Effect of Intrathecal Dexmedetomidine and Magnesium Sulphate on the Characteristics of Bupivacaine Spinal Block - A Comparison

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ABSTRACT

Background: Prolongation of spinal analgesia extends not only the duration of surgical anaesthesia but also provides postoperative analgesia. The effects of adjuvants like dexmedetomidine and magnesium sulphate to intrathecal bupivacaine are compared in this study.

Materials and Methods: In a prospective randomized double-blinded placebo-controlled study, 90 adult patients of American Society of Anaesthesiologists (ASA) physical status I and II scheduled for lower abdominal and lower limb surgeries were randomly allocated to one of three groups: Group-D (n=30) received 12.5mg(2.5ml) hyperbaric bupivacaine 0.5% plus 10µg (0.1ml) dexmedetomidine, Group-M(n=30) received 12.5mg(2.5ml) hyperbaric bupivacaine plus 50mg (0.1ml) magnesium sulphate 50%, and Group-C (n=30) received 12.5mg (2.5ml) hyperbaric bupivacaine plus 0.1ml normal saline 0.9% without preservative intrathecally. The onset times to reach T₁₀ sensory and Bromage 3 motor block, peak sensory block level, time to reach peak block, time to two segment regression, the regression times to reach S₁ sensory level and modified Bromage 0 motor scale, side-effects, and time to first analgesic request after surgery were assessed.

Results: The onset time of sensory and motor blockade were significantly shortened in group D (2.53±0.57 min.) and prolonged in group M (8.00±1.29 min.) compared to group C (4.10±0.55 min.).Dexmedetomidine group showed significantly prolonged time to two segment regression (group D vs group M -132.33 ±12.51 min. vs. 91.83 ±9.69 min.; p<0.001) and significantly delayed time to first analgesic request (group D vs. group M – 356.50±30.82 min vs 193.00±18.78min. p<0.001).

Conclusion: Dexmedetomidine had faster onset of anesthesia and provided prolonged postoperative analgesia compared to magnesium sulphate.

Key Words: spinal anesthesia, adjuvant, dexmedetomidine, magnesium sulphate, analgesia

INTRODUCTION

The use of central neuraxial blockade with hyperbaric bupivacaine for surgeries of the lower abdominal and the lower extremities are widely acknowledged. Spinal anaesthesia has the advantage of simplicity of technique and rapid onset, but has drawbacks of shorter duration of block and lack of postoperative analgesia. Prolongation of spinal analgesia not only extends the duration of surgical anaesthesia but also provides postoperative analgesia for
a considerable duration. A variety of adjuvants have been tried, yet no agent has been identified to specifically inhibit nociception without associated side-effects. \[1\]

Dexmedetomidine is a newer prototype of \( \alpha_2 \)-adrenergic receptor agonist, with a relatively higher selective ratio of \( \alpha_2 \)-to-\( \alpha_1 \) receptor (1620:1 as compared to 220:1 for clonidine). \[2\] It has been the focus of interest in anaesthetic procedures, as it produces dose-dependent sedation, anxiolysis and analgesia (involving spinal and supraspinal sites) without respiratory depression, secondary to activation of central \( \alpha_2 \)-adrenoceptors in the locus coeruleus. \[3\] Dexmedetomidine has been used in the epidural space as well as intravenously resulting in a significant opioid-sparing effect. \[4\]

Magnesium, the fourth most plentiful cation in the body and known for its efficacy in the treatment of arrhythmia, acute asthma and pre-eclampsia, has recently been highlighted in anaesthetic practice, due to its antinociceptive action without increased adverse effects \[5\] based on its antagonist properties for the \( N \)-methyl-\( D \)-aspartate (NMDA) receptor and its inhibitory properties for calcium channels. There are considerable evidences that intrathecally administered magnesium potentiate opioid nociception and prolongs duration of anaesthesia. \[6\]

Based on the earlier studies, it was hypothesized that intrathecal 10\( \mu \)g Dexmedetomidine or 50 mg magnesium sulphate would provide the effective characteristics of bupivacaine spinal anaesthesia with minimal side-effect. The purpose of this study was to compare the effect of intrathecal dexmedetomidine and magnesium sulphate on the characteristics of bupivacaine spinal block in patients undergoing lower abdomen and lower extremity surgeries.

