ORIGINAL RESEARCH

A Comparative Study of Ropivacaine with Fentanyl versus Ropivacaine with Fentanyl and Clonidine for Postoperative Epidural Analgesia in Total Knee Replacement Surgery

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ABSTRACT

Background: Total knee replacement, a common surgical procedure today, is linked to severe postoperative pain. The present study was conducted to compare ropivacaine and fentanyl versus ropivacaine and fentanyl with clonidine for postoperative epidural analgesia in total knee replacement surgery. **Materials & Methods:** 90 patients undergoing total knee replacement surgery of both genders were divided into 2 groups. Group I (n=40) patients received postoperative continuous epidural infusion of ropivacaine (2mg/ml) plus fentanyl (2 µg/ml) with clonidine (2 µg/ml) whereas Group II (n=50) patients received epidural infusion of Ropivacaine (2mg/ml) plus Fentanyl (2 µg/ml) in the range of 3-7 ml/hr. Parameters such as postoperative VAS scores, haemodynamic parameters, motor block, sedation were noted. **Results:** Group I had 20 males and 20 females and group II had 28 males and 22 females. The mean duration of surgery was 104.1 mins in group I and 110.9 mins in group II. The mean time to onset of sensory analgesia was 7.4 minutes in group I and 4.2 minutes in group II. The time taken for regression of sensory block to T12 was 150.2 minutes in group I and 198.7 minutes in group II. The mean time to first postoperative analgesic requirement was 264.4 minutes in group I and 354.4 minutes in group II. The mean time taken to achieve complete motor blockade was 13.2 minutes in group I and 12.8 minutes in group II. The mean VAS in group I was 4.7 and in group II was 3.2. The difference in VAS score among both group ($P< 0.05$) was significant. **Conclusion:** When clonidine at a concentration of 2µg/ml was combined with ropivacaine at 2 mg/ml and fentanyl at 2 µg/ml, it enhanced postoperative epidural analgesia and improved haemodynamic stability in total knee replacement surgery patients, without causing other significant side effects.

Key words: Clonidine, Dexmedetomidine, fentanyl

INTRODUCTION

Total knee replacement, a common surgical procedure today, is linked to severe postoperative pain. Pre-emptive analgesia, neuraxial anaesthesia, peripheral nerve blockade, periarticular analgesic injections, and intravenous patient-controlled analgesia have all been documented as methods for postoperative pain relief in these patients.[1] When regional anaesthesia is conducted effectively, it greatly enhances joint function and promotes early rehabilitation.

Epidural analgesia offers outstanding pain relief for these patients and correlates with a reduced occurrence of postoperative myocardial infarction and enhanced local tissue perfusion.[2]

Tamsen A and Gordh T reported in 1984 that clonidine, an alpha 2 adrenoceptor agonist, exhibited analgesic properties when administered via the epidural or intrathecal route. Since that time, many studies have employed intrathecal or epidural clonidine for postoperative pain relief across different types of surgery.[3] It works through the stimulation of alpha-2 adrenoceptors in the dorsal horn and simulates the activation of descending inhibitory pathways. Reports indicate that it interacts with other analgesic medications via serotonergic mechanisms, spinal muscarinic receptors, and local nitric oxide synthesis. This interaction may enhance analgesia through additive or synergistic mechanisms.[4]

It has been reported that clonidine can reduce heart rate through two mechanisms: a vagomimetic effect and presynaptic inhibition of norepinephrine release at the neuroreceptor junction. Reports indicate that it can lead to hypotension and reduce noradrenaline levels in the locus coeruleus, resulting in sedation and anxiolysis.[5]

Ropivacaine, an amide local anesthetic, received approval from the Food and Drug Administration (FDA). As it is regarded as having a lower risk of cardiac toxicity and a higher threshold for CNS toxicity on a milligram basis compared to bupivacaine, it may serve as an appropriate substitute for long-acting local anesthetic.[6]

AIM & OBJECTIVES

The present study was conducted to compare ropivacaine and fentanyl versus ropivacaine and fentanyl with clonidine for postoperative epidural analgesia in total knee replacement surgery.

