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Continuous Perioperative Thoracic Epidural Fentanyl-Bupivacaine Infusion *vs.* Continuous Perioperative Fentanyl Intravenous Infusion in Patients Undergoing Major Upper Abdominal Cancer Surgeries

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Abstract

Background: Major upper gastrointestinal cancer surgeries induce postoperative pain, that if not controlled may cause various organ dysfunctions and prolonged hospital and ICU stay. Thus an appropriate pain therapy to those patients must be applicated.

Objective: To compares the effects of continuous perioperative thoracic epidural Fentanyl-bupivacaine infusion versus continuous perioperative Fentanyl intravenous infusion in patients undergoing major upper gastrointestinal cancer surgery.

Methods: 60 patients (ASA II) of either sex were scheduled for elective upper gastrointestinal cancer surgeries. Patients were allocated randomly into two groups (30 patients each) to receive: continuous peri-operative epidural infusion with bupivacaine 0.132 and fentanyl (TEA group), or continuous peri-operative intravenous infusion with fentanyl (control group). Postoperative pain was assessed over 72 h using visual analogue scale (VAS). The intra and post-operative haemodynamic, sedation score and overall patient fentanyl consumption were recorded. Any concomitant events like nausea; vomiting, pruritus or respiratory complications were recorded postoperatively.

Results: There was a significant decrease in pain sensation in TEA group during first day postoperative. Patient haemodynamics was significantly decreased in TEA group. As regard sedation scale, patients of the TEA group were significantly less sedated than control group at immediate postoperative only.

Conclusion: Continuous perioperative thoracic epidural Fentanyl-bupivacaine infusion was much better in pain relief, less sedating effect and shorter duration of hospital and ICU stay than continuous perioperative fentanyl intravenous infusion in patients undergoing major upper gastrointestinal cancer surgery.

Keywords: Thoracic epidural analgesia; Major Upper gastrointestinal cancer surgeries; Postoperative pain; VAS scale

Introduction

Recent estimates indicate that millions of major surgical procedures are performed worldwide each year and patients undergoing gastrointestinal surgery for malignancy are typical representatives of such high-risk patients [1]. Major abdominal surgeries induce neuro-hormonal changes responsible for postoperative pain, various organ dysfunctions and prolonged hospitalization. Inadequate pain control is harmful and costly thus an appropriate pain therapy must be used to those patients (Table 1) [2]. Some of the main complications of under controlled postoperative pain are cardio-circulatory complications like tachycardia, hypertension, increase of cardiac output, increase of heart work and dysrhythmias, increasing the risk of ischemia or myocardial infarction in the postoperative period [3]. The presence of high-quality analgesia in the postoperative period is very important, to relieve post-surgical pain and improve well-being, and also because inadequate pain control may increase morbidity, lead to prolonged hospital stays, and increase medical costs [4].

Patient-controlled epidural analgesia (PCEA) is a widely used postoperative analgesic strategy because it is very effective and safe method of acute postoperative pain relief [5]. In these surgeries Epidural analgesia is effectively applied to improve perioperative pain; epidural analgesia is coupled with improved analgesia, earlier extubation time, better hemodynamics, less respiratory complications, and superior left ventricular function [6].

However, TEA is occasionally contra indicated and may also lead to serious risks as, high incidence of failure rate, premature catheter dislodgement, motor block involving lower limbs preventing early mobilization of patient and hypotension with risk of hypervolemia or prolonged use of vasopressors [7]. Also TEA may cause rare but serious a neurologic complications (hematoma, abscess and paraplegia) [8]. This study compares the effects of continuous perioperative thoracic epidural Fentanyl-bupivacaine infusion versus continuous perioperative Fentanyl intravenous infusion in patients undergoing major upper gastrointestinal cancer surgery.

