Original Research Article

A comparison of ropivacaine with fentanyl to bupivacaine with fentanyl for post-operative patient controlled epidural analgesia in patients undergone lower abdominal cancer surgery

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Abstract

Background: PCEA (patient controlled epidural analgesia) is a safe and effective technique for post-operative analgesia on routine surgical wards. Use of the epidural catheter as part of a combined epidural-general anesthetic technique results in less pain and faster patient recovery immediately after surgery than general anesthesia followed by systemic opioids does.

Aim: In this prospective, randomized, double – blind study, we compared the analgesic effectiveness, hemodynamic changes and other side effects of epidural analgesia with drug combination – bupivacaine with fentanyl and ropivacaine with fentanyl in different concentrations.

Material and methods: It was a prospective, randomized, double – blind study. Sixty patients of ASA I-II and age group 18-65 years divided in four groups 15 patients in each group (Group B1 bupivacaine 0.1%; Group B2 bupivacaine 0.05%; Group R1 ropivacaine 0.1%; Group R2 ropivacaine 0.05% with fentanyl 5micrograms/ml in each groups). After taking consent from patients epidural catheter was placed and study drugs were given to every patient. Visual analogue scale, heart rate,

blood pressure, sedation score, modified bromage scale and other side effects were noted for the next 48 hours. Statistical analysis was done by using Medcalc 12.2.1.0 version statistical analysis software.
Results: All four groups were comparable in terms of analgesia but group B1 patients had significant decrease in blood pressure at all time intervals. This group also had loss in motor power of lower extremity p value 0.020 than all other three groups.
Conclusions: We concluded that ropivacaine 0.1% with fentanyl 5 µg/mL after major abdominal surgery provides optimal dynamic analgesia without significant adverse effects.

Key words

Patient controlled epidural analgesia (PCEA), Ropivacaine, Bupivacaine, Fentanyl, Visual analogue scale (VAS).

Introduction

The goal of analgesia is to achieve analgesia at rest as well as on movement, at the same time minimizing the side effects of analgesics. Use of the epidural catheter as part of a combined epidural-general anesthetic technique results in less pain and faster patient recovery immediately after surgery than general anesthesia followed by systemic opioids does [1].

The use of continuous epidural or peripheral catheter techniques may be able to actively participate in postoperative rehabilitation, which may improve short- and long-term recovery after surgery [2].

The pharmacodynamic profile of ropivacaine was reported to be superior to that of bupivacaine, especially in clinical settings where early ambulation is required. Therefore, we conducted this study to evaluate the efficacy of different concentrations of ropivacaine with fentanyl for postoperative patient controlled epidural analgesia as compare to bupivacaine with fentanyl, to assess the safety of use of epidural ropivacaine with fentanyl as compare to bupivacaine with fentanyl and to test the hypothesis that epidural ropivacaine produces less cardio toxicity, less neurotoxicity and less motor block than bupivacaine.

The intensity of acute postoperative pain is a significant predictor of chronic postoperative pain [3]. Control of acute postoperative pain may improve long-term recovery or patient-reported outcomes (e.g., quality of life). Patients whose pain is controlled in the early postoperative period (especially with the use of continuous epidural or peripheral catheter techniques) may be able to actively participate in postoperative rehabilitation, which may improve short- and long-term recovery after surgery [2]. Optimizing treatment of acute postoperative pain can improve HRQL [4].

Materials and methods

It was a prospective, randomized, double – blind study. Randomization is done by sealed envelope technique. Blinding Technique – Observers who recorded the data i.e. pain and motor scores were blinded with respect to patient's group allocation. The observers were never be anesthesiologist providing clinical care to the patient.

We included 60 patients of age between 18 yrs to 65 yrs, ASA physical status I and II, weight 40 – 100 kg, lower abdominal surgery and patients who can be explained and was able to use patient controlled analgesia effectively.

Patients with history of allergy to amide local anesthetic and fentanyl, chronic opioid use, chronic alcoholic, motor disorders of lower limb and inability to comprehend or perform verbal or physical assessments were excluded from the study.

After taking Institutional Ethics Committee approval and informed consent from all 60 patients undergoing lower abdominal surgery

including wertheim's hysterectomy, low anterior resection and retroperitoneal lymph node dissection were randomly divided into Bupivacaine 0.1% with fentanyl 5 µg/ml (Group B1); Bupivacaine 0.05% with fentanyl 5 µg /ml (Group B2); Ropivacaine 0.1% with fentanyl 5 µg/ml (Group R1); Ropivacaine 0.05% with fentanyl 5 µg/ml (Group R2).

We explained each patient regarding use of patient controlled analgesia (PCA) device during the preanesthetic check up. An anesthesiologist who was not one of the observers prepared solutions of the study drug according to group allocation.

