Section: Anaesthesiology

Original Research Article

EFFECT OF EPIDURAL DEXMEDITOMEDINE VERSUS CLONIDINE FOR POSTOPERATIVE ANALGESIA IN LOWER LIMB SURGERIES: A PROSPECTIVE STUDY

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ABSTRACT

Background: The lower limb long bone fractures contribute to severe pain in the postoperative period leading to morbid conditions in the patients. Epidural block, even though a widely used regional anesthetic technique in orthopedics, is limited by its short duration of action when local anesthetics alone injected via epidural route. Hence adjuvants are added along with local anesthetics to prolong the duration of analgesia. The objective is to evaluate and compare the analgesic effects of clonidine vs dexmedetomidine through epidural route in patients undergoing lower limb surgeries by prospective randomized double blinded study. **Materials and Methods:** 100 patients aged 21-60 years belonging to American society of anesthesiologists Physical status 1 and 2 undergoing surgeries for lower limb long bone fractures were randomly divided into two groups of 50 each. After the surgery, the group BD received bupivacaine and dexmedetomedine and group BC received bupivacaine and clonidine in the elastomeric pump through epidural route. VAS score was assessed at 0,12,24,36 and 48 hours and time to rescue analgesic was noted. Data was entered on Microsoft Excel and analysed using STATA version 14. A p value less than 0.05 was considered significant in all analytical tests. **Result:** The clonidine group showed a higher median VAS score than dexmedetomedine group after 12 hours. (p value<0.001)The time to rescue analgesic was higher in dexmedetomedine group (mean=37.2, SD=1.9) compared to those who received clonidine (mean=29.5, SD=1.7), and this difference was statistically significant. The occurrence of significant decrease in pulse rate was similar across both groups. Survival analysis demonstrated a hazard ratio of 0.60, and this was not found to be statistically significant (95% CI 0.14 – 2.51). The occurrence of significant increase in pulse rate was similar across both groups. Survival analysis demonstrated a hazard ratio of 1.1 and this was not found to be statistically significant (95% CI 0.45 – 2.73). **Conclusion:** Dexmedetomidine was found to provide better post-operative analgesia than clonidine as demonstrated by VAS scores and time taken to start rescue analgesia. Dexmedetomidine and clonidine provided similar levels of sedation and hemodynamic stability, and did not differ in terms of side effects like nausea and vomiting.

INTRODUCTION

Epidural anesthesia is the most commonly used technique for providing not only peri-operative surgical anesthesia but postoperative analgesia in lower abdominal and limb surgeries.[1] Many techniques and drug regimens, with partial or greater success, have been tried from time to time to calm the patients and to eliminate the anxiety component during regional anesthesia.[2] Many a time for achieving desired effect, invariably large volumes of local anesthetics are used with deleterious consequences or the impulsive use of large doses of sedation or even general anesthesia defeats the novel purpose of regional anesthesia.[3] To overcome these problems there is an ongoing effort to find a better adjuvant in regional anesthesia.

α 2-adrenergic receptor agonists have been the focus of interest for their sedative, analgesic, peri-operative sympatholytic, anesthetic-sparing, and hemodynamic

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-stabilizing properties.[4] α-2adrenoreceptor agonists produce analgesia by depressing release of C - Fiber transmitters and by hyperpolarization of postsynaptic dorsal horn neurons. The complementary action of local anesthetics and α-2 adrenoreceptor agonists accounts for their profound analgesic properties. Dexmedetomidine is a highly selective α-2 adrenergic agonist with an affinity eight times greater than that of clonidine.5 There is no such study which has compared the dose equivalence of these drugs, but the observations of various studies have stated that dose of clonidine is 1.5- 2 times higher than Dexmedetomidine when used in epidural route. The present double-blind prospective randomized study aims at comparing the hemodynamic, sedative, and analgesia potentiating effects of epidurally administered clonidine and dexmedetomidine when combined with bupivacaine.

