

A comparative evaluation of Clonidine, Fentanyl and Combination of both as Adjuvants to Ropivacaine in Epidural block for Perineral and lower limb Surgeries

Anita Vig Kohli, Swati Bhan, Smriti Gulati, Arti Mahajan

Abstract

The current study evaluated the effect of fentanyl and clonidine as adjuvants with Ropivacaine in epidural block. In our study, 120 patients were randomly allocated to one of the four study groups i.e. Group I (R)-20 ML of .75% of Ropivacaine + 2ml NS; Group II (RC)-20 ML of .75% of Ropivacaine + 2ml of NS containing 75u of Clonidine, Group III (RF) -20 ML of .75% of Ropivacaine + 2ml of NS containing 75u of Fentanyl; Group IV (RCF)- 20 ML of .75% of Ropivacaine + 2ml of Saline containing 37.5u Clonidine + 37.5u Fentanyl. After observing various sensory and motor blockade characteristics in the four groups, it was found that addition of Clonidine and Fentanyl hastened the onset of sensory and motor block and also provided longer, complete and effective analgesia in adjuvant groups than control group. A significant incidence of side effects was noted in RF and RC groups. A reduction in doses of Clonidine and Fentanyl in RCF group did not make any significant difference in block characteristics but there was significant decrease in the incidence of side effects.

Key Words

Ropivacaine, Clonidine, Fentanyl and Epidural

Introduction

Epidural anesthesia is a central neuraxial block with many applications ranging from analgesia with minimal motor block to dense anesthesia with full motor block. Epidural block can be used as a single shot technique or with a catheter that allows intermittent boluses and/or continuous infusion. Bupivacaine is the most commonly used amide local anesthetic agent for intrathecal/epidural analgesia but its potential toxicity led to the introduction of pure agonists with less toxic potentials such as Ropivacaine and Levobupivacaine.

Ropivacaine is the stereoisomer of bupivacaine showing less central nervous system and cardio toxicity than bupivacaine. (1) Also its decreased propensity for motor block is useful for rapid patient mobilization in the postoperative period. (2) But a slightly larger dose of ropivacaine is required to achieve the analgesic and anesthetic effects, leading to quite a few side effects. A number of drugs have been used as adjuvants in epidural blocks. These include opioids (tramadol, morphine, fentanyl, etc.) and a wide variety of non opioids (alpha adrenergic agonists: clonidine; benzodiazepines: midazolam; steroids: methyl prednisolone, etc.). The addition of an adjuvant not only increases the

effectiveness of a local anaesthetic by prolonging and intensifying the sensory blockade but also causes reduction in the dose of local anaesthetic agents. (3) Fentanyl is a commonly used synthetic opioid used as adjuvant to local anesthetics solution and is seen to produce a rapid onset of sensory and motor block during epidural anesthesia. (4) As fentanyl has no effect on sympathetic and motor neurons, it has advantages over local anesthetics. However, when used alone, analgesia is not enough and overdose will lead to side effects like itching, nausea, vomiting and urinary retention. Clonidine, an alpha adrenergic agonist is also commonly used as an adjuvant to improve the quality of epidural block. (5) Although, unlike neuraxial opioids; it does not produce pruritus or respiratory depression, at higher doses, it may exert its toxic effects resulting in profound hypotension, bradycardia and deep sedation. At low doses, epidural clonidine improves the quality of anesthesia, reduces the dose requirement of the anesthetic agent and provides a more stable cardiovascular course during anesthesia. (6)

Our aim in the present study, is to evaluate and compare the relative effectiveness of Clonidine-Ropivacaine

From the Department of Anesthesiology and Critical Care, Government Medical College Jammu. (J&K)-India

Correspondence to : Dr Anita Vig Kohli, Assistant Professor, Deptt. of Anesthesiology & Critical Care, Govt. Medical College Jammu. (J&K)

combination with Fentanyl-Ropivacaine combination. We also used a mixture of Fentanyl and Clonidine in reduced doses as an adjuvant to Ropivacaine in epidural block to see whether addition of alpha-2 agonist can help in dose sparing of an opioid while preserving the analgesic quality at the same time.

