Original Article

Comparison of two different doses of dexmedetomidine for continuous epidural analgesia for lower limb surgeries: A randomized double-blind study

Pranjali Kurhekar, Sam Blessy Sheba[1], Sathyasuba Meenakshisundaram, Raghuraman M. Sethuraman, Neeta Parlikar

Department of Anesthesiology, Sree Balaji Medical College and Hospital, Chromepet, Chennai, [1]Shri Sathya Sai Medical College and RI, Kancheepuram, Tamil Nadu, India

Abstract

Background and Aims: Bolus epidural dexmedetomidine provides potent analgesia but the incidence of hemodynamic instability is high. There are only a few studies that have evaluated the efficacy of epidural dexmedetomidine infusion but none of them compared different doses to find the optimum safe dose. We compared the analgesic efficacy and safety of two different doses of dexmedetomidine in continuous epidural for postoperative analgesia.

Material and Methods: Patients undergoing lower limb surgeries were divided randomly into two groups: Group I (n = 36) received an epidural infusion of 0.1% ropivacaine + 0.5 μg/kg/24 h of dexmedetomidine and Group II (n = 36) received epidural infusion 0.1% ropivacaine + 1 μg/kg/24 h of dexmedetomidine. Both groups received epidural infusion at the rate of 5 ml/h over 48 h postoperatively. Pain scores, demand for rescue analgesics, hemodynamic parameters, and sedation scores were compared between the groups. Statistical analysis was done using an independent t-test and Chi-square test.

Results: 1 μg/kg group (Group II) had a significantly reduced pain score at all time intervals and less demand for rescue analgesia (P = 0.03). The severity of pain was more in the 0.5 μg/kg group (Group I), at all times (P = 0.000). Incidence hypotension was higher in Group II. Bradycardia was seen in two patients in Group II and none in Group I.

Conclusion: Dexmedetomidine in a dose of 1 μg/kg/24 h with 5 ml of 0.1% ropivacaine through epidural infusion provides better analgesia with a safe hemodynamic profile.

Keywords: Dexmedetomidine, epidural analgesia, hemodynamic stability, ropivacaine

Key message: Epidural dexmedetomidine can cause profound hypotension. The optimum, safe dose of dexmedetomidine is not known. In our study, we observed that continuous epidural infusion of 1 μg/kg/24 h dexmedetomidine provides better analgesia with acceptable hemodynamic variations.

Introduction

Epidural analgesia continues to be the superior method for providing effective analgesia during the postoperative period. Adequate analgesia can be achieved with only local anesthetic agents (LA) given through an epidural route. But may require larger doses and volume which carries the risk of sympathetic blockade and systemic toxicity. The addition of adjuvants to epidural LA helps to decrease the dose of LA and hence reduction in the systemic manifestation of LA while providing potent analgesia.[1] Opioids are the most commonly used additives with local anesthetic agents due to their potent

Address for correspondence: Dr. Sathyasuba Meenakshisundaram, Department of Anesthesiology, Sree Balaji Medical College and Hospital, Chromepet, Chennai - 600044, Tamil Nadu, India.
E-mail: drsathyasuba@gmail.com

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analgesic properties but have certain adverse effects like pruritis, respiratory depression, nausea, and vomiting.[2,3] Dexmedetomidine is a potent selective α2 adrenergic agonist with analgesic and sedative properties which has become a popular adjuvant due to its synergistic action with LA.[4] Previous studies have proven that a bolus dose of epidural dexmedetomidine provides prolonged analgesia. A bolus dose of epidural dexmedetomidine can cause hypotension and bradycardia and may not provide long-lasting analgesia.[5] Epidural infusion of dexmedetomidine can give long-lasting analgesia with dose-dependent hemodynamic stability.[6] A couple of studies used continuous epidural analgesia with dexmedetomidine for labor analgesia, in which both the average duration and dose for infusion were low.[6,7] Besides, only a few studies evaluated the analgesic efficacy of dexmedetomidine in continuous epidural infusion.[8-10] The dosages used in these studies were not based on the weight of the patient; instead, the rate of infusion varied from 2 to 6 μg/h and they reported with a high incidence of hemodynamic instability. Hence an effective, yet safe dose for continuous epidural infusion remains unclear. Till now, no previous study has compared different dexmedetomidine doses in continuous epidural infusion to find an optimum safe analgesic dose. We hypothesized that a dose of 1 μg/kg of dexmedetomidine through continuous epidural infusion can provide better analgesia with hemodynamic stability.

