Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Anaesthesiology and Intensive Care

Comparison of Dexmedetomidine Vs Buprenorphine as Adjuvants to Intrathecal Bupivacaine for Bilateral Total Knee Replacement Surgeries - Randomised Controlled Trail

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DOI: 10.36347/sjams.2022.v10i09.021 | **Received:** 11.08.2022 | **Accepted:** 18.09.2022 | **Published:** 22.09.2022

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Abstract **Original Research Article**

***Introduction*:** The duration of analgesia produced by local anaesthesia is limited if administered alone. Therefore, supplementation of local anaesthetics with adjuvants helps to improve the efficacy of the sub-arachnoid block, especially in long-duration surgeries like bilateral total knee replacement. The most preferred drugs used are opioids, but due to new drug development like dexmedetomidine has been introduced and proved to be effective adjuvant. ***Aim*:** This study was conducted to evaluate and compare the characteristics of subarachnoid blockade and hemodynamic stability. The VAS was used pre-operatively, after intrathecal, immediately post-operatively, and on the basis of the need for rescue analgesia or epidural. ***Materials and Methods*:** A total of 150 patients were taken aged between 30-80 years classified as American Society of Anesthesiologists (ASA) undergoing bilateral TKR under neuraxial anaesthesia were included in the study. The patients were randomly allotted to two groups to receive 4.0 mL of 0.5% hyperbaric bupivacaine with 0.2 mL of dexmedetomidine (5 µg) intrathecally (Group D; n = 75) and another group to receive 4.0 mL of 0.5% hyperbaric bupivacaine with 0.2 mL of buprenorphine (60 µg) intrathecally (Group B; n = 75). ***Results*:** There was no significant difference between groups regarding demographic characteristics, no significant difference in hemodynamic variables. The motor, sensory, blockade, and time of rescue analgesia were significantly prolonged in Group D compared to Group B. Hence, Group D was far better than Group B in terms of duration of analgesia, time of onset of sensory block, time for maximum levels of sensory block, and modified bromage score. ***Conclusion*:** Intrathecal dexmedetomidine, compared to intrathecal buprenorphine, causes prolonged anaesthesia and analgesia with a reduced need for sedation and rescue analgesics. Also, reduced adverse effects are seen with intrathecal dexmedetomidine. Complications with Group D were less as compared to Group B.

Keywords: Intrathecal, α_2 adrenoreceptor agonist, opioid, Bilateral total knee replacement, Postoperative analgesia.

1. INTRODUCTION

Pain is the most common complaint after major surgeries such as total knee replacement attributing to long-term comorbidity in the patient. Premptive analgesia and an adequate plan for postoperative pain management are prerequites for early ambulation and a better outcome following knee replacement. Neuraxial anaesthesia is commonly used for lower limb surgeries. The duration of action of local anaesthetics is limited and adjuvants such as opioids, epinephrine, α2 agonist, ketamine, and magnesium sulphate are added to potentiate as well as prolong the duration of block [1]. Therefore, adding these adjuvants to the local anaesthesia intensifies the block in the intra-operative period, prolongs the duration of post-operative analgesia and also reduces the volume of local anaesthesia, thereby minimising the adverse-effects.

Dexmedetomidine, i.e., the d-enantiomer of medetomide, belongs to the imidazole subclass of the selective alpha-2 receptor agonists which act by hyper-

polarisation of activated cation channels [2, 3]. Intrathecal dexmedetomidine (5-10 µg) is used as an adjuvant to bupivacaine for its excellent analgesic efficacy [4]. Prolonged duration of neuraxial blockade and improved postoperative analgesia without significant adverse effects such as hypotension have been noted when used at dosage up to 5µg [5, 6].

Buprenorphine is a partial mu receptor agonist, a delta receptor agonist, and a weak kappa receptor agonist. It is a potent analgesic that acts on the central nervous system. Buprenorphine detaches slowly from the µ-opioid receptor and has a longer duration of action with a lower potential for addiction.

Buprenorphine has also been used in intrathecal dose 60µg in lower abdominal and lower limb surgeries without significant side effects [5, 7]. Pruritus, nausea, vomiting, and respiratory depression are commonly seen with the use of neuraxial opioids, which require the lowest dosage usage for the least adverse effects. Pruritus associated with the majority of opioids responds to use of naloxone while the availability of doxapram is required for reversal of respiratory depression with use of buprenorphine.

Studies using both of these drugs have shown that their equipotency dose is 5µg dexmedetomidine and 60 µg buprenorphine [7].

2. MATERIAL AND METHODS

2.1 Study Design

This study was conducted at the Adesh Institute of Medical Sciences and Research (AIMSR), Bathinda, Punjab. An interventional prospective double-blind randomised study in 150 patients meeting inclusion criteria, undergoing total knee replacement surgeries (TKR) at Adesh hospital Bathinda, was conducted after approval from the institutional ethical committee (IEC). The study was registered in the CTRI (Clinical Trail Registry of India) as CTRI/2019/09/021327.

