Original Research Paper

Volume - 12 | Issue - 05 | May - 2022 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Anaesthesiology

EPIDURAL ROPIVACAINE: EFFECTS OF HIGH-VOLUME/ LOW-CONCENTRATION VERSUS LOW-VOLUME/ HIGH-CONCENTRATION IN RENAL TRANSPLANT PATIENTS

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ABSTRACT

Background: Choice of an appropriate analgesic regimen is especially important in ESRD patients. Regional analgesia technique such as epidural with local anaesthetic drugs has been found suitable in such patients. This study was designed to compare a high-volume/low-concentration with low-volume/high concentration ropivacaine regimen in ESRD transplant patients.

Materials And Methods: This prospective, open level randomized control study was conducted on 40 end stage renal disease (ESRD) patients, aged between 20- 60 years of either sex who underwent live-related renal transplant surgery.GROUP A Low volume/High concentration group received 6 ml of 0.75% ropivacaine and GROUP B High volume/Low concentration group received 12 ml of 0.375% ropivacaine.Total dose of ropivacaine needed for postoperative pain control and for achieving T6 to S5 sensory block, Level of motor blockade and Dose of vasopressors needed for haemodynamic stability was compared.

Results: Total dose of ropivacaine required to achieve T6 to S5 sensory block and total dose of vasopressor used was higher in low volume high concentration group at initiation of block. Postoperative quality of analgesia as assessed by VAS score and top up requirements (total dose of postoperative ropivacaine used) was comparable in both the groups.

Conclusion: We conclude no added advantage of using low volume high concentration ropivacaine drug regimen in renal transplant recipients in terms of quality of analgesia and haemodynamic stability.

KEYWORDS : Ropivacaine, Analgesia, Epidural, Renal, Vasopressors

INTRODUCTION

Renal transplantation is a well accepted treatment modality for patients with end stage renal disease (ESRD).[1] An ideal anaesthetic technique for the renal allograft recipient should assure haemodynamic stability, enhance graft reperfusion and provide good post-operative pain control[2]. Combination of epidural with general anaesthesia has been found to maintain a steady intra-operative haemodynamic state and also prolong analgesia in lower abdominal surgeries.[3,4,5]Choice of an appropriate analgesic regimen is especially important in ESRD patients, where intravenous opioids need to be administered cautiously and NSAIDs may have adverse effects on ischaemic kidney.[6,7] Regional analgesia technique such as epidural with local anaesthetic drugs is very suitable under such circumstances. Ropivacaine is a local anaesthetic with an epidural potency similar to bupivacaine which displays an improved cardiotoxicity profile and reduced motor block at doses which provide analgesia.[8,9,10]

Administration oflow concentrations and high volumes of local anaesthetics is common, clinical studies have shown conflicting results as to whether the same effect can be reached by highly concentrated solutions infused at low volumes.[11,12,13] However, clinical effects related to the concentration, dose and volume of local anaesthetics during continuous epidural infusion are still not completely understood and validated in ESRD patients. There are no randomised controlled studies comparing analgesic and haemodynamic effects of same local anaesthestic dose of ropivacaine given as high-volume/low-concentration versus a low-volume/high-concentration regimen in ESRD patients undergoing renal transplant surgery under combined epidural general anaesthesia technique. Hence, we designed this study to compare a high-volume/low-concentration with low-volume/high concentration ropivacaine regimen in ESRD transplant patients.

MATERIALS AND METHODS

After approval of institutional ethical committee and written informed consent from the participants, this prospective, open level randomized control study was conducted on 40 end stage renal disease (ESRD) patients, aged between 20- 60 years of either sex who underwent live-related renal transplant surgery under combined epidural and general anaesthesia. The exclusion criteria included height < 150 cm, contraindication to epidural anaesthesia, h/o hypersensitivity to study drug/local anaesthetic, compensated or decompensated myocardial insufficiency, serum K+ > 5.5 meq/ l, accidentalduralpuncture, persistent high BP > 170/100 mm hg.

