Dexmedetomidine versus morphineas an adjuvants for spinal anaesthesia A double blind controlled study

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Abstract

Background: Intrathecal adjuvants has gained popularity with the aim of prolonging the duration of block, quality of block,postoperative analgesia, 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, postoperative analgesia as well as adverse effects of adding Dexmedetomidine or morphine to hyperbaric bupivacaine for spinal anesthesia. objective of the study was to evaluate and compare the anaesthetic properties of intrathecal dexmedetomidine with time tested morphine.
Design : randomized double blind trail.
Setting : hospital based study
Method : 90 Patients between the period of march to june 2013 were randomly allocated to three groups of 30 each to receive intrathecally either 15 mg hyperbaric bupivacaine + saline (group B) or 5µg of dexmedetomidine + 15 mg hyperbaric bupivacaine (group D) or 100 µg morphine + 15 mg hyperbaric bupivacaine (group M). The onset time to reach T10 sensory and Bromage 3 motor level, the regression time for S1 sensory and Bromage 0 motor block, Sedation scores, hemodynamic changes and side effects were recorded.
Results: Onset of bromage 3 motor block and time to reach T10 sensory dermatome level was statistically significant between group D and group M, B ($P < 0.05$, D vs M,B). The time for regression of sensory block to S1 dermatome and bromage 0 motor block was prolonged by addition of dexmedetomidine . ($p < 0.001$, DvsM,B).
Conclusion: onset of both sensory and motor block was rapid and regression of sensory and motor block was prolonged with the addition of Dexmedetomidine without any side effects .duration ofPost operative analgesia was longer in morphine group but it was associated with minor adverse effect like pruritus.

Keywords: Dexmedetomidine, bupivacaine, morphine,intrathecal, spinal anesthesia.

Introduction

Lower limb surgeries are mostly performed under spinal anaesthesia. It has the advantage of being free from the risks of intubation but its duration of action is limited. Various intrathecal adjuvants to local anaesthetics have found to improve the quality, extend duration of spinal block and post operative analgesia.Opioids are considered a gold standard in clinical practice for treatment of pain. Morphine was the first opioid approved by the US food and drugs administration for spinal administration. All opioids probably produce analgesia, at least in part by a spinal mechanism through opioid receptors [1]. Morphine is a potent analgesic widely used for treatment of acute pain and for longterm treatment of severe pain. Bioavailability of hydrophilic drugs like morphine is

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superior to that of lipophilic opioid [2]. Hydrophilic opioids like morphine crosses blood-brain barrier slowly and this results in prolonged rostral spread(resuting in delayed respiratory depression), slow onset and long duration of action.Intrathecal morphine was studied between dose range of 100-4000 µg. morphine as adjuvant in spinal anaesthesia is associated with side effects like pruritus ,urinary retention, respiratory depression and nausea and vomiting. Several trails have examined intrathecal doses between 50 -300 µg and found it safe with limited side effects. Low incidence of adverse events reported by the respondents along with the popularity of the technique suggests that low dose spinal opioid administration is safe [3,4,5]. intrathecal morphine dose of 100µg has been defined as the optimal dose in a qualitative and quantitative systematic review of randomized controlled trails for caesarean section [6]

Dexmedetomidine is a highly selective α2-adrenergic agonist which has been used as pre-medication and as an adjuvant to general anesthesia.[7]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 andopiod requirement, cause sedation and analgesia. Dexmedetomidine was first introduced into clinical practice as a short term intravenous sedative in intensive care [8,9]. 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 [10].

Various animal studies have been conducted using intrathecal dexmedetomidine at a dose range of 2.5 to 100 µg without any neurological complications [11,12,13]. Antinociceptive effect of dexmedetomidine, a highly selective alpha 2 adrenergic agonist was evaluated in animal studies [14,15] 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 [16]. Dexmedetomidine showed protective or growth promoting properties in tissues, including nerve cells from cortex and has aneuroprotective effect similar to methylprednisolone in spinal cord injury when used intrathecally [17,18].

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 [19,20]. In 1990s dexmedetomidine a highly selective alpha 2 agonist with a 1600:1 ratio of alpha2:alpha1 receptor binding (8 -10 fold stronger binding then clonidine) was introduced as a short term intravenous sedation in intensive care.[9,20] Even after extensive study of both the drugs the optimal dose of clonidine and dexmedetomidine remains unknown [19].

Different agents, such as epinephrine, phenylephrine, adenosine, magnesium sulfate, and clonidine have been used as adjuvant for prolonging the duration of spinal anesthesia. The mechanism by which intrathecal alpha 2-adrenergic agonists prolong the motor and sensory block of local anesthetics is not clear. It may be an additive or synergistic effect secondary to the different mechanisms of action of local anesthetic and alpha 2 adrenergic agonist. The local anesthetics 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 realease of C fibre transmission by hyperpolarization of post synaptic dorsal horn neurons [21]. 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 [22]. Intrathecal injection of alpha 2 adrenergic agonists produces potent antinociceptive effects by altering spinal neurotransmitter release and effectively treats acute pain [21,22].

