Clonidine versus Tramadol as Adjuvant to Epidural Anaesthesia With 0.5% Bupivacaine for Lower Limb Orthopaedic Procedures

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Abstract

Background: Epidural anesthesia is safe to provide surgical anesthesia and postoperative analgesia. Its efficacy can be improved with diversity of adjuvants. The aim of the study was to compare the clonidine versus tramadol as epidural adjuvant to 0.5% bupivacaine for lower limb orthopaedic procedures. Subjects and Methods: Sixty adult patients were enrolled and divided in two equal groups of 30 patients each to receive 14 mL of 0.5% bupivacaine with either 1ml (50µg) clonidine (Group I) or 1ml (50mg) tramadol (Group II), through lumbar epidural catheter at L3-L4 intervertebral space. The onset and duration of sensory and motor blockade with highest cephalic spread and duration of postoperative analgesia were assessed as primary objectives. Hemodynamic changes, respiration, sedation level or any adverse events were assessed as secondary end points. Results: Mean onset time and two dermatome sensory regression was comparable. The mean duration of sensory analgesia was 216.08±46.18min in patients of Group I and 251.33 ± 58.5 min in patients of Group II with statistically highly significant difference between the groups (P=0.000). Mean onset time and duration of motor blockade was comparable. The hemodynamic parameters remained stable, though 4 patients of Group I developed manageable hypotension. No episode of respiratory depression, shivering, pruritus, nausea and vomiting was observed. Conclusion: Tramadol (50mg) as epidural adjuvanento0.5%bupivacainewas better than clonidine for enhancing the duration of postoperative analgesia in patients undergoing lower limb orthopedic procedures.

Keywords: Bupivacaine, Clonidine, Epidural Anesthesia, Tramadol.

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Introduction

Epidural anaesthesia is widely used regional anaesthetic technique for lower limb orthopaedic procedures. It attenuates the stress response to surgery with enhanced duration of anaesthesia by means of an indwelling epidural catheter. Epidural anaesthesia is also useful when patient is suffering from comorbid conditions or anticipated difficult airway and adverse effects of general anaesthesia can be avoided to reduce the morbidity in high risk patients. Moreover, the consciousness can be preserved during surgery. Epidural blockade can be performed virtually at any level of spine but lumbar epidural blockade is simplest to perform by midline approach and its efficacy can be exalted with range of adjuvants, used either intravenously or by neuraxial route. Among adjuvants, opioids and alpha 2-adrenergic agonists could provide effective enhancement of postoperative analgesia. Opioid analgesics activate opioid receptors located on the primary afferent neurons, resulting in the activation of pain modulating systems and suppression of action potential transmission of ascending pain pathways. Tramadol is an opioid and lacks the respiratory depressant effects despite an analgesic potency. It causes inhibition of neuronal reuptake of norepinephrine and serotonin, resulting in anti-nociceptive effect. Clonidine is centrally acting α2-adrenergic agonist and decreases the sympathetic nervous system outflow of norepinephrine by inhibiting the voltage gated sodium channels and prevents action potential generation in dorsal horn cells, leading to analgesia, sedation and anxiolysis without respiratory depression. Considering the above facts, this study was designed to compare the clinical efficacy of clonidine versus tramadol as epidural adjuvant to 0.5% bupivacaine in patients undergoing lower limb orthopaedic procedures.
Subjects and Methods

After approval from the Institutional Ethical Committee and written informed consent, 60 patients of American Society of Anaesthesiologists (ASA) physical status I and II, aged between 28 to 58 years of either gender weighing less than 65 kg and scheduled for elective lower limb orthopaedic procedures under epidural anesthesia, were enrolled for this prospective randomized double blind study. All patients underwent pre anesthetic assessment and patients with history of severe cardiac or pulmonary disease, uncontrolled hypertension, morbid obesity, hepatic or renal dysfunction, endocrinial or metabolic disorders or any coagulation disorder, were excluded from the study. Patients with deformity of spinal column, known hypersensitivity to study drugs or using any drug that modifies pain perception, infection at site of lumbar puncture were also excluded from the study.

