

Randomized Controlled Study to Evaluate Comparative Efficacy of Intrathecal Clonidine and Dexmedetomidine as Adjuvants to Hyperbaric Bupivacaine for Spinal Anaesthesia for Lower Limb Surgeries

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Abstract

Background: Various adjuvants are being used with local anaesthetics for prolongation of intra operative and post-operative analgesia. Dexmedetomidine, the highly selective alpha-2 adrenergic agonist is a new neuraxial adjuvant gaining popularity.

Setting and Design: The study was conducted in prospective, double blind manner. It included 90 ASA grade I and II patients undergoing lower limb surgery under Spinal anaesthesia, after approval from hospital ethical committee with written and informed consent of patients.

Material and Method: The patients were randomly divided into 3 groups (30 each) Group BS received 12.5 mg hyperbaric bupivacaine with normal saline. Group BC received 12.5 mg hyperbaric bupivacaine with 30 mcg clonidine and Group BD received 12.5 mg hyperbaric bupivacaine with 5mcg dexmedetomidine. The onset time to reach peak sensory and motor level, the regression time of sensory and motor block, hemodynamic changes and side effects were recorded.

Results: Patients in group BD had significantly longer sensory and motor block duration than patients in group BC and BS. The mean time of two segment sensory block regression was 146.67 minutes in BD, 127 minutes in group BC and 102minutes in BS groups respectively ($p > 0.0001$). The regression time of motor block to reach modified Bromage zero (0) was 273.33 minutes in BD, 198.67 minutes in BC and 160.50minutes in BS groups respectively ($p > 0.0001$). Dexmedetomidine group showed significantly less and delayed requirements of rescue analgesia.

Conclusion: Intrathecal dexmedetomidine is associated with prolonged sensory and motor blockade, haemodynamic stability and reduced demand of rescue analgesia in 24 hours as compared to clonidine and hyperbaric bupivacaine without any serious side effects.

Keywords: alpha-2 adrenoceptor agonist, hyperbaric bupivacaine, clonidine, dexmedetomidine and spinal anaesthesia.

Introduction

Subarchanoid blockade is the most commonly used regional anaesthesia technique for lower limb surgery. Over the last decade, there has been considerable revival of interest in the use of adjuncts to local anaesthetic agents in central neuraxial block with the aim of prolonging the duration of sensory and motor block and reducing post-operative analgesia requirement. However, their use is thwarted either due to the adverse effects of

adjuvants or unreliable post-operative analgesia.

Most of the clinical studies about intrathecal alpha-2 adrenergic agonists are related to clonidine [1]. Dexmedetomidine, a highly selective alpha-2 adrenergic agonist has evolved as a panacea for various applications in procedures in perioperative and critical care settings [2]. It is also emerging as a valuable adjunct in regional anaesthesia and analgesia, where studies have built the evidence for its safe use in central neuraxial blocks [3]. Based on earlier human studies, it is hypothesized that intrathecal 5mcg Dexmedetomidine would produce more post-operative analgesic effects with hyperbaric bupivacaine in spinal anaesthesia with minimal side effects [4-7].

In view of few evidences [4-7] of dexmedetomidine

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efficacy as an adjuvant to hyperbaric bupivacaine in spinal anaesthesia, we strived to explore its usefulness and also compare this new alpha-2 adrenergic agonist with the previously established and widely used adjunct clonidine, for patients for lower limb surgery.

Material & Method

Pre-operative

After getting informed consent, 90 patients of either sex belonging to ASA grade I and II and scheduled for lower limb surgery under subarachnoid block were enrolled in this prospective randomized and double blind study. To calculate the sample size, a power analysis of $\alpha = 0.05$ and $\beta = 1.00$ showed that 30 patients were needed per study group to detect an increase of 30 min. difference between the median duration of spinal sensory block between the groups. Data was expressed as means, standard deviation (SD), medians, ranges or numbers and percentages.

Patients with contraindications for regional anaesthesia, history of any co-existing disease like Ischaemic heart disease, hypertension, impaired renal functions, rheumatoid arthritis and severe liver disease were excluded from the study.

All patients were examined and investigated a day prior to surgery and were familiarized with visual analogue scale (VAS) and its use for measuring the post-operative pain.

They were advised fasting for 6 hours and received Alprax 0.5 mg a night before and 0.25 mg on the day of surgery.

Intraoperative

In operation theatre base line parameters like ECG, pulse oximetry, non-invasive blood pressure were recorded and monitoring was initiated. Intravenous access was secured and all the patients were preloaded with ringer lactate 10ml/kg. These patients were randomly assigned, using sealed envelope technique to either of three groups in double-blind manner.

