Comparison of Epidural Clonidine and Dexmedetomidine for Perioperative Analgesia in Combined Spinal Epidural Anesthesia with Intrathecal Levobupivacaine: A Randomized Controlled Double-blind Study

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Abstract

**Background:** Epidural administrations of α2 agonists are being used as adjuvants as they lead to anxiolysis, sedation, analgesia, and hypnosis. **Aim:** This study aims to evaluate the analgesic effects of epidural α2 agonists-dexmedetomidine and clonidine in conjunction with intrathecal levobupivacaine in combined spinal epidural anesthesia (CSEA). **Methods:** A prospective, randomized controlled study was done to assess and compare the efficacy and clinical profile of two α2 adrenergic agonists, clonidine, and dexmedetomidine administered epidurally in combination with intrathecal levobupivacaine in CSEA. The study was conducted for 1 year. Sixty adult patients physical status Class I and II undergoing below umbilical surgeries under CSEA were included in the study after a valid consent. Patients were randomly assigned into two groups, to receive either epidural dexmedetomidine (1.5 μg/kg) or clonidine (2 μg/kg) in 10 ml normal saline along with 0.5% isobaric levobupivacaine 15 mg (3 ml). Block characteristics, ability to provide sedation, duration, and quality of analgesia and side effects were studied and compared between the groups. **Results:** The characteristics of intraoperative block were comparable among two groups. As compared to clonidine, dexmedetomidine provided a better sedation and prolonged analgesia, evidenced by the distribution of visual analog scale scores and requirement rescue analgesic among two groups. The side effect profile of the two drugs was comparable. **Conclusion:** Dexmedetomidine at 1.5 μg/kg epidurally with intrathecal levobupivacaine is a better adjuvant compared to clonidine at 2 μg/kg epidurally in CSEA because of better sedation, prolonged analgesia, and safe side-effect profile.

Keywords: Analgesia, clonidine, combined spinal epidural anesthesia, dexmedetomidine, levobupivacaine

**INTRODUCTION**

Neuraxial blockade can be achieved through many techniques. Among them, combined spinal epidural anesthesia (CSEA) commands a unique place. The singularity lies in its ability to combine the density, rapidity, and reliability of the subarachnoid block with the added advantage of flexibility of continuous epidural block which help to titrate a desired sensory level, vary the intensity of the block, control the duration of anesthesia, and deliver postoperative analgesia. [1] This procedure has come back in a big way off late, with its use extended to pediatric and even infant laparotomies, apart from its use in orthopedic surgery, obstetrics, and geriatric patients and in other high-risk patients. Combined spinal epidural (CSE) technique appears to be more complicated at first sight than either epidural or spinal block, intrathecal drug administration and placement of the epidural catheter are both facilitated by the various modifications of the combined spinal epidural technique. [2-4] Although at first sight, the CSE technique appears to be more complicated than either epidural or spinal block, intrathecal drug administration, and placement of the epidural catheter

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are both facilitated by the various modifications of the combined spinal-epidural technique.\textsuperscript{[4]}

**Methods**

A prospective randomized double-blind controlled study was conducted on sixty patients physical status Class I and II in our hospital, who were aged between 18 and 60 years and scheduled to undergo elective surgery after hospital ethical committee approval.

Patients satisfying all the inclusion criteria (American Society of Anesthesiologists [ASA] Grade I and II status, 18–60 years of age and patients giving informed written consent) were enrolled in the study. The exclusion criteria were ASA III and above, age more than 60 years and <18 years, pregnant and lactating women, uncooperative patients, hypotension, previous spinal surgeries, spine abnormalities, local site infection and coagulation abnormalities, poorly controlled hypertension, angina, and cardiopulmonary disease, hematological disease, neurologic, psychiatric disease, severe renal or hepatic derangement, patients taking tricyclic antidepressants, any antipsychotic drugs, \(\alpha_2\) adrenergic agonists, opioids, antiarrhythmic agents, beta-blockers, and anticoagulants.

Patients were randomly allocated into two groups of thirty each.

