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Comparison of epidural bupivacaine-fentanyl and ropivacaine-fentanyl for postoperative analgesia in major abdominal surgeries - a prospective, randomised study

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Abstract

Introduction and Aims: The pain after major abdominal surgeries, if treated inadequately, may lead to increased postoperative morbidity and delayed recovery. The present study aims to compare continuous epidural infusion of ropivacaine-fentanyl with bupivacaine-fentanyl for postoperative analgesia in major abdominal surgeries.

Materials and Method: This prospective, randomised, double blind study was conducted in 112 patients undergoing major abdominal surgeries. The patients were divided into two groups: each involving 56 patients. One group received 0.125% bupivacaine + 1µg/ml of fentanyl and the other received 0.2 % ropivacaine + 1 µg/ml of fentanyl. Both the infusions were started at a constant rate of 5 ml/h at the end of surgery. The Visual analogue scale (VAS) to assess pain, heart rate, systolic blood pressure, diastolic blood pressure, duration of surgery and anaesthesia, amount of crystalloids used and side effects were noted and compared at different time intervals. The data was analysed using SPSS 20.0 (trial version).

Results: The mean of VAS pain score after 1,2,4,6,8,12 and 24 hours of surgery was less in RF group as compared to BF group and the total rescue analgesia consumption in 24 hours after surgery was 2.4 g (mean) in BF group and 1.3 g(mean) in RF group and the difference was statistically significant ($P < 0.0001$). There were no statistically significant differences in haemodynamic or physiologic variables when compared with both the groups.

Conclusion: Analgesic potency and motor sparing effect of ropivacaine-fentanyl is better than bupivacaine-fentanyl at doses used in our study.

Keywords: Bupivacaine, Epidural analgesia, Ropivacaine, Endotracheal intubation.

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Introduction

Postoperative pain, despite considerable concurrent advancement in the field continues to be a challenge and is often inadequately treated, leading to patient anxiety, stress and dissatisfaction.[(1)]

Ropivacaine is a local anaesthetic that may be superior to bupivacaine for epidural analgesia as it has been claimed that ropivacaine produces less motor block but equipotent analgesia compared with bupivacaine in similar doses, although this is controversial.[(2)]

Recently, few studies have compared bupivacaine with ropivacaine for postoperative analgesia.[(3)] However, most of these studies have been in the context of labour analgesia and the results have been contradictory.[(4)] A dose finding study for postoperative analgesia in patients undergoing abdominal surgeries demonstrated that 0.2% ropivacaine provides the best balance between analgesia and motor block[(5)] and as we know that ropivacaine is 40% less potent than bupivacaine, we decided to compare 0.2% ropivacaine with 0.125% bupivacaine, which should be equipotent, to compare analgesia, duration of action and haemodynamic changes in the two groups.

Materials and Method

This prospective, randomised, double blind study, approved by the institutional ethical committee was carried out from March 2014 to March 2015. Informed consent was taken from all the patients prior to the study. A total of 112 patients of American Society of Anesthesiologists (ASA) grade 1 and 2, of either sex and aged between 20 to 60 years scheduled for major abdominal surgeries under general anaesthesia were selected for the study. Sample size calculation was done using the formula; $N = t^2 \times p\ (1-p) / M^2$ {where**: N** = required sample size. **t** = confidence level at 95% (standard value of 1.96) **p** = estimated proportion of major abdominal surgeries out of all other surgeries which were performed in our hospital in last 12 months, total 180 cases of major abdominal surgeries were performed out of 2000 total surgeries in last 12 months (p=9%), **M** = margin of error at 5% (standard value of 0.05). Hence, required sample size was calculated by using above formula, which was 112. The patients were randomly allocated into two groups of 56 each to be started on one of the following continuous epidural infusions: BF group was started with 0.125% bupivacaine + 1 µg/ml of fentanyl or RF group with 0.2 % ropivacaine + 1 µg/ml of fentanyl. Both the infusions were started at a constant rate of 5 ml/h. Patients with allergy to study drugs (bupivacaine,

ropivacaine and fentanyl), those on anticoagulants or history of bleeding diathesis, haemodynamic instability, local infection at the site of epidural needle insertion or those undergoing emergency surgeries were excluded from the study.

