Original Article

Comparison of intravenous dexmedetomidine versus ketamine-dexmedetomidine combination on spinal block characteristics in patients undergoing lower limb orthopaedic surgery - A randomised clinical trial

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ABSTRACT

Background and Aims: One major limitation of the spinal block remains the inability to extend the duration of the block intraoperatively unless planned before with spinal or epidural catheters and/or intrathecal additives. This study was designed to compare the effects of intravenous dexmedetomidine versus low-dose ketamine–dexmedetomidine combination infusion on spinal anaesthesia in lower limb orthopaedic surgeries. **Methods:** This randomised study was conducted in 60 patients scheduled for unilateral lower limb surgeries under spinal anaesthesia. Patients were randomised into Group D (n = 30) (0.5 μg/kg of intravenous (IV) dexmedetomidine bolus followed by maintenance infusion at 0.5 μg/kg/h) and Group LKD (n = 30) (IV bolus of 0.5 μg/kg of dexmedetomidine and 0.2 mg/kg of ketamine, followed by maintenance infusions of dexmedetomidine and ketamine at 0.5 μg/kg/h and 0.2 mg/kg/h, respectively). Ramsay Sedation Scale score of 3–4 was maintained. The t-test or the Wilcoxon–Mann–Whitney U test was used to compare the parameters between groups. **Results:** The mean sacral segment 1 (S1) regression time was 390.3 [standard deviation (SD):84.38] [95% confidence interval (CI): 360.13, 420.53] versus 393.23 (SD: 93.01) (95% CI: 363.04, 423.43) min in Group D versus Group LKD respectively ((P = 0.701). The number of episodes of hypotension was significantly higher in Group D (19 patients) compared to Group LKD (nine patients) (P = 0.001). Pre- and postoperative stress markers (24 h) and the incidence of postoperative nausea and shivering were comparable between the two groups (P > 0.05). Tramadol requirement in the postoperative period was significantly less in Group LKD compared to Group D (P = 0.003). **Conclusion:** The duration of S1 regression was similar between group dexmedetomidine (Group D) and group low-dose ketamine and dexmedetomidine (Group LKD).

Keywords: Dexmedetomidine, haemodynamic, hypotension, ketamine, motor regression, postoperative period, sensory blockade, spinal anaesthesia

INTRODUCTION

Spinal anaesthesia is a standard anaesthetic technique for lower limb surgeries. One major limitation is the inability to extend the duration of the block intraoperatively.[1-3] Intravenous (IV) adjuvants are being studied for their effectiveness in the outcomes of spinal block.[3,4] IV dexmedetomidine prolongs the duration of the spinal block.[1-4] However, its sympatholytic activity can lead to bradycardia and

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hypotension. IV ketamine is effective in providing sedation and prolonging the spinal block, mainly when used in infusions and low doses; it does not lead to adverse effects like hallucinations, increased secretion and salivation.[2,5]

Therefore, it is clinically expected that a combination of IV low-dose ketamine and dexmedetomidine in spinal anaesthesia should provide stable haemodynamics and have a synergistic effect on prolonging the spinal block and improving other outcomes.

We hypothesised that low-dose ketamine and dexmedetomidine infusion would provide a longer duration of sensory block, better haemodynamics and fewer complications compared to dexmedetomidine infusion alone. The primary objective was to compare the time of regression of sensory blockade to S1 in patients receiving an IV infusion of dexmedetomidine and low-dose ketamine–dexmedetomidine infusions undergoing femur fracture surgeries under spinal anaesthesia. The secondary objectives were to compare the intraoperative haemodynamic stability, change in perioperative stress markers and discharge readiness from the post-anaesthesia care unit (PACU).

METHODS

The study was a randomised, double-blinded clinical trial carried out from May 2021 to February 2022. Ethical approval was obtained from the Institutional Ethical Committee (vide approval number IEC/017/2021, dated 19/03/2021), and trial was registered with Clinical Trials Registry – India (vide registration number CTRI/2021/05/033549, www.ctri.nic.in/). The study was carried out in accordance with the Declaration of Helsinki, 2013 and Good Clinical Practice. Written informed consent was obtained from all the patients before they participated in the study and for the use of the patient data for research and educational purposes.