Consenting patients in the age group of 30–80 years classified as American Society of Anesthesiologists (ASA) Physical Status I/II/III willing to undergo bilateral TKR under neuraxial anaesthesia were included in the study. Patients with a history of previous spinal surgery, infection at the injection site, hypersensitivity to amide local anesthetics, buprenorphine or dexmedetomidine, mental disturbance or neurologic disease were excluded from the study.

2.2 Block Intervention

In the operating room, the electrocardiogram monitoring (leads II and V_5), noninvasive blood pressure, pulse oximeter, and temperature probe were attached and baseline vitals recorded. An anaesthesiologist not involved in the study prepared the study drug. Under aseptic precautions, following epidural insertion, the subarachnoid block was performed and the study drug was administered by one of the investigators who was unaware of the drug. In circumstances with prolongation of surgery, the epidural was activated with bupivacaine 0.5% intraoperatively and rescue analgesia was kept ready (injection ketorolac 30mg iv in 100ml NS over 15 min).

2.3 Sample Size Calculation

Based on the key article "Time to Rescue Analgesia," the effect size was calculated as 0.5635, with alpha error set to 0.05 and power required at 90%, resulting in a sample size of 68 in each group. Giving consideration to dropout, the final sample was considered as 75 for each group.

2.4 Patient Randomisation

On the morning of surgery, patients will be allocated to one of two groups based on a computer-generated random number table.

- Group D (dexmedetomidine Group): 75 patients will receive 4.0 mL of 0.5% hyperbaric bupivacaine with 0.2 mL of dexmedetomidine (5 µg) intrathecally.
- Group B (Buprenorphine Group): 75 patients will receive 4.0 mL of 0.5% hyperbaric bupivacaine with 0.2 mL of buprenorphine (60 µg) intrathecally.

2.5 Evaluation of the Adjuvant and Outcome:

The anesthesiologist who was blinded to the study drug recorded the following study parameters:

- Hemodynamic parameters at different intervals
- VAS - T0: preoperative; T1: post-intrathecal; T2: immediately postoperative; T3: at first request for epidural or rescue analgesia
- Onset time of sensory: loss of pinprick sensation to 23G hypodermic needle
- Maximum Sensory Block Level
- Time for maximum level of sensory block
- Motor blockade: Modified bromage score ;onset time of motor blockage to modified bromage grade 3; time for complete motor block
- Duration of analgesia: Time at which first epidural bolus was given/required
- Regression of sensory block level to S1

2.6 Statistical Analysis

IBM SPSS Version 23.0, R software environment for statistical computing and graphics (version 4.2.1) and Microsoft Office Excel 2007.

3. RESULTS

A total of 167 patients were enrolled in the study who underwent bilateral total knee replacement. Of which 17 patients (7 patients in group B and 10 patients in group D) were excluded. 150 patients were randomly assigned using a computer-generated

randomization with 75 patients in Group B and 75 patients in Group D.

Both groups were compared with respect to the demographic parameters (like age, sex, and duration of surgery), hemodynamic parameters (like heart rate, SBP, DBP, and mean arterial pressure) and various other parameters (like time of onset of sensory block, motor blockage, etc).

Hemodynamic parameters such as heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure were accessed in both Group B and Group D. These parameters were assessed at 0mins, 10mins, 20mins, 30mins, 60mins, 120mins, 150mins, and 180mins. On comparing the groups, there was no significant difference between both groups. Only a slight difference was seen during the first 10 mins to 20 mins (Table 1-3). The mean HR decreased over time in both the groups. It was lower in Group B when compared to Group D, but the difference was statistically insignificant.

Table 1: Comparison of Heart Rate

Heart Rate	Group B (Mean ± SD	Group D (Mean ± SD)	P-value
0 mins	75.581 ± 4.0713	75.856 ± 3.5587	0.6346
10 mins	72.488 ± 4.3025	70.367 ± 2.1224	< .00001
20 mins	73.593 ± 4.4468	72.244 ± 4.254	0.0414
30 mins	72.802 ± 3.8343	72.922 ± 4.4095	0.8478
60 mins	73.291 ± 4.0377	72.189 ± 4.383	0.0844
120 mins	73.174 ± 4.4357	72.289 ± 4.1333	0.1724
150 mins	72.047 ± 4.0841	72.433 ± 3.9207	0.5232
180 mins	71.988 ± 3.7464	73.033 ± 4.4758	0.0956