Material and Methods

After obtaining approval from the hospital ethical committee the present study was undertaken in the Department of Anesthesiology and Intensive Care, Government Medical College Jammu. 120 patients of either sex, ranging in age from 18-60 years, belonging to ASA Grade I and II, scheduled for perineal and lower limb procedures were included in the study. The patients with bleeding or coagulation abnormalities, local skin infection at spinal or lumbar region and raised intracranial pressure were excluded from the study. Informed written consent was taken from all patients to be enrolled in the study. In the Preanaesthetic checkup demographic profile including weight, height, age and sex were recorded. All patients were subjected to detailed general physical as well as systemic examination and all routine investigations were carried out. VAS was explained to all patients.

The patients were randomly assigned to one of the following four groups, taking 30 patients in each group
Group I (R)-20 ML of .75% of Ropivacaine + 2ml NS;
Group II (RC)-20 ML of .75% of Ropivacaine + 2ml of NS containing 75u of Clonidine,
Group III (RF) -20 ML of .75% of Ropivacaine + 2ml of NS containing 75u of Fentanyl;
Group IV (RCF)- 20 ML of .75% of Ropivacaine + 2ml of Saline containing 37.5u Clonidine + 37.5u Fentanyl.

All patients were kept fasting overnight. They received tablet alprazolam 0.25mg orally the night before surgery. After receiving the patient in the operation theatre, intravenous line with 18G cannula was established and Ringer Lactate drip started. Baseline heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), arterial saturation (SPO₂), and respiratory rate (RR), were recorded. All patients were given epidural anesthesia for undergoing the proposed surgery. After aseptically preparing the site, epidural needle (Portex 20G) was introduced in L2-L3 inter-vertebral space in sitting position into epidural space using loss of resistance to air technique. Test dose of 3ml of 1.5% lignocaine hydrochloride solution containing adrenaline 1:200,000 was given after aspiration. After waiting for 2-3 minutes to see the effect of test dose and to rule out intravascular or intrathecal injection. the drug combination depending upon the group was slowly injected. Thereafter, patients were placed in supine position for surgery.

Haemodynamic variables were monitored and recorded every 5 minutes after the block for half an hour

and then every 10 minutes until the end of surgery. Time was calculated considering the time of epidural injection as zero. The sensory block was assessed by bilateral pin prick method using blunt 25G needle every 5 minutes for the first 30 minutes. The onset of sensory block, peak sensory level and the time to reach peak sensory level was recorded before surgery. Thereafter, the sensory level was checked every 10 minutes till the point of two segment regression was reached. The motor block was assessed using modified Bromage Scales (BS) (0 - no block, 1 -inability to raise extended leg, 2 - inability to flex knee and 3 - inability to flex ankle and foot). Time to reach BS 3 motor block was also recorded before surgery.

Sedation was assessed by modified Ramsay Sedation Score as Score I: Anxious and agitated or restless, or both; Score II: Co-operative, oriented and tranquil; Score III: Drowsy, but responds to commands; Score IV: Asleep, brisk response to light glabellar tap or loud auditory stimulus, Score V: Asleep, sluggish response to light glabellar tap or loud auditory stimulus and Score VI: Asleep and unarousable.

The incidence of adverse effects such as hypotension, bradycardia, respiratory depression, nausea, vomiting, headache, dry mouth, shivering, urinary retention and pruritus were recorded. Postoperatively, sedation score, sensory level and BS was recorded every 30 minutes in the recovery room. The time from epidural injections to two dermatome sensory regression, sensory regression to S1 dermatome and motor block regression to modified BS 0 was recorded. Pain intensity was assessed every 30 minutes by using VAS scale using a 10 centimeter line, 0 denoting 'no pain' while 10 denoting 'worst possible pain'. Duration of analgesia was taken as time period till VAS of 4 was recorded. I.V. diclofenac 75mg was given as rescue analgesia.