MATERIALS & METHODS

Study Design

This was a prospective, randomized, double-blind comparative clinical study conducted to evaluate the efficacy of ropivacaine-fentanyl versus ropivacaine-fentanyl with clonidine for postoperative epidural analgesia in patients undergoing total knee replacement (TKR).

Study Population

A total of 90 adult patients, both male and female, undergoing elective unilateral total knee replacement surgery under spinal anaesthesia were included in the study. All participants provided written informed consent prior to enrollment.

Study Place

The study was conducted in the Department of Anaesthesiology, Department of Anaesthesia, Sri Krishna Medical College & Hospital, Muzaffarpur, Bihar, India.

Study Duration

The study was carried out over a period of one year from March 2017 to February 2018.

Inclusion Criteria

- Patients aged between 40 to 80 years
- Either gender
- ASA physical status I–III
- Scheduled for elective unilateral total knee replacement
- Willing to give informed consent

Exclusion Criteria

- Patient refusal
- Known allergy or contraindications to study drugs (ropivacaine, fentanyl, clonidine)
- Preexisting neurological disorders
- Coagulopathies or anticoagulant therapy
- Severe hepatic, renal, or cardiac disease
- Local infection at the epidural site
- Chronic opioid use or substance abuse

Ethical Considerations

- Approval was obtained from the Institutional Ethics Committee prior to initiation.
- All patients were given detailed information about the study, and written informed consent was taken.
- The study complied with the Declaration of Helsinki and relevant ethical guidelines.

Study Procedure

Patients were randomly allocated into two groups, using computer-generated random numbers:

- **Group I: Ropivacaine + Fentanyl + Clonidine, (n = 40)**: Received continuous epidural infusion of Ropivacaine 0.2% (2 mg/ml) + Fentanyl 2 μg/ml + Clonidine 2 μg/ml.
- **Group II: Ropivacaine + Fentanyl, (n = 50)** : Received continuous epidural infusion of Ropivacaine 0.2% (2 mg/ml) + Fentanyl 2 μg/ml.

Infusion was given postoperatively at a rate of 3–7 ml/hr based on patient response and VAS scores.

Blinding: Both patients and observers were blinded to the group allocation. Drug preparation was done by an anaesthesiologist not involved in data collection.

Surgical Technique

All patients underwent standardized total knee arthroplasty (TKA) by the same surgical team under spinal anaesthesia, using identical protocols for anaesthesia induction, maintenance, and intraoperative care.

Outcome Measures

1. Primary Outcome:
   - Postoperative pain intensity assessed using Visual Analogue Scale (VAS) at 2, 4, 8, 12, 24, and 48 hours postoperatively.
2. Secondary Outcomes:
   - Hemodynamic parameters: HR, BP at baseline and at scheduled intervals postoperatively.
   - Motor block: Graded using Modified Bromage Scale.
   - Sedation level: Assessed by Ramsay Sedation Scale.
   - Incidence of side effects: Nausea, vomiting, bradycardia, hypotension, pruritus, urinary retention.

Statistical Analysis

- Data were analyzed using SPSS version 20.0.
- Continuous variables were expressed as mean ± SD.
- Categorical variables were presented as number and percentage.
- Student's t-test was used for comparison of continuous variables.
- Chi-square test/Fisher's exact test was used for categorical variables.
- P value < 0.05 was considered statistically significant.

RESULTS

Table 1: Gender wise distribution of Patients

Groups	Group I: Ropivacaine + Fentanyl + Clonidine, (n=40)	Group II: Ropivacaine + Fentanyl, (n=50)
Method	continuous epidural infusion of ropivacaine (2 mg/ml) plus fentanyl (2 µg/ml) with clonidine (2 µg/ml)	epidural infusion of Ropivacaine (2 mg/ml) plus Fentanyl (2 µg/ml)
M:F	20:20	28:22

Table 1 show that group I had 20 males and 20 females and group II had 28 males and 22 females.