The study solutions were prepared in 5 ml syringe by an anaesthesiologist who then handed them over in a coded form to the attending anaesthesiologist blinded to the nature of the drug given to him/her. Subarachnoid block was administered at the L 2-3 or L 3-4 vertebral level using 23G Quincke spinal needle with patients in sitting position, under all aseptic precautions. Patients were made supine following the block. The anaesthesiologist performing the block recorded the intraoperative data.

The onset and duration of sensory block, highest level attained, time to reach the highest dermatome, motor

Table 1: Groups for Study

GROUP BS	Intrathecal(I/T) hyperbaric bupivacaine 12.5 mg(2.5 ml) + Preservative Free Normal Saline(NS) (0.5 ml)
GROUP BC	Intrathecal(I/T) hyperbaric bupivacaine 12.5 mg(2.5 ml) + Clonidine 30mcg (0.2ml) + Preservative Free Normal Saline(NS) (0.3 ml)
GROUP BD	Intrathecal(I/T) hyperbaric bupivacaine 12.5 mg (2.5 ml) + Dexmedetomidine 5mcg (0.05ml) + Preservative Free Normal Saline(NS) (0.45 ml)
	BS - Bupivacaine Saline
	BC - Bupivacaine Clonidine
	BD - Bupivacaine Dexmedetomidine

block onset, time to complete motor block, recovery and duration of spinal anaesthesia were recorded. Onset of sensory block was defined as a time between injection of intrathecal anaesthetic and absence of pain at T8 dermatome assessed by sterile pinprick every 2 minutes till T8 dermatome was reached. The highest level of sensory block was evaluated by pinprick at midclavicular line anteriorly every 5 minutes for 20 minutes after injection and thereafter every 15 minutes.

Duration of sensory block was defined as a time of regression of 2 segments in maximum block height, evaluated by pinprick. Motor level was assessed according to modified Bromage score [9].

- **Bromage 0** - patient can move hip, knee and ankle
- **Bromage 1** - unable to move hip, but can move knee and ankle.
- **Bromage 2**- unable to move hip and knee but can move ankle.
- **Bromage 3**- unable to move hip, knee and ankle.

Complete motor block recovery when Bromage is 0.

Duration of sensory block was defined as time of regression of 2 segments in maximum block height, evaluated by pin prick. Duration of spinal anaesthesia was defined as the period of spinal injection to first occasion when patient complained of pain in post - operative period.

Surgery was started, achieving adequate sensory height (T8), vitals were recorded 5 minutes before intrathecal (I/T) injections at 5, 10,15,20,25 minutes interval and then every 15 minutes subsequently during intraoperative period. Pain score using VAS was recorded 5 minutes before intrathecal injections and start of surgery in subsequently, every 15 minutes till surgery was completed and thereafter VAS was assessed in post-

operative period. Intravenous fluids were given to maintain the blood pressure. Hypotension was defined as a fall in systolic blood pressure by 30% from base line and was treated with intravenous bolus of mephenteramine or crystalloid fluids. Heart rate less than 50 beats/minute was treated with 0.6 mg intravenous atropine sulphate. The incidence of nausea, vomiting pruritis and sedation were recorded. De Kock sedation scale was used [10].

- 1-patient is somnolent but responding to verbal commands
- 2-patient is somnolent but not responding to verbal commands
- 3-patient is somnolent, not responding to verbal commands or manual stimulation.

Postoperative

Motor block recovery (modified bromage score of 0 and sensory block regression were assessed every 15 minutes after completion of surgery till the time of regression of two segments in maximum block along with vital signs and VAS score. Any patient showing VAS more than 3 was administered supplemental dose of tramadol 50mg. Amount required by the patient in next 24 hours was recorded in all the groups. Descriptive statistic was done for all data and suitable statistical tests for comparison was done. Categorical variables (sex, nausea/vomiting, use of additive analgesia, hypotension and bradycardia) were analysed with Chi-square test and Fisher exact test. Statistical significance was taken as p value < 0.05. The observations were depicted in tables. Continuous co-variates (age and duration of surgery) were compared using analysis of variance (ANOVA).

Observations

In this study age, sex, height, weight, ASA grade of patients were comparable among all the groups & statistically insignificant and p= 0.19.

Table 2: Mean time of onset of sensory block (mins.)

	Mean	SD
BS	6.8	1.355
BC	4.92	1.104
BD	4.45	1.12
Significance	P value <0.05 (Significant)	

Table 3: Mean time of onset of motor blockade (mins.)