All study drugs were prepared by an anaesthesiologist not involved in the study and data collection. Randomisation was done by random number table to select the first group out of two groups. The cases were allocated then by systematic way (systematic randomised allocation method). Data collection, analysis and study drugs instillation were done by two separate anaesthesiologists who were not involved in the conduct of anaesthesia. So in this way, both patients as well as investigator were unaware about the study drugs.

Procedure was explained and written informed consent was taken from all the patients. Assessment of postoperative analgesia was done using Visual analogue scale. Patients were educated about the standard VAS pain score of 0-10, 0 being 'no pain' and 10 being 'worst imaginable pain' during preanaesthetic evaluation visit. A VAS score of 1-3 was considered as mild pain, 4-7 as moderate pain and 8-10 as severe pain. A common anaesthesia protocol was followed in all patients which included ranitidine 50 mg orally and alprazolam 0.25 mg orally, the evening before surgery, standard monitoring with pulse oximetry, non-invasive blood pressure, capnography and three lead electrocardiogram.

An epidural catheter was placed under aseptic conditions at T9-T11 interspaces for upper abdominal surgeries and L1-L3 interspaces for lower abdominal surgeries and a length of 5 cm of epidural catheter was fixed inside. Subsequently, a test dose (3 ml of 2% lignocaine with 1 in 200,000 adrenaline) was injected to detect inadvertent intrathecal or intravascular placement of catheter after negative aspiration for CSF or blood. Induction was done with intravenous (IV) midazolam (0.05mg/kg), followed by fentanyl (2 µg/kg) and propofol (1.5 mg/kg). Muscle relaxation was achieved by IV vecuronium bromide (0.1mg/kg). After Endotracheal intubation, general anaesthesia was maintained with isoflurane 1 to 2% with oxygen and nitrous oxide 50:50 ratio. Ventilation was adjusted to maintain end tidal CO_2 between 35-40 mmHg. After surgery, patients were successfully extubated and shifted to post-operative recovery room. When the patients started complaining of pain as assessed by VAS score, and when VAS score was > 3, all patients received an initial bolus dose of 8 ml of study drug followed by epidural analgesia infusion, started using either 0.2 % ropivacaine + 1µg/ml fentanyl or 0.125% bupivacaine + 1µg/ml fentanyl at the constant rate of 5 ml/h. VAS pain score was recorded at 1, 2, 4, 6, 8, 12, 24 hours after surgery. Time duration of first demand for rescue analgesia and total dose consumption in 24 hours were recorded. 1g paracetamol IV was given as rescue analgesic on demand up to a maximum dose of 4g in 24 hours. Regular use of analgesic drugs could have masked the actual effect of the study drugs; therefore we used the analgesics on demand only. Injection tramadol IV in a dose of 50 mg was reserved, apart from the rescue analgesic, for the interim management of inadequate analgesia. Rescue analgesia was given when VAS score was > 3 on a scale of 0 - 10. Monitoring of vitals including heart rate (HR), blood pressure were recorded at intervals of 15 min, 30 min, 1 h, 2h, 6h, 12h & 24h after start of epidural infusion postoperatively.

Modified Bromage scale was used to assess motor block. Motor block was assessed at intervals of 30 min, 60 min, 2 hrs, 4hrs, 6 hrs, 12 hrs and 24 hrs after start of epidural infusion. Patients having motor block more than grade 1 were considered as significant motor block in our study. Following side effects of the studied drugs were also observed during postoperative period after start of epidural infusion at 30min, 60 min,2 hrs,4 hrs, 6 hrs, 12 hrs and 24 hrs; nausea and vomiting (NV), hypotension (H) defined as more than 20% reduction of systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) from baseline and motor blockade (M) (motor block more than grade 1) Patients were followed up for an additional period of 24 hours for any post operative or untoward complications before finally removing the epidural catheter.