MATERIALS AND METHODS

Study Design: Prospective randomised double blinded study

Sample Size

Sample size is done by the formula

$n=(Z\alpha^2 + Z\beta^2)SD^2 \times 2/d2$

where $Z\alpha=1.96, Z\beta=0.84$, SD=standard deviation, d=effect size

In a study conducted by Kaur S et al,[6] standard deviation was found to be 0.76. To detect a difference of 0.5 between groups, the sample size required, using the above formula was 50 in each group.

Study Setting: Govt. Medical College, Kozhikode

Inclusion Criteria

1. Age between 21-60 years.
2. ASA 1-2
3. Posted for lower limb long bone fractures.

Exclusion Criteria

1. Patient refusal
2. History of asthma, cardiac, renal and liver disease.
3. Coagulation disorder
4. Metabolic and endocrine disease
5. Obesity (BMI>30)
6. Infection at site of epidural puncture.

Materials And Methods

After ethical committee clearance and obtaining written informed consent, 100 subjects who satisfied the inclusion criteria were randomly divided into two groups either receiving bupivacaine and clonidine (BC group) or bupivacaine and dexmeditomedine (BD group). After preoperative assessment by detailed history, physical examination and laboratory evaluation, informed written consent were taken from legal guardian for participation to study.

On arrival to the operation theatre pre induction monitors – ECG, pulse oximeter and non invasive blood pressure was attached and base line values recorded. All the cases were given combined spinal epidural block and we compared the epidural component of the block for post op analgesia.

Lumbar epidural block was done using 18G Touhy needle with patients in lateral position in L1-L2 or L2-L3 interspace and location of epidural space confirmed by loss of resistance technique. A test dose of 3 ml 2% lignocaine with adrenaline was administered into the epidural space and thereafter the catheter was secured 3-5 cm into the epidural space. Next, under strict asepsis and local anesthesia a preferential subarachanoid block was performed with the operative limb in the dependent position at the level of either L3-L4 or L4-L5 intervertebral space using 25 G quince needle. Following the subarachnoid block the subject was put in supine position after 5 minutes. Both groups received hyperbaric 0.5% 2ml bupivacaine. All the partial action and failed epidural cases were neglected and were not taken up for study. Heartrate, blood pressure, SPO2 and respiratory rate were monitored throughout the surgery.

At the end of surgery, an elastomeric pump (125ml) was filled with 0.125% (60 ml 0.25% bupivacaine + 60 ml sterile water) bupivacaine to which either clonidine or dexmeditomedine was added.

Group BD received 0.125% bupivacaine + dexmeditomedine 1mics/kg through epidural catheter via elastomeric pump Group BC received 0.125% bupivacaine + clonidine 2 mics/kg through epidural catheter via elastomeric pump.

The outcome of study was measured by assessing postoperative analgesia in both groups. Postoperative analgesia was assessed by using visual analogue score (VAS score). The scoring was done by the same anesthesiologist who performed the block. The heart rate, postoperative nausea vomiting, sedation score was assessed at 0,12 hour,24 hour,36 hour and 48 hours. Sedation score was assessed by Ramsay Sedation scale. Any bradycardia occurring was treated using atropine 0.6 mg and any hypotension occurring in the perioperative period was treated using fluids and Inj.ephedrine 6mg.

Statistical Analysis: Data was entered on Microsoft Excel and analysed using STATA version 14. A p value less than 0.05 was considered significant in all analytical tests.

RESULTS

Demographic details such as age, gender, weight and ASA grading were comparable among participants of both the groups. There were no statistically significant difference.

There was no significant difference between the two groups in terms of duration of surgery.

Table 1: Comparison of hemodynamic parameters between the two groups (N=100)

Variable	Number of participants, n (%)		P-value
	Clonidine Group	Dexmedetomidine Group	
Baseline Heart Rate (bpm)			

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Range	56 – 90	67 - 92	
Mean (SD)	74.1 (9.0)	80.3 (6.7)	<0.001
Baseline mean arterial pressure (mmHg)			
Range	60 – 82	62 – 80	
Mean (SD)	70.5 (5.1)	69.3 (4.0)	0.191