Patients and Methods

This prospective randomized study was approved by the local ethics committee of the South Egypt Cancer Institute, Assiut University,

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Patients characters	Control group (n=30)	TEA group (n=30)	P. value
Male	18(60%)	20(66.7%)	0.592
Female	12(40%)	10(33.3%)	
Age (year), mean ± SD (range)	66.4+5.61	61.73+6.07	0.191
	(55-74)	(55-74)	
Weight (kg.), mean ± SD(range)	68.7+10.01	73.67+8.58	0.474
	(55-88)	(56-84)	
Height(cm.), mean ± SD(range)	170.9+6.58	163.87+5.99	0.967
	(156-177)	(154-173)	
Operative duration (hours),mean ± SD (range)	5.64+0.7	5.41+0.68	0.196
	(4.4-7)	(4.3-7)	
Type of Surgery			
pancreatic surgery	7(23.3%)	8(26.7%)	0.998
Lower Oesophagectomy	6(20.0%)	7(23.3%)	0.976
Partial Gastrectomy	17(56.7%)	15(50.0%)	0.795

Table 1: Patients characters.
Data are expressed as mean ± SD, TEA: Thoracic Epidural Analgesia Group. P. value<0.05 considered statistically significant. Between two groups there was no significant different regarding patient's characteristics.

Egypt, from October 2013 till October 2015, after written consent, ASA II 60 patients were scheduled for elective major abdominal gastrointestinal cancer surgery. Exclusion criteria were the following: Patients who refused the study, contraindications to epidural analgesia (coagulopathy, recent-less than 1 week-treatment with thrombolytic or potent antiplatelet drugs as clopidogrel, and local infection), allergy to local anaesthetic solutions or opioids. Patient whose ability to use PCEA pump or who cannot be taught how to evaluate their own pain intensity were also excluded from the study.

Preoperative data were taken within a 2 days before surgery included; demographic data, medical, surgical history, physical examination and routine laboratory investigations. The day before surgery, all patients were taught how to evaluate their own pain intensity using the Visual Analog Scale (VAS) (Table 2) [9], scored from 0-10 (where 0=no pain and 10=worst pain imaginable) and how to use the PCA device (Abbott Pain Management Provider. S. No: 96450292. Abbott Laboratory, North Chicago. IL: 60064, USA)®. The Patients were randomly assigned into two groups (30 patients each)by using opaque sealed envelopes containing computer generated randomization schedule, the opaque sealed envelopes are sequentially numbered that were open before application of anaesthetic plan. Patients of both groups were pre-medicated with midazolam 0.05 mg/kg and ranitidine 50 mg. After shifting the patient to the induction room, ECG, pulse oximeter, non-invasive blood pressure and invasive blood pressure monitors were attached. Peripheral Venous line and subclavian vein catheter were established-if indicated- and an infusion of lactated ringers' solution was started as a preload (Figure 1).

Group 1(control group No=30)

-Surgery was performed under standard general anesthesia.

-Postoperative analgesia was provided through patient Intravenous-controlled analgesia (PICA) for 72 hours postoperatively.

Group 2 (TEA group No=30)

-Surgery was done under standard general anaesthesia and additionally Thoracic Epidural catheter was inserted and tested prior induction of GA.

-Postoperative analgesia will provided through Patient-Controlled Epidural Analgesia (PCEA) using TEA for 72 hours postoperatively.

