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Admixture of Clonidine and Fentanyl to Ropivacaine in Epidural Anaesthesia for Lower Abdominal Surgery and Lower Limb Surgery

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ABSTRACT

Aims and Objectives: *To evaluate and compare the clonidine-ropivacaine combination with fentanyl-ropivacaine in epidural anaesthesia and also to find out whether addition of clonidine can reduce the dose of fentanyl in epidural anaesthesia.*

Methodology 60 patients of ASA grade I and II between the ages of 21 and 55 years, who underwent lower abdominal surgeries and lower limb surgeries, were included randomly into three clinically controlled study groups comprising 20 patients in each. They were administered epidural anaesthesia with ropivacaine-clonidine (RC), ropivacaine-fentanyl (RF), or ropivacaine-clonidine-fentanyl (RCF). Pre-operative and postoperative block characteristics as well as hemodynamic parameters were observed and recorded. Statistical data were compiled and analyzed using non-parametric tests and P<0.05 was considered as significant value.

Results: *The demographic profile of the patients in all the three groups was similar as were the various block characteristics. The reduction of clonidine and fentanyl in the RCF group did not make any significant difference (P>0.05) in the analgesic properties of drug combination and hemodynamic parameters as compared to RC and RF groups. However, there was significant reduction of incidence of side effects in the RCF group (P<0.05) and it resulted in increased patient comfort.*

Conclusions: *The analgesic properties of the clonidine and fentanyl when used as adjuvant to ropivacaine in epidural anaesthesia are almost comparable and both can be used in combination at lower dosages without impairing the pharmacodynamic profile of the drugs as well as with a significant reduction in side effects.*

KEYWORDS : Epidural anaesthesia, Ropivacaine, Clonidine, Fentanyl

INTRODUCTION

Feeling of pain is one of the most important emotional determinants which dominate the perception of patients who undergo the surgical procedures. The thoughts of pain create a lot of unknown fears, anxiety and stress in the minds of such patients despite administration of adequate premedication. Even the post-operative period can acquire the dimensions of a nightmare once a patient starts experiencing the agony of excruciating pain if not given proper attention.

Epidural anaesthesia and analgesia is widely regarded as a boon for such patients as it can provide a relief from pain for a longer duration and the facility of further top-ups and continuous infusion of the analgesic drugs through epidural catheter thus provides an uneventful and smooth recovery. Epidural ropivacaine has increasingly replaced bupivacaine because of its similar analgesic properties, similar motor blockade and decreased propensity of cardiotoxicity. Local anaesthetic and opioid combination was shown to be more effective in epidural analgesia for post-operative pain as their effects started rapidly and lasted longer when compared with local anaesthetic given alone.[1]

Epidural fentanyl has been widely used in neuraxial blockades as a better alternative to morphine as far as opioid-induced complications and side effects are concerned. The main site of action of fentanyl is the substantia gelatinosa in the dorsal horn of spinal cord, where it blocks the neural fibers carrying pain impulses both at pre-synaptic and post synaptic levels. As fentanyl has no effect on sympathetic and motor neurons, it has advantages over local anaesthetics. Addition of opioid to local anaesthetics gives the opportunity to use more diluted local anaesthetic solutions for better analgesia, and reduces systemic toxicity risk and motor block incidence of local anaesthetics.[2]

Clonidine is a partial alpha-2 adrenergic agonist that has a variety of different actions including antihypertensive effects as well as the ability to potentiate the effects of local anaesthetics. It has been used as an adjuvant to epidural local anaesthetics and opioids to improve the quality of analgesia after major abdominal surgeries and lower limb surgeries. It can provide pain relief by an opioid independent mechanism as it directly stimulates pre- and postsynaptic 2-adrenoceptors in the dorsal horn gray matter of the spinal cord, thereby inhibiting the release of nociceptive neurotransmitters. At low doses, epidural clonidine improves the quality of anaesthesia, reduces the dose requirement of the anaesthetic agent and provides a more stable cardiovascular course during anaesthesia.[3]

MATERIALS AND METHODS

After obtaining approval from the institution, the present study was done in our institution and a informed written consent was taken from the patients after explaining to them in detail about the implications of the anaesthetic and the surgical procedure.

INCLUSION CRITERIA-

60 patients of ASA grade I and II between the ages of 20 and 50 years, who underwent lower abdominal surgeries and lower limb surgeries.

EXCLUSION CRITERIA-

- Patients with hematological disease,
- bleeding or coagulation test abnormalities,
- psychiatric diseases,
- diabetes,
- history of drug abuse and
- allergy to local anaesthetics of the amide type.

Patients were assigned to one of the following three treatment groups:

1. Ropivacaine + clonidine (RC)
2. Ropivacaine + fentanyl (RF)
3. Ropivacaine + clonidine + fentanyl (RCF)

All patients were explained about the sequence of anaesthetic procedure and a good IV access was secured in the operation theater and all monitoring devices were attached which included devices measuring heart rate, ECG, SpO2, non invasive blood pressure and respiratory rate. Baseline hemodynamic parameters, respiratory rate, ECG and SpO2 were recorded.

