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Clonidine, Fentanyl or their Combination for Postoperative Epidural Analgesia in Lower Limb Surgeries: Comparative Study

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Abstract

Background: Prolonged post-operative analgesia helps in early ambulation and prevents chronic post-surgical pain. Hence, effectiveness of using a combination of two adjuvants with ropivacainefor epidural analgesia is required to be known. *Objectives:* To compare the effectiveness, duration of post-operative analgesia and side effects of fentanyl and clonidine used alone with ropivacaine or in combination. *Materials and Methods:* 105 American Society of Anaesthesiologists physical statusclass1 and 2 patients with 18 to 70 years of age posted for elective lower limb surgeries under combined spinal epidural technique were randomly assigned into 3 equal groups. Surgery was done under spinal anaesthesia and postoperatively, Group RC received 8ml 0.2% Ropivacaine + Clonidine 60mcg, Group RF received 8ml 0.2% Ropivacaine + Fentanyl 75mcg and Group RFC received 8ml 0.2% Ropivacaine + Clonidine 30mcg + Fentanyl 37.5mcg epidurally. The Visual Analogue Scores, onset of analgesia, peak effect of analgesia, duration of analgesia, haemodynamic parameters and side effects in each group were recorded and statistically analysed with $p<0.05$ considered as significant. *Results:* Group RFC had faster onset of analgesia, earlier peak analgesic effect and longer duration of analgesia compared to group RC and RF. VAS scores were comparable between group RC and RFC. No statistically significant difference between the groups was noted with respect to haemodynamic parameters. Only one patient had nausea and vomiting in group RFC. *Conclusion:* Both clonidine and fentanyl can be used as adjuvants in lower doses without compromising the analgesic efficacy and also lower the incidence of side effects.

Keywords: Postoperativeanalgesia; Epidural; Ropivacaine; Fentanyl; Clonidine.

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Introduction

Post-operative pain may have a great impact on post-surgical outcomes.Adequate analgesia is important to ease patient suffering, improve well-being and to prevent cardiovascular and respiratory complications. Improved pain control can shorten the length of hospital stay, early ambulation and reduce postoperative complications and improve patient satisfaction. Multimodal or balanced analgesia is an ideal approach to prevent postoperative pain. Epidural analgesia is a critical component of multimodal perioperative pain management and improves patient outcome [1,2,3].

Ropivacaine is replacing bupivacaine for epidural analgesia because of its similar analgesic properties, lesser motor blockade and less cardiotoxicity. Decreased motor blockade without pain will help in early ambulation of the patients and prevent complications like deep venous thrombosis,

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pulmonary thromboembolism and pneumonia [4]. Addition of an adjuvant further enhances the analgesic efficacy. Opioids are the gold standard as adjuvants along with local anaesthetics in the central neuraxial blocks. They provide adequate pain relief when given in low doses but can also cause nausea and vomiting, pruritus and respiratory depression when given in high doses. Shorter acting lipophilic opioid like fentanyl is popular as an adjuvant to local anaesthetics. Clonidine inhibits the descending pathway of pain and also acts on spinal α -2 receptors to produce analgesia. It is one of the most popular adjuvant used for paediatric caudal epidural analgesia [5,6].

Since clonidine and fentanyl act through different mechanisms to produce analgesia, the rationale to combine these drugs is that the component drugs may produce analgesia by additive or synergistic mechanisms. And the combination of the adjuvants may allow the usage of reduced doses of each drug with correspondingly fewer dose-related side effects [7].

After searching the literature, we found that very few studies [8,9] have used a combination of clonidine-fentanyl along with ropivacaine for epidural post-operative analgesia. Thus, we conducted a study to evaluate the analgesic efficacy and duration of analgesia along with side effects profile when ropivacaine is added with clonidine or fentanyl or in combination in low doses administered as intermittent boluses via epidural route.

Materials and Methods

One hundred five (105) patients posted for elective lower limb surgeries were selected for the study after taking an informed written consent. Approval from the ethical committee was obtained. The study was conducted from November 2015 to July 2017. The study population was divided by simple random sampling using shuffled sealed opaque envelope method into 3 equal groups (n=35).