Result

The demographic parameters including age, weight, height and sex of all the patients were comparable and type and duration of surgery was also comparable. No statistical difference was observed in all the four groups. The hemodynamic parameters including SBP, DBP, MAP and HR recorded in the preoperative period and intra-operatively were found to be statistically comparable in the four groups.

The mean time in minutes for onset of sensory block at T10 dermatome (*Table 1*) was found to be significantly decreased in RC, RF and RCF groups when compared to Group R ($p < 0.001$). However, no significant difference was found among RC, RF and RCF groups on intergroup comparisons according to Bonferroni's test.

Similarly the time taken to attain peak level of sensory block was maximum in R group as compared to RC, FR and RCF groups which was highly significant by ANOVA test ($p < 0.001$).

Table 1. Time Taken For Onset and Peak Level of Sensory Block.

Group	Time in minutes for onset at T10 dermatome	Time in minutes to attain peak level of block
RC	12.33±4.69	17.50±4.50
RF	12.00±4.28	17.17±4.30
RCF	11.33±3.20	16.50±3.65
R	15.67±3.20	20.83±3.96
Significance	F value = 6.851 p=<0.001 : HS	

Table 2. Time Taken to Attain Complete Motor Block

Group	Time in minutes (Mean ±SD)
RC	21.50±4.38
RF	20.83±3.96
RCF	21.83±4.04
R	26.17±3.13
Significance	F value = 11.560 p=<0.001 : HS

Table 3. Duration of Analgesia in Minutes

Group	Time in minutes (Mean ±SD)
RC	276.67±26.11
RF	286.00±29.40
RCF	271.67±33.20
R	161.33±21.61
Significance	F value = 132.673 p=<0.001 : HS

Table 4. Incidence of Common Side Effects

Side Effects	Number of patients (%age)				Statistical inference
	RC	RF	RCF	R	
Hypotension	3(10%)	2(6.67%)	2(6.67%)	2(6.67%)	X ² = 0.360 P=0.948:NS
Bradycardia	3(10%)	2(6.67%)	0	0	X ² = 5.63 P=0.13:NS
Shivering	1(3.33%)	1(3.33%)	2(6.67%)	2(6.67%)	X ² = 0.702 P=0.872:NS
Nausea/Vomiting	2(6.67%)	10(33.33%)	2(6.67%)	0	X ² = 19.08 P=0.001:HS
Dry mouth	7(23.33%)	0	1(3.33%)	0	X ² = 18.21 P=0.001:HS
Respiratory depression	0	0	0	0	Zero incidence
Urinary retention	0	0	0	0	Zero incidence
Pruritus	0	0	0	0	Zero incidence
Headache	0	0	0	0	Zero incidence

For purpose of statistical analysis block level was divided as T7 or higher and less than T7. Number of patients with a block level > T7 were 21, 19, 19, 13 in Group RC, RF, RCF and R respectively. In all the four groups the maximum level of sensory block obtained was comparable and statistically insignificant.

The mean time in minutes for establishment of complete motor block (Table 2) was found to be statistically significant by ANOVA test (p<0.001) where control group took longer time to establish motor block. However, no significant difference was found among RC, RF and RCF groups on intergroup comparison (p0.05).

Time taken to two segmental regression of sensory block was recorded in minutes. In Group RC mean time taken to

two segmental regression was 153.00±10.22, in Group RF it was 157±9.24, in Group RCF the time taken was 151.33±10.33 and in Group R, it was 109.67±9.99. The observations were found to be statistically significant by ANOVA test (p<0.001) where sensory block was prolonged in study groups with adjuvants as compared to control group/ Same observations were noted for segmental regression to S1 dermatome, where it was 252.67±23.03, 263.00±33.93, 246.67±33.79, 154.33±20.11 I minutes for RC, RF, RCF and R group respectively The duration of analgesia as defined by the time to reach a VAS of 4 was found to be significantly prolonged in all the study groups as compared to the control group (Table 3).

