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Elastomeric Infusion Pump: Evaluation of Different Infusion Rates for Postoperative Epidural Analgesia

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Abstract

Introduction: The continuous epidural infusion of local anesthetic and fentanyl using a multirate elastomeric infusion pump provides the good analgesic option to treat the postoperative pain following the major abdominal surgery. The aim of the present study is to compare the different infusion rates of 0.1% bupivacaine with fentanyl as continuous epidural infusion using Baxter's multirate elastomeric infusion pump in patients undergoing laparotomy under general anesthesia. *Materials and Methods:* Seventy five patients, in age group of 25–60 year with ASA Grade I and II undergoing intraabdominal surgery under general anesthesia were randomly divided into three groups. The epidural catheter was placed in L1–2 interspace with six cm of catheter length in epidural space before induction of GA. At the time of closure of peritoneum a bolus of 8 ml of 0.1% bupivacaine with fentanyl 2 mcg/ml was given in epidural space and the continuous infusion was started at specified rate depending upon the group. In Gp I the infusion was @ 5 ml/hr while in Gp II and Gp III infusion rate was 7 ml/hr and 12 ml/hr respectively. An independent observer visited the patient at regular intervals to enquire about VAS score in postoperative period, extending up to 48 hours. *Statistical Analysis:* Parametric and nonparametric data were collected and relevant data of each patient was entered in Microsoft Excel Worksheet© and were analyzed statistically by using IBM SPSS© software. p - value < 0.05 was taken statistically significant. *Results:* Analysis of postoperative VAS score showed that all the patients have 0 VAS at the time of extubation. Gp I showed higher VAS scores while Gp II and Gp III had a comparable VAS scores. Mean morphine consumption in Gp I was 0.96 ± 1.136 (total 5.7 mg), in Gp II was 0.48 ± 0.714 (total 2.88 mg) and in Gp III was 0.24 ± 0.663 (total 1.44 mg). All groups demonstrated the height of sensory block at T5 dermatome level in immediate postoperative period and the regression was faster in Gp I and II. The mean height of sensory blockade was much higher in Gp III (T7 dermatome) as compared to Gp I & II (T 9 dermatome). Gp III had mild weakness in hip flexion after 20 hrs of continuous infusion. Statistically higher sedation scores were noted in Gp III, but all patients were responsive to commands at all times. Gp III had higher incidence of bradycardia and hypotension (5/25, 20 %), shivering (13/25, 52%), pruritus (14/25, 56%), nausea and vomiting. The mean hospital stay was 5.106 ± 1.203 days. *Conclusion:* For adequate postoperative pain relief following laparotomy under general anesthesia, the administration of bupivacaine 0.1% with fentanyl 2 mcg/ml @7 ml/hr is ideal rate for continuous epidural infusion. The multi rate elastomeric pump used in the study performed satisfactorily and no mal function was reported.

Keywords: Infusion pump; Epidural analgesia.

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Introduction

Pain is an inevitable consequence of surgery and it disrupts the normal physiological and psychological homeostasis. Acute pain after surgery has a distinct patho physiology that reflects peripheral and central sensitization as well as humoral factors.[1] Peri operative pain is a potent trigger for the stress response, activates the autonomic system and is thought to be an indirect cause of adverse effects on various organ systems.[2] Uncontrolled acute pain is associated with the development of chronic pain, prolonged rehabilitation and reduction in quality of life.[3,4] Moreover, failure to relieve pain is morally and ethically unacceptable. Goals for the same are to relieve suffering, achieve early mobilization after surgery, shorten hospital stays, reduce hospital costs and increase patient satisfaction.[5] Laparotomy performed under general anesthesia with a mid line vertical incision is best choice as it provides a rapid and safe entry into the peritoneum and provides relatively bloodless field but is associated with intense pain in the immediate postoperative period. Early postsurgical pain typically peaks on the first postoperative day and shows some improvement over the first 72 hours.[6] This pain has a major impact on patients' satisfaction and may negatively interfere with the postoperative recovery course.[7] Many options are available for treatment of postoperative pain, the main stay of postoperative pain therapy in many settings is still opioids.[8] All opioids have significant side effects limiting their use.[9] Primary opioid-based regimens are being challenged by other agents and approaches to postoperative pain management.[10] Regional neuraxial anesthesia is an effective method of producing effective postoperative analgesia.[11] Effective analgesia for postoperative pain relief after major surgery with epidural administration has been a proposition since early 1980s.[12] The ideal epidural analgesic technique for major surgery would provide effective pain relief with minimal side effects and high levels of patient satisfaction. It would also obtund central sensitization and pain-induced organ dysfunction, leading to improved outcome.[13] Continuous infusion of local anesthetics and opioids in the epidural space helps to maintain a constant level of analgesia while minimizing the cardiovascular and respiratory effects of bolus doses.[14] For this purpose, disposable pumps that use an elastomeric reservoir remain widely used, while the operational complexity of electronic pumps raises concerns about potentially introducing dangerous programming errors.[15]

Potential long-term benefits from reduction in morbidity associated with epidural analgesia may outweigh total costs.[16] Further, studies are needed to identify the full extent of potential benefits from epidural analgesia, optimal techniques and especially the minimum effective dosage with less side effects. Hence, we compared different infusion rates of 0.1% bupivacaine with fentanyl 2 mcg/ml as continuous epidural infusion using elastomeric multirate infusion pump for postoperative analgesia in patients undergoing laparotomy under general anesthesia.