Inclusion criteria were patients between 18 to 70 years of age with American Society of Anaesthesiologists Physical Status (ASAPS) class 1 & 2.

Exclusion criteria were any contraindications to neuraxial anaesthesia, sensitivity or allergy to any of the study drugs, pregnant patients, BMI more than 30kg/m^2 and patients shorter than 150 cm and taller than 180 cm.

A routine pre-anaesthetic evaluation was conducted on the evening before surgery and relevant investigations done. The patients were pre-medicated with tablet alprazolam 0.5 mg and tablet ranitidine 150 mg orally at bed time on the previous night before surgery. They were kept nil orally for 6 hours prior to surgery for solid food and 2 hours for clear liquids.On the day of surgery, patient's basal vital parameters were recorded. Monitoring was done using multiparameter monitor having pulse oximetry, Electrocardiogram (ECG), Non-invasive Blood pressure (NIBP). Intravenous line was obtained with an 18-gauge cannula.

With the patients in sitting position under aseptic precautions, epidural space was identified by loss of resistance technique using 18G Tuohy needle via the midline approach at L2-3 inter spinous space. An epidural catheter was threaded for 3 cm inside the epidural space. A test dose of 3ml of 2% lidocaine with 1:200000 adrenaline was injected through the catheter after negative aspiration of blood and cerebrospinal fluid. After waiting for 5 min to rule out intravascular or intrathecal placement of the catheter, lumbar puncture was performed at the level of L3-4 through a midline approach using 25G Quincke spinal needle and 3ml of hyperbaric bupivacaine was injected after confirming free flow of clear cerebrospinal fluid. Epidural catheter wasfixed, patients were turned to supine position and surgery was allowed to be started. If the surgery outlasted the spinal anaesthesia and patient required epidural top-ups, such patients were excluded from the study.

After the surgery, patients were shifted to post-operative recovery room. Analgesia effect was measured using Visual analogue scale (VAS). First epidural top-up of the study drug was given once the VAS score was 5 and above.

Group RC – received 8ml of 0.2% Ropivacaine + Clonidine 60mcg

Group RF – received 8ml of 0.2% Ropivacaine + Fentanyl 75mcg

Group RFC – received 8ml of 0.2% Ropivacaine + Fentanyl 37.5mcg + Clonidine 30mcg

The study drug was prepared by an anaesthesiologist who was involved with randomisation, but was not involved further in the study. The anaesthesiologist who administered the test drug was also the observer of the parameters. Thus, the observer and the patients were blinded for the study drug. The total volume of the drug injected was made to 10ml in all three groups by adding 0.9% normal saline.

The VAS score, heart rate, systolic, diastolic and mean arterial blood pressure, respiratory rate, SpO_2

and ECG were monitored at 0, 5, 15, 30 and 60 min and then hourly from the time of giving the study drug tillpatient's VAS score was 5 or more and the rescue analgesic as top-up with 0.2% ropivacaine with 75 mcg of fentanyl was given.

The following parameters were studied based on the VAS scores

- Onset of analgesia- From the administration of the first epidural top-up to the time required for the VAS score to decrease by two from the initial VAS score
- Peak effect of the drug- From the administration of the first epidural top-up to the time required for the VAS score to decrease to 1 or 0.
- Duration of analgesia- From the administration of the first epidural top-up until the patient requires a rescue analgesic top-up.

Patients were also monitored for any side effects like nausea, vomiting, sedation, respiratory depression and pruritus.Ramsay sedation scoring was used to assess the sedation

Based on the previous study [10] and considering a prolongation of duration of analgesia of 60 minutes as significant with α =0.05 with power of 80% sample size was calculated to be 29 in each group. A sample size of 105 with 35 patients in each group were taken to compensate for the drop outs.

All the statistical calculations were done using SPSS version 21 for windows. Descriptive statistics were done by calculating mean, standard deviation, range and proportion appropriately. The inferential statistics were done using Chi-square test, Repeated measure ANOVA, One-way ANOVA with post hoc test and Kruskal-Wallis test.

Significant figures: $p>0.05$ is not significant, $p<0.05$ is significant, $p<0.01$ is highly significant.