- **Group A** \((n = 30)\) = Patients receiving 0.5% isobaric levobupivacaine 15 mg (3 ml) intrathecally and clonidine 2 \(\mu\)g/kg in 10 ml 0.9% normal saline epidurally
- **Group B** \((n = 30)\) = Patients receiving 0.5% isobaric levobupivacaine 15 mg (3 ml) intrathecally and dexmedetomidine 1.5 \(\mu\)g/kg in 10 ml 0.9% normal saline epidurally.

Identical syringes containing each drug were prepared by one of the anesthesiologists who did not participate in the study. Patient and anesthesiologist who would deliver the combined spinal-epidural anesthesia were blinded by the study solutions. All preanesthetic evaluation of all patients was performed by an anesthesiologist a day before the surgery. In operation theater, a peripheral intravenous access was secured using 18G cannula and ASA standard monitors were attached-non-invasive blood pressure (BP), electrocardiograph, pulse rate, and SPO\(_2\), were recorded. As a standard premedication, injection Metoclopramide 10 mg intravenous was given. All patients were preloaded with Ringer lactate solution 20 ml/kg before the block. Intravenous fluids were given as per body weight intraoperatively and operative loss requirement.

The patient was put in sitting position under aseptic precautions, epidural space of L2–L3 interspaces was located, and with the 18-gauge Tuohy needle, using midline approach and loss of resistance technique, an epidural catheter of 18-gauge was placed in epidural space. A test dose of 3 ml of lignocaine with adrenaline 1:200,000 was administered to exclude intrathecal or intravascular placement of the needle.

Using 24–26-gauge Quincke spinal needle, subarachnoid block was performed at L3 L4 interspace and 3 ml of 0.5% isobaric levobupivacaine was administered to both groups. Intraoperative block characteristics such as time taken for motor block, time taken to reach T 10 dermatome, and maximum level of block were recorded.

After 20 min of administering intrathecal levobupivacaine, patients in Group A received clonidine 2 \(\mu\)g/kg body weight in 10 ml 0.9% normal saline and Group B received dexmedetomidine 1.5 \(\mu\)g/kg body weight in 10 ml 0.9% normal saline epidurally.

Cardiorespiratory parameters were monitored continuously, and recordings made every 5 min until 30 min and every 10 min until 60 min and then every 15 min for the next hour and finally at 30 min till the end of surgery.

Intra- and post-operatively, the incidence of bradycardia (heart rate <50 beats/min) will be treated with 0.6 mg of injection atropine, and hypotension (systolic BP falling more than 20% mm of Hg) will be treated with injection mephetnermine 6 mg in bolus.

Sedation scores were recorded just before the initiation of surgery and every 30 min.

Ramsay sedation scale was used to assess the level of sedation.\textsuperscript{[5]}

- 1 - Anxious and agitated
- 2 - Alert and wide awake
- 3 - Arousable to verbal commands
- 4 - Arousable to gentle tactile stimulation
- 5 - Arousable to vigorous shaking
- 6 - Unarousable.

During surgical procedure, adverse effects such as anxiety, nausea, vomiting, dry mouth, dizziness, headache, respiratory depression, pruritus, and shivering will be recorded.

Duration of analgesia will be recorded as time interval from the completion of anesthesia to the time when the patient complains of pain. Postoperatively, patients will be assessed at 30 min, 2 h, 6 h, and 24 h for postoperative analgesia. The intensity of postoperative pain will be assessed using visual analog scale (VAS), 0 is no pain and 10 is maximum pain. Rescue analgesia will be provided by intramuscular injection of tramadol 75 mg, when patient complains of pain or VAS of >4.\textsuperscript{[6]}

**Statistical analysis**

Sample size was based on the previous studies, with 21 minimum in each group and with \(\alpha\) error of 1%, beta error of 10%, confidence interval of 99%, and power of the study was 90%.

A commercial software package - SPSS version 19, was used for statistical analysis. Perioperative data on various parameters
in Group A and Group B were expressed in the tables as mean ± standard deviation.

The parametric data were statistically analyzed using the paired t-test for comparison of within-group data, and the unpaired t-test for comparison of between-group data.

Mann–Whitney U-test was used to analyze nonparametric data.

*P* value was considered statistically significant if <0.05.

**RESULTS**

The patients in the two groups were comparable with regard to age, sex, weight, height, ASA grading, and duration of surgery [Table 1].

