.562
BMI (cm/kg^2)	22.165±3.58	23.15±3.37	0.362
Duration of surgery (min)	114.85±2.725	125.9±34.055	0.156

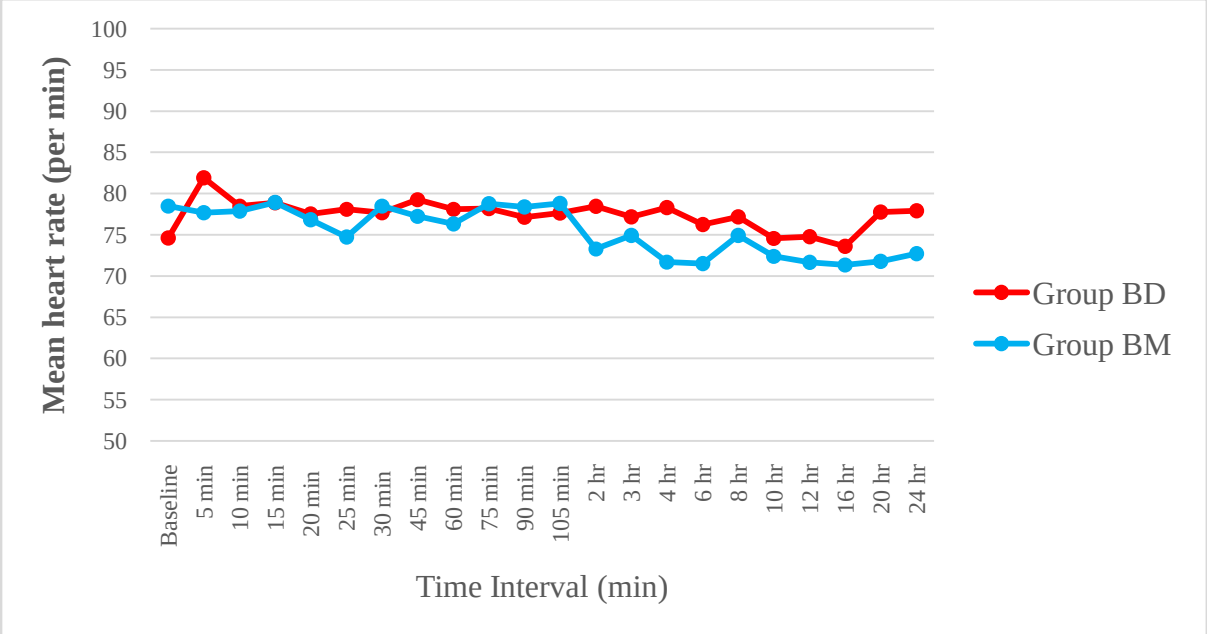
Table 2: Characteristics of subarachnoid block

Parameters	Group BD (Mean±SD)	Group BM (Mean±SD)	p Value
Onset of sensory block	3.275±0.498	3.690±0.736	0.044
Onset of motor block	3.873±0.206	4.348±0.974	0.039
Duration of sensory block	361.35±45.565	343.65±30.608	0.004
Duration of motor block	318.2±32.734	287.1±19.452	0.024
Duration of analgesia	373.85±49.497	350.05±34.509	0.08

