ORIGINAL ARTICLE

Comparison of dexmedetomidine and clonidine as an adjuvant to intrathecal bupivacaine in lower limb surgery: A randomised, double-blind, placebo controlled trial

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ABSTRACT

Background: We compared the duration of analgesia and adverse effects along with the hemodynamic changes, following intrathecal administration of dexmedetomidine or clonidine with bupivacaine.

Methodology: Seventy five patients of ASA grade I or II, ages between 20-50 years, were enrolled in the study. Patients were randomly allocated to three equal groups, Group B received hyperbaric bupivacaine (0.5%) 12.5 mg with normal saline as a placebo, group D received bupivacaine with 3 μg of dexmedetomidine and Group C received bupivacaine with 30 μg of clonidine. All solutions were made up to 3 ml with addition of normal saline and injected at L3-L4 using a 25G spinal needle. The onset and duration of sensory and motor blockade, time to reach peak sensory and motor level and the sensory and motor regression times were recorded. Hemodynamic changes and time to use first rescue analgesia, diclofenac sodium 75 mg IM, were also recorded. In post anaesthesia care unit (PACU), pain scores were recorded using visual analogue scale (VAS), initially every 30 minutes for 8 hours, then every 2 hours till 24 hours. Descriptive statistics was used for describing frequencies, mean and standard deviation. Analysis of variance (ANOVA) test was used to compare the quantitative variables in between the three groups which were independent of each other. Chi square test was used to compare categorical variables. All the data was analysed using SPSS vs. 17. P value < 0.05 was considered statistically significant.

Results: There was no significant difference in patients demographics or duration of surgery, in the time to onset of sensory block but motor block was early in Group D and Group C as compared to Group B. Duration of sensory and motor blockade was prolonged in Groups C and D, compared with Group B. The mean regression time to S1 segment was 306.6 ± 52 min in Group D, 278.6 ± 27 min in Group C and 199.8 ± 33 min in Group B. The regression of motor block to Bromage zero was 253.2 ± 38.40 min in Group D, 229.00 ± 42.57 min in Group C and 175.00 ± 29 min in Group B. The time to analgesia was significantly prolonged in Group D compared with Group C the latter being longer than Group B.

Conclusion: The addition of dexmedetomidine to intrathecal bupivacaine prolongs the motor and sensory block and postoperative analgesia when compared to bupivacaine with or without clonidine, with preserved hemodynamic stability in lower limb surgeries.

Key words: Anesthesia, Spinal; Adjuvants, anaesthesia; Adrenergic alpha-Receptors, Adrenergic alpha-2 Receptor Agonists; Clonidine; dexmedetomidine; Surgical Procedures, Operative

Citation: Suthar O, Sethi P, Sharma UD. Comparison of dexmedetomidine and clonidine as an adjuvant to intrathecal bupivacaine in lower limb surgery: A randomised, double-blind, placebo controlled trial. Anaesth Pain & Intensive Care 2015;18(2):149-154

***Declaration:** This study was conducted for preparation of my thesis as a part requirement of MD examination in our institute.*

INTRODUCTION

Subarachnoid blockade is the most commonly used regional anaesthetic technique for lower limb surgery. Intrathecal use of hyperbaric 0.5% bupivacaine is appropriate for surgeries of short duration and may lead to early analgesic intervention in the postoperative period.[1]

In search for adjuvants that prolong the duration of analgesia with lesser side effects various drugs as opioids, alpha agonists and midazolam have been tried with local anesthetics.[2]

For intrathecal alpha agonist, most of literature is for clonidine and there are very few studies about intrathecal use of dexmedetomidine.[3] Dexmedetomidine is a potent α2 agonist and is approximately eight-times more selective towards the α2 adrenergic receptor than clonidine. Dexmedetomidine is now emerging as an adjuvant to regional anesthesia and analgesia, where evolving studies can build the evidence for its safe use in central neuraxial blocks.[4]

In view of few studies[5-8] about efficacy of dexmedetomidine as an adjuvant to intrathecal hyperbaric bupivacaine, we planned a double blind randomized control study to compare the spinal block characteristics and side effects along with hemodynamic changes following intrathecal bupivacaine vs. intrathecal bupivacaine supplemented with a low dose of either dexmedetomidine or clonidine in patients scheduled for lower limb surgery.