Post-operative VAS	Control (n=30)		TEA (n=30)		P. value
	Range	Mean ± SD	Range	Mean±SD	
VAS 0 h	01-Apr	2.6 ± 1	01-Feb	2.1 ± 0.9	0.049*
VAS 4 h	01-Mar	2.1 ± 0.9	01-Feb	2.6 ± 0.5	0.006*
VAS 8 h	01-Mar	2 ± 0.5	01-Feb	2.4 ± 0.5	0.002*
VAS 12 h	02-Mar	3 ± 0.8	01-Mar	2.4 ± 0.8	0.006*
VAS 16 h	02-Apr	3.1 ± 0.8	01-Mar	2.7 ± 1.1	0.177
VAS 20 h	01-Apr	2.5 ± 0.9	01-Mar	2.3 ± 0.7	0.527
VAS 24 h	01-Apr	3.2 ± 1	02-Mar	2.7 ± 0.9	0.058
VAS 28 h	02-Apr	3.1 ± 0.8	01-Mar	2.7 ± 1.1	0.177
VAS 32 h	01-Apr	2.5 ± 0.9	01-Mar	2.3 ± 0.7	0.527
VAS 36 h	01-Mar	2.4 ± 0.6	01-Mar	2.6 ± 0.9	0.319
VAS 40 h	01-Mar	2.3 ± 0.7	01-Mar	2.1 ± 0.9	0.383
VAS 44 h	01-Mar	2.5 ± 1	01-Feb	2 ± 0.9	0.059
VAS 48 h	01-Mar	2.4 ± 1.2	01-Feb	2.5 ± 0.7	0.798
VAS 52 h	01-Mar	2.5 ± 0.8	01-Feb	2.3 ± 0.7	0.178
VAS 56 h	02-Mar	2.5 ± 0.5	01-Feb	2.6 ± 0.8	0.705
VAS 60 h	01-Mar	2.4 ± 1.2	01-Feb	2.5 ± 0.7	0.798
VAS 64 h	01-Mar	2.5 ± 0.8	01-Feb	2.3 ± 0.7	0.178
VAS 68 h	02-Mar	2.5 ± 0.5	01-Feb	2.6 ± 0.8	0.705
VAS 72 h	02-Mar	2.5 ± 0.5	01-Feb	2.6 ± 0.8	0.705

Table 2: Post-operative VAS.
Data are expressed as mean ± SD, TEA: Thoracic Epidural Analgesia Group; VAS: Visual Analogue Scale. P. value<0.05 considered statistically significant.

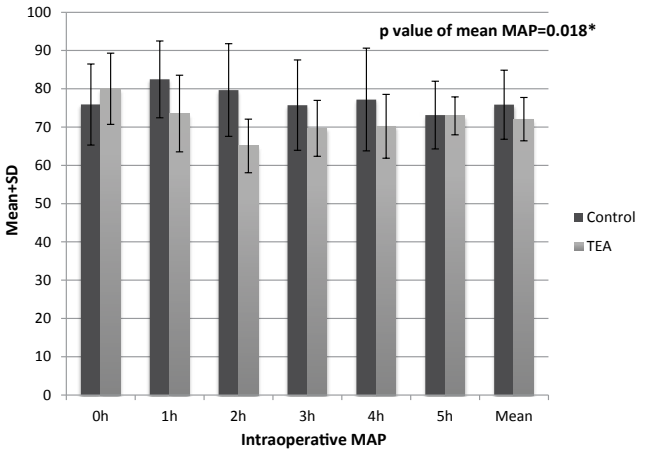

Figure 1: Patient's intraoperative mean arterial pressure.
Data are expressed as mean ± SD, TEA: Thoracic Epidural Analgesia Group, MAP: Mean Arterial Pressure; P. value<0.05 considered statistically significant. Between two groups there was significant difference regarding patient's Intraoperative MAP.

Standard general anaesthesia

After pre-oxygenation for 3 minutes, intravenous anaesthesia (propofol 2.5 mg/kg) induced with fentanyl 1-2 μg/kg administered over min. Tracheal intubation will be performed after adequate neuromuscular blockade with cisatracurium 0.15 mg/kg. Anaesthesia was maintained by isoflurane 1-1.5 MAC, cisatracurium 0.03 mg/kg given when indicated. Patients were mechanically ventilated to maintain ETCO2 between 35-40 mmHg. The inspired oxygen fraction (FIO_2) was 0.5 using oxygen-and-air mixtures. At the end of surgery neuromuscular block was antagonized in all patients with neostigmine 0.05 mg/kg and atropine 0.02 mg/kg and trachea was extubated in the operating room. Tracheal extubation will be performed when patients meet the following criteria: Hemodynamic stability, adequate muscle strength, full consciousness, and adequate ventilation breathing rate:

10 to 30 breaths/min, PaO_2/IFO_2 ≥ 80/0.4, $PaCO_2$, 30 to 45 mmHg). Intra operative analgesia in control group: Intra operative analgesia: By continuous intravenous fentanyl infusion 1 µg g/kg/hr intra operatively along with a bolus dose of fentanyl 0.5 µg/kg to maintain heart rate (HR) and blood pressure within 20% of the basal value. Rescue analgesia of 0.5 µg/g/kg was given. Fentanyl infusion was continued until shifting the patient to ICU (Figure 2).