All patients were admitted prior to day of surgery and were given tab. alprazolam 0.5 mg and tab. ranitidine 150 mg, the night before surgery and their nil per oral status for 6 h was upheld on the day of surgery.

Randomization Schedule

All 60 patient were divided into two equal group of 30 patients each, according to computer generated random number table and allocation of concealment was ensured with sealed opaque envelop. Patients of Group I received 14 mL of 0.5% bupivacaine (70mg) with 1ml of clonidine (50µg) and patients of Group II received 14 mL of 0.5% bupivacaine (70mg) with 1ml of tramadol (50mg). The study drug solution was premixed with isotonic saline to a total volume of 15 mL for both groups, prepared by resident anaesthesiologist who was restricted to collect the intraoperative data. The study was conducted in double blind manner by using coded syringes.

Epidural blockade Technique

On arrival to operation theatre, standard monitoring for heart rate, systemic blood pressure and electro cardiogram (ECG) with peripheral oxygen saturation (SpO2) was commenced. Lactate Ringer solution was started after securing an intravenous line before initiation of the epidural blockade. Patients were explained about the procedure and instructed on the methods of sensory and motor blockade assessments along with VAS score agreement.

Under strict aseptic precaution, the epidural Tuohy needle was inserted between the L2-3or L3-4 intervertebral spaces along with VAS score agreement. All patients were explained about the procedure and instructed about the methods of sensory and motor blockade assessments along with VAS score agreement.

Under strict aseptic precaution, the epidural Tuohy needle was inserted between the L2-3or L3-4 intervertebral spaces along with VAS score agreement. All patients were explained about the procedure and instructed about the methods of sensory and motor blockade assessments along with VAS score agreement. The sensory blockade was assessed by pin prick method bilaterally along the mid clavicular line by using short bevelled hypodermic needle and the motor blockade of the lower extremities was evaluated bilaterally by using Modified Bromage Scale (0-3): 0=full movement and able to raise straight leg against resistance; 1=unable to raise extended leg at the hip but able to flex the knee; 2=unable to flex the knee but able to move the ankle joint; 3=unable to move hip, knee or ankle (no motor activity).

These blocks were assessed at every 2 minutes intervals till surgical anaesthesia was achieved. After achieving the highest dermatome level, the sensory blockade was assessed every 20 minutes.

Postoperative monitoring for pain was done using Visual analogue scale (VAS) Score, in which patient specified their level of pain by indicating a position along a continuous line between two end points of 0-10, where 0 means no pain and 10 means worst possible pain. Visual Analogue Scale (VAS) score was recorded at every 30 minutes for first hour, followed by at every15 min for next two hours. At VAS score of ≥4, epidural top up (8mL of 0.125% bupivacaine with 50µg fentanyl) was given for pain relief.

Hemodynamic parameters

Heart rate, systemic blood pressure, peripheral oxygen saturation (SpO2) were recorded at baseline, after epidural blockade and thereafter at every 5 min interval till 30 minutes, then at 15 min intervals up to the end of surgery and postoperatively, at every 30 minutes interval. Any increase or decrease of more than 20% from baseline in heart rate and blood pressure was considered significant. Respiratory depression was defined when respiratory rate was less than 10 breaths/min. Intra operative incidence of bradycardia (heart rate <60 b/m) was treated with 0.5 mg of atropine and hypotension (fall in SBP > 20% of baseline value or below 90 mm Hg) was treated by increasing the infusion rate of lactate Ringer solution and additionally with vasopressor, if required.

Sedation score

Intraoperative sedation was recorded just after giving the epidural medication and then at every 15 minutes intervals during the surgery. Level of sedation was assessed using a five point sedation scale: 1- Alert and wide awake; 2- Arousable to verbal commands; 3- Arousable to gentle tactile stimulation; 4- Arousable to vigorous shaking and 5- Unarousable even on vigorous shaking.

Adverse effects

Adverse effects of nausea, vomiting, dry mouth, dizziness, respiratory depression, pruritus and shivering were recorded and managed accordingly.