Materials and Methods

After approval by the research ethics committee and written informed valid consent of the patients, the proposed study was carried out over a period of one year, in ASA-I and ASA-II patients, aged between 25 and 60 years of either sex, weight ranging from 40 to 70 kg, posted for intraabdominal surgery. The study was conducted in a prospective, double blind and randomized manner.

Inclusion Criteria

Included ASA Grade I & II patients posted for abdominal surgery under general anesthesia.

Exclusion Criteria

Included Patient refusing consent, patients with ASA Grade III and IV, history of peripheral neuropathy, low backache and spinal pathologies, pregnant women, patients with coagulation disorders, history of drug allergy or hypersensitivity to drugs, infection at the site of epidural injection, patients with psychiatric disorder and patients aged less than 25 years and more than 60 years. All patients underwent a routine preanesthetic check up. Study protocol was explained to all the patients during preanesthetic evaluation and informed consent was taken and signed. The patients were made familiar with visual analog score, VAS (0 for no pain and 10 for the worst imaginable pain). The patients were instructed for a fasting period of 6 hrs.

Patients were divided into Three Groups depending upon the rate of continuous epidural infusion of 0.1% bupivacaine with fentanyl 2 mcg/ml, as follows, Group I: @ 5 mL/hr, Group II: @ 7 mL/hr and Group III: @ 12 mL/hr. The epidural infusion at specified rates was continued for next 48 hrs in postoperative period. The patients were assigned to their respective groups using random allocation software. The number allocated was kept

in a sealed envelope and kept under lock and key. The envelope was opened at the time of surgery and the patient was assigned to the respective group. The epidural catheter was placed at L1/2 interspace with 6 cms of catheter in epidural space before giving general anesthesia and test-dose of 3 ml of 2% lidocaine with 1:200000 adrenaline was given to rule out intrathecal or intravascular placement of catheter.

Intravenous fentanyl 2 mcg/kg and ondansetrone 0.1 mg/kg were administered just before induction of anesthesia. All the patients were preoxygenated with 100% oxygen for 3 minutes. Induction of anesthesia was provided by injection Propofol 1–2.5 mg/kg intravenously. Injection Atracurium 0.5 mg/kg was used to facilitate tracheal intubation after 3 minutes of assisted ventilation. Anesthesia was maintained with 1% Isoflurane with 33% oxygen and 66% nitrous oxide. Muscle relaxation was maintained by intermittent boluses of Atracurium 0.1 mg/kg as required. At the time of closure of peritoneum, patients were given a bolus of 8 ml of 0.1% bupivacaine with 2 mcg/ml of fentanyl and thereafter, the continuous epidural infusion was started as per group allocated using elastomeric infusor pump. At the end of the procedure, prior to extubation residual neuromuscular blockade was reversed with intravenous Neostigmine 0.05 mg/kg and Glycopyrrolate 0.01 mg/kg. The time of extubation was considered as 0 minutes. The epidural infusion at specific rate was kept for 48 hrs in postoperative period and patients were observed for pain relief and side effects, if any, at regular intervals. Subsequent refilling of the infusion pump was done by the same anesthetist who started the infusion.

The independent observer visited the patient at regular intervals to monitor and enquire about VAS score in postoperative period extending up to 48 hours; the observer had no access to covered infusion pump.

The quality of postoperative analgesia was assessed according to VAS score at 0, 30, 60 minutes and 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48 hrs. It was considered satisfactory if the patient does not complain of any pain or discomfort after surgery. When the patient began to experience pain more than 4 on VAS it was considered that the analgesic action of the drug is inadequate and rescue analgesia was given as injection morphine sulphate 6 mg intravenously, waited for 15 minutes and repeated at a dose of 3 mg, if necessary.

The level of sensory block was assessed postoperatively at above intervals, according to pin prick method. (Grade-0 Sharp pain felt, Grade-1 - dull sensation felt, Grade-2 - no sensation felt). The infusion was stopped if sensory block level reaches above T4. It was restarted after it recedes back to T5 or below. The level of motor block was assessed postoperatively, by asking the patient to move his/her limb in accordance with the Modified Bromage Scale. Sedation score was assessed by using Ramsay Sedation Scale postoperatively at the same time intervals. Monitoring of heart rate, mean arterial pressure, SpO_2 and respiratory rate was done at same time intervals. Side effects were monitored.

Results

Parametric and nonparametric data were collected and were analyzed statistically by using IBM SPSS® software. The following observations were made:

The mean age (in years) was 38.64 ± 9.83, 41.60 ± 8.11 and 38.56 ± 9.81 in Group I, II and III respectively. The mean weight (in kg) was 65.12 ± 5.95 in Gp I, 64.2 ± 7.39 in Gp II and 65.88 ± 6.72 in Gp III. The mean height (in cm) was 167.68 ± 6.26, 166.92 ± 6.38 and 166.00 ± 5.53 in Gp I, II and III respectively. No statistically significant difference was found between the Three Groups with respect to age, weight and height (p - value: > 0.05). In this study, more number of male patients were present in all the Three Groups and the difference was statistically insignificant (p – value > 0.05). Out of the total patients, 18.7% (14/75) were females and 81.3% (61/75) were males. The quality of analgesia was assessed by VAS scoring for 48 hours postoperatively. All the patients at the time of extubation (time 0) recorded a VAS of '0'. There after the VAS values showed a 'rise and fall' trend. When the Gp I and II were compared for pain scores at different points of postoperative period, the VAS recorded were significantly lower in Gp II up to 10 hours and the changes were statistically highly significant (p - value < 0.001). Only at 12^{th} hour (p - value = 0.371) and 16^{th} hour (p - value = 0.346) the groups had comparable pain scores. While comparing Gp I and III for analgesic efficacy, the VAS recorded for Gp III were significantly lower throughout the study period, and the changes were statistically highly significant (p - value < 0.001). No significant changes in VAS scores were noted on comparing pain between Gp II and Gp III except between 8 and 20 hours of postoperative period. The p - values were consistently more than 0.05, except between 8 and 20 hours (p - value < 0.001). During this period Gp III demonstrated a significantly lower pain scores, (Table 1, Fig. 1).

