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Research Communication

ADDITION OF CLONIDINE REDUCE DOSE OF FENTANYL AND ROPIVACAINE IN EPIDURAL ANAESTHESIA

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Abstract:
Aim of Study: *To find out effect of clonidine on fentanyl and Ropivacaine requirement to produce Epidural Anesthesia.*
Material and Method: *After Institute ethical clearance and consent from patient, 60 patients of ASA I and II were studied in 3 groups. All patients were premedicated with ranitidine and metoclopramide. In operation room epidural catheter was placed. After recording base line hemodynamic parameters, drugs were mixed in 20ml syringe according to 3 different groups and given through epidural catheter.*
Observation and Result: *All patients were monitored for hemodynamic changes and recorded at different time interval. Data were analyzed using different tests. Patients of all 3 group have similar level of anesthesia with lower adverse effects hypotension which was more in clonidine, fentanyl and ropivacaine group.*
Conclusion: *With this study we concluded that adition of clonidine in fentanyl and ropivacaine significantly reduces the amount of ropivacaine and fentanyl required to produce epidural anesthesia.*

Keywords: *Anesthesia epidural, clonidine, fentanyl, ropivacaine.*

Background

The thoughts of pain create fears, anxiety and stress in the minds of patients despite administration of adequate premedication. Epidural anesthesia and analgesia 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. In recent years, ropivacaine has replaced bupivacaine for epidural anesthesia because of its similar analgesic properties, lesser motor blockade and decreased propensity of cardiotoxicity[1]. Though a slightly larger dose of ropivacaine is required as compared to bupivacaine to achieve the analgesic and anesthetic effects, the addition of an adjuvant can decrease the dose of ropivacaine required, thereby eliminating side effects associated with larger doses of ropivacaine. [2,3]

Opioids, given by epidural route to relieve post-op pain, provide adequate analgesia when given in low doses, but can also cause mental confusion, somnolence, nausea and vomiting, itching and respiratory depression when given in high doses.[4,5] Local anesthetic and opioid combination was shown to be more effective in epidural analgesia for post-op pain as their effects started rapidly and lasted longer when compared with local anesthetics given alone.[6] 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 anesthetics. It has been used as an adjuvant to epidural local anesthetics and opioids to improve the quality of analgesia after major abdominal surgeries.[7,8] 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.[9]

Aim of Study

To find out effect of clonidine on fentanyl and Ropivacaine requirement to produce Epidural Anesthesia.

Material and Method

After taking Institute ethical committee clearance and written informed consent from the patients a double blind randomized study was performed. The study was conducted in department of Anesthesiology, Institute of Medical Sciences, Banaras Hindu University in 60 ASA grade I and II patients of either gender, aged between 16 to 60 years scheduled for various infra umbilical surgeries. The patients with hematological disease, bleeding or coagulation test abnormalities, psychiatric diseases, diabetes, history of drug abuse and allergy to local anesthetics of the amide type were excluded from the study. The sample size was decided by previous study with α =0.05, β=0.20 and power of 80%. Consequently, 60 patients were allocated by computer generated random number system to one of three groups, each group comprising 20 patients.

Group RC : Inj. Ropivacaine (0.75%) 20mL & clonidine 50µg.
Group RF : Inj. Ropivacaine (0.75%) 20mL + fentanyl 50µg.
Group RFC : Inj. Ropivacaine (0.50%) 20mL + clonidine 25µg + fentanyl 25µg.

Confirming of eligibility for inclusion and obtaining of written inform consent, the patients were explained about the sequence of anesthetic procedure in the pre-op room and a good IV access was secured. Thereafter, the patients were shifted to the operation theater and all monitoring devices were attached which included measuring heart rate (HR), ECG, SpO2 , noninvasive blood pressure (NIBP) and respiratory rate. Baseline hemodynamic parameters, respiratory rate, ECG and SpO2 were recorded. The anesthesia resident who prepared the syringes was given a written set of guidelines about the drug preparation, and was unaware of the operation theater team and the patients. 1hr. before proposed surgery Inj. Ranitidine 50mg + Inj. Metoclopramide (10mg) was given to all patients through intra venous route. Patients were preloaded with 10mL/kg of crystalloid before the proposed procedure.

