Continuous paravertebral infusion of ropivacaine with or without fentanyl for pain relief in unilateral multiple fractured ribs

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ABSTRACT

Background: Continuous thoracic paravertebral block (TPVB) provides effective analgesia for unilateral multiple fractured ribs (MFR). However, prolonged infusion of local anaesthetic (LA) in high doses can predispose to risk of LA toxicity, which may be reduced by using safer drugs or drug combinations. This study was conducted to assess efficacy and safety of paravertebral infusion of ropivacaine and adrenaline with or without fentanyl to provide analgesia to patients with unilateral MFR. **Methods:** Thirty adults, having ≥ 3 unilateral MFR, with no significant trauma outside chest wall, were studied. All received bolus of 0.5% ropivacaine 0.3 ml/kg through paravertebral catheter, followed by either 0.1-0.2 ml/kg/hr infusion of ropivacaine 0.375% with adrenaline 5 μg/ml in group RA or ropivacaine 0.2% with adrenaline 5 μg/ml and fentanyl 2 μg/ml in group RAF. Rescue analgesia was provided by IV morphine. **Results:** Statistical analysis was performed using unpaired Student *t*-test, Chi-square test and repeated measures ANOVA. After TPVB, VAS scores, respiratory rate and PEFR improved in both groups with no significant inter-group differences. Duration of ropivacaine infusion, morphine requirements, length of ICU and hospital stay, incidence of pulmonary complications and opioid-related side-effects were similar in both groups. Ropivacaine requirement was higher in group RA than group RAF. No patient showed signs of LA toxicity. **Conclusion:** Continuous paravertebral infusion of ropivacaine 0.375% with adrenaline 5 μg/ml at 0.1-0.2 ml/kg/hr provided effective and safe analgesia to patients with unilateral MFR. Addition of fentanyl 2 μg/ml allowed reduction of ropivacaine concentration to 0.2% without decreasing efficacy or increasing opioid-related side-effects.

Key words: Fentanyl, local anaesthetic toxicity, rib fractures, ropivacaine, thoracic paravertebral block

INTRODUCTION

Effective analgesia is the most important aspect of management of patients with multiple fractured ribs (MFR). It allows deep breathing, effective cough and compliance with chest physiotherapy.[1] Continuous thoracic paravertebral block (TPVB) produces sustained improvement in respiratory parameters and oxygenation[1,2] and is as effective as thoracic epidural analgesia[3] for providing pain relief in patients with unilateral MFR. It has low incidence of complications[4]

and very few absolute contraindications.[5] However, local anaesthetic (LA) agents are rapidly absorbed from paravertebral space and can accumulate in blood.[6] Therefore, prolonged infusion of LA in high doses through paravertebral catheter can predispose to risk of LA toxicity. Use of safer drugs or drug combinations can reduce the risk of toxicity and maximum benefits of TPVB can be obtained.

Ropivacaine is a relatively newer long-acting enantiomerically pure (S-enantiomer) amino-amide

LA agent.[7] It has desirable properties of racemic bupivacaine along with greater margin of safety due to its reduced potential for neurotoxicity and cardiotoxicity. Thus, it is a good option for regional anaesthesia and analgesia techniques requiring large volume and infusion rate.[8] Ropivacaine infusions have been used by various routes for different purposes in concentrations varying from 0.1% to 0.5%;[9-13] however, the most effective concentration in terms of analgesia and side-effects is ill defined.[13] A thorough search of English literature could not reveal any randomised controlled trial using ropivacaine infusion through paravertebral route for providing analgesia to patients with multiple fractured ribs. As the recommended concentration of bupivacaine to be used for this purpose is 0.25%[1,3] and the potency ratio of ropivacaine to bupivacaine is 1:1.5,[8] ropivacaine concentration of 0.375% is expected to provide the best results in this group of patients.

Addition of adrenaline to ropivacaine delays its systemic absorption.[14] Use of fentanyl as adjuvant allows reduction of LA dose and thus risk of toxicity.[15] Higher doses of fentanyl (at 4-10 µg/ml concentrations) have been associated with increased incidence of opioid-related side-effects like vomiting and pruritus.[15,16]

Keeping the above facts in mind, the present study was conducted to test the hypothesis that a combination of ropivacaine 0.375% and adrenaline, when given as a continuous thoracic paravertebral infusion, provides good analgesia with minimal side effects in patients with unilateral MFR; and addition of fentanyl in low dose of 2 µg/ml allows reduction of ropivacaine concentration to 0.2% without affecting analgesic efficacy or increasing incidence of opioid-related side effects.