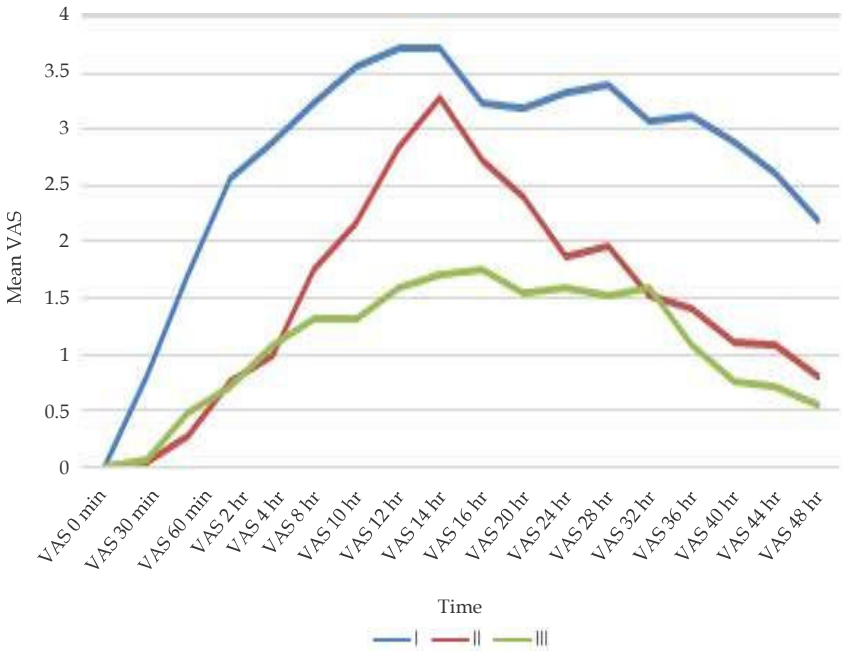

Fig. 1: VAS values in three groups at different point of time

Table 1: VAS values in three groups at different point of time

	Gp I		Gp II		Gp III		*p* - value* (*t*- test)		
	Mean	SD	Mean	SD	Mean	SD	Group I Vs Group II	Group I Vs Group III	Group II Vs Group III
VAS 0 min	0.000	0.0000	0.000	0.0000	0.000	0.0000	–	–	–
VAS 30 min	0.800	0.5000	0.040	0.2000	0.080	0.2769	.000	.000	.914
VAS 60 min	1.720	0.7371	0.280	0.4583	0.480	0.5859	.000	.000	.475
VAS 2 hr	2.560	0.8206	0.760	0.5972	0.720	0.7371	.000	.000	.979
VAS 4 hr	2.880	0.9713	1.000	0.6455	1.080	0.7024	.000	.000	.931
VAS 6 hr	3.240	0.9695	1.760	0.6633	1.320	0.9452	.000	.000	.181
VAS 8 hr	3.560	0.9609	2.160	0.6245	1.320	0.5568	.000	.000	.000
VAS 10 hr	3.720	0.9798	2.840	0.8981	1.600	0.7638	.002	.000	.000
VAS 12 hr	3.720	1.3077	3.280	1.1733	1.720	0.9363	.371	.000	.000
VAS 16 hr	3.240	1.5078	2.720	1.3077	1.760	1.0909	.346	.000	.031
VAS 20 hr	3.200	1.1902	2.400	0.8165	1.560	0.5066	.006	.000	.004
VAS 24 hr	3.320	1.0296	1.880	0.7257	1.600	0.5000	.000	.000	.419
VAS 28 hr	3.400	0.8660	1.960	1.2741	1.520	0.8226	.000	.000	.277
VAS 32 hr	3.080	0.8124	1.520	1.1944	1.600	1.2247	.000	.000	.964
VAS 36 hr	3.120	0.5260	1.400	0.6455	1.080	0.7024	.000	.000	.177
VAS 40 hr	2.880	0.7810	1.120	0.7810	0.760	0.5972	.000	.000	.192
VAS 44 hr	2.600	0.8165	1.080	0.7024	0.720	0.6137	.000	.000	.184
VAS 48 hr	2.200	0.5000	0.800	0.5774	0.560	0.7118	.000	.000	.342

(**p* - value inference: > 0.05- insignificant, < 0.05- significant, < 0.001- highly significant)

The mean dose of Inj. Morphine consumed as rescue analgesic in Gp I, Gp II and Gp III was 0.96 ± 1.136, 0.48 ± 0.714 and 0.24 ± 0.663 respectively. Intergroup analysis showed a statistically insignificant *p* - value of 0.129 between Gp I and Gp II, and 0.591 between Gp II and Gp III. But the difference was statistically significant with a *p* - value of 0.012 between Gp I and Gp III. The total amount of morphine consumed over 48 hours per patient was 5.76 mg in Gp I, 2.88 mg in Gp II and 1.44 mg in Gp III, (Table 2, Fig. 2).

