

# A Comparison of Patient Controlled Epidural Analgesia With Intravenous Patient Controlled Analgesia for Postoperative Pain Management After Major Gynecologic Oncologic Surgeries: A Randomized Controlled Clinical Trial

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**Background:** Postoperative pain after major open gynecologic surgeries requires appropriate pain management.

**Objectives:** This study aimed at comparing perioperative patient controlled epidural analgesia (PCEA) and patient controlled intravenous analgesia (PCA) after gynecologic oncology surgeries.

**Patients and Methods:** In this clinical trial study, 90 patients with American society of anesthesiologists (ASA) class I or II scheduled for gynecologic oncologic surgeries were randomly allocated to two groups (45 patients each group) to receive: patient-controlled epidural analgesia with bupivacaine and fentanyl (PCEA group), or patient controlled intravenous analgesia (IV PCA group) with fentanyl, pethidine and ondansetron. Postoperative pain was assessed over 48 hours using the visual analog scale (VAS). The frequency of rescue analgesia was recorded. Occurrence of any concomitant events such as nausea, vomiting, ileus, purities, sedation and respiratory complications were recorded postoperatively.

**Results:** There were no statistically significant differences in demographic data including; age, weight, ASA physical status, duration of surgery, intraoperative bleeding, and the amount of blood transfusion ( $P > 0.05$ ), between the two studied groups. Severity of postoperative pain was not significantly different between the two groups ( $P > 0.05$ ); however, after first patient mobilization, pain was significantly lower in the epidural group than the IV group ( $P < 0.001$ ). There was no significant difference between the two groups regarding the incidence of complications such as nausea, vomiting, purities or ileus ( $P > 0.05$ ). Nevertheless, the incidence and severity of sedation was significantly higher in the IV group ( $P < 0.001$ ). Respiratory depression was higher in the IV group than the epidural group; this difference, however, was not significant ( $P = 0.11$ ). In the epidural group, only 10 patients (22.2%) had mild and transient lower extremities parenthesis.

**Conclusions:** Both intravenous and epidural analgesic techniques with combination of analgesics provide proper postoperative pain control after major gynecologic cancer surgeries without any significant complications. Regarding lower sedative and respiratory depressant effects of epidural analgesia, it seems that this method is a safer technique for postoperative pain relief in these patients.

**Keywords:** Pain, Postoperative; Gynecologic Surgical Procedures; Analgesia, Epidural

## 1. Background

A revolution in the management of acute postoperative pain has occurred during the past three decades. Although, clinical practice guidelines for acute postoperative pain management were developed, provision of effective analgesia for surgical patients continues to be undertreated (1). Postoperative pain has been a major concern for physicians in both traditional and modern medicine (2, 3). Numerous methods (3-5) and medications, from analgesics (6) to local anesthetics (7), have been introduced to overcome postoperative pain. Postoperative pain, especially when poorly controlled, results in harmful acute and chronic effects, adverse physiologic responses, delayed long-term recovery and chronic pain

(3, 4). Gynecologic cancer surgery includes a wide variety of surgical procedures such as radical pelvic dissection, upper abdominal exploration, tumor reduction, and bowel resection, all of which are associated with potential complications of blood loss, thromboembolic events, and delayed return of bowel function (8-11). Various analgesic techniques have been developed to treat postoperative pain after open gynecologic cancer surgeries. Epidural analgesia is an effective therapy for the management of pain after major abdominal surgeries. Epidural opioid improves the potency of analgesia, decreasing most of the aforementioned complications (12).

Patient-controlled analgesia with intravenous opioids

(IVPCA) and patient-controlled epidural analgesia (PCEA), with a local anesthetic or an opioid either alone or in combination, are two major advances in the management of pain after major surgery, which enable patients to self-titrate bolus doses of analgesics to their desired levels of pain relief using a programmable infusion pump (13-15). Although PCEA using a mixture of bupivacaine and opioid has been compared with IVPCA for gynaecological surgeries, the optimal drug combination for infusion in the two techniques has not been defined (7, 14).

## 2. Objectives

In this study, we compared the effects of patient controlled analgesia with intravenous or epidural routes using protocols of combinational analgesics on postoperative pain control.

## 3. Patients and Methods

This randomized, clinical trial was performed at Al-zahra obstetrics and gynecology educational hospital, Tabriz, Iran. The code of this research protocol was 91222, and the registration ID in IRCT was IRCT2013071411700N2.

