Comparison Between Two Methods of Patient-Controlled Analgesia Through Intravenous and Thoracic Epidural to Control Pain and Complications After Surgery in Esophageal Cancer Patients: A Randomized Controlled Trial

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Abstract- The aim of this study was to compare the post-operation analgesic effects of patient-controlled epidural analgesia and patient-controlled intravenous analgesia for patients who were undergoing esophageal cancer surgery. This was a randomized clinical trial. 80 patients undergone esophagostomy were randomly divided into two groups: 40 patients in the epidural PCA and 40 patients in the intravenous PCA group were evaluated. Post-operation pain score was assessed using the universal pain assessment tool (UPAT) in both groups at 24 and 48 hours after surgery. Secondary outcomes included AKI, MI, CVA, pulmonary complications, ICU stay and three months survival. Mean pain scores were similar in the two groups (P>0.05). There was no significant difference between the two groups for rescue treatment, three months' survival, CVA, MI and AKI. However, ICU stay (P=0.008) and pulmonary complications (P=0.05) were greater in PCIA group. The results indicate that none of the PCEA and PCIA methods have any superiority in terms of pain control and the incidence of analgesic-related side effect complications after surgery in patients undergoing esophagostomy and confirm sufficient analgesia by both.

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Introduction

Today, the prevalence of cancer is increasing due to the lifestyle of people and modernization. One of these prevalent cancer types is esophageal cancer which counts as one of the fatal malignancies worldwide, with a dramatic increase in incidence over the past few decades (1).

Surgery is the leading curative option for esophageal carcinoma to improve patient survival. Patients who are candidates for surgery need a low-risk and beneficial method to control pain and maintain the patient's condition stable with better results (2). The right choice of pain control will be led to less damage and will eventually less hospitalization period after surgery. Nowadays, two methods of analgesia are used extensively for pain control; patient-controlled epidural analgesia (PCEA) and patient-controlled intravenous analgesia (PCIA).

In most studies, injection through the epidural catheter was mentioned as the common approach. However, catheter implantation has more complications than the intravenous method, including spinal cord injury (3,4).

In the present study, we report the results from a

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randomized clinical trial that assessed the efficacy of both methods of PCEA and PCIA in pain score and secondary outcomes such as AKI, MI, CVA, pulmonary complications, hospitalization in ICU and three-month survival.

Materials and Methods

Trial design

This study was registered in the cancer institute of Imam Khomeini hospital (Tehran, Iran) registration number IR.TUMS.IKHC.REC.1397.199, 22/07/2018, with approval from the hospital's ethics committee.

Participants

80 esophageal cancer patients with ages ranging from 20 to 80 who were scheduled for esophagostomy were enrolled in this study. We excluded patients with coagulation disorders, skin infection of epidural catheter insertion site, severe hemodynamic disorders, severe movement disorders, chest disorders, neurological disorders, ASA grade 3 or above (systematic changes due to cancer like anemia, malnutrition and…), and drug addicts from the study (Figure 1).

Data collection

After entering the patient to ICU, the patient's condition and information were recorded and the patient's hemodynamics were considered. The items recorded on the monitor were noted. The second- and third-days' VAS score (visual analog scale) using UPAT (universal pain assessment tool) and probable complications were recorded. The amount of hospitalization in the intensive care unit and three-month survival of the patient were also monitored.

Intervention

In the first group, before the start of anesthesia, the epidural catheter (Arrow flex tip plus) from the thoracic space (T6-T8 space) was implanted and in the last half an hour of operation, epidural analgesia pump with local anesthetic using bupivacaine 0.125 with a dose of 4 ml per hour was also used for the patient. We implemented epidural test dose of 3 mg lidocaine 1.5% with epinephrine 1:200 000 for detecting incorrect placement of epidural catheter. In the second group, after anesthesia and surgery in the last half an hour of operation, the venous pump from the peripheral vein was connected to the patient and the patient was on intravenous infusion of morphine 10 mcg/kg/hr. and Ketorolac 120 mg/day (ketorolac does not pose risk for acute kidney injury or bleeding postoperatively) (5). Patients, after surgery, intubated and were transferred to the ICU.