As shown in Table 2, there was no statistical difference between two groups with respect to mean time taken for loss of pinprick sensation at T10 and mean time taken to achieve modified Bromage grading of motor block 3 as both groups received intrathecal levobupivacaine.

As shown in Graphs 1 and 2, a statistically significant fall in the pulse rate and mean arterial pressure (MAP) was noticed 20 ± 5 min following epidural clonidine and dexmedetomidine injection in both groups and persisted for all time intervals thereafter, until the end of the study period. However, the pulse rate and MAP remained in the normal physiological range throughout the study period.

Patients in both groups were sedated after 20 ± 5 min following epidural drug administration. Sedation scores were higher following the administration of dexmedetomidine in the epidural space compared to epidural clonidine and sedation lasted for 45 ± 5 min [Graph 3].

As shown in Table 3, there was a significant prolongation of the mean time taken for sensory regression to S1 in Group A, 350.87 min and Group B, 367.37 min, with *P* value of 0.0001. There was a significant prolongation of the mean time taken to regression to Bromage 0 in Group A 306.17 min and Group B 325 min with *P* = 0.00001.

In our results, we found that during initial 270 min, i.e., from baseline to 270 min, *P* value being >0.05, it was statistically insignificant. The difference in VAS scores of two Groups A and B becomes statistically significant at 300–450 min time intervals with *P* < 0.05.

VAS score was higher in clonidine group requiring rescue analgesia at 300 min and maximum VAS scores at 360–390 min, whereas in dexmedetomidine group VAS score started to increase only after 390 min and maximum

### Table 1: Demographic profile of Group A and B

| Variables                        | Group A | Group B | *P*  |
|----------------------------------|---------|---------|------|
| Age (years)                      | 35.17   | 33.18   | 0.34 |
| Sex (male + female)              | 15 + 15 | 15 + 15 | 1    |
| Weight (kg)                      | 65.76   | 67.77   | 0.29 |
| Height (cm)                      | 161.4   | 159.9   | 0.36 |
| American Society of Anesthesiologist (I and II) | 22 + 8  | 25 + 5  | 0.34 |
| Duration of surgery (min)        | 113.37  | 108.83  | 0.30 |

*P* < 0.05 is statistically significant

### Table 2: Intraoperative characters in Group A and B

| Variables                                              | Group A | Group B | *P*  |
|--------------------------------------------------------|---------|---------|------|
| Time taken for loss of pinprick sensation at T10 in min| 5.90    | 5.70    | 0.26 |
| Time taken to achieve modified Bromage grading of motor block | 9.83    | 9.93    | 0.78 |

*P* < 0.05 is statistically significant
scores of VAS was seen at 450–480 min. Dexmedetomidine group had lower scores of VAS even at 360, 390, and 420 min.

Mean time taken for rescue analgesia in Group A was 363.73 min and that of Group B was 456.87 min with statistically significant \( P < 0.001 \) [Graph 4].

**DISCUSSION**

The CSE technique has gained increasing importance for patients undergoing below the umbilical level surgery who require effective and prolonged postoperative analgesia. CSE anesthesia combines the density, rapidity, and reliability of a subarachnoid anesthetic with added advantage of the flexibility of continuous epidural anesthesia to extend the duration of analgesia.\(^{[1]}\)

Levobupivacaine, the \( S \)-enantiomer of bupivacaine has significantly less cardiac and neural toxic effects than bupivacaine, while still possessing a similar duration of sensory blockade. Levobupivacaine has been shown to be safe and effective for epidural and spinal anesthesia.\(^{[7-9]}\)

Epidural administrations of \( \alpha \)2 agonists are being used as adjuvants as they lead to anxiolysis, sedation, analgesia, and hypnosis. The pharmacological actions are extensively studied as these agents can be used instead of opioids which are known to cause many side effects such as nausea, vomiting, pruritus, and urinary retention.\(^{[10]}\)

The analgesic and the analgesic requirement get reduced to a large extent by the use of \( \alpha \)2 agonists because of their analgesic properties and augmentation of local anesthetic effects as they cause hyperpolarization of nerve tissues by altering transmembrane potential and ion conductance at locus coeruleus in the brainstem.\(^{[11]}\)

Sedation is due to action on locus coeruleus, which inhibit the release of norepinephrine.\(^{[12,13]}\) Sedation after epidural \( \alpha \)2 agonists is due to its systemic absorption and vascular redistribution to higher centers.\(^{[14-16]}\) Sedation is an add-on advantage for regional anesthesia to bring down the stress associated with the surgery.