A baseline assessment of vital signs, pain, nausea, pruritus, sedation scores and lower-extremity motor strength was performed on all patients in a preoperative holding area. All patients received a standard premedication of midazolam (≤0.02-0.04 mg/kg) and/ or fentanyl (≤1 µg/kg) IV before placement of an epidural catheter 4–6 cm into the epidural vertebral interspaces. A 3-mL 2% lidocaine test dose containing 15 µg epinephrine was given from the catheter. If no intrathecal or intravascular injection was evident 5 min later a further 10 mL of 1% lidocaine with epinephrine 1 in 200000 is dosed. Sensory block (to cold) covering the area of the proposed incision (T10) was confirmed before surgery. An additional 5 mL of 1% lidocaine with epinephrine 1 in 200000 was given if an adequate block is not demonstrated by 15 min. After sensory blockade was substantiated, patients were randomized in a double-blinded manner by an anesthetist to receive one of four epidural infusions: according to group allocated. General anesthesia was achieved with propofol (2-2.5 mg/kg), fentanyl (≤2 µg/kg) and muscle relaxation at the discretion of the primary anesthesia team. After 1 h of induction, the epidural infusion with the blinded solution was commenced at 5mL/h after a bolus of 5ml of the study solution.

General anesthesia was maintained with isoflurane in 60% nitrous oxide and 40% oxygen. Additional muscle relaxation was administered as required. IV opioid supplementation was restricted to i.v. fentanyl during intra-operative period. During intra-operative period if patients developed hypotension (systolic pressure ≤90 mm Hg and 20% below baseline systolic blood pressure) then it was treated with mephentermine (vasopressor).

On admission to the post anesthesia care unit, patients received a standard teaching regarding use of the PCEA device. The standard settings include a fixed bolus of 2 mL of study solution, 15 min lockout time and a background infusion of 5 mL/h. Patients with inadequate analgesia (visual analogue scores (VAS) for pain at rest >3/10) received a 4mL bolus of study drug and a 2 mL/h increase in the rate of infusion and then reassessment was done in 20 min. The same intervention was repeated until patients reported a VAS at rest <3/10 upto maximum of 13 ml/hour. All patients received paracetamol 1 g every 6 hourly either orally, via a nasogastric tube, or rectally. All patients received injection Ondansetron 4 mg IV 8 hourly for three days. Patients were transferred to standard nursing care on the hospital ward when standard post anesthesia care unit discharge criteria were met. Inadequate analgesia in hospital ward was treated as described above. The nursing team was instructed to call an anesthesiologist to assess the patient if more than two increases in the infusion rate for inadequate analgesia were required, if motor block develops, if patients develops hypotension (systolic pressure ≤90 mm Hg and 20% below baseline systolic blood pressure) or postural hypotension impairing ambulation. Hypotension on the ward was treated with a 500-mL bolus of normal saline. In addition, for hypotension or for motor-block impairing ambulation, the infusion was held for 1 h then restarted lower hourly rate. If inadequate pain relief because of unilateral block is suspected, or if unilateral motor block is assessed, the epidural catheter was withdrawn 1 cm from the epidural space or the catheter is replaced. For interim treatment of inadequate analgesia, fentanyl IV will be administered. No other analgesics,

including nonsteroidal anti-inflammatory drugs (NSAIDs), were administered during the infusion of the study drug. If analgesia was inadequate with the infusion rate at 13mL/h and the patient had received two additional 4-mL bolus doses at least 30 min apart, the case was considered as an "efficacy failure," and alternate analgesia was provided.

All patients were assessed by a blinded investigator for 1hour after completion of surgery to assure adequate analgesia, proper equipment function, and stable vital signs and then every 4 hourly till 24 hours and then every 6 hourly till next 24 hours. In addition to the preoperative baseline assessment, patients underwent subsequent assessments for motor functions (modified Bromage scale) three times in a day for first 48 hours in postoperative period morning (7 A.M. – 9 A.M.) afternoon 2 P.M. – 4 P.M and night 7 P.M. to 9 P.M. Study measurements includes the following: blood pressure and heart rate; pain scores at rest, with coughing and with mobilization (supine to standing), and with lower-extremity motor function assessments (modified Bromage Scale), pruritus and nausea scores (VAS 0–10 scale); observer-rated sedation score 0–4 (0 = no sedation, 1 = mildly sedated, 2 = sleeping but easily aroused, 3 = sleeping but difficult to arouse, 4 = not arousable); and ability to ambulate (yes/no). For occurrence measurements pruritus and nausea were considered to be present if VAS >5. Side effects were considered clinically significant if they persist for two consecutive measurement periods despite adjustments to the analgesic regimen as described above.