Study population size and statistical analysis

The sample size was calculated in consultation with statistician who computed that 25 to 27 patients should be
included in each group for detecting clinically meaningful difference in duration of postoperative analgesia of 30 minutes between groups for detecting type I error of 0.05 and power of 80% with confidence limit of 95%. Thus, finally 60 patients were incorporated in the study for equal distribution of patients in both groups.

The obtained data was expressed as Mean and Standard Deviation and analyzed using Stat Graphic Centurion, version 16 (Stat point technologies, IMC, Warrenton, Virginia). The demographic data for categorical variables were compared using chi-square test and statistical significance in mean difference between groups was done using student’s t test and one way analysis of variance (ANOVA). A ‘p’ value < 0.05 was considered statistically significant and ‘p’ value < 0.001 was considered statistically highly significant.

Results

Total 100 patients, aged between 28 to 58 years of either gender belonging to ASA physical status I and II, weighing less than 65 kg who scheduled for lower limb orthopaedic procedures under epidural anaesthesia, were enrolled. Out of which, 25 patients were excluded as they were not fulfilling the eligibility criteria, while 10 patients were not willing to participate and 5 patients were declined due to other reasons. Finally 60 patients were included in this study, who were randomized in two study groups by double blind manner.

Demographic Profile

The demographic data for age, weight, height, BMI, ASA physical status and duration of lower limb orthopaedic procedures were comparable between the groups. [Table 1]

Sensory and Motor Blockade Profile

The mean time required for onset of sensory blockade in patients of Group I was 10.06 ± 2.03 minute and in patients of Group II was 12.6 ± 2.01. The onset of sensory blockade and time to achieve T6 sensory block was faster in patients with epidural clonidine than patients of Group II, but with comparable difference (p=0.157). Time from epidural medication to two dermatome sensory regression was 141.83±11.02 minutes and 142.23 ± 17.1 minutes in patients of Group I and Group II respectively with comparable difference between the groups. The mean duration of sensory analgesia in patients of Group I, was 216.08 ± 46.18 minute and in patients of Group II, was 251.33 ± 58.5 minute with statistically highly significant difference between the groups (p<0.001).

The onset time of motor blockade was also comparable in patients of Group I (13.2±4.30 min) and patients of Group II (13.93±2.74 min). The total duration of motor block was 160.83 ± 38.26 minutes and 169.33±35.03 minutes in patients of Group I and Group II respectively with statistically insignificant difference. [Table 2]

Rescue analgesia was not required in any patient till 3 hours after giving epidural analgesia. The patients of Group I required first rescue analgesia after 216.08 ± 46.18 min, while in patients of Group II, analgesia lasted longer (251.33 ± 58.5 min) when they required first rescue analgesia. Duration of effective analgesia was maximum in patients of tramadol group.

Hemodynamic changes

The hemodynamic changes in patients of both groups were recorded just before commencement of epidural blockade and then at every 5 min interval still 30 minutes, then at 15 min intervals up to the end of surgery and postoperatively, at every 30 min interval.

Preoperative mean heart rate of patients of Group I and II was 91.13±14.44 beats/min and 86.06±14.22 beats/min, respectively. After 5 min of epidural blockade, the mean heart rate in patients of Group I was decreased to 79.26±10.36 beats/min where as it increased to 89.43±15.20 beats/min in patients of Group II. Thereafter, the heart rate showed gradual decline in patients of both groups. After 30 min of epidural anesthesia, the heart rate became stable in patients of both groups. The changes in the mean heart rate were statistically insignificant between the groups and there was no episode of tachycardia or bradycardia in any patient. [Table 3]

Preoperative mean systolic blood pressure was 127.57±10.73 mmHg in patients of Group I and 125.13±15.63 mmHg in patients of Group II. After 5 min of epidural blockade, the systolic blood pressure decreased to 123.50±9.93 mmHg in patients of Group I and 118.00±11.84 mm Hg in patients of Group II with statistically insignificant difference. Thereafter, it declined constantly in patients of both groups with comparable difference. After 90 min of epidural anesthesia, there appeared an upwards trend in patients of Group II whereas downward trend continued in patients of Group I. The difference in mean systolic blood pressure between the groups was statistically not significant (p > 0.05). [Table 4]

Sedation score

The mean sedations core in patients of Group I was 2.16±0.37 and 2.20±0.40 in patients of Group II, which remained constant till two hours after giving study drug in patients of both the groups. All patients were calm and sedated.