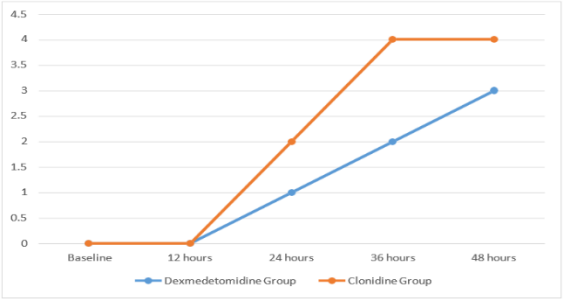

Figure 1: Comparison of Visual Analogue Scale across the two groups (N=100)

There was a significant difference in the mean baseline heart rate between the study groups. But the baseline arterial pressure was comparable across the groups.

The clonidine group showed a higher median VAS score than dexmedetomedine group after 12 hours.

There was a significant difference in VAS scores between the two groups at 24, 36 and 48 hours, with the score being higher in the clonidine group.

Table 2: Distribution of study participants by time to rescue analgesia (N=100)

Variable	Number of participants, n (%)		P-value
	Clonidine Group	Dexmedetomidine Group	
Time to rescue anaesthetic (in minutes)			
Range	26 – 33	32 – 40	
Mean	29.5	37.2	<0.001
Standard Deviation	1.7	1.9	

The time to rescue analgesic was higher in dexmedetomedine group compared to those who received clonidine, and this difference was statistically significant.

There was no significant difference in Ramsay Sedation Score scores between the two groups at any point of time.

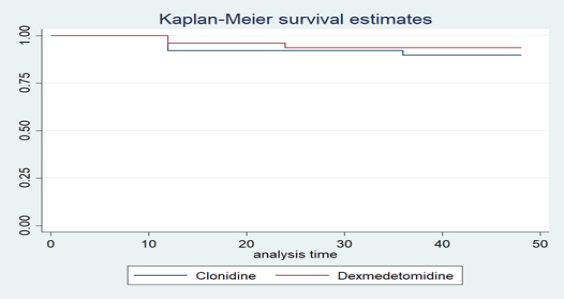

Figure 2: Kaplan Meier Curve for occurrence of any significant decrease in pulse rate (N=100)

The occurrence of significant decrease in pulse rate was similar across both groups. Survival analysis demonstrated a hazard ratio of 0.60, and this was not found to be statistically significant (95% CI 0.14 – 2.51).

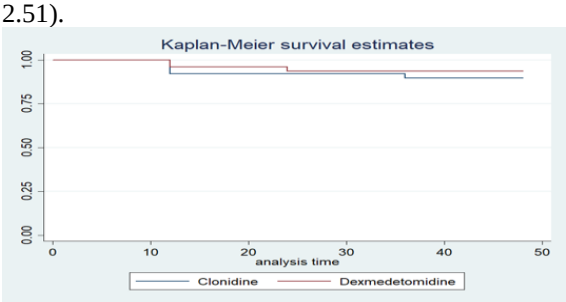

Figure 3: Kaplan Meier Curve for occurrence of any significant increase in pulse rate (N=100)

The occurrence of significant increase in pulse rate was similar across both groups. Survival analysis demonstrated a hazard ratio of 1.1 and this was not found to be statistically significant (95% CI 0.45 – 2.73).

Two participants in the clonidine group and one participant in the dexmedetomidine group had post-operative nausea and vomiting. The difference was not statistically significant.

DISCUSSION

Dexmedetomidine and clonidine are both alpha-agonists that have analgesic and anaesthetic properties and similar pharmacological properties. An early study by Takano et al. found that intra-thecal dexmedetomidine has a higher intrinsic efficacy than clonidine.[7] Many studies have since documented their use in comparison with placebo as well as with each other, in terms of hemodynamic stability, block characteristics, sedation and side effect profile. The various studies that have looked at epidural/ intra-thecal administration of clonidine and dexmedetomidine in adults is discussed here.