Pain was measured using a visual analog scale (VAS) (0 = no pain, 10 cm = worst pain imaginable). Motor block was measured using the modified Bromage scale [5] (0 = no motor block, 1 = inability to raise extended leg, 2 = inability to flex knee, 3 = inability to flex ankle). Twice daily mobilization (walking bed to chair) was encouraged and the VAS score was recorded and if patients were unable, the reason for inability to do so. All other aspects of care were left to the patient's own clinicians. The duration of surgery was also noted. Specific daily patient questioning include quality of analgesia (1 = poor, 2 = fair, 3 = good, 4 = excellent), the presence of pruritus or nausea as an index of recovery and all adverse events were recorded.

Sample size was calculated at 80% of study power, alpha (α) error of 0.05 and beta (β) error of 0.2 assuming standard deviation of 1.5 in VAS score immediately after shifting the patient. For minimum detectable difference of 2 in VAS score sample size required comes to 14 patients in each group. This was further enhanced to 15 patients in each group considering dropout or attrition due to adverse reactions, hypersensitivity reactions and other effects. Chi – square test was used for demographic variables and for comparative study of all four study groups one way AnoVA test was applied on observation tables summarized as mean(SD) or as percentages. The statistical analysis was carried out using Medcalc 12.2.1.0 version (***MedCalc*** Software Mariakerke, Belgium). P value < 0.05 was considered statistically significant.

Results

Demographic variables age, sex, ASA grade, and weight did not differ significantly among the four groups respective **Tables - 1, 2, 3, and 4**. No patients were excluded from the study. Hemodynamic data were as per **Graphs - 1, 2, 3, and 4**. Pulse rate was not significantly different in all the four groups at all the time intervals (**Graph - 1**). SBP was significantly low in group B1 at all time intervals after start of study solution from all other three groups except for immediately after shifting the patient (p value 0.096) (**Graph - 2**). DBP was significantly low in group B1 patients except for the five minute (p value 0.266), sixty minute (p value 0.093) and at fourty eight hours (p value 0.347) after start of study solution (**Graph - 3**). MBP was also significantly low in group B1 patients at all time intervals (**Graph - 4**).

Table 1

Age (Yrs)

Group	Mean	Std. Deviation	p' value*
B1	46	11	0.251
B2	52	8	
R1	47	11	
R2	52	10	

Graph – 1

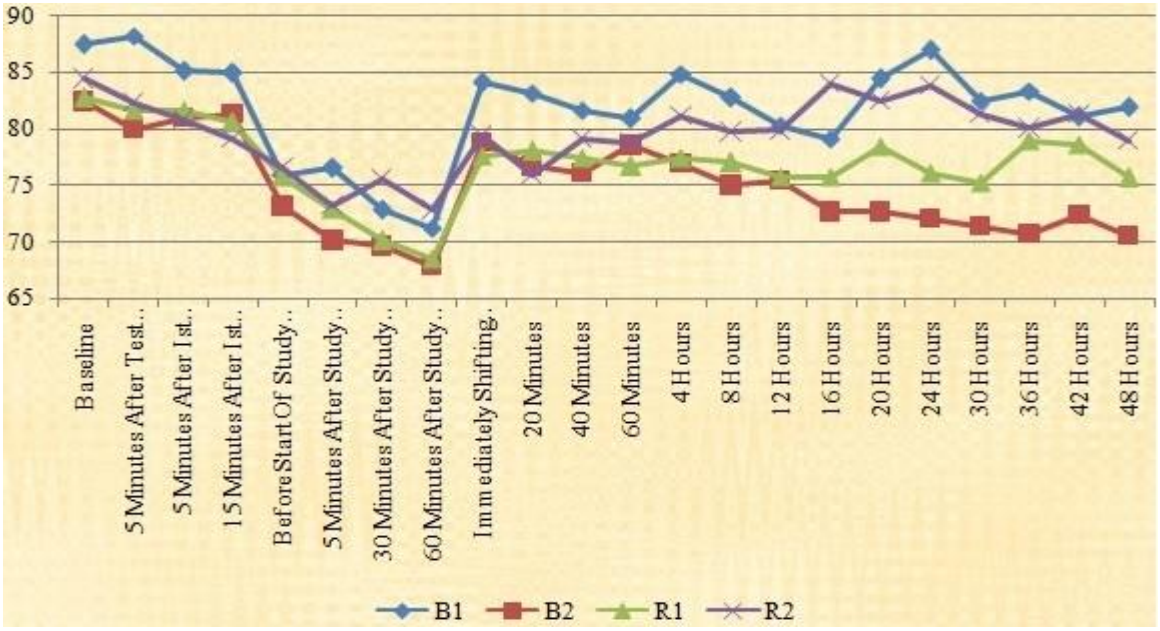


Table 2

SEX

Sex	B1		B2		R1		R2		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
MALE	2	13.33	3	20.00	3	20.00	5	33.33	13	21.67
FEMALE	13	86.67	12	80.00	12	80.00	10	66.67	47	78.33
Total	15	100.00	15	100.00	15	100.00	15	100.00	60	100.00

