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Research Article

Clonidine versus fentanyl as adjuvant to 0.75% ropivacaine for epidural anesthesia for lower limb surgeries: a comparative evaluation

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ABSTRACT

Background: Epidural adjuvants to local anaesthetic are used to enhance the quality and duration of surgical anaesthesia. The present study was aimed to compare the clinical efficacy of clonidine with fentanyl as adjuvant to epidural ropivacaine for block characteristics and hemodynamic changes during lower limb surgeries.
Methods: Sixty adult consenting patients of both gender of ASA physical status I and II scheduled for lower limb surgeries under epidural anaesthesia, were randomized into two groups of 30 patients each to receive either 15 ml of 0.75% ropivacaine with 1 ml of clonidine, 50 µg (Group RC) or with 1 ml of fentanyl 50 µg (Group RF). All patients were assessed for onset and duration of sensory and motor blockade and time to first rescue analgesia as primary end points. The hemodynamic variations, sedation, pruritus, respiratory depression or any other adverse events were recorded as secondary end points.
Results: Onset of sensory block to T10 was comparable between the groups. Time to achieve maximum sensory level at T6-7 and maximum motor block was faster when fentanyl was used as compared to clonidine with statistically significant difference between the group ($p<0.05$). Duration of sensory analgesia was enhanced with epidural clonidine, delaying the need for rescue analgesia. In clonidine group, side effects of sedation, bradycardia and hypotension were also observed. Only 5 patients of fentanyl group suffered from pruritus.
Conclusions: Clonidine was more effective than fentanyl as epidural adjuvant to 0.75% ropivacaine for prolonging the duration of analgesia with fewer manageable side effects.

Keywords: Clonidine, Epidural anesthesia, Fentanyl, Ropivacaine

INTRODUCTION

Epidural anesthesia is well established regional anesthetic technique and commonly used for all surgical procedures carried on lower abdomen, pelvis and lower limbs. It has the ability to maintain continuous anesthesia after placement of an epidural catheter, thus suitable for procedures of long duration. Epidural anesthesia has a definite advantage over general anesthesia by blocking nociceptive impulses from the operative site, reduced blood loss and decreased incidence of deep vein thrombosis but there is always a possibility of local anaesthetic toxicity due to use of large volumes of epidural local anaesthetic solution.[1]

Bupivacaine is commonly used local anesthetic but fear of inadvertent intravascular injection may result in systemic toxicity. Ropivacaine, a long acting amide, showed physiochemical profile close to bupivacaine in terms of onset, quality and duration of sensory block but

with lesser cardiovascular and central nervous system toxicity. The clinical data has shown its efficacy and safety for regional anaesthetic techniques with minimal hemodynamic changes and greater sensory- motor differentiation by blocking sensory nerve fibres more readily than motor fibre. Early recovery of motor function is associated with early postoperative mobilization.[2,3]

The addition of epidural adjuvants like opioids or α 2-adrenoreceptor agonist can further enhanced the effectiveness of local anaesthetics by intensifying the block and prolonging the duration of analgesia. They also decrease the dose requirement of local anesthetic thus prevents side effects associated with large doses. Fentanyl is μ-opioid receptor agonist and its main site of action is substantia gelatinosa in the dorsal horn of spinal cord. Though fentanyl enhances the neuraxial analgesia but is associated with increased incidences of pruritus, nausea, vomiting and respiratory depression.[4] Clonidine is α 2-adrenoreceptor agonist and it directly stimulates the pre and post synaptic sympathetic nerve terminal and central nervous system in the dorsal horn grey matter of the spinal cord, thereby inhibiting the release of nociceptive neurotransmitters. Clonidine is used as an adjuvant to epidural local anesthetic to improve the quality of analgesia after major abdominal surgeries and reduces the dose requirement of local anesthetics. It is associated with sedation, hypotension and bradycardia but no respiratory depression or other opioids related side effects.[5]

Considering the merits of ropivacaine and epidural adjuvants, the present study was undertaken to compare the clinical efficacy of clonidine with fentanyl as adjuvant to epidural ropivacaine 0.75% for block characteristics and duration of postoperative analgesia in patients scheduled for lower limb surgeries.

METHODS

After approval by the Institutional Ethical Committee and written informed consent, 60 patients of American Society of Anaesthesiologist (ASA) physical status I and II, aged 21 to 58 years of both genders, scheduled for lower limb surgeries under epidural anesthesia, were enrolled for this prospective double blind randomized study. All patients were subjected to pre-anaesthetic assessment prior to enrolment for the study and patients with history of diabetes mellitus, severe cardiac or pulmonary disease, uncontrolled hypertension, spinal deformity, skin infection at site of injection, coagulation disorders, allergy to local anaesthetic, history of opioid dependence or neurological disorders and patient's refusal to technique were excluded from the study. Before enrolment for the study, patients were properly explained about the epidural technique with catheter in situ, its advantages and disadvantages, along with method of sensory and motor assessments.