All the participants underwent haemodialysis the day prior to surgery as per our institutional protocol. They were instructed to fast for a minimum of eight hours. Premedication advised was tablet alprazolam 0.5 mg orally the night before surgery. Tablet ranitidine 150mg and tablet metoclopromide 10 mg orally was also administered the night before and two hours prior to shifting to the operating room. Perioperative antihypertensives were omitted on the morning of surgery and immunosuppressant therapy was administered as per the institutional practice.

In operating room, a 16G cannula was secured in a peripheral vein and maintenance normal saline infusion was started at 2ml/kg/hour. All the patients were monitored by ECG, pulse rate, invasive blood pressure (IBP), CVP and SpO2. A 20 G arterial cannula was inserted into radial artery for continuous IBP monitoring. The mean of first three recordings of monitored haemodynamics at 5 minute interval were considered baseline values for subsequent comparison. Peripheral venous access and arterial cannulation for invasive pressure monitoring was not done in limb with arterio-venous fistula.

Later, under all aseptic precautions with patient in left lateral position 18G epidural catheter was placed in T12-L1space. Not more than 5cm of catheter was placed inside the epidural space. Correct placement of catheter was confirmed by injecting a test dose of 3ml of 2% lignocaine with adrenaline 1:2,00,000. Patients were made supine and ropivacaine was given through epidural catheter. Based on concentration and volume of ropivacaine patients were randomly divided into 2 groups. Dose of ropivacaine in mg used for initial loading and subsequent top ups (if required) was same in both the groups.

GROUP A. Low volume/High concentration group - 6 ml of 0.75% ropivacaine.(LVHC group) Total dose = 45 mg.

GROUP B. High volume/Low concentration group - 12 ml of 0.375% ropivacaine.(HVLC group) Total dose = 45 mg.

Onset of sensory block was checked after 5 minutes and every minute thereafter for 20 minutes with cold spirit swab. Subsequently after 20 minutes additional boluses of 3 ml ropivacaine in HVLC group and 1.5 ml ropivacaine in LVHC group were given if required until sensory analgesia is achieved between T6 to S5 dermatomes. Duration, total dose and volume required to achieve the block between T6 to S5 was recorded.

After initiation of epidural block, hemodynamic monitoring was done and records of 5 minute interval were kept till 60 minutes of combined anaesthesia. Subsequently haemodynamic recording for study purpose was done every 20 minutes till the end of surgery.

General anaesthesia technique was same in both the groups. Fentanyl 1µg/kg intravenous was given to all patients, following which induction was done with propofol 1.5-2 mg/kg slow i/v. Endotracheal intubation was facilitated by intravenous suxamethonium 2 mg/kg. After intubation, atracurium 0.5 mg/kg was given and intermittent positive pressure ventilation was commenced with a mixture of 50% Nitrous oxide in oxygen and isoflurane 0.5% – 1.5%, using a closed circuit with a circle absorber. Ventilation was adjusted to maintain end-tidal carbon dioxide (EtCO2) between 35-40mm Hg and combined MAC between 0.8-1.1 throughout the procedure. Continuous intraoperative monitoring included IBP, HR through ECG, SpO2, EtCO2, CVP and MAC and these parameters were recorded for study purpose as per intervals mentioned before. Any episode of hypotension defined as fall of mean blood pressure > 20% of baseline and total dose of vassopressors used to maintain haemodynamics was recorded. Urine output was monitored every half hourly after revascularisation of the graft. The target BP (SBP > 130 mm hg and mean BP > 80 mm hg) was maintained during declamping and any fall less than these values was managed by fluid administration and vasopressor therapy as per the situation.