Intra operative analgesia in TEA group: By slowly injection of epidural bolus dose of 0.1 ml/kg of 0.125% bupivacaine/Fentanyl 10 µg/ml. After a negative response to test dose-was administered, epidural were considered to be adequately working if there is decreased pin prick sensation at the expected dermatomal level, decreased blood pressure from its basal level and absence of stress response to surgical incision. Then, the bolus dose is followed by continuous infusion of 0.1 ml/kg of 0.125% bupivacaine/Fentanyl 8 µg/ml until the end of surgery guided by patient hemodynamic. All patients were transmitted post-operative ICU.

Thoracic epidural catheter

Under strict aseptic precautions thoracic epidural was performed using a 16 gauge Tuhy epidural needle by a paramedian approach. T7-T8 or T8-T9 interspace was chosen for the injection (with air) after skin wheal of lidocaine local anesthetic 2%. The catheter was introduced approximately 4 cm into the epidural space. The epidural space was identified by the loss of resistance technique. A 3 ml test dose of 2% Lidocaine with 1: 200,000 Adrenaline was given after the placement of the epidural catheter.

Patient-controlled I.V analgesia

Using Fentanyl 10 µg/ml solutions through PCA device that programmed to give a bolus dose 2 ml/dose with a minimal lockout interval of 10 min with no background infusion. The analgesic regimen was adjusted to achieve a visual analog scale score <3.

Patient-controlled epidural analgesia

In the PCEA group, postoperative pain treatment was achieved by background epidural infusion of 0.1 ml/kg/h of the mixture 1.25 mg/ml bupivacaine plus 5 µg/ml Fentanyl, and 3 ml as top up dose of this mixture with lockout interval of 20 min. The analgesic regimen was adjusted to achieve a visual analog scale score <3.

Intra operative data collection includes (MAP, HR, and duration of anaesthesia and surgery) (Figures 3 and 4).

Post-operative all patients were admitted to surgical ICU and beside routine follow up, the following were recorded:

- Sedation was assessed one day postoperatively by 5 points Sedation score (at the same time intervals of VAS) as follows 0=aware, 1=drowsy, 2=asleep/easily respond to verbal command, 3=asleep/difficulty responding to verbal command, 4=asleep/no respond to verbal command (Table 3).
- HR, MAP and were recorded every one hour in ICU.
- Any concomitant events like nausea; vomiting, pruritus or respiratory depression (decrease oxygen saturation ≥ 90%) were recorded postoperatively
- Duration of hospital and ICU (Table 4).
- Visual analogue scale- every 4 hours for 3 days-for pain measurement. And total doses of Fentanyl consumption (both intra and post-operative) were calculated (Table 5).

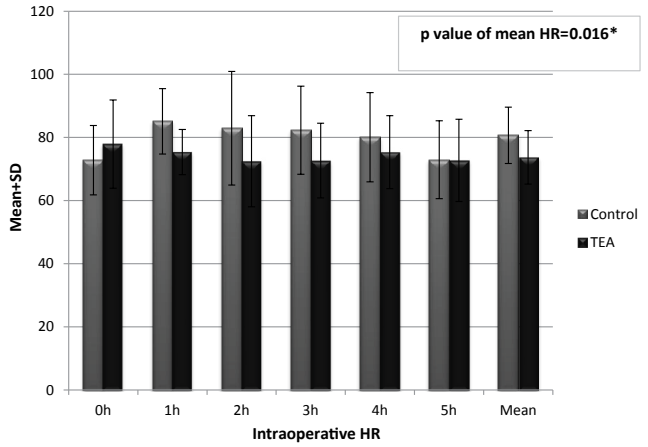

Figure 2: Intraoperative Heart Rate.
Data are expressed as mean ± SD, TEA: Thoracic Epidural Analgesia Group; H.R.: Heart Rate. P. value <0.05 considered statistically significant. Between two groups there was significant difference regarding patient's Intraoperative H.R.