METHODOLOGY

This randomized double blinded placebo controlled trial was conducted at a tertiary care centre in western Rajasthan, India. Patients with contraindication to regional anesthesia, history of significant coexisting diseases like ischemic heart disease, hypertension, diabetes, impaired renal functions, LVF, valvular heart disease, rheumatoid arthritis and severe liver disease were not included in the study. Body weight more than 120 Kg, height less than 140 cm, patient on adrenergic receptor agonist or antagonist therapy, with known hypersensitivity to local anaesthetic, drugs, pregnant patients, chronic alcoholics and malnourished patients were excluded from the study.

Seventy five patients of ASA-I or II and ages between 20-50 years were enrolled in the study. Simple randomization was done with computer generated random number sequence. Subjects were randomised with a 1:1:1 allocation ratio. The allocated interventions were written on paper slips, placed in serial-numbered, opaque envelopes and sealed. As consecutive eligible subjects got enrolled, the envelopes were serially opened and the allocated intervention was implemented. Group B received subarachnoid block with injection hyperbaric bupivacaine (0.5%) 12.5 mg with normal saline as a placebo to make 3 ml. In Group C, the patients received hyperbaric bupivacaine (0.5%) 12.5 mg with 30 μg (0.2 ml) clonidine and the total volume of the drug was made 3 ml by adding 0.3 ml of normal saline. In Group D, the patients received subarachnoid block with injection hyperbaric bupivacaine (0.5%) 12.5 mg with 3 μg dexmedetomidine. Normal saline was added to 1 ml (100 μg/ml) of dexmedetomidine to make it 10 ml (10 μg/ml). From this, 0.3 ml (3 μg) of solution was taken with 1 ml tuberculin syringe with 0.01 ml marking for intrathecal use. One anaesthesiologist prepared the intrathecal drugs just prior to positioning the patient for spinal anesthesia. Patient and the anaesthesiologist who attended patient intraoperatively and collected data in the postoperative period were blinded to the study drug.

All patients were examined and investigated a day prior to surgery and were familiarized with visual analogue scale [9] (VAS) and its use for measuring the postoperative pain and were advised fasting for 6 h. Sedatives and hypnotics were avoided in premedication drugs as well as during intraoperative period. All these patients were premedicated with antiemetic ondansetron (4 mg IV). In operating room, patients were preloaded with Ringer Lactate solution 10-15 ml/kg. Baseline hemodynamic parameters heart rate (HR), oxygen saturation (Spo_2) and mean blood pressure (MBP) were noted. After aseptic precautions, lumbar puncture was performed at L3–L4 using a 25 G spinal needle with the patient in sitting position and the study drug solution (3 ml) was injected as per the groups allocated. The patients were placed supine after injection and the sensory level was assessed by pinprick sensation using a blunt 25-gauge needle along the mid-clavicular line bilaterally at three-minute intervals for 30 minutes and then every 15 minutes after. The time to reach T10 dermatome (onset time), the maximum sensory level achieved, time for two segment and S1 segment regression (the duration of sensory block) were recorded. The motor block was assessed according to the modified Bromage scale[10] (0–3), for onset (time to reach maximum Bromage level) and duration (time to Bromage 0 regression). In the intraoperative period, vital parameters (HR, MBP and Spo_2) were recorded after the block, every 3 minutes for half an hour then every 15 minutes up to 3 hours. On achieving T10 sensory blockade level, surgery