Patients aged 18–65 years, with a body mass index (BMI) 18.5–34.9 kg/m^2 and of American Society of Anesthesiologists (ASA) physical status I or II, scheduled for elective femur fracture surgeries under spinal anaesthesia were included. Patients with prior addiction or analgesic abuse, a history of psychiatric/neurological disease, or deafness were excluded. Patients requiring supplementation with general anaesthetics and surgeries of expected duration less than 1.5 h and more than 4 h were also excluded.

All consecutive eligible patients were enroled. Random group allocation was done using computer-generated random numbers, and allocation concealment was ensured using sequentially numbered opaque, sealed envelopes. Participants were randomised into two groups: Group D (IV dexmedetomidine infusion) and Group LKD (IV low-dose ketamine and dexmedetomidine infusion). An independent anaesthesiologist prepared the study drugs in syringes – drug 1 was dexmedetomidine and drug 2 was normal saline (Group D) or ketamine (Group LKD).

Administration of spinal anaesthesia, intraoperative monitoring, drug infusion titration and postoperative follow-up were done by another anaesthesiologist who was blinded to the syringes. Spinal anaesthesia was performed with 12.5 mg of 0.5% hyperbaric bupivacaine and 25 μg of fentanyl, and supplemental oxygen was provided at 2 l/min. Loading dose infusions were started when a sensory level of T10 was achieved. Drug 1 was given at a loading dose of 0.5 μg/kg over 10 min and a maintenance dose of 0.5 μg/kg/min. Drug 2 was given at 0.2 mg/kg as a bolus over 2–3 min and an infusion of 0.2 mg/kg/h. In both groups, drug 1 was titrated by 0.1 μg/kg/h every 30 min to maintain a Ramsay Sedation Scale (RSS) score of 3–4. If the RSS score was >4 at 0.2 μg/kg/h of Drug 1, both drug infusions were stopped. The drug infusions were restarted at the lowest doses at RSS of 3. RSS of 3–4 was maintained.

Recordings were taken considering the time of spinal anaesthesia as zero. The sensory blockade was checked using cold sensation using an alcohol swab. The extent of motor blockade was assessed with a modified Bromage scale.[6] RSS was measured preoperatively, just before starting infusion, immediately after the loading dose and every 30 min after starting maintenance infusion.

An increase of 20% in heart rate (HR) and blood pressure (BP) from the baseline was considered tachycardia and hypertension, respectively. HR <50 beats/min was considered as bradycardia. Systolic BP <20% of baseline or mean arterial pressure <65 mmHg was considered hypotension. Hypotension and bradycardia were treated with mephentermine 6 mg and atropine 0.6 mg IV, respectively. Total episodes of haemodynamic instability during surgery were recorded. Time of regression of motor blockade to modified Bromage 6 (MB6) using the modified Bromage scale and other

complications, including postoperative nausea and shivering, were recorded.[6] Drug infusions were stopped at skin closure, and patients were shifted to PACU. The patient was discharged from the PACU when the patient achieved a modified Aldrete score of 9 and the sensory level regressed to T10. On the first analgesic demand or when NRS was >4, diclofenac 75 mg IV was given, followed by diclofenac 75 mg IV every 8 h. Tramadol 100 mg IV was administered as a rescue analgesic, repeated at 12 h if needed. Serum albumin, random blood sugar (RBS), neutrophil-lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) were monitored preoperatively and at the 6th and 24th hour postoperatively. PACU discharge time was recorded based on the modified Aldrete's score.

The study's primary outcome was to compare the time of regression of sensory blockade to S1 in both groups. The secondary outcomes were motor blockade duration, the haemodynamics in the intra- and immediate postoperative periods, changes in perioperative stress markers, measurements preoperatively and at the 6th and 24th hour postoperatively, and PACU discharge time.