Side Effects

Hypotension was observed in 4 (13.33%) patients of clonidine group, which was treated by increasing the infusion rate of lactate Ringer solution only. No vasopressor medication was required. No patients suffered from bradycardia, shivering, respiratory depression, pruritus, dry mouth, nausea and vomiting.

Table 1: Demographic Profile

| Demographic data | Group I   | Group II  | Pravalue |
|------------------|-----------|-----------|----------|
| Age(year)        | 35.83±6.7 | 39.66±15.09 | 0.209    |
| Weight(kg)       | 55.23±10.65 | 54.06±9.4   | 0.655    |
| Height(cm)       | 164.6±5.37 | 162.2±6.58  | 0.128    |
| BMI(kg/m²)       | 20.35±3.5  | 20.47±2.88  | 0.894    |
| ASA(I/II)        | 28/2      | 27/3      | 0.640    |
| Duration of surgery (min) | 128.45±6.31 | 131.63±5.82 | 0.526    |

Data are expressed as Mean and Standard deviation (SD) or numbers; P value<0.05 is statistically in significant.
Epidural anesthetic techniques are preferred for lower limb orthopedic procedures as duration of surgical anesthesia and postoperative analgesia could be extended by indwelling epidural catheter. Different local anesthetic can be used, but 0.5% bupivacaine is preferred. In this study, 70 mg bupivacaine was used to establish the epidural blockade as it was more effective for prolonging the duration of sensory blockade without affecting the two segment regression time. Though sensory blockade profile was significantly better in patients of tramadol group, but mean on set of complete sensory blockade was faster in patients of clonidine group. Gupta S et al evaluated the analgesic effect of combination of epidural clonidine with bupivacaine and concluded that the mean onset time of sensory analgesia was significantly faster (493.8 ± 31.66 seconds) in patients of clonidine group as compared to patients of control group (686.4 ± 47.42 seconds). The results of their study was in agreement with present study.

In this study, addition of clonidine and tramadol to epidural bupivacaine produce rapid onset and prolong the duration of sensory blockade without affecting the two segment regression time. Though sensory blockade profile was significantly better in patients of tramadol group, but mean on set of complete sensory blockade was faster in patients of clonidine group. Gupta S et al evaluated the analgesic effect of combination of epidural clonidine with bupivacaine and concluded that the mean onset time of sensory analgesia was significantly faster (493.8 ± 31.66 seconds) in patients of clonidine group as compared to patients of control group (686.4 ± 47.42 seconds). The results of their study was in agreement with present study.

Data are expressed as Mean and Standard deviation (SD). E A: Epidural Anaesthesia P value<0.05 is statistically significant.

Discussion

Epidural anesthetic techniques are preferred for lower limb orthopedic procedures as duration of surgical anesthesia and postoperative analgesia could be extended by indwelling epidural catheter. Different local anesthetic can be used, but 0.5% bupivacaine is preferred. In this study, 70 mg bupivacaine was used to establish the epidural blockade as it was more effective for prolonging the duration of sensory analgesia. Therefore, clonidine and tramadol were used as epidural adjuvants 0.5% bupivacaine to enhance efficacy of epidural blockade and postoperative analgesia. Clonidine induced analgesia by activation of α2 adrenergic agonist on the dorsal horn of the spinal cord. It also rapidly absorbed into systemic circulation to reach its target sites to exert its antinoceptive action for both somatic and visceral pain. The prolongation of epidural anesthesia may result from synergism between bupivacaine and clonidine on dorsal horn neurons.

