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Impact of Continuous Intra and Post operative Thoracic Epidural Fentanyl–Bupivacaine Infusion on Patients Undergoing Major Upper Gastrointestinal Cancer Surgery

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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 investigate the effects of Continuous intra and post operative thoracic epidural Fentanyl–bupivacaine 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, beside GA: continuous intra and post -operative intravenous infusion with fentanyl for 72 hours post-operatively (control group) or continuous intra and post -operative epidural infusion with bupivacaine 0.125% and fentanyl (TEA group) for 72 hours post-operatively. Intra-operative haemodynamics and fluid shift (blood loss, blood transfusion and colloid transfusion) were recorded. Postoperative pain was assessed over 72 h using visual analogue scale (VAS). And post-operative haemodynamics, sedation score and overall fentanyl consumption were recorded. Any concomitant side effects like nausea; vomiting, pruritus or respiratory complications were recorded postoperatively.

Results: There was a significant decrease in pain scores (p. value =0.049*) with less sedating effect (p. value 0.01*) especially in early postoperative hours in TEA group in comparison to control group. Intra-operative haemodynamics (MAP and HR) were increased not markedly but significantly in control group with p. value of mean MAP=0.018* and p value of mean HR=0.016* respectively.
Postoperative haemodynamics (MAP and HR) and also Intra-operative fluid shift (blood loss, blood transfusion and colloid transfusion) were comparable in both groups.

Conclusion: Continuous intra and post operative thoracic epidural Fentanyl–bupivacaine infusion was associated with decreased in fentanyl consumption, better pain relief, less sedating effect and optimized peri-operative haemodynamics than continuous perioperative fentanyl intravenous infusion in patients undergoing Major Upper gastrointestinal cancer Surgery.

Key Words: 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 neurohumoral 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. [2]

Some of the main complications of untreated postoperative pain are cardiocirculatory 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 may effectively applied to improve perioperative pain; epidural analgesia was coupled with improved analgesia, earlier extubation time, better haemodynamics, less respiratory complications, and superior left ventricular function. [6]

In this study we aimed to investigate the effects of Continuous intra and post operative thoracic epidural Fentanyl–bupivacaine infusion in patients undergoing Major Upper gastrointestinal cancer Surgery, Regarding analgesic efficacy, intraoperative fluid shifts, side effects and peri-operative haemodynamics.

Patients and Methods:

This prospective randomized study was approved by the institutional ethics committee of the South Egypt Cancer Institute, Assiut University, Assiut, Egypt. In the duration from October 2013 till October 2015, after written informed consent, ASA II 60 patients were scheduled for elective major abdominal gastrointestinal cancer surgery.

We excluded from the study; Patients with 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 anesthetic solutions or opioids were excluded from the study. Patient whose ability to use PCA pump or who cannot be taught how to evaluate their own pain intensity were also excluded from the study.

Preoperative data were collected one day before surgery as; 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) [7], scored from 0-10 (where 0= no pain and 10=worst pain imaginable).and how to use the PCA device (B Braun patient controlled analgesia. S. No: 267466. Melsungen Laboratory, AG: 60064, Germany) ®.

All patients were premedicated with midazolam 0.05 mg/kg and ranitidine 50 mg. After transferring the patients to the operative room; Peripheral Venous line was established and an infusion of lactated ringers' solution was started. ECG, pulse oximeter, non-invasive blood pressure and invasive blood pressure monitors were attached. Then subclavian vein catheter was inserted.

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 were sequentially numbered that were opened before application of anesthetic plan. Thoracic Epidural catheter was inserted prior induction of GA in patients of TEA group.

Group 1 (control group No. =30): Surgery was performed under standard general anesthesia and postoperative analgesia was provided through patient controlled Intravenous - analgesia (PCIA) using fentanyl for 72 hours.

Group 2 (TEA group No. =30): Surgery was done under standard general anesthesia and postoperative analgesia was provided through Patient-Controlled Epidural Analgesia (PCEA) using bupivacaine / Fentanyl for 72 hours postoperatively.