Dexmedetomidine is a highly selective \( \alpha \)2 adrenergic agonist with an affinity of 8 times greater than clonidine and hence allows the use of higher doses with less \( \alpha \)1 effect. There is no such study which has compared the dose equivalence of these drugs, but the observations of various studies have stated that the dose of clonidine is 1.5–2 times higher than dexmedetomidine when used in epidural route.\(^{[11]}\)

Neuraxial clonidine enhances the action of local anesthetics, increases the intensity and duration of analgesia. It is known to have sedative properties, and the side effects are hypotension and bradycardia.\(^{[17]}\)

A study conducted by Jain et al.\(^{[18]}\) showed similar results to our study with fall in pulse rate and BP 5–10 min following administration of epidural dexmedetomidine. There was statistically significant fall in pulse rate in dexmedetomidine group compared to saline group, at all time intervals. They also had higher sedation scores in dexmedetomidine group and also prolonged sensory and motor blockade with a reduced dose of rescue analgesia.

Fukushima et al. were the first to report the use of epidural dexmedetomidine in patients undergoing surgery under general anesthesia. They found that after 10 min of epidural injection of 2 \( \mu \)g/kg dexmedetomidine resulted in decreased heart rate and BP, which was correlating with our study.\(^{[19]}\)

Salgado et al. studied the synergistic effect of dexmedetomidine with 0.75% ropivacaine and observed that epidural dexmedetomidine 1 \( \mu \)g/kg enhances motor and sensory blockade, and prolongs analgesia duration.\(^{[20]}\)

The analgesic effect of dexmedetomidine is produced by the stimulation of the \( \alpha \)2 receptors at spinal cord level. At the dorsal root neuron, \( \alpha \)2 agonists inhibit the nociceptive pathway by releasing substance \( P \) and by inhibiting the release of norepinephrine, which may have a possible role in analgesia. Even with the evidence of both the supraspinal and peripheral sites of action of dexmedetomidine, the spinal mechanism may be mainly responsible for the analgesic effects.\(^{[21,22]}\)

In a study done by Bajwa et al., time for rescue analgesia was comparatively lesser (310.76 ± 23.75 min) in the patients who were administered clonidine \( (P < 0.05) \) when compared to dexmedetomidine (342.88 ± 21.86 min) which was similar to our study.\(^{[11]}\)

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**Graph 4:** Visual analog scale scores of two Group A and B at different time intervals. \( P < 0.05 \) is statistically significant

**Table 3: Perioperative block characteristics Group A and B**

| Variables                        | Group A | Group B | \( P \)  |
|----------------------------------|---------|---------|---------|
| Time taken for sensory regression to S1 | 350.87  | 367.37  | 0.0001  |
| Time taken to regression to Bromage 0 | 306.17  | 325.00  | 0.00001 |
| Time taken for rescue analgesia  | 363.73  | 456.87  | 0.00001 |

\( P < 0.05 \) is statistically significant.
Summary of our study is that dexmedetomidine administered epidurally had superior and prolonged analgesia with superior anesthetic effects with respect to the duration of sensory blockade, and motor blockade compared to epidural clonidine. Epidural dexmedetomidine also had higher sedation scores compared to clonidine.

Limitation of our study is that we had no placebo group and further scope will be to design the study with different doses of α2 agonists.