	Mean	SD
BS	9.17	2.96
BC	9.83	3.59
BD	9.67	3.20
Significance	P value >0.05 (Nonsignificant)	

Table 4: Mean duration of sensory block (mins.)

	Mean	SD
BS	102.38	17.16
BC	127	21.84
BD	146.67	20.57
Significance	P value = 0.0001 (significant)	

BS had statistically significant shorter duration, when compared to BC & BD groups.

BC & BD were comparable with statistically no difference between the two.

Table 5: Mean duration of motor block (mins.)

	Mean	SD
BS	160.50	19.88
BC	198.67	26.39
BD	273.33	24.58
Significance	P value < 0.0001 (Highly significant)	

Duration of motor blockade was prolonged in BD group as compared to BS & BC. BS had a significant shorter duration of motor block as compared to BC & BD. Groups BC & BD were however comparable.

Table 6: Mean time of rescue analgesia (mins.)

	Mean	SD
BS	160.46	11.87
BC	242.33	54.21
BD	290.01	40.30
Significance	P value = 0.0001 (significant)	

Time for analgesia request was earlier in BS as compared to BC & BD and this was statistically significant with p value 0.0001. Prolonged duration of analgesia with significantly delayed time of rescue analgesia was observed in group BD whereas BS & BC was statistically insignificant.

Trends in intraoperative hemodynamic parameters among subjects in different groups.

HEART RATE

During intra-operative period there was no statistical significant difference in HR in any of the groups with p value > 0.05 at all points of time. In post-operative period too, no statistically significant difference was seen in any of the groups and all groups were comparable.

SYSTOLIC BLOOD PRESSURE (SBP) / MEAN ARTERIAL PRESSURE (MAP)

No statistically significant difference in pre-operative MAP in all groups and it remained comparable at all times intra-operatively & post-operatively too.

SpO₂

There was no statistically significant difference in intra-operative and post-operative subjects of all groups.

All patients had a sedation score of 1 i.e. were somnolent but responded to verbal commands. Hence, all groups were comparable with regard to post-operative sedation.

No patient had pruritis at anytime intra/post-operatively.

VAS SCORE

VAS score was comparable with p value < 0.05 and no patient required intra-operative rescue analgesia.

At ½ hr, BS group patients had a higher VAS score as compared to BC & BD groups.

At 1, 1.5, 3 hrs, BS group had statistically significant higher VAS score as compared to BC & BD groups. At all points group BD had a minimal Vas score.

Discussion

Since most of the studies have compared the use of dexmedetomidine as an adjuvant to hyperbaric bupivacaine, we have compared the onset & duration of sensory and motor blockade, hemodynamic changes, total 24 hrs rescue analgesic requirement of 5 mcg of dexmedetomidine with 30 mcg of clonidine when added as adjuvants to hyperbaric bupivacaine for spinal anaesthesia.

In our study, in BD group we observed longer duration of both sensory and motor block, stable hemodynamic condition, good patient satisfaction. Findings were same as observed by Al-Mustafa et.al who studied the effect of dexmedetomidine 5 and 10 mcg doses with bupivacaine in urological procedures and found that dexmedetomidine prolongs the duration of spinal anaesthesia in dose dependent manner [6].

The mechanism by which intrathecal α_2 adrenergic agonist prolong the sensory and motor block of Local Anaesthetics is spectacular. Local anaesthetics act by blocking sodium channels and α_2 adrenergic agonists act by binding to the pre-synaptic C fibers and post synaptic dorsal horn neurons [4,5,11]. They produce analgesia by decreasing the release of C fiber transmitters and by hyperpolarisation of post synaptic dorsal horn neurons. The prolongation of motor block by these agents may also be because of this reason.

A lot of clinical experience in the use of intrathecal clonidine has been in use [19-22] and thus there has been a need to clinically study intrathecal dexmedetomidine to prove its efficacy, safety and suitable dose for supplementation to spinal local anaesthesia. In our study the dose of dexmedetomidine was selected on previous human studies wherein no neurotoxic effects have been observed [4-6].

Time of onset of Sensory block (Table 2)

It was observed that the time of onset of sensory block was early in BC & BD groups with 6.8 mins SD 1.35 in BS group, 4.92 mins SD 1.104 in BC group and 4.45mins SD 1.12 in BD group respectively. Strebel S et al 2004⁽³¹⁾ also concluded these findings in their study that intrathecal clonidine added to bupivacaine for spinal anaesthesia shortened the sensory block onset time. Kanazi et al [4] also studied intrathecal clonidine added to bupivacaine for spinal anaesthesia, shortened the sensory block onset time. These findings too go in favour of our results.