Table 2: Comparison of SBP and DBP in Both the groups

Time Interval	SBP			DBP		
	Group B	Group D	p-Value	Group B	Group D	p-Value
0 mins	120.105 ± 11.5901	131.378 ± 8.1207	< .00001	79.093 ± 6.1312	82.433 ± 6.2063	0.0004
10 mins	122.919 ± 12.6354	120.489 ± 10.9875	0.1746	81.977 ± 6.3561	75.389 ± 4.1481	< .00001
20 mins	122.919 ± 12.0139	118.644 ± 11.9252	0.019	83.058 ± 7.9267	79.867 ± 5.8984	0.0028
30 mins	123.14 ± 11.3699	118.533 ± 11.9213	0.0096	81.733 ± 6.6958	81.267 ± 8.1141	0.679
60 mins	126.221 ± 10.9549	119.911 ± 12.1236	0.0004	79.744 ± 7.1541	79.567 ± 6.9055	0.8676
120 mins	122.267 ± 11.4619	118.1 ± 10.5831	0.013	81.093 ± 6.3461	82.522 ± 7.3702	0.1708
150 mins	125.779 ± 10.7577	124.233 ± 11.6108	0.3614	80.663 ± 5.814	82.356 ± 8.0801	0.1138
180 mins	121.198 ± 12.737	126.556 ± 11.4951	0.0038	81.326 ± 7.2167	80.367 ± 7.0447	0.3736

Table 3: Comparison of Mean Arterial Pressure

Mean Arterial Pressure	Group B (Mean ± SD	Group D (Mean ± SD)	P-value
0 mins	92.764 ± 5.8163	98.748 ± 5.0603	< .00001
10 mins	95.624 ± 6.2866	90.422 ± 4.4623	< .00001
20 mins	96.345 ± 6.7594	92.793 ± 5.3161	0.0002
30 mins	95.535 ± 6.2698	93.689 ± 5.789	0.0438
60 mins	95.236 ± 6.6097	93.015 ± 6.3729	0.0244
120 mins	94.818 ± 4.7614	94.381± 6.2426	0.6034
150 mins	95.702 ± 5.2299	96.315 ± 6.1972	0.4802
180 mins	94.616 ± 6.4821	95.763 ± 5.4062	0.2032

The time for sensory regression to S1 was considerably slower in Group B, with 231.477 ± 31.8007 minutes compared to Group D, which was 518.633 ±90.7917 minutes. The difference was statistically significant (p<0.00001). The time for Modified Bromage 0 in Group B was 219.535 ± 42.8235 minutes and in Group D was 412.944 ± 18.1593 minutes, that's statistical difference of p<0.00001. A total of 11 patients in Group B required an additional dose of sedation, and a total of 12 patients in Group D required an additional dose of sedation (Table 4).

The duration of analgesia was compared in both the groups; Group B (295.547 ±45.1462 mins) and Group D (581.933 ±122.0251 mins) with a statistical difference of p < 0.00001 (Table 4). The duration of analgesia in Group D was far longer as compared to Group B. The time for maximum level of sensory block was measured, which was earlier in Group D (3.828 ±0.1722 mins) as compared to Group

B (5.272 ±0.5728 mins). There was no significant difference in the time of onset of sensory block or the duration of surgery between the two groups (Table 4).

Table 4: Comparison of Various Parameters in both the Groups

Various Parameters	Group B	Group D	P-value
Duration of Surgery	187.558 ± 9.1749	186.922 ± 9.6736	0.6554
Time of onset of sensory block (mins)	3.49 ± 0.5174	3.406 ± 0.2111	0.157
Time for maximum levels of sensory block	5.272 ± 0.5728	3.828 ± 0.1722	< .00001
Motor blockade: Modified Bromage Score (mins)	219.535 ± 42.8235	412.944 ± 18.1593	< .00001
Duration of Analgesia (mins)	295.547 ± 45.1462	581.933 ± 122.0251	< .00001
Regression of sensory block to S1 (mins)	231.477 ± 31.8007	518.633 ± 90.7917	< .00001

On comparing the visual analogue scale in both groups, there was not much of a significant difference in the VAS Score. Both groups showed a decrease in the intensity of pain as compared to pre-operative and immediate post-operative (Table 5).

Table 5: Comparison of Visual Analogue Scale in both the groups

Visual Analogue Scale	Group B	Group D	P-Value
T0 (Preoperative)	5.953 ± 0.8665	6.044 ± 0.923	0.5014
T1 (After intra-thecal)	3.541 ± 0.9704	3.422 ± 0.9238	0.407
T2 Immediate Postoperative)	2.616 ± 0.6356	2.544 ± 0.621	0.4482
T3 (Request of epidural or rescue)	11	12	

Various complications such as nausea, vomiting, pruritis, hypotension, bradycardia were assessed in both the groups. Group D showed much fewer complications and side-effects as compared to Group B (Table 6).

