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Originalan rad **Original article**

CONTINUOUS EPIDURAL INFUSION OF LARGE CONCENTRATION WITH SMALL VOLUME VERSUS SMALL CONCENTRATION WITH LARGE VOLUME OF LEVO-BUPIVACAINE FOR POSTOPERATIVE ANALGESIA AFTER LAPAROTOMY (Effect of epidural levobupivacaine small versus large volume)

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Abstract

Introduction: *Epidural analgesia after abdominal surgery is most effective mode of postoperative pain relief. Relative effects of the volume and concentration of local anaesthetic used for epidural analgesia are still under debate. We compared postoperative analgesic efficacy and adverse effects with continuous epidural infusion of 0.5% levobupivacaine at 3 ml/h and 0.15% levobupivacaine at 10 ml/h after abdominal surgery.* **Methodology:** *Sixty patients in the age group of 18-60 yrs of either sex belonging to ASA I and II scheduled for abdominal surgery under general anaesthesia were randomly equally divided into two groups. Patients of group-A received continuous epidural infusion of 0.5% levobupivacaine at 3 ml/h and group-B received continuous epidural infusion of levobupivacaine 0.15% at 10 ml/h for 24hrs in postoperative period. Intra-operative hemodynamic, HR, SBP, DBP, MAP, quality of postoperative analgesia using VAS score, time for first rescue analgesia, consumption of rescue analgesic drug, motor blockade, sensory loss and side effects were observed during the study period.* **Results:** *No statistically significant difference was observed in VAS score in group-A and Group-B at rest and at cough at all times. Motor block was significantly higher in group-A after 16 hours. Heart rate, SBP, DBP and MAP were significantly lower in group-A as compared to group-B in postoperative period.* **Conclusion:** *Continuous epidural infusion of 0.5% levobupivacaine at 3 ml/h and 0.15% levobupivacaine at 10 ml/h provided equal postoperative analgesia after abdominal surgery. We observed that postoperative analgesia depends on total dose of local anaesthetic agent and not on the concentration or volume.*

Key words: *Epidural analgesia; Levobupivacaine; postoperative analgesia*

Introduction

Inadequate control of postoperative pain following abdominal surgery can adversely affect patient's recovery outcomes.[1] It can cause impairment in coughing and breathing which may affect pulmonary function and decrease vital capacity.[2] Administering continuous epidural analgesia is a reliable and beneficial approach that facilitates early patient mobilization and supports recovery.[3] Local anaesthetic drugs which are given through epidural route, block the nociceptive input into the CNS thus provides greater analgesic effect.[4] In contrast to bupivacaine, levobupivacaine, the S-enantiomer of bupivacaine, exhibits reduced sodium channel blocking activity and offers lower cardiac and central nervous system toxicity than its racemic form and produces less arrhythmia.[5] Thus, levobupivacaine is a widely used local anaesthetic due to its favourable safety and efficacy profile.[6]

There is a lack of consensus regarding the optimal concentration of levobupivacaine used for the purpose of epidural analgesia. Concentrations of levobupivacaine ranging from 0.0625% to 0.5%

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have been used for epidural analgesia. Raising the total administered dose, whether by concentration or volume, enhances the onset speed, prolongs the effect, and intensifies motor blockade.[7,8,9] The relative impact of concentration versus volume on analgesic quality during epidural administration remains uncertain when the total dosage is fixed.[3,10]

We hypothesized that a larger-volume, lower-concentration infusion would provide comparable analgesia with better hemodynamic stability compared to a smaller-volume, higher-concentration regimen. With above mentioned hypothesis, we planned this randomized, double blinded, prospective study to evaluate and compare the analgesic quality, hemodynamic stability and adverse effects caused by continuous epidural analgesia of levobupivacaine 0.5% at 3 ml/h (small volume) and levobupivacaine 0.15% at 10 ml/h (large volume) keeping the total dose 15 mg/hr constant after lower abdominal surgery for postoperative analgesia. Patients underwent elective gynaecological, urological and oncological surgeries under general anaesthesia. These surgeries were interval debulking surgery, exploratory laparotomy, nephrectomy, total abdominal hysterectomy with bilateral salpingo-oophorectomy, low anterior resection in carcinoma rectum patients and staging laparotomy in gynaecological cancer patients.

Objective

We hypothesized that a larger-volume, lower-concentration infusion would provide comparable analgesia with better hemodynamic stability compared to a smaller-volume, higher-concentration regimen. Our objective was to compare quality of analgesia, hemodynamic stability, motor blockade, sensory loss, duration of analgesia and adverse effects between two groups during post-operative period.