In all the patients, CVP was gradually increased to 12-15mm Hg with crystalloids (up to 50ml/kg) & colloids (2-4ml/kg of 20% albumin) till the revascularization is complete. Intravenous injection of frusemide 2mg/kg and 20% mannitol 2ml/kg was given to all patients before reperfusion of grafted kidney as per our institutional protocol. Once graft diuresis is established, intravenous fluid therapy was continued to maintain CVP 8-10mm Hg. Blood transfusion was considered according to estimated blood loss and blood hemoglobin levels. In case of no urine output (poor graft function) fluid administration was restricted. Ondansetron (0.1mg/kg) was administered approximately half an hour before completion of the surgery. Patients were reversed with neostigmine (0.05mg/kg) and glycopyrolate (0.01mg/kg) and extubated on meeting the standard criteria and shifted to post renal transplant intensive care unit.

Primary output variables:
1. Total dose of ropivacaine needed for achieving T6 to S5 sensory block.
2. Total dose of ropivacaine needed for postoperative pain control.
3. Dose of vasopressors needed for haemodynamic stability.

Secondary output variables:
1. Level of motor blockade.

Hemodynamic monitoring was continued in postoperative period and hourly records were kept for first 24 hours. Parameters compared were analgesia, assessed using 10 point visual analogue scale (VAS), where 0 is no pain and 10 is worst imaginable pain. Participants were made familiar with VAS preoperatively. Postoperative pain was treated with boluses of 10 ml of 0.1857% ropivacaine in HVLC group and 5 ml of 0.375% ropivacaine in LVHC group on demand (VAS = 4). Dose of ropivacaine was compared.

Preinduction dose of ropivacaine for achieving T6-S5 sensory level was compared. Dose of vasopressors used for haemodynamic stability was compared. Motor blockade was assessed by modified bromage score. Epidural catheter was removed after 24 hours postoperatively. The collected data was compared between the groups and from baseline values with in each group.

The statistical analysis was carried out using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 15.0 for Windows). All quantitative variables were estimated using measures of central location (mean or median) and measures of dispersion (standard deviation or IQR). Measures of Kolmogorov Smirnov tests of normality was used to check normality of data. In normally distributed data student's t-test was used to compare two groups. For skewed data or for scores (for VAS score or Bromagescore) Mann –Whitney test was applied. Categorical or qualitative variables were described as proportions and frequencies. Proportions were compared using Chi square or Fisher's exact test whichever was applicable. For time related variables (within group) comparisons, One-Way ANOVA followed by Dunnet t test was applied. For time related scores Friedman test was used followed by Wilcoxon Signed Rank test. All statistical tests were two-sided and performed at a significance level of α=.05

RESULTS

Forty patients fulfilling the eligibility criteria planned for elective renal transplant surgery were enrolled in our study and randomly allocated into two groups [Figure 1]. Both the groups were comparable in their demographic data such as age, height, weight, gender distribution and duration of anaesthesia as well as surgery (Table 1). All the patients in the study received haemodialysis the day prior to the surgery. The weight before and after dialysis were comparable in both the groups.The baseline investigations Hb, serum sodium, serum potassium, RBS, urea and creatinine were comparable in both the groups. The baseline haemodynamic parameters i.e. mean of three readings taken 5 minutes apart inside the operation theatre before the start of anaesthesia for heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure and central venous pressure were comparable in both the groups.

Ropivacaine dose required to achieve desired T_6 to S_5 sensory block was significantly higher in LVHC group as compared to HVLC group (50.62 IQR 45-56.25 mg versus 45 IQR 45-45 mg respectively; P<0.001). Similarly the time required to achieve desired T_6 and S_5 sensory block was also significantly more in LVHC group compared to HVLC group. The median time difference between the two groups for achieving T_6 level was statistically more significant as compared to median time required for sensory block level S_5 between both the groups (*p<0.001 versus *P=0.017) (Table 2).