METHODS

This prospective, randomised, double-blind study was conducted after obtaining permission from the Institutional Ethics Committee and informed consent from all the patients. The trial was registered at Clinical Trials Registry of India (CTRI/2012/12/003187). A total number of 30 adult patients of either sex, having >3 unilateral fractured ribs and visual analogue scale (VAS) pain score greater than 30 mm at admission to hospital were included in the study. To randomise these 30 patients, a total of 43 patients were assessed for eligibility [Figure 1].
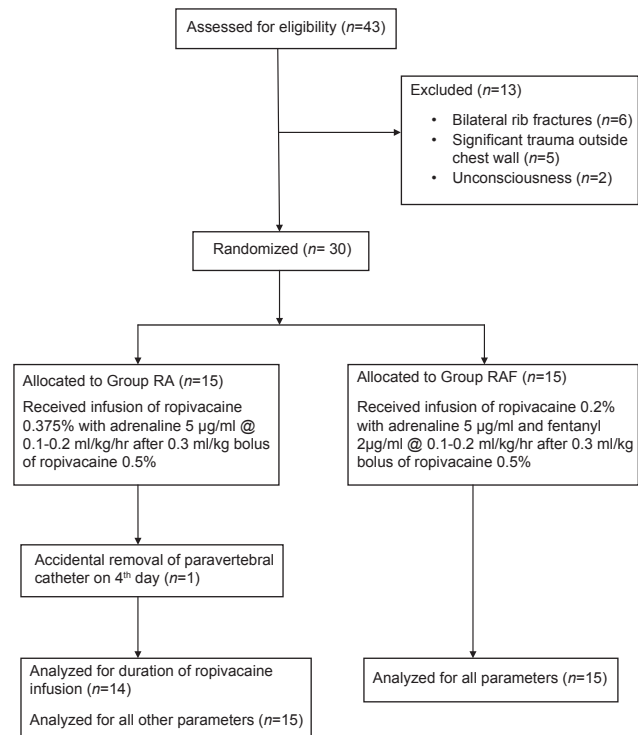

Figure 1: Consort flow diagram

Unconscious patients, patients having unstable cardiac or severely altered mental status, known liver/kidney disease, known allergy to LA drugs, infection at site of needle insertion, pre-existing spinal deformity and those with significant trauma outside chest wall, (e.g., acute spine or pelvic fracture, severe fracture, severe traumatic brain or spinal cord injury or abdominal visceral injuries) were excluded.

The patients were randomly allocated, using sealed envelope technique, to one of the two groups of 15 patients each. All patients received continuous thoracic paravertebral infusion for pain relief. Patients in both groups received bolus of 0.3 ml/kg of ropivacaine 0.5% which is the usual LA dose recommended in the literature for management of multiple rib fractures,[6] followed by continuous infusion at rate of 0.1-0.2 ml/kg/hr. Patients in Group RA received infusion of ropivacaine 0.375% with adrenaline 5 µg/ml; whereas Group RAF patients received ropivacaine 0.2% with adrenaline 5 µg/ml and fentanyl 2 µg/ml through paravertebral catheter. The person preparing solutions for infusion was different from the person recording pain scores and other parameters in intensive care unit (ICU).

Cardiovascular stability was achieved and surgical procedures e.g., drainage of pneumothorax or haemothorax, if required, were performed. Patients'

demographic data, injury data and haemodynamic status on admission were recorded. Selected patients were shifted to ICU and written informed consent was taken. Monitoring during and after TPVB included non-invasive blood pressure, electrocardiogram and arterial oxygen saturation (SpO_2).

TPVB was performed under aseptic conditions with the patient in sitting position, using the classical technique eliciting loss of resistance, at a spinal level midway between the uppermost and the lowest fractured ribs. In case of involvement of more than four ribs, one level higher than the middle level was chosen. Following test dose of 2% lignocaine with adrenaline (1:2,00,000) 3 ml to rule out intravascular or subarachnoid injection, the bolus dose was administered. Non-invasive blood pressure and heart rate were recorded every 5 minutes until 30 minutes after drug injection. Bradycardia was defined as heart rate <50 beats/minute and hypotension as a fall of >30% from baseline readings or an absolute value of <80 mmHg systolic blood pressure. Any episodes of bradycardia or hypotension were recorded and managed with atropine, fluids and vasopressors as required.