After the approval of the study by the ethical committee of Tabriz university of medical sciences, 90 patients with ASA physical status of I, II or III, aged 40 to 60 years, undergoing major gynecologic oncologic surgeries were randomly allocated to either the general anesthesia with placement lumbar epidural and postoperative opioid/bupivacaine (PCEA) group or general anesthesia with postoperative IV PCA group. The sample size was calculated based on the study of Ferguson et al. (18). A power analysis was performed using postoperative pain as the primary outcome. This analysis indicated that a sample size of 42 patients/group was necessary. To allow for potential drop-outs, it was decided to recruit 55 patients per group. Randomization was carried out by a computer-generated list of random numbers. All patients provided informed written consents to participate in this study. Exclusion criteria were contraindications to epidural catheter placement, history of anaphylaxis or contraindication to bupivacaine or fentanyl. All patients received general anesthesia as follows: all patients received premedication with midazolam 1 - 2 mg/kg and fentanyl 1  $\mu$ /kg. Induction was performed with thiopental 5 - 6 mg/kg and atracurium 0.5 - 0.6 mg/kg to facilitate tracheal intubation. Anesthesia was maintained with isoflurane (1 - 1.5%) in 50% oxygen and 50% N<sub>2</sub>O; controlled ventilation was continued.

Group 1 (PCEA) had placement of an epidural catheter at the L2 - L3 intervertebral space and only test doses (1.5% lidocaine 3 - 4 mL and epinephrine 1/200000) were administered, before induction of general anesthesia. After surgery, in the recovery room, group 1 (PCEA), received 0.5% bupivacaine 120 mg (24 mL) (bupivacaine hydrochloride vials as 50 mg/20 mL, DELPHAN Tours, La Baraudiere, 37172 Chambray Les Tours Cedex France) fentanyl 150  $\mu$ g (3 mL) in normal saline with a total volume of 100 mL.

Rate of infusion was 6 - 8 mL/hour with bolus administration of 2 mL every 15 minute as needed. Group IV PCA received IV analgesia, which contained 300  $\mu$ g (6 mL) fentanyl, 200 mg (4 mL) pethidine and 8 mg (2 mL) ondansetron in 0.9% normal saline with a total volume of 100 mL, through a PCA device (Forina disposable infusion pump, type: WZ-US joint venture maximum capacity of 100 mL. Basal rate: 0.3, 0.5, 0.6, 0.8 mL/hour and effective infusion dose: 98 mL). First the speed of infusion was set to 6 to 8 mL/hour, with bolus administration of 2 mL every 15 minutes, as needed. Patients not being satisfied with the pain control in either of the groups received pethidine (0.5 mg/kg IV) PRN, as the supplementary analgesia.

The primary outcome was pain at rest and while ambulating. Pain was measured by the ten-point visual analogue scale (VAS) graded from 1 cm (no pain) to 10 cm (the worst possible pain) daily. All secondary outcomes including need for additional analgesia, nausea/vomiting using the Bellville scoring system (0: without nausea and vomiting, 1: sensation of nausea, 2: sensation of nausea with retching, 3: vomiting), purities, postoperative ileus, respiratory depression (SaO<sub>2</sub>) or arterial oxygen saturation < 92%, sedation using the Ramsay scoring system (1: anxious and agitated, 2: cooperative, oriented and tranquil, 3: sleepy, drowsy and respond easily to commands, 4: sleepy and respond slowly to pressure on glabella or loud auditory stimulus, 6: sleepy without response to pressure on glabella or loud auditory stimulus) and lower extremities paresthesia were assessed and recorded daily for each patient.

The statistical analysis of data was performed using the SPSS software version 17. The results were presented in the form of mean  $\pm$  standard deviation (SD) for parametric data. Analysis of data was performed to test the statistical difference between groups using Student's t-test and Mann-Whitney test to compare between groups while Chi-square test was used for qualitative data. P values of less than 0.05 were considered statistically significant.

## 4. Results

A total of 100 patients enrolled in this study. According to the Consort flow diagram, four patients were excluded; two because of technical difficulty and two patients because of early catheter withdrawal. Six patients were excluded due to incomplete, unavailable or missing data for a complete review.

