Section: Anesthesiology

Original Research Article

THE EFFECT OF ADDING EPINEPHRINE TO THE COMBINATION OF 0.5% HYPERBARIC BUPIVACAINE AND DEXMEDETOMIDINE IN INTRATHECAL ANESTHESIA FOR LOWER LIMB SURGERY-A PROSPECTIVE, DOUBLE-BLINDED, RANDOMIZED CONTROL STUDY

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Received : 10/12/2023
Received in revised form : 21/01/2024
Accepted : 06/02/2024

Keywords:
Intrathecal, Bupivacaine, Dexmeditomedine, Epinephrine, Analgesia.

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DOI: 10.47009/jamp.2024.6.1.252

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2024; 6 (1); 1269-1274

Abstract

Background: In multiple previous studies, dexmedetomidine or epinephrine have been used as adjuvants with intrathecal bupivacaine to improve the quality and duration of spinal anesthesia. This study aims to investigate the effects of adding epinephrine to the combination of dexmedetomidine and bupivacaine for intrathecal anesthesia. **Materials and Methods:** Sixty patients were included in the study. Patients were randomly assigned to receive either 10mg hyperbaric bupivacaine plus 10µg dexmedetomidine and epinephrine 100µg (Group BDA, N = 30) or 10mg hyperbaric bupivacaine plus 10µg dexmedetomidine and normal saline (NS) (Group BDN, N = 30). Onset and duration of sensory and motor blockade were observed intraoperatively along with heart rate and mean arterial blood. The duration of analgesia and complications were also recorded in the postoperative period. **Result:** The total length of analgesia was 360 (62) min in group BDA, which was significantly greater than from group BDN 297 (38) min. The mean duration of sensory regression at S1 was 281 (40) min for the BDA group and 230 (46) min for the BDN group. The regression time for the motor block to achieve the Bromage score of 0 was 299(41) min in the group BDA and 252 (46) min in the group BDN. The hemodynamic changes and side effects were comparable at different time intervals. **Conclusion:** The addition of epinephrine to the combination of bupivacaine and dexmedetomidine for intrathecal anesthesia shows higher efficacy for the duration of sensory and motor blockade, prolongation of analgesia and hemodynamic stability with fewer side effects.

INTRODUCTION

Intrathecal anesthesia is the most commonly performed regional anesthetic technique and is widely used in various below umbilical surgeries because it provides rapid onset of action, adequate analgesia, proper muscular relaxation, is very economical, and is easy to administer. For this purpose, bupivacaine is largely used for intrathecal anesthesia, mainly in the hyperbaric form, but using it alone results in a shorter duration and is inadequate for visceral pain. So, various adjuvants, such as morphine, epinephrine (ADR), fentanyl, dexmedetomidine, ketamine, midazolam, and clonidine, are very commonly used with it, to improve the quality and duration of analgesia. A highly selective α2-agonist which is Dexmedetomidine is now being used to improve the quality and duration of spinal anesthesia due to its antinociceptive benefits by diminishing the noxious stimuli evoked liberation of nociceptive substances.[1] Along with these, it diminishes both intra- and postoperative anesthetic utilization and prolongs the postoperative pain-free period.[2] Its

sympatholytic action causes bradycardia and hypotension at higher doses, which usually limits its use for various surgeries. Whereas epinephrine enhances LA action via vasoconstriction, preventing systemic reabsorption of local anesthetics.[3] Due to its sympathomimetic action, it leads to tachycardia and hypertension after administration. In addition, it can exert its analgesic effect mediated by the activation of α-2 adrenergic receptors.[4] There have been no studies evaluating epinephrine's effect in combination with dexmedetomidine and hyperbaric bupivacaine.

So, we hypothesize that adding epinephrine as another adjuvant to the combination of dexmedetomidine and bupivacaine will improve the efficacy of intrathecal anesthesia along with the hemodynamic changes and side effects that are often observed with these adjuvants when used individually with bupivacaine. The study aims to evaluate the effect of adding epinephrine to the combination of 0.5% hyperbaric bupivacaine and dexmedetomidine in lower limb surgeries for the duration of analgesia as the primary outcome and the sensory and motor blockade as secondary outcomes, including hemodynamic stability, and side effects.