was allowed. All episodes of pulse rate and blood pressure variations more than 20 % of baseline were noted in all groups. Hypotension was treated with ephedrine 6mg bolus and bradycardia was treated with IV atropine. The sensory and motor blockade were assessed intraoperatively The onset and duration of sensory block, highest level of sensory block, time to reach the highest dermatomal level of sensory block, motor block onset, time to complete motor block recovery and duration of pain relief were recorded. All durations were calculated in relation to the time of subarachnoid block. In post anesthesia care unit (PACU), pain scores were recorded using visual analogue scale (VAS), by nursing staff that were unaware of the group assignment. Initially every 30 minutes for 8 hours, then every 2 hours till 24 hours. Duration of pain relief (effective analgesia) was defined as the time from spinal injection to the first request for rescue analgesics or VAS was >4. Postoperative analgesic rescue was provided by diclofenac sodium 75 mg intramuscularly. The time to request rescue analgesia (the duration of analgesia) was noted. This was taken as the time of wearing off analgesia. Patients discharged from PACU after sensory regression to S1 dermatome and Bromage score reached to zero. Side-effects such as nausea, vomiting, bradycardia, hypotension, respiratory depression (RR <8/min) and pruritus were noted and treated accordingly.

Statistical analysis: We took a convenient sample size of 75 patients as it was a pilot study. Descriptive statistics was used for describing frequencies, mean and standard deviation. Analysis of variance (ANOVA) test was used to compare the quantitative variables in between the three groups which were independent of each other. Chi square test was used to compare categorical variables. All the data was analysed using SPSS vs. 17. P value < 0.05 was considered statistically significant.

RESULTS

Ninety two patients posted for lower limb surgeries were enrolled the study. Eight patients refused to participate in the study and nine patients were found to be on beta blockers, anticoagulation drugs and had uncontrolled diabetes mellitus. The remaining 75 patients fulfilling the inclusion criteria were randomly assigned to one of the three groups. All patients (n = 75) completed the study, there was no statistical difference in patients demographics or duration of surgery (Table 1).The numbers of patients for each type of surgery of the lower limb was equal among the groups.

The time of onset of sensory block (to reach T10) was statistically insignificant in all the three groups. T10 sensory level was achieved in all patients. In Groups B, C and D sensory block to a level of T10 reached at 6 ± 1.28, 6.00 ± 1.25 and 6.32 ± 1.4 min after the injection (statistically insignificant). However, there were patients with level progressing further to the highest sensory level of T4. T6 was the mean level of sensory block attained at 16 ± 3.8, 14 ± 4.18, 17 ± 4.52 min after injection in 40, 60 and 68% patients in Group B, C and D respectively. Onset of motor block (time to achieve Bromage score 3) was statistically significant between Group B and C as well as between B and D, but not between C and D (Table 2). Difference between duration of sensory and motor block was statistically significant in the three groups. (Table 2) The mean values of systolic, diastolic, mean arterial pressure (MAP) and heart rate (HR) were comparable between the three groups throughout the intraoperative and postoperative periods (Figure 1 & 2). All patients had SpO_2 greater than 95% at all the times and did not require additional oxygen in PACU.

Table 1: Patients demographics

Variable	Group B (Mean ± SD)	Group C (Mean ± SD)	Group D (Mean ± SD)
Age(years)	33 ± 8.8	31 ± 8.8	33 ± 6.8
Sex(male)	15	17	16
ASA 1: 2	13:12	12:13	11:14
Height (cm)	160 ± 4.1	164 ± 8.5	160 ± 7.6
Weight (kg)	57 ± 6.3	58 ± 7.4	57 ± 9.4
Duration of surgery (min)	93 ± 26.3	83.2 ± 23.6	85.6 ± 25.9