In total, 90 patients were studied who were females undergoing major abdominal operations for gynaecological cancers. They were allocated to two groups of IV PCA (n = 45) and PCEA (n = 45). There were 85 patients with ovarian cancer, 43 patients of which (96.5%) were in the IV PCA group, and two patients (4.4%) in the PCEA group. Four patients had endometrial cancer, two (4.4%) were in the IV PCA group, and the other two (4.4%) in the PCEA group. One patient in the IV PCA group (2.2%) had cervical carcinoma. Demographic data are shown in Table 1.

Severity of postoperative pain at different times after

surgery and during the first ambulation period was assessed using the VAS system (Table 2). Pain severity, at 2, 4, 8, 12, 24, 36 and 48 hours after surgery was not significantly different between the two groups ( $P > 0.05$ ). Further and accurate evaluation with the chi-square test, also showed no significant difference in pain severity (VAS) at different times between the two groups ( $P = 0.96$ ); however, the mean severity of pain at first ambulation times was significantly lower in the PCEA group when compared to the IVPCA group ( $P < 0.001$ ) (Table 1). Considering additional postoperative analgesic consumption (VAS  $> 4$ ), seven patients (15.6%) in the PCEA group received pethidine (0.5 mg/kg IV) and 38 patients (84.4%) did not require further analgesics. In the IVPCA group, ten patients (8.9%) required additional analgesia while 35 patients (77.8%) did not. There were no statistically significant differences between both groups regarding the number of patients requiring additional analgesics. With a confidence interval of 95% (0.532 - 4.519), an odds ratio of 1.155 was achieved for IVPCA/PCEA regarding further analgesic requirement. Other postoperative complications, including postoperative nausea, vomiting, purities, ileus and respiratory depression were evaluated; there were no significant differences between the two groups ( $P = 0.46$ ,  $P = 0.21$ ,  $P = 0.49$ ,  $P = 0.11$  and  $P = 0.11$ , respectively).

The PCEA group was also evaluated for having paresthesia or motor weakness in their lower extremities. Only 10 patients (22.2%) had mild and transient paresthesia without any motor blockade and 35 patients (77.8%) were without any sensory or motor complications. Postoperative sedation using Ramsay scoring system was significantly higher in the IVPCA group compared with the PCEA group ( $P < 0.001$ ) (Table 3).

**Table 1.** Demographic Characteristics of Two Groups <sup>a,b,c</sup>

Patients (n = 90)	IVPCA (n = 45)	PCEA (n = 45)	P Value
Age, y	53.8 ± 11.4	49.9 ± 8.8	0.73
Weight, kg	67.96 ± 8.45	69.84 ± 7.7	0.78
ASA			0.20
I	22 (48.8)	16 (35.5)	
II	23 (51.1)	29 (64.4)	
Operation time, h	3.08 ± 0.85	3.7 ± 0.79	0.001

<sup>a</sup> Abbreviations: ASA, American Society of Anesthesiologists; IVPCA, Intravenous Patient-controlled Analgesia; PCEA, Patient Controlled Epidural Analgesia.

<sup>b</sup>  $P < 0.05$  is considered significant.

<sup>c</sup> Values are presented as mean ± SD or No. (%).

**Table 2.** Pain Severity at Different Times <sup>a,b</sup>

Pain Severity	IVPCA (n = 45)	PCEA (n = 45)	Total (n = 90)
VAS 2 hours after surgery	3.71 ± 0.89	2.87 ± 1.23	3.29 ± 1.15
VAS 4 hours after surgery	3.20 ± 1.29	2.91 ± 3.20	3.06 ± 1.24
VAS 8 hours after surgery	2.67 ± 1.36	2.53 ± 0.99	2.60 ± 1.18
VAS 12 hours after surgery	2.11 ± 1.15	2.24 ± 0.83	2.18 ± 1.00
VAS 24 hours after surgery	0.69 ± 0.73	1.51 ± 1.14	1.10 ± 1.03
VAS 36 hours after surgery	0.31 ± 0.59	0.31 ± 0.66	0.31 ± 0.63
VAS 48 hours after surgery	0.20 ± 0.50	0.56 ± 0.01	0.38 ± 0.15
VAS at the first ambulation	2.67 ± 0.02	1.89 ± 0.93	NA

<sup>a</sup> Data are shown as mean ± standard deviation.