Methods

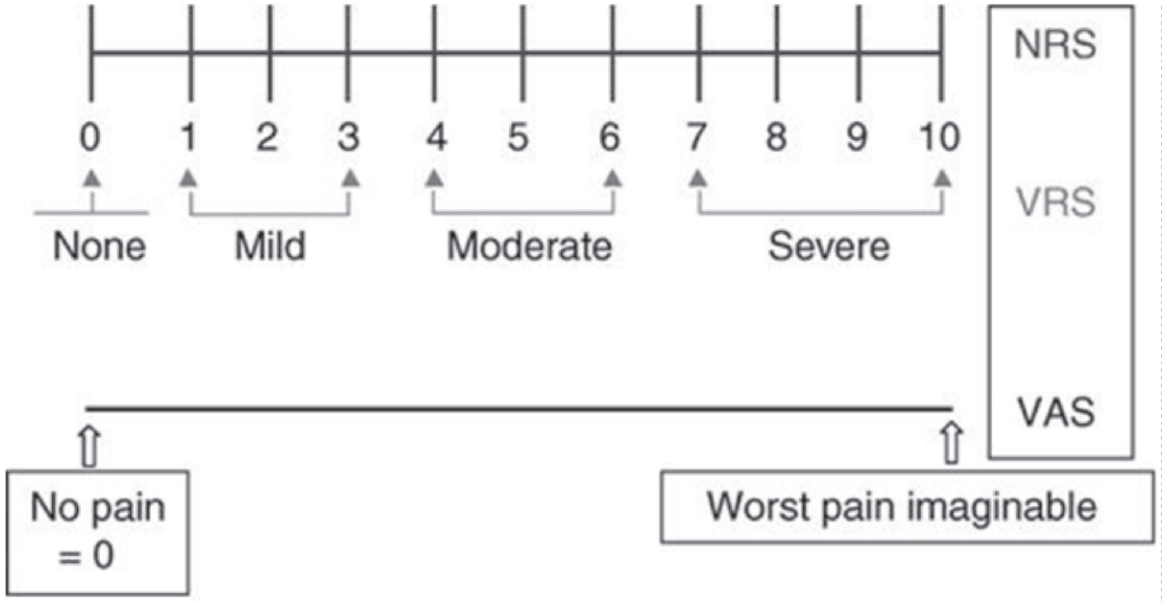
This study was a randomized, prospective, comparative study. After obtaining the Ethical Committee approval and written informed consent, 90 patients ASA (American Society of Anesthesiologists) grade I-II scheduled for lower limb surgeries, between march – june 2013 were enrolled for the study. Patients 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 mothers ,pregnant woman, 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 were excluded from the study. 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 500 ml 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) +1 ml was identical in all study groups. Patients allocated to group D received 3 ml hyperbaric 0.5% bupivacaine15 mg + 1 ml of preservative free normal saline containing 5 µg dexmedetomidine. Patients allocated to group M received 3 ml hyperbaric 0.5% bupivacaine 15 mg + 1 ml of preservative free normal saline containing 100 µg morphine. Patients allocated to group B received hyperbaric 0.5% bupivacaine 15 mg + 1 ml preservative free normal saline. The intrathecal drug formula was prepared by a separate anaesthesialogist under a sterile technique.

The anesthesiologist performing the block was blinded to the study drug and recorded the perioperative data. anaesthetist 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 23gauge 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 sensory regression to the S1 segment, and Bromage scale of 0.

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. Pain was assessed using visual analogue scale (VAS) every hourly in post operative period. Analgesia was given whenever VAS score was >4 (inj diclofenac 75 mg intramuscularly).inj tramadol 100 mg was supplemented whenever required. Patientsneurological assessment was done every day and recorded during hospital stay.

Figure1. Visual analogue scale.



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, nausea/vomiting, pruritus, hypotension, bradycardia, use of ephedrine, atropine, postoperative analgesia requirement, 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 S1 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

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

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

Demographic data	B	D	M	P value	significanc
Age[yrs]	35.2 ± 11.8	36.5±12.2	37.8 ± 10.6	>0.05	NO
Male	17	17	18	>0.05	NO
Female	13	13	12	>0.05	NO
ASA Grade I	23	24	25	>0.05	NO
ASA Grade II	7	6	5	>0.05	NO
Height	160±6	162±8	161±7	>0.05	NO
Weight[kg]	66±8	65±7	62±5	>0.05	NO
Orthopedic surgery	25	26	24	>0.05	NO
General Surgery	5	4	6	>0.05	NO

The time to reach T10 sensory dermatome, Bromage 3 scale were statistically significant between group D and group B, M but comparable among B and M groups. The regression of the sensory block to S1 dermatome and motor block to Bromage scale 0 were affected by the addition of Dexmedetomidine significantly, but comparable between group B and M [Table 2].

