

Comparison of Dexmedetomidine, Fentanyl and Magnesium Sulfate as Adjuvants with Hyperbaric Bupivacaine for Spinal Anesthesia: A Double Blind Controlled Study

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Research Article

Abstract: Background: Intrathecal adjuvants has gained popularity with the aim of prolonging the duration of block, quality of block and decreased resource utilization compared with general anaesthesia. The purpose of this study was to evaluate the onset and duration of sensory and motor block as well as adverse effects of adding dexmedetomidine, fentanyl or magnesium to hyperbaric bupivacaine for spinal anesthesia. **Design:** randomized double blind trial. **Setting:** hospital based study during the period, march-june 2013. **Method:** 90 Patients were randomly allocated to three groups of 30 each to receive intrathecally either 15 mg hyperbaric bupivacaine plus 10 µg dexmedetomidine (group D) or 15 mg hyperbaric bupivacaine plus 25 µg fentanyl (group F) or 15 mg hyperbaric bupivacaine plus 50 mg magnesium (group M). The onset time to reach T10 sensory and Bromage 3 motor level, the regression time for L1 sensory and Bromage 0 motor block, Sedation scores, hemodynamic changes and side effects were recorded. **Statistical analysis:** Performed using computer statistical software system SPSS version 16. Data were expressed as either mean and standard deviation or numbers and percentages. Continuous covariates (age, height, weight and duration of surgery) were compared using analysis of variance (ANOVA). For categorical covariates (gender, ASA class, blood transfusion, nausea/vomiting, hypotension, bradycardia, use of ephedrine, additive analgesia, atropine and type of surgery) a Chi-square test was used, with the p value reported at the 95% confidence interval. For the time to reach T10 dermatome, Bromage 3 scale, and the regression of the sensory block to L1 dermatome and Bromage scale 0, ANOVA test was used to compare the means. The level of significance used was p<0.05. The total sample size was calculated to be 90 (30 patients in each group). **Results:** Onset of bromage 3 motor block and time to reach T10 sensory dermatome level was statistically significant between group D, group M and group F .onset time for sensory and motor block was significantly earlier in group D but delayed in group M .(P<0.001, DvsM. P<0.05, DvsF and FvsM). The time for regression of sensory block to L1 dermatome and bromage 0 motor block was significantly prolonged in group D compared to group M, which was greater than group F . (p <0.001, F vs D,M and DvsM). **Conclusion:** addition of dexmedetomidine prolonged the sensory and motor block significantly when used with hyperbaric bupivacaine for spinal anesthesia. Onset of both sensory and motor block was earlier and

significant in Dexmedetomidine group. In magnesium sulfate group although onset of sensory and motor block was delayed, the regression was significantly prolonged then fentanyl group, good haemodynamic stability was observed and there was no significant side effects in three groups during study period.

Keywords: Dexmedetomidine, bupivacaine, spinal anesthesia, intrathecal, fentanyl, magnesium sulfate

Introduction

Various intrathecal adjuvants to local anaesthetics have found to improve the quality and extend duration of spinal block. Prolongation of duration of spinal block is desirable both for long procedures and for postoperative pain relief. Different agents, such as opioids, epinephrine, phenylephrine, adenosine, magnesium sulfate, and clonidine have been used as adjuvant for prolonging the duration of spinal anesthesia. Fentanyl a mu receptor agonist, phenylpiperidine compound is increasingly used as adjuvant to spinal anaesthesia. Newer opioids are highly lipid soluble and have higher affinity for opioid receptor. they improve the quality of intraoperative anaesthesia, permit lower doses of local anaesthesia ,provides faster onset and prolong the duration of post operative analgesia with fewer side effects.^[1] intrathecally opioids acts synergistically with local anaesthetics.^[2] addition of opioid to local anaesthetics for spinal block have disadvantages such as pruritis ,urinary retention and respiratory depression. Addition of fentanyl to hyperbaric bupivacaine prolongs the duration of post operative sensory block.^[3] Antinociceptive effect of magnesium appears to be relevant not only for chronic pain^[4] but also in post operative pain.^[5] These effects are primarily based on regulation of calcium influx in to the cell. Magnesium blocks calcium influx and non competitively antagonizes NMDA channels.^[6] NMDA receptor signalling may be important in determining the duration of acute pain.^[5] addition of magnesium to spinal