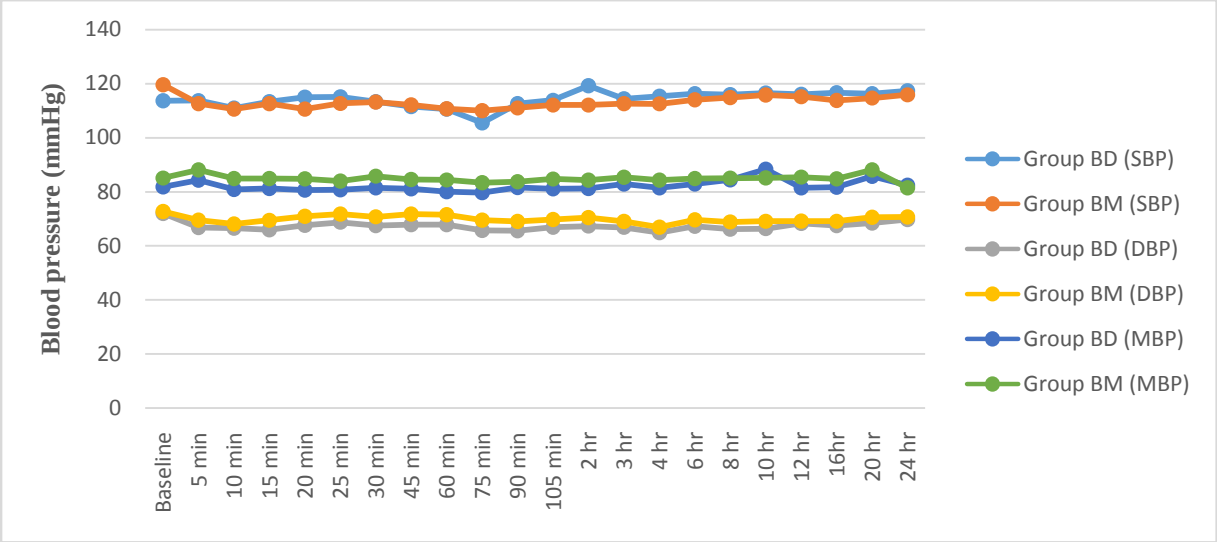
Table 3: Side effects and complications

Side effects and complications	Group BD n (%)	Group BM n (%)	p Value
Nausea	3 (15)	1 (5)	>0.05
Vomiting	2 (10)	1 (0)	>0.05
Hypotension	3 (15)	0 (0)	>0.05
Bradycardia	0 (0)	0 (0)	>0.05
Pruritus	0 (0)	0 (0)	>0.05
Respiratory Depression	0 (0)	0 (0)	>0.05
Shivering	0 (0)	0 (0)	>0.05

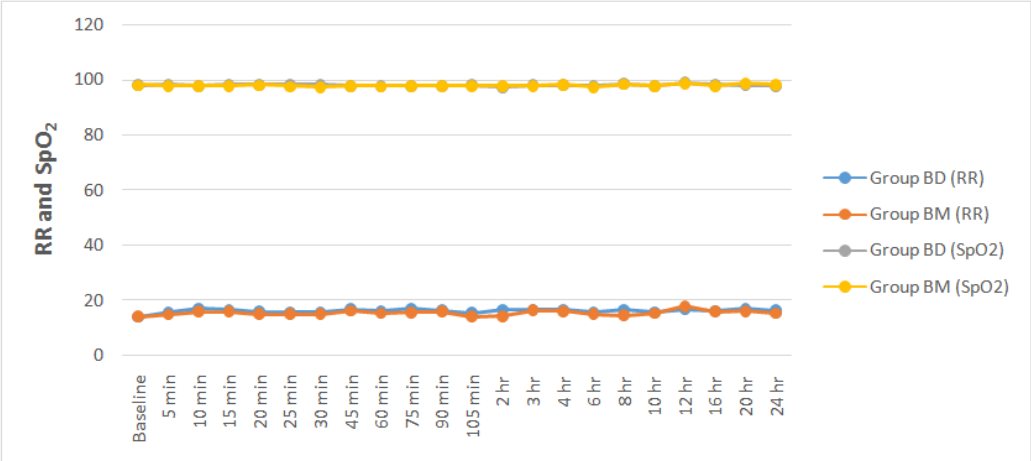
Graph 1: Mean heart rate



Graph 2: Mean SBP, DBP, and MBP



Graph 3: Mean respiratory rate (per min) and SpO_2 (%)



IV. Discussion

Neuraxial dexmedetomidine and magnesium sulfate provide good analgesia similar to systemic administration, but in small doses and concentrations with less risk of systemic side effects[15]. Dexmedetomidine has been the focus of interest for its sedative, analgesic, sympatholytic and haemodynamic stabilizing properties. It has been recently used as a systemic analgesic and regional anaesthetic adjuvant for both intrathecal and epidural administration to intensify and prolong the action of local anaesthetics. Magnesium is a non-competitive antagonist to NMDA receptor. Anti-nociceptive action of magnesium appears to be relevant not only to chronic pain but also determines the duration & intensity of acute post-operative pain[16].

