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BMH Med. J. 2019;6(2):47-57. **Editorial**

Effect Of Intravenous Dexmedetomidine On Subarachnoid Block Characteristics, Using 0.5% Hyperbaric Bupivacaine, In Patients Undergoing Unilateral Knee Arthroscopy - A Prospective Randomized Double Blinded Placebo Controlled Study

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Abstract

Introduction: Many techniques and drug regimens, with partial or greater success, have been tried from time to time to eliminate the anxiety component, to improve the quality of regional anesthesia and prolong the postoperative analgesia. Alpha 2-adrenergic agonists have both analgesic and sedative properties, when used as an adjuvant to regional anesthesia. They potentiate the effect of local anesthetics and prolong the duration of motor and sensory spinal blockade and postoperative analgesia. Dexmedetomidine is a selective alpha 2-adrenoreceptor agonist; it has a alpha 2/alpha 1 selectivity ratio which is ten times higher than that of clonidine. So we hypothesised that a premedication with intravenous dexmedetomidine 0.5mcg/kg will prolong sensory and motor block with hyperbaric bupivacaine and significant postoperative analgesia with minimal side effects.

Material and Methods: In our study, 70 patients undergoing elective unilateral knee arthroscopic surgeries were randomly allocated into two groups A and B. Group A received intravenous dexmedetomidine 0.5mcg/kg bolus over 10 minutes prior to subarachnoid block and group B received similar volume of normal saline. The time of onset of sensory block, duration of sensory block, peak sensory level attained, time to reach peak sensory level, time of onset of motor block, duration of motor block, hemodynamic characteristics, duration of postoperative analgesia, sedation, side effects and other outcomes were recorded and compared between the two groups. We presumed that premedication with dexmedetomidine will prolong the quality of spinal block without significant hemodynamic alterations and side effects.

Results: We concluded that intravenous dexmedetomidine 0.5 mcg/kg administered 30 minutes before subarachnoid block as loading dose alone will shorten the onset of both sensory and motor block of subarachnoid block with hyperbaric 3 ml 0.5% bupivacaine and provide adequate intraoperative sedation without significant hemodynamic alterations and harmful side effects.

Key words: isobaric, 0.5% bupivacaine, Dexmedetomidine, Knee arthroscopy, Subarachnoid Block

Introduction and background

Subarachnoid block(SAB) is a widely used regional anesthetic technique, particularly advantageous for lower abdominal and lower limb surgeries. Main advantage of subarachnoid block are rapid onset, superior blockade, reduced side effect, shortened stay in post anesthesia care unit and cost effectiveness. But these advantages can be short lived and limited by the relatively short duration of action of currently available local anesthetics, resulting in inadequate post operative analgesia. In recent years, use of adjuncts has gained popularity with the aim of prolonging the duration of block and post operative analgesia. Alpha 2 agonists are used as the major adjuvant drugs to local anesthetics in potentiating the effect of local anesthetics and allowing a decrease in the dose of local anesthetic required.

Dexmedetomidine, a highly selective alpha 2 adrenergic agonist has evolved as a panacea for various applications and perioperative procedures in the perioperative and critical care settings. Though approved for intensive care unit sedation, studies are being conducted on its off label use. Previous animal and human studies suggest a 1:10 dose ratio between dexmedetomidine and clonidine. Dexmedetomidine, a highly selective Alpha 2 - adrenoreceptor agonist with a relatively high ratio of Alpha 2/Alpha 1 activity, possesses sedative, analgesic, perioperative sympatholytic, anesthetic sparing and hemodynamic stabilizing properties, but lacks respiratory depression [3,4], making it a useful and safe adjunct in diverse clinical applications.

In the spinal cord, activation of both alpha 2A and 2B adrenoreceptors situated in the neurons of the superficial dorsal horn (especially lamina II) [6-8], directly reduces pain transmission by reducing the release of pro-nociceptive transmitter, substance P and glutamate from primary afferent terminals and by hyperpolarizing spinal interneurons via G protein mediated activation of potassium channel.

Post synaptic activation of alpha 2-adrenoreceptors results in sympatholytic effect leading to hypotension and bradycardia, an effect judiciously used to attenuate the stress response of surgery [10-12]. Other useful effects of activation of Alpha 2A receptors include decreased salivation, increased glomerular filtration, decreased intraocular pressure and decreased shivering threshold. The hypnotic and supraspinal analgesic effects of dexmedetomidine is mediated by the hyperpolarisation of nor adrenergic neurons, which suppresses neuronal firing in the locus ceruleus along with inhibition of norepinephrine release and activity in the descending medullospinal noradrenergic pathway, secondary to activation of central alpha 2 adrenergic receptors.