Patients were randomized according to computer generated random number table into two equal groups of 30 patients each. Patients of Group RC received epidural study solution of 15 ml of 0.75% ropivacaine with 1 ml of clonidine (50 μg) and patients of Group RF received epidural study solution of 15 ml of ropivacaine 0.75% with 1 ml of fentanyl (50 μg). The drug was prepared by an anaesthesiologist who was blinded to study protocol and was not involved for further assessment of patient.

All patients were admitted a day prior to surgery and were premedicated with tablet alprazolam 0.5 mg with tab ranitidine 150 mg orally. Their 6 hours fasting was ensured before surgery. After arrival of patient into operation theatre, routine monitoring of non- invasive blood pressure (NIBP), heart rate (HR), electrocardiogram (ECG) and pulse- oximetry (SpO2) was commenced. An intravenous line was secured and patients were preloaded with lactated Ringer solution at rate of 10 ml kg^{-1} 20 minutes prior to initiation of epidural blockade.

Under all aseptic condition, lumber epidural anesthesia was administered in the sitting position at L2-3 or L3-4 inter-vertebral disc space with an 18 G Touhy needle and location of epidural space was confirmed by loss of resistance technique. With the bevel of Touhy needle in cephalic direction, a test dose of 3 ml of 2% lidocaine with adrenaline 1: 2, 00,000 was administered to detect intrathecal or intravenous injection. Thereafter an epidural catheter was secured 3-5 cm into the epidural space. After confirming the correct placement of the catheter, the epidural anesthesia was activated with 15 mL of 0.75% ropivacaine either with 1 mL of clonidine (50 μg) or fentanyl (50 μg) according to the randomization schedule at rate of 3 ml /10 seconds by epidural catheter. Vital parameters of heart rate, blood pressure, ECG and pulse oximetry were continuously monitored.

The onset of sensory blockade with maximal cephalic spread was assessed by bilateral pin prick method along the mid-clavicular line using a short bevelled 26-G hypodermic needle. The onset of sensory block was defined as the time from epidural injection to the occurrence of loss of pinprick sensation at the site of surgical incision. The onset of motor blockade was assessed by observing toes movements and modified Bromage scale: 0- able to flex the whole lower limb at the hip (full motor activity), 1- able to flex the knee but unable to raise the leg at the hip, 2- able to planter flex the ankle but unable to flex the knee, 3- no movement of lower limb (no toes movements).[6] The onset of motor block was defined as the time from epidural injection to the absence of toes activity.

Surgical procedure was initiated after establishment of adequate surgical anesthetic effect at T10 dermatome. Duration of analgesia was taken from the time of epidural drug administration to the time of first supplementation

with rescue analgesic, assessed by VAS score. When VAS score was >3, rescue analgesia with 3ml of 0.75% ropivacaine with 50 mg tramadol, diluted to 10 ml with saline was given by epidural catheter along with intravenous ondansetron 4mg.

Intraoperative monitoring for pulse oximetry, ECG and arterial blood pressure were continuously observed and recorded at every 5 min in the first hour and thereafter at every 10 min until the patient transferred to the post anesthesia room. Supplemental oxygen at rate of 4 L/min was administered via venti mask throughout the surgery. For the present study, hypotension was defined as a fall in systolic blood pressure of more than 20% of base line or less than 100 mm Hg and was treated with additional lactated Ringer solution and if needed, incremental dosages of mephenteramine 3-6 mg in boluses. Bradycardia (heart rate < 55 beats/min) was treated with intravenous atropine sulphate 0.6 mg bolus doses.

Sedation was assessed using Ramsey sedation scale [7]: 1=awake, conscious, no sedation; 2= calm and compose; 3= awake on verbal command; 4= brisk response to gentle tactile stimulation; 5= awake on vigorous shaking; 6= unarousable or exhibits no response, initially at interval of 20 minutes during intraoperative period then at intervals of 1 hour during postoperative period. Side effects of pruritus, nausea, vomiting, respiratory depression, shivering and urinary retention were recorded during the study period and managed according to clinical protocol.

The sample size was calculated with standard programme which computed that approximately 23-25 patients should be included in each group to detect clinically significant difference of 30 min in mean duration of block and postoperative analgesia between the groups for type I error of 0.05 with power of 80% and 95% confidence limit. Assuming a 5% dropout rate, the total number of patients was set at 60 for better validation of result.