comparison of dexmedetomidine and clonidine as an adjuvant

Table 2: Characteristics of spinal block

Variable	Group B (Mean ± SD)	Group C (Mean ± SD)	Group D (Mean ± SD)	P value
Time of onset of motor block(Bromage score 3)*(min)	15 ± 3.4	9 ± 1.8	10 ± 1.7	< 0.001
Time of onset of sensory block (up to T10) (min)	6 ± 1.28	6.00 ± 1.258	6.32 ± 1.474	0.345
Maximum height of sensory block(Thoracic level)	6 ± 1.52	6 ± 1.47	6 ± 1.155	0.0893
Time to reach maximum height of sensory block (min)	16 ± 3.85	14 ± 4.11	17 ± 4.51	0.839
Duration of motor block (regression to Bromage score zero)*	175 ± 28.8	229 ± 42.57	253 ± 38.40	0.0001
Duration of sensory block(two segment regression time)(min) ±	99.4 ± 29.2	120.00 ± 30.9	139.8 ± 30.9	0.0001
Regression to s1 dermatome (min) ≠	199.8 ± 32.9	278.6 ± 26.4	306.6 ± 51	0.0001
Duration of analgesic effect of spinal anesthesia ≠	204 ± 16.9	309 ± 51.5	336 ± 55.9	0.0001

*Intergroup comparison B to C and B to D; P value was significant (< 0.001).Whereas C to D was not significant (p > 0.05).

± Intergroup comparison B to D was significant (< 0.001).Whereas B to C and C to D was not significant > 0.05.

≠Intergroup comparison B to C and B to D was significant (< 0.001).Whereas C to D was not significant > 0.05.

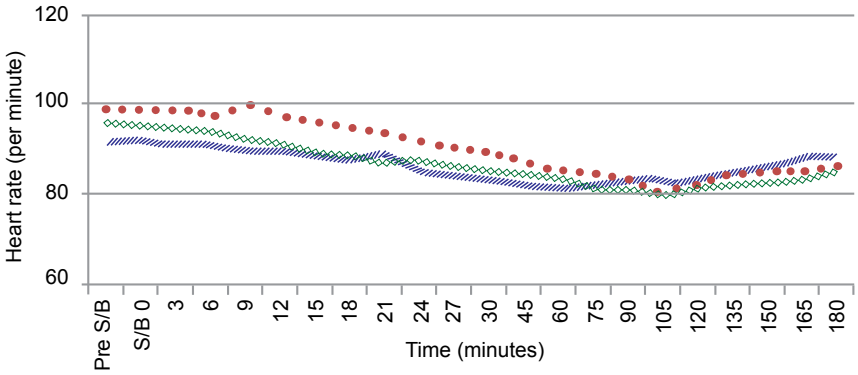

Figure 1: Trend of heart rate

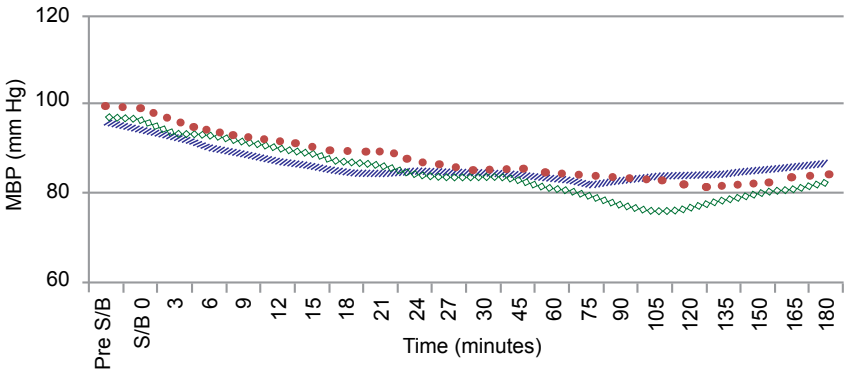

Figure 2: Trend of mean BP

Two patient in Groups B and D and four patients in Group C received one dose of ephedrine .One patient in Group D required atropine. VAS values were less than 3 observed in all the groups during the whole duration of the surgery and none of the patients required additional analgesics. Intra-operative or post-operative nausea or vomiting occurred in 3 patients in Group B and 2 patients in Group D. There was statistically significant difference in time of first rescue dose requested by patient, it was 204±16.9 min. in Group B, 309±51.5 min. in Group C and 336±55.9 min. in Group D with p value < 0.05.