Table 6: Comparison of Complication

Complication	Group B	Group D
Nausea	5	2
Vomiting	5	1
Pruritis	6	2
Hypotension	9	7
Bradycardia	8	5

4. DISCUSSION

Various adjuvants like morphine, buprenorphine, fentanyl, clonidine, ketamine have been used in anaesthetic practise for a long time for the improvement of peri-operative analgesia. In spite of various adjuvants in the literature, dexmedetomidine and buprenorphine have been compared in only a handful of studies. Alpha-2 receptors are currently being explored in the anaesthetic field for their sedative, analgesic, sympatholytic, anaesthetic-sparing and favourable hemodynamic properties. In this study, we have compared the addition of Buprenorphine (60 µg) and Dexmedetomidine (5 µg) to 4.0ml of 0.5% Hyperbaric Bupivacaine as an adjuvant in local anaesthesia in patients undergoing total knee replacement surgery. It acts on the locus ceruleus of the brain stem, producing sedative and anxiolytic effects [8].

Dexmedetomidine acts by stimulating the alpha 2 receptors on dorsal horn neurons of the spinal cord, reducing the sympathetic discharge and also modulating the release of substance P, causing hyperpolarization of dorsal horn neurons [9-13].

Buprenorphine is an opioid that acts by stimulating the kappa and mu opioid receptors and inhibiting the delta opioid receptor.

In this study, we found that the dexmedetomidine 5µg used as an adjuvant with bupivacaine prolongs the duration of action of sensory and motor blockade significantly as compared to buprenorphine 60µg.

Dexmedetomidine also increased the quality and duration of anaesthesia. Also, the requirement for an additional dose of sedative was reduced in the case of Group D [13, 14]. Intravenous Dexmedetomidine has an anti-shivering effect [16].

Dexmedetomidine was found to have fewer side effects in patients, which is thought to be due to its high lipid solubility.Because of its high lipophilic nature, it diffuses faster in neural tissue and reduces the possibility of rostral effect [3].

In spinal anesthesia, Mahima Gupta *et al*., [5] compared the onset of sensory and motor blockade in

both dexmedetomidine and buprenorphine.The duration of motor and sensory block in the dexmedetomidine group was 413 minutes and 451 minutes, which was significantly different from 205 minutes and 226 minutes in the buprenorphine group. Hence, intrathecal dexmedetomidine 5µg when compared to intrathecal buprenorphine 60µg causes a prolonged duration of sensory and motor block.

Amitha S *et al*., [8] conducted this comparison during spinal anaesthesia for tibial interlocking nailing surgeries and concluded the addition of dexmedetomedine (5µg) to 15mg of 0.5% heavy bupivacaine for spinal anaesthesia provides a longer duration of sensory and motor blockade than compared to that of buprenorphine (30µg) to 15mg of 0.5% heavy bupivacaine for spinal anaesthesia.

Ashem Jack *et al*., [17] conducted a similar study and found an increase in the duration of postoperative analgesia in the dexmedetomidine group of patients.

Vaghela *et al*., 2020 [18] also conducted a similar study in pregnant women that concluded sedation scores were achieved higher in patients receiving dexmedetomidine, and so the requirement for further intraoperative sedation is less in the dexmedetomidine group compared with the buprenorphine group.

P M A & Hussain, 2019 [19] concluded that bupivacaine along with intrathecal dexmeditomidine when compared to intrathecal buprenorphine caused early onset of sensory anaesthesia with prolonged duration of anaesthesia, which could be beneficial in long duration surgeries and prolonged analgesia with reduced need for sedation and rescue analgesics with fewer side effects. Our study also proved the fact.

Sisinti Sanjeeb Patro *et al*., [20] conducted an evaluation of Dexmedetomidine as an Adjuvant to Intrathecal Bupivacaine in Infraumbilical Surgeries, which concluded that "Addition of dexmedetomidine potentiates bupivacaine spinal anesthesia".

5. CONCLUSION

Dexmedetomidine as an adjuvant has shown an early onset of sensory block and motor block with a longer duration of action as compared to buprenorphine. The duration of analgesia was compared in both the groups; Group B (295.547 ±45.1462 mins) and Group D (581.933 ±122.0251 mins), which has a statistical difference. Also, the duration of analgesia in Group D was far longer as compared to Group B. The time for maximum level of sensory block was measured, which was earlier in Group D (3.828 ±0.1722 mins) as compared to Group B (5.272 ±0.5728 mins). Hence, we concluded that intrathecal dexmedetomidine 5µg when compared to intrathecal buprenorphine 60µg causes a prolonged duration of sensory and motor block. The requirement for additional sedation and rescue analgesia is less in the dexmedetomidine group and the hemodynamics are similar in both groups. The complications in Group D were decreased as compared to Group B.

Funding: No Funding sources.

Conflict of interest: None Declared.

Ethical Approval: The study was approved by the institutional ethics committee.

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