On intergroup comparisons, however the difference in total duration of analgesia was not found to be statistically significant.

Time taken to attain complete motor regression was noted in four groups and mean time in minutes recorded for Group RC was 212.50 ± 39.06 , for RF 232.17 ± 30.64 , for RCF 213.17 ± 27.15 and for R was 133.83 ± 14.84 minutes. The groups with adjuvants had prolonged duration of motor block which was statistically highly significant.

..... Table 4) show that none of the patients in any group had respiratory depression, headache, urinary retention or pruritus. Hypotension and Bradycardia was seen in insignificant number, however, a significant number of patients in RF group (33.33%) developed nausea and vomiting, Dry mouth was another side effect found in significant (23.3%) number of patients in RC group, .

Sedation was found to be more in RF group where 70% patients had sedation score of 2 and 30% patients had sedation score 3. Group RC had 90% patients with sedation score 2 and only 10% patients had sedation score 3. In Group RCF 93.33% patients had sedation score 2 with only 6.67% patients having sedation score 3. In Group R, 100% patients had sedation score 2. The difference was found to be statistically highly significant on intergroup analysis.

Discussion

Epidural blockage is one of the most useful and versatile procedures in modern anaesthesiology. Local anesthetics, mostly used for epidural blockade are bupivacaine, levobupivacaine and ropivacaine. Ropivacaine is relatively new amide type, long acting, pure S-enantiomer local anesthetic, structurally related to bupivacaine. It was developed for purpose of reducing potential toxicity for cardiovascular and central nervous system seen with bupivacaine and improving relative sensory and motor blockade profile (7).

A variety of drugs have been studied as adjuvants to try to improve the quality of neuraxial blockade with epidural technique. These include opioids (tramadol, morphine, fentanyl (8) and a wide variety of non opioids (alpha adrenergic agonists, clonidine (9): benzodiazepines, midazolam; steroids: methyl prednisolone).

The quest for finding optimal dose of either an opioid or alpha blocker as an adjuvant in regional anaesthesia is never ending but there are few studies which have tried to compare the potential benefits of either the two combinations or tried to evaluate the synergistic effect of these two in lower concentrations (5,6,10).

In our study, the time taken for onset of sensory block at T10 was found to be decreased in adjuvant groups as compared to control group which was found to be statistically significant. Similar results were obtained in

other studies (4,8,9). In contrast to our study, Cho Y H, *et al* (11) studied the effect of addition of clonidine to ropivacaine and did not observe any significant difference in the onset of sensory block. We observed that the time taken for establishment of highest level of sensory block was significantly decreased in study group which was in accordance with study by Bajwa SJS, *et. al* (8). However, the number of patients reaching sensory level of T7 or higher at 30 minutes was found to be comparable. In various studies (8,9,11,12), the results were same. The mean time in minutes for two segmental regression of sensory block was found to be significantly increased in RC, RF and RCF groups when compared to group R. However, no significant difference was found on intergroup comparisons with study drugs .in accordance with other studies (8,11,12).

The mean time for establishment of complete motor block was significantly decreased by addition of fentanyl and clonidine in study groups as compared to control group, which is consistent with most of the studies (4,8,9). As in these studies the total duration of motor block was also prolonged in our study. Engel JM, *et al* (13) concluded that clonidine significantly enhanced the duration of analgesia of epidurally administered ropivacaine as is seen in our study. Our results are also in accordance with the results of other studies (3,6,14).