Chi-square = 1.866 with 3 degrees of freedom; P = 0.599

Graph – 2

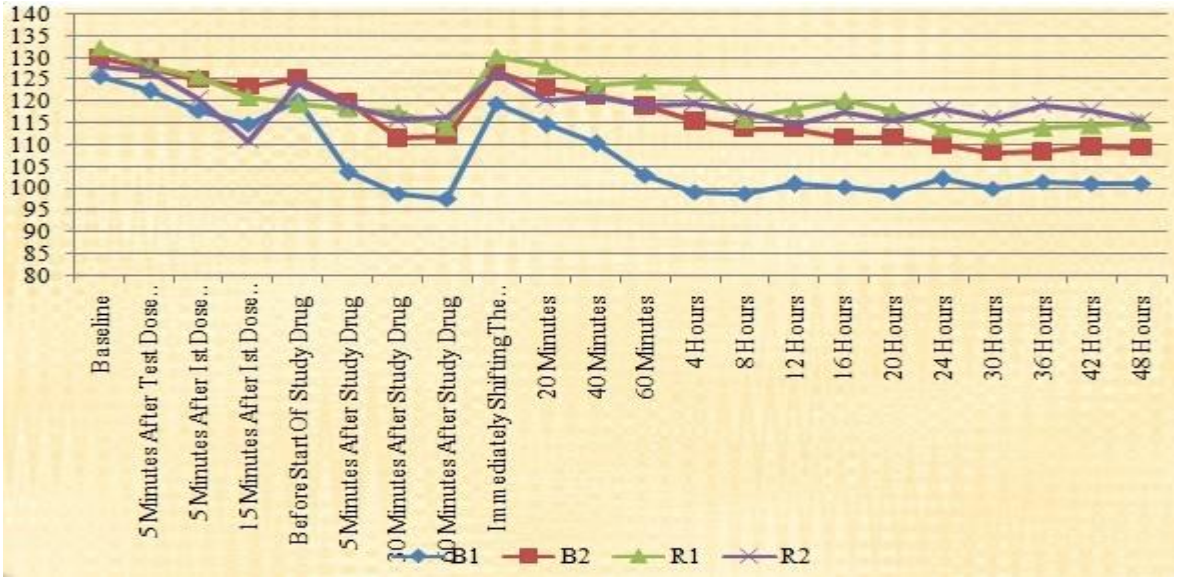


Table 3

ASA Grade

ASA grade	B1		B2		R1		R2		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
I	12	80.00	9	60.00	12	80.00	7	46.67	40	66.67
II	3	20.00	6	40.00	3	20.00	8	53.33	20	33.33
Total	15	100.00	15	100.00	15	100.00	15	100.00	60	100.00