Continuous paravertebral infusion was started according to group allocation 30 minutes after administration of bolus dose. Initial rate of infusion was 0.1 ml/kg/hr in all patients which was gradually increased in steps of 1-2 ml/hr up to a maximum of 0.2 ml/kg/hr, in case adequate pain relief was not achieved. If, despite the maximum rate of paravertebral infusion, VAS score exceeded 40 mm or if the patient requested additional analgesia at any time during the study period, rescue analgesia was provided by intravenous morphine in increments of 1.5 mg. All the patients received diclofenac 1 mg/kg 12 hourly intramuscularly. The patients having any contraindication to diclofenac administration were to receive intravenous tramadol 1 mg/kg along with an antiemetic.

VAS scores at rest and on coughing, respiratory rate (RR), peak expiratory flow rate (PEFR), SpO_2 and arterial oxygen partial pressure to inspired oxygen concentration (PaO_2/FiO_2) ratio were measured before administration of block, 30 minutes after initiation of block, every 6 hours on 1st day and then every 8 hours 2nd day onwards. Ropivacaine infusion was continued until pain relief was complete and consistent i.e., VAS scores at rest and on coughing not more than 10 to

15 mm for more than 8 hours. Thereafter the infusion was gradually tapered off in steps of 1-2 ml/hour and the patients were shifted to surgical ward when they were completely off LA infusion. The end of ropivacaine infusion constituted the end-point of the study. Any complications of the technique or side effects of the drugs were noted and appropriately managed. Development of pneumonia or other pulmonary complications and duration of ICU and hospital stay were also recorded.

In the previous data on use of TPVB using bupivacaine infusion in similar group of Indian patients with MFR, 14 out of 15 (93%) patients required rescue analgesia with intravenous morphine.[3] Considering a 50% reduction in number of patients requiring additional rescue analgesia with morphine to be clinically significant, sample size required to detect this reduction at 5% level of significance and 90% power was calculated as 14 patients per group. Therefore, 15 patients were included in each group. Statistical analysis was performed using SPSS version 17.0. Unpaired Student *t*-test was used to compare mean age, weight, number of fractured ribs, chest AIS, ISS, duration of infusion, lengths of ICU and hospital stay and ropivacaine requirements between the two groups. Pearson Chi-Square and Fisher's exact test were used to compare sex ratio, proportion of presence of chest tube drainage, pulmonary contusion, flail segment, haemothorax, pneumothorax and subcutaneous emphysema. Repeated measures ANOVA followed by post-hoc analysis with Tukey's test at 5% significance level was done to perform inter and intra-group comparisons for heart rate, blood pressure, VAS at rest and coughing, RR, PEFR and PaO_2/FiO_2 ratio.

RESULTS

The two groups were comparable with respect to age, weight and sex ratio. The mean age of the patients in groups RA and RAF was 46.8 ± 14.6 years and 37.9 ± 10.9 years, respectively ($P = 0.070$). The mean weight was 53.7 ± 7.2 kg in Group RA and 53.1 ± 5.3 kg in Group RAF ($P = 0.796$). Out of 15 patients, there were 11 males and 4 females in group RA; and 14 males and 1 female in group RAF ($P = 0.330$). Road traffic accident (RTA) was the most common mechanism of injury in both groups. No patient had any contra-indication to diclofenac injection and all patients received the same drug throughout the study period.

Injury data of patients in the two groups was comparable [Table 1].

VAS scores at rest and coughing, RR, PEFR, SpO_2 and PaO_2/FiO_2 ratio were measured at frequent intervals. Till 32 hours, data of all the patients in both groups was analysed to compare all these parameters. Thereafter the number of patients started decreasing in both groups so that in group RA, 14 patients remained at 48 hours and 12 at 72 hours. In group RAF, 15 and 13 patients could be studied at 48 and 72 hours, respectively.