Shukla U, *et al* (15) in his study showed that efficacy of clonidine and fentanyl as additive to ropivacaine are comparable. Topcu I (16) comparing fentanyl and clonidine with ropivacaine in PCEA in patients in labour concluded that fentanyl provides superior analgesia than clonidine. Forster JG *et al*, (17) studied the effect of fentanyl and clonidine mixture to Ropivacaine and concluded that the quality of analgesia was better than when used alone. The synergistic effect of opiates, local anaesthetics and alpha2 adrenergic agonists are due to separate mechanism. Opiates produce analgesia by specifically binding and activating the opiates receptors in substantia gelatinosa whereas local anaesthetics provide analgesia by blocking impulse transmission at nerve roots and dorsal root ganglia. The lipophilic opioids injected into epidural space as bolus shows biphasic pattern of absorption leading to increased duration of analgesia. Clonidine on the other hand produces analgesia by action on alpha2 adrenergic agonists and enhances analgesia from intra spinal opioids. Side effects like hypotension and bradycardia was seen only in 10% of patients in RC group and 6.67% in RF, RCG and R which was not significant. On results are in accordance with other studies (4,8,12,17) however, in contrast to our study, Gupta *et al* (9) reported 25% incidence of hypotension in Clonidine group when used in dose of 1ug per kg. None of the patients had pruritis, headache and urinary retention which is similar

to results as shown in other studies (3,8,9). In contrast to our study Cuchiaro et al observed 85% and 54% patients in RF and RCF group having pruritus respectively. Shivering was observed in insignificant number of patients. On monitoring respiratory rate and saturation, we found none of the patients developed respiratory depression which is in accordance to the study by Malik P *et al* (18). Nausea and vomiting was observed in 33.33% of patients in Group RF as compared to 6.67% in RC and RCF groups whereas no patients had similar complaints in Group R, which was statistically significant. Cucchiario *et. al* (10) also came to the same conclusion in his study. He showed that nausea and vomiting in clonidine group (27%) was significantly less than in fentanyl group (69%) and fentanyl and clonidine group (55%). However in contrast, the studies by Cherng CH *et. al* (4), Topcu I *et. al* (16) and Forster JG (17) did not show any increased incidence of nausea and vomiting with fentanyl. A total of 23.33% of patients in our study complained of dry mouth in RC group in contrast to other groups, which was highly significant. Dry mouth as a side effect is also seen in other studies (8,9,17). In our study, patients were most of the time cooperative, oriented and tranquil with sedation score 2. On intergroup comparison, sedation was seen maximally in Fentanyl (30%) and less in Clonidine group (10%). However, the sedation score of more than three was not seen in any patient. These results show that use of Clonidine and Fentanyl in epidural space is associated with higher incidence of sedation than when ropivacaine is used alone for epidural block. The same results were observed in other studies also (9,12,13,17,19,20).

The significant prolongation of epidural block by addition of adjuvants like fentanyl or clonidine as compared to control group is a potential advantage both for the patient as well as the care takers. This long duration of analgesia allows better patient satisfaction and decreased use of post operative analgesics. However, fentanyl or clonidine, when used alone in optimal doses via epidural route with ropivacaine do produce an array of side effects which includes sedation, nausea / vomiting, dry mouth, etc. The side effects become almost non-existent, while the analgesic quality is preserved when both these are used in combination with ropivacaine with their doses reduced to half of optimal dose.

Conclusion

Our study helped us to conclude that addition of clonidine or fentanyl to epidural ropivacaine in patients undergoing lower limb or perineal surgeries prolongs the duration of analgesia when compared to ropivacaine alone. Combination of clonidine and fentanyl in reduced doses with epidural ropivacaine provides equally effective analgesia while significantly reducing the incidence of side effects.