**MATERIALS AND METHODS**

After obtaining institutional ethical committee approval and written informed consent from the patients, 90 ASA \[7\] physical status I and II patients aged 18-60 years of both sexes, scheduled for elective lower abdominal and lower limb surgeries under spinal anaesthesia were included in this prospective, randomized, double-blind, placebo-controlled study. Based on previous studies, \[8\] it was calculated that a sample size of 30 patients would be required per group to demonstrate a clinically significant difference among the groups, at \( \alpha = 0.05 \) with a power (1-\( \beta \)) of 80%. Patients were randomly allocated into three groups by computer generated randomisation chart to receive the drugs during the study as follows:

**Group D** (n=30): received 2.5 ml (12.5 mg) hyperbaric bupivacaine 0.5% plus 0.1ml (10\( \mu \)g) dexmedetomidine intrathecal;

**Group M** (n=30): received 2.5ml (12.5mg) hyperbaric bupivacaine 0.5% plus 0.1ml (50mg) magnesium sulphate 50% intrathecal and

**Group C** (n= 30): received 2.5ml (12.5 mg) hyperbaric bupivacaine 0.5% plus 0.1ml preservative free normal saline intrathecal as control.

-the injections were made over a period of 15 seconds.

Exclusion criteria were - patient’s refusal, history of uncontrolled labile hypertension, infection at the site of injection, post spinal surgeries, spinal deformity, neurological disorder, coagulopathy, hypovolemia or bradycardia, patients on calcium channel blockers or adrenergic receptor blockers, history of hypersensitivity to the study drugs.

After pre-anesthetic evaluations, upon arrival in the operating room the patient were preloaded with lactated Ringer’s solution at 15mL/kg. The patients were monitored with electrocardiogram
(ECG), pulse oximetry (SpO₂) and noninvasive blood pressure (NIBP).

Under full aseptic conditions in the sitting position, lumbar puncture was performed at the level of L₂-L₄ through a midline approach using a 25-gauge Quincke spinal needle (Spinocan, B Braun Medical, Melsungen, Germany) with the bevel pointing cephalad. The investigator performing the block and collecting the data was blinded to the study drug.

After performing the spinal block, patients were positioned in the supine position and received 4L/min of oxygen via a face mask. Heart rate, mean arterial blood pressure and oxygen saturation were monitored in the baseline and every 15 minutes until the end of surgery and during shifting. All durations were calculated considering the time of intrathecal injection as time “0” (zero).

Sensory block levels were assessed bilaterally by pin-prick sensation using a blunt 25-gauge needle along the mid-clavicular line. Sensory blockade were assessed every 2 minutes until the highest level has stabilized for four consecutive tests, and then every 10 minutes until the point of two segment regression of the block. Further testing was performed at 30 minutes interval until the recovery of S₁ dermatome. The times to reach the T₁₀ dermatome sensory block, the peak sensory block level, a two-dermatome regression and sensory regression to the S₁ dermatome were recorded.

Motor blockade were assessed by using the Modified Bromage Scale [9]: (Bromage 0 – able to move hip, knee and ankle; Bromage 1 – unable to move the hip, but is able to move the knee and ankle; Bromage 2 – unable to move the hip and knee but is able to move the ankle; Bromage 3 – unable to move the hip, knee and ankle). Motor blockade were assessed every 2 min. before the onset of the surgery and then every 15 minutes thereafter. The times to reach modified Bromage 3 motor blockade and regression to modified Bromage Scale 0 were noted.

Intraoperative side-effects like nausea/vomiting, hypotension, bradycardia or respiratory depression, and any additive analgesia were recorded. Hypotension, defined as systolic blood pressure lower than 90 mmHg or a decrease in systolic blood pressure by 30% from baseline values, were corrected with fluids or injection mephentermine intravenously. Bradycardia, defined as heart rate less than 50 beats per minute, were treated with intravenous 0.6mg atropine sulphate.

The data collected were analyzed using Statistical Package for Social Sciences (SPSS Inc. Chicago, IL, USA) Windows based version 16.0. The comparisons of normally distributed continuous variables amongst the groups were performed using one-way analysis of variance (ANOVA) and, if appropriate, followed by the Bonferroni test for post hoc analysis. Nominal categorical data between study groups were compared using the chi-squared test or Fisher’s exact test as appropriate. ‘p’ < 0.05 values were considered statistically significant. Data were expressed as either means and standard deviations, or numbers and percentages.