Figure 2 shows trends of VAS scores at rest and on coughing till 72 hours. VAS scores at rest decreased significantly from baseline values at all time points in both groups. On intergroup comparison,
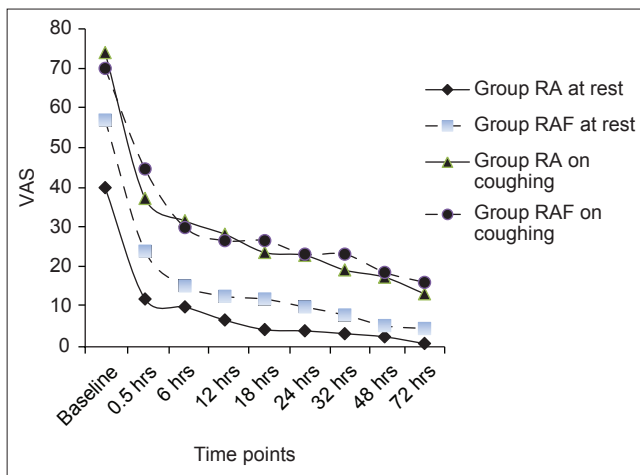

Figure 2: Trends of VAS scores at rest and on coughing

scores till 32 hours appeared to be higher in group RAF ($P = 0.029$). However, on application of Tukey's test, the difference could be detected only in the baseline values. VAS scores at 48 and 72 hours also showed no difference between the groups ($P = 0.200$ at 48 hours; $P = 0.078$ at 72 hours). Similarly, VAS scores on coughing decreased significantly from baseline values at all time points in both groups but there was no difference between the groups ($P = 0.737$ till 32 hours, $P = 0.756$ at 48 hours, $P = 0.372$ at 72 hours).

Effect on respiratory function was assessed by studying changes in RR, PEFR and PaO_2/FiO_2 ratio. A significant decrease in mean RR was noted at all time points in comparison to baseline values in both groups. However, the values were statistically similar in two groups ($P = 0.882$ till 32 hours, $P = 0.525$ at 48 hours, $P = 0.273$ at 72 hours). An increasing trend with time in mean PEFR was seen in both groups but without any intergroup difference ($P = 0.950$ till 32 hours, $P = 0.483$ at 48 hours, $P = 0.608$ at 72 hours). PaO_2/FiO_2 values could not demonstrate any definite trend with time in either of the groups. However, SpO_2 was maintained above 90% after institution of TPVB in all patients and PaO_2/FiO_2 values were comparable in the groups ($P = 0.583$ till 32 hours, $P = 0.700$ at 48 hours, $P = 0.779$ at 72 hours).

No patient in any group developed hypotension or bradycardia after paravertebral administration of ropivacaine. Mean values of heart rate and blood pressure at various time points did not differ within or between the groups ($P > 0.05$).

The catheter was accidentally pulled out on fourth day in one patient in group RA whose pain was subsequently controlled with inj. diclofenac. Therefore, mean duration of infusion (89.1 ± 39.9 hours) in this group was calculated after excluding this case. This was statistically comparable to group RAF with duration 98 ± 30.8 hours ($P = 0.433$).

In group RA, three patients required morphine administration in doses of 7.5, 4.5 and 1.5 mg. On the other hand, only one patient in group RAF required morphine 3 mg. Due to most of the patients not requiring morphine administration, mean/median morphine requirement could not be calculated. However, the proportion of patients requiring morphine in both groups was compared using Fisher's exact test, which was statistically similar ($P = 0.598$).

Table 1: Injury data of the study groups			
Parameters	Group RA (*n*=15)	Group RAF (*n*=15)	*P* value
Mean number of fractured ribs (range)	3.9±1.1 (3-6)	4.1±1.2 (3-7)	0.533
Mean chest AIS (range)	2.7±0.6 (2-4)	2.9±0.6 (2-4)	0.391
Mean ISS (range)	12.8±6.1 (6-29)	13.3±4.6 (6-20)	0.788
Patients with flail segment (no.)	5	6	0.705
Patients with pulmonary contusion (no.)	2	2	1.000
Patients with haemothorax (no.)	7	6	0.713
Patients with pneumothorax (no.)	7	10	0.269
Patients with chest tube (no.)	9	11	0.233
Patients with S/C emphysema (no.)	5	5	1.000

no – Number; AIS – Abbreviated injury score; ISS – Injury severity score; S/C – Subcutaneous; RA – Ropivacaine+Adrenaline; RAF – Ropivacaine+Adrenaline+Fentanyl

Total amount of ropivacaine required in each patient was noted and ropivacaine requirement per kg patient's weight was calculated. Mean values of both these parameters were higher in group RA than RAF [Table 2].

The outcome of treatment in terms of length of ICU and hospital stay and pulmonary and other complications was comparable in two groups [Tables 3 and 4]. No patient in either group developed pneumonia or other serious pulmonary complications.