Results

The demographic profile of the patients comparing age, sex, weight, height and also type of surgeries show no statistically significant difference and were comparable in all the three groups in our study. All base line vital parameters were similar in all three groups (Table 1).

The mean onset of analgesia and peak analgesic effect were achieved faster in group RFC (Table 2). Mean onset of analgesia in group RC was 7.92±1.21 min, in group RF is 6.51±1.53 min and in group RFC is 5.9±1.24 min. There was statistical significant difference between group RC and RFC (P=0.03) but there was no significant difference between group RF and RFC (P=0.1) and group RC and RF (P=0.09). The peak effect in group RC was seen at 18.23±2.21 min, in group RF at 16.11±1.96 min and in group RFC at 15.34±2.36 min. There was statistically significant difference between Group RC and RFC (p=0.02) and between group RC and RF (p=0.03).The difference was insignificant between group RF and RFC (p=0.07)

Table 1: Comparison of baseline haemodynamic parameters and duration of surgery between the three groups

	Group						P
	Ropivacaine with clonidine		Ropivacaine with fentanyl		Ropivacaine with clonidine and fentanyl		
	Mean	SD	Mean	SD	Mean	SD	
VAS_baseline	5.89	.87	6.20	.80	6.06	.80	0.3
HR_baseline	85.11	13.45	82.03	10.50	89.91	12.17	0.05
SBP_baseline	128.49	14.13	130.26	12.93	130.74	9.25	0.7
DBP_baseline	75.60	9.40	72.51	11.33	76.40	8.71	0.2
MAP_baseline	92.77	9.96	91.80	10.22	94.40	8.28	0.5
RR_baseline	13.20	1.08	13.11	1.05	13.71	1.20	0.06
Duration of surgery	183.65	10.12	187.24	9.87	190.05	6.31	0.07

Table 2: Comparison of mean onset of analgesia, mean peak analgesic effect and mean duration surgery (minutes) between the three groups

	Ropivacaine with Clonidine (RC)	Ropivacaine with Fentanyl (RF)	Ropivacaine with Clonidine and Fentanyl (RFC)	P value
Mean onset of analgesia	7.92±1.21	6.51±1.53	5.9±1.24	0.01
Mean peak analgesic effect	18.23±2.21	16.11±1.96	15.34±2.36	0.02
Mean duration of analgesia	188.40±27.60	187.29±15.90	199.77±13.21	0.017

Group RFC had longer duration of analgesia compared to the other two groups (Table 2). The mean duration of analgesia in Group RC was 188.40±27.60 min, in Group RF was 187.29±15.90 min and in Group RFC was 199.77±13.21 min. There was statistically significant difference between group RC and RFC (p=0.017) and between group RF and RFC (p=0.03). There was no significant difference between group RF and RC (p=0.12)

We observed a decreasing trend in the VAS scores over time in all three groups. There was statistically significant difference in the VAS scores between RC and RF groups (p=0.001) and RF and RFC groups (p=0.011). The analgesia with RC and RFC were almost comparable (p=0.9). The results of our study indicate that patients in RC and RFC group had better analgesia. All the patients in the three groups had VAS score less than 1 upto 120 minutes. Although statistically significant difference was there among the groups, clinically it was not significant.

There was no statistical significant difference in the incidence of side effects between the three groups (p=0.055) (Table 3). 14.3% of the patients in RC group and 5.4% in RF group had sedation (score ≥4). Nausea and vomiting was seen in 2.7% of the patients in RF group. Only one patient (2.85%) in RFC group had significant sedation.

The haemodynamic parameters like heart rate, systolic, diastolic and mean arterial blood pressure and respiratory rate were comparable in all three groups and were not statistically significant (Figure 1,2,3,4). There was no significant bradycardia, hypotension or respiratory depression observed in any group.