Our study compared dexmedetomidine (10 µg) and magnesium sulphate (50 mg) as an intrathecal adjuvant to local anaesthetic (15 mg bupivacaine 0.5% heavy) for infraumbilical surgeries. The mean onset of sensory and motor block is consistent with the studies of Shukla D et al[10] and Farooq Z et al[17] who observed that the onset of sensory and motor block was rapid in the dexmedetomidine group and also noted a similar delay in onset of spinal anaesthesia when magnesium was added to hyperbaric bupivacaine. Their results were similar to our study because T10 level block was considered as the onset of sensory block and time to reach Modified Bromage 3 was considered as onset of motor block in both the studies. Also, the same amount and volume of drug was used for subarachnoid block in both the studies. Gupta R et al[18], Sunil BV et al[19] and Amr SA et al[20] found slightly delayed onset of sensory and motor block which could be explained by dilution of adjuvant in normal saline in their studies. In addition Gupta R et al used ropivacaine which itself has delayed onset as compared to bupivacaine. Rashid AE et al[21] also found delayed onset which might be because of use of 0.5 ml of 10% magnesium sulphate.

Shukla D et al[10] and Routtray SS et al[22] observed mean duration of sensory and motor block similar to our findings. They found that prolongation of duration of sensory and motor block with 10 µg intrathecal dexmedetomidine was more as compared to that with 50 mg intrathecal magnesium sulphate. This could be attributed to use of same amount and volume of drug for subarachnoid block in their studies as well as in ours. In the studies of Khan AL et al[23], Rashid AE et al[21] and Sunil BV et al[19] duration of sensory and motor block were shorter which could be explained by dilution of study drug by normal saline. In another study, Mahendru V et al[24] used 12.5 mg of bupivacaine with dexmedetomidine and found shorter duration of action.

The duration of analgesia was slightly prolonged in group BD but it was statistically not significant in our study. Gupta R et al[18] found prolonged duration of analgesia which is consistent with their use of ropivacaine which has prolonged duration of action as compared to bupivacaine. Bhure AR et al[7] also found prolonged duration of analgesia because they used 3.4 ml 0.5% bupivacaine and we used 3 ml 0.5% bupivacaine. Wapang A et al[25] and Suresh G et al[15] reported shorter duration of analgesia as compared to our study may be because they used less dose and volume of drug i.e. 2.5 ml bupivacaine+0.1 ml dexmedetomidine or 0.1 ml magnesium sulphate (total 2.6 ml) while we used 3 ml bupivacaine +0.1 ml dexmedetomidine or 0.1 ml magnesium sulphate (total 3.1 ml).

In group BM, where magnesium is added to bupivacaine, showed less duration of analgesia as compared to group BD. There are a few possible reasons why magnesium failed to prolong the time to the first analgesic requirement because it has been claimed that the effect of magnesium sulphate on the NMDA receptor complex is weaker than those of some other NMDA receptor antagonists. Second reason is that magnesium sulphate might activate bupivacaine hydroxylation by cytochrome P450. Therefore, the addition of intrathecal magnesium sulphate to spinal bupivacaine may alter bupivacaine pharmacokinetics and cause a more rapid elimination of bupivacaine.

No statistically significant difference was observed in hemodynamic parameters like heart rate, systolic blood pressure, diastolic blood pressure and mean blood pressure. RR and SpO_2 of both the groups were also comparable at all time intervals. There was no statistically significant difference in side effects like nausea, vomiting, hypotension, bradycardia, respiratory depression, shivering and pruritus.

Limitations of our study were that the study design was an observational one, a randomized controlled trial with large sample size would have been better. The analgesic effect of intrathecal dexmedetomidine in healthy patients of ASA I and II were considered. The effect on patients of ASA III and IV and those having comorbidities is yet to be studied. Follow up was not done after 24 hours for any delayed complications like neurological deficit etc.

V. Conclusion

Dexmedetomidine and magnesium sulphate significantly prolongs the duration of sensory and motor block when used as an adjuvant to bupivacaine in subarachnoid block for infraumbilical surgeries. Although onset of sensory and motor block was significantly delayed in magnesium sulphate as compared to dexmedetomidine, both the drugs provide good postoperative analgesia with minimal side effects.

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