anaesthesia improved post operative analgesia in orthopedic setting.^[7,8] addition of intrathecal magnesium sulfate to 10 mg bupivacaine plus 25µg fentanyl prolonged spinal anaesthesia in patients undergoing lower extremity surgery.^[8] Dexmedetomidine is a highly selective α_2 -adrenergic agonist which has been used as pre-medication and as an adjuvant to general anesthesia.^[9] Dexmedetomidine have several beneficial actions during perioperative period. They decrease sympathetic tone with attenuation of the neuroendocrine and haemodynamic response to anaesthesia and surgery, reduce anaesthetic and opioid requirement, cause sedation and analgesia. Dexmedetomidine was first introduced into clinical practice as a short term intravenous sedative in intensive care.^[10,11] Like any other adjuvant dexmedetomidine is not free from adverse effects. Use of dexmedetomidine is often associated with a decrease in heart rate and blood pressure.^[12]

Various animal studies have been conducted using intrathecal dexmedetomidine at a dose range of 2.5 to 100 µg without any neurological complications.^[13,14,15] Antinociceptive effect of dexmedetomidine, a highly selective alpha 2 adrenergic agonist was evaluated in animal studies.^[16,17] Dexmedetomidine was used to enhance the analgesic property of local anaesthetics like lidocaine, bupivacaine and ropivacaine. In vivo and in vitro studies indicated that these local anaesthetics had significant neurotoxicity.^[18] Dexmedetomidine showed protective or growth promoting properties in tissues, including nerve cells from cortex. Intrathecal dexmedetomidine has a neuroprotective effect similar to methylprednisolone.^[19,20] Clonidine, another alpha 2 adrenergic receptor agonist with a 200:1 ratio of alpha2:alpha1 receptor binding has been widely used as analgesic adjuvant for pain therapy. Clonidine is extensively used intrathecally at a dose range of 15 -150 µg as an adjuvant to local anaesthetic agents.^[21,22] In 1990s dexmedetomidine a highly selective alpha 2 agonist with a 1600:1 ratio of alpha2:alpha1 receptor binding (8 -10 fold stronger binding than clonidine) was introduced as a short term intravenous sedation in intensive care.^[11,22] Even after extensive study of both the drugs the optimal dose of clonidine and dexmedetomidine remains unknown.^[21] The mechanism by which intrathecal alpha 2-adrenergic agonists prolong the motor and sensory block of local anaesthetics is not clear. It may be an additive or synergistic effect secondary to the different mechanisms of action of local anaesthetic and alpha 2 adrenergic agonist. The local anaesthetics act by blocking sodium channels, whereas the alpha 2 adrenergic agonist acts by binding to pre synaptic C fibre and post synaptic dorsal horn neurons. Intrathecal alpha 2 adrenergic agonist produce analgesia by depressing the

release of C fibre transmission by hyperpolarization of post synaptic dorsal horn neurons.^[23] Li *et al* observed that Glutamate is involved in excitatory neurotransmission nociception and plays an essential role in relaying noxious stimuli in the spinal cord. Intrathecal injection of alpha 2 adrenergic agonists produces potent antinociceptive effects by altering spinal neurotransmitter release and effectively treats acute pain.^[23,24]

Methods

This study was a randomized, prospective, comparative study. After obtaining the Ethical Committee approval and written informed consent, 90 patients, belonging to ASA (American Society of Anesthesiologists) grade I-II scheduled for lower limb surgeries, between march – june 2013 were enrolled for the study. Exclusion criteria includes Patients with Hypertension or ischemic heart disease using beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, or noted to have dysrhythmias on the electrocardiogram (ECG), hypothyroidism, lactating mother, pregnancy, uncontrolled diabetes or chronic obstructive lung disease, a body weight of more than 100 kg, or height less than 150 cm, spinal deformity and h/o drug allergy. Premedication was avoided to the study group patients prior to surgery. Standard monitoring was used, including non-invasive arterial blood pressure (BP), ECG, heart rate (HR) and pulse oximetry (SpO₂). Preloading was done with 10 ml/kg of crystalloid solution. With the patient in the sitting position, spinal anesthesia was performed at the level of L3-L4 through a midline approach using a 25-gauge Quincke spinal needle which was inserted with the bevel pointing upwards. Patients were randomized into three groups using sealed envelope technique. The dose of hyperbaric 0.5% bupivacaine, 15 mg (3.0 ml) and total spinal volume (3.5 ml) was identical in all study groups. Patients allocated to group F received 3 ml hyperbaric 0.5% bupivacaine 15 mg + 0.5 ml of preservative free normal saline containing 25 µg Fentanyl. Patients allocated to group D received 3 ml hyperbaric 0.5% bupivacaine 15 mg + 0.5 ml of preservative free normal saline containing 10 µg dexmedetomidine. Patients allocated to group M received hyperbaric 0.5% bupivacaine 15 mg + 0.5 ml preservative free normal saline containing 50 mg magnesium sulphate. The intrathecal drug formula (total volume 3.5 ml) was prepared by a separate anaesthesiologist under a sterile technique.