Reference

1. Hansen TG Ropivacaine: A pharmacological review. *Expert Rev Neurother* 2004; 4: 781-91.
2. Hogdson PS, Liu SS. A comparison of Ropivacaine with fentanyl to bupivacaine with fentanyl for postoperative patient controlled epidural analgesia. *Anaesth Analg* 2001; 92: 1024-28.
3. Landau R, Schiffar E, Morles M, *et. al*. The dose sparing effect of clonidine added to Ropivacaine for Labour epidural analgesia. *Anaesth Analg* 2005; 95: 729-34.
4. Cherng CH, Yang CP, Wong CS. Epidural fentanyl speeds the onset of sensory and motor blocks during epidural Ropivacaine anaesthesia. *Anaesth Analg* 2005; 101: 1834-7.
5. Curatolo M, Schnider TW, Petersen Felix S, *et al*. A direct search procedure to optimize combinations of epidural bupivacaine, fentanyl and clonidine for post operative analgesia. *Anaesthesiology* 2000; 92: 325-27.
6. De Negri P, Ivani G, Visconti C, *et al*. The Dose response relationship for clonidine added to a postoperative continuous epidural infusion of ropivacaine in children. *Anaesth Analg* 2001; 93: 71-76.
7. Kuthiala G, Chaudhary G. Ropivacaine. A review of its pharmacology. *Indian J Anesth* 2011; 55: 104-10.
8. Bajwa SJS, Bajwa SK, Kaur J, *et.al*. Admixture of clonidine and fentanyl to ropivacaine in epidural anaesthesia for lower abdominal surgery. *Anesth Essays Res* 2010; 4: 9-14.
9. Gupta S, Raval D, Patel M. Addition of Epidural clonidine enhances post operative analgesia. *Anesth Essays Res* 2010; 4: 70-4.
10. Cuchiaro G, Adzick SN, Rose JB, *et.al*. A comparison of Epidural Bupivacaine - Fentanyl and Bupivacaine clonidine in children undergoing the Nuss procedure. *Anaesth Analg* 2006; 103: 322-27.
11. Cho YH, Lee JH, Lee SG, *et. al*. Effects of clonidine added to Ropivacaine in epidural Anesthesia. *Korean J Anesthesiol* 2001; 41: 428-33.
12. Azevedo TCA, Braz JRC. Effects of the association of clonidine to ropivacaine in epidural anaesthesia. *Rev Bras Anaestesiol* 2002; 52: 410-19
13. Engel JM, Hussmann R, Gurtler KH, *et. al*. Dose response relationship of clonidine with epidural administration of ropivacaine in orthopedic procedures of the lower extremities. *Anesthesist* 1998; 47: 565-70.
14. Jyothi, Verma H, Safiya S. A prospective randomized study of combination of epidural bupivacaine with clonidine and bupivacaine for post operative analgesia. *Intern J Anaesthesiol* 2012; 30.
15. Shukla U, Prabhakar T, Malhotra K. Postoperative analgesia in children when using clonidine or fentanyl with ropivacaine given caudally. *J Anesthesiol Clin Pharmacol* 2011; 27: 205-10.
16. Topcu I, Erincler T, Tekin S, *et.al*. The comparison of efficiency of Ropivacaine and Addition of fentanyl or clonidine in patient controlled Epidural Analgesia for Labour. *Int J Anaesthesiol* 2007; 11
17. Forster JG, Rosenberg PH. Small dose of clonidine mixed with low dose ropivacaine and Fentanyl for epidural analgesia after total knee arthroplasty. *Br J Anaesth* 2001; 93: 670-77.
18. Malik P, Manchanda C, Malhotra N. Comparative evaluation of epidural fentanyl and butorphanol for post operative analgesia. *J Anaesth Clin Pharmacol* 2006; 225: 337-82.
19. Azevedo TCA, Braz JRC. Effects of the association of clonidine to Ropivacaine in epidural anaesthesia. *Rev Bras Anesthesiol* 2002; 52: 410-19.
20. Vieira AM, Schnaider TB, Costa AF. Analgesia and sedation of the association of clonidine and Ropivacaine 0.75% for epidural post operative open cholecystectomy. *Rev Bras Anaestesiol* 2003; 53: 586-90.