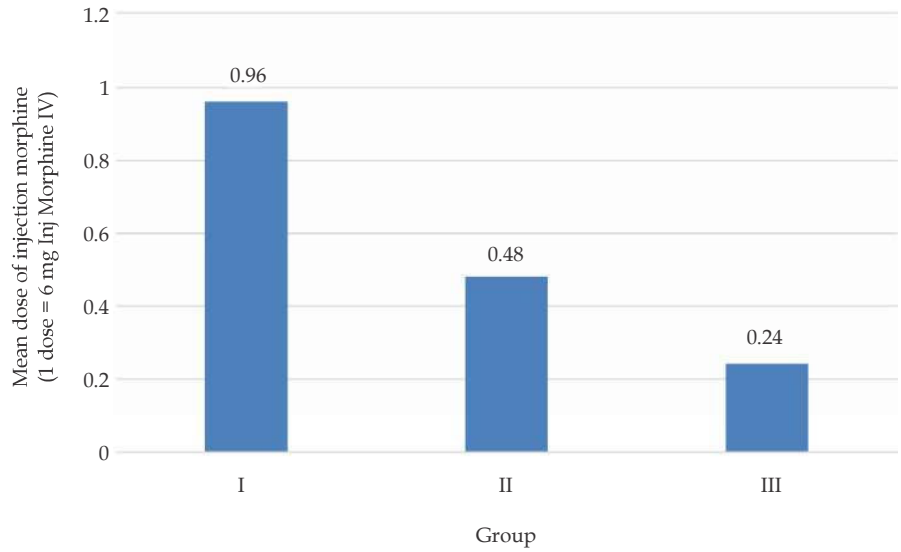

Fig. 2: Comparison of number of rescue analgesic doses (Inj. Morphine sulphate 6 mg IV).

Table 2: Comparison of number of rescue analgesic doses (Inj. Morphine sulphate 6 mg I/V)

Groups	N	Mean dose of Inj. Morphine	SD	Mean consumption of morphine over 48 hours (mg)	*p* - value (*t*- test)
I	25	0.96	1.136	5.76	Group I v/s Group II = 0.129
II	25	0.48	0.714	2.88	Group I v/s Group III = 0.012
III	25	0.24	0.663	1.44	Group II v/s Group III =0.591

At the time of extubation, all the patients demonstrated a comparable sensory block level corresponding to dermatomes T4/T5. Thereafter, the height of the sensory block showed a regression to lower levels in all the Groups. The rate of regression of sensory block height was higher in Gp I. Gp III showed a relatively consistent sensory block level during the study period, (Fig. 3). Gp I and II till 28 hrs showed no significant difference in sensory block height (*p* value >0.05), but thereafter Gp I showed significant regression of sensory block (*p* - value < 0.001). At the end of the study period, the mean height of sensory blockade achieved by Gp I and II was dermatome level T9, whereas for Gp III it was T7. While comparing Gp I and III, and Gp II and Group III, the regression of the sensory block observed for Gp III was significantly lower throughout the study period, and the changes were statistically highly significant (*p* - value < 0.001), (Fig. 3).

The level of motor block was assessed in accordance with the Modified Bromage Scale. Gp I and Gp II consistently demonstrated no motor block. But Gp III after 20 hrs was characterized by Modified Bromage Scale values between 5 and 6, corresponding to mild weakness in hip flexion, and the changes were statistically significant (*p* - value < 0.05).

In Gp I the patients showed Ramsay sedation scale less than 2 during most of the study period. The sedation scale in Gp II was consistently between 2 and 3, whereas Gp III showed significantly higher levels of sedation. The sedation scores between Gp I and Gp II were comparable throughout the study period (*p* - value > 0.05). The comparison between All Groups showed a statistically significant high sedation score in Gp III after 12 hrs (*p* - value < 0.05).

Patient's Heart Hate (HR), Mean Arterial Blood Pressure (MABP), respiratory rate, Oxygen Saturation (SpO_2) were recorded Preoperative mean heart rate were 94.280 ± 6.0520, 95.760 ± 7.8437, and 96.320 ± 7.7175 in Gp I, II and III respectively, with no statistically significant difference in the Three Groups (*p* - value: > 0.05). Comparison between Gp I and Gp II showed a statistically comparable HR between 8 hours and 32 hours (*p* - value: > 0.05). Rest

of the time period, Gp II showed a significant lower HR compared to Gp I. Whereas the comparison between Gp III with Gp I and Gp II showed a statistically highly significant fall in HR in Gp III throughout the study period (*p* - value : < 0.001). MABP before induction of anesthesia in Gp I, II and III were 80.480 ± 5.0259, 80.640 ± 2.9844 and 85.200 ± 4.8477 mm Hg respectively, with no statistically significant difference between the groups (*p* - value: > 0.05). In the postoperative period, Gp I showed a consistently elevated MABP, ranging between 99.440 ± 4.9840 mm Hg to 104.400 ± 6.8496 mm Hg, whereas it was between 83.360 ± 4.8809 mm Hg to 91.000 ± 13.0671 mm Hg in Gp II and 68.720 ± 5.3659 mm Hg to 80.120 ± 10.7017 mm Hg in Gp III. Highly significant fall in MABP was observed within Gp III (*p* - value: < 0.001).