In this study, epidural clonidine in dose of 50μg was chosen to fasten the onset of sensory blockade, which was favored by the study of Prabha P et al, who concluded that this dose of clonidine has significantly increased the spread and duration of analgesia as compared to bupivacaine alone in their study. 

Tramadol is centrally acting, μ-receptor opioid agonist and exerts its effect by combining with opioid receptors in the dorsal horn of spinal cord. It enhances the function of the spinal descending pathways by inhibiting the neuronal reuptake of serotonin and norepinephrine along with presynaptic stimulation of 5-hydroxytryptamine release. In this study, tramadol in dose of 50 mg was used as epidural adjuvant to 0.5% bupivacaine to enhance the efficacy of epidural blockade. Ramchandra VS et al also used the same dose and concluded that addition of 50 mg tramadol to epidural bupivacaine provided good postoperative analgesia with less sedation.

In this study, addition of clonidine and tramadol to epidural bupivacaine produce rapid onset and prolong the duration of sensory blockade without affecting the two segment regression time. Though sensory blockade profile was significantly better in patients of tramadol group, but mean on set of complete sensory blockade was faster in patients of clonidine group. Gupta S et al evaluated the analgesic effect of combination of epidural clonidine with bupivacaine and concluded that the mean onset time of sensory analgesia was significantly faster (493.8 ± 31.66 seconds) in patients of clonidine group as compared to patients of control group (686.4 ± 47.42 seconds). The results of their study was in agreement with present study.

Yaun-Shiou Huang et al conducted a dose-response study of epidural clonidine for postoperative pain after total knee arthroplasty. They divided the patients in four groups of 20 patients each, to receive patient control epidural analgesia (PCEA) with clonidine 0, 1.0, 2.0, 4μg/ml respectively and morphine 0.1 mg/ml in 0.2% ropivacaine and concluded that the highest concentration of clonidine (4μg/mL) produced effective sensory and motor blockade and best analgesia, but with marked sedation, when compared to lower concentrations of clonidine. 

Agarwal S, Gupta K et al compared the clonidine with fentanyl as adjuvant to 0.75% ropivacaine for epidural anesthesia for lower limb surgeries. They observed that time to achieve highest sensory level and motor block was faster in patients of fentanyl group, but the duration of sensory analgesia was extended with epidural clonidine, thus delaying the need for rescue analgesia and concluded that clonidine was more effective for prolonging the duration of analgesia.

### Table 2: Sensory and Motor Blockade Profile

| Time Interval | Group I | Group II | P value |
|---------------|---------|----------|---------|
| Pre-op        | 127.57±10.73 | 125.13±15.63 | 0.485 |
| After EA      | 128.20±12.93 | 124.60±17.44 | 0.06 |
| 5 min         | 123.50±9.93  | 118.00±11.84 | 0.061 |
| 10 min        | 124.27±7.70  | 117.73±12.97 | 0.078 |
| 15 min        | 120.97±9.17  | 117.47±16.05 | 0.073 |
| 30 min        | 113.57±12.10 | 112.80±20.99 | 0.863 |
| 45 min        | 108.43±9.61  | 109.07±10.93 | 0.813 |
| 60 min        | 112.43±11.55 | 110.33±9.21  | 0.901 |
| 90 min        | 110.80±11.42 | 111.33±12.79 | 0.865 |
| Post-op       | 107.77±10.42 | 113.07±13.17 | 0.089 |

Data are presented as Mean and Standard deviation; E A: Epidural Anaesthesia; P value<0.05 is statistically significant.

### Table 3: Changes in Heart Rate (beats/min)

| Time Interval | Group I | Group II | P value |
|---------------|---------|----------|---------|
| Pre-op        | 91.13±14.44 | 86.06±14.22 | 0.176 |
| After EA      | 89.10±16.07 | 86.60±15.36 | 0.062 |
| 5 min         | 79.26±10.36 | 85.43±15.20 | 0.065 |
| 10 min        | 78.86±12.77 | 84.53±15.51 | 0.083 |
| 15 min        | 79.00±10.54 | 88.26±16.56 | 0.102 |
| 30 min        | 75.86±10.11 | 82.67±11.11 | 0.054 |
| 45 min        | 75.26±9.01  | 82.43±8.34  | 0.073 |
| 60 min        | 74.73±11.39 | 80.16±5.48  | 0.291 |
| 90 min        | 72.53±8.00  | 81.16±2.34  | 0.081 |
| Post-op       | 73.60±9.88  | 80.83±3.47  | 0.054 |

