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Original Article

Anaesthesia Section

Comparative Evaluation of Ropivacaine and Fentanyl Versus Ropivacaine and Fentanyl with Clonidine for Postoperative Epidural Analgesia in Total Knee Replacement Surgery

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ABSTRACT

Introduction: Clonidine an alpha 2 adrenoceptor agonist possesses analgesic properties and has been used as an adjuvant in epidural analgesia. The addition of clonidine to other analgesics may result in enhanced analgesia through additive mechanisms or synergistic mechanisms. The enhanced analgesia may lead to a decrease in the dosage of analgesic drugs along with reduction of side effects.

Aim: The purpose of this study was to evaluate the effect of adding clonidine to epidural ropivacaine and fentanyl mixture in terms of quality of analgesia and side effects in patients of total knee replacement surgery.

Materials and Methods: A prospective randomised double blind study was conducted on 60 patients of ASA physical status I, II and III who underwent unilateral total knee replacement surgery under combined spinal epidural anaesthesia. Patients were divided into two Groups A and B randomly. Postoperatively Group A received continuous epidural infusion of ropivacaine 2 mg.ml $^{-1}$ and fentanyl 2 µg.ml $^{-1}$ along with clonidine 2 µg.ml^{-1} in the range of 3-7 ml.hr^{-1} while Group B received the ropivacaine and fentanyl epidural solution. The postoperative VAS scores, haemodynamic parameters, motor block, sedation, nausea, vomiting and any other significant side effects were noted. The two groups were compared with student's t-test, Pearson's Chi square test and t-test using SPSS statistical software.

Results: Visual analog scale scores were lower in Group A (3.38) than in Group B (3.72). The average infusion rate was lower in Group A (4.7 ± 0.7 ml.hr $^{-1}$) than in Group B (5.5 ± 0.7 ml.hr^{-1}). Patients in Group A required less dosage of rescue pain medication Paracetamol (1g i.v.), diastolic pressure and heart rate were lower in Group A. The groups were comparable in terms of sedation, motor block and nausea vomiting.

Conclusion: Clonidine added to a ropivacaine and fentanyl mixture augmented the postoperative epidural analgesia without significant side effects.

Keywords: Haemodynamic parameters, Side effects, Visual analog scale

INTRODUCTION

With the advancement of medical science, total knee replacement is a common surgical procedure now a days and is associated with severe pain in the postoperative period. Pre-emptive analgesia, neuraxial anaesthesia, peripheral nerve blockade, periarticular analgesic injections and intravenous patient controlled analgesia have all been reported as modalities for postoperative analgesia in these patients [1]. A well conducted regional anaesthesia significantly improves the joint function and facilitates early rehabilitation [2,3]. Epidural analgesia provides excellent pain relief in these patients [4] and is associated with lower incidence of postoperative myocardial infarction [5] and improved local tissue perfusion [6].

Clonidine an alpha 2 adrenoceptor agonist was first reported to have analgesic properties when administered through the epidural or intrathecal route by Tamsen A and Gordh T in 1984 [7]. Since then numerous studies have used intrathecal or epidural clonidine for postoperative analgesia in various surgeries [8-16]. It acts by stimulation of alpha-2 adrenoceptors in the dorsal horn and mimics the activation of descending inhibitory pathways. It has been reported to interact with other analgesic drugs through serotonergic mechanisms, spinal muscarinic receptors, and local nitric oxide synthesis [17,18] and may result in enhancement of analgesia through additive or synergistic mechanisms. Clonidine has been reported to decrease the heart rate by a vagomimetic effect and also by presynaptic mediated inhibition of norepinephrine release at the neuroreceptor junction [19]. It has been reported to cause hypotension [20,21] and decreases the noradrenaline concentration in the locus coeruleus causing sedation and anxiolysis [22].

In the present study, we evaluated the efficacy of addition of clonidine to a mixture of epidural ropivacaine and fentanyl for postoperative analgesia in patients undergoing total knee replacement surgery, along with its side effects.