In group RA, one patient developed nausea and vomiting following rescue morphine injection and pruritus 4 hours later. He was treated with antiemetic and antihistaminic. Two patients in group RAF had nausea which was managed with antiemetic. None of these patients had received morphine.

No patient in either group showed any signs of LA-induced neurotoxicity or cardiotoxicity.

DISCUSSION

The present study was conducted to find an efficacious yet safe drug combination that could minimise the risk of LA toxicity associated with TPVB and the

Table 2: Ropivacaine requirements

Ropivacaine requirement	Group RA (*n*=15)	Group RAF (*n*=15)	*P* value
Total ropivacaine requirement (mg)	1570±736	940±286	0.006
Ropivacaine requirement/kg (mg/kg)	29±14	17±6	0.009

Values are mean±SD. RA – Ropivacaine+Adrenaline;
RAF – Ropivacaine+Adrenaline+Fentanyl

Table 3: Length of ICU and hospital stay

Parameters	Group RA (*n*=15)	Group RAF (*n*=15)	*P* value
Length of ICU stay (days)	4.2±1.5	4.3±1.3	0.899
Length of hospital stay (days)	7.3±3.2	8.8±5.3	0.349

Values are mean±SD. RA – Ropivacaine+Adrenaline; RAF – Ropivacaine+Adrenaline+Fentanyl; ICU – Intensive care unit

Table 4: Patients developing pulmonary and other complications

Complications	Group RA (*n*=15)	Group RAF (*n*=15)	*P* value
Delayed haemothorax	0	1	0.50
Fever	0	1	0.50
Nausea	1	2	0.50
Vomiting	1	0	0.50
Pruritus	1	0	0.50

RA – Ropivacaine+Adrenaline; RAF – Ropivacaine+Adrenaline+Fentanyl

drugs used, without compromising the efficacy of the technique.

Ropivacaine was used in this study as it is known to be safer than bupivacaine, being less neurotoxic and cardiotoxic.[7,8] Various studies using paravertebral ropivacaine infusions have used concentrations ranging from 0.1% to 0.5%;[9-13] however, most of them were conducted in thoracotomy, breast surgery or knee surgery. Therefore, their results may not be applicable to patients with MFR. In case of bupivacaine infusions in paravertebral space for providing analgesia to MFR patients, a concentration of 0.25% has been used most often.[1,3] Considering the equipotent dose ratio of ropivacaine and bupivacaine to be 1.5:1,[8] we used 0.375% ropivacaine in group RA in the present study.

Epinephrine 5 µg/ml was added to ropivacaine to delay its systemic absorption. Karmakar *et al.* studied pharmacokinetics of ropivacaine with and without epinephrine after TPVB.[14] They found significantly delayed systemic absorption and reduced peak plasma concentrations of ropivacaine after addition of epinephrine.

Meyer *et al.* found an infusion of 0.375% ropivacaine to be safe.[17] However, it was administered at a fixed rate of 0.1 ml/kg/hr and for a fixed time of 71.5 hours. Patients with MFR usually need pain relief for longer periods and paravertebral infusion rates range from 0.1 to 0.2 ml/kg/hr. Hence, further reduction in the concentration of ropivacaine used, if possible without compromising efficacy of the technique, may present an even safer option. Various adjuvants added to LA agents improve the quality of analgesia and spare the LA,[18] thus allowing a decrease of LA dose to safer, nontoxic levels.[19] Fentanyl is used very often for this purpose. Burlacu *et al.* added fentanyl 4 µg/ml to levobupivacaine in paravertebral infusion for breast surgery.[15] This drug combination was effective in providing analgesia and thus reducing postoperative morphine consumption. However, it was associated with an increased incidence of nausea and vomiting. Bimston and colleagues administered fentanyl 10 µg/ml combined with 0.1% bupivacaine in continuous paravertebral infusion to patients undergoing thoracotomy.[16] Adequate postoperative pain relief was provided; however, a high incidence of opioid-induced side-effects was noted. Thus, it is clear that addition of fentanyl improves analgesia and can allow reduction in dose of LA, but in high doses,

it predisposes to side-effects. Therefore, in the present study, fentanyl was added in a low concentration i.e., 2 μg/ml so as to reduce the incidence of opioid-induced side effects.

The main aim of the study was to compare the analgesic efficacy of paravertebral infusion of two different ropivacaine solutions. Considering this fact, the end of ropivacaine infusion was taken as the end point of the study because beyond this time point the patients remained pain free on systemic analgesics without requiring any paravertebral infusion.