Chi-square = 5.40 with 3 degrees of freedom; P = 0.144

Graph - 3

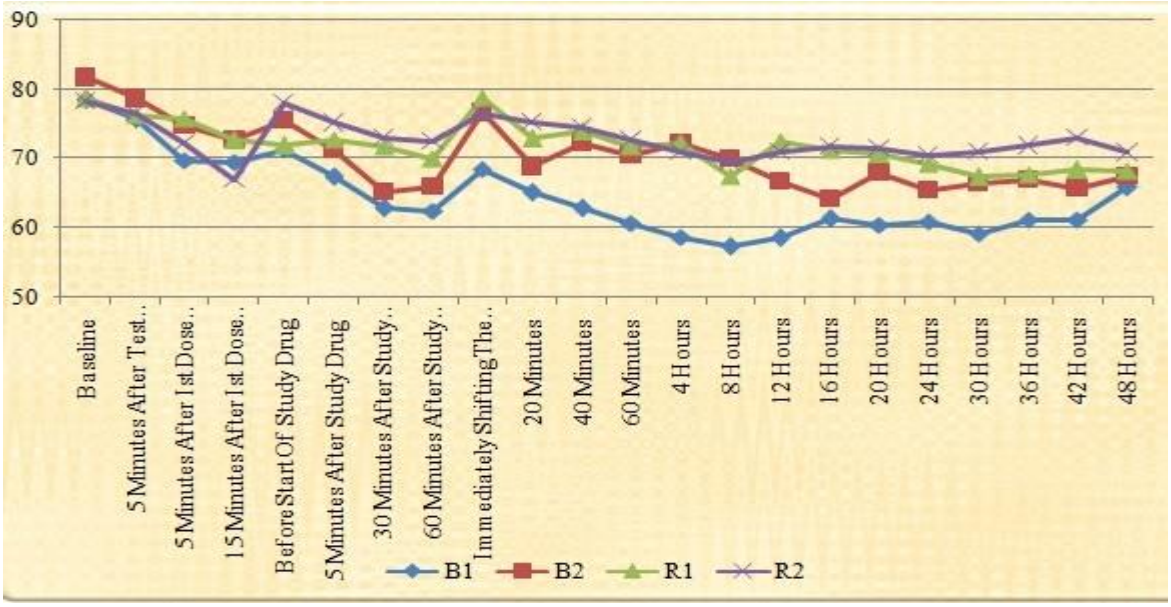
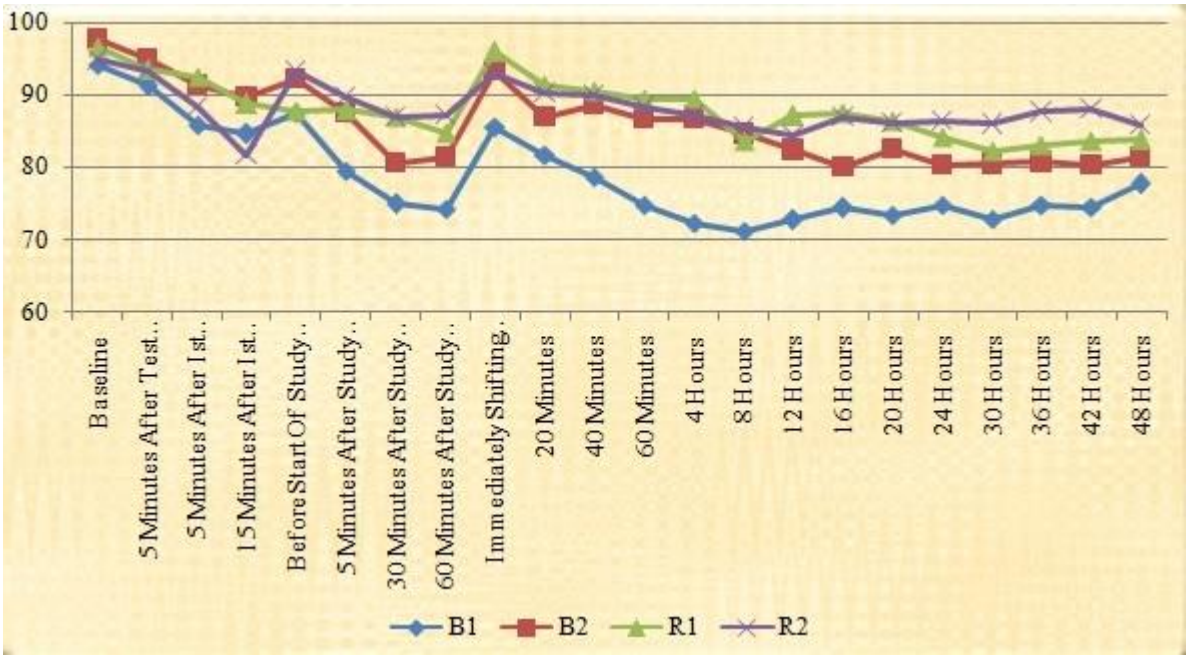


Table 4

Weight (Kg)

Group	Mean	Std. Deviation	p' value*
B1	58	8.2	0.908
B2	60	8.7	
R1	58	7.2	
R2	59	7.9	

Graph – 4



Patients in all the four groups experienced adequate pain relief during the 48 hours after surgery, but pain score at rest was significantly different at immediately shifting the patient (p value 0.000), twenty minutes (0.000), fourty minutes (p value 0.013), Four hours (p value 0.081), twelve hours (p value 0.010), sixteen hours (p value 0.012), twenty hours (p value 0.021), twenty four hours (p value 0.001) in first 24 hours with maximum pain relief in group R1 and minimum pain relief in group B2 at all time intervals, but it was not significantly different after twenty four hours in all the four groups (**Graph - 5**).

Pain at cough was significantly different at eight hours (p value 0.000), sixteen hours (p value 0.000), twenty four hours (p value 0.043) and thirty six hours (p value 0.013) with minimum pain score in group R1 and maximum pain score in group B2 (**Graph - 6**).

Pain score at movement from supine to sitting was significantly different at four hours (p value 0.003), sixteen hours (p value 0.021) and twenty four hours (p value 0.029) with minimum pain score in group R1 and maximum pain score in group B2 but it was not significantly different after twenty four hours in all the four groups (**Graph - 7**).

Post-operative nausea vomiting, sedation score and total volume of study solution used and patient satisfaction were not statistically different in all the four groups. None of the patient had complained of pruritus for all three PODS.

All the patients had indwelling urinary catheter for three days. Therefore, urinary retention as side effect could not be evaluated.

Motor power loss was significantly high (p value 0.020) in group B1 as compare to all the other three groups on all three days of observation (**Table - 5**). The total volume of study solution used was minimum for group R1 patients and maximum for group R2, and it was statistically significant after 48 hours (p value 0.022) (**Table - 6**).