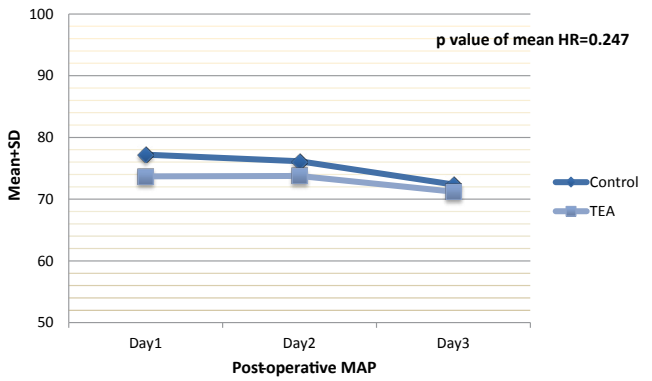

Figure 3: Post-operative MAP.
Data are expressed as mean ± SD, TEA: Thoracic Epidural Analgesia Group, MAP: Mean Arterial Pressure. P. value<0.05 considered statistically significant. Between two groups there was no significant difference regarding patient's post-operative MAP.

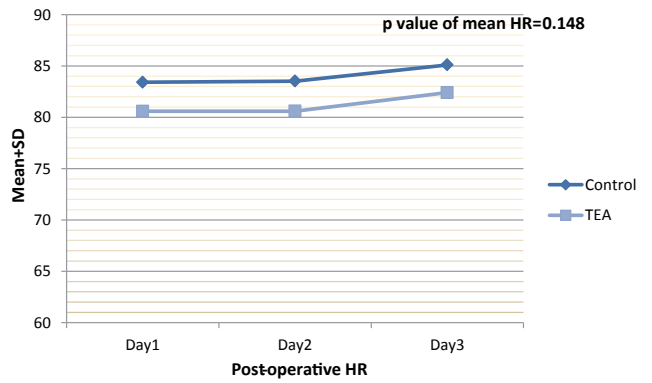

Figure 4: Post-operative HR.
Data are expressed as mean ± SD, TEA: Thoracic Epidural Analgesia Group, H.R: Heart Rate. P. value <0.05 considered statistically significant. Between two groups there was significant difference regarding patient's post-operative H.R.

Post-operative sedation score	Control (n=30)		TEA (n=30)		P value
	Range	Mean ± SD	Range	Mean ± SD	
0 h	(2–1)	2	(1–1)	1	0.00*
4 h	(2–1)	2	(1–1)	1	0.00*
8 h	(2–1)	2	(1–1)	1	0.956
12 h	(1–1)	1	(1–1)	1	0.943
16 h	(1–1)	1	(1–1)	1	0.948
20 h	(1–1)	1	(1–1)	1	0.943
24 h	(1–1)	1	(1–1)	1	0.956

Table 3: Post-operative sedation score.
Data are expressed as mean ± SD, TEA: Thoracic Epidural Analgesia Group, P value<0.05 considered statistically significant.

	Control (n=30)	TEA (n=30)	P. value
No complication	17(56.7%)	24(80%)	0.319
Vomiting	3 (10%)	0(0%)	0.383
Pruritus	2 (6.6%)	0(0%)	0.059
Respiratory depression	4 (13%)	1(3.3%)	0.798
Bradycardia	4 (13%)	5(16.7%)	0.178

Table 4: Post-operative complication.
Data are expressed as mean ± SD, TEA: Thoracic Epidural Analgesia Group, P. value<0.05 considered statistically significant. There was no significant difference between two groups.