Data are expressed as Mean and Standard deviation (SD); E A: Epidural Anaesthesia P value<0.05 is statistically significant.
Sutariya M et al randomised 90 patients into three groups of 30 patients each, to receive either bupivacaine with saline, or bupivacaine with tramadol, or bupivacaine with clonidine. They concluded that onset of sensory blockade was fastest in patients of clonidine group but total duration of sensory blockade was longest in patients of tramadol group, therefore tramadol was superior.\(^{[12]}\) The results of their study was in agreement with present study.

In this study, significantly lower VAS scores were observed in patients receiving epidural tramadol, indicating good postoperative analgesic effect. The time required for first rescue analgesia was 251.33 ± 58.5 min with statistically highly significant difference between the groups (p < 0.001).

Demiraran Y et al. compared the postoperative analgesic efficacy of single dose epidural tramadol (2 mg/kg) versus morphine (0.1 mg/kg) in children undergoing urological surgery. They observed that supplementary analgesia was not needed for 16 hours in the tramadol group and for 18 hour in the morphine group. Thus concluded that pain score and average time for analgesia were comparable in children of both groups.\(^{[13]}\)

Prakash S et al. have also evaluated the analgesic efficacy of three different doses of tramadol, administered caudally with bupivacaine to provide postoperative pain relief in 80 children. They observed that duration of analgesia was longer (12±0.9 h) when 0.25% bupivacaine (0.75 ml/kg) with tramadol 2 mg/kg was given by caudal route with statistically significant difference among the groups.\(^{[14]}\)

In this study, the mean onset and total duration of motor block was neither affected by clonidine nor by tramadol, when used as epidural adjuvant to 0.5% bupivacaine. Noha Sayed Hassien \(^{[14]}\) and Tammoj Ghatak et al \(^{[15]}\) also observed no difference in the quality of motor blocks between the groups. The result of their study was consistent with the present study. In contrast to present study Yaun-Shiou Huang et al. observed that higher concentration of clonidine produced prolonged motor blockade.

During the present study, the sedation score remained constant till two hours after giving study drug in patients of both groups. All patients were calm and sedated during the lower limb orthopedic procedures. Grand he et al also used 75 µg clonidine with 0.5% hyperbaric bupivacaine and observed no significant sedation or respiratory depression in clonidine combination group.\(^{[16]}\)

Epidural clonidine has been reported to result in intra operative hypotension. In this study, hypotension was observe din 4 patients of clonidine group which was treated by increasing the rate of crystalloid solution infusion only. No vasopressor medication was required to manage the hypotension. No other patient showed fall in blood pressure. This could be explained by adequate pre loading which was done in all patients prior to establishment of epidural blockade. No incidence of respiratory depression or changes in the respiratory rate and peripheral oxygen saturation were observed in any patient. There was no episode of nausea, vomiting or pruritus in either group. Similarly bradycardia did not occur in either group reflecting the safety of lower doses of clonidine and tramadol as epidural adjuvants in the present study.

**Conclusion**

Both tramadol and clonidine as epidural adjuvant to 0.5% bupivacaine could prolonged the duration of analgesia after lower limb orthopedic procedures, but sensory blockade profile of tramadol was better when compared clonidine. Hence, this study validates the use of tramadol in doses of 50 mg as epidural adjuvant to 0.5% bupivacaine for enhancing the sensory and motor block along with post-operative analgesia. It could also provide are usable sedation without respiratory depression and maintained the intra operative hemodynamic stability.

**Limitation of study**

The sample size of this study was small and a larger sample size might have more impact. The end point of this study, was demand of first rescue analgesia. Requirement of total number of analgesic doses in 24 hours could have been evaluated.

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