The anesthesiologist performing the block was blinded to the study drug and recorded the perioperative data. he recorded the baseline value of vital signs (BP, HR, SpO₂,) before performing the spinal anesthesia, and once in every 5 minutes inside the O T, then after every 15 minutes in the Post Anesthesia Care Unit (PACU) till the

recovery of sensory and motor function. For the purpose of the study, hypotension was defined as a systolic blood pressure of <90 mm Hg and Bradycardia was defined as HR <50 beats/minute. The sensory dermatome level was assessed by pin prick sensation using 23 gauge hypodermic needle along the mid clavicular line bilaterally. The motor dermatome level was assessed according to the modified Bromage scale: Bromage 0, the patient is able to move the hip, knee and ankle; Bromage 1, the patient is unable to move the hip, but is able to move the knee and ankle; Bromage 2, the patient is unable to move the hip and knee, but is able to move the ankle; Bromage 3, the patient is unable to move the hip, knee and ankle. The sensory level and Bromage scale were recorded pre-spinal injection and every two minutes after the spinal injection up to the 10th minute and after that every 3 minutes until the highest dermatome was reached. In the PACU, the sensory level and Bromage scale were recorded every 15 minutes until the patient

was discharged from the PACU. All durations were calculated considering the time of spinal injection as time zero. When sensory levels of anesthesia were not equal bilaterally, the higher level was used for the statistical analysis. Patients were discharged from the PACU after complete recovery of sensory and motor function. No premedication was given to the study patients on the previous night of surgery. The level of sedation was evaluated just before surgery, intra operatively and post-operatively every 15 minutes using the Ramsay sedation scales: scale 1 - patient anxious, agitated, or restless; scale 2 - patient cooperative, oriented, and tranquil alert; scale 3, Patient responds to commands; scale 4, Asleep, but with brisk response to light glabellar tap or loud auditory stimulus; scale 5 - Asleep, sluggish response to light glabellar tap or loud auditory stimulus and scale 6- asleep, no response. Patient’s neurological assessment was done every day and recorded during hospital stay.

Results

90 patients were enrolled in the study. All the patients completed the study protocol and were included in the data analysis. Thus group F, group M and group D consisted of 30 patients each. There was no significant difference in the demographic data between the three study groups [p >0.05] (Table 1).

Table 1: Demographic data (mean±SD) in three study groups

| Demographic data | F | M | D | P value | Significance |
|--------------------|-------------|-----------|-------------|---------|--------------|
| AGE | 39.2 ± 12.6 | 37.4±12.1 | 36.3 ± 10.8 | >0.05 | NO |
| Male | 15 | 17 | 16 | >0.05 | NO |
| Female | 15 | 13 | 14 | >0.05 | NO |
| ASA Grade I | 24 | 25 | 26 | >0.05 | NO |
| ASA Grade II | 6 | 5 | 4 | >0.05 | NO |
| Height | 158±6 | 161±7 | 160±6 | >0.05 | NO |
| Weight | 64±7 | 63±4 | 66±5 | >0.05 | NO |
| Orthopedic surgery | 21 | 21 | 22 | >0.05 | NO |
| General Surgery | 9 | 9 | 8 | >0.05 | NO |

The time to reach T10 sensory dermatome, Bromage 3 motor block and regression of the sensory block to L1 dermatome, motor block to Bromage scale 0 were statistically significant between group D, group M and group F. onset of sensory block was rapid and regression of motor block was prolonged significantly in group D. whereas onset of both sensory and motor block was delayed in group M which is highly significant (p <0.001) when compared to group D. regression of sensory dermatome to L1 and motor block bromage 0 was highly significant (p<0.001) between three study group.

Table 2: sensory, motor block onset and regression time in minutes (mean ± SD). P values, after comparing to group F.