Thoracic Epidural catheter

Under strict aseptic precautions thoracic epidural catheter was inserted in T8-T9 or T9-T10 interspace, using a 16 gauge Tuhy epidural needle through a paramedian approach, after skin wheal of lidocaine local anesthetic 2%. The epidural space was identified by the loss of resistance technique (using saline). The catheter was introduced approximately 4 cm into the epidural space. A 3ml test dose of 2% Lidocaine with 1: 200,000 Adrenaline was given after the placement of the epidural catheter to confirm its position. After a negative response to test dose, epidural analgesia was considered to be adequately working if there is decreased pin prick sensation at the expected dermatomal level and decreased blood pressure.

General anesthesia was conducted as following;

After pre-oxygenation, intravenous induction was done by propofol (1.5 mg/kg) and fentanyl 1-2 μg/kg administered over one minute. Tracheal intubation was performed after adequate neuromuscular blockade with cisatracurium 0.5 mg/kg. Anesthesia 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 (FIO2) was 0.5 using oxygen-and-air mixtures. At the end of surgery neuromuscular block was reversed 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 was performed when patients met the following criteria: hemodynamic stability, adequate muscle strength, full consciousness, and adequate ventilation breathing rate: 10 to 30 breaths/min, PaO2 /IFO2 ≥80/0.4, PaCO2, 30 to 45 mmHg).

Intra operative analgesia in (control group): by continuous intravenous fentanyl infusion 1 μg g/kg/hr

intra operatively along with bolus doses of fentanyl 0.5 µg /kg to maintain heart rate (HR) and blood pressure within 20% of the basal value. Fentanyl infusion was continued until transferring the patient to ICU.

Intra operative analgesia in (TEA group): by epidural bolus dose of 0.1 ml ⁄ kg of 0.125% bupivacaine ⁄ Fentanyl 10 µg ⁄ ml. Then, the bolus dose was 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.

Postoperative Analgesia was performed using Fentanyl (10 µg /ml solutions through PCA device that was programmed to give a bolus dose 2 ml/dose with a minimal lockout interval of 15 min with no background infusion) in control group. And 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 minutes in TEA group. The analgesic regimen was adjusted to achieve a visual analog scale score < 3.

Intra operative assessment was done using data as MAP, HR, volumes of (colloid, and blood transfusion), volumes of blood loss and duration of anesthesia.

Post operative all patients were admitted to surgical ICU and were assessed by:

- HR and MAP every one hour in ICU.
- Visual analogue scale [7] - every 4 hours for 3 days-for pain measurement.
- Total intra and post operative Fentanyl consumption was calculated.
- 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.
- Any concomitant events like nausea; vomiting, pruritus or respiratory depression (decrease oxygen saturation ≥90% or decreased respiratory rates≤10) were recorded postoperatively
- Duration of hospital and ICU stay and patients outcome (living or dead).

The primary outcome of our study was the analgesic efficacy of continuous Epidural fentanyl/ bupivacaine infusion that was assessed by VAS in comparison to control group. The secondary end points were calculation of total fentanyl consumption and hospital and ICU stay in patients of both 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 <.05 at confidence interval 95%.

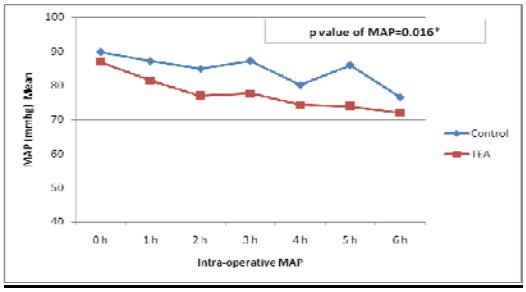
Results:

Table (1): Demographic data, type and duration of surgeries.