Methods

After getting the hospital ethical committee's approval (IRC/24/2020), a randomized, double blinded prospective study was done on sixty patients of either sex, aged 18 to 60 years belonging to ASA I-II, undergoing elective laparotomy. Surgical types were evenly distributed between groups. Exclusion criteria were patient's refusal, weight > 90kg, allergy to local anaesthetic agent, coagulation abnormalities, local infection, uncontrolled hypertension, diabetes mellitus, renal insufficiency, hepatic insufficiency, cardiac or respiratory disease, spine abnormality, emergency surgeries and neurological or psychological disorder which interfere in communication for postoperative pain assessment. Patients were distributed randomly into two groups by sealed envelopes (containing 30 patients in each). One anaesthesiologist from our institute who did not participate in study prepared levobupivacaine infusion in two different concentrations. Anaesthesiologists who did post-operative observation was blinded to the concentration and infusion rate of levobupivacaine. Patients of group A received 0.5% levobupivacaine at 3 ml/h and patients of group B received 0.15% levobupivacaine at 10 ml/h as continuous infusion for 24 hours in postoperative period after 2 hours of last dose of levobupivacaine in intraoperative period.

During preanaesthetic check-up, a detailed history and complete physical examination including thorough airway and spine was carried out. Patient's written informed consent was taken. All routine investigations including chest x-ray (PA view), electrocardiogram (ECG) and 2-D echo were done. Patients were briefed about the epidural technique with catheter in situ and educated with a 10 cm visual analogue scale (VAS) device for assessment of pain intensity (0 indicates no pain, 10 indicates worst pain).

Patients were premedicated with tablet lorazepam 1 mg at night before surgery. Standardized general anaesthesia was administered with thiopentone, vecuronium, fentanyl and sevoflurane in a 50:50 O_2/N_2O mixture. Epidural catheter of 18-G was inserted through 16-G Tuohy needle into the epidural space in lumbar region and was directed cephalad for a 4 cm distance and fixed at back. We injected 5 ml of 0.5% levobupivacaine via epidural catheter before surgical incision in all the patients. We repeated 2.5 ml of 0.5% levobupivacaine via epidural catheter for surgery lasting longer than 2 hours, if patient remained hemodynamically stable. ECG, HR, SpO2, NIBP, EtCO2, urine output and blood loss was monitored. This study was done in cancer institute and cancer surgeries sometimes can extend so we opted general anaesthesia rather than sole epidural anaesthesia for surgery. We used fentanyl only once during induction of anaesthesia.

Patients were transferred to postoperative ICU and observed for 24 hours. The intensity of pain was assessed using VAS score at rest and at cough

in immediate post-operative period and then 2 hourly for 24 hours from the time when the epidural analgesia was started. Patients received randomly either 0.5% levobupivacaine at 3ml/hour in group A or 0.15% levobupivacaine at 10ml/hour in group B through epidural catheter in post-operative period as continuous infusion after 2 hours of last intra-operative dose of levobupivacaine. Patients were given 15 mg levobupivacaine per hour in both the groups. Intravenous inj. tramadol 100 mg as rescue medication was given if VAS score ≥ 4. HR, SpO2, SBP, DBP, MAP, motor block, sensory block and adverse effects were monitored. Total dose of rescue medication used and time for first rescue analgesia were recorded during the study period. Incidence of vomiting and nausea was also recorded. Modified Bromage scale was used for assessment of motor blockade. Ramsay sedation score was used for assessment of sedation. Primary outcome was VAS score, and secondary outcomes were motor and sensory blockade, total dose of rescue medication, time for first rescue analgesia, hemodynamic stability, nausea and vomiting.

A fall of 20% in SBP from baseline value was considered as hypotension. It was treated with inj. RL 500 ml fast infusion and inj. mephentermine 6mg if required. Bradycardia was defined as HR < 50 bpm and treated with inj. atropine 0.6 mg. Nausea and vomiting were treated with inj. Ondansetron 8mg. No active intervention done to treat motor blockade.

Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA, version 19.0 for Windows) was used for statistical analysis with all data available always. Results on continuous measurements were presented as mean ± SD and results on categorical measurements were presented in number and percentages (%). Paired and unpaired t-tests were used for analysis of parametric data. Chi-square test or Fisher's exact test was used for comparison of qualitative or categorical variables. All statistical tests were performed at a significance level of $\alpha = 0.05$ and were two-sided. Calculation of sample size was done based on mean VAS 0.6 ± 0.6cm in LV (low volume) group and 0.6 ± 0.7cm in HV (high volume) group as per reference study.[7] Total number of patients to be included in the study was calculated on the basis of a power calculation assumption on a 20% difference with $\alpha = 0.05$ and $\beta = 0.20$. Results were considered as significant if the critical level is 5% ($p < 0.05$).

Results

This study included 60 patients of ASA grade I and II who underwent abdominal surgery under general anaesthesia. Patients were divided randomly into two groups (30 patients in each). No patient was excluded from study. Patients of both groups were comparable with respect to sex, height, age, weight and duration of surgery (Table 1). No statistically significant difference was observed in type of surgery, HR, MAP, systolic and diastolic BP between the groups at baseline and in intra operative period. Patients received mean 34.16 ± 5.62 mg levobupivacaine in group A and 32.50 ± 6.23 mg levobupivacaine in group B intra operatively. No statistically significant difference was observed ($p = 0.2811$).

Table 1: Demographic data of both groups

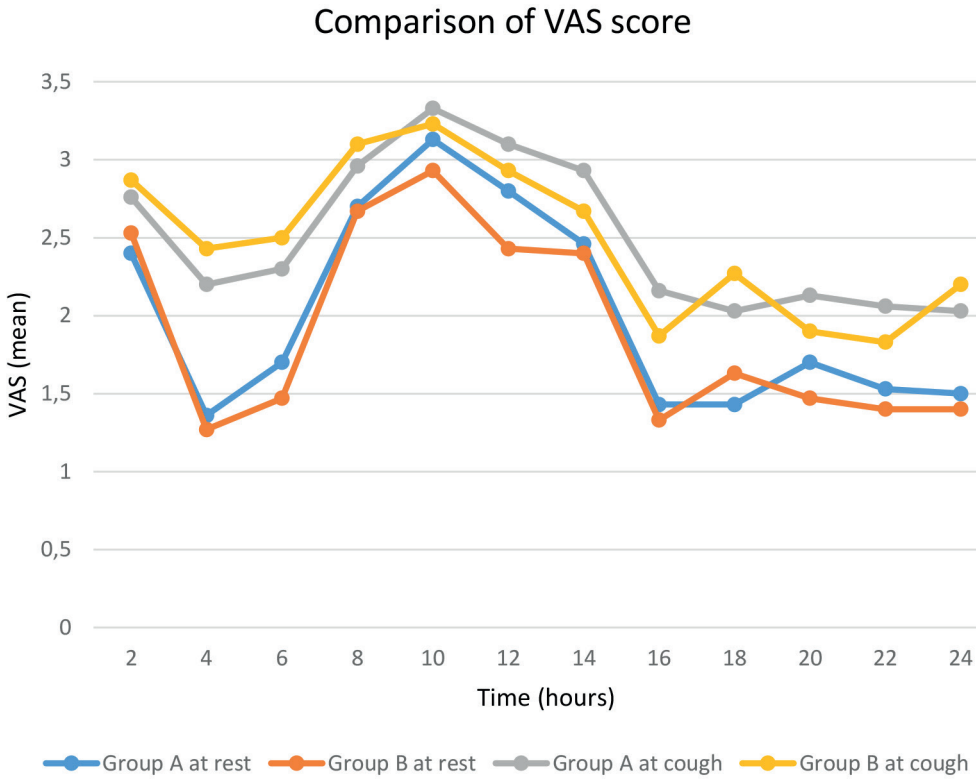
Variables	GroupA (n=30)	GroupB (n=30)	p value
Age (years), mean±SD	38.13±11.65	39.30±9.58	0.6734
Sex Male Female	7 23	6 24	-
Height (cm), mean±SD	156.16±6.86	153.93±6.43	0.1986
Weight(kg), mean±SD	61.86±9.76	62.93±8.64	0.6557
Duration of surgery(min), mean±SD	170.00±36.39	159.00±37.91	0.2562
Intra operative dose of levobupivacaine (mg), mean±SD	34.16±5.62	32.50±6.23	0.2811

n = number, cm = centimetre, kg = kilogram, min = minute, mg = milligram
(Values are expressed as Mean ± SD, $p < 0.05$ considered as significant)

No statistically significant difference was observed in VAS scores at rest and at cough between groups during first 24 hours in post-operative period indicating comparable analgesic efficacy (Graph 1).