MATERIALS AND METHODS

The study was approved by the university's institutional review board (IRB number: Dean/2020/EC/2266) and was conducted in Department of Anesthesiology and Critical care, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India. Written informed consent was obtained from all subjects participating in the trial after explaining the procedure and purpose of the study. The trial was registered prior to patient enrollment at clinicaltrials.gov (CTRI/2021/01/030357, http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=50312, Date of registration: 11.01.2021). This clinical trial was conducted following Good Clinical Practice guidelines and the Declaration of Helsinki. Patients aged 15-60 years with the American Society of Anesthesiologists (ASA) physical status classifications of I and II, posted for lower limb surgery of a probable duration of 2 hours, were *included*. The *exclusion criteria* were contraindications to regional anesthesia, history of significant coexisting diseases like ischemic heart disease, hypertension, impaired renal functions, severe liver disease, cardiac conduction blocks, intake of beta-blockers, and those who did not give consent. The sample size was calculated based on $\alpha = 0.05$, and $\beta = 0.20$, with the help of a sealed envelope sample size calculator, including a minimum expected difference of 30% so that the results would be statistically significant. The total number of patients was distributed into two groups, each consisting of 30 patients. The patients who fulfilled the eligibility criteria were reviewed a day before and were familiarized with the visual analog scale (VAS).[5] On the day of surgery, after the arrival of the patient in the operation theater, preloading with 500 ml of lactated Ringer's solution was done through an 18 gauge cannula with no premedication, and ASA-specific monitors were attached. The total volume of the drug combination in both groups was taken to be 3 ml. In Group BDA (N=30)- freshly prepared combination of bupivacaine heavy 0.5% 2.0 ml (10.0 mg), dexmedetomidine 0.1 ml (10 mcg), epinephrine 1:1000 , 0.1 ml (100mcg) and saline was used as required to give a total volume of 3 ml solution. In Group BDN (N = 30), a freshly prepared combination of bupivacaine heavy 0.5% 2.0 ml (10.0 mg), dexmedetomidine 0.1 ml (10 mcg), and saline was used as required to give a total volume of 3 ml of solution. A 25G Quincke needle was used to administer the intrathecal anesthetic solution at the L3-4 or L4-5 level while the patient was seated, under strict aseptic conditions. The patient was immediately placed in the supine posture after receiving spinal anesthetic solution. An impartial anesthesiologist who was not connected to the study prepared and administered the medication solutions, and the investigator collected the outcome variables. The onset of sensory block to level T10, the onset of the motor blockade to Bromage scale 3, the regression of sensory level to dermatome S1, the return of motor activity to Bromage score 0, and the total duration of analgesia were recorded, preoperatively, 2.5 minutes after intrathecal injection, then every 10 minutes until the operation was complete, and postoperatively every 10 minutes till the sensory blockade was tapered off. The vital signs, such as heart rate, mean arterial pressure, and oxygen saturation, were all monitored. Prior to being returned to their wards, patients were brought to the postanesthesia care unit to be checked for vital signs and problems. The onset and duration of sensory block were assessed by the pinprick test and motor blockade by the Bromage Scale,[6] (Bromage 0- Full mobility of the hip, knee, and ankle. Bromage 1- The patient is unable to move his hip, but can move his knees and ankles. Bromage 2- The patient is unable to move his hip or knee, but can move his ankle. Bromage 3-Patient is unable to move his hip, knee, or ankle). The duration of analgesia was assessed by VAS and ranged between 0 and 10 (0 = no pain, 10 = most severe pain), VAS > 3 was considered a regression of analgesia. The time recorded is the total duration of analgesia. As a rescue analgesic, injections of 15 mg/kg of paracetamol were given intravenously to treat pain. If the pain persisted, injections of 1 mg/kg of tramadol were given intravenously. In the case of hypotensive episodes, systolic blood pressure less than 30% of its baseline value or ≤90 mmHg, was treated with inj. Ephedrine, 6 to 12 mg, with increased intravenous fluid administration. And for bradycardia, 0.6 mg of Atropine, along with oxygen

ISSN (O): 2687-5365; ISSN (P): 2753-6556

administration via a face mask (4 l/min). The intraoperative and recovery phase complications, including nausea, vomiting, shivering, respiratory depression, and sedation, were also recorded. The pH for the BDA group 5.4 (0.08) and the BDN group 5.3 (0.08) were determined by a pH meter, and it was observed that they came under the range of Bupivacaine Heavy 0.5% (4.0-6.5).[7] Also, the density (by volumetric method), specific gravity (relative to water at 37°C), and baricity (relative to human CSF at 37°C) were found to be similar among the groups. So the anesthetic solutions would show similar physicochemical changes as with 0.5% bupivacaine heavy.