Dexmedetomidine has poor bioavailability due to extensive first pass metabolism. It exhibits linear pharmacokinetics over dose range of 0.2-0.7mcg/kg/hr intravenous infusion. It is 94% protein bound and does not displace most of the protein bound drugs used in anesthesia and intensive care [13]. It undergoes complete biotransformation by glucoronidation and by cytochrome P450 mediated aliphatic hydroxylation to inactive metabolites. These metabolites are excreted in urine (95%) and in feces (4%). The dose needs to be adjusted in hepatic failure owing to lower rate of metabolism.

The clinical utility of dexmedetomidine is expanding with the availability of more and more literature from various studies carried out across the globe. In 1999, FDA approved [13] dexmedetomidine as a sedative in the intensive care unit owing to its favourable properties of a linear pharmacokinetic profile, short elimination half-life and absence of any respiratory depression. Because of its anxiolytic, analgesic sympatholytic and sedative effects, dexmedetomidine has found its application in the perioperative period for premedication, prevention of stress response to laryngoscopy, and for the prevention of emergence delirium [9]. It has also been found to potentiate the effects of all anaesthetics namely intravenous and inhalational agents and opioids thereby reducing the doses required. It can also help in reducing the oxygen requirements of the body and help in the prevention of intraoperative myocardial ischemia.

Materials and methods

After obtaining approval from hospital ethical committee along with written and informed consent, 70 adults of either sex belonging to ASA grade 1 or ASA grade 2 scheduled for unilateral knee arthroscopy under subarachnoid block were enrolled in this prospective randomized double blinded study.

All patients were examined one day prior to surgery as part of the preanesthetic check up where a detailed history was taken, the patient physically examined, the body weight and height measured and relevant routine and special investigations asked for. All patients were familiarised with visual analogue scale (VAS) and its use for measuring the postoperative pain. Patients were divided into two groups by computer software generated randomisation into group A and group D. They were advised fasting for 6 hours and received tab. ondansetron 8 mg tab. ranitidine 150 mg as a premedication at night before and in morning on the day of surgery. All patients were receiving tab. midazolam 7.5 mg in the morning of surgery to relieve anxiety. After securing a suitable peripheral cannulation, all patients were preloaded with ringer lactate 10ml/kg.

Study solution A: It was prepared by taking 100 ml of normal saline
Study solution D: It was prepared by taking dexmedetomidine at 0.5mcg/kg diluted to 100 ml with normal saline.

Under all aseptic precautions, after local infiltration with 2 ml of 1% Lignocaine a subarachnoid block was performed with 3 ml of 0.5% (hyperbric) Bupivacaine using a 25G Quincke's spinal needle in the L3-L4 intervertebral space with the patient lying in the lateral position after confirmation of the free flow of clear CSF.

Recording of block dynamics

Characteristics of sensory block

1. Time of onset of sensory block at T10

The onset of sensory block was defined as the time duration between administration of the subarachnoid block and the absence of pain at the T10 dermatome. It was assessed by a sterile pinprick at the midclavicular line anteriorly every minute till the T10 dermatome is achieved.

2. Maximum sensory level achieved

The highest level of sensory block was evaluated by a sterile pin prick at the midclavicular line anteriorly every minute till the maximum sensory level is achieved.

3. Time taken to achieve maximum sensory level

Time duration between the administration of the subarachnoid block and the achievement of the maximum sensory level was noted.

4. Time to two segment regression

The duration of sensory block was defined as the time to regression by two segments from the maximum block height. It was evaluated by pinprick at the midclavicular line anteriorly every 15 minutes in the intraoperative period.

Characteristics of motor block

1. Time to reach Modified Bromage Scale 3

The degree of motor block was assessed by the patient's leg and feet movement. This was classified into four grades according to the criteria described by the Modified Bromage Scale:

Grade 0 : No paralysis

Grade 1 : Unable to raise extended leg

Grade 2 : Unable to flex knee

Grade 3 : Unable to flex ankle

Time to reach Modified Bromage scale grade 3 i.e: time elapsing from administration of subarachnoid block to failure to flex ankle on command, was noted. It was evaluated every minute for the first 10 minute.

2. Duration of motor block

Motor block duration is the time elapsing from administration of subarachnoid block to return to the Modified Bromage scale 1, ie patient unable to raise extended leg. It was evaluated every 15 minute in the intraoperative and post operative periods

Recording of hemodynamic characteristics

1. Mean arterial pressure and heart rate

It was recorded before premedication, 5 minutes after premedication with the study drug, immediately before the subarachnoid block, then every minute after the subarachnoid block till 10 minutes then at 30 minutes, 45 minutes, 60 minutes and then every 30 minutes till the end of surgery.