Table 2 shows mean consumption of inj. tramadol in group A was 53.33 ± 50.74 mg and in group B was 43.33 ± 56.83 mg. No statistically significant difference was observed (p = 0.4750). No statistically significant difference was observed in

Graph 1: Comparison of VAS score at rest and at cough between two groups during post-operative period



mean first rescue analgesia time between group A (11.38 ± 2.70hr) and group B (10.17 ± 1.99 hr) (p = 0.2041).

As shown in Table 3, MAP was lower in group A in comparison to Group B throughout post-operative observation period. Hypotension was observed in 13 patients in group A while 6 patients in group B (p = 0.05). Heart rate was significantly lower in group A as compared to group B at 14, 16, 22 and 24 hours post operatively. Bradycardia was noticed in 10 patients in group A (33.33%) while in 4 patients in group B (13.33%) (p = 0.06).

As shown in Graph 2, Bromage score was higher in group A in the comparison of group B. It was significantly higher at 14 hours and was highest at 22 hours. No statistically significant difference was observed in sensory blockade between both the groups. Mean upper dermatome level of sensory block was observed at different time points are as follows; time (in hours) [group A: group B]: 2hr [T12, T12], 4hr [L1, L2], 8hr [T12, L1], 12hr [L2, L2], 16hr [L2, L1], 20hr [L3, L2] and 24hr [L3, L3].

5 patients had nausea in group A (16.66%) while 3 patients had nausea in group B (10%). Similar incidence of vomiting was observed in both the groups. Sedation, dizziness, pruritus, allergic reaction or any life-threatening complication was not observed in our patients.

Discussion

Different modalities are in use for postoperative pain management.[3] Studies have showed that local anaesthetic agent as epidural analgesia provides superior postoperative analgesia for lower abdominal surgery including laparoscopic gynaecological surgery in comparison with IV-PCA.[11,4]

M Dernedde et al. (2003)[7] evaluated and compared the analgesic quality produced by 0.5% levobupivacaine as continuous epidural infusion with

Table 2: Comparison of rescue analgesia requirement between both groups

Variable	Group A(n=30) Mean±SD	Group B(n=30) Mean±SD	p value
Time for first rescue analgesia (hr)	11.38±2.70	10.17±1.99	0.2041
Mean consumption of tramadol (mg)	53.33±50.74	43.33±56.83	0.4750

mg – milligram, hr- hour
(Values are expressed as Mean ± SD, p < 0.05 considered as significant)

Graph 2: Comparison of motor blockade - Modified Bromage scale during postoperative period

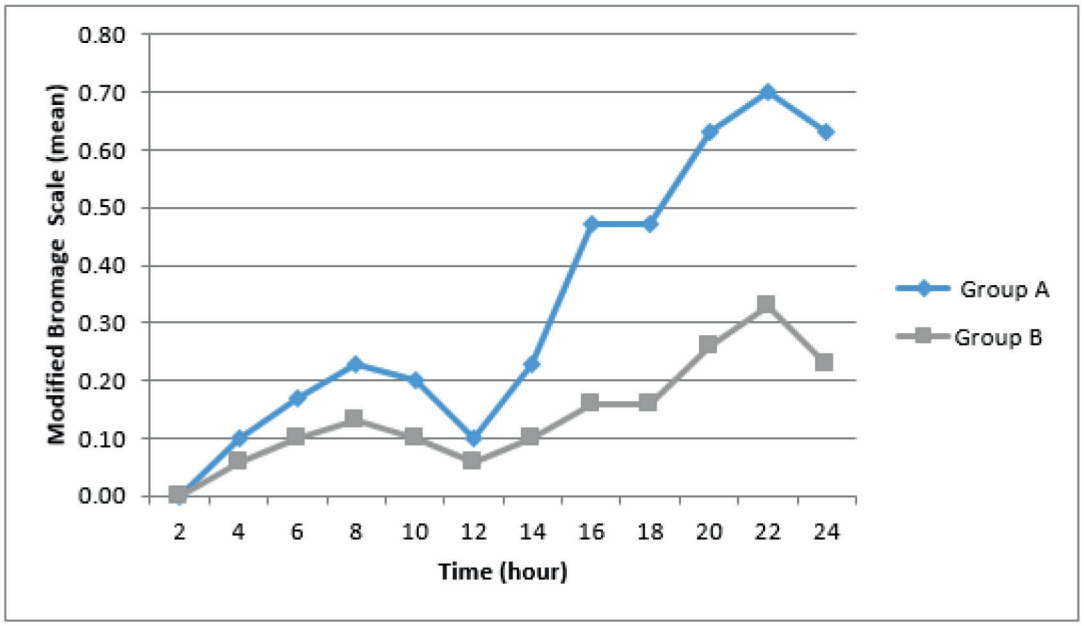


Table 3: Comparison of changes in MAP (mm of Hg) during post-operative period in both groups