Table 2. Sensory, motor block onset and regression time in minutes (mean ± SD). P values after comparing with group D.

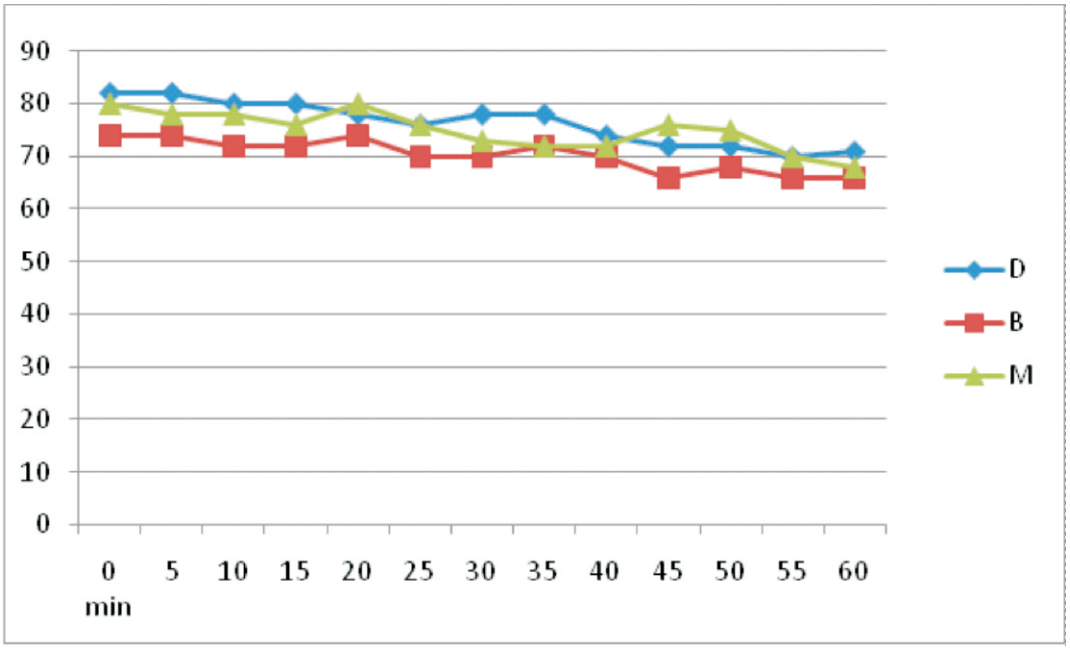
Group	B	D	M	P value	significant
Time to reach T10[min]	4.7±1.1	3.1±0.8	4.4±0.5	<0.05	yes
Time to Bromage 3[min]	5.6±1.4	4.4±1.1	5.3±1.2	<0.05	yes
Time to reach S1[min]	159.2±19.9	249.6+26.8	165.2±22.4	<0.001	yes
Time to Bromage 0[min]	149.4±17.5	225.0+23.3	151.1±21.5	<0.001	yes

.The median and range of Highest sensory level recorded were T5(T4 -T7) in group B, T4(T3-T7) in group D, T5(T4 –T8) in group M 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, urinary retention and nausea or vomiting in the intraoperative or n PACU were comparable in the three groups (*p*>0.05) (Table 3). Itching and pruritus was observed in six patients belonging to group M (P<0.05) which is significant when compared and responded promptly to antihistamines. . All patients in groups B and D and four patients in group M received inj Diclofenac. Doses of Diclofenac taken over the24-hour study duration was Significantly lower in group M (p <0.001) than ingroups D, B but the difference between group D and B were comparable. Five patients in group B received tramadol (total amount received 600 mg) whereas no patients in either group D or M required tramadol. The mean time of the first analgesic request was significantly prolonged in group M(20. 2±2.2 hrs, p<0.001) and group D (3.6±0.65 hrs, p<0.05) when compared to group B (2.7 ±0.21hrs)

Table 3. Perioperative characteristics (mean±SD) in three study groups

Perioperative characteristics	B	D	M	P value	significance
Intravenous fluid[ml]	1146.7±251.5	1310.0+236.7	1163.6±251.3	>0.05	NO
Surgical duration[min]	92.9 ± 27.0	98.4±32.5	96.0±24.5	>0.05	NO
Itching and pruritus	0	0	6	<0.05	NO
Diclofenac/tramadol[no of doses]	65/5	57/0	4/0	<0.001	NO
PONV	1	0	1	>0.05	NO
Bradycardia	2	1	1	>0.05	NO
Hypotension	1	0	1	>0.05	NO
Atropine	2	1	1	>0.05	NO
Ephedrine	1	0	1	>0.05	NO
Respiratory depression	0	0	0	>0.05	NO
Urinary retention	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 2 and 3 show graphical representation of H R and MAP measured during 1 st hour of study.