At the end of study, all recorded data were compiled systematically in tabulated manner. The results are expressed as mean ± SD considering later being best predictor and analyzed using Stat graphic centurion, version 16.2 (Stat point Technologies INC, Warrenton, Virginia). Parametric data were analyzed using Student's t-test and nonparametric data using chi-square test. Epidural block characteristics were compared using Mann Whitney U test. A p value of <0.05 was considered statistically significant.

RESULTS

The present study was successfully conducted on 60 adult patients with no protocol deviation. All patients were cooperative with their subsequent assessment. The demographic profile of the patients in term of their age, weight, height, ASA physical status and duration of surgery was comparable (Table 1).

Table 1: Demographic profile of patients.

Parameters	Group RC	Group RF
Age (years)	45.61±2.8	49.17±1.2
Weight (kg)	62.56±8.37	64.36±7.54
Height (cm)	156±4.5	159±3.5
Sex (M/F)	18:12	14:16
ASA Grade I/II	19/11	21/9
Duration of surgery (Min)	105. 97±17.34	108.78±16.25

Data are presented as mean ±SD or whole numbers. RC- Ropivacaine with Clonidine; RF- Ropivacaine with Fentanyl; ASA- American Society of Anaesthesiologist.

Onset time of sensory analgesia at T10 dermatome was 13.5±3.8 min in patients of group RF and 15.4±4.7 min in patients of group RC with no clinically or statistically significant difference between the groups. Time to attain maximum sensory level (T6-7) was faster in group RF when compared to group RC with statistically significant difference (p=0.047*). Onset of maximum motor block was also rapid in patients of group RF when compared to clonidine group with statistically significant difference (p=0.031*). However, once the sensory level to T6-7 was established, there was no noticeable difference in sensory anesthesia in both the groups throughout the surgical procedure.

Two segment regressions were prolonged in patients of group RC when compared to group RF with statistically highly significant difference (p<0.001**). Time to complete motor recovery was significantly longer in group RF when compared to group RC. Addition of fentanyl has intensified the motor block while clonidine showed no influence on duration of motor blockade. The duration of analgesia was prolonged in patients of group RC (372.07±7.13 min versus 357.23±9.36 min) when compared to group RF with statistically significant difference (p<0.001) (Table 2).

The baseline heart rate and systolic blood pressure were comparable between the groups. Intraoperative fall in heart rate was statistically significant in patients of group RC when compared to group RF at 15 min and 30 min. Bradycardia (<55beats/min) was observed in 6 patients of RC group which was treated by single dose of inj. atropine 0.6 mg intravenously.

The hypotension was observed in 12 patients of study group and was treated initially by increasing the rate of lactated Ringer solution. Only 7 patients needed incremental doses of mephenteramine in 3 mg boluses to manage the hypotension.

The incidence of sedation was more in patients of group RC as compared to group RF. Mild pruritus was observed in only five patients of group RF which required no

treatment. The ventilatory frequency and peripheral oxygen saturation were comparable between the groups. No patients suffered from shivering, nausea, vomiting, urinary retention or dry mouth.

Table 2: Sensory and Motor blockade profile.

Parameters	Group RC	Group RF	P value
Onset time of sensory block at T10 dermatome (min)	15.4±4.7	13.5±3.8	0.063
Median maximal sensory level	T6 (4-8)	T6 (4-7)	0.076
Time taken to achieve maximal sensory level (min)	27.3±1.6	24.3±1.9	0.047*
Time taken to achieve complete motor block (min)	29.2±3.2	25.6±4.7	0.031*
Two segment regression (min)	118.7±9.6	106.7±12.3	0.001**
Duration of motor block (min)	167.3±12.6	182.7±10.9	0.001**
Duration of Analgesia (min)	372.07±7.13	357.23±9.36	0.001**

Data are presented in mean±SD; *P value is statistically significant; ** P value is statistically highly significant.

DISCUSSION

Epidural blockade prior to surgical stimuli from lower limb reduces the stress response by preventing the central sensitization for pain and postoperative dynamic pain, when it is used as sole anesthetic technique for lower limb surgeries. Local anesthetics in the epidural space provide sufficient surgical anesthesia with muscular relaxation and minimum central nervous system or cardiovascular toxicities. Epidural anaesthesia has the added benefits of prolonged duration of surgical anesthesia and postoperative pain management.[1]

Bupivacaine is commonly used for epidural anesthesia but associated with few undesirable adverse effects. Ropivacaine shares many physiochemical properties with bupivacaine without its undesirable toxic effects. The onset of sensory anesthesia begins at 10-25 minutes after epidural administration of 2 to 4 hour duration.[8,9] Peduto et al reported that epidural injection of 15 ml of either 0.5% levobupivacaine or 0.75% ropivacaine produced similar epidural blockade in patients undergoing lower limb surgery.[10] In the present study, epidural anesthesia with 0.75% ropivacaine either with clonidine or fentanyl as adjuvant provided adequate surgical analgesia in patients of both the groups.