2. No of bolus doses of vasopressors required

Hypotension, defined as a decrease in systolic blood pressure of more than 20% from baseline and was treated with an intravenous bolus dose of 6mg ephedrine. The total no. of bolus doses required throughout the intraoperative period was noted.

3. No. of doses Atropine (0.6mg) given for bradycardia

Heart rate <50, defined as bradycardia, was treated by a bolus dose of 0.6mg atropine. The total no of doses of atropine required was noted.

Sedation score

Degree of sedation was closely monitored in patients of both the groups. Sedation scoring was based on Ramsay sedation score .It was done before giving the premedication drug, 5 minutes after premedication,then 30minutes, 60 minutes, 90 minutes, 120 minutes, 180 minutes after premedication. The Ramsay Sedation Score is defined as follows:

Ramsay score 1: Patient is anxious agitated or restless or both

Ramsay score 2: Patient is cooperative,oriented and tranquil

Ramsay score 3: Patient responds to commands only

Ramsay score 4: Patient exhibits brisk response to light glabellar tap or loud auditory stimulus

Ramsay score 5:Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus

Ramsay score 6:patient exhibits no response

Duration of the surgery

In this study surgeons were allowed to start the operation once analgesia is attained at T10 dermatome confirmed by the pin prick method. Duration of surgery in this study was taken as time from surgical incision to the skin closure.

Monitoring of postoperative analgesia

Assessment of post operative pain was done by the attending nurse using the visual analogue scale (VAS, **Figure 1**) [26]. In this, the patient was first educated about the scale and then allowed to mark a point on the scale of 0-10, depending on the degree of pain he/she receiving at that moment

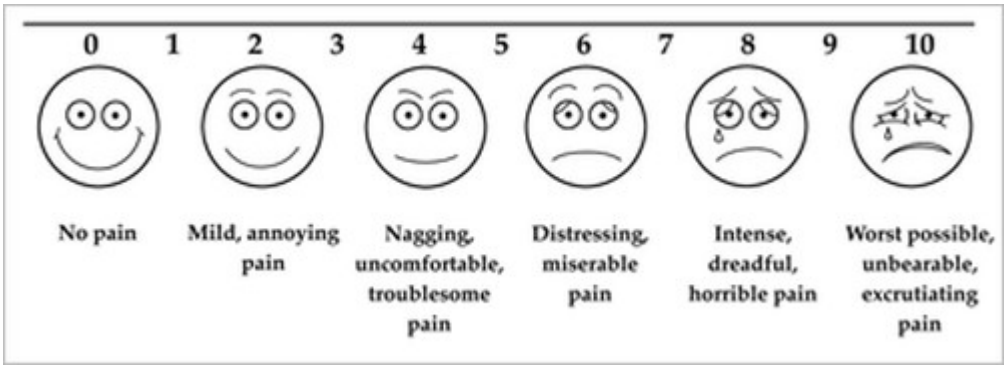

Figure 1: Representation of visual analogue scale

At every assessment, a fresh scale was shown to the patient. Recording was done every hour in the postoperative care unit, till the patient demands a rescue analgesic.

Duration of spinal anesthesia

The duration of spinal anesthesia is defined as the period from administration of the subarachnoid block to the first occasion when the patient demands a rescue analgesic in the postoperative care unit.

Time of administration of rescue analgesic for pain relief

When the pain was complained by the patient or when the patient had visual analogue scale (VAS) >4, they were given the rescue analgesic i.e: Inj. Tramadol 100 mg iv and the time elapsed from the time of administration of the subarachnoid block was noted. Once a patient received rescue analgesia, subject is no more part of the study.

Complications and other outcome

Patient was closely observed post operatively for 6 hours for complications like nausea, vomiting,

shivering, headache, dry mouth etc which were subsequently managed as per standard institutional protocols.

Results

Comparison of demographic variables

Demographic data analysis of the study population on the basis of age, sex, weight, height and duration of surgery did not reveal any statistically significant difference between the two groups ($p>0.05$) A and D (**Table 1**). Hence, the groups were found to be comparable.

The baseline heart rate and mean arterial pressure among two groups A and D also showed no significant difference (p value>0.05). This analysis confirmed that both groups were comparable.