Overall patient satisfaction concerning the pain management regimen was good to excellent in all the four groups. There is no statistically significant difference between all the four groups (p value 0.659) (**Table - 7**).

Table 5

MOTOR POWER LOSS (Mean ± SD)

Group	POD	POD1	POD2
B1	0.20 ±0.41	0.33 ±0.49	0.40 ±0.51
B2	0.00 ±0.00	0.07 ±0.26	0.07 ±0.26
R1	0.00 ±0.00	0.07 ±0.26	0.07 ±0.26
R2	0.00 ±0.00	0.00 ±0.00	0.07 ±0.26
'p' Value	0.021	0.020	0.018
	S	S	S

Graph – 5

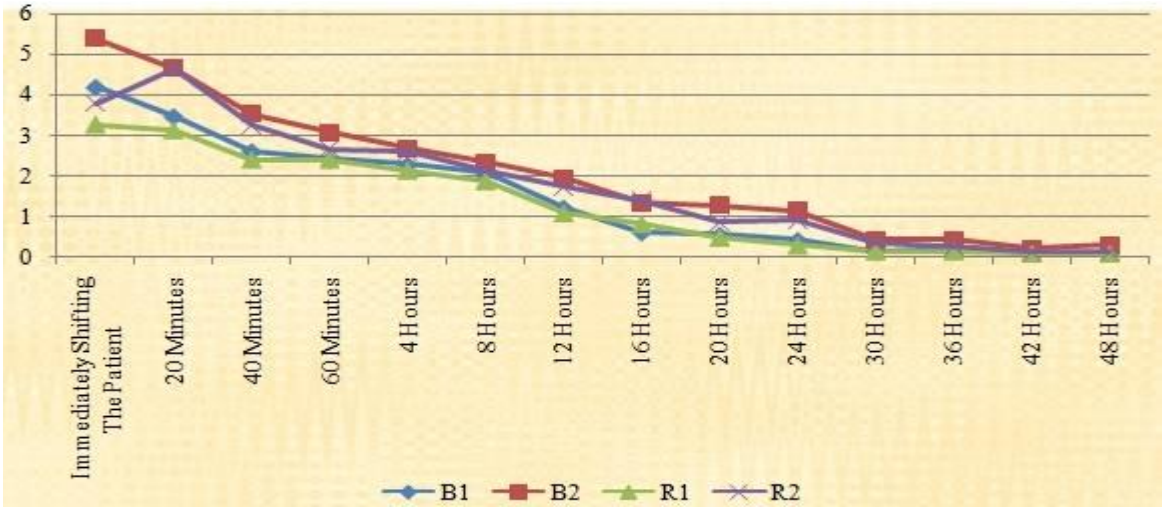


Table 6

Total Volume of Study solution used (Mean ± SD)

Group	First 24 Hours	Second 24 Hours
B1	152.00 ±20.69	140.80 ±32.50
B2	162.00 ±23.87	165.47 ±27.03
R1	148.53 ±17.80	141.93 ±19.72
R2	172.93 ±48.37	170.4 ±44.34
'p' Value	0.128	0.022
	NS	S