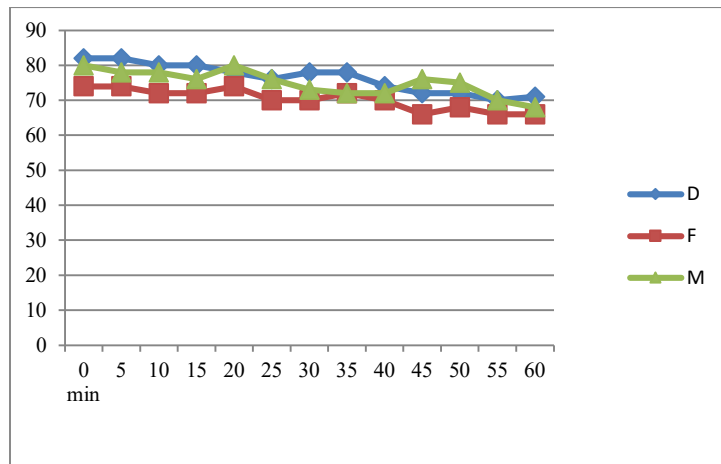
| Group | F | M | D | P value | Significant |
|-------------------|------------|------------|------------|---------|-------------|
| Time to reach T10 | 4.27±1.19 | 6.36±1.36 | 3.17±0.86 | <0.05 | yes |
| Time to Bromage 3 | 4.91±1.30 | 7.28±1.21 | 3.86±1.06 | <0.05 | yes |
| Time to reach L1 | 182.5±24.9 | 239.6±36.5 | 348.2±44.5 | <0.001 | yes |
| Time to Bromage 0 | 165.7±22.5 | 221.0±23.3 | 322.1±41.5 | <0.001 | yes |

The median and range of Highest sensory level recorded were T5 (T4 –T7) in group F, T4 (T3-T7) in group M, T5 (T3 – T6) in group D were statistically comparable (p>0.05) among three study groups. The total amount of fluids administered following spinal anesthesia, the duration of surgery, amount of ephedrine or atropine, bradycardia, hypotension, need of additive analgesia, blood transfusion, shivering and nausea or vomiting in the intraoperative or in PACU were comparable in the three groups; p>0.05 (Table 3). Values are in mean ± SD.

Table 3: perioperative characteristics (mean±SD) in three study groups

| Perioperative characteristics | F | M | D | P value | Significance |
|-------------------------------|--------------|--------------|--------------|---------|--------------|
| Intravenous fluid(ml) | 1076.7±251.5 | 1214.0±236.7 | 1123.6±251.3 | >0.05 | NO |
| Duration of surgery | 89.9 ± 22.0 | 94.4±26.5 | 92.0±24.5 | >0.05 | NO |
| Blood Transfusion | 0 | 0 | 0 | >0.05 | NO |
| Additive analgesia | 0 | 0 | 0 | >0.05 | NO |
| PONV | 1 | 0 | 0 | >0.05 | NO |
| Bradycardia | 2 | 1 | 2 | >0.05 | NO |
| Hypotension | 1 | 0 | 1 | >0.05 | NO |
| Atropine | 2 | 1 | 2 | >0.05 | NO |
| Ephedrine | 1 | 0 | 1 | >0.05 | NO |
| Respiratory depression | 0 | 0 | 0 | >0.05 | NO |
| Shivering | 0 | 0 | 0 | >0.05 | NO |

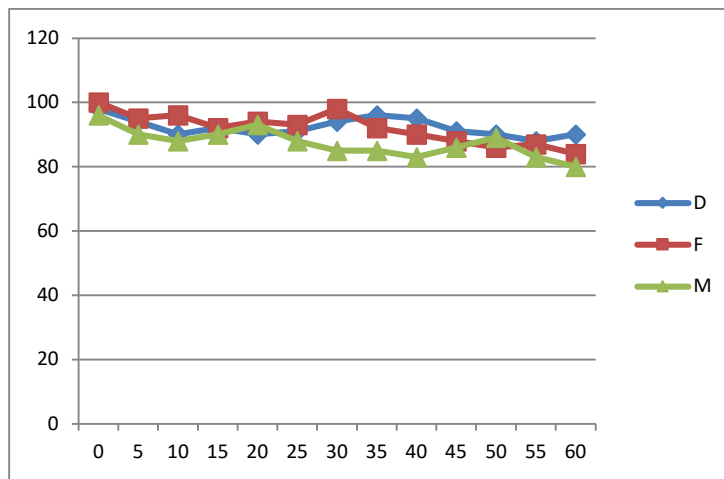
The mean ±SD values of heart rate (H R) and mean arterial pressure (MAP) measured in O T and PACU were comparable between three groups. Figure 1 and 2 show graphical representation of H R and MAP measured during 1 st hour of study.