Time (hour)	Group A(n=30) Mean±SD	Group B(n=30) Mean±SD	p value
2	80.55±11.58	87.03±8.31	0.0164
4	79.75±12.85	86.66±10.05	0.0253
6	79.76±11.90	86.33±9.21	0.0205
8	79.53±11.40	86.44±8.62	0.0092
10	80.47±10.63	87.36±8.84	0.008
12	80.23±10.51	87.42±9.31	0.0071
14	79.8±10.88	86.66±9.42	0.0127
16	79.98±10.95	86.89±9.00	0.0098
18	79.45±11.07	87.41±9.33	0.0033
20	79.74±10.65	87.66±9.43	0.0037
22	79.48±11.33	87.32±9.09	0.0049
24	85.76±6.73	85.59±10.19	0.9408

(Values are expressed as Mean±SD, P<0.05 is considered as significant)

dose equivalent 0.15% levobupivacaine as continuous epidural infusion after lower-abdominal surgery and no statistically significant difference was observed in VAS scores at rest during the first 48 hours postoperative period between both groups. We also used same concentrations in two groups and confirmed these findings in our study. No statistically significant difference was observed in VAS score at rest and at cough during first 24 hours postoperative period between both groups at all times.

In 2008, C. Mendola et al[12], did a randomized, prospective, double blinded comparative study of three different concentrations of 10 mg/hr levobupivacaine 0.5%, 0.25% and 0.15% in combination with sufentanil at 2.6 mg/h for thoracic epidural analgesia in patients undergoing thoracotomy and found equal analgesic quality and incidence of adverse effects in all groups. We also noticed equal analgesic quality using 0.5% and 0.15% concentrations of levobupivacaine 15 mg/h. Our results contradict these findings regarding adverse effects. We found higher incidence of motor blockade, hypotension and bradycardia in 0.5% group with similar incidence of nausea and vomiting in both groups.

In 2009, G Danelli et al.[13], evaluated the effects of levobupivacaine (10.5 mg/h) with either levobupivacaine 0.125% at 8.4 ml/h (n = 35, low concentration group) or levobupivacaine 0.75% at 1.4 ml/h (n = 35, high concentration group) in 70 patients undergoing total hip replacement. No statistically significant difference was observed in pain relief between both groups at rest. Our results also support these findings with no statistically significant difference in VAS score between both groups at rest and at cough.

The effect of local anaesthetic agent injected via the epidural space depends on a concentration gradient achieved between the extraneural and intraneural spaces that allows the diffusion of local anaesthetic agent into nerve. A critical length of the nerve fiber must be blocked by local anaesthetic agent for achieving desired effect. Long, thick motor fibers have twice critical blocking length in comparison to short, thin pain fibers. High concentration of local anaesthetic agent is needed to produce motor blockade. Lower incidence and intensity of motor blockade is produced by lower concentration of local anaesthetic agent because the lake of sufficient total amount of local anaesthetic agent inside the nerve. When epidural catheter is placed more proximal to lumbar spinal segments, it increases the risk of motor block in comparison to more cephalic approach.[14]

In our study, we observed higher motor block in group-A (0.5%, low volume) as compared to group B (0.15%, high volume). Placement of epidural catheter was done at lumbar region, proximal to motor innervation of the lower extremities that might had increased the risk of motor blockade. M Dernedde et al. (2003)[7,15] evaluated the analgesic quality and side effects exerted by a continuous epidural infusion of levobupivacaine 0.5% and compared it with a dose equivalent 0.15% levobupivacaine after lower-abdominal surgery. In contrast to our study, they observed that there was significantly less motor blockade in the LV (low volume, 0.5% group) as compared to HV (high volume, 0.15%) group ($p = 0.025$). They concluded that altering the volume and the concentration while maintaining equivalent total doses of levobupivacaine produced the same analgesic quality at rest and after coughing. We also confirmed these findings in our study.