Graph – 6

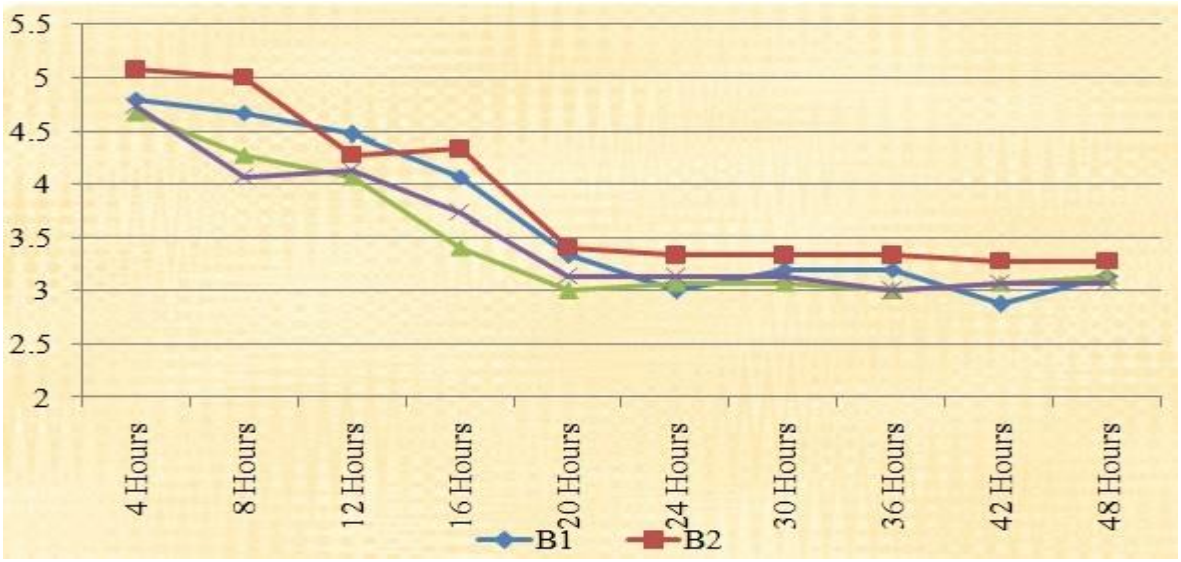
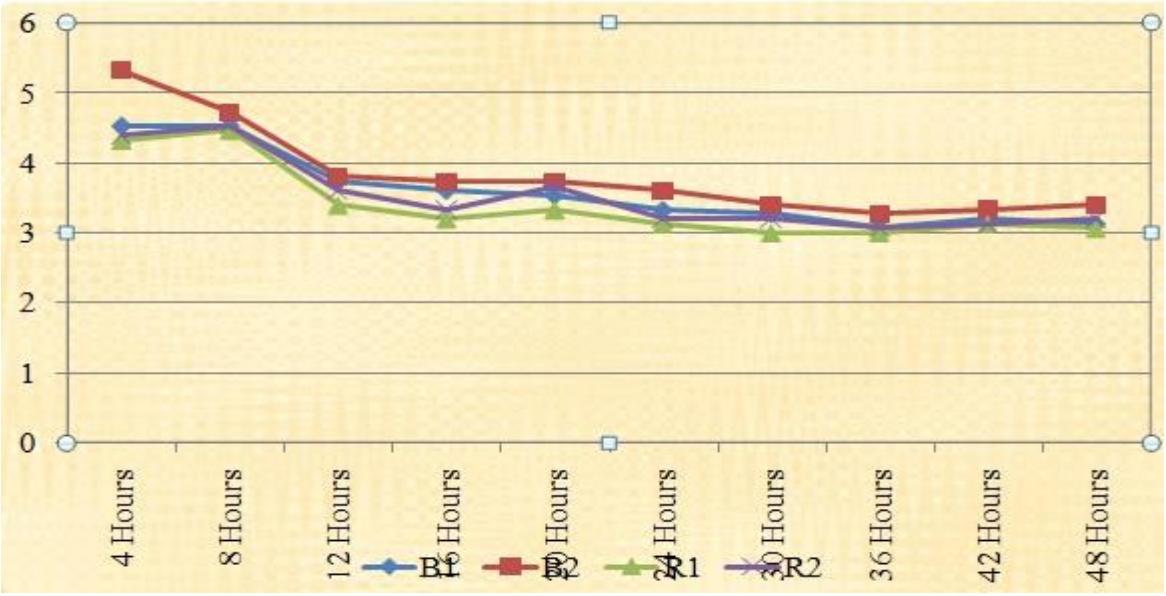


Table 7

Patient satisfaction

Group	Mean	Std. Deviation	p' value*
B1	2.93	0.59	0.659
B2	2.8	0.68	
R1	3.07	0.46	
R2	3.00	0.65	

Graph – 7



Discussion

After institutional Ethics Committee approval study was conducted in a tertiary care cancer centre from May 2010 to May 2012. Sixty patients of age group 18-65 years and ASA grade I–II undergoing lower abdominal cancer surgery such as wertheim's hysterectomy, low anterior resection and retroperitoneal lymph node dissection were included in our study. Patients with history of allergy to amide local anesthetic or fentanyl, h/o chronic opioid use, or any motor disorder of lower limb were excluded.

Good pain control in the postoperative period has a role in improving the surgical outcome with reduced morbidity and mortality, and there is a common consensus that optimal dynamic pain relief is a prerequisite for early postoperative recovery. This is more important in cancer patients who are physiologicaly and psychologically more comprised. Surgeries are more intense with lymph node dissection which causes more pain, often needs i.v. opioids in high doses that can cause sedation and respiratory depression. This delays patient's ambulation and recovery.

In our study, we compared different concentrations of ropivacaine with fentanyl for postoperative patient controlled epidural analgesia with bupivacaine and fentanyl.

Continuous epidural infusion of a local anesthetic-opioid combination provide analgesia superior to that of intravenous PCA with opioids [6] and also decreases postoperative pulmonary complications in patients undergoing abdominal and thoracic surgeries [7]. Use of a continuous or background infusion in addition to the demand dose is more common with PCEA than with intravenous PCA and may provide analgesia superior to that with the use of a demand dose alone [8].