Table 1

PARAMETER	GROUP A	GROUP D	P VALUE
AGE IN YEARS	35.86±8.171	35.84±6.792	0.862
HEIGHT IN CENTIMETERS	168.7±4.674	166.8±7.162	0.177
WEIGHT IN KILOGRAMS	72.83±8.797	69.51±8.624	0.116
BASELINE HR	69.86±5.094	70.09±7.298	0.880
BASELINE MEAN ARTERIAL PRESSURE	93.63±4.346	94.80±5.229	0.312
DURATION OF SURGERY IN MINUTES	76.49±20.37	79.97±17.38	0.444

Block characteristics

Onset of sensory blockade

Mean time of onset of sensory block was shorter in group D (study group) which was 4.31±0.963 minutes, while that in group A(control group) was 5.23±1.352 minutes(p value =0.002).

Peak sensory level achieved Comparison of level of highest sensory blockade level showed that 71.4% in group A (control group) had peak sensory level of blockade at T6 and 28.6% patients had peak sensory level at T4. In group D (study group) 60% had peak sensory level at T6, while 40% had peak sensory level at T4 (**Table 1**). It means there is no significant difference between the two groups in terms of peak sensory level achieved (p value = 0.314). Time taken to reach maximum sensory level Comparison of time taken to reach highest sensory blockade in Group A (control group) and Group D (study group) showed that mean time taken for highest sensory blockade was 7.80±1.922 minutes for control group (Group A) and 7.46±2.077 minutes for study group (Group D). 'p' value was found to be 0.476 i.e. statistically insignificant ($p> 0.05$).

Duration of sensory blockade

Analysis of duration of sensory blockade showed that Group D(study group) had slightly longer duration of sensory blockade ie 120.9±24.39 minutes compared to Group A (control group) ie 112.1±22.76 minutes. But the difference was not statistically significant Single bolus dose of intravenous dexmedetomidine follows zero order linear pharmacokinetics, meaning that a constant amount of the drug is eliminated per hour rather than a constant fraction of the drug eliminated per hour,which is characteristic of first order kinetics. After intravenous administration in healthy adult volunteers, dexmedetomidine has an onset of action after approximately 15 minutes. Peak concentrations are usually achieved within 1 hour after drug administration and the duration of action is 60-120 minutes and is dose dependent.

Based on the inferences from present study, we found that intravenous dexmedetomidine 0.5 mcg/kg administered 30 minutes before subarachnoid block as loading dose alone may not produce sufficient plasma concentration of the drug to prolong the duration of sensory block with hyperbaric 3 ml 0.5% bupivacaine.

Motor block characteristics

Onset of motor blockade:

Analysis showed that onset of motor blockade in group D (study group) is shorter ie 7.29±1.619 minutes compared to group A (control group) ie 8.46±1.462 minutes and this difference is statistically significant with p value <0.002

Duration of motor blockade:

Analysis revealed that mean time duration in group D (study group) was slightly higher (194.1±28.63 minutes) compared to the group A (control group)(186.4±20.99 minutes). But the p value was 0.203, statistically insignificant.

Comparison of motor block in our study compared with other authors is given in **Table 2**.

Table 2

Authors	Duration of motor block (minutes)	Duration of motor block (minutes)	
	Dexmedetomidine	**Saline**	**P value**
Reddy VS et al (n=25) (2013)	146.53±31.62	139.89±32.18	0.4112
Kaya et al (n=25) (2010)	193±27	180±34	>0.05
Annamalai A et al (n=30) (2013)	196±33	184±24	>0.05
Lee MH et al (n=20) (2014)	132.9±434	98.8±34.1	<0.05
Present study (n=35)	**194.1±28.63**	**186.4±20.99**	**0.203**

Conclusions

Analysis of our recorded observations revealed the following:

1. The demographic data including age, gender, body weight, height and duration of surgery, baseline heart rate and baseline mean arterial pressure among the two groups were comparable.(p values >0.05)

2. There was a significant difference in the onset of sensory blockade between the two groups. The data revealed that onset of sensory blockade was shorter in group D (study group) ie 4.31±0.963minutes than group A (control group) ie 5.23 ± 1.352 minutes. (p value 0.002)

3. Analysis of onset of motor blockade between the two groups revealed that onset of motor blockade was shorter in group D (study group) 7.29±1.619minutes than group A (control group) ie 8.46 ± 1.462 minutes (p value 0.002).

4. There is no statistically significant difference in the peak sensory level achieved after subarachnoid block between the two groups (p value >0.05).

5. There is no statistically significant difference in the time to reach peak sensory level after subarachnoid block between the two groups (p value >0.05).

6. There is no statistical difference between the two groups in terms of the duration of sensory and motor blockade (p value >0.05).

7. Hemodynamic alterations after the premedication were comparable in both the groups and didn't require any intervention (p value >0.05).

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