With proper explanation to patient and under strict aseptic measures L_{3-4} interspace was palpated. Local anesthetic infiltration of skin and subcutaneous tissues was performed at lumbar level L_{3-4} with lignocaine + adrenaline 2% 1-2 ml. Thereafter, the epidural space was localized and confirmed with the loss of resistance to saline technique using an 18-gauge Tuohy needle. An epidural catheter was then inserted into the epidural space in a cephalic direction and aspirated for detection of cerebrospinal fluid or blood. After the catheter was secured to skin surface, patients were repositioned. Thereafter, 3ml of 2% lignocaine hydrochloride with 1 in 2 lakh adrenaline solution was administered as a test dose to look for any untoward effect and confirmation of correct placement of catheter. After 4-6 minutes of test dose, patients in group RC received 20ml of 0.75% ropivacaine and 50µg of clonidine. Group RF patients were administered 20ml solution of 0.75% ropivacaine and 50µg of fentanyl, while group RCF patients received 20ml of 0.50% ropivacaine, 25µg of clonidine and 25µg of fentanyl. Surgical procedures were initiated only after establishment of adequate surgical anesthetic effect with minimum level up to T6-7 dermatome. The sensory level was checked and confirmed with pin-prick method bilaterally at 5, 10, 15, 20, 25 and 30 minutes.

Time of onset and degree of sensory block was noted by loss of discrimination to pinprick [Gromley & Hill classification] as follows:

Normal sensation = 0
Blunted sensation = 1
No sensation = 2

The 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, the time to two segment regression of analgesic level from T6 dermatome, regression of analgesic level to L5 dermatome and time to complete recovery. Hemodynamic parameters (HR, ECG, mean arterial pressure (MAP), SpO_2 and respiratory rate) were monitored at every 5 minutes until 30 minutes, and thereafter at 10minute intervals for another 30 minutes, and then at 15 minute intervals for the rest period. Hypotension (defined as systolic arterial pressure

falling more than 20% mm Hg) was treated with Inj. Mephenteramine 5 mg in bolus doses and HR less than 50 beats/min was treated with injection 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 venturi 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 Ondansetron.

After completion of surgery patients were shifted to post anaesthesia care unit. 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 top-up doses of 8 ml of 0.2% ropivacaine and 50µg of clonidine in RC group while 50µg of fentanyl was added to the same volume of ropivacaine in RF group. The patients in RCF group received 25µg each of clonidine and fentanyl along with 8 ml of 0.2% ropivacaine during the first top-up dose. Later on, all the patients received 8 ml of 0.2% ropivacaine for relief of post-op pain.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 (hemodynamic parameters and block characteristics). For all statistical analysis, the value of $P<0.05$ was considered as significant.

Observation and Results

Sixty patients were enrolled and completed the study without any dropout. All three groups RC, RF and RCF were comparable (Table 1). There was no statistically significant variation between the three groups with regard to age, weight, height and body mass index ($P>0.05$). Duration of surgery was comparable in both the groups and did not show any significant variation.

Table1:
Demographic profile of RC, RF& RCF groups

Groups	RC(n=20)	RF(n=20)	RCF(n=20)	p-value
Age(years)	36.70±5.859	38.20±7.223	38.20±7.245	0.725
Height(cm)	163.85±7.876	169.25±9.846	166.00±12.153	0.244
Weight (kg)	64.05±12.094	66.30±12.612	60.65±12.946	0.365
BMI	23.61±2.84	22.87±2.39	22.67±2.77	0.507
ASA(I/II)	8/12	7/13	9/11	0.812
Mean duration of surgery (minutes)	38.62	34.54	35.72	0.053
Gender M/F	9/11	13/7	12/8	0.414

(R-ropivacaine, C-clonidine, F-fentanyl, BMI-body mass index)

Onset of anesthesia was faster in group RF as compared to group RC and RCF as shown in Table 2. Block characteristics were similar in all three groups. Hypotension was treated with incremental doses of mephentermine 3-6mg bolus doses, but the total dose did not cross 18mg in any of the groups. Mephentermine dose used was lowest in the RCF group and statistically significant on intergroup comparison ($P<0.05$) [Table 2].

Table2:
Comparison of initial block characteristics in RC, RF & RCF group

Groups	RC(n=20)	RF(n=20)	RCF(n=20)	**INTERGROUP - COMPARISON**		
Anesthetic characteristics(mean)				**RC-RF**	**RC-RCF**	**RF-RCF**
Onset time at T10-T11(minutes)	11.45±1.93	9.70±2.99	10.75±2.26	0.081	1.000	0.536
Maximum sensory level	T6-7	T5-6	T6-7	_	_	_
Time to maximum sensory blockade level(minutes)	16.75±1.57	16.80±2.41	16.95±2.32	1.000	1.000	1.000
Time to complete motor block(minutes)	20.36±2.85	19.94±3.89	21.45±2.84	1.000	1.000	1.000
Mephentermine requirement (mg)	10.25±3.09	10.65±3.10	7.50±2.56	1.000	0.013	0.004