Statistical Analysis: The data was analysed using SPSS 20.0 (trial version) and the variables were expressed as mean ± standard deviation. The comparison of normally distributed continuous variables within the groups was performed using ANOVA test. We used the unpaired student t test for comparing the means of both groups and chi-square test was used to find the association between two groups. For all statistical tests, a P value less than 0.05 was considered significant.

Results

Both the groups were comparable with regards to age, sex distribution, weight and height. The percentage of females was found to be higher than males in each group showing no statistically significant difference (P =0.315). We also analysed the total IV fluids required for patients in both groups during anaesthesia and found that the difference was not statistically significant. There was no statistically significant difference between the groups regarding duration of anaesthesia (P = 0.427) and duration of surgery as well (P = 0.590). [Table 1]

Table 1: Demographic data

	Group	N	Ratio	Mean	Std. Deviation	T Value	P value
Age	BF Group	56	-	48.2143	9.35310	0.920	0.360
	RF Group	56	-	49.7321	8.06224		
BMI	BF Group	56	-	23.0800	2.32234	0.709	0.480
	RF Group	56	-	23.3867	2.25856		
IV crystalloids	BF Group	56	-	1769.6429	261.06052	1.391	0.167
	RF Group	56	-	1710.7143	179.82676		
Duration of Surgery	BF Group	56	-	156.3571	10.05336	0.541	0.590
	RF Group	56	-	155.4643	7.17309		
Duration of Anesthesia	BF Group	56	-	173.9107	11.25615	0.798	0.427
	RF Group	56	-	175.3393	7.27206		
Gender(M:F)	BF Group	56	16:40	-	-	-	0.315
	RF Group	56	21:35				

Regarding post-operative analgesia, we analysed the VAS score seven times in 24 hours; out of which the mean of VAS pain score after 1, 2, 4, 6, 8, 12 and 24 hours of surgery was less in RF group as compared to BF group and the difference was statistically significant at 1, 2, 4, 6 and 24 hours. [Table 2]

Table 2: Mean of VAS pain scores at different time intervals in the two groups

	Group	N	Mean Rank	Sum of Ranks	U Value	P value
VAS 1 Hours	BF	56	74.33	4162.50	569.50	<0.0001*
	RF	56	38.67	2165.50		
VAS 2 Hours	BF	56	70.68	3958.00	774.00	<0.0001*
	RF	56	42.32	2370.00		
VAS 4 Hours	BF	56	68.46	3834.00	898.00	<0.0001*
	RF	56	44.54	2494.00		
VAS 6 Hours	BF	56	62.74	3513.50	1218.5	0.035*
	RF	56	50.26	2814.50		
VAS 8 Hours	BF	56	62.01	3472.50	1259.5	0.057
	RF	56	50.99	2855.50		
VAS 12 Hours	BF	56	61.46	3442.00	1290.0	0.082
	RF	56	51.54	2886.00		
VAS 24 Hours	BF	56	75.54	4230.00	502.0	<0.0001*
	RF	56	37.46	2098.00		

The mean time interval of first rescue analgesia (paracetamol) demand was also longer in RF group as compared to BF group, which was also statistically significant ($P < 0.0001$). BF group had mild to moderate pain and most of the patients in RF group had mild pain in first 24 hours of surgery. Total rescue analgesia consumption in 24 hours was analysed. BF group had 2.4643 g (mean) and RF group had 1.3750 g (mean) of paracetamol (rescue analgesia) consumption in 24 hours which was statistically significant ($P < 0.0001$). [Table 3]

Table 3: Rescue analgesia demand times

	Group	N	Mean	Std. Deviation	T Value	P value
First rescue analgesia demand time (hours)	BF	56	4.9643	1.52511	6.884	<0.0001*
	RF	56	7.7500	2.61638		
Total rescue analgesic consumption in 24 hours (grams)	BF	56	2.4643	0.57094	10.848	<0.0001*
	RF	56	1.3750	0.48850		