RESULTS

The demographic profile was comparable among the three study groups. [Table 1] and changes in the mean arterial pressures [Fig 1] were comparable amongst the three groups throughout the perioperative period.

The mean onset time of block, both sensory upto T₁₀ dermatome and motor to Bromage 3 scale, was rapid in the group D (2.53±0.57 and 3.60±0.62) and delayed in the group M (8.00±1.29 and 9.80±1.63) in
comparison with the control group C (4.10±0.55 and 5.37±0.56). The difference between the groups, conducted through one way ANOVA with post hoc Bonferroni tests was statistically significant in both sensory (F=312.601, P<0.001) and motor (F= 274.618, P<0.001). The regression time of block, both sensory upto S1 dermatome and motor to Bromage 0 scale, was prolonged in the group D (339.00±21.06 and 306.50±19.57) and in the group M (184.50±11.92 and 156.50±12.26) when compared with the control group C (175.50±11.25 and 148.50±12.05). However, the duration was longest in the group D among the three groups. The difference between the groups conducted through one way ANOVA with post hoc Bonferroni tests was statistically significant in both sensory (F=1067, p<0.001) and motor (F=1051, p<0.001). These groups were similar in the maximal dermatome heights achieved and ‘Time taken for the peak sensory block’ to achieve were also statistically significant (F=212.63, p<0.001). The time to the first patients demand for rescue analgesic after surgery was significantly longer in group-D i.e., 356.50±30.82: 193.00±18.78: 158.00±12.42 in groups D: M: C; p< 0.001 respectively.

Table 1: Demographic profile

<table>
<thead>
<tr>
<th>Patient Profile</th>
<th>Group D (n=30)</th>
<th>Group M (n=30)</th>
<th>Group C (n=30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>35.93 ± 14.38</td>
<td>36.27 ± 11.26</td>
<td>34.80 ± 10.82</td>
<td>0.889</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>10/20</td>
<td>13/17</td>
<td>12/18</td>
<td>0.655</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>53.90 ± 7.55</td>
<td>55.13 ± 7.82</td>
<td>54.30 ± 8.60</td>
<td>0.331</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.67 ± 5.85</td>
<td>161.77 ± 6.16</td>
<td>159.40 ± 6.34</td>
<td>0.831</td>
</tr>
<tr>
<td>ASA (I/II)</td>
<td>26/4</td>
<td>27/3</td>
<td>27/3</td>
<td>0.225</td>
</tr>
<tr>
<td>Type of surgeries (Lower abdominal/ Lower limb)</td>
<td>19/11</td>
<td>20/10</td>
<td>18/12</td>
<td>0.287</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or number of patients.

Table 2: Characteristics of Spinal Anaesthesia

<table>
<thead>
<tr>
<th></th>
<th>Group D (n=30)</th>
<th>Group M (n=30)</th>
<th>Group C (n=30)</th>
<th>F value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory onset to reach T10 (min)</td>
<td>2.5±0 .57⁷</td>
<td>8.00±1.29⁹</td>
<td>4.10±0 .55</td>
<td>312.601</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Motor onset to modified Bromage 3 (min)</td>
<td>3.60±0 .6²</td>
<td>9.80±1.63³</td>
<td>5.37±0.56</td>
<td>274.618</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak Sensory Block (Thoracic segment)</td>
<td>5.43±0 .86</td>
<td>5.73±0.83</td>
<td>5.80±0.71</td>
<td>1.777</td>
<td>0.175</td>
</tr>
<tr>
<td>Time taken for peak Sensory Block (min)</td>
<td>9.83±1.23⁷</td>
<td>17.53±1.72²</td>
<td>13.07±1.36</td>
<td>212.630</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time taken for Two segment Regression (min)</td>
<td>132.33±12.5¹</td>
<td>91.83±9.69</td>
<td>97.67±10.06</td>
<td>122.685</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sensory regression to S1 (min)</td>
<td>339.00±21.06⁶</td>
<td>184.50±11.9²</td>
<td>175.50±11.25</td>
<td>1067</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Motor regression to Modified Bromage 0 (min)</td>
<td>306.50±19.5⁷</td>
<td>156.50±12.26¹</td>
<td>148.50±12.05</td>
<td>1051</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to rescue analgesia (min)</td>
<td>356.50±30.82²</td>
<td>193.00±18.78²</td>
<td>158.00±12.42</td>
<td>693.237</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Post hoc analysis using the Bonferroni test: *significantly different from other groups
** not found significant compared to group C