Time –x axis[min], heart rate – y axis[mm of Hg]

Figure 2. Heart rate measured during 1st hour. (Mean±SD)

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

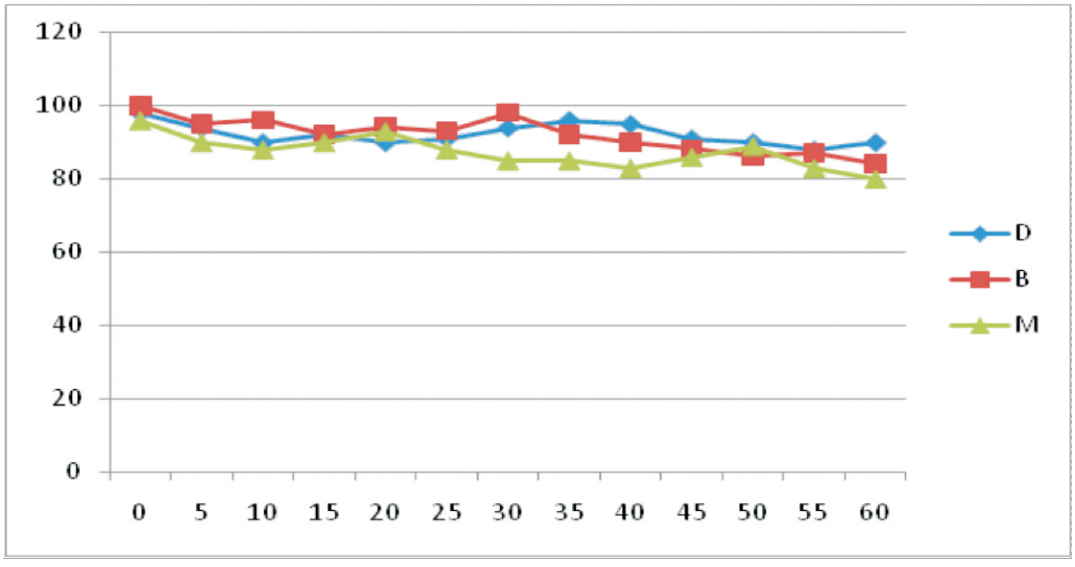


Figure 2. Mean Arterial pressure during first hour (Mean ± SD)
Time - X axis, MAP - Y axis

Figure 2 shows the (mean ± SD) MAP 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 period .

Discussion

Prolongation of duration of spinal block is desirable both for long procedures and for postoperative pain relief. Dexmedetomidine was used in a smaller doses in the spinal block combined with bupivacaine, leading to fast onset and prolongation of block without any significant hemodynamic instability or sedation [23,24]. Previous Studies revealed haemodynamic stability with 3 and 5 µg of dexmedetomidine as intrathecal adjuvant.[23,24] .Kanazi et al. found that the supplementation of bupivacaine (12.0 mg) spinal block with dexmedetomidine (3 µg) produces significantly shorter onset of motor block, and a significantly longer sensory and motor block with preserved haemodynamic stability and lack of sedation[2,4]. Mohamed et al found intrathecaldexmedetomidine 5µg improved the quality and duration of post operative analgesia and also provides analgesic sparing effect in patients undergoing major abdominal cancer surgery [25]. Satoh et al observed, 0.1-0.2 mg of intrathecal morphine is usefull for pain relief after trans vaginal hysterectomy and occompanies no major side effects.[26] Uchiyama et al recommended 100 µg of intrathecal morphine as optimal dose for post operative analgesia in caesarean section[27]. In our study with the usage of 5 µg of intrathecal dexmedetomidine with 15 mg hyperbaric bupivacaine there is a prolongation of duration for regression of sensory and motor block in group D which is comparable to Kanazi and Mohamed et al [18,19]. First analgesic request was significantly prolonged in Morphine group with very less consumption of analgesic drugs during first 24 hours which is comparable to Damevski et al and Matsuda et al [28,29]. In our study we did not pre-medicate any patients and got similar Ramsay sedation scores in group D, M and group B which is comparable to kanazi et al [24]. Dexmedetomidine also have anti shivering property and there was no shivering in the entire study group [30].

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 5 µg 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. Morphine produces prolong analgesia in post operative period with minimal side effect like pruritus. We recommend further study in this direction.

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