<sup>b</sup> Abbreviations: IVPCA, Intravenous Patient-controlled Analgesia; PCEA, Patient Controlled Epidural Analgesia; VAS, Visual Analogue Scale.

**Table 3.** Other Postoperative Complications <sup>a</sup>

Complication	IVPCA (n = 45)	PCEA (n = 45)	P Value <sup>b</sup>
Nausea	13 (28.9)	10 (22.2)	0.46
Vomiting	4 (8.9)	8 (17.8)	0.21
Pruritus	2 (4.4)	0 (0)	0.49
Ileus	4 (8.9)	0 (0)	0.11
Sedation	4 (8.9)	22 (48.8)	< 0.001
Paresthesia or motor weakness	0 (0)	10 (22.2)	< 0.001
Respiratory depression	4 (8.9)	0 (0)	0.11

<sup>a</sup> Values are presented as No. (%).

<sup>b</sup>  $P < 0.05$  is considered significant.

## 5. Discussion

This study showed that both patient-controlled intravenous and epidural techniques with combination of analgesics provide proper postoperative pain control in patients undergoing gynaecological oncologic surgery. Moreover, pain in movement was better controlled with the epidural technique with less sedation than intravenous controlled analgesia. As previously mentioned, PCA is a safe and effective analgesic technique for postoperative analgesia and is known as the gold standard for pain relief after major abdominal operations. Furthermore, PCA makes it possible for patients to benefit proper pain control by themselves with titrated doses of analgesics (16, 17).

Ferguson et al. showed that in patients who received thoracic epidural analgesia after gynaecological surgery, postoperative pain relief was better controlled at rest and after coughing, when compared to patients with IV PCA. Nevertheless, pain at rest was similar in both groups at different postoperative times in our study (18). Bartha et al. used ropivacaine and morphine for PCEA in comparison with IV morphine for IV PCA in patients undergoing major abdominal surgeries (19). They suggested that postoperative pain was better controlled with PCEA than IV PCA. Also, Chen et al. compared these two analgesic techniques after gynaecological laparotomies and recommended that PCEA provided better pain relief, especially after patient movement, when compared to IV PCA (1). They also used intravenous morphine in PCA similar to the studies of Ferguson et al. and Bartha et al. (18, 19). Nonetheless, we used the combination of low-dose analgesics in our study; this might have contributed to the better quality of analgesia in the IV group in comparison to other studies.

In this study, we used pethidine as additional analgesia when VAS was higher than four. Ferguson et al. used ketorolac as the additional analgesic. In their study, similar to ours, there was no difference in additional analgesic consumption between the two groups (18). Also, in the PCEA group, we used 0.125% bupivacaine with fentanyl as the analgesic. Regarding very low and mild paresthesia without any motor block, it seems that this diluted solution in combination with opioids can provide better analgesia without any neural complications.

Perioperative interventions like epidural analgesia with local anesthetics and opioids can block afferent pain stimulations and efferent sympathetic responses. Consequently, they can excel intestine motility and prevent postoperative ileus. In our study, and also in the studies of Ferguson et al. (18) and Chen et al. (1), postoperative ileus was not reported.

Regarding sedation, 22 patients in the IV PCA group, had different degrees of sedation (using the Ramsay sedation scoring system), due to direct intravenous infusion of opioids. Only three patients had high sedation scores. In the PCEA group, despite infusion of opioid (fentanyl) with bupivacaine, no patient experienced sedation. Although respiratory depression was not statistically different be-

tween the two groups, in the IV PCA group, four patients had respiratory depression, i.e. decrease in SaO<sub>2</sub> levels to less than 91%, which was controlled rapidly, lowering the infusion rate. In the PCEA group, no one had respiratory depression. It appears that PCEA is safer than IV PCA regarding these complications.

Both PCEA and IV PCA are effective in pain relief after major gynaecological cancer surgeries, especially when combination therapy with low dose agents is used. It appears that PCEA is superior in pain relief with less sedation effects. The limitation of this study was that it compared two different techniques, thus it was not a double-blinded study, which may cause some bias in the data collection.

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## Authors' Contributions

Farnaz Moslemi and Samad EJ Golzari provided the hypothesis and the draft, Sousan Rasooli and Ali Baybordi collected the data and revised the final draft, Farnaz Moslemi and Samad E.J. Golzari provided the revised manuscript, collected the data and performed the analysis.

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