The sample size was estimated using the software G*Power version 3.1.9.2. The sample size was based on the study by Dinesh *et al.*,[7] who had considered the mean sensory regression time to the S1 segment in the dexmedetomidine group as 261.5 [standard deviation (SD): 34.8] min and in the control group as 165.2 (SD: 31.5) min. Therefore, taking the minimum expected difference as 20 min at a minimum two-sided 95% confidence interval (CI) and 90% power of the study, the required sample size in each group (1:1 ratio) was 21. Considering dropouts, 30 patients were included in each group.

Package for the Social Sciences statistics software version 22.0 (IBM Corp, Armonk, NY, USA) was used for statistical analysis, and the results were tabulated in a Microsoft Office Excel worksheet. Clinical parameters were presented as mean (SD) and median (interquartile range) for quantitative variables and frequency for qualitative variables. The Chi-squared test was used to test the statistical significance of cross tabulation between categorical variables like gender, postoperative nausea vomiting and need for rescue analgesia. An independent *t*-test or Mann–Whitney *U* test was used to compare continuous variables like age, BMI, time to S1 regression, HR, BP, change in stress markers and time of PACU discharge between the two groups. W is the Wilcoxon test statistic that was used to compare PACU discharge time and total tramadol requirement. P value < 0.05 was considered statistically significant.

RESULTS

Seventy-three patients were assessed for eligibility, and 60 were included in the study [Figure 1]. Both groups' demographic profiles, ASA physical status and baseline vitals were comparable [Table 1].

All patients in both groups achieved a sensory blockade between T4 and T6 within 4–8 min and a motor blockade of modified Bromage level 1 or 2 within 4–6 min. There was no significant difference between the groups regarding sensory regression to S1 or recovery to MB6 ($P > 0.05$) [Table 2, Figure 2].

The number of patients who developed bradycardia and hypotension was comparable between the two groups [Table 2]. The stress markers (NLR, PLR, albumin and RBS) were comparable between the two groups (P = 0.941, 0.294, 0.562 and 0.677, respectively). There was a significant difference between the two groups in terms of PACU discharge time from the completion of surgery (min) (W = 882.500, $P < 0.001$) [Table 2]. There was no significant difference between groups regarding the first demand for rescue analgesia. However, there was a significant difference between the groups regarding tramadol required in 24 h (W = 614.50, P = 0.003), with a higher requirement in Group D [Table 2]. The two groups had no significant difference regarding postoperative shivering and nausea.

DISCUSSION

This study found that patients of both groups, Group D and Group LKD, had comparable sacral (S1) sensory regression. Compared to the IV infusions of dexmedetomidine, patients who received a low dose of ketamine–dexmedetomidine under spinal anaesthesia had a significantly lower incidence of hypotension intraoperatively, had shorter PACU discharge times and had significantly less postoperative tramadol consumption. No significant difference was noted in the time of attaining the highest level of sensory blockade, duration of sensory blockade, motor blockade, incidence of bradycardia, stress markers, time of first rescue analgesia, postoperative nausea and shivering in the two groups.