Two patients from group D and one patient from group C received one dose of mephenetamine and one patient from group C had shivering during intraoperative period, but statistically insignificant (p>0.05). There was no incidence of respiratory depression and nausea or vomiting. [Fig 2]
DISCUSSION

In this study, we compared the effects of intrathecal dexmedetomidine and magnesium sulphate on the characteristics of bupivacaine spinal block. The intrathecal dose of 10µg dexmedetomidine was selected based on previous human studies wherein no neurotoxic effects have been observed. [10,11] The use of dexmedetomidine has been studied as an epidural adjunct by various authors who have observed its synergism with local anaesthetic without any reports of neurological deficits. [12]

The selected dose of 50 mg intrathecal magnesium sulphate in our study was based on previous studies that the use of such a dose could prolong the duration of intrathecal opioid analgesia without additional side effects. [13,14] Furthermore, Khalili et al. [15] also demonstrated that the application of a larger dose (100 mg) could not produce any further desirable effects compared to 50 mg magnesium sulphate except prolonging the duration of sensory block with no effect on duration of motor block or duration of spinal analgesia.

Our findings of significantly shorter onset of sensory and motor block, and a significantly longer sensory and motor blocking effects of spinal bupivacaine when supplemented with intrathecal 10 µg dexmedetomidine is in consonance with the results of Kanazi et al. [16] Similar findings were observed by Gupta et al [10] and Al-Ghanem et al. [17]

The duration of motor block to Bromage 0 as observed in our study was markedly prolonged (306.50± 19.57 min, \(p <0.001\)) when compared to the duration of motor block observed in the study of Kanazi et al. [16] (250 ± 76 min, \(p < 0.001\)) and Al-Ghanem et al. [17] (240 ± 64 min, \(p < 0.001\)). The possible explanation may be attributed to use of larger dose of intrathecal dexmedetomidine (10 µg) and larger volume of drug (2.6 ml) in our study as compared to 3 µg and 5 µg dose, and 1.9 ml and 2.5 ml drug used in the respective studies. Al-Mustafa et al. [11] observed in urological procedures that the shorter onset of sensory and motor block, and the prolonged duration of spinal anaesthesia with dexmedetomidine are dose-dependent.

In the magnesium group, the onset time of sensory to reach T10 dermatome and motor blockage to Bromage 3 was prolonged compared with the dexmedetomidine group and control group, without significantly prolonging the duration of motor and sensory block compared to the control group. Similar observations were made by Unlugence et al. [13] and Khezri et
al. [14] who have shown that the addition of magnesium sulphate to hyperbaric spinal bupivacaine (0.5%) did not shorten the onset time of sensory and motor blockade, nor prolong the duration of spinal anesthesia when compared with the fentanyl group. Our results are also supported by Hung et al., [18] who reported that the addition of magnesium sulphate to amide local anaesthetic significantly shortened the duration of sciatic nerve blockade in rats which might be due to the difference in pH and baricity of magnesium solution contributing to the delayed onset.

This study has not demonstrated the effect on duration of spinal anaesthesia with addition of magnesium to local anaesthetic bupivacaine alone. However, in a study by Khalili et al.,[15] contrary to ours, addition of 100 mg intrathecal magnesium sulphate to 15 mg of isobaric 0.5% bupivacaine caused a significant prolonged duration of sensory block (106.5 vs 85.5 min, p<0.001) in patients undergoing lower extremity orthopaedic surgery. Ozalevli et al. [19] observed a similar delay in onset of spinal anesthesia but prolonged period of anaesthesia by adding magnesium sulphate 50 mg to the intrathecal combination of bupivacaine and fentanyl. The difference could be due to co-administration of magnesium to intrathecal local anaesthetic and opioid mixture, unlike in our study, where magnesium was added only to lone bupivacaine. These results are consistent with study conducted by Buvanendran et al. [20] in patients requesting labour analgesia, in which the addition of intrathecal magnesium (50 mg) to 25 μg fentanyl citrate prolonged the period of spinal analgesia.