Both the groups show no statistically significant ($P > 0.05$) changes in HR at any point of time from baseline to 24 hrs postoperatively. [**Fig. 1**]

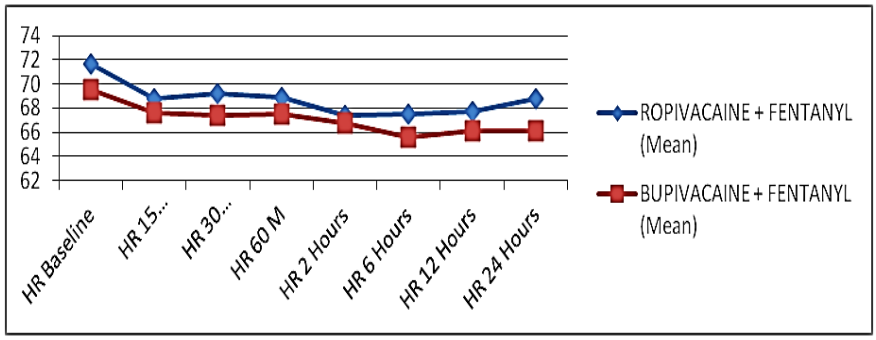

Fig. 1: Comparison of mean heart rate during the observation period

Both the groups show no statistically significant (P > 0.05) changes in SBP from baseline to 6 hrs postoperatively, though the values at 12 and 24 hrs show statistical significance (P = 0.019 and 0.023 respectively).[**Fig. 2**]

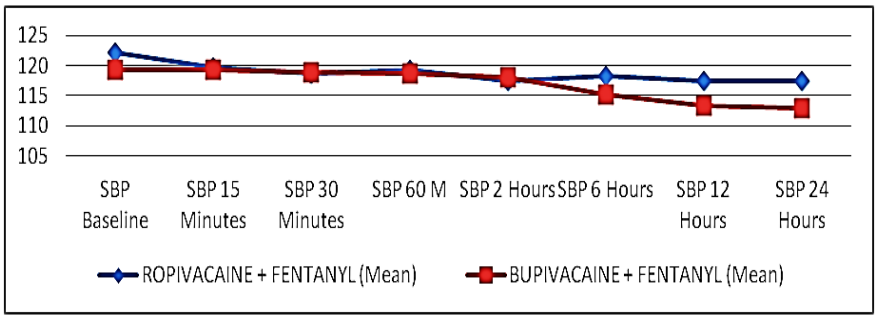

Fig. 2: Comparison of mean systolic blood pressure during the observation period

Both the groups show no statistically significant (P > 0.05) difference in baseline DBP. However, BF group shows statistically significant less DBP than RF group (P < 0.0001) at 15 min, 30 min. 1h, 2h, 6h, 12h and 24 h of surgery. [**Fig. 3**]

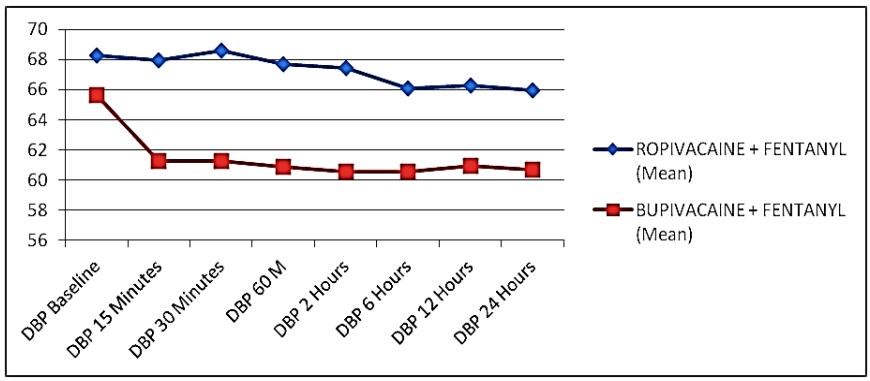

Fig. 3: Comparison of mean diastolic blood pressure during the observation period