Table 2: Comparison of Intraoperative and Postoperative Parameters

Parameter	Group I, (n=40) (Mean ± SD)	Group II, (n=50) (Mean ± SD)	P-value
Duration of surgery (minutes)	105.1 ± 9.3	106.4 ± 10.1	0.82
Onset of sensory analgesia (minutes)	5.4 ± 1.2	8.2 ± 1.6	0.02
Time taken for regression of sensory block to T12 (minutes)	158.2 ± 14.7	190.7 ± 18.2	0.05
Time to first postoperative analgesic requirement (minutes)	260.2 ± 25.6	358.4 ± 30.1	0.01
Time to achieve complete motor blockade (minutes)	11.2 ± 2.1	13.5 ± 2.4	0.05

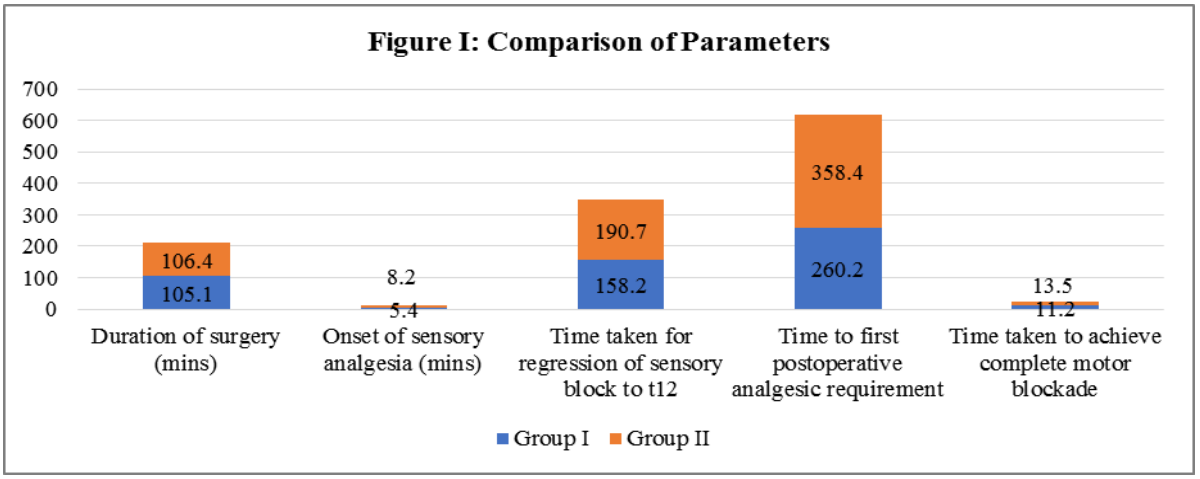

Table 2, figure I shows that the mean duration of surgery was comparable between Group I (105.1 ± 9.3 minutes) and Group II (106.4 ± 10.1 minutes), with a P-value of 0.820, indicating no statistically significant difference. The onset of sensory analgesia in Group I showed a faster onset of sensory analgesia (5.4 ± 1.2 minutes) compared to Group II (8.2 ± 1.6 minutes). The P-value of 0.020 indicates a statistically significant difference, suggesting that the addition of clonidine slightly delays the onset. The time taken for regression of the sensory block to T12 shows the sensory block regressed faster in Group I (158.2 ± 14.7 minutes) than in Group II (190.7 ± 18.2 minutes). The P-value of 0.050 is on the threshold of statistical significance, indicating that clonidine prolongs sensory block duration. Time to First Postoperative Analgesic Requirement in Group II had a significantly longer analgesia duration (358.4 ± 30.1 minutes) compared to Group I (260.2 ± 25.6 minutes), with a P-value of 0.010. This suggests that the addition of clonidine enhanced postoperative analgesia, delaying the need for additional pain medication. Time to Achieve Complete Motor Blockade shows the motor block onset was slightly delayed in Group II (13.5 ± 2.4 minutes) versus Group I (11.2 ± 2.1 minutes). The P-value of 0.050 indicates a borderline significant difference, suggesting that clonidine may slightly prolong the time to achieve a full motor block.