Patients were administered epidural block in a sitting position with an 16 gauge Touhy needle and epidural space was localized and confirmed by loss of resistance. Epidural catheter was secured 3-5 cm into the epidural space and confirmation for correct placement of the catheter was done by injecting 3 ml of 2% lignocaine HCl solution containing adrenaline 1:200,000. After 4-6 minutes of test dose, patients in group RC received 20 ml of 0.75% ropivacaine and 75 µg of clonidine.

- Group RF patients were administered 20 ml of 0.75% ropivacaine and 75 µg of fentanyl, while
- Group RCF patients received 20 ml of 0.75% ropivacaine and 37.5 µg of clonidine and 37.5 µg of fentanyl.

Surgical procedures were initiated only after the establishment of adequate surgical anaesthetic effect with minimum level up to T6-7 dermatome. The bilateral pin-prick method was used to evaluate and check the sensory level while a modified Bromage scale

- 0 - no block
- 1 - inability to raise extended leg
- 2 - inability to flex knee and
- 3 - inability to flex ankle and foot

was used to measure the motor blockade effect at 5, 10, 15, 20, 25 and 30 minute intervals after the epidural administration of the drugs.

The following block characteristics were observed and recorded :
Initial period of onset of analgesia, The highest dermatomal level of sensory analgesia, The complete establishment of motor blockade, Hemodynamic parameters, included HR, ECG, mean arterial pressure, SpO2 and respiratory rate were monitored continuously.

Initial bolus dose timing was assumed to be the baseline time. Recordings were made every 5 minutes until 30 minutes and at 10 minute intervals, and thereafter up to 60 minutes and then at 15 minute intervals for the next hour and finally at 30 minutes in the third hour. Hypotension was treated with inj. mephenteramine 3-6 mg in bolus doses and HR<55 beats/min was treated with 0.3 mg of inj. atropine. Intravenous fluids were given as per the body weight and operative loss requirement, with no patient requiring blood transfusion. The patients were given supplementary O_2 with the help of face mask.

During the surgical procedure, any adverse event like anxiety, nausea, vomiting, pruritis, shivering, bradycardia, or hypotension was recorded. Nausea and vomiting were treated with 4-6 mg of i.v. ondansetron. During and at the end of surgery, the vitals were recorded in the recovery room also at 1, 5, 10, 20 and 30 minute interval.

Sedation was evaluated by five-point scale
1 - wide awake
2 – drowsy
3 – dozing
4 – mostly sleeping
5 – awakening only when aroused.

The onset of pain was managed by 50 mg tramadol diluted up to 5 ml and given slowly via epidural catheter. Comparability of the groups was analyzed with analysis of variance test (ANOVA). Student's two tailed "t" test and chi square test were applied to analyze the parametric data (monitored hemodynamic parameters and block characteristics).For all statistical analysis, the value of *P*<0.05 was considered as significant.

RESULTS
Sixty patients were enrolled in this study and their data were eligible and were processed for statistical analysis. The three groups RC, RF, RCF were comparable with regard to demographic data as shown in table.

	RC (n=20)	RF (n=20)	RCF (n=20)
Age (years)	29.28 ± 8.64	28.94 ± 7.48	27.20 ± 9.36
Height (cm)	168.70 ± 6.62	171.04 ± 5.88	170.92 ± 6.34
Weight (kg)	44.84 ± 8.32	42.16 ± 6.94	43.22 ± 7.56
ASA (I/II)	15/5	14/6	16/4
Mean duration of surgery (minutes)	98.86	96.78	97.54
Gender M/F	17/3	18/2	19/1

There was no statistically significant variation between the three groups with regard to age, height and weight (*P*>0.05). Duration of surgery was comparable in all the groups and did not show any significant variation.

Onset of anaesthesia was faster in group RF as compared to group RC and RCF as shown :

Anaesthetic characteristics (mean)	RC (n=20)	RF (n=20)	RCF (n=20)	Intergroup comparison		
				RC-RF	RC-RCF	RF-RCF
Onset time at T_{10}-T_{12} (minutes)	8.24 ± 3.56	7.04 ± 2.08	9.02 ± 3.42	–	–	Significant
Maximum sensory level	T6-7	T5-6	T6-7	–	–	–
Time to maximum sensory blockade level (minutes)	13.38 ± 5.22	10.16 ± 3.94	14.86 ± 3.80	–	–	–
Time to complete motor block (minutes)	20.58 ± 4.96	16.92 ± 3.84	21.64 ± 3.80	–	–	Significant
Mephentesamine requirement (mg)	Not required	Not required	Not required	–	Significant	Significant

However, once sensory level was established at T6-T7 level, there was no noticeable difference in sensory anaesthesia in any of the three groups throughout the surgical procedure.The establishment of complete motor blockade was earlier in the RF group which was statistically significant, when compared to RCF (*P*<0.05).Mean arterial pressure and mean heart rate were comparable in all the three groups during the entire procedure as well as post-op, which was a non-significant value on statistical comparison (*P>0.05)*. Similarly, pulse oximetry trends did not show any significant variation in patients of all the three groups.