The monitored haemodynamic parameters and CVP were comparable between the two groups at all study points during intraoperative and postoperative period.As per our study protocol the mean arterial pressure was not allowed to fall below 20% of baseline by the use of mephentramine. Total dose of mephentramine used intraoperatively was significantly higher in LVHC group than HVLC group (LVHC group- 11.7±9.021 mg versus HVLC group- 3.60±5.29 mg respectively; *P=0.001). None of the groups required mephentramine for haemodynamic stability during postoperative period (Figure2). The mean blood loss in LVHC group was 270.0 ± 52.31484 ml whereas that in HVLC group was 255.0±42.61208 ml which was comparable between both the groups. The intra operative colloid and crystalloid requirements were also comparable in both the groups.

Postoperatively pain was assessed with VAS score every hourly for first 24 hours. VAS score was comparable in both the groups (Figure 3). Modified bromage score was compared at rest in both the groups. Modified bromage score was comparable in both the groups (Table III). The total dose of ropivacaine used and total number of boluses given were comparable in both the groups.Patients in both the groups recieved epidural boluses of ropivacaine in the post operative period for 24hrs. The epidural catheter was removed after 24 hours.

DISCUSSION

The results of this study demonstrated that equal doses of ropivacaine given as low volume/ high concentration (LVHC) in lumbar epidural space blocks less number of sensory dermatomes as compared to that given as high volume/ low concentration (HVLC) at the time of initiation of sensory block. This is evident in our study by the fact that in LVHC group we had to give repeat dose of ropivacaine as top up to achieve sensory block in T6 to S5 dermatomes in the beginning. Due to need for repeat epidural top up in LVHC group, the time required to achieve T6 to S5 sensory block was also significantly more than HVLC group. However, during postoperative period quality of analgesia (as assessed by VAS) achieved after top ups given as LVHC or HVLC for same dose of ropivacaine was comparable. Also, the total dose and number of top ups required by patients in post operative period for

comparative pain relief were not statistically significant. This implies that once epidural space is filled with required volume of local anaesthetic drug to achieve block of desired sensory dermatomes; subsequently only total dose as LVHC or HVLC of ropivacaine is important to continue analgesia.

In this study the explanation for increased requirement of vasopressor in LVHC group could be more dense sensory and motor block produced in this group leading to more blood pooling in muscle vessel group and also because of more systemic absorbtion of drug which could have vasodilatory effects. Moreover more drug dose given in this group could have lead to more wide sympathetic block as compared to HVLC group, where the total dose given was less. Chamberlain et al[14] and Malmqvist et al[15] has shown wide variation in the dermatomal spread of sympathetic block above sensory level after central neuraxial block. However, in the postoperative period there were no statistically significant difference between the two groups in terms of haemodynamic stability and motor blockade as assessed by modified Bromage scale.

The results of our study showing high dose requirement of ropivacaine in LVHC group to achieve T6 to S5 sensory block are consistent with other studies, supporting the view that dermatomal sensory block level was higher in HVLC group than LVHC group.[12,15,16] Dernedde et al[12] in their study compared three different regimens of 10 ml/hr, 3 ml/hr and 2 ml/hr of levobupivacaine keeping the total dose same in all regimens for post operative analgesia as continuous infusion and found that sensory block was more extensive (up to T_7) in the 10 ml/hr group as compared with the two other groups (up to T_9) (P<0.001). They explained the wider cephalad extend of sensory block being due to high infusion rate of 10 ml/hr in HVLC group. However, the caudal spread of drug was not assessed in their study. Liu et al[17] compared 10 ml 3% of 2-chloroprocaine bolus with 30 ml 1% of 2-chloroprocaine bolus (keeping the total drug dose same) given as lumbar epidural bolus. They found that number of dermatomes blocked to pinprick, cold and touch was significantly greater with the 1% solution due to greater cephalad spread of the HVLC 1% solution.Hong et al[16]found that the median spread level was T11 (range T8-L2) with 1 mL/kg of 0.225% ropivacaine and T6 (range T3-11) with 1.5 mL/kg of 0.15% ropivacaine which was statistically significant.