Material and Methods

This study was conducted over 18 months, in a tertiary teaching hospital after approval from the Institutional Ethical Committee. The trial was registered with Clinical Trials Registry – India (CTRI No: CTRI/2019/02/017895). Patients belonging to the American Society of Anesthesiologists (ASA) I and II, between the age groups of 18–60 years, posted for elective lower limb orthopedic surgeries with the willingness to participate in the study were included in the study. Patients with known cardiac illness, hypertension, coagulation abnormalities, extremes of body mass index, and pregnant/lactating patients were excluded from the study.

Patients were randomly allocated into two groups using computer-generated random numbers. After shifting to the operating room, standard monitors like electrocardiogram (ECG), non-invasive blood pressure (NIBP), and pulse oximetry (SpO_2) were connected. Baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), oxygen saturation, and respiratory rate (RR) were recorded. An epidural block was given at L1-L2/L2-L3 intervertebral space with an 18-gauge Tuohy needle using the loss of resistance technique. A test dose of 3 ml of 2% lignocaine with adrenaline was given, after which the subarachnoid block was administered in the lower lumbar space with an appropriate LA dose.

After the completion of the surgery, the patients were started on epidural infusion based on their allocated group. Group I received 0.1% Ropivacaine with the addition of 0.5 μg/kg of dexmedetomidine. 50 μg (0.5 ml) of dexmedetomidine (Dextomid 50, Neon Laboratories India) was diluted with 1.5 ml of normal saline. From this 0.5 μg/kg of dexmedetomidine was added to 24 ml 0.5% ropivacaine (Ropin 0.5% Neon Laboratories, India). Then the drugs were diluted with normal saline to a total volume of 120 ml. Thus each milliliter contained 0.1% ropivacaine with 0.20–0.29 μg of dexmedetomidine, depending upon the weight of the patient. The total volume of 120 ml was loaded in two syringes of each 60 ml capacity and given through epidural infusion at the rate of 5 ml/h through the syringe pump. This infusion was continued at the same rate for 48 h. Group II received 0.1% ropivacaine with 1 μg/kg of dexmedetomidine. 100 μg (1 ml) of dexmedetomidine (Dextomid 50, Neon Laboratories India) was diluted with 1 ml of normal saline. From this 1 μg/kg of dexmedetomidine was added to 24 ml 0.5% ropivacaine (Ropin 0.5% Neon Laboratories, India). Then the drugs were diluted with normal saline to a total volume of 120 ml. Thus, each milliliter contained 0.1% ropivacaine with 0.4–0.5 μg dexmedetomidine depending upon the weight of the patient. The total volume of 120 ml was loaded in two syringes of each 60 ml capacity and given through epidural infusion at the rate of 5 ml/h through the syringe pump (Akas Infusions, India). This infusion was continued at the same rate for 48 h. The drug syringes were prepared by the investigator who was not involved in monitoring patients and was handed over to the operation room ~~theater~~ anesthesiologist.

The next day another two syringes loaded with study drugs were handed over to the postoperative nursing staff who did the monitoring under the investigators' supervision. The time of starting of infusion was taken as zero hour and HR, SBP, DBP, MAP, SpO2, and RR were noted as baseline parameters. From then patients were evaluated every fourth hour for the first 24 h and then every eighth hour for the next 24 h for pain and sedation scores, HR, SBP, DBP, SpO2, and RR in the postoperative ward. Assessment of pain was done using the numeric pain rating scale (NPRS), where 0 = No pain and 10 = Unimaginable pain.[11] Pain scores from 0 to 3 were taken as mild pain, 4 to 7 were taken as moderate pain, and > 7 were taken as severe pain. Incidence of mild, moderate, and severe pain was noted. If NPRS was four, it was taken as the presence of pain and 5 ml of 0.2% of ropivacaine was given through the epidural catheter as a

rescue analgesic. The incidence of pain and the total number of rescue analgesics needed were noted. Ramsay sedation score was used for monitoring postoperative sedation.[12] HR of < 50/min was taken as bradycardia and was treated with atropine 0.6 mg intravenous (IV). MAP of < 20% of baseline value (0-hour value) was taken as hypotension and was treated with intravenous fluids or vasopressors like ephedrine 6 mg IV. Patients sustaining persistent hypotension intraoperatively were not started on epidural infusion and were considered dropouts.

The primary outcome of the study was to compare analgesic efficacy in terms of pain scores. The secondary outcomes were to compare the safety profile measured by sedation score and hemodynamic parameters and the total number of rescue analgesics required.