MATERIALS AND METHODS

After Institutional Ethics Committee approval and written informed consent from patients, this prospective randomised double blinded study was conducted on 60 American Society of Anaesthesiology physical status I-III patients during the period, June 2010 to December 2011. Patients of either sex, aged 20-65 years undergoing unilateral total knee replacement surgery were enrolled. Patients with history of allergy to any of the study drugs, contraindications to neuraxial anaesthesia, cardiovascular disease (NYHA Grade III and IV), psychiatric illness or mental retardation, renal or hepatic impairment were excluded.

Patients were randomly allocated to one of the two groups by computer generated random selection. Group A (n=30) patients received postoperative continuous epidural infusion of ropivacaine (2mg.ml^{-1}) plus fentanyl (2 µg.ml^{-1}) with clonidine (2 µg.ml^{-1}) whereas Group B (n=30) patients received epidural infusion of Ropivacaine (2mg.ml^{-1}) plus Fentanyl (2 µg.ml^{-1}) in the range of 3-7 ml.hr^{-1}. The patients along with the primary investigator and pain clinic nurse involved in the treatment of the patients were blinded regarding the study group allocation through out the study period.

Preanaesthetic evaluation was done and the entire procedure was explained to the patient one day prior to the surgery. Patient was taught about the Visual Analog Scale (VAS) and was taught how to express the degree of pain on the scale. Score 0 indicated no pain and a score of 10 indicated worst pain imaginable. Premedication consisted of oral alprazolam 0.25-0.5 mg night before and on the morning of surgery. All patients received their routine medications except diuretics, ACE inhibitors and diabetes mellitus medications. Patients were shifted to the operation theatre and routine monitors like non invasive blood pressure, electrocardiography and pulse oximetry were attached. Baseline non invasive blood pressure, heart rate, respiratory rate and oxygen saturation on room air were recorded. A 18 Gauge intravenous line was secured and ringer lactate infusion was started. Patients were administered injection midazolam 0.04 $mg.kg^{-1}$ body weight intravenous as premedication before the procedure. Patients were placed in the sitting position and local anaesthesia infiltrated at the Lumbar 2-3 or Lumbar 3-4 intervertebral space. Lumbar epidural space was identified by using loss of resistance to air technique. The epidural catheter was threaded through the Tuohy needle and advanced 4 cm into the epidural space. After a negative aspiration for blood and cerebrospinal fluid a test dose of 3 ml of 2% lignocaine and 15 µg of adrenaline was given to confirm the position of the catheter in the epidural space. A test dose of 3 ml of 2% lignocaine and 15 mg of adrenaline was given to confirm the position of the catheter in the epidural space. The subarachnoid block was given one lumbar intervertebral space below that of the epidural puncture site with 25 Gauge Quincke Babcock needle using 2.75 to 3 ml of 0.5% hyperbaric bupivacaine. Urinary catheter was inserted and surgery was allowed to proceed when adequate anaesthesia had been achieved. Intraoperative intravenous fluid therapy consisted of ringer lactate and hydroxyethyl starch as clinically indicated. A thigh tourniquet was used during the surgery and tranexemic acid 0.75 grams infusion was started before the surgical incision.

Postoperatively patients were transferred to the postanaesthesia care unit. The epidural solution was prepared by a trained anaesthesia nurse who was not involved in treatment of the patients. The epidural infusion was started when the sensory block had descended to T12-L1. Patients were initially administered a 5 ml epidural bolus of the solution and then epidural infusion was started at 4 $ml.hr^{-1}$ via an infusion pump. Epidural infusion rate was adjusted within the range of 3-7 $ml.hr^{-1}$ as per the requirement of the patient. Infusion rate was decreased if the patient developed systolic blood pressure less than 90 mm Hg or heart rate was less than 50beats/min, or if motor block Grade-2, or sedation Score-2 developed. Patient was administered injection ephedrine 6 mg i.v. if the systolic blood pressure was less than 90 mm Hg. Injection atropine 0.5 mg i.v. was administered if heart rate was less than 50 beats/minute. The epidural infusion continued for 24 hours postoperatively.