In our study, side effects were also observed after starting the infusion and it was found that nausea and vomiting occurred only in 2 patients out of 56 at 30 min in the BF group, which was statistically not significant (P = 0.153) and were treated with Palonosetron 0.25 mg IV. Hypotension and motor blockade were observed more in BF group, but that was also found to be statistically not significant. (Table 4)

Table 4: Intergroup comparison of side effects at different time intervals

		Group						Chi sq	P value
		Bupivacaine + Fentanyl		Ropivacaine + Fentanyl		Total			
		N	N%	N	N%	N	N%		
S/E 30 Minutes	A	53	94.6%	56	100.0%	109	97.3%	3.083	0.214
	H	1	1.8%	0	0.0%	1	0.9%		
	NV	2	3.6%	0	0.0%	2	1.8%		
S/E 60 M	A	56	100.0%	56	100.0%	112	100.0%	-	-
S/E 2 Hours	A	55	98.2%	56	100.0%	111	99.1%	1.009	0.315
	H	1	1.8%	0	0.0%	1	0.9%		
S/E 6 Hours	A	56	100.0%	55	98.2%	111	99.1%	1.009	0.315
	H	0	0.0%	1	1.8%	1	0.9%		
S/E 12 Hours	A	53	94.6%	55	98.2%	108	96.4%	1.037	0.309
	M	3	5.4%	1	1.8%	4	3.6%		
S/E 24 Hours	A	50	89.3%	54	96.4%	104	92.9%	2.287	0.319
	H	4	7.1%	1	1.8%	5	4.5%		
	M	2	3.6%	1	1.8%	3	2.7%		

Discussion

In our country, practices of pain management are still in infancy. Lack of awareness, public illiteracy, associated misconception and shortage of trained personnel could be some of the reasons. Safe and effective methods for pain relief in postoperative period are demanding. Epidural analgesia has the ability to maintain continuous analgesia after placement of an epidural catheter. Apart from providing pain relief, it also helps in attenuation of stress responses (autonomic hyperactivity, cardiovascular stress, pulmonary dysfunction). Maintenance of analgesia postoperatively by means of continuous epidural infusion is one of the proven techniques which allows the patient to ambulate early and recover faster.

In our study, we compared the analgesic effects of 0.125 % bupivacaine + 1µg/ml fentanyl versus 0.2% ropivacaine + 1µg/ml fentanyl through a continuous epidural infusion in patients undergoing major abdominal surgeries in post operative period. When the patients started complaining of pain in the postoperative recovery room, epidural analgesia infusion was started at the rate of 5 ml/h and continued up to a period of 24 hrs postoperatively. We, then, tried to compare the analgesic potency with the help of VAS pain scores and in terms of different haemodynamic variables and physiological variables. Our results show that the continuous epidural infusion of 0.2 % ropivacaine with 1µg/ml fentanyl provides better relief from postoperative pain compared to patients who were given 0.125 % bupivacaine with 1µg/ml fentanyl after major abdominal surgeries.

Bupivacaine, a racemic mixture of 2 stereo isomers, is the most widely used long-acting local amide anesthetic, along with ropivacaine, a propyl homologue of bupivacaine (a pure S-enantiomer). Previous studies have suggested that use of single enantiomers is more desirable than racemic agents.[6] Ropivacaine is a levorotatory (left-isomer) and although it possesses a relatively low potency, it has been found to be less toxic to the nervous system and heart when compared with bupivacaine.[(7)]

Epidural injection of ropivacaine with fentanyl decreased postoperative pain with stable vital signs as compared to bupivacaine or ropivacaine alone in a study by Kanai A, et al, possibly because of the maintenance of sensory blockade by ropivacaine and enhancement of this sensory blockade by fentanyl.**[(8)]** Our study also shows similar results.