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	66.4 ± 5.61 (55 - 74)	61.73 ± 6.07 (55 - 74)	0.191
Weight (kg.), mean±SD	68.7 ± 10.01 (55 - 88)	73.67 ± 8.58 (56 - 84)	0.474
Height(cm.), mean±SD	171 ± 6.56 (156 -177)	163.87 ± 5.99(154 - 173)	0.967
Operative duration (hours), mean±SD	5.64 ± 0.7 (4.4 - 7)	5.41 ± 0.68 (4.3 - 7)	0.196
Type of Surgery			
• Pancreatic surgery	7 (23.3%)	8 (26.7%)	0.998
• Partial Oesophagectomy	6 (20.0%)	7 (23.3%)	0.976
• Partial Gastrectomy	17 (56.7%)	15 (50.0%)	0.795

Data are expressed as mean ± SD, TEA =Thoracic epidural analgesia group. Between the two groups there were no significant differences regarding patient's characteristics.

Figure (1): patient's Intraoperative Mean Arterial Pressure (MAP).



Data are expressed as mean, TEA =Thoracic epidural analgesia group MAP= Mean Arterial Pressure, h=hour interval, 0h=baseline reading, P. value **0.016**. Significant decrease in Intraoperative MAP, all over the operation in TEA group.

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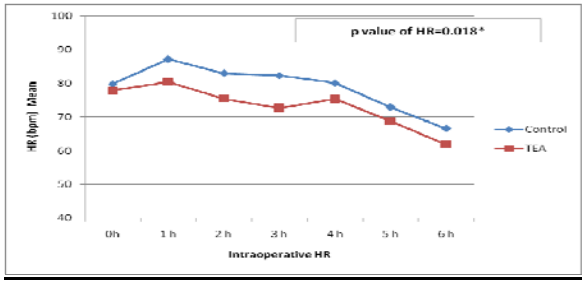
Figure (2): Intraoperative Heart Rate (HR).



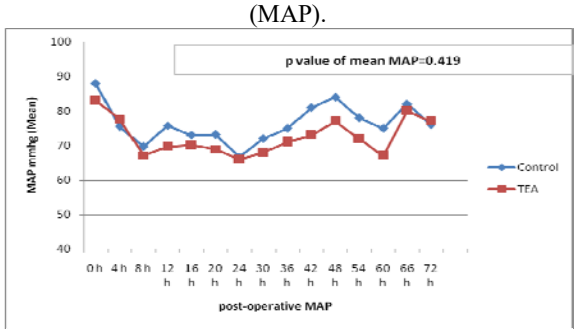
Data are expressed as mean, TEA =Thoracic epidural analgesia group H.R. = heart rate, h=hour interval, 0h=baseline reading, P. value 0.018. Significant decrease in Intraoperative HR all over the operation in TEA group.

Table (2): Intra-operative fluid shift;

Intra-operative:	Control group (n=30)	TEA group (n=30)	P. value
Blood loss (liter)	2.09 ± 0.38 (1.5 - 3)	2.05 ± 0.41 (1.4 -3)	0.696
Blood transfusion (liter)	1.4 ± 0.28 (1 - 2)	1.33 ± 0.3 (1 - 2)	0.376
Colloid transfusion (liter)	0.53 ± 0.39 (0-1)	0.47 ± 0.39 (0 - 1)	0.513

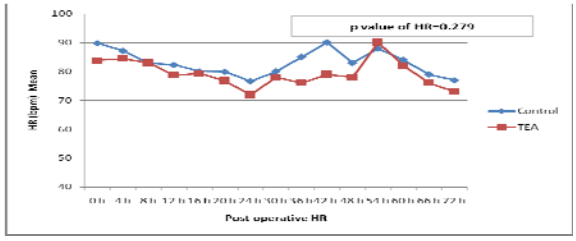
Data are expressed as mean ± SD. TEA =thoracic epidural group, there was no significant difference between control and TEA group.

Figure (3): Post-operative Mean Arterial Pressure (MAP).