The potency of ropivacaine may be altered by adjuvants like opioids or α 2 adrenoreceptor agonist by accelerating the onset time and increasing the duration of epidural blockade. The combination of local anaesthetic and adjuvants effectively inhibit multiple areas of neuronal excitability to provide a dose sparing effects of local anaesthetics. The synergistic interaction between local anaesthetics and adjuvants during epidural administration is reported in many previous studies.

Fentanyl acts primarily as μ-opioid receptors agonist and enhances the analgesia. Fields *et al* showed that dorsal roots (primary afferent tissues) contain opioid binding sites and fentanyl may have either act directly on the spinal nerve or by penetrating the duramater to act at the spinal roots.[11]

Clonidine acts on pre and post synaptic sympathetic nerve terminal and central nervous system to decrease the sympathetic outflow and nor-epinephrine release to augment the effects of local anaesthetics in regional block. It produces analgesia through an opioid independent mechanism and may be an alternative to opioids. Clonidine also exerts vasoconstricting effect on smooth muscles, which results in a decreased absorption of the local anesthetic agent and eventually prolongs the duration of analgesia.[12]

In the present study, onset of sensory and motor blockade was accelerated with epidural fentanyl when compared to epidural clonidine. Time to attain maximum sensory level of T6-7 was also less in group RF when compared to group RC. Bajwa et al also studied the clonidine and fentanyl as adjuvant to epidural anesthesia and concluded that onset of sensory block was faster with epidural fentanyl as compared to clonidine.[13] Our results are in concurrence with their results. These studies showed that epidural adjuvants like clonidine or fentanyl to epidural ropivacaine fastens the onset of sensory and motor blockade.

In the present study, mean time to maximum motor block was faster with fentanyl when compared to clonidine. Mean time to complete motor recovery was significantly longer in patients of group RF than in patients of group RC. It is observed that addition of fentanyl has intensified the motor block but clonidine showed no much influence on duration of motor block. Same results were reported by Bajwa et al and Cherng et al.[4,13] In our study, the mean duration of analgesia was significantly extended in patients who were given clonidine as adjuvant to epidural ropivacaine when compared to fentanyl.

The episode of hypotension occurred in 12 patients of present study, which was effectively managed by rapid infusion of lactated Ringer and only 7 patients needed incremental doses of mephenteramine 3mg bolus doses, but the total dose of mephenteramine was not more than 15 mg in any patient. Hypotension was more common in the RC group, may be due to hypotensive action of

clonidine. In the present study, 6 patients of clonidine group also showed fall in heart rate which was managed by bolus dose of atropine 0.6 mg. No patient of fentanyl group showed incidence of bradycardia.

Bajwa et al conducted a study with epidural ropivacaine and clonidine in caesarean delivery and observed manageable bradycardia and hypotension with statistically significant difference between both the groups.[14] Topcu et al also compared the efficiency of ropivacaine with addition of fentanyl or clonidine in patient control epidural analgesia in labour where mean arterial pressure was monitored which was significantly lower in patients of clonidine group.[15]

No incidences of nausea, vomiting, headache, shivering, dry mouth or urinary retention occurred in any patients during the study period. Pulse oximetry trends did not show any significant variation in peripheral oxygen saturation. None of the patient in any group suffered from respiratory depression. Five patients of ropivacaine with fentanyl suffered with mild pruritus which required no treatment except assurance. All patients were calm and comfortable during surgical procedures. The sedative-hypnotic effect of α 2 adrenergic agonist is caused by action on locus coeruleus. Our results are in agreement with study done by Filos et al.[12]

Fentanyl is replacing the traditional opioid morphine as an adjuvant in regional anesthesia, but side effects like nausea and vomiting still persist even used in optimal dose, which is quite discomforting for the patients and defeats the purpose of providing a smooth uneventful recovery.

CONCLUSION

Onset of anesthesia was hastened when epidural adjuvants like clonidine or fentanyl was used with 0.75% ropivacaine with dose sparing action on local anaesthetics. Duration of motor blockade was prolonged with fentanyl while duration of analgesia was extended with clonidine delaying the need for rescue analgesia during lower limb surgery. Clonidine as adjuvant to epidural ropivacaine was more effective than fentanyl with manageable bradycardia and hypotension.

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