Patient Characteristics: The current study was done in a group of participants belonging to ASA grades 1 and 2, in which more than 50% were males and participants were aged around 40 years in both groups. The two groups were comparable with respect to all baseline characteristics. Almost all previous studies on the topic have been done in a similar demography, with samples with more male participants than female. The studies by Kanazi et al. only had male participants. The exceptions are studies based on gynaecological procedures done by Channabasappa et al., Bajwa et al., and Li et al. which

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all participants were female, and the study by Venkatraman et al. in which the sample had a higher proportion of females than males.[8-11] But gender-based differences in study sample is not expected to make a difference to objective measurements in sedation and hemodynamic characteristics. All studies recruited only patients with ASA grades 1 and 2 similar to the current study, except Kanazi et al, in which ASA grade 3 was also included. The baseline characteristics of age, gender, weight, proportion of ASA grade and duration of surgery were reported to be similar across study groups by all studies.

Procedures Done: The current study was done in patients undergoing lower limb orthopaedic procedures. The bulk of the previous studies were based on lower limb surgeries, like those of Arunkumar et al, Zeng et al and Kaur et al.[6,12,13]

Hemodynamic Stability: The current study found that significant fluctuation in heart rate was comparable for both groups. Almost all previous studies have found hemodynamic parameters to be comparable across groups. Even in the case of significant fluctuation, the values stayed within normal range in the study by Shaikh et al but comparable across both groups.[14] A significant difference in heart rate was reported by Sarma et al. at almost all time points with the rate being lower in dexmedetomidine.[15]

Pain Scores: Pain scores were assessed using Visual Analogue Scale and found to be significantly lower in dexmedetomidine at 24, 36 and 48 hours in the current study. This is consistent with the findings of Kaur et al and Li et al.[6,10] A few studies, like Kanazi et al. found the two groups to be comparable.[8]

Sedation: No significant difference was picked up in the Ramsay sedation score between the two groups in the current study. Similar comparable results were reported by Kanazi et al., Li et al,[8,11] Other studies have all reported sedation scores to be better for dexmedetomidine group at various time points. Maximum sedation was reported at 20 and 40 minutes by Channabasappa et al.[9] Some studies also report dexmedetomidine to reach maximum/peak effect faster than clonidine.

Rescue Analgesia: The current study did not look at block characteristics across the two groups, but the same has been reported by most of the studies. Overall, dexmedetomidine is reported to have earlier onset of sensory blockade, longer duration of blockade and a later regression of recovery. This is reported in the systematic review and meta-analysis published by Zhang et al.[16] This is also reflected by the duration before rescue analgesic is required. In the current study, the time to rescue was significantly higher for the dexmedetomidine group. All studies report the time to rescue analgesia in the clonidine group to be either lower or comparable to that of dexmedetomidine. The consumption of rescue dosage is also reported by Zeng et al., Mahendru et al., and Kaur et al. to be lesser for dexmedetomidine.[13,16] The current study did not look at block characteristics across the two groups, but the same has been reported by most of the studies. Overall, dexmedetomidine is reported to have earlier onset of sensory blockade, longer duration of blockade and a later regression of recovery. This is reported in the systematic review and meta-analysis published by Zhang et al.[16]

Complications/ Side Effects

Post-operative nausea and vomiting (PONV) was found to be present by comparable across both groups in the current study. Only 2 patients in the clonidine group and 1 patient in the dexmedetomidine group reported PONV. All studies have reported consistent results, with post-operative side effects being comparable for both groups, with low incidence of the same as well. Other side effects that are usually reported include shivering, dizziness, dry mouth and headache.[12,13,17]

CONCLUSION

To conclude, dexmedetomidine was found to provide better post-operative analgesia as demonstrated by VAS scores and time taken to start rescue analgesia. Dexmedetomidine and clonidine provided similar levels of sedation and hemodynamic stability, and did not differ in terms of side effects like nausea and vomiting. The findings of the current study are consistent with other studies done previously.

Strengths And Limitations

The strengths of the study are as follows:

1. Since all the measurements were done by a single researcher, there were no inter-observer error.
2. The required sample size was achieved.

The limitations of the study are as follows:

1. It is a single centre study.
2. It is not generalisable to patients of ASA grades more than 2.
3. Effect on block characteristics was not looked at in detail.

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