Al -Ghanem et al [5] however observed no difference time of onset in patients receiving dexmedetomidine (7.5 ± 3.4 min) and fentanyl (7.4±3.3min) as adjuvants to hyperbaric bupivacaine. The onset of time observed in the study by Al -Ghanem et al could be different from those of our study due to their use of isobaric bupivacaine and also could be due to patients positioning (lithotomy v/s supine in our study).

The duration of sensory block (Table 4), defined as two sensory segment regression, was significantly prolonged in BD group as compared to BS & BC groups respectively. This finding was similar to the study by Gupta et al [7] and Kanazi et al [4].

Time of onset of Motor block (Table 3)

In our study the time of onset of motor blockade was comparable among all 3 groups. Same results were obtained by Kanazi et al [4], Ghanem et al [5] and Gupta et al [7].

Duration of motor blockade (Table 5) was significantly prolonged in BD group. Significant motor blockade was

also seen in BC group as compared to BS group where bupivacaine was used alone. The group BS had significant shorter duration of motor block as compared to BC & BD groups but BC & BD groups when compared were comparable. Our results showed marked prolongation of motor block as compared to studies conducted by other authors which could be attributed to larger intrathecal volume of drug used in our study.

Requirement of Rescue Analgesia (Table 6)

It was seen that patients who received only bupivacaine i.e. BS group had the earliest request. This period was significantly prolonged in BD group, whereas BC & BD groups showed comparable results.

Gupta et al [7] showed results comparable to our study. Our results were also in concordance with Marziehlak et al 2015 [30] and Anil thakur et al 2015 [15] who found statistically significant increase in duration of analgesia with addition of clonidine to intrathecal bupivacaine.

H Saxena et al [17] (2009) and Singh R et al [29] (2012) also found similar results with increasing doses of clonidine.

Greater VAS scores in BC group when compared with BD group suggested that dexmedetomidine has better analgesic efficacy. The results were comparable with that of Gupta et al [7] who found significantly less requirement of rescue analgesia in 24hrs in dexmedetomidine group as compared to fentanyl group.

Kanazi et al [4] observed comparable analgesic effects of 3mcg dexmedetomidine to 30mcg clonidine but we noted significantly less requirement of rescue analgesia with 5mcg dexmedetomidine to 30mcg clonidine which could be due to dose dependent analgesic efficacy of dexmedetomidine.

Haemodynamic profile

Heart Rate(HR), Systolic Blood Pressure/Mean Arterial Pressure, Respiratory Rate (RR), SpO₂ were comparable in all 3 groups. No incidence of bradycardia or significant hypotension in any of the patients. All patients maintained their SpO₂ between 96-99% at all points of time. No respiratory depression occurred in any patient. These findings were in favour of various studies conducted [4,29] using low doses of dexmedetomidine.

Peri-operative side effects

Sedation was greater with dexmedetomidine as compared to clonidine but statistically insignificant. Sedation produced by dexmedetomidine differs from other sedatives as patient may be easily aroused and remain co-operative. These findings were in concordance with

those observed in study by Velayudha Srida Reddy [27], Nawaz Ahmed Shaik and VenkatsivaJangam J Anaesthesiol Pharmacol 2013; 29/3: 342-47 and Ustun Y et al [28], Gunduz M, Erdogan O, Benlidayi ME. Dexmedetomidine v/s Midazolam in out-patient 3rd molar surgery. J Oro Maxillofacial Surgery 2006; 64: 1353-8 (PubMed)

Mean HR of both BC & BD groups was more than 70/min indicating haemodynamic stability in BC & BD groups at given doses. No significant difference was observed with regard to post-operative sedation, vomiting and pruritis, all patients had sedation score of 1. These findings were comparable to studies conducted by Kanazi [4], Subhi M and Ghanem Al [5], Mustafa et al [6].

Conclusion

To conclude, our study report shows that the use of intrathecal dexmedetomidine as an adjuvant to hyperbaric bupivacaine seems to be an attractive alternative to clonidine and even fentanyl for longer duration surgeries due to its profound anaesthetic and analgesic properties combined with minimal side effects. Higher cost of dexmedetomidine could be the reason for preference for clonidine.

Effect of adding dexmedetomidine to other local anaesthetics like Ropivacaine or Levobupivacaine in other neuraxial blocks needs further research.

As dexmedetomidine produces long motor blockade, its use for day care surgeries should be restricted & it is undesirable for short term surgical procedures or ambulatory surgeries.

To conclude, Intrathecal dexmedetomidine is associated with prolonged motor block and sensory block haemodynamic stability and reduced demand of rescue analgesic in 24 hours as compared to clonidine and lone bupivacaine groups.

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