DISCUSSION

In our study we found that, dexmedetomidine 3 µg supplemented to intrathecal bupivacaine significantly prolonged the duration of

Table: 3 Description of side effects

Side effect	Group B n (%)	Group C n (%)	Group D n (%)
Hypotension	02 (8)	04 (16)	02 (12)
Bradycardia	0	0	01(4)
Shivering	4 (16)	2 (8)	2 (8)
Nausea/Vomiting	3 (12)	0	2 (8)

postoperative analgesia compared with the addition of clonidine 30 μg. Both dexmedetomidine and clonidine prolonged both sensory and motor blockade and reduced the need of rescue analgesia for the first 24 postoperative hours. Many studies are published about intrathecal use of clonidine.[11,12] but literature is scarce about intrathecal dexmedetomidine as an adjuvant to spinal local anesthetics. Intrathecal α2-adrenoceptor agonists produce analgesia by binding and depressing the release of pre-synaptic C-fibre neurotransmitters and also by hyperpolarisation of post-synaptic dorsal horn neurons.[13,14] This anti nociceptive effect may explain the prolongation of the sensory block while prolongation of motor block may be due to the binding of α2-adrenoceptor agonists to motor neurons in the dorsal horn.[15]

The binding affinity of dexmedetomidine is approximately ten times higher than clonidine to spinal α2-adrenergic receptor. Intrathecal dexmedetomidine and clonidine, when used in 1:10 dose ratio, produce similar effects in animals.[16] In our study, the intrathecal dose of dexmedetomidine selected was based on previous human studies wherein no neurotoxic effects have been observed.[5-7] Kanazi et al[5] and Al Ghanem et al [6] found that dexmedetomidine and clonidine added to bupivacaine produced a similar prolongation in the duration of the motor and sensory block, with preservation of hemodynamic stability. Time of onset of sensory block was comparable among all the groups. Al-Mustafa et al.[7]and Hala et al[17] observed dose dependent prolongation of motor and sensory blockade with reduced analgesic requirement with increasing dosages of intrathecal dexmedetomidine.

There was statistically no change in perioperative BP and HR in three groups. The sympathetic blockade is near maximal at the usual doses used for spinal anesthesia so it is not or only minimally affected by an inclusion of a low dose of α2-agonist. Strebel et al[18] and Solanki et al[15] examined the effects of small doses of intrathecal clonidine with hyperbaric bupivacaine 0.5% lower limb surgeries patients and found that it prolonged the anesthetic and analgesic effects of bupivacaine. Bradycardia and hypotension are most important side effect of intrathecal α adrenergic receptor agonists.[19] In our study, these side effects were not significant, may be because of small dose of intrathecal dexmedetomidine and clonidine used in our study.

Kanazi et al[5] and Ghanem et al[6] also used intrathecal dexmedetomidine without any adverse neurological consequences. Various preclinical animal neurotoxicity studies, using dexmedetomidine in a dose range from 2.5–100 μg failed to show any untoward neurological effects.[20-22]

LIMITATIONS

This study adds to the current knowledge on dexmedetomidine but the results should be considered taking into consideration the various limitations. As all patients were either ASA physical status I or II, so results cannot be generalised to ASA physical status III and IV patients. Our patients were young and otherwise healthy ones, free of significant comorbidities that might have exaggerated the cardiovascular side effects of intrathecal clonidine or dexmedetomidine. Hence, further studies that compare the effect of intrathecal clonidine and dexmedetomidine on the spinal bupivacaine with large sample size are needed.

CONCLUSION

Our study concluded that the supplementation of hyperbaric bupivacaine with low dose of dexmedetomidine in subarachnoid block produces an early onset of motor block and a significantly longer sensory and motor block than bupivacaine plus clonidine or bupivacaine alone.

Conflict of interest: The authors declare that they have no conflict of interest related to the publication of this manuscript.

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