Postoperatively in terms of pain, respiratory complications, hemodynamic disorders (within first 24 hours), time of discharge from ICU, critical complications such as AKI, MI, CVA, extra dose of narcotic and three-month survival were followed. AKI in terms of increased blood creatinine more than at least 1.5 times of the Baseline, MI in terms of positive troponin or corresponding electrocardiographic symptoms and CVA in terms of clinical signs were diagnosed and the necessary measures were taken to treat.

On the first day, due to intubation and receiving sedatives, it was not possible to assess the amount of pain. Six patients were not able to be extubated. On the second day, when they were excluded from the study, six other patients entered the study instead of them. From the second day after extubation, patients' pain was measured based on VAS score for 48 hours by UPAT. IF it was supposed the patient had a score of six or higher; In the PCIA method, static doses of morphine (3 mg) were used and in the PCEA method, the amount of agent received increased one unit per hour, and if the patient still had a pain, higher than six, another unit of the agent was used. It was raised to the desired level of analgesia. If the pain score is still higher than 6, static dose morphine (3 mg) is also used. If the average arterial blood pressure is less than 70 mmHg and the heart rate is less than 60 beats per minute, the medication admiration was held temporarily for getting back to stable hemodynamic.

As mentioned, because of the patient's intubation on the first day, the UPAT method wasn't used to assess pain. The second and third days after the operation were used to assess pain. The hemodynamic status of the patient was checked during the first day.

Considering that the pain can affect a patient's blood pressure and heart rate, in the first 24 hours after the operation the patient's hemodynamics status, including blood pressure and heart rate, were recorded and the patient's pain score was also recorded on the second and third days.

Average systolic, diastolic blood pressure and HR in the first 24 hours in the two study groups at 2, 4, 6, 12, 18 and 24 hours were examined.

Sample size

Based on a previous study (6), considering 95% confidence level, test power 80%, standard deviation (SD1)=1.4, SD2=1.5, based on $\alpha = 0.05$ and $\beta = 0.1$, using the following formula, the final sample size was estimated at 40 patients in each intervention group.

$$n = \frac{(\sigma_1^2 + \sigma_2^2)(Z_1 - \frac{\alpha}{2} + Z_1 - \beta)^2}{(\mu_1 - \mu_2)^2}$$

Randomization

Enrolled patients were randomly assigned to receive either PCEA or PCIA analgesia during surgery. Odd and even date of the surgery was used to allocate patients respectively (odd for PCEA, even for PCIA). When the number of patients for PCEA reached 40, the number of patients undergoing PCIA was 35 and the subsequent five patients were assigned for PCIA. In both groups, the induction method of anesthesia and maintenance were the same. Type of surgery was also the same in these patients.

Analysis

The SPSS version 25.0 was used to analyze the data. Descriptive analyses were carried out to explore the data. The chi-square test was used to compare categorical variables. An independent t-test was used to compare pain scores between two groups. A significant level of alpha 0.05 or lower was adopted for all main analyses.

Ethics

Approval for the study was obtained from the Office for Protection of Research Subjects at Tehran University of Medical Sciences. Written informed consent was obtained from all the patients.

Results

The RCTs selection process is outlined in Figure 1. Out of 80 patients who were screened for eligibility criteria, 40 patients were allocated to each group of intervention.

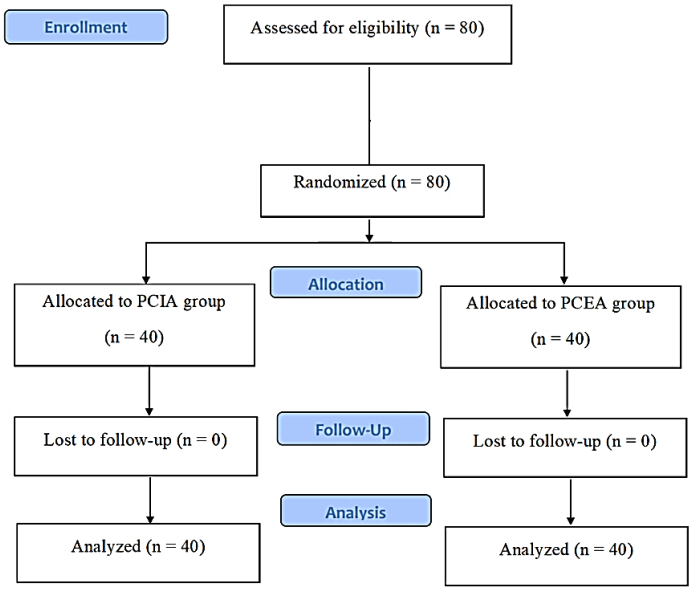

Figure 1. Consort flow chart. Out of 80 patients who were screened for eligibility criteria, 40 patients in each group were analyzed