The mean respiratory rate in the preoperative assessment were 20.320 ± 1.9088, 21.200 ± 1.9365 and 20.560 ± 2.4166 in Gp I, II and III respectively, which was comparable to each other (*p* - value: > 0.05). Comparison between Gp I and Gp II showed a statistically comparable mean respiratory rate (*p* - value : > 0.05) between 10 hours and 32 hours of postoperative period. Rest of the time period, Gp II showed a significantly low respiratory rate than that of Gp I. Whereas the comparison between Gp III with Gp I and II showed a statistically highly significant fall in respiratory rate in Gp III throughout the study period (*p* - value: < 0.001).

Intergroup comparison of mean SpO_2 between the groups revealed comparable values till 24 hours of postoperative time period (*p* - value: > 0.05). After that the saturation of oxygen showed a significant fall in Gp III compared to Gp I and II (*p* - value: < 0.05).

Side effects such as postoperative hypoxemia, hypotension, bradycardia, shivering, pruritus, nausea, vomiting, signs of local anesthetic toxicity/ arrhythmia and any other untoward side effect was monitored. Incidence of hypoxia (SpO_2 < 94%) was considerably higher in Gp III (13/25, 52%) whereas in Gp II only 2 patients (8%) and none in Gp I had fall in saturation values (*p* - value: < 0.001). Five patients (20%) in Gp III suffered hypotension (MABP < 65 mm Hg) and bradycardia (HR < 60 bpm) but no patient in Gp I and II had significant fall in heart rate and blood pressure (*p* - value: < 0.05). Thirteen patients (52%) reported shivering in Gp III whereas two patients (8%) in Gp I and five

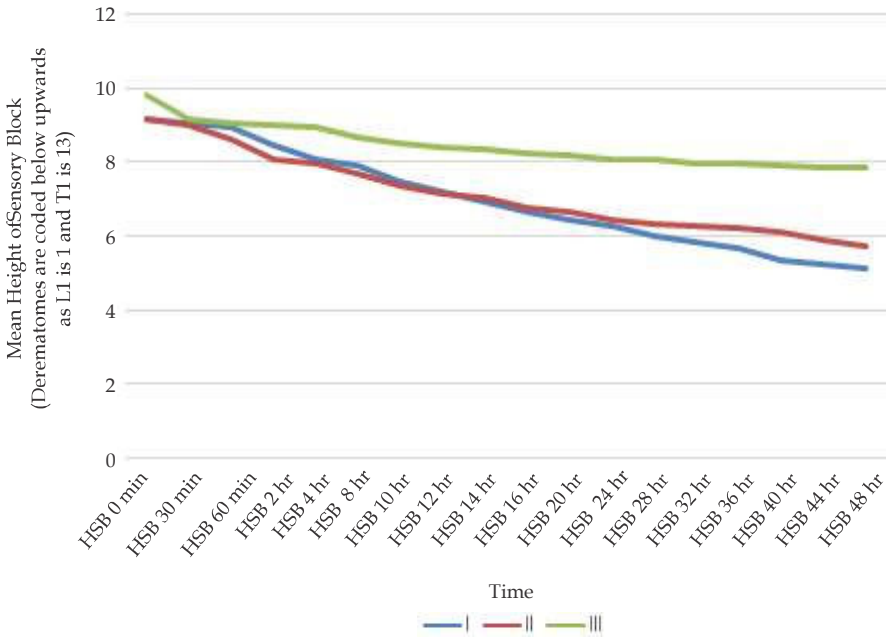

Fig. 3: Mean heights of the sensory block (HSB) in three groups at different point of time

patients (20%) in Gp II reported shivering (*p* - value: < 0.05). Pruritus was present in all the Groups with highest incidence in Gp III (14/25, 56%), followed by Gp II (8/25, 32%) and Gp I (4/25, 16%) (*p* - value: < 0.05). Gp I showed a less incidence of nausea (4/25, 16%), whereas Gp II (5/25, 20%) and Gp III (10/25, 40%) showed a higher incidence, but the differences were statistically insignificant (*p* - value:

>.05). Incidence of vomiting was highest in Gp III (7/25, 28%), followed by Gp II (4/25, 16%) and Gp I (3/25, 12%) (p - value: > 0.05). None of the patients in the study showed any signs of local anesthetic toxicity or arrhythmia during the study period, (Table 3, Fig 4).

Table 3: Incidence of side effects

	Group						Total		
	I		II		III				
Side effects	**Count**	**% within Group**	**Count**	**% within Group**	**Count**	**% within Group**	**Count**	**Total %**	***p*-value***
Hypoxia (SpO_2 < 94%)	0	0.0%	2	8.0%	13	52.0%	15	20.0%	.000
Hypotension (MAP < 65 mm Hg)	0	0.0%	0	0.0%	5	20.0%	5	6.7%	.005
Bradycardia (HR < 60 bpm)	0	0.0%	0	0.0%	5	20.0%	5	6.7%	.005
Shivering	2	8.0%	5	20.0%	13	52.0%	20	26.7%	.001
Pruritis	4	16.0%	8	32.0%	14	56.0%	26	34.7%	.011
Nausea	4	16.0%	5	20.0%	10	40.0%	19	25.3%	.112
Vomiting	3	12.0%	4	16.0%	7	28.0%	14	18.7%	.312
Signs of LA toxicity/ arrhythmia in first 30 min	0	0%	0	0%	0	0%	0	0%	–