Study Parameters

Study parameters blood pressure, heart rate and respiratory rate were recorded in a double-blinded fashion by the primary investigator or the pain clinic nurse on duty at 6,12,18 and 24 hours postoperatively. Pain intensity at rest and during motion (flexion of the knee, about 30 degree) was assessed using the VAS score. If VAS score was >3 at any time in the postoperative period epidural infusion was increased by 1-2 $ml.hr^{-1}$. Paracetamol 1gm i.v. was used as the rescue medication. If injection paracetamol did not provide sufficient pain relief then a 3-7 ml bolus of the epidural solution was given by the anaesthesiologist on duty. If the patient still complained of severe pain then injection meperidine 50 mg was given intravenously. If the patient required meperidine rescue then the epidural catheter was removed and the patient was excluded from the study. The above medications were documented by the pain clinic nurse. Pain relief was estimated from the VAS scores [23] and total amount of epidural analgesic solution consumed postoperatively.

Motor Block was assessed at the above time intervals using the Bromage scale [24] (0= Free flexion of knees and feet, 1= Just able to flex knees with free movement of feet, 2= Unable to move knees with some flexion of feet, 3= Unable to move legs and feet.

Sedation was assessed at the above time intervals with the scoring 0= awake, 1= snoozing and easy to wake up, 2= Drowsy, 3= Sleeping and difficult to wake up.

Nausea and vomiting score was used to assess the same during visits at above mentioned interval (0=no nausea/vomiting in past time interval, 1= nausea in past time interval, 2= retching/vomiting in past time interval).

Side Effects

Any adverse effect like pruritis, nausea, vomiting was noted in the postoperative period. Since patients were catheterised preoperatively, urinary retention as a side effect was not taken into consideration. All patients received injection ondansetron 4 mg intravenous every eight hours postoperatively. Postoperative nausea lasting for more than 10 minutes or vomiting were treated additionally as required with injection metoclopramide 10 mg intravenous. The use of antiemetics was documented by the pain clinic nurse on duty and was noted on subsequent visits at above mentioned intervals. Pruritus was treated with injection naloxone 0.1 mg intravenous.

STATISTICAL ANALYSIS

The statistical tests applied were two-tailed student's t-test for finding significant difference in parameters such as VAS score, consumption of post operative systemic analgesics between the two groups. The categorical variables such as nausea and vomiting score, sedation score were computed by Pearson's Chi-square test. The comparison of the observations at different periods of time was assessed by t-test. The p-*value* <0.05 was taken as cut point for level of statistical significance and the data was analysed by using the SPSS statistical software.

RESULTS

The mean demographic profile of the two groups were comparable [Table/Fig-1].

Parameters	Group A	Group B
Sex (M/F)	16/14	17/13
Age (years)	54.5 ± 6.1	54.1 ± 7.4
Height (cm)	166.1±8.5	165.1±7.6
Weight (kg)	75.4 ± 8.2	75.6 ± 7.9
Body mass index	27.3 ± 1.7	27.8 ± 2.8

[Table/Fig-1]: Demographic data.
*Statistical test used was t-test

Analgesia and Total Epidural Analgesia Consumption

No patient required rescue meperidine and none of the patient were excluded from the study. Two patients in the clonidine group experienced less pain and had lower VAS scores on rest [Table/Fig-2] and on knee flexion [Table/Fig-3] as compared to the control group during the study period.

The total epidural solution consumption at 24 hours postoperatively was 130.9±15.7 ml in Group B (control) and 113.9±16.4 ml in Group A (study group) and the difference was found to be statistically significant (p< 0.05) [Table/Fig-4].

Rescue analgesia: The average paracetamol dosage was 1.2±0.81 grams in Group A vs 1.87±0.68 grams in Group B, and was significantly lower (p=0.017).

Patients in the clonidine group required epidural bolus rescue analgesia as compared to six patients in the control group. The epidural bolus provided pain relief in the above patients and indicated appropriate position of the epidural catheter.

Time	Group A		Group B		p-value
	Mean	SD	Mean	SD	
6 hours	3.20	0.89	3.30	0.95	0.67
12 hours	2.73	0.64	3.26	0.86	0.008
18 hours	2.46	0.78	2.93	0.69	0.02
24 hours	2.27	0.52	2.50	0.51	0.08

[Table/Fig 2]: VAS Score (at rest) at various intervals.
*VAS scores at rest were significantly higher in the Group B as compared to the Group A at 12 and 18 hours postoperatively. The values are ± S.D. * $p < 0.05$ compared with the clonidine group. Statistical test used was two-tailed student's t-test.