Table 3: Comparison of Hemodynamic Parameters and Pain Scores

Parameter	Group I, n=40 (Mean ± SD)	Group II, n=50 (Mean ± SD)	P-value
VAS score at rest	2.6 ± 0.5	2.9 ± 0.6	0.05
VAS score on movement	3.4 ± 0.7	4.8 ± 0.8	0.02
Systolic Blood Pressure (mmHg)	112.8 ± 8.2	126.2 ± 9.4	0.01
Diastolic Blood Pressure (mmHg)	70.2 ± 6.3	76.4 ± 7.1	0.05
Heart Rate (beats/min)	70.4 ± 5.8	78.2 ± 6.7	0.05

Table 3 compares pain scores (VAS) and haemodynamic parameters between Group I (Ropivacaine + Fentanyl) and Group II (Ropivacaine + Fentanyl + Clonidine) during the postoperative period in total knee replacement patients. The mean VAS at rest was 2.62 ± 0.5 and 2.9 ± 0.6, P = 0.050 (borderline significance). This suggests slightly higher pain levels at rest in Group II, likely due to delayed onset of analgesia with clonidine, but the difference is borderline significant. VAS Score on Movement was 3.4 ± 0.7 in Group I and 4.8 ± 0.8 in Group II, P = 0.020 (statistically significant). Pain during movement was significantly higher in Group II, indicating that despite clonidine's prolonged analgesia, it may not have offered superior dynamic pain relief, or it could reflect initial delayed analgesic onset. Systolic Blood Pressure (SBP) was 112.8 ± 8.2 mmHg in Group I and 126.2 ± 9.4 mmHg in Group II, P = 0.010 (statistically significant). Group II showed higher systolic BP, possibly due to the sympathomimetic effect or incomplete attenuation of stress response with clonidine initially. Diastolic Blood Pressure (DBP) was 70.2 ± 6.3 mmHg in Group I and 76.4 ± 7.1 mmHg in Group II, P = 0.050 (borderline significant). There is a borderline rise in DBP in Group II, again potentially linked to variable autonomic modulation by clonidine. Heart rate was 70.4 ± 5.8 bpm in Group I and 78.2 ± 6.7 bpm in Group II, P = 0.050 (borderline significant). Slightly higher heart rates in Group II suggest a mildly increased sympathetic tone or a less pronounced reduction in heart rate by clonidine at this dose.

DISCUSSION

Although minimally invasive surgery is used, providing effective postoperative analgesia is a beneficial addition for facilitating early physiotherapy and rehabilitation in patients who have had total knee replacement surgery. Epidural analgesia is a widely used method for delivering postoperative pain relief in these patients, with evidence suggesting it leads to fewer thromboembolic complications and reduced blood loss during orthopaedic surgery.[7] Intrathecal clonidine has been used as an adjuvant to local anaesthetics in various surgical procedures without any clinically significant side effects. Previous studies have described the use of clonidine in a wide range (15—150 mcg).[8] The present study was conducted to compare ropivacaine and fentanyl versus ropivacaine and fentanyl with clonidine for postoperative epidural analgesia in total knee replacement surgery.

We found that group I had 20 males and 20 females and group II had 28 males and 22 females. Panwar et al.[9] evaluated 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 on 60 patients of ASA physical status I, II and III. Patients were divided into two Groups A and B randomly. Postoperatively Group A received continuous epidural infusion of ropivacaine 2 mg/ml and fentanyl 2 µg/ml along with clonidine 2 µg/ml in the range of 3-7 ml/hr while Group B received the ropivacaine and fentanyl epidural solution. 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.