Statistical Analysis

The information was recorded as a number (proportion) or as a mean ±SD/median (range). Statistical analysis was done using appropriate tools. SPSS version 23 was used to analyze all of the data. We used Student t-tests and Chi-square tests to examine the significance of differences between continuous and categorical variables. P-value < 0.001 was considered to be extremely statistically significant, while $p < 0.05$ was significant.

RESULTS

Among 70 patients enrolled, 10 patients got excluded, as they declined to participate or did not meet the inclusion criteria. After the follow-up of remaining 60 patients the study was closed [Figure 1]. For demographic data, in terms of age, weight, height, and ASA physical status classification both the group were comparable. The primary outcome of our study, i.e., the meantime for rescue analgesia, was significantly exceeded for group BDA as compared to group BDN shown in [Figure 2].

Secondary outcomes, such as the onset of sensory block to level T10 and motor blockade to Bromage scale 3 [Figure 3] were recorded for both groups, and when compared, there were no statistically significant or clinically meaningful differences between them. Sensory level regression to dermatome S1 [Figure 4] was longer in group BDA as compared to group BDN. The return of motor activity to a Bromage score of 0 (Figure 4) was significantly longer in the BDA group than in the BDN group. Vitals such as heart rate (HR) and mean blood pressure (MAP) were recorded after intrathecal injection for up to 2 hours, and there were no statistical differences between the two groups at any time points. Variations in vitals are represented in [Figure 5].

In the BDN group, one patient had an oxygen saturation of less than 95%, requiring oxygen administration for a short period. In this study, out of 30 patients of group BDA, only one patient complained of nausea with no episodes of vomiting in any patient, whereas in BDN group two patients complained of nausea and one had vomiting episodes. Hypotensive episodes were reported in two patients, and bradycardia in one patient, which was treated by inj. ephedrine and atropine, respectively. Furthermore, other side effects like shivering, respiratory depression, sedation were not found in any patients of the study groups.

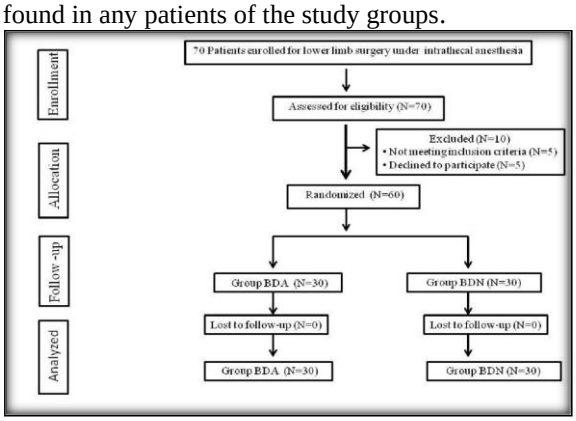

Figure 1: Flow chart, estimates for sample size, and randomization for the study groups

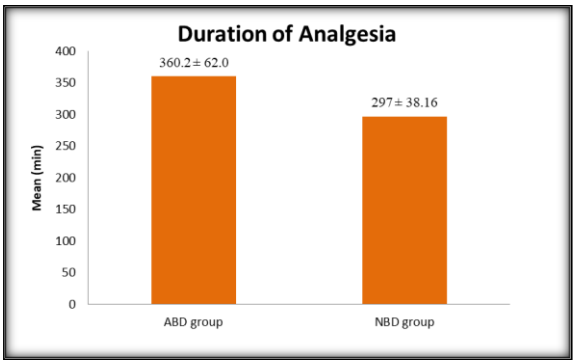

Figure 2: Bar diagram showing the Mean Duration of Analgesia in the study groups

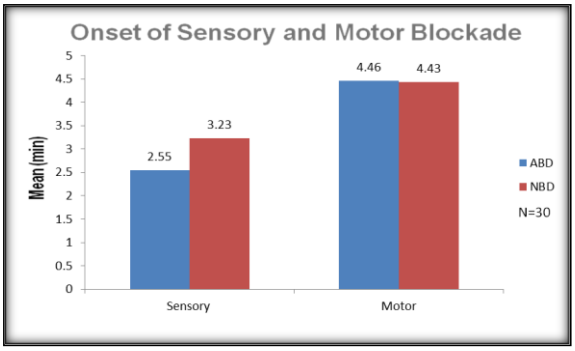

Figure 3: Bar diagram showing the Mean Onset of Sensory and Motor blockade in the study groups