The regression of block height was similar in all three groups while time for supplementary analgesic doses was prolonged in RCF group, which was statistically significant on analysis (P<0.05). [Table 3]

Table3:
Comparison of per-op and post-op block characteristics in RC, RF & RCF group

Groups	RC(n=20)	RF(n=20)	RCF(n=20)	**INTERGROUP-COMPARISON**		
				RC-RF	**RC-RCF**	**RF-RCF**
Time to two segmental regression (minutes)	85.55±5.29	88.05±3.53	88.60±6.32	0.154	0.169	0.171
Time to segmental regression (L5)	132.30±9.21	130.55±12.41	129.05±6.91	0.521	0.412	0.511
Time to first feeling of pain(minutes)	136.75±6.828	137.80±8.770	135.15±6.635	1.000	1.000	1.000
Time interval b/w postop supplementary analgesic doses(hours)	4.00±.795	4.05±.686	4.80±.894	1.000	0.007	0.013
Total dose of Ropivacaine postop (mg)	160.22±5.74	162.78±4.55	150.43±3.47	0.126	<0.001	<0.001

Table 4 shows that MAP and mean HR were comparable in all the three groups during the entire procedure while post-op MAP was lower in RCF group, which was significant value on statistical comparison (P<0.05) as compared to RF group. Similarly, pulse oximetry trends did not show any significant variation in patients of all the three groups.

Table 4:
Comparison of vital parameters in patients of RC, RF & RCF group

Groups	RC(n=20)	RF(n=20)	RCF(n=20)	**INTERGROUP-COMPARISON**		
				RC-RF	**RC-RCF**	**RF-RCF**
Pre-op HR	87.35±14.132	83.45±16.535	80.75±8.391	1.000	0.465	1.000
Intra-op HR	80.35±10.394	76.50±11.209	75.60±9.428	1.000	0.399	1.000
Post-op HR	79.25±10.814	79.85±12.062	77.45±8.134	1.000	1.000	1.000
Pre-op MAP	84.65±9.304	85.20±8.370	84.35±9.544	1.000	1.000	1.000
Intra-op MAP	78.80±6.396	79.40±3.119	83.60±3.016	1.000	1.000	0.477
Post-op MAP	74.90±4.962	75.70±4.646	64.45±3.265	1.000	<0.001	<0.001
Intra-op Spo2	98.85±1.182	99.00±.918	98.85±.933	1.000	1.000	1.000
Post-op Spo2	99.10±.788	98.80±.768	98.85±.875	1.000	1.000	1.000

Table 5 outlines the various side effects observed during the entire study with all the three drug groups. In the RF group, 40% of the patients experienced nausea/vomiting as compared to 25% in group RC and 5% in RCF, which was statistically significant (P<0.05). Similarly, we observed sedation in 30% of the patients in group RF as compared to 20% in RC group and none in RCF group, which was again statistically significant (P<0.05).The incidence of dry mouth was higher in group RC but was non-significant (P>0.05). The incidence of other side effects like shivering, headache and respiratory depression was almost comparable and statistically non-significant.

Table 5:
Incidence of side effects in patients of all three groups

Groups	RC(n=20)		RF(n=20)		RCF(n=20)		**p-value**
Side effects	**No.**	**%**	**No.**	**%**	**No.**	**%**	
N/V	5	25.0	8	40.0	1	5.0	0.040
Sedation	4	20.0	6	30.0	0	0	0.034
Respiratory depression	0	0	0	0	0	0	
Headache	2	10.0	4	20.0	0	0	1.150
Dry mouth	4	20.0	1	5.0	2	10.0	0.478
Shivering	2	10.0	1	5.0	2	10.0	1.000

Discussion

About 60 patients ASA grade I and II of either gender (Adult age group between 16-60 years) undergoing infra umbilical surgeries were allocated by computer generated random number system to one of three groups (RC,RF,RCF).The attempts made earlier for dose determination concluded that 75µg of 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.[10] But we administered single clonidine dose of 50µg with 0.75% ropivacaine for operative purpose while top-up doses of 50µg clonidine were administered with 0.2% ropivacaine and fentanyl, ropivacaine 0.75% and clonidine 25 µg for the post-op pain relief.