**CONCLUSION**

Epidural dexmedetomidine in a dose of 1.5 μg/kg with intrathecal levobupivacaine causes significant prolongation in the duration of analgesia and thus decreasing the need for additional analgesic agents.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Rawal N, Schollin J, Wesström G. Epidural versus combined spinal epidural block for cesarean section. Acta Anaesthesiol Scand 1988;32:61-6.
2. Yousef AA, Atef AM, Awais WM. Comparison of fentanyl versus meperidine as supplements to epidural clonidine-bupivacaine in patients with lower limb orthopedic surgery under combined spinal epidural anesthesia. BMC Anesthesiol 2015;15:146.
3. Tummala V, Rao LN, Vallury MK, Sanapala A. A comparative study-efficacy and safety of combined spinal epidural anesthesia versus spinal anesthesia in high-risk geriatric patients for surgeries around the hip joint. Anesth Essays Res 2015;9:185-8.
4. Xiao F, Xu WP, Zhang YF, Liu L, Liu X, Wang LZ. The dose-response of intrathecal ropivacaine co-administered with sufentanil for cesarean delivery under combined spinal-epidural anesthesia in patients with scarred uterus. Chin Med J (Engl) 2015;128:2577-82.
5. Sessler CN, Grap MJ, Ramsay MA. Evaluating and monitoring analgesia and sedation in the Intensive Care Unit. Crit Care 2008;12 Suppl 3:S2.
6. Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH, et al. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: A systematic literature review. J Pain Symptom Manage 2011;41:1073-93.
7. Bajwa SJ, Kaur J. Clinical profile of levobupivacaine in regional anesthesia: A systematic review. J Anaesthesiol Clin Pharmacol 2013;29:530-9.
8. Leone S, Di Cianni S, Casati A, Fanelli G. Pharmacology, toxicology, and clinical use of new long acting local anesthetics, ropivacaine and levobupivacaine. Acta Biomed 2008;79:92-105.
9. Burlacu CL, Buggy DJ. Update on local anesthetics: Focus on levobupivacaine. Ther Clin Risk Manag 2008;4:381-92.
10. Afonso J, Reis F. Dexmedetomidine: Current role in anesthesia and intensive care. Rev Bras Anestesiol 2012;62:118-33.
11. Bajwa SJ, Bajwa SK, Kaur J, Singh G, Arora V, Gupta S, et al. Dexmedetomidine and clonidine in epidural anaesthesia: A comparative evaluation. Indian J Anaesth 2011;55:116-21.
12. Liu N, Bonnet F, Dелаunay L, Kermarec N, D’Honneur G. Partial reversal of the effects of extradural clonidine by oral yohimbine in postoperative patients. Br J Anaesth 1993;70:515-8.
13. MacDonald E, Kobilka BK, Scheinin M. Gene targeting – Homing in on alpha 2-adrenoceptor-subtype function. Trends Pharmacol Sci 1997;18:211-9.
14. Ruokonen E, Parviainen I, Jakob SM, Nunes S, Kaukonen M, Shepherd ST, et al. Dexmedetomidine versus propofol/midazolam for long-term sedation during mechanical ventilation. Intensive Care Med 2009;35:282-90.
15. Guinter JR, Kristeller JL. Prolonged infusions of dexmedetomidine in critically ill patients. Am J Health Syst Pharm 2010;67:1246-53.
16. Gerlach AT, Murphy CV, Dasta JF. An updated focused review of dexmedetomidine in adults. Ann Pharmacother 2009;43:2064-74.
17. Arunkumar S, Hemanth Kumar VR, Krishnaveni N, Ravishankar M, Jaya V, Aruloli M. Comparison of dexmedetomidine and clonidine as an adjuvant to ropivacaine for epidural anaesthesia in lower abdominal and lower limb surgeries. Saudi J Anaesth 2015;9:404-8.
18. Jain D, Khan RM, Kumar D, Kumar N. Perioperative effect of epidural dexametomidine with intrathecal bupivacaine on haemodynamic parameters and quality of analgesia. South Afr J Anaesth Analg 2012;18:105-9.
19. Fukushima K, Nishini Y, Mori K, Takeda J. Effect of epidurally administered dexametomidine on sympathetic activity and postoperative pain in man. Anesth Analg 1996;82:5121.
20. Salgado PF, Sabbag AT, Silva PC, Brientz SL, Dalto HP, Módolo NS, et al. Synergistic effect between dexametomidine and 0.75% ropivacaine in epidural anesthesia. Rev Assoc Med Bras 2008;54:110-5.
21. Ishii H, Kohno T, Yamakura T, Ikoma M, Baba H. Action of dexametomidine on the substantia gelatinosa neurons of the rat spinal cord. Eur J Neurosci 2008;27:3182-90.
22. Langer SZ, Duval N, Massingham R. Pharmacologic and therapeutic significance of alpha-adrenoceptor subtypes. J Cardiovasc Pharmacol 1985;7 Suppl 8:S1-8.