The incidence of other side effects like shivering, headache, urinary retention and respiratory depression was almost comparable and statistically non significant.

Side effects	RC	RF	RCF
Nausea/vomiting	0	1	1
Sedation	0	0	1
Respiratory depression	0	0	0
Headache	1	1	0
Dry mouth	6*	0	1
Shivering	2	1	1
Urinary retention	0	1	0

DISCUSSION
The present study evaluate rigorously the effects of clonidine on dose reduction concentration of fentanyl, when administered as an adjuvant to ropivacaine in epidural anaesthesia for lower abdominal surgeries and lower limb surgeries .The analgesic effects of the ropivacaine-clonidine combination are equivalent to those of the ropivacaine-fentanyl.

The results of the present study demonstrate that it is possible to decrease the unwanted side effects of epidural fentanyl by reducing the dose of fentanyl and adding an equivalent dose of clonidine to the epidural solution, and that too without impairing the analgesic effect. The reduction in opioid requirement does have a significant effect on reduction of incidence of nausea and vomiting, beneficial effects on respiratory functions as well as reduction of other opioid-related side effects.

Turner G, Scott DA et al did a comparison of epidural ropivacaine infusion alone and with three different concentration of fentanyl for 72 hours of postoperative analgesia following major abdominal surgery. He also studied the variables studied by us in three groups and used same statistical analysis.[3]

Forster JG, Rosenberg PH studied small dose of clonidine mixed with low-dose ropivacaine and fentanyl for epidural analgesia after total knee arthroplasty. The purpose of this study was to characterize the pharmacodynamics and pharmacokinetics of three concentrations

of the new long-acting amide local anesthetic, ropivacaine, given for elective, lower-extremity orthopedic procedures. Three groups of five patients each received either 0.57%, 0.75%, or 1.0% ropivacaine. Upper and lower levels of analgesia to pinprick were determined at frequent intervals until normal sensation had completely returned. Motor blockade assessed by use of a modified Bromage scale after each determination of level of analgesia. No significant differences were found between the three groups in terms of onset or recovery of motor and sensory blockade. Total durations of sensory blockade were 5.4 +/- 0.7, 6.5 +/- 0.4, and 6.8 +/- 0.8 h, respectively. No statistically significant differences were noted between the three groups in term of clearance (CL). Pharmacokinetic and pharmacodynamic characteristics of epidural ropivacaine are similar to those of epidural bupivacaine in humans. The observations are comparable to our study[4]

De Negri P, Ivani G, Visconti C et al did their work on the dose-response relationship for clonidine added to a postoperative continuous epidural infusion of ropivacaine in children. They concluded that epidurally administered clonidine enhances the quality and duration of postoperative analgesia when it is used as an adjunct to local anesthetics in children. A clear dose-response relationship could be identified for a continuous infusion of epidural clonidine, with clonidine dosages in the 0.08–0.12 $\mu g \cdot kg^{-1} \cdot h^{-1}$ range providing improved postoperative analgesia. Analgesia was improved without any signs of increased sedation or other side effects. The adjunct use of epidural clonidine in the dosage range of 0.08–0.12 $\mu g \cdot kg^{-1} \cdot h^{-1}$ appears effective and safe for use in children. These findings are in close relation to our study[5]

Bajwa SJ et al did a study with admixture of clonidine and fentanyl to ropivacaine in epidural anesthesia for lower abdominal surgery. The reduction of clonidine and fentanyl in the RCF group did not make any significant difference ($P>0.05$) in the analgesic properties of drug combination and hemodynamic parameters as compared to RC and RF groups. However, there was significant reduction of incidence of side effects in the RCF group ($P<0.05$) and it resulted in increased patient comfort. The analgesic properties of the clonidine and fentanyl when used as adjuvant to ropivacaine in epidural anesthesia are almost comparable and both can be used in combination at lower dosages without impairing the pharmacodynamic profile of the drugs as well as with a significant reduction in side effects. Their findings are almost similar to our study [6]

We did not observe a single case of respiratory depression in our study and this probably may be due to smaller dose of fentanyl we used in our study. Alpha-adrenergic agonists produce pain through an opioid independent mechanism and may be alternatives to opioid for combination with local anaesthetics for analgesia during surgery.

The 75 µg clonidine is the optimal epidural dose when added to bupivacaine for analgesia, as smaller doses were not serving the purposes of adequate analgesia while larger doses were associated with bradycardia, hypotension, sedation and other side effects.

CONCLUSIONS

The study helped us to conclude the established facts about the epidural usage of clonidine and fentanyl, when added as an adjuvant to ropivacaine. Though both the drugs have side effects when used in epidural route in optimal doses, the spectrum of side effects of clonidine is much narrower than that of fentanyl.

Combination of clonidine with fentanyl does allow the reduction of individual doses of these drugs through epidural route. The combination of clonidine and fentanyl in half than the optimal doses has almost similar pharmacokinetic and pharmacodynamic profile when used with ropivacaine in epidural anaesthesia. Therefore, we recommend that the combination of fentanyl and clonidine can be safely used with ropivacaine and that too in half the doses as they have got a synergistic adjuvant effect.

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