Table 3: Comparison of side effects between the three groups

	Ropivacaine with Clonidine (RC)		Ropivacaine with Fentanyl (RF)		Ropivacaine with Clonidine and Fentanyl (RFC)	
	Number of patients	Percentage	Number of patients	Percentage	Number of patients	Percentage
Nil	30	85.7	32	91.9	34	97.15
Sedation (score≥4)	5	14.3	2	5.4	1	2.85
Nausea and Vomiting	0	0	1	2.7	0	0

P=0.055

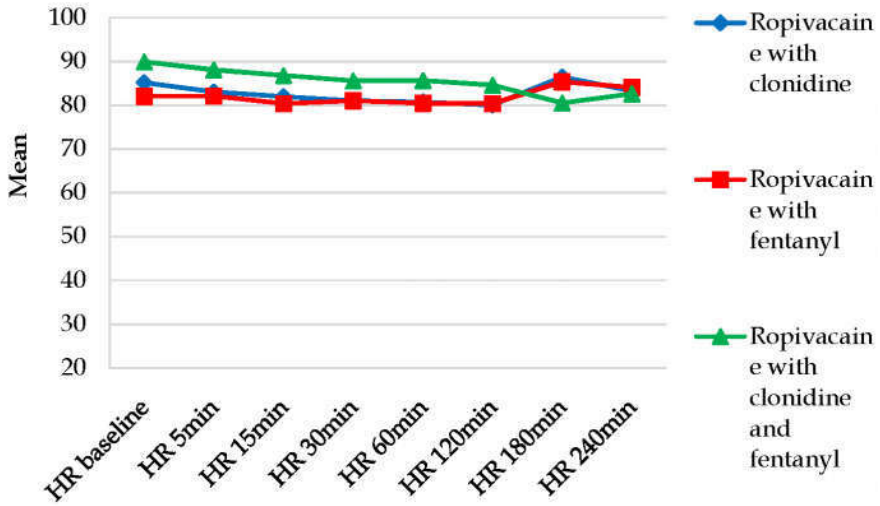

Fig. 1: Mean Heart rate (per min) at various time intervals

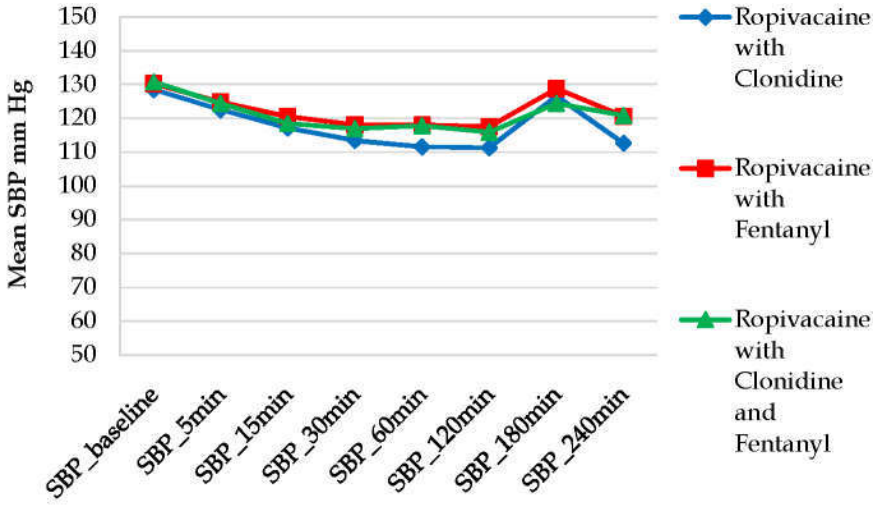

Fig. 2: Mean Systolic Blood Pressure (SBP) at various time intervals (mm Hg)