Time –x axis, heart rate – y axis

Figure 1: heart rate measured during 1st hour. (Mean±SD)

Figure 1 show the (mean ± SD) HR in the OT measured during 1st hour, showing no significant difference among the groups. H R was comparable among three groups in PACU as well.



Time – x axis, MAP –y axis

Figure 2: Mean arterial pressure measured during 1st hour (Mean±SD)

Figure 2 shows the (mean \pm SD) MAP in the OT measured during 1st hour, showing no significant difference among the groups .MAP values were comparable among three groups in PACU also

Ramsay sedation score was 2 in all the study subjects during their stay in O T and PACU .The SpO₂ was higher than 95% in all patients in the three groups both in the intraoperative and in the PACU. Study patients did not show any neurological impairment related to spinal anesthesia such as back, buttock or leg pain or weakness, headache or any new neurological deficit. No patients suffered from respiratory depression or shivering during the study.

Discussion

Prolongation of duration of spinal block is desirable both for long procedures and for postoperative pain relief. Different agents, such as epinephrine, phenylephrine, adenosine, magnesium sulfate, and clonidine have been used as adjuvant for prolonging the duration of spinal anesthesia.

Dexmedetomidine was used in a smaller dose in the spinal block combined with bupivacaine, leading to fast onset and prolongation of block without any significant hemodynamic instability or sedation.^[25,26] Largest dose of dexmedetomidine used intrathecally in humans was 10 μ g²⁷ .Previous Studies revealed haemodynamic stability with 5 and 10 μ g of dexmedetomidine as intrathecal adjuvant. ^[25,26] gupta *et al* and al ghanem *et al*. found intrathecal dexmedetomidine with bupivacaine is associated with prolonged motor and sensory block with haemodynamic stability when compared to intrathecal fentanyl(25 mics).^[28,29] . Kanazi *et al*²⁶ found that the supplementation of bupivacaine (12.0 mg) spinal block with dexmedetomidine (3 μ g) produces significantly shorter onset of motor block, and a significantly longer sensory and motor block with preserved haemodynamic stability and lack of sedation.^[26] Al-Mustafa *et al*²⁷ compared the doses of dexmedetomidine 5, 10 μ g in isobaric bupivacaine 12.5mg (total volume:3 ml) with plain isobaric bupivacaine without premedication and found the effect to be dose dependent on the onset and regression of sensory and motor block with comparable sedation scores among three groups.^[27]

On the other hand in magnesium group the onset time to reach sensory dermatomal level T10 and motor block to bromage 3 was delayed. Ozalevli *et al* observed asimilar delay in onset of spinal anaesthesia when adding intrathecal magnesium to fentanyl and isobaric bupivacaine.^[8] shukla *et al* found rapid and prolonged duration of surgical anaesthesia in dexmedetomidine group when compared to intrathecal magnesium. They also found that there was a delay in onset of sensory and motor block in magnesium group, but the regression of

block was prolonged as compared to plain hyperbaric bupivacaine.^[30]

In our study with the usage of 10 μ g of intrathecal dexmedetomidine with 15 mg hyperbaric bupivacaine (total volume :3.5 ml) there is a quicker onset and prolong duration of sensory and motor block when compared to magnesium and fentanyl which is similar to Al-ghanem *et al* and shukla *et al*.^[29,30] The onset of sensory block was statistically prolonged in magnesium sulfate group compared to group D and group F, which is similar to the observations made by Ozalevli *et al*. and malleeswaran *et al*.^[8,31] reason for this delayed onset of action in magnesium group may be due to change in p^h and baricity of bupivacaine due to addition of magnesium sulfate .haemodynamic stability was maintained in all the three study groups. Dexmedetomidine has anti shivering effect^[32] and there was no incidence of perioperative shivering among study groups.

Conclusion

In conclusion, addition of dexmedetomidine prolonged the sensory and motor block significantly when used with hyperbaric bupivacaine intrathecally, without increasing the incidence of significant adverse effects. We support the addition of dexmedetomidine 10 μ g with bupivacaine in spinal anesthesia when prolongation of spinal anesthesia is desired. Addition of dexmedetomidine avoids general anesthesia in few unexpected cases when surgical duration prolongs. Intrathecal magnesium also prolongs the duration of sensory and motor block regression compared to fentanyl group, but lesser then dexmedetomidine group and is with a delayed onset. We recommend further study in this direction to know the ideal dose of drug for safe spinal anaesthesia.

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