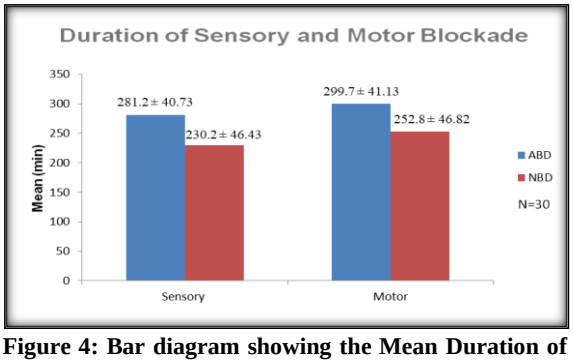

Figure 4: Bar diagram showing the Mean Duration of Sensory and Motor blockade in the study groups

ISSN (O): 2687-5365; ISSN (P): 2753-6556

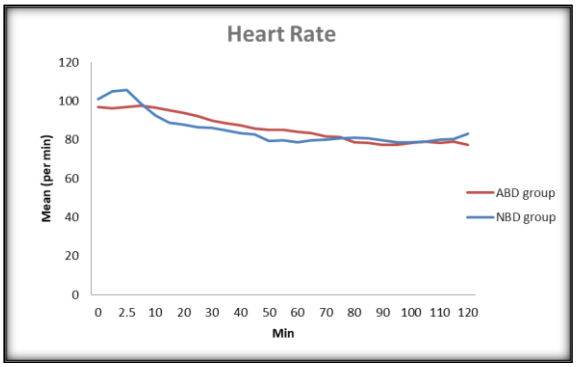

Figure 5A: Graph showing changes in Heart rate (HR) between BDA and BDN Group

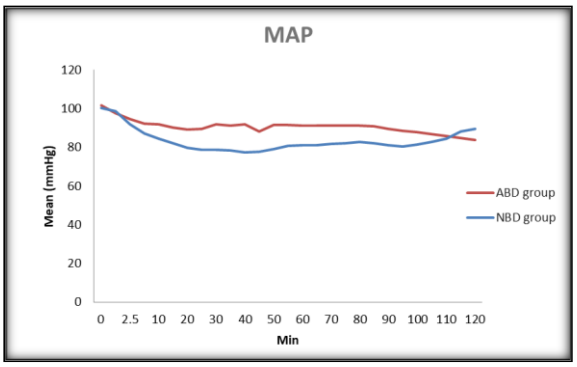

Figure 5B: Graph showing changes in Mean Blood pressure (MAP), between BDA and BDN Group

DISCUSSION

Dexmedetomidine's analgesic properties are dependent on its ability to activate receptors in the dorsal horn of the spinal cord, in particular, α2-C and α2-AR located in the superficial dorsal horn, especially lamina II.[8,9,10] n intrathecal a-2-receptor agonist is antinociceptive for both somatic and visceral pain.[11] While Epinephrine also potentiates the effect of LA. In the dorsal horn of the spinal cord, the substantia gelatinosa contains α-2 adrenoreceptors, through which epinephrine indirectly mediates its antinociceptive properties by reducing the release of transmitters from Aδ and C fibers. In addition, its vasoconstrictive action also limits its systemic absorption, which ensures a longer duration of action.[12]

In our study, we found that there was a prolonged duration of analgesia in the group BDA 360.2 (62.06) min, which is significantly more than in the BDN group 297 (38.16) min. Gupta et al noticed less diclofenac sodium consumption postoperatively in the group where dexmedetomidine and bupivacaine were administered intrathecally than fentanyl and bupivacaine.[13] In a study by Eid HEA et al. a dose-dependent decrease in diclofenac consumption was observed.[14]

This effect of dexmedetomidine was supported by Saadalla AET et al,[15] who compared 10 µg of dexmedetomidine with 25 µg of fentanyl to 10 mg isobaric bupivacaine intrathecal and concluded that there is less need for postoperative analgesia in the dexmedetomidine group with a similar safety profile. Based on earlier human studies, Dexmedetomidine doses for intrathecal anesthesia used were between 3 and 15 µg.[16] Even 3 µg /kg of dexmedetomidine can prolong motor and sensory block without hemodynamic compromise.[17] That would produce higher postoperative analgesic effects with hyperbaric bupivacaine in spinal anesthesia and fewer adverse effects.[18,19,20] In our study, we used 10µg dexmedetomidine in both groups, which prolongs the duration of spinal anesthesia, supported by Al-Mustafa et al,[19] where the effect of dexmedetomidine 5 and 10 µg was studied with bupivacaine in urological procedures and found that 10µg dexmedetomidine shows reduced demand for rescue analgesics in 24 h, this was also shown by studies done by Halder S et al.[21] Similarly, in many other studies, dexmedetomidine was used as an adjuvant to intrathecal anesthesia, and the most common dosage used was 10 mcg. Furthermore, DC Campbell et al,[22] added 0.2 mg epinephrine to the intrathecal combination of 10mcg sufentanil and 2.5mg bupivacaine significantly prolonged labor analgesia without causing adverse effects to the mother or fetus. Again, Gurbet A et al,[23] in CSE for labor, found that intrathecal epinephrine significantly increases the duration of analgesia than the control group who received an intrathecal solution containing local anesthetic-opioid only, in the same study, they concluded that the low dose of epinephrine (12.5 mcg) showed prolonged intrathecal analgesia to a degree comparable to that observed with doses as high as 100 mcg. Whereas when epinephrine (200mcg) was compared with phenylephrine (2-5mg) as adjutants to lidocaine and tetracaine, it was found that both prolongs the effect of spinal anesthesia to a similar extent.[24] As a result, we used epinephrine at the dose of 100mcg in this study.