Patients in all the four groups experienced adequate pain relief during the 48 hours after surgery, but pain score at rest was significantly different at immediately shifting the patient (p value 0.000), twenty minutes (0.000), forty minutes (p value 0.013), four hours (p value 0.081), twelve hours (p value 0.010), sixteen hours (p value 0.012), twenty hours (p value 0.021), twenty four hours (p value 0.001) in first 24 hours with maximum pain relief in group R1 and minimum pain relief in group B2 at all time intervals, but it was not significantly different after twenty four hours in all the four. Our all patients had good pain scores (<4 on POD1) with least sedation scores were able to sit in bed on

very next day morning and were able to do spirometry. Neither any patient developed complications related to epidural analgesia, nor any patient developed pulmonary infections, any cardiac morbidity, ileus or acute renal failure in perioperative period.

Epidural administration of local anesthetic-opioid combination provides superior postoperative analgesia (including dynamic pain relief), limits regression sensory blockade, and possibly decreases the dose of local anesthetic administered [9].

C. N. H. Tan, et al. [10] found in their study the optimal concentration of fentanyl in bupivacaine 0.1% after thoracotomy is 5 µg/mL. They compare the concentration of fentanyl 2 µg/mL, 5 µg/mL and 10 µg/mL. They found 16 patients in-group 10 were having sedation score >1 as compare to 10 each in group 2 and group 5. Number of patients with episodes of unsatisfactory pain VAS score > 30 mm and Observer verbal rating scale (OVRS) > 1 at each of four hour assessment was significantly higher (p value< 0.01) in group 2 than in group 5 and group 10. We also used the concentration of fentanyl 5 µg/mL and it was associated with sedation score 1 in Four to ten patients (6.67%-16.67%) which is desirable in the postoperative period.

Peter S. Hodgson, et al. [11] was found same findings in study to compare the ropivacaine with fentanyl to bupivacaine with fentanyl for patient controlled epidural analgesia in abdominal surgery. They found PCEA with bupivacaine/fentanyl 4 µg/mL and ropivacaine/ fentanyl 4 µg/mL as 0.05% and 0.1% solutions appears clinically equipotent. Lower-extremity motor function decreases during PCEA (10-35%decrease from preoperative, P<0.001) and was equivalent among groups. Lower extremity motor function decreases, but is unlikely to result in prolonged inability to ambulate. Use of a 0.05% solution may be advantageous to decrease local anesthetic use and prevent transient motor block.

We assessed the motor power by modified bromage scale, and ropivacaine fentanyl group had less motor blockade than bupivacaine – fentanyl group. None of the patient had vomiting only a few patients had mild nausea in the postoperative period and it was not statistically different. None of our patient had pruritus.

A review article by Gerg C. Meister, et al. [12] to compare the effect of epidural analgesia with 0.125% ropivacaine with fentanyl to 0.125% bupivacaine with fentanyl during labour demonstrated no differences in verbal pain scores, local anesthetic use, patient satisfaction, or side effects between groups and the ropivacaine/ fentanyl group developed significantly less motor block than bupivacaine/fentanyl.

Ayad, et al. [13] found in their study to compare epidural ropivacaine/ fentanyl versus bupivacaine/fentanyl for postoperative analgesia following lumbar disc surgery that patients in group I ropivacaine 0.125% and fentanyl 2 mcg/mL were having least incidence of motor blockade than group II bupivacaine 0.125% and fentanyl 2 mcg/mL and group III bupivacaine 0.0625% and fentanyl 4 mcg/mL respectively 3%, 22 % and 6 %. This study also showed that the decreasing concentration of local anesthetic reduces the chances of motor blockade and patients in group I developed less hypotension (14.3%) as compare to group II (19.4%) and group III (18.8%) with p value of <0.05 for group II or III versus group I.

In our study heart rate was not significantly different in all the four groups. Systolic Blood pressure, diastolic blood pressure and mean blood pressure was significantly lower in group B1 at all time intervals as compare to all other three groups. Ropivacaine group patients developed less hypotension as compare to Bupivacaine group patients ‘p’ value (< 0.05) at all time intervals except for immediately shifting the patients for SBP. For DBP it was significant at all time intervals (‘p’ value <0.05) except for at fourty two hours. For MBP at all time intervals

it was statistically significant ('p' value <0.05). Respiratory rate and pulse oximetry were not significantly different among the groups.

Patient satisfaction is an important consideration in the field of postoperative pain management. Postoperative pain management by anesthesiology team in our hospital was satisfactory, which is evident by the fact that in our study overall satisfaction concerning the pain management regimen was good to excellent in all four groups. This may also be due to frequent monitoring, patient involvement in self-care and their control over pain. There is no statistically significant difference between satisfaction level in all four groups (p=0.659).

Conclusion

Our study demonstrated that, when infused through a epidural catheter a solution of ropivacaine 0.1% with fentanyl 5 µg/mL provide optimal analgesia after lower abdominal surgery without significant adverse effects like hypotension and motor power loss.

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