Statistical analysis was done with a Statistical Package for Social Sciences (SPSS Version 23.0, IBM, Armonk, NY, USA). The Kolmogorov–Smirnov test was used to assess the distribution of the data. Demographic parameters, NPRS scores, rescue analgesics, hemodynamic, and respiratory parameters were analyzed with an independent *t*-test and were expressed as mean ± standard deviation (SD). The incidence of bradycardia, hypotension, and sedation was compared using the Chi-square test and expressed as frequency and percentage. *P* values < 0.05 were considered statistically significant for a two-sided test. Sample size calculations were drawn based on a previous study where complete analgesia was achieved in 76% of patients.[5] Considering the higher dose of dexmedetomidine given in our study continuously via epidural, anticipated complete analgesia in 99% of patients. A sample size of 32 per group was needed with a significance of 5% and a power of study of 90%. 36 patients per group were included to allow possible dropouts.

Results

A total number of 86 patients were eligible for the study [Figure 1]. Out of which, ten did not meet the inclusion criteria and four patients declined to participate in the study. The remaining 72 patients were randomized for the study. After randomization, 36 patients were included in each group and all were analyzed. Patients' characteristics and types of surgeries were comparable between the groups. [Table 1] The NPRS scores were significantly lower in Group II at all time intervals [Table 2]. All the patients in Group II had only mild pain at all the time intervals while a significant number of patients in Group I had moderate pain ($P = 0.000$). Six patients in Group I had severe pain at various time intervals ($P = 0.00$). The total number of rescue analgesics needed was more in Group I on day 1 [Table 3]. No patient in either group required more than one rescue analgesic. A total of ten patients in Group I and seven in Group II required rescue analgesics on day 1. This difference was statistically significant ($P = 0.03$). Sedation scores were more in Group II after 24 h, but the difference was not statistically significant. A maximum number of patients had a score of 3 in both groups on day 1. After 24 h, the maximum number of patients in Group II had a score of 4. The highest score was 4 in both groups and the lowest was 2. SBP and DB*P* values over the period are depicted in Figure 2. At the 4th, 8th, 16th, 24th, and 32nd hour, the SB*P* values were comparable between the groups. At the 12th, 20th, 40th, and 48th hour, SBP was significantly low in Group II. The incidence of hypotension was significantly more in Group II at all time intervals [Table 4]. At all time intervals, 16 patients had hypotension in Group II. Out of them, ten patients responded to fluid boluses and only four patients needed vasopressors and no patient required discontinuation of epidural infusion. Bradycardia was seen in two patients in Group II and was not seen in any patient in Group I.

Discussion

In this study, we compared the analgesic efficacy and safety of two different doses (0.5 μg/kg/24 h and 1 μg/kg/24 h) of dexmedetomidine for continuous epidural postoperative analgesia. We observed that pain scores and requirements for rescue analgesics were lower with the 1 μg/kg group. Sedation scores were similar between the groups. Dexmedetomidine, when administered epidurally, produces analgesia by preventing the release of substance *P* in the nociceptive pathway and hyperpolarization of unmyelinated C fibers.[13,14] Along with profound analgesic properties, dexmedetomidine is also known to produce bradycardia and hypotension with increments in its dosages, hence it is vital to have an optimal dose to be administered epidurally.[15] Previous studies have used epidural dexmedetomidine in doses of 0.5 and 1 μg/kg as a bolus and reported a high incidence of hypotension.[16,17] The dosages used in studies involving continuous dexmedetomidine epidural infusion were not based on the weight of the patient instead, varied from 2 to 6 μg/h and a high incidence of hemodynamic instability was reported.[8-10] Hence we decided to study 0.5 μg/kg and 1 μ/kg as a continuous infusion over 24 h.

Agamohammdi *et al.*[8] studied the effect of continuous infusion of dexmedetomidine given through thoracic epidural and found that pain scores were significantly lower with the dexmedetomidine group at all time intervals. Our results are similar to their study.