In our study arterial pressure was lower in RCF group in post op period that may be attributed to better pain reduction as well as lesser dose of drugs used in combination. Similar modest haemodynamic changes have been described consistently in many previous studies utilizing clonidine for epidural analgesia.[11, 12, 13] Obviously, in addition to clonidine there are several other factors, which may have influenced arterial pressure and heart rate in our patients, such as fluid loss as a result of bleeding and diuresis, the amounts of administered fluids, and use of diuretics. Nevertheless, in the clinical sense, the lower arterial pressure and heart rate had no obvious deleterious impact on our patients. Sedation is a frequent side effect of clonidine in postoperative analgesia when used in conjunction with opioids.[14] Probably the low dose of clonidine used here does not contribute to sedation in RCF group.

Shukla et al[15] compared the efficacy of clonidine and fentanyl as an additive to ropivacaine given via single shot caudal epidural in 90 children of ASA-I-II aged 3-8 years scheduled for infraumblical surgical procedures were randomly allocated to two groups to receive either ropivacaine 0.25% 1ml/kg + clonidine 2µg/kg (group I) or ropivacaine 0.25% 1 ml/kg + fentanyl 1µg/kg (group II). Caudal block was performed after the induction of general anesthesia. Postoperatively patients were observed for analgesia, sedation, hemodynamics, and side effects/complications. Both the groups were similar with respect to patient and various block characteristics. The analgesic properties and hemodynamics were also comparable in both groups (P > 0.05). Side effects such as respiratory depression, vomiting bradycardia were significantly less in group I than group II (P < 0.05) ensuing more patient comfort. They concluded that the analgesic properties of clonidine and fentanyl as additives to ropivacaine in single shot caudal epidural in children are comparable but clonidine offers a more favourable side effect

profile. The use of clonidine as additive to ropivacaine in caudal epidural is superior choice to fentanyl because of lack of unwanted side effects and increased patient comfort.

Triple combinations of local anesthetic, opioid, and clonidine have been used as intrathecal boluses, either with or without[10, 13] slight improvement of analgesia.[16] Clonidine doses have ranged between 15 and 75μg. In all these studies, the addition of clonidine caused significant hypotension. The advantage of such a single-shot technique may be that no spinal or epidural catheter is required but, on the other hand, hypotension seems to be a problem with the large intrathecal clonidine doses.

Bajwa et al[17] determined the qualitative and quantitative aspects of epidural block of ropivacaine 0.75% versus ropivacaine 0.75% with clonidine for 51 healthy parturients, scheduled for elective cesarean section. Epidural block was administered with 20 ml of ropivacaine 0.75% (group R) and ropivacaine 0.75% and clonidine 75μg (group RC) and anesthetic level was achieved minimum until T6-T7 dermatome.

Onset time of analgesia, sensory and motor block levels, maternal heart rate and blood pressure, neonatal Apgar scores, postoperative analgesic dose and adverse events were recorded. Groups were comparable with regard to demographic data, neonatal Apgar scores and incidences of side effects except for the higher incidence of dry mouth in patients of RC group. Onset of analgesia was much shorter in RC group along with prolonged duration of analgesia. The incidence of bradycardia and hypotension was more in RC group as compared to RF group which was statistically significant. The dose requirement for postoperative pain relief was significantly lesser in RC group. They concluded that the addition of 75μg clonidine to isobaric epidural ropivacaine results in longer, complete and effective analgesia with similar block properties and helped to reduce the effective dose of ropivacaine when compared with plain ropivacaine for caesarean delivery. In our study the total dose consumption of ropivacaine in postoperative period was significantly lesser in RCF group as compared to RF and RC group which may be attributed to longer time interval between supplementary analgesic doses and prolonged effect. Other factor may be the type of surgical procedure. Both fentanyl and clonidine, when used alone in optimal doses in epidural route with ropivacaine, may produce an array of side effects which include sedation, nausea/vomiting, dry mouth, etc. In our study 40% of the patients in RF group experienced PONV as compared to 25% in RC and 5% in RCF group. Sedation was observed in 30% of the patients in RF group, 20% in RC group while in RCF group none of the patient had sedation as the side effect. So the side effects became almost nonexistent when these drugs were used in combination with their dose reduced to half. As a result, the patient in group RCF felt more comfortable in the post-op period and described the anesthesia as the most pleasing experience.

The results of our study demonstrate that it is possible to decrease the unwanted side effects of epidural fentanyl and clonidine 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. Also the total dose consumption of ropivacaine can be significantly reduced when used in conjuction with fentanyl and clonidine in epidural anesthesia.

There are certain limitations of our study. Potential limitation is whether clonidine supplemented analgesia in RCF group is an additive or a synergistic effect. Another possible limitation may be the small sample size.

Conclusion

With this study we concluded that addition of clonidine in fentanyl and ropivacaine significantly reduces the ropivacaine required to produce satisfactory epidural anesthesia.

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