Our study demonstrated that at same dose of ropivacaine given as low volume/ high concentration boluses versus high volume/ low concentration boluses resulted in same quality of analgesia after lumbar epidural administration during postoperative period. There are many previous studies which supports the view that the quality of epidural analgesia depends on the total dose of local anaesthetic drug and not on the volume or concentration.[18,19,20]However, Whiteside et al[21]and Snijdelaar et al[22]showed that HVLC appeared to reduce dose of drugs required for analgesia. Our study differs from their study because we did not add any epidural opioids.

In this study total dose of propofol and atracurium, intravenous fluids, blood loss, and MAC of inhalational agents were comparable in both the groups. None of the patients had any cardiovascular or neurological side effects of ropivacaine. No anaesthesia or surgery related complications were noted during the study period. There was no accidental dural puncture, epidural haematoma, neurological deficits, hyperacute graft rejection, bleeding, anuria, injury to bowel or other vascular structures.

CONCLUSIONS

In conclusion, the results of the present study show that there is no added advantage of using low volume high concentration ropivacaine drug regimen in renal transplant recipients in terms of quality of analgesia and haemodynamic stability. Moreover this regimen may lead to unnecessary requirement of high dose of ropivacaine and more vasopressor consumption after induction of general anaesthesia in renal transplant recipient patients.

Table I: Demographic Data

PARAMETER	LVHC Group (n=20)	HVLC Group (n=20)	P-Value
Age(Yrs)	36.2±9.51	33.2±12.22	0.392
Height (cm)	164.75±5.379	163.7±6.554	0.583
Weight(kg)	53.75±6.669	51.509±6.5538	0.291
Gender (M:F)*	20:0	18:2	0.487
Duration of surgery (min)	144.4±10.0755	139.6±9.05771	0.121
Duration of anaesthesia (min)	174.25±12.904	170.0±10.513	0.261

P>0.05All the data are represented as mean ± SD except *gender distribution shown in numbers.

Statistical test - independent t- test. *Statistical test- Chi- square test.

Table II: Ropivacaine Dose And Time Requirement For Achieving T6 – S5 Sensory Block

	LVHC Group (n=20) MEDIAN(IQR)	HVLC Group (n=20) MEDIAN(IQR)	P- Value
ROPIVACAINE DOSE(mg)	50.62(45-56.25)	45(45-45)	<0.001*
T_6 Level	20.5(17-23.75)	8(7.25-9)	<0.001*
S_5 Level	7(6-7)	6(5-6.75)	0.017*

*P<0.05.
Data expressed as median (IQR).
Data for these parameters was not normally distributed, hence analysed by Mann Whitney test.

Table III: Post Operative Modified Bromage Score

Time (hrs)	LVHC Group (n=20) Median (IQR)	LVHC Group (n=20) Mean±SD	HVLC Group (n=20) Median (IQR)	HVLC Group (n=20) Mean±SD	P-Value
1	1.0(0-1)	0.65±0.489	0(0-1)	0.45±0.51	0.209
2	0(0-0)	0.05±0.224	0(0-0)	0.2±0.41	0.157
3	0(0-0)	0.1±0.308	0(0-0)	0.1±0.308	1.000
4	0(0-1)	0.35±0.489	0(0-1)	0.45±0.51	0.524
5	0(0-0)	0.20±0.41	0(0-1)	0.3±0.470	0.471
6	0(0-0)	0.1±0.308	0(0-0)	0.05±0.224	0.553
7	0(0-1)	0.35±0.489	0(0-1)	0.35±0.489	1.000
8	0(0-0)	0.15±0.366	0(0-1)	0.3±0.47	0.262
9	0(0-0)	0.15±0.366	0(0-1)	0.3±0.47	0.262
10	0(0-1)	0.35±0.489	0(0-1)	0.3±0.47	0.739
11	0(0-0)	0.20±0.41	0(0-0)	0.15±0.366	0.681
12	0(0-1)	0.3±0.47	0(0-0.75)	0.25±0.444	0.727
13	0(0-1)	0.4±0.503	0(0-0.75)	0.25±0.444	0.317
14	0(0-0)	0.2±0.410	0(0-0.75)	0.25±0.444	0.708
15	0(0-0)	0.1±0.308	0(0-0)	0.05±0.224	0.553
16	0(0-0.75)	0.25±0.444	0(0-1)	0.3±0.47	0.727
17	0(0-0)	0.2±0.41	0(0-0)	0.15±0.366	0.681
18	0(0-0)	0.1±0.308	0(0-0)	0.15±0.366	0.637
19	0(0-0.75)	0.25±0.444	0(0-0)	0.15±0.366	0.435
20	0(0-0)	0.2±0.41	0(0-0)	0.2±0.41	1.000
21	0(0-0)	0.15±0.366	0(0-0)	0.2±0.41	0.681
22	0(0-1)	0.35±0.489	0(0-1)	0.35±0.489	1.000
23	0(0-0)	0.15±0.366	0(0-0)	0.15±0.366	1.000
24	0(0-0)	0.2±0.41	0(0-0.75)	0.25±0.444	0.708