In our study both dexmedetomidine and magnesium sulphate provided good quality intraoperative analgesia and hemodynamic stability. The time of the first rescue analgesic requirement was significantly prolonged in both the dexmedetomidine group (356.50± 30.82 min mins) and the magnesium group (193±18.78 mins) compared to the control group (158±12.42 mins). We noted significantly delayed requirement of “first analgesic request” in dexmedetomidine group when compared to magnesium group and only bupivacaine group (p < .001) which supports the analgesic efficacy of dexmedetomidine as an intrathecal adjunct. Similarly, significant improved analgesic efficacy was seen by Gupta et al. [10] on comparison of dexmedetomidine (251.7± 30.69 min.) and fentanyl (168.96± 15.96 min.) as intrathecal adjuvant (p<0.001). Eid et al. [3] and Al-Mustafa et al. [11] observed dose dependent prolongation of motor and sensory blockade with reduced analgesic requirement with increasing dosages of intrathecal dexmedetomidine (5, 10, and 15μg). The complementary action of local anesthetics and α2-adrenoreceptor agonists may account for their profound analgesic properties.

Although magnesium failed to prolong the sensory and motor regression time, the “time to first analgesia” request was increased by mean 35 minutes as compared to the control group, and was statistically significant which concurs with the findings of Khalili et al. [15] Shoeibi et al. [21] showed a 48 minutes longer time free of analgesics when intrathecal magnesium was associated to lidocaine (p<0.001). The possible explanation to this finding could be augmentation by intrathecal magnesium sulphate of the opioid effects, used as postoperative pain relief, and thereby preventing the subsequent N-methyl-D-aspartate (NMDA) activation. The addition of magnesium might have reduced the activation of C-fibers by inhibiting the slow excitatory post-synaptic currents produced by NMDA receptor activation. [22]

In our study, the peak sensory block levels among the groups were comparable as found in the study by Shukla et al. [8] The
two segment sensory block regression was significantly slower with the addition of intrathecal dexmedetomidine (132.3±12.5) as compared with magnesium (91.8±9.7) and control (97.7±10.1). These observations were found to be similar to the studies of Gupta et al. [10] and Kanazi et al. [16] in the dexmedetomidine group, compared to clonidine and fentanyl group respectively, which might be due to the synergistic action of α2-adrenoceptor agonist with the local anaesthetics. [23]

Although none of the patients in magnesium group of the study showed a hypotensive episode requiring treatment, the overall difference between the three groups were statistically insignificant (p=2.069). These findings of insignificant hemodynamic changes were consistent with that reported of Shukla et al. [8] Gupta et al. [10] Kanazi et al. [16] and Al-Ghanem et al. [17] who found that the addition of dexmedetomidine to bupivacaine is associated with hemodynamic stability.

The reasons for the hemodynamic stability in our study could be attributed mainly to good preloading. Furthermore, the associated sympathetic block is usually near-maximal with the doses used for spinal anesthesia. The addition of either dexmedetomidine or magnesium sulfate as adjuvants did not further influence the near maximal action of sympathetic block of bupivacaine. [21] The gradual onset of sympathetic blockade in the magnesium group in our study could be a contributing factor.

Magnesium causes peripheral vasodilation which improves the cutaneous circulation thereby decreasing the incidence of shivering. [24] In our study there was only one incidence of shivering in the control group. Also, the antishivering property of α2-adrenergic agents have been observed by Talke et al. [25]

**CONCLUSION**

Dexmedetomidine combined with bupivacaine for spinal anaesthesia may be particularly useful in surgeries where a prompt onset and long duration of analgesia is required but prolonged duration of motor blockade may be a hindrance for short-term surgical procedures or ambulatory surgeries whereas magnesium with a longer onset time but with shorter duration might be preferred.

**Limitations:**

There were some limitations to the present study, viz. different doses of the local anesthetic with the same adjuncts or different doses of the adjuncts could have been studied with the same local anesthetic.

**Future direction:**

Further, clinical study with different dosages of dexmedetomidine and magnesium sulphate required for supplementation of spinal local anesthetics is needed to determine the ideal safe and efficient dose.

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How to cite this article: Wapang A, Singh NR, Singh SS et al. Effect of intrathecal dexmedetomidine and magnesium sulphate on the characteristics of bupivacaine spinal block - a comparison. Int J Health Sci Res. 2014;4(12):169-177.

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