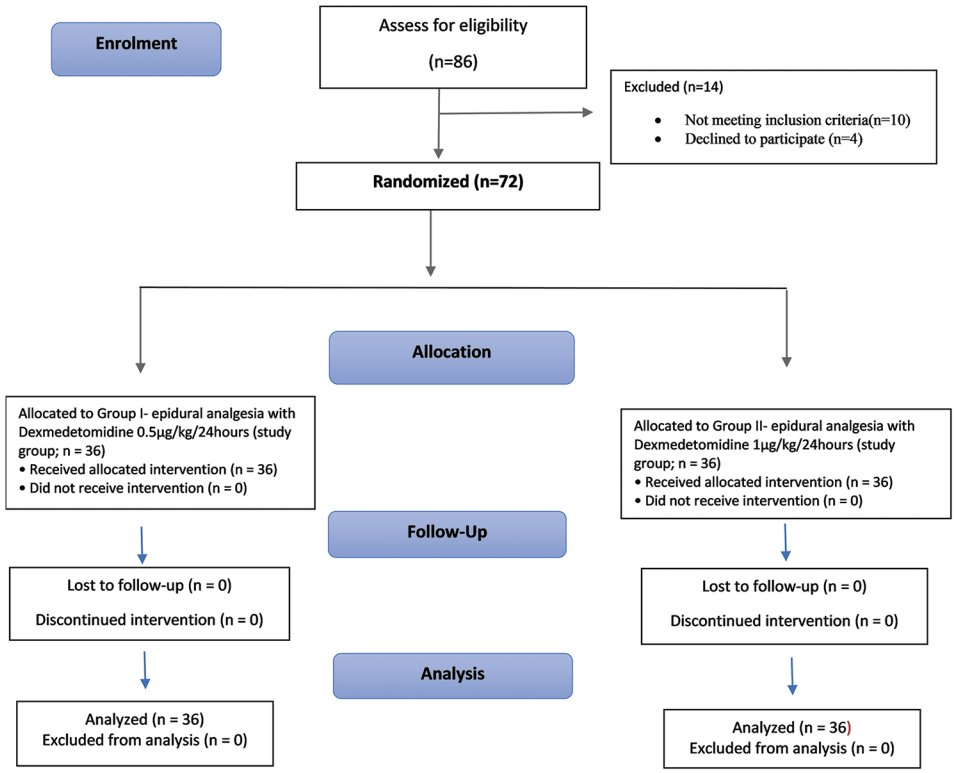

Figure 1: CONSORT Diagram

Table 1: Comparison of patient's characteristics

Variable	Group I Mean±SD	Group II Mean±SD
Age (in years)	37.39±12.71	39.78±10.61
Weight (in kg)	55.86±9.47	60.89+12.99
Gender (M/F)	18/18	19/17
Type of surgeries		
Proximal femoral nailing (PFN)	16 (45.5%)	18 (50%)
Hemiarthroplasty	6 (16.5%)	5 (14%)
Nailing for both bone fracture (Leg)	10 (27%)	11 (30.5%)
Dynamic hip screw fixation (DHS)	4 (11%)	2 (5.5%)

Table 2: Numeric pain rating score

Time interval	Group I Mean±SD	Group II Mean±SD	*P*-value Confidence interval (CI)
4th Hour	4.42±0.60	2.36±0.49	0.001 (1.79–2.31)
8th Hour	4.56±0.65	2.33±0.48	0.000 (1.95–2.49)
12th Hour	4.22±0.54	2.19±0.40	0.001 (1.80–2.25)
16th Hour	4.14±0.49	2.39±0.49	0.003 (1.51–1.98)
20th hour	4.06±0.33	2.39±0.49	0.001 (1.47–1.87).
24th Hour	4.36±0.54	2.31±0.47	0.001 (1.81–2.29)
32nd Hour	4.28±0.70	2.31±0.47	0.001 (1.81–2.19)
40th Hour	4.25±0.60	2.33±0.53	0.00 (1.64–2.18)
48th Hour	4.06±0.23	2.44±0.56	0.00 (1.64–2.18)

Hetta *et al.*[9] found that epidural infusion of 3 µg dexmedetomidine with 0.1% bupivacaine at an infusion rate of 6 ml/h provided a significant reduction in pain scores, demand

Table 3: Number of rescue analgesics required

	Group I (Mean±SD)	Group II (Mean±SD)	*P*-value
Day 1	0.27±0.45 (0–1)*	0.08±0.2 (0–1)*	0.03
Day 2	0.19±0.40 (0–1)*	0.05±0.2 (0–1)*	0.07

**Minimum to maximum*

Table 4: The incidence of hypotension

Time interval	Group I No. of patients (% in group)	Group II No. of patients (% in group)	*P*-value
4th Hour	7 (19.4%)	16 (44.4%)	0.02
8th Hour	5 (13.9%)	16 (44.4%)	0.004
12th Hour	5 (13.9%)	16 (44.4%)	0.004
16th Hour	5 (13.9%)	16 (44.4%)	0.004
20th hour	10 (27.8%)	16 (44.4%)	0.008
24th Hour	10 (27.8%)	16 (44.4%)	0.008
32nd Hour	10 (27.8%)	16 (44.4%)	0.008
40th Hour	10 (27.8%)	16 (44.4%)	0.008
48th Hour	5 (13.9%)	16 (44.4%)	0.004

for rescue analgesics, and pain intensity but was associated with hypotension and bradycardia. In our study, we found in Group II pain intensity and scores were significantly less with hypotension than in Group I. In our study, we used rescue analgesics as epidural bolus rather than IV analgesics because epidural bolus provides better analgesia with reduced opioid requirements as compared to IV analgesics.[18] When different doses of epidural dexmedetomidine ranging from 0.25 to