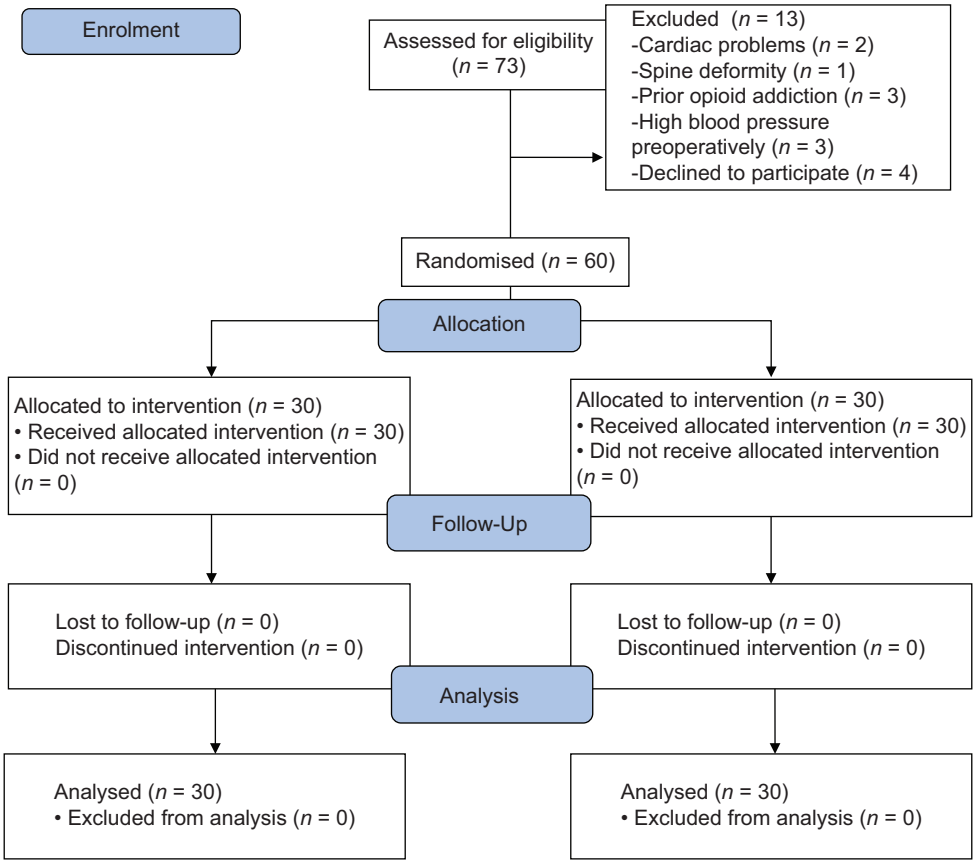

Figure 1: Consolidated Standards of Reporting Trials flow diagram

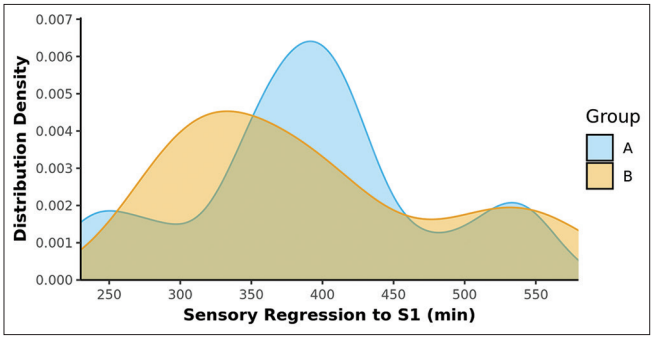

Figure 2: Density plot depicts the association between groups and distribution of sensory regression to S1 (min). S1 = sacral 1 segment

Dexmedetomidine has a role in modulating pain and inhibiting transmission and perception of pain. Likewise, ketamine is also known to combine with *N*-methyl-D-aspartate receptors and affect the voltage-sensitive calcium channels with opiate and monoaminergic receptors to cause analgesic and anaesthetic effects. Therefore, dexmedetomidine and ketamine are considered to have a synergic effect with intrathecal bupivacaine. Many studies have shown that both IV and intrathecal dexmedetomidine prolong spinal anaesthesia. Choudhary *et al.*[8] reported that the time taken for two dermatomal regressions was prolonged in the dexmedetomidine group compared to normal saline under bupivacaine spinal anaesthesia. Watanabe *et al.*[9] reported that the time for regression to L2 was significantly prolonged in the dexmedetomidine group compared to the midazolam ($P = 0.008$) group.

In our study, although the incidence of bradycardia was comparable, it was observed that the incidence of hypotension and the number of hypotensive episodes were significantly higher in Group D compared to Group LKD. Choudhary *et al.*[8] reported that the incidence of bradycardia was significantly higher in the dexmedetomidine group than in the normal saline group ($P < 0.001$). Fatima *et al.*[10] reported that low-dose IV ketamine (0.3 mg/kg) provides haemodynamic stability and reduces the crystalloid volume requirement after spinal anaesthesia. Hence, combining low-dose ketamine with dexmedetomidine infusion can significantly reduce the incidences of hypotensive episodes. Our study showed no significant difference in the attenuation of the surgical stress response measured by NLR, PLR, albumin and RBS between groups, which is comparable to previous studies.[11,12]