In 2018, EL Shaarawy Ahmed Mostofa et al.[9], compared the effects of three different concentrations of levobupivacaine (0.125%, 0.25% and 0.0625%) on mode of delivery during epidural labour analgesia, characteristics of sensory and motor block and pharmacokinetic profile of the different three concentrations throughout the labour. Levobupivacaine concentrations of 0.25% and 0.125% had significantly lower VAS than 0.0625%. 39% of parturients who received levobupivacaine 0.25% had motor block (Bromage score 1). 43% of them were converted to caesarean delivery. Remaining two concentrations had no observation of motor blockade.

Mohammad H et al.[19] compared effects of 0.0625%, 0.1% and 0.125% bupivacaine mixed with fentanyl 1 mcg/ml as thoracic epidural analgesia administered through Baxter elastomeric pump at 5 ml/h in upper abdominal surgeries. They observed that hypotension was significantly higher in 0.125% group than in other groups. The incidence of other side effects including motor block, pruritus, postoperative nausea and vomiting, were found to be highest in 0.125% compared to the other groups. We also support these findings with our

study that higher concentration group had higher incidence of motor block and other adverse effects.

Halliday L et al.[20] compared ultra-low, low and high concentration local anaesthetic (bupivacaine or equivalent) for labour epidural analgesia and observed that 30 or 60 min VAS pain scores and maternal satisfaction scores were similar between the three groups. Parturients receiving ultra-low concentration were significantly less likely to have a Bromage score > 0 and increased likelihood of spontaneous vaginal delivery compared with high concentration. Our findings are also consistent with this finding regarding motor blockade.

M Dernedde et al. (2003)[7] observed no difference in median upper level of sensory blockade at different times in post-operative period between the two groups (levobupivacaine 0.5% and 0.15%). Similarly, we also observed no difference in upper dermatome level of sensory block between both the groups in our study.

These results are in accordance with previous studies that support the concept that the quality of epidural analgesia depends on the total dose of local anaesthetic agent and not on the concentration or volume.[7,16,17,18] We also observed that the quality of epidural analgesia was similar while using levobupivacaine infusion as large concentration with small volume and small concentration with large volume with constant total dose.

M Dernedde et al. in another study[17] observed that all the three groups had similar morphine consumption as rescue analgesia with same dose (5 mg/ml, 1.5 mg/ml and 0.75 mg/ml). Similar to this, no statistically significant difference was observed in requirement of rescue analgesia as inj. tramadol between two groups: group-A (53.33 ± 50.74 mg) and group-B (43.33 ± 56.83 mg) (p = 0.4750).

In other study, M Dernedde et al (2003)[7] noticed that hypotension was the most frequent adverse event in their study, that occurred in 5 patients in HV group and 2 patients in LV group. Observation of bradycardia was higher in the LV group (11 patients) than HV group (3 patients). We observed hypotension significantly higher in group A (low volume, 0.5% group) in our study. Hypotension was observed in 13 patients (43.33%) in group-A and 6 patients (20%) in group-B (high volume, 0.15%) (p = 0.05). We observed higher incidence of bradycardia, 10 patients (33.33%) in group-A in comparison to 4 patients (13.33%) in group B (p = 0.06). The higher incidence of hypotension and bradycardia in the low-volume high-concentration group may be attributed to more extensive sympathetic blockade caused by denser local anaesthetic spread at higher concentration.

In our study, we observed similar incidence of nausea in both groups (p = 0.4474). Incidence of vomiting was similar in both the groups (p = 1). M Dernedde et al. (2003)[7] observed no difference between the two groups for incidence of nausea and vomiting. Nausea was observed in five patients in the HV group, compared with four in the LV group (p = 0.72). Danelli G et al.[13] observed higher incidence of nausea in low concentration group (13.3%) versus high concentration group (6.2%, p = 0.025). Sedation, pruritus or respiratory depression was not observed in any group in our study.

Limitation of our study was that we had not used PCEA. That might give better and precise calculation of total consumption of LA to achieve adequate analgesia. We could not observe urinary retention because catheterization was done in all patients during the observation period. Other limitations were small sample size, single centre study and absence of plasma levobupivacaine concentration monitoring.

Conclusion

Continuous epidural analgesia of 0.5% levobupivacaine at 3ml/h and 0.15% levobupivacaine at 10ml/h are equally effective for postoperative analgesia at rest and at cough after abdominal surgery with similar haemodynamic parameters and incidence of side effects. The study demonstrated that postoperative analgesia depends on total dose of local anaesthetic agent and not on the concentration or volume.

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