We found that mean duration of surgery was 105.1 minutes in group I and 106.4 minutes in group II. The mean time to onset of sensory analgesia was 5.4 minutes in group I and 8.2 minutes in group II. The time taken for regression of sensory block to T12 was 158.2 minutes in group I and 190.7 minutes in group II. The mean time to first postoperative analgesic requirement was 260.2 minutes in group I and 358.4 minutes in group II. The mean time taken to achieve complete motor blockade was 11.2 minutes in group I and 13.5 minutes in group II. The efficacy of dexmedetomidine and fentanyl as intrathecal adjuvants to 2.5 ml of 0.75% isobaric ropivacaine was compared by Ravipati et al.[10] Sixty patients who were chosen and randomized received either 2.5 ml of 0.75% isobaric ropivacaine with dexmedetomidine at 5 mcg (Group RD) or 20 mcg of fentanyl (Group RF) intrathecally for lower limb surgeries, and block characteristics, hemodynamic changes, and adverse effects were compared. The effectiveness of both medications when administered intrathecally was examined. The average duration required for sensory blockade at T10 was 156.46 ± 33.78 seconds in the RD group and 185.20 ± 35.17 seconds in the RF group. The outcomes have significance both clinically and statistically. In Group RD, the average total duration of sensory block was 194.40 minutes, whereas in Group RF it was 139.90 minutes. This difference was both clinically and statistically significant. The duration until the onset of motor block was nearly identical for both groups. In Group RD, the average total duration of motor block was 136.73 minutes, whereas in Group RF it was 94.87 minutes. This difference was both clinically and statistically significant.

We found that mean VAS at rest was 2.6 and 2.9, VAS at motion was 3.4 and 4.8, SBP was 112.8 mm Hg and 126.2 mm Hg, DBP was 70.2 mm Hg and 76.4 mm Hg and heart rate was 70.4 beats/min and 78.2 beats/min in group I and in group II respectively. Martin et al.[11] reported that when Clonidine was used intrathecally with ropivacaine at three different doses (15, 45, and 75 µg) for ambulatory knee arthroscopy, the small 15 µg dose significantly enhanced anaesthesia quality without causing delays in sensory and motor recovery. It was also observed that a Clonidine dose of 45 µg extends the sensory blockade with no effect on motor blockade, whereas a 75 µg dose leads to delayed sensory and motor recovery and noticeable side effects like hypotension and sedation.

In a study by Mahendru et al.[12] involving fifty patients undergoing lower abdominal surgeries, the intrathecal administration of clonidine and dexmedetomidine was compared to hyperbaric ropivacaine. The results showed that the dexmedetomidine group experienced a longer duration of analgesia compared to the clonidine group, with this difference being statistically significant. Forster JG et al[13] studied whether a small dose of clonidine added to a ropivacaine-fentanyl mixture improves epidural analgesia without provoking side effects typically related to larger amounts of epidural clonidine. In this randomized, double-blinded study, patients (≤85 yr, ASA I-III) underwent total knee arthroplasty (TKA) performed under spinal anaesthesia. After the operation, patients received an epidural infusion consisting of ropivacaine 2 mg/ml and fentanyl 5 microg/ml either without (Group RF, n=33) or with clonidine 2 microg/ml (Group RFC, n=36). The infusion rate was adjusted within the range 3-7 ml/ h. Average rate of infusion was slightly smaller in Group RFC than in Group RF (mean (SD) 4.7 (0.72) vs 5.2 (0.8) ml/ h, P=0.004). Compared with the RF group, patients in the RFC group required significantly less rescue pain medication, that is i.m. oxycodone (median (25th, 75th percentile) 0 (0, 7) vs 7 (0, 12) mg, P=0.027). Arterial pressure and heart rate were slightly lower in Group RFC throughout the study period (mean difference

between the groups 5 mm Hg (P<0.002) and 3 min (-1) (P=0.12), respectively). The groups did not differ statistically with respect to nausea, motor block, and sedation.

LIMITATIONS OF THE STUDY

- Single-centre study: Limits generalizability to other populations or settings.
- Short follow-up period: Long-term effects of clonidine addition were not assessed.
- Subjective pain scoring: VAS is patient-dependent and may vary.
- Limited dosage range: Only one dosage regimen was evaluated for each group.
- Fixed infusion rate range: Patient-controlled epidural analgesia (PCEA) was not used, which may offer more individualized pain control.
- Sedation scoring was observer-based and might have variability.
- Sample size may not be sufficient to detect rare side effects or complications.

CONCLUSION

Author found that the addition of clonidine to ropivacaine and fentanyl for postoperative epidural analgesia in total knee replacement resulted in faster onset of analgesia, improved dynamic pain control, and better hemodynamic stability, though with a shorter duration of analgesia requiring earlier rescue medication. This regimen may be advantageous in settings where rapid recovery and early ambulation are desired.

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