P> 0.05.
Values represented as mean ± SD.
Statistical test – Mann Whitney test and independent t- test.

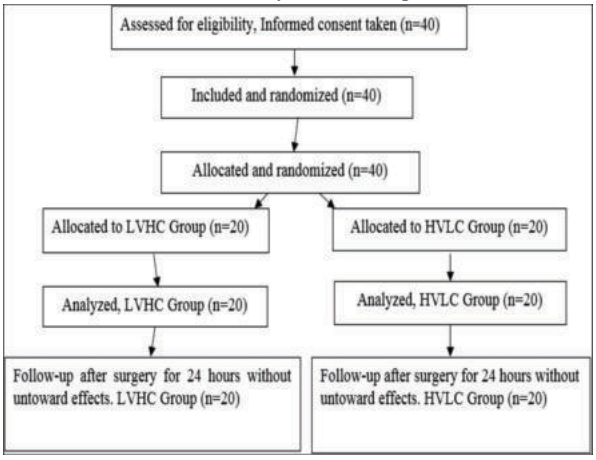

Figure 1: Consort Diagram Of Study

Figure 2 Total Dose Of Vasopressor Used (mephentramine)

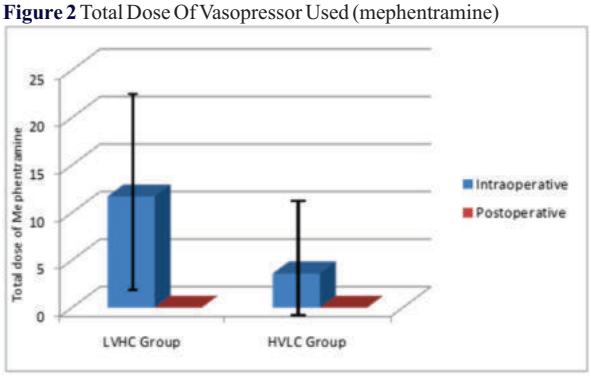

Figure 8- Comparision of total dose of mephentramine during the study period in both the groups. No drug used in postoperative period.

***P<0.05.**

Values are represented as mean± SD.

Statistical test - independent t- test.

Figure 3 Post operative Pain (VAS Score)

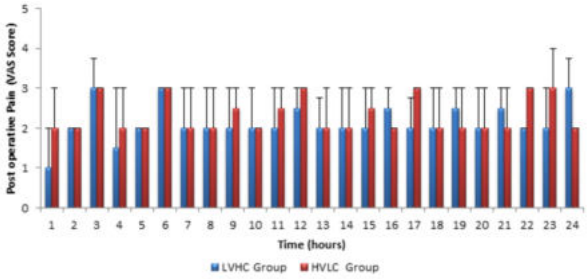

Figure 9- Comparision of postoperative VAS score between the groups.
P>0.05.

Values represented as median(IQR).

Statistical test– Mann Whitney test.

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