Table 1: Demographic profile and baseline parameters

Parameters	Group D (*n*=30)	Group LKD (*n*=30)
Age (years), mean (SD)	34.17 (13.35)	36.87 (8.69)
Gender (male/female), *n*	25/5	22/8
Weight (kg), mean (SD)	67.93 (8.43)	64.57 (8.87)
Height (cm), mean (SD)	168.17 (6.80)	166.23 (8.38)
BMI (kg/m^2), mean (SD)	23.87 (1.78)	23.20 (1.58)
Heart rate (bpm) (baseline), mean (SD)	87.43 (13.44)	86.70 (9.64)
Systolic BP (mmHg) (baseline), mean (SD)	122.97 (15.38)	128.87 (13.49)
Diastolic BP (mmHg) (baseline), mean (SD)	80.50 (13.34)	80.77 (7.38)
MAP (mmHg) (baseline), mean (SD)	95.80 (17.19)	96.53 (8.92)

Data expressed as mean (SD) or numbers. BMI=body mass index, BP=blood pressure, MAP=mean arterial pressure, SD=standard deviation, *n*=number of patients

Table 2: Study parameters

Parameters	Group D (*n*=30)	Group LKD (*n*=30)	*P*
Total dose of dexmedetomidine (μg), mean (SD) (95% CI)	93.80 (13.03) (89.14, 98.46)	100.37 (32.12) (88.88, 111.86)	0.917
Total dose of ketamine given (mg), mean (SD) (95% CI)	-	37.24 (9.52) (33.83, 40.65)	-
Postoperative shivering (yes)	0	0	1
Nausea (yes)	3	2	1
Bradycardia (yes)	9	3	0.053
Hypotension (yes)	19	9	0.009
Tachycardia (yes)	5	6	0.739
Hypertension (yes)	6	2	0.254
Recovery to modified Bromage 6 (min), mean (SD) (95% CI)	193.60 (71.90) (167.87, 219.33)	195.63 (47.36) (178.68, 212.58)	0.898
Sensory regression to S1 (min), mean (SD) (95% CI)	390.33 (84.38) (360.14, 420.53)	393.23 (93.01) (363.04, 423.43)	0.701
Duration of drug given (minutes), mean (SD) (95% CI)	131.90 (36.66) (118.78, 145.02)	130.03 (30.72) (119.04, 141.023	0.832
PACU discharge from the completion of surgery (min), mean (SD) (95% CI)	37.17 (5.68) (35.14, 39.20)	22.20 (4.50) (20.59, 23.81)	<0.001
Rescue analgesic (min), mean (SD) (95% CI)	291.77 (70.55) (266.52, 317.02)	301.73 (76.88) (274.22, 329.24)	0.767
Total tramadol required in 24 h (mg), mean (SD) (95% CI)	130.00 (53.50) (110.86, 149.14)	83.33 (59.21) (62.14, 104.52)	0.003

Data expressed as mean (SD) (95% CI). CI=confidence interval, *n*=number of participants, PACU=postoperative care unit, S1=sacral 1 segment, SD=standard deviation

Kaur *et al.*[13] conducted a study on discharge readiness comparing dexmedetomidine and ketamine premedication. They found that the number of patients ready for discharge was higher with ketamine and dexmedetomidine premedication compared to the saline premedication. In our study, PACU discharge time was significantly higher in Group D than in Group LKD. This might be due to haemodynamic stability in the LKD group, as other criteria like spinal regression, postoperative nausea, and vomiting were comparable in both groups.

Our study's limitations include the absence of a control group and the inclusion of ASA I and II patients only.

CONCLUSION

Low-dose ketamine–dexmedetomidine infusion during spinal anaesthesia does not increase the onset and duration of sensory or motor block compared to dexmedetomidine infusion.

Statement on data sharing

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared after approval as per the authors' institution policy.

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Conflicts of interest

There are no conflicts of interest.

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