Time	Group A		Group B		p-value
	Mean	SD	Mean	SD	
6 hours	4.73	0.944	4.73	0.98	1.00
12 hours	4.2	0.71	4.8	1.13	0.016
18 hours	3.73	0.91	4.43	0.85	0.003
24 hours	3.63	0.76	4.2	0.71	0.004

[Table/Fig 3]: VAS (at motion) Score at various intervals.
*VAS scores during knee flexion were significantly higher in the Group B as compared to the Group A at 12, 18 and 24 hours postoperatively. The values are means ± S.D. *$p < 0.05$ compared with the clonidine group. Statistical test used was two-tailed student's t-test.

Time	Group A		Group B		p-value
	Mean	SD	Mean	SD	
6 hours	30.5	2.8	32.2	3.7	0.026
12 hours	57.8	7.1	62.8	8.4	0.003
18 hours	86.0	11.5	96.0	12.3	< 0.001
24 hours	113.9	16.4	130.9	15.7	< 0.001

[Table/Fig-4]: Cumulative volume (in ml) infused epidurally.
*The total epidural solution volume infused epidurally was significantly higher in the control Group (B) as compared to the study Group (A) at all times postoperatively. *$p < 0.05$ as compared to the clonidine group. Statistical test used was two-tailed student's t-test.

Haemodynamic Effects

Lower mean systolic and diastolic blood pressure [Table/Fig-5,6] and lower mean heart rate [Table/Fig-7] was observed in the clonidine group than control group but the differences were not significant. The systolic blood pressure was more than 80 mm Hg in all the patients postoperatively. Heart rate less than 50 beats per minute requiring injection atropine was seen in eight patients in the clonidine group as compared to three patients in the control group.

Time	Group A		Group B		p-value
	Mean	SD	Mean	SD	
0 hours	122.7	9.6	123.5	10.6	0.74
6 hours	118.7	12.8	123.0	14.0	0.22
12 hours	114.5	16.6	118.9	15.6	0.30
18 hours	114.5	20.8	118.8	15.6	0.37
24 hours	115.1	16.8	120.1	15.0	0.24

[Table/Fig-5]: Mean systolic blood pressure (mmHg) at various intervals.
*Statistical test used was t-test

Effect of Clonidine on Sedation, Respiration and Motor Blockade

None of the patient in our study suffered from respiratory depression. Three patients in the clonidine group felt drowsy as compared to one patient in the control group. However, the sedation scores were comparable in both the groups. The motor block was comparable in both the groups at all time intervals postoperatively. Four patients in the clonidine group felt nausea requiring antiemetic as compared to five patients in the control group. However, the difference was not significant. None of our patients suffered from pruritus and none required meperidine rescue.

Time	Group A		Group B		p-value
	Mean	SD	Mean	SD	
0 hours	74.9	8.0	76.1	6.5	0.53
6 hours	72.7	8.2	75.5	9.2	0.22
12 hours	71.4	9.3	74.1	9.4	0.26
18 hours	71.2	12.5	74.1	9.5	0.31
24 hours	72.0	10.5	74.4	9.0	0.35

[Table/Fig-6]: Mean diastolic blood pressure (mmHg) at various intervals.
*Statistical test used was t-test

Time	Group A		Group B		p-value
	Mean	SD	Mean	SD	
0 hours	72.5	9.7	73.2	5.6	0.73
6 hours	69.9	9.9	73.9	8.2	0.10
12 hours	69.0	13.0	72.7	9.2	0.21
18 hours	68.0	13.8	72.3	9.0	0.15
24 hours	69.6	13.5	73.8	9.0	0.17

[Table/Fig-7]: Mean heart rate at various intervals.
*Statistical test used was t-test

DISCUSSION

The primary aim of the present study was to determine the effect on analgesia and side effects upon adding epidural clonidine to a ropivacaine and fentanyl mixture in patients of total knee replacement surgery. Clonidine enhanced the analgesia and decreased the postoperative consumption of analgesics. Its use was not associated with significant side effects in our study.