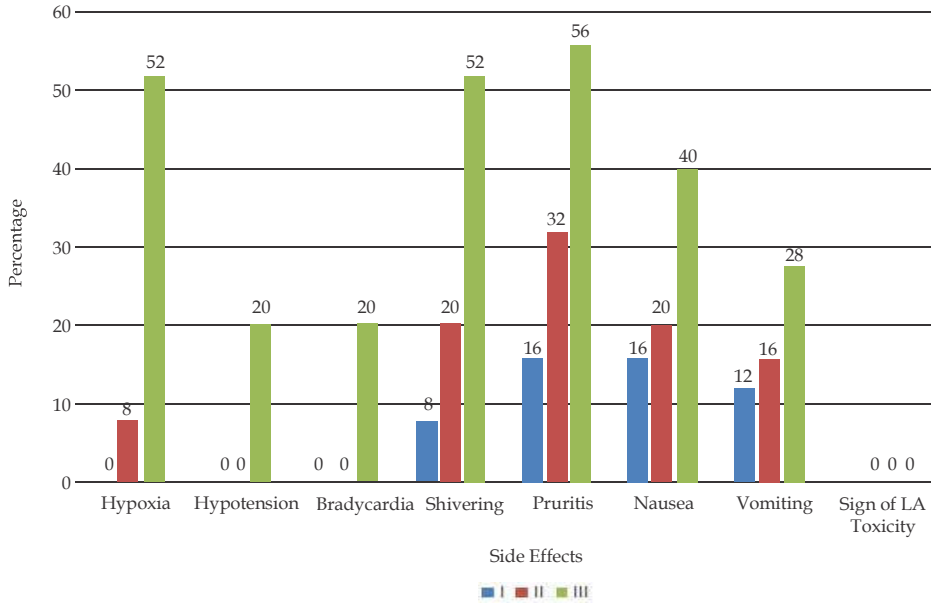

Fig. 4: Incidence of side effects

Apart from the proposed objectives of the study, we also performed a retrospective comparative analysis of mean length of hospital stay between our subjects and 75 other subjects in a similar patient population who were not given CEA. Length of hospital stay was defined as the time period beginning with admission to the Postanesthesia Care Unit (PACU) until the day of discharge. The mean hospital stay of the subjects who have received CEA was 5.106 ± 1.203 days whereas it was 9.106 ± 3.747 days in subjects who received only GA (p - value < 0.001).

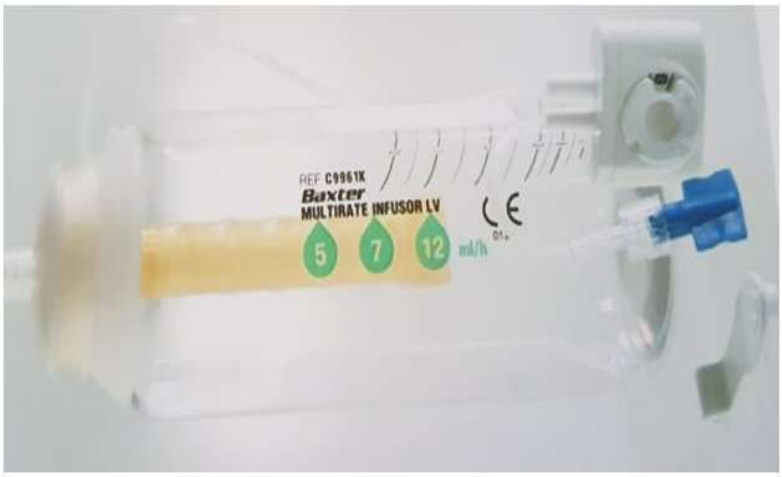

Fig. 5: Baxter's Multirate Elastomeric Infusion Pump

Discussion

Epidural analgesia is a safe and well-established technique, commonly regarded as the gold standard in postoperative pain management.[17] It provides superior pain relief while retaining adequate spontaneous respiration and hemodynamic stability. Christopher L Wu et al.[18] and Salicath JH et al.[19] suggested that an epidural technique provides better pain relief.

Routinely isobaric bupivacaine is used in a concentration of 0.1–0.25% for postoperative analgesia.[20] Addition of fentanyl has synergistic analgesic action and increases the pain free period postoperatively.[21] When administered in combination with opioids and other additives, the minimum effective concentration of bupivacaine can be as low as 0.0625% to 0.1% for epidural analgesia and side effects related to higher concentration of bupivacaine and fentanyl are less.[22,23] The mean VAS score at the time of extubation (0 min) was zero in all the Three Groups and can be attributed to the effect of bolus dose of epidural bupivacaine and fentanyl given at the time of peritoneum closure as well as the residual effect of intraoperative analgesia. Results showed that Gp II and Gp III have better pain relief than Gp I as far as quality of analgesia is concerned. Gp II and Gp III had comparable VAS during most of the study period. This shows that infusion of test solution @ 5 ml/hr was inadequate for postoperative analgesia. A similar pattern of pain scores were observed in a study conducted by SS Patil et al., Neal H Badner and Rakesh Bhandari and Paech MJ et al.[24-26]

The morphine consumption was maximum in Gp I. Intergroup analysis demonstrated a statistically significant difference between Gp I and Gp III. This could be attributed to fact that in Gp III the rate of infusion is 12 ml/hr which covers wide area in epidural space providing better pain control and also due to fact that more amount of fentanyl is being given i.e. 24 mcg/hr resulting in less consumption of morphine. This fentanyl acts locally on opioids receptors present at spinal cord level and also gets absorbed from epidural space and thus acting centrally.