In this study, the BDA group showed an early onset of sensory and motor blocks with an increased duration of the blocks as compared to the BDN group. Halder S et al,[21] compared 5µg and 10µg dexmedetomidine with bupivacaine and concluded that intrathecal dexmedetomidine increases the sensory and motor block duration in a dose-dependent manner. In humans, even little doses of intrathecal dexmedetomidine (3mcg) combined with bupivacaine have been demonstrated to reduce the onset of motor block and extend the duration of motor and sensory block while maintaining hemodynamic stability and avoiding sedation.[20] Al-Ghanem et al,[18] also found a similar result with 5mcg dexmedetomidine for sensory and motor block when they compared it with 25 µg fentanyl intrathecal in vaginal hysterectomy. The study, conducted by Gupta R et al,[13] and Saadalla AET et al,[15] showed that dexmedetomidine prolongs both the duration of sensory and motor blockade with good hemodynamic stability and patient satisfaction. In the present study, good quality intraoperative and postoperative analgesia and hemodynamic stability

ISSN (O): 2687-5365; ISSN (P): 2753-6556

were observed in the BDA group at all-time points when drugs were used in combination at an optimal dosage intrathecally. When dexmedetomidine was used alone with bupivacaine in the BDN group, heart rate was initially increased to compensate for hypotension caused by bupivacaine, and then they both settled near the baseline [Figure 5]. Postsynaptic activation of central α2-Adrenergic receptors results in a sympatholytic effect leading to hypotension and bradycardia, an effect judiciously used to attenuate the stress response of surgery.[25,26] Halder S et al,[21] compared two doses of dexmedetomidine and observed that patients who received 10 mcg suffered more from bradycardia than those who received 5 mcg, which was statistically significant. According to Esmaoglu et al,[27] the side effects were similar without significant differences between the two groups. However, in the present study, there were no episodes of bradycardia in either of the groups, whereas hypotension was observed in a few patients in the BDN group, but the difference was statistically insignificant. Incidences of complications in the current trial, like shivering, respiratory depression, and sedation, were not observed in either of the groups. In contrast, a study done by Safari F et al,[28] showed significant sedative effects of dexmedetomidine when used in intrathecal injections. Talke et al,[29] discovered that dexmedetomidine, as an α2-adrenergic agent, has anti-shivering properties.

De Oliveira et al,[30] found that doses of 100 µg or less were associated with a greater incidence of hypotension or postoperative nausea and vomiting (PONV) than doses greater than 100 µg with similar prolongation of sensory and motor block duration. However, in our study, we found that at doses of 100 mcg epinephrine, there was a lower frequency of nausea and vomiting in the BDA group in comparison to the BDN group, but the difference was not statistically significant. The antiemetic effect of dexmedetomidine may be induced by the direct antiemetic properties of α2 agonists through inhibition of catecholamine by parasympathetic tone.[31]

There are very few studies that have used a triple combination of drugs as described above for intrathecal administration for better efficacy and safety of anesthesia. Therefore, further research is needed to investigate this. In addition, the exact mechanism of the analgesic action of adjuvants in combination should be explored with larger randomized controlled studies to achieve increased analgesic efficacy with minimal adverse effects

CONCLUSION

In conclusion, the current trial demonstrated that the addition of epinephrine, at optimal dosage, to dexmedetomidine and bupivacaine increases the duration of sensory and motor block and analgesic rescue time. In addition, it provides stable hemodynamics with minimal side effects, so we do recommend a combination of dexmedetomidine and epinephrine to bupivacaine for intrathecal anesthesia to increase the duration of analgesia.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556