Data are expressed as mean (of 4 hours readings), TEA =Thoracic epidural analgesia group MAP= Mean Arterial Pressure, h=hour interval, 0h= reading at recovery, there was no significant difference between control and TEA group (P. value 0.419).

Figure (4): Post-operative heart rate (HR).



Data are expressed as mean (of 4 hours readings), TEA =Thoracic epidural analgesia group H.R. = heart rate, h=hour interval, 0 h= reading at recovery. there was no significant difference between control and TEA group (P. value 0.279).

Table (3): Post-operative VAS;

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

Data are expressed as mean ± SD, TEA =Thoracic epidural analgesia group VAS = visual analogue scale. h=hour interval, 0 h= reading at recovery. Significant decrease in post-operative VAS values especially at the first 16 hours post-operatively in TEA group.

Table (4): Post-operative sedation score;

Post-operative sedation score	Control group (n=30)		TEA group (n=30)		P. value
	Range	Mean±SD	Range	Mean±SD	
0 h	(1-2)	2	(1-1)	1	0.01*
4 h	(1-2)	2	(1-1)	1	0.01*
8 h	(1-2)	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

Data are expressed as mean ± SD, h=hour interval, 0 h= reading at recovery. Significant decrease in sedation score values especially at the first hours post-operatively in TEA group.

Table (5): Post-operative side effects;

SIDE EFFECTS	Control group (n=30)	TEA group (n=30)	P. value
No complication	17 (56.7%)	21(70%)	0.319
Vomiting	3 (10%)	0 (0%)	0.383
Pruritus	2 (6.6%)	1 (3.3%)	0.059
Respiratory depression	2 (6.7%)	1 (3.3%)	0.798
Bradycardia	2 (6.7%)	5 (16.7%)	0.178

Data are expressed as mean ± SD. There was no significant difference between two groups.

Table (6): ICU, Hospital stay and Fentanyl consumption;

	Control group (n=30)		TEA group (n=30)		P. value
	Range	Mean±SD	Range	Mean±SD	
ICU stay	3 - 11	7.47 ± 2.16	3 - 8	5.6 ± 1.57	0.000*
Hospital stay	3 - 31	22.13 ± 7.62	10 - 25	18.13 ± 4.12	0.014*
Total Fentanyl (mic/72h) consumption	1200 - 2000	1646.67 ± 234.5	600 - 1000	753.33±122.43	0.001*

Data are expressed as mean ± SD, ICU= intensive care unit, the total doses of peri-operative fentanyl and stay in (ICU and hospital) were significantly lower in the TEA group.

Discussion:

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. [8]

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. [9]

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. [10]

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. [11]. 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. [12]

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. [13]

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. [14]

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. [15]

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. [16]

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. [17]

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. [18]

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 side effects are caused by the

presence of drug either in CSF or 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. [19]

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. [20]

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. [21]

Intraoperative fluid shift as (blood loss, fluid and red blood cell transfusion) were increased in control group compared to TEA group, but the difference was not statistically significant as a recent study by Skinner et al that concluded that TEA decrease intraoperative blood loss and transfusion demand, although these data are insufficient for meta-analysis. [22]

The total dose of intraoperative 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 anesthesia with thoracic epidural analgesia than those receiving general anesthesia alone. [23]

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 than in the PCIA group. [24]

In Conclusion, Continuous intra and post operative thoracic epidural Fentanyl–bupivacaine infusion was associated with much decrease in fentanyl consumption, better pain relief, less sedating effect and optimized peri-operative haemodynamics than continuous intra and post-operative fentanyl intravenous infusion in patients undergoing Major Upper gastrointestinal cancer Surgery.

List of Abbreviations:

ECG	Electrocardiogram
GA	General anesthesia
HR	Heart rate
IV	Intravenous
MAP	Mean arterial pressure
PCA	Patient controlled analgesia
PCEA	Patient controlled epidural analgesia
PCIA	Patient controlled Intravenous – analgesia
TEA	Thoracic epidural analgesia
VAS	Visual analogue scale

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