	Control (n=30)		TEA (n=30)		P. value
	Range	Mean ± SD	Range	Mean ± SD	
ICU STAY	03-Nov	7.47 ± 2.16	03-Aug	5.6 ± 1.57	0.000*
Hospital stay	Mar-31	22.13 ± 7.62	Oct-25	18.13 ± 4.12	0.014*
Post op. Fentanyl (mic/72h) consumption	1200-2000	1646.67 ± 234.5	600-1000	753.33 ± 122.43	0.000*
Intra op. Fentanyl (mic/72h) consumption	280-480	384.8 ± 92.5	65.6-120	80.9 ± 22	0.000*

Table 5: ICU, Hospital stay, ICU stay and Fentanyl consumption.
Data are expressed as mean ± SD, TEA: Thoracic Epidural Analgesia Group, ICU: Intensive Care Unit P. value <0.05 considered statistically significant. There was significant different between two groups.

Statistical analysis

The required sample size was calculated using Epi Info software version 7 (CDC, 2012)®. Using post hoc power analysis with accuracy mode calculations with VAS as the primary objective and therefore, it was estimated that minimum sample size of 29 patients in each study group would a chive a power of 80% to detect an effect size of 0.8 in the outcome measures of interest, assuming a type I error of 0.05. All analyses were performed with the SPSS 20.0® software. Categorical variables were described by number and percent (N, %), where continuous variables described by mean and standard deviation (Mean, SD). And Mann-Whitney test were used to compare between two groups while Chi square test was used for qualitative data. Where compare between continuous variables by t-test. P was considered significant if 60.05 at confidence interval 95%.

Discussion

Since the discovery of a pain inhibitory system modulated specially in the spinal cord by neurotransmitters like endorphins, serotonin and others, there were possibilities of using substances 8-10 that imitate the action of these inhibitory neurotransmitters in the epidural or subarachnoid spaces as means for controlling postoperative pain [9]. This randomized clinical study showed that the quality of postoperative analgesia was better and sedation scores were significantly decreased especially at immediate postoperative period in patients of the TEA group in comparison to control group. We believe in the concept of preemptive analgesia which is to prevent altered sensory processing. Therefore we started our pain control strategy in intraoperative period; preemptive may not simply mean "before incision" An insufficient afferent blockade cannot be preemptive, even if it is administered before the incision [10]. PCA is considered one of best methods in controlling pain and can be used either intravenously or epidural. Advantages of PCA over conventional pain management are that the therapy is individualized to the patient. Patients are the best to assess their pain and they can get medication as and when required by pressing a button of PCA pump. Thus it reduces overdose and also reduces nursing aid [11].

We used in this study PCEA using both bupivacaine and fentanyl because Epidural LA drugs administered alone have never become widely used for routine postoperative analgesia because of the significant failure rate resulting from regression of the sensory block and the unacceptable incidence of motor blockade and hypotension [12].

Consistent with us, Mann et al, who compared the effectiveness on postoperative pain and safety of PCEA and intravenous PCA after major abdominal surgery, they found pain relief was better at rest and after coughing in the PCEA group during the five postoperative days [13]. And in the study done by Behera et al, the number of patients with analgesic failure was significantly less in PCEA group as compared to IV PCA group [14]. Moreover a study performed on patients undergoing upper abdominal surgery; despite the infusion of bupivacaine 37.5 ± 50 mg/h via a thoracic epidural 30% of patient's required opioid supplementation for inadequate analgesia and 80% had significant hypotension [15]. So, opioids must be added either morphine or fentanyl and our choice of fentanyl based on the higher lipophilicity of fentanyl that makes it shorter duration of action, lower incidence of side effects, and reduced risk of respiratory depression [16].

Fentanyl is more preferred than morphine as proved by a study conducted by Teng et al. who concluded that patients receiving epidural fentanyl bupivacaine PCA experienced better overall pain relief, while morphine PCA, either epidural or intravenously, caused more side effects [17].