To provide rescue analgesia, usually an agent with rapid onset and offset is preferred. However, we preferred to use morphine as in patients with multiple rib fractures, good pain relief is required for a prolonged period which may be even a week or more. Therefore, morphine, with a relatively longer duration of action as compared to shorter acting agents e.g., fentanyl, was considered to be the better choice. The slightly longer onset of action of morphine than that of fentanyl did not present any problems as these patients were also receiving continuous paravertebral ropivacaine infusion and round the clock administration of diclofenac. Moreover, Group RAF patients were already receiving fentanyl 2 μg/ml along with infusion of ropivacaine and adrenaline. Therefore, it was considered better to use a drug other than fentanyl for rescue analgesia.

Both paravertebral drug combinations in the present study provided good analgesia to MFR patients. However, no significant difference could be found in two groups at any time point after institution of block. Respiratory function in terms of RR and PEFR improved and was comparable with both RA and RAF. These results demonstrated that addition of fentanyl 2 μg/ml improved the analgesic efficacy of 0.2% ropivacaine so as to make it comparable to effect of 0.375% ropivacaine.

Morphine requirement in the present study was minimal, with only three patients in group RA and one in group RAF requiring morphine administration for rescue analgesia. Only one study in English literature has calculated morphine requirement in MFR patients receiving TPVB.[3] In this study, TPVB group patients had received bolus of 0.3 ml/kg bupivacaine 0.5% followed by continuous infusion of bupivacaine 0.25% at 0.1-0.2 ml/kg/hr. No other analgesic was administered along with this. Mean morphine requirement in these patients was 11.2 ± 9.5 mg, with 14 out of 15 patients

requiring rescue analgesia. One major difference in these two studies was that all patients in the present study received diclofenac every 12 hours throughout study period. This would have reduced the analgesic requirements in both groups. Moreover, difference in nature of the drugs infused in paravertebral space could have contributed to the difference.

The total ropivacaine requirements as well as ropivacaine requirements per kg body weight of the patients were significantly higher in group RA as compared to group RAF [Table 2]. Although the patients in group RA received a higher concentration of ropivacaine as compared to the patients in group RAF, this cannot be the only reason for difference in ropivacaine requirements. Ilfeld *et al.* stated that local anaesthetic dose (mass) is the primary determinant of perineural infusion effects.[20] Infusion rate in the present study could be varied between 0.1 ml/kg/hr and 0.2 ml/kg/hr, depending on the patient's requirements. Despite this titration, group RA patients needed more ropivacaine to achieve the desired results. This demonstrates the role of fentanyl in improving analgesic efficacy and thus lowering requirement of ropivacaine in group RAF.

The occurrence of opioid induced side-effects e.g., nausea, vomiting, pruritus etc., is a major concern when fentanyl is added to LA infusion.[15] However, only 2 out of 15 patients in group RAF complained of nausea which was easily managed with antiemetic. On the other hand, one patient in group RA suffered nausea, vomiting and pruritus despite having no fentanyl in the infusion. Thus, addition of 2 μg/ml fentanyl to ropivacaine infusion appears to be quite safe.

No patient in either group showed any signs of LA induced neurotoxicity or cardiotoxicity. In a previous study in MFR patients, one patient developed convulsions after 68 hours of paravertebral bupivacaine infusion.[3] Lack of any such complications in the present study can be attributed to use of safer drugs and drug combinations.

The present study has certain limitations. First, it would have been ideal to measure plasma ropivacaine levels as many patients received infusions for a prolonged period. However, it was not possible to do so due to lack of facilities for the same. Secondly, the study was not adequately powered to compare the incidence of opioid-induced side-effects in the two groups. However, despite this limitation, very low

incidence of side-effects supports the safety of fentanyl infusion at a low dose i.e., 2 μg/ml.

CONCLUSION

Both drug combinations used for paravertebral infusion in the present study, i.e., ropivacaine 0.375% with adrenaline 5 μg/ml and ropivacaine 0.2% with adrenaline 5 μg/ml and fentanyl 2 μg/ml, provided good analgesia with minimal side effects in patients with unilateral MFR. Addition of fentanyl in low concentration i.e., 2 μg/ml to the combination of ropivacaine and adrenaline allowed reduction of ropivacaine requirement without affecting the analgesic efficacy or the incidence of opioid-induced side-effects.

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