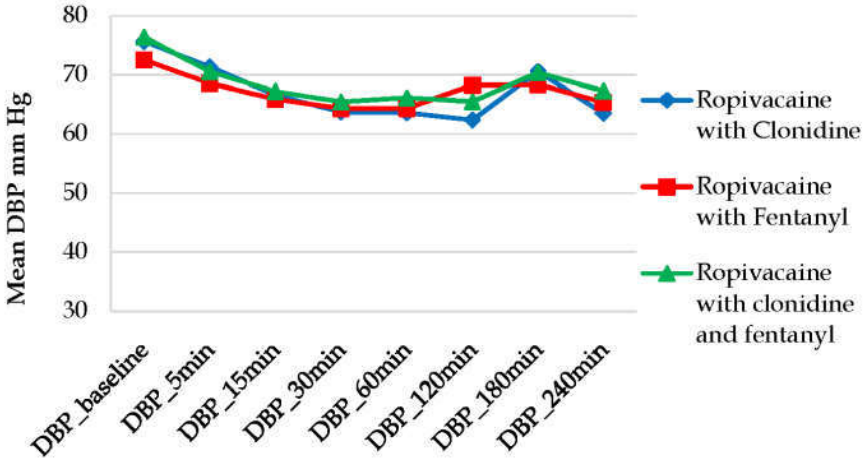

Fig. 3: Mean Diastolic Blood Pressure (DBP) at various intervals (mm Hg)

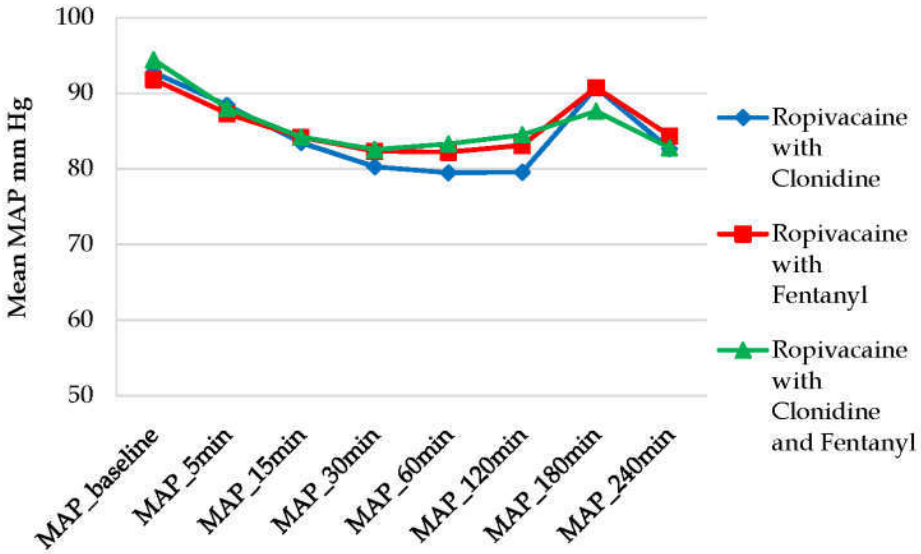

Fig. 4: Mean Mean Arterial Pressure (MAP) (mm Hg) at various intervals

Discussion

Epidural analgesia is a very effective route for post-operative pain relief. The most commonly used epidural local anaesthetic for post-operative analgesia is ropivacaine because of its less motor blockade and decreased cardiotoxicity. The duration of action of ropivacaine when used alone will be short and hence requires adjuvants to prolong the analgesia. Opioids like fentanyl and α2 agonists like clonidine are the most commonly used adjuvants along with ropivacaine.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 [10,11].

Many studies have found that 0.2% ropivacaine is better for providing effective post-operative analgesia without producing motor blockade [12,13]. Many studies have found the ideal concentration of ropivacaine for post-operative analgesia is 8 ml of 0.2% for intermittent boluses. Hence we have taken 8ml of 0.2% ropivacaine which was recommended for lumbar epidural analgesia [14]. 8ml of 0.2% ropivacaine with adjuvants like clonidine and fentanyl for postoperative analgesia was found it to be effective [8,15,16].

The mean onset of analgesia was achieved faster in group RFC compared to the other two groups. Similar results were found in Agarwal et al study [20]. However, in a study done by Ahirwar A et al. [19] comparing 0.125% ropivacaine with addition of fentanyl or clonidine there was no significant difference in the onset of analgesia between the three groups.

The peak analgesic effect was achieved faster in group RFC in our study compared to the other two groups but there is no statistically significant difference between RF and RFC group. This shows that even after reducing the dose of fentanyl combining clonidine will improve the time for peak effect of analgesia.