At the time of extubation (0 minute) all Three Groups showed comparable sensory block level reaching up to dermatome T5 as all the patients in our study received a bolus dose of 8 ml of bupivacaine and fentanyl at the time of closure of peritoneum. Thereafter, a steady regression of sensory block was seen throughout the study period in all the groups. The regression was faster in Gp I and Gp II as compared to Gp III. The height of sensory blockade at a given time was much higher in Gp III throughout the study period. At the end of the study period the mean height of sensory blockade achieved by Gp I and Gp II was at dermatome level T9, whereas for Gp III it was at T7. The regression of sensory analgesia always corresponded with an increase in pain score, further supporting the trends in VAS score analysis discussed above.

Our results suggest that when drug is given as a bolus dose, it ascends two to three segments higher as compared to continuous infusion because all patients have sensory block up to T5 dermatome with 8 ml of bolus and then showing gradual regression to various levels depending upon the rate of infusion. Continuous epidural infusion of bupivacaine at a higher rate induces a slower regression of sensory blockade compared with

lower infusion rates. Tachyphylaxis in continuous or repetitive epidural anesthesia manifests as either a diminished response to a standardized dose of local anesthetic or an increased dose requirement to maintain a constant level of sensory block. The lipid soluble bupivacaine penetrates the epidural fat and nerve fibers and deposit in the injecting region without diffusing longitudinally. Bigler et al. hypothesized that tachyphylaxis is due to a relative reduction in the efficiency of the neurogenic blockade by local anesthetics secondary to a posttraumatic increase in afferent neurogenic input, thereby overriding the neurogenic blockade.[27] Also, bupivacaine contains parahydroxyl benzoate as a preservative, which might alter the structural integrity of the epidural space, resulting in either a true reduction in effect at the receptor level, or a decrease in the fraction of local anesthetic reaching the receptor, causing a steady regression in sensory block height.[28] In a study conducted by Akifumi Kanai et al. and SS Patil et al.[24,29], a similar pattern of regression of sensory blockade was reported. In the study by SS Patil et al., they demonstrated that bupivacaine with fentanyl maintained a higher level of sensory blockade compared to ropivacaine and fentanyl.

None of the patients in Gp I and Gp II developed motor blockade, whereas Gp III showed a higher incidence after 20 hours of continuous infusion. Motor block is usually not seen with intermittent bolus injections of dilute local anesthetic. However, continuous infusion of anesthetic solution it may become anesthetized with time and this is probably why patients in Gp III developed a motor block. The motor block developed was considered as mild. Moreover the motor blockade developed after a period of time, reflecting the accumulated effect of the local anesthetic used. Christopher L Wu et al.[18] showed the overall incidence of motor block associated with CEA to be 28.3%.

Higher sedation scores were observed in Gp III after 12 hrs but all patients were responsive to commands at all times and it can be due to the systemic effect of fentanyl getting absorbed from epidural space. A Scott et al. and Leonardo Teixeira Domingues Duarte et al.[30,31] demonstrated a rising incidence of sedation with increase in fentanyl concentration.

Preoperative and intraoperative mean HR and MABP were comparable in three groups with no statistically significant difference. Five out of twenty five (20%) patients in Gp III developed bradycardia and hypotension but none in other groups. Epidural blockade causes vasodilatation with decrease in venous return and blockade of sympathetic fibers (T1-4), leading to bradycardia and hypotension depending upon the amount and volume of drug given as continuous infusion. Also, enhanced analgesia may abate the sympathetic discharge associated with pain perception, leading to lower heart rates. Fentanyl also has a vagotonic effect on heart causing decrease in heart rate by itself. This explains the significant decrease in HR in Gp III throughout the study period. The well settled HR in Gp II and III are in concordance with the well-controlled pain profile observed in these groups. Similar results were seen in study by Kumar Lakshmi et al.[32] None of the patient received any blood transfusion or vasopressors in the postoperative period though Inj. Mephentermine 3 mg IV was sometimes given during surgery. A similar study conducted by SS Patil et al.[34] demonstrated a comparable incidence of hypotension (13.3%).

Respiratory depression is one of the most feared adverse effects following CEA with opioids and can be classified as early and late.[35] Due to the different definitions of respiratory depression adopted by the authors, the incidence described in the literature varies considerably.[36] In our study, we defined respiratory depression by a reduction in peripheral oxygen saturation (SpO_2), determined by the pulse oximetry, less than 94%. The mean respiratory rate and mean SpO_2 in the preoperative assessment were comparable to each other. Highly significant fall in respiratory rate in Gp III was observed throughout the study period. The respiratory centre may get depressed due to increased systemic absorption of fentanyl from epidural space or its direct spread as more amount of fentanyl (24 mcg/hr) is being administered in Gp III with higher infusion rate and enhanced analgesia in that group. Also, the incidence of hypoxia was considerably higher in Gp III (52%), whereas Gp II showed 8% and none in Gp I. The difference was statistically highly significant.