In all 80 patients who were studied (40 in the PCEA group and 40 in the PCIA group) as shown in Table 1, there were no significant differences between the two groups concerning demographic characteristics, including age and sex ($P > 0.05$).

This study demonstrated a non-significant difference in 2nd and 3rd-day pain scores between the two groups, as depicted in Table 2.

As shown in tables 3-5, no significant difference was seen between the average of diastolic and systolic BP as well as HR.

Based on results in Table 6, no significant difference was observed between the two groups of study in measured parameters after surgery, such as three-month survival and AKI. Likewise, rescue treatment was the same in both groups (Table 7).

Table 1. Demographic characteristics of patients who undergo esophageal surgery

Variable	Group PCEA	Group PCIA	*P*
	Mean±SD	Mean±SD	
Age	62.6±7.5	62.6±9.4	0.83
Sex (M/F)	17/23	24/16	0.11

Table 2. Pain evaluation in two studied groups in 2nd and 3rd days after surgery

Variable	Group PCEA	Group PCIA	*P*
	Mean±SD	Mean±SD	
2nd day pain score	3.8 ± 1.1	4.1 ± 1.1	0.27
3rd day pain score	2.8 ± 0.7	3.1 ± 0.9	0.12

Table 3. Comparison between the average of systolic blood pressure in first 24 hours after surgery in two studied groups

Time (hr)	Group PCEA	Group PCIA	*P*
	Mean±SD	Mean±SD	
2	128.2±15	129.1±13.3	0.78
4	125.4±13	126.4±13.9	0.74
6	126.4±12.5	123.3±12.8	0.28
12	119.4±10.5	119.5±13.2	0.95
18	117.8±11	117.5±11.3	0.89
24	114.3±11.8	113.7±13.5	0.813

Table 4. Comparison between average diastolic blood pressure in first 24 hours after surgery in two studied groups

Time (hr)	Group PCEA	Group PCIA	*P*
	Mean±SD	Mean±SD	
2	72.1±12.6	71.63±8.6	0.83
4	70.4±13.6	69±6	0.61
6	69.7±12.7	67.9±10.6	0.50
12	65.7±11	63.4±10.3	0.35
18	63.13±12.7	62.8±11	0.91
24	64±12.3	62.8±12.3	0.68

Table 5. Comparison between average heart rate in first 24 hours after surgery in two studied groups

Time (hr)	Group PCEA	Group PCIA	*P*
	Mean±SD	Mean±SD	
2	86.2±14.9	85.7±13.1	0.86
4	82.7±11.1	82.7±13.5	> 0.9
6	80.2±9.9	83±10.6	0.21
12	80.5±12.2	81±10.6	0.83
18	78.7±9.4	80.9±8.9	0.28
24	77.5±9.6	77.8±7.8	0.87

Table 6. After surgery, complications in two studied groups

Variable	Group PCEA	Group PCIA	*P*
	N=40	N=40	
Three-months survival rate	30 (75 %)	26 (65 %)	0.32
AKI	2 (5 %)	7 (17.5 %)	0.15
Pulmonary complication	0 (0 %)	5 (12.5%)	0.05

Table 7. Comparison of rescue treatment in two studied groups after surgery

Variable	Group PCEA	Group PCIA	*P*
	Mean±SD	Mean±SD	
Rescue treatment	0.2±0.8	0.45±1.44	0.39

However, pulmonary complications were statistically higher in the PCIA group.