The mean duration of analgesia was prolonged in group RFCcompared to group RC and RF.Addition of Fentanyl and clonidine to ropivacaine 0.75% for epidural anaesthesia showed longer duration of action than with addition of fentanyl alone [9]. There is no statistically significant difference between RF and RC group but there is statistically significant difference between RFC and RC/RFC and RF group. VAS score was better with RFC compared to RF and RC groups which was significant statistically (p value 0.01). Although statistically significant difference was there among the groups, clinically it was not significant.

Clonidine produces dose dependent spinal cord anti-nociception mainly through stimulation of α2 adrenoceptors in the dorsal horn, mimicking the activation of descending inhibitory pathways [17]. Fentanyl when given through central neuraxis acts on spinal opioid receptors and also being highly lipophilic gets into circulation faster and acts on supraspinal opioid receptors. So both these drugs when used as adjuvants to local anaesthetics produce a better and longer duration of analgesia. This has been confirmed by various studies. When these drugs have to be used alone with local anaesthetics, the dose required is higher. This was found out by our study when we used 75 mcg fentanyl and 60 mcg clonidine. When these drugs used in dose mentioned in our study the side effects would also increase. This was again found in our study where in there was increase in sedation in patients with clonidine group and increased incidence of nausea and vomiting in patients with fentanyl group.

Hence anhypothesis was made that the combination of these two adjuvants would produce minimal side effects without comprising either the quality or duration of analgesia. The same thing was observed by various authors when they combined clonidine and fentanyl along with ropivacaine either administered as single doses or as infusions. Study done by Foster et al who compared combination of clonidine 2 mcg/ml and fentanyl 5 mcg/ml with 0.2% ropivacaine used as infusion with a rate 3 to 7 ml/hr in patients with Total Knee Arthroplasty for post-operative analgesia. In this study authors found out that clonidine produces prolonged duration of analgesia and reduces the need for rescue pain medication and decreases the incidence of post-operative nausea and vomiting.

In another study done by Bajwa et al. who used either fentanyl or clonidine alone in the dose of 75 mcg or a combination of these two drugs in dose of 37.5 mcg each along with 0.75% ropivacaine as epidural anaesthesia for lower abdominal surgeries. The authors found out that the combination of fentanyl and clonidine in half the doses have the same quality and duration of analgesia in comparison with fentanyl group and significant decrease in the

incidence of post-operative nausea and vomiting (40% in fentanyl group vs 10% in RCF group).

In another study conducted by Bahaddur Singh et al. who used 0.75% ropivacaine along with 50 mcg fentanyl alone or a combination of 50 mcg fentanyl and 50 mcg clonidine. In this study the dose of fentanyl in combination group was not reduced. The authors found out that there is a significant prolongation of analgesia without reduction in incidence of nausea and vomiting in the combination group. This shows that the fentanyl dose if not reduced would produce the same incidence of nausea and vomiting in spite of adding clonidine. 14.3% of the patients in RC group and 5.4% in RF group had sedation (score ≥ 4). Nausea and vomiting was seen in 2.7% of the patients in RF group. One patient in RFC group had significant sedation. Ropivacaine plus fentanyl caused higher incidence of sedation thanropivacaine plus clonidine and ropivacaine + fentanyl + clonidine [8]. 40% of the patients had nausea/vomiting and 30% of the patients had sedation in the ropivacaine fentanyl group. They have used epidural fentanyl intraoperatively and for postoperative analgesia which might be the reason for higher incidence of side effects. However, there was no significant difference in side effects between ropivacaine-fentanyl and ropivacaine-fentanyl-clonidine groups in one of thesimilar studies [17].

Thus, the addition of low doses of both fentanyl and clonidine to ropivacaine has resulted in reduction of side effects without affecting the quality of analgesia.

The sample size may not be adequate to observe a statistically significant difference between the groups with regard to side effects. The duration of action and side effects were lesser compared to other studies, as we have studied the effects of only one top-up. The study might have given significant results because of the additive effects of multiple top-ups if the study period had been longer.

Conclusion

Thus, it can be concluded that addition of small dose clonidine and fentanyl to 0.2% ropivacaine produced a faster onset of action, earlier peak analgesic effect, prolonged duration of analgesia, stable haemodynamic parameters and also lower incidence of side effects when given epidurally for post-operative pain relief in lower limb surgeries.

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