Side effects such as shivering, pruritus, nausea, vomiting and signs of local anesthetic toxicity/ arrhythmia and any other untoward side effect were monitored and the incidence was significantly more in Gp III. Epidural anesthesia and analgesia is associated with a high incidence of intra and postoperative shivering, which is sometimes difficult to control. Increased temperature loss induced by the sympathetic block-induced vasodilatation and epidural infusion at ambient atmospheric temperature may lead to shivering.[37] Mild to moderate hypothermia (35.9 to 34°C) during general or regional anesthesia triggers the activation

of thermoregulatory mechanisms responsible for decreasing temperature loss and increasing heat generation: Muscle shivering, sympathetic centers hyperactivity promoting vasoconstriction in the area above sympathetic block, increase in enzyme reactions by catecholamines, among others. Abreu MP et al.,[38] conducted a comparative study to analyze the incidence of intra and postoperative shivering and other complications of epidural block. In their study, 41% patients who received epidural bupivacaine/fentanyl solution developed shivering; this is in agreement with our study. They also demonstrated that, addition of fentanyl to LA solution did not abolish shivering but is able to decrease its incidence. Shivering during CEA can be prevented by measures such as warming infused fluids to 37°C, maintaining room temperature between 21 and 24°C and using thermal mattresses and blankets to cover the patient. Pharmacological therapy shows varying success rates.[39]

The use of opioids by intrathecal or epidural route frequently results in itching. The incidence of pruritus is 83% in postpartum patients and 69% in nonpregnant patients including males and females.[40] The central mechanism of intrathecal and epidural opioid-induced itching may be related to direct absorption of opioids into blood or due to cephalic spread of the drug in the cerebrospinal fluid and its action on the medullary dorsal horn and a trigeminal nucleus in the medulla.[41] Neuraxial opioids can also cause itching by acting on central 5-HT3 receptors. In our study, pruritus was present in all the groups with highest incidence in Gp III followed by Gp II and Gp I, which was statistically significant. The overall incidence was 34.7%. In a similar study conducted by Saito et al.,[42] the incidence of pruritus with epidural bupivacaine/morphine and bupivacaine/ fentanyl was found to be 36% and 10% respectively. In another study conducted by Tan et al.,[43] to compare the analgesic and adverse effects of three commonly used concentrations of thoracic epidural fentanyl with bupivacaine, 41.37% of patients who received bupivacaine 0.1% with 2 mcg/ml fentanyl developed pruritus. These studies are in concordance with our results. Naloxone, the classic μ-receptor antagonist, is effective in preventing or treating intrathecal or epidural opioid-induced itching. Gurkan and Toker[44] have shown that ondansetron reduces the incidence of intrathecal fentanyl–induced pruritus. Because intrathecal or epidural opioids do not produce itching by the release of histamine, H1 blockers (such as diphenhydramine) have little effect on centrally induced itching.

Even though lipophilic opioids such as fentanyl are taken up quickly into the spinal cord, a continuous infusion of the same can cause ascension into medulla, triggering CTZ. Moreover, epidural administration of drugs leads to rapid vascular uptake that provides access to the CTZ Hypotension may lead to brain stem ischemia, which is thought to activate the circulatory, respiratory, and vomiting centers grouped together in the medulla. Consequently, supplemental oxygen and strategies avoiding hypotension can relieve nausea in such circumstances.[45] In our study, incidence of nausea and vomiting was highest in Gp III followed by Gp II and Gp I. Rucci et al.[46] demonstrated the higher incidence of PONV when fentanyl was added to the bupivacaine. Crocker and Vandam[47] found out that hypotension (systolic blood pressure < 80 mm Hg), a block higher than the T5, and the anesthetic mixture increased the incidence of PONV during spinal anesthesia. Young age group and female gender are the other documented risk factors.

The signs of systemic local anesthetic toxicity or arrhythmia during the study period were specifically sought and none were seen. The infusion of a local anesthetic drug over a long-period into the epidural space can lead to potentially toxic plasma concentrations. Felicity Reynolds[48] compared bupivacaine, lignocaine and mepivacaine and found bupivacaine to have the widest safety margin. Moreover, it is possible that toxic signs would be virtually absent in patients receiving CEA with low concentration of local anesthetics because the rise in plasma concentration would be very slow.[49]

All the patients in our study had a urinary catheter *in situ* preoperatively as part of our institute protocol, so, incidence of urinary retention was not able to assess. The causative association between epidural local anesthetics and opioids with Postoperative Urinary Retention (POUR) is well-documented and is probably due to combination of the central and peripheral effect of the opiate involving altered autonomic activity and the effect of epidural local anesthetics on the sacral and lumbar nerve fibers, blocking the transmission of impulses from and to the bladder.[50,51] It can be minimized by using lower concentrations of local anesthetic. Naloxone per se has no effect on normal bladder function; However, it has been shown to reverse the uro dynamic effects associated with epidural opioids.[51]

We also performed a retrospective comparative analysis of mean length of hospital stay between our subjects and 75 other subjects in a similar patient population who were not given CEA. Length of

stay was defined as the time period beginning with admission to the Postanesthesia Care Unit (PACU) until the day of discharge. The mean hospital stay of the subjects who have received CEA was 5.106 ± 1.203 days whereas it was 9.106 ± 3.747 days in subjects who received only GA shown in Fig. 5, with a p - value of < 0.001 (highly significant). Baxter's multirate elastomeric infusion pump worked satisfactorily in all Groups without causing any problem regarding flow of anesthetic drug.

In our experience, continuous epidural infusion of 0.1% bupivacaine with fentanyl 2 mcg/ ml @7 ml/hr offers the best infusion rate for managing postoperative pain following abdominal operations. It requires careful supervision. A quiet, reliable infusion pump is not cheap. The epidural catheter might penetrate a blood vessel or the duramater, though if this happened it is probable that the patient would be in less danger from a low-concentration of drug delivered slowly by infusion than from a larger mass of drug delivered as a bolus.

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