Despite minimally invasive surgery, supplementation of effective postoperative analgesia makes a valuable adjunct for early physiotherapy and rehabilitation in patients undergoing total knee replacement surgery. Epidural analgesia is a popular technique for providing postoperative analgesia in these patients with evidence of fewer thromboembolic complications and reduced blood loss in orthopaedic surgery [25].

Epidural analgesia with local anaesthetics and opioids however is associated with side effects like motor blockade, pruritus, nausea and vomiting, urinary retention and respiratory depression [26]. A combination of antinociceptive drugs results in enhancement of analgesia through synergistic mechanisms and may lead to a decrease in dosage of the epidurally infused drugs and reduced number of side effects [27-32]. In this randomised and double blinded study, we added clonidine to a mixture of epidural ropivacaine and fentanyl in an attempt to reduce the dosage and side effects of these drugs and evaluate the analgesia provided.

Intrathecal clonidine added to bupivacaine morphine spinal anaesthetic mixture improves postoperative analgesia in total knee arthroplasty [8]. Gupta S et al., reported enhancement of postoperative analgesia and prolongation of sensory and motor blockade when epidural clonidine was added to bupivacaine in patients of total knee replacement surgery [9]. Huang YS et al., studied the effect of adding clonidine to epidural ropivacaine and morphine mixture for postoperative analgesia in total knee arthroplasty patients and reported enhanced analgesia with clonidine without significant haemodynamic derangement in any patient [10]. Similar results were noted by Foster JG et al., who added clonidine to epidural ropivacaine and fentanyl in patients of total knee arthroplasty [11].

Krishnamoorthy K et al., too reported enhanced postoperative analgesia with minimal side effects when clonidine was added to epidural bupivacaine in patients undergoing lower limb orthopaedic surgeries [12]. Similarly other studies have reported enhancement of analgesia after the addition of clonidine in patients undergoing various surgeries [13-16].

In our study, we observed reduced dosage of epidurally administered drugs and reduced need for rescue analgesia (Paracetamol i.v.) as compared to the control group. Lower pain scores were seen in

the clonidine group at all time intervals postoperatively which was consistent with the findings reported by other authors [10]. However, Forster JG et al., reported significantly lower pain scores only at 24 hours postoperatively [11].

In our study, we observed bradycardia and atropine usage in eight patients in the study group and three patients in the control group. However, the difference was not statistically significant which was consistent to the findings reported by other authors [10,11]. In our study, only four patients felt drowsy postoperatively whereas drowsiness was observed in one third of the patients postoperatively in the study by Forster JG et al., [11].

Clonidine did not increase the motor blockade in our study as observed in other studies too [11]. This could be attributed to the low dose of ropivacaine and clonidine used which enabled postoperative physiotherapy in all but three patients. However, we did not observe pruritus in any of our patients postoperatively. This was in sharp contrast to the study by Forster et al., where they observed significant pruritus at all times postoperatively [11]. This could be attributed to the low of fentanyl used in our study as compared to 5 $\mu g.ml^{-1}$ fentanyl used by them. As our patients were already administered prophylactic antiemetics we observed nausea and vomiting in only 15% of our patients.

LIMITATION

Our study had a potential limitation as pain is a subjective sensation and different patients have different threshold and response towards the same degree of pain. Hence, the visual analogue scores could be different for different patients with the same degree of pain. This could have led to an unwanted bias in our study.

CONCLUSION

We conclude that clonidine 2 $\mu g.ml^{-1}$ when added to ropivacaine 2 $mg.ml^{-1}$ and fentanyl 2 $\mu g.ml^{-1}$ augmented the postoperative epidural analgesia and provided better haemodynamic stability in patients of total knee replacement surgery without other significant side effects.

ABBREVIATIONS

NYHA:	New York Heart Association
VAS:	Visual Analog Scale
mm Hg:	Millimetres of mercury
$ml.hr^{-1}$:	millilitre per hour
$mg.ml^{-1}$:	milligrams per millilitre
$\mu g.ml^{-1}$:	micrograms per millilitre

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