Regarding postoperative complications, CVA and MI were not seen in any patients. Nine patients showed renal impairment, two patients in the PCEA group, were at risk (R) according to the RIFLE criteria (7). There were seven cases in the intravenous group, five of them were at risk and two were injured as (I) criteria. However, this result was not significant. There were five cases of pulmonary complications in the PCIA group, including two cases of pneumonia and three cases of atelectasis. But no case was seen in the epidural group, which was significantly different between the two groups. Six patients were also excluded from the study on the second day due to intubation. Pulmonary complications and the surgery itself, including pleural effusion, dilatation of the organs in the thoracic space, and poor functioning of the chest tube, were the reasons for their non-acquisition. Three patients were in the epidural group and three were in the intravenous group, which were replaced with other patients.

Surprisingly, the hospitalization rate was more in the PCIA group (P =0.008) as reported in Table 8.

Table 8. The hospitalization rate in two studied groups after surgery

Variable	Group PCEA	Group PCIA	*P*
	Mean±SD	Mean±SD	
Hospitalization	3±0.1	3.2±0.5	0.008

Discussion

In this randomized controlled trial study, we found that both methods of PCEA and PCIA were the same about 2nd and 3rd-day pain scores or other after surgery complications such as three-month survival rate among patients undergoing esophagostomy.

In the study by Wu *et al*., in 2005, two methods of PCIA and PCEA with narcotics were used to control postoperative pain in a meta-analysis from 1966 to 2004. Pain control was better in the epidural group. Based on the result, patients receiving continuous epidural infusion had a significantly higher incidence of nausea-vomiting and motor block but a lower incidence of pruritus (8).

In 2005, M Zutshi *et al*., reported that in colon cancer surgery, comparing PCEA and PCIA for postoperative analgesia found no differences in pain control, complications, costs, and hospital stay. In the epidural method, bupivacaine was used with fentanyl and in the intravenous method, morphine was used (9). The results from Tseng study confirmed that both intravenous analgesia and epidural analgesia can provide sufficient pain control and are safe strategies for treating acute post-thoracotomy pain in patients (10).

With comparing the experience of change in systolic and/or diastolic blood pressure and heart rate after anesthesia, Table 3-5 showed that there were no statistically significant differences between two groups.

The results of the study of Ham showed that the two groups had postoperative hemodynamic differences. Patient hemodynamics were recorded for up to three days after surgery. The PCEA group had systolic and diastolic hypertension, while the heart rate was higher in the PCIA group. We hypothesize that similar pain control in both groups in our study could be the reason for no difference in patients' hemodynamic profiles. Despite significant differences in the postoperative hemodynamics, the incidence of AKI was similar between the two groups in the Ham study, which was in line with our results (11).

In our study, the incidence of respiratory complications was higher in the PCIA group, with a P-value of 0.05. Previously, some studies reported PCEA superiority, or no difference was found between the two groups (12,13). In the epidural method of anesthesia, by blocking the sympathetic nervous systems and preventing the release of cortisol and other inflammatory factors, fewer pulmonary complications are seen, and the immune system is inactivated. Residual functional capacity is maintained, and respiratory depression will be lower due to less narcotic use (14).

Rescue treatment in this study was not different between two groups. In this study, the time of hospitalization in the ICU was statistically greater in the PCIA group. Li *et al*., also reported that the PCEA group had a shorter hospital stay in patients with esophageal cancer undergoing open thoracotomy (14). The length of hospital stay in the PCEA group was shorter than PCIA group in the study by Zhu *et al*., in 2013 in patients after gastrectomy for gastric cancer (15).

Implantation of an epidural catheter can be challenging and can sometimes fail. Hence the

intravenous method can be an effective as well as a

safe alternative to the epidural method. Especially in patients who are contraindicated for PCEA.

There are also some limitations in this study. For instance, this is a single-center with a limited number of cases. Alternatively, we planned to perform an additional study with an appropriately calculated sample size based on the results of the present study.

Patients were intubated on the first day after surgery and they needed sedation to tolerate the endotracheal tube. Therefore, a small amount of sedative agent (fentanyl 50-100 mcg per hour) was administered for patients with the thoracic epidural. Since this confounding factor may interfere with our analyses, we relied on the difference in pain on the second and third days after surgery. After extubation, sedatives were discontinued and the only analgesic for the epidural group was the same as the infusion of bupivacaine through the epidural catheter.

The findings from this study suggest that both methods of PCEA and PCIA are effective in pain reduction, and also causes a similar analgesic effect for post-operative pain management in esophageal cancer patients.

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