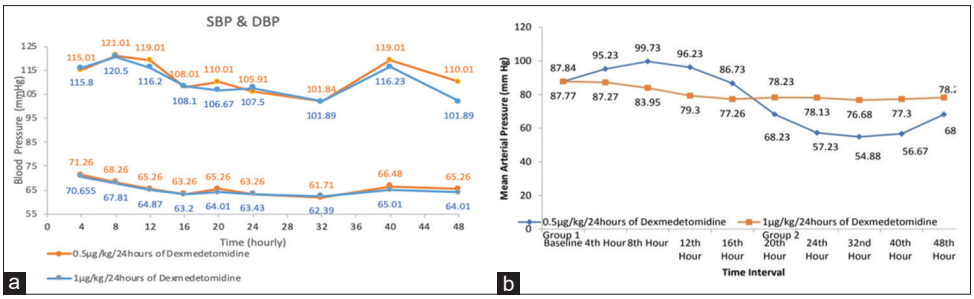

Figure 2: (a) SBP and DBP distribution among the groups. (b) MAP distribution among the groups at different time periods

1 µg/ml were added to ropivacaine for epidural labor analgesia, it was found that pain scores were reduced with an increase in the dose of dexmedetomidine.[7] Ramsay sedation scores were similar in the four different doses of dexmedetomidine during labor, ranging from 2 to 4.[12] In our study, sedation scores were comparable between 1 and 0. 5 µg/kg and ranged from 2 to 4. Previous studies have reported an incidence of hypotension as high as 52% with 0.5 µg/kg bolus epidural dexmedetomidine.[16] Zeng *et al.*[10] found that epidural dexmedetomidine in a dose of 0.5 0.5 µg/kg bolus followed by 5–6 µg/h, provided analgesia comparable to epidural morphine infusion. The incidence of hypotension was 27% and bradycardia was 17% in that study. In our study, the incidence of hypotension in Group I (0.5 µg/kg) was 13–27% and in Group II (1 µg/kg) was 44%, while no patient in Group I and only two patients in Group II developed bradycardia (HR < 50/min). Zeng *et al.*[10] considered hypotension as a fall of 30% from baseline, while we took a fall of 20% from baseline. This could be the reason for the increased incidence of hypotension in our study. The incidence of a fall in MAP after intravenous dexmedetomidine is documented as 13–27% and with higher maintenance doses, the fall is more.[19,20] In our study, although the incidence of hypotension was statistically significant in the 1 µg/kg group, the SBP and DBP showed a steady trend [Figure 2 and 2b]. The incidence of hypotension with 0.5 µg/kg was more on day 2 than on day 1 as this group required more top-up boluses as rescue analgesics [Tables 3 and 4]. Considering this, we believe that the analgesic benefit of 1 µg/kg outweighs this minimal risk of hypotension, thus making the hemodynamic variations acceptable. We used dosages of dexmedetomidine based on body weight. Based on mean body weight and rate of infusion, the dilution of dexmedetomidine in our study was approximately 1 µg/h in Group I and 2.5 µg/h in Group II. Previous studies have reported pain scores < 3 with a dexmedetomidine infusion rate of 3–6 µg/h.[9,10] Our study found that with a 1 µg/kg dose (2.5 µg/h), pain scores were < 3 at all intervals with hemodynamic stability.

There were some limitations of the study. First, we did not monitor the time for onset of analgesia after starting the infusion which could have helped to assess the efficacy of both doses better way. Also, the inclusion of one more group with 0.75 µg/kg/24 h of dexmedetomidine would have given a better understanding of the optimal dose. Not monitoring patients' satisfaction scores was another limitation of our study. Further studies are needed with different doses of dexmedetomidine to understand the dose-dependent effects of dexmedetomidine through continuous epidural infusion.

Conclusion

We conclude that dexmedetomidine in a dose of 1 µg/kg/24 h with 5 ml/h of 0.1% ropivacaine through epidural infusion provides better analgesia with lower pain scores and less demand for rescue analgesic than 0.5 µg/kg/24 h with acceptable hemodynamic variations.

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Conflicts of interest
There are no conflicts of interest.

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