The application of opioids by epidural analgesia delivers the drug close enough to the spinal cord so that the opioids can inhibit pain transmission from afferent nerves to the central nervous system through interaction with pre- and postsynaptic opioid receptors in the dorsal horn When the same amount of an opioid is used, epidural application of PCA should achieve more effective analgesia than systemic administration [18].

At the end of the 24 h postoperatively there was no significant difference in VAS between both groups as the plasma level of fentanyl was constant in controlling pain in both groups.

Very similar to our results a study done by Privado et al, comparing epidural versus intravenous fentanyl for postoperative analgesia following orthopedic surgery, they found that epidural fentanyl is more efficient than intravenous fentanyl administration during first day postoperative and no significant difference between both groups after 24 h [19]. But against us, Welchew and Breen who found that both routes of fentanyl administration resulted in equally satisfactory analgesia but the total dose of fentanyl in intravenous group was twice the total dose of fentanyl in epidural group during the first 24 h postoperatively [20]. TEA by its sympathetic inhibition may cause hypotension. As found in a study conducted by Komatsu et al. who agree with us- found five

episodes of postoperative hypotension occurred in the PCEA group versus none in the PCA group. The patients were treated by simple fluid loading [21]. In the present study, the incidence of side effects were increased in control group compared to TEA group, but the difference was statistically significant only in sedation.

Epidural administration of opioids was associated with side effects like sedation, delayed respiratory depression, nausea, vomiting, pruritus, urinary retention. These sideeffectsarecausedbythepresence ofdrugeitherin CSFor systemic circulation. In the study conducted by Cooper et al, concluded that side effects were less in bolus PCEA group and all the patients were arousable, the findings of which were similar to our study [22].

Agree with, Chen who found that nausea and vomiting were more frequent in the epidural analgesia than the intravenous group; this may be due to the rostral spread of epidural opioid to the chemoreceptor trigger zone [23].

But against us, Arunotai et al who found that, Patients in the TEA group developed pruritus, which may be due to histamine release, activation of peripheral opioid receptor, or production of excitatory morphine metabolites. Although these side effects occurred more likely with morphine, they might be due to fentanyl or tramadol [24].

TEA decrease both HR and MAP due to sympathetic block as we noticed in our study and agree with us Loick et al. [25], who evaluated the effect of TEA on haemodynamic parameters and reported that the heart rate in patients decreased significantly during the intra and postoperative period following administration of TEA, as compared to preoperative values, but there was not a difference between the patients of control groups [26].

But it was proved that, both TEA and intravenous analgesia were found to reduce pulmonary and cardiac complications, and improve tissue oxygenation and tissue reperfusion [27].

In our study, no patient of TEA group developed Bradycardia and hypotension. Similar findings were noted in previous studies five episodes of postoperative hypotension occurred in the PCEA group versus none in the PCA group. The patients were treated by simple fluid loading [28].

The total dose of intra and post-operative fentanyl was significantly lower in the (TEA group) than in the (control group). This was consistent with Mehta et al., who found that fentanyl requirement in patients undergoing off-pump CABG surgery was lower in patients receiving general anaesthesia with thoracic epidural analgesia than those receiving general anaesthesia alone [29].

Shorter hospital and ICU stay were observed in TEA group. Van Boerum et al. reported that the patients in the epidural PCA group were discharged earlier in one and half days on average than the PCIA group. Also, patients in the epidural PCA group started ambulation earlier and fewer Incidences of ileus than in the PCIA group [30].

There were no cases of serious epidural catheter-related complications, such as respiratory depression, epidural hematoma or abscess, local inflammation, or permanent neurologic damage in our study.

Study Limitations

Study limitations were**,** the study was not blind and small sample size that prevent to provide more powerful results with smaller statistical error and more solid conclusion and short duration of follow up period.

Conclusion

This study concluded that both Continuous perioperative thoracic epidural Fentanyl-bupivacaine infusion and Continuous perioperative fentanyl intravenous infusion in patients undergoing Major Upper gastrointestinal cancer Surgery were effective in pain relief but Continuous perioperative thoracic epidural infusion was much better in pain relief with less sedating effect.

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