Ropivacaine as a sole epidural analgesic requires relatively concentrated solutions (0.2%–0.3%) and is often unsatisfactory because of inadequate analgesia or excessive motor block.[(9)] In a prospective, randomized, and nonblinded comparative study by Lakshmi K, et al, it was concluded that ropivacaine 0.2% with fentanyl administered as an epidural infusion provides better intraoperative and postoperative analgesia with hemodynamic stability in abdominal surgery compared with bupivacaine 0.2% with fentanyl.**[(10)]**

However, some studies have found similar efficacy for post operative analgesia between bupivacaine and ropivacaine. No significant differences were found in the block parameters using 0.75% ropivacaine and 0.5% bupivacaine epidurally in a study by Chandran S, et al but ropivacaine was associated with relatively longer duration of postoperative analgesia.**[(11)]**

A double blind study was conducted by Korula, et al to compare the clinical efficacy of equipotent doses of ropivacaine 0.75% and bupivacaine 0.5% for epidural anaesthesia and ropivacaine 0.2% and bupivacaine 0.125% for postoperative epidural analgesia in patients undergoing bilateral mesh hernioplasty. For postoperative analgesia, 0.2% ropivacaine and 0.125% bupivacaine were given as

continuous epidural infusion. VAS and motor block profile were similar in both groups during the post-operative period.[12] In our study, we also found that motor blockade was less in ropivacaine group, however that was statistically not significant.

The values of SBP in our study at 12, and 24 hrs shows statistical significance which can be attributed to the use of additional analgesics given at or near the time of readings taken. In our study we also measured heart rate, systolic blood pressure and diastolic blood pressure. Both groups were hemodynamically stable throughout 24 hrs during epidural infusion. Although in Bupivacaine group initially diastolic blood pressure fell, but later it was found to be stable in entire 24 hrs.

A meta-analysis of relevant randomised clinical trials was conducted by Yiyang Li, et al to compare the effectiveness of bupivacaine and fentanyl and ropivacaine and fentanyl in epidural analgesia for labour pain. In combination with fentanyl, bupivacaine and ropivacaine exhibit comparable efficacy and safety. It has been suggested that ropivacaine possesses low lipophilic characteristics and is therefore resistant to the rapidly penetrating myelinated nerve fibres and thus is less likely to cause a motor blockade and neurotoxicity.[13]

The analgesic efficacy and extent of motor block using 0.125% ropivacaine or 0.125% bupivacaine in continuous epidural infusion during labour in 60 ASA 1-2 women was compared by Fernandez C, et al. Both drugs were equally effective for controlling the pain accompanying labour. Ropivacaine's reduced motor block effect at the doses administered may offer an advantage in some situations, such as when a walking epidural is provided.[14] our study shows similar results. In our study we also found that, less rescue analgesia was required in ropivacaine group compared to bupivacaine group.

However, in contrast to the result from our study, Pouzeratte, et al reached to a conclusion that after major abdominal surgery, bupivacaine was more effective than ropivacaine when mixed with sufentanil.[15]

In a study by Ahmed A, et al with the aim to determine pain management strategies employed after major abdominal surgeries and their efficacy and safety, epidural analgesia, Patient controlled analgesia and opioid infusions were used for pain relief. It was concluded that regular assessments and appropriate dose adjustments by acute pain management service (APMS) and use of multimodal analgesia lead to a high level of patient satisfaction. They recommended that this feedback to the primary anesthesiologists by APMS is of utmost importance to enable improvement in practice.[16]

One limitation of our study could be that the time of giving rescue analgesics was not fixed so it could have affected the VAS assessment. The other limitation could be that we have not assessed the incidence of postoperative complications, either surgery related or anaesthesia related which can act as confounding factors in our study.

Conclusion

The analgesic potency as well as the motor sparing effect of ropivacaine in combination with fentanyl is better than bupivacaine with fentanyl as assessed by VAS score at doses used in our study. It also offers an advantage of less rescue analgesic drug consumption, although haemodynamic and physiological variables were comparable in both the groups.

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