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Improved Postoperative Pain Control for Cytoreductive Surgery in Women With Ovarian Cancer Using Patient-Controlled Epidural Analgesia

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Objective: Many studies have compared different methods of postoperative pain management in abdominal laparotomy patients; however, the conclusions have been inconsistent and controversial. This study aimed to compare the pain scores and complications of patients who underwent cytoreductive surgery for ovarian cancer and used either patient-controlled epidural analgesia (PCEA) or patient-controlled intravenous analgesia (PCA) for postoperative pain management. We hypothesized that PCEA would be superior to PCA for postoperative pain management in ovarian cancer surgery.

Materials and Methods: The medical records of women who underwent ovarian cancer surgery in 2014 were reviewed retrospectively. Pain scores for postoperative days (PODs) 0 to 5 days and the incidence of complications were examined and compared in patients who received PCEA and PCA. Means were compared using an independent sample *t* test or Wilcoxon rank sum test, and proportions were compared using Fisher exact test or a χ^2 test at each time point. A mixed-effects model was applied to determine correlations among repeated measurements. A *P* value less than 0.05 was considered significant.

Results: Of the 105 study patients, 38 received PCEA and 67 received PCA. Pain scores were significantly lower in the PCEA group than the PCA group at POD 0 (2.47 ± 1.75 vs 4.39 ± 1.17 ; $P < 0.001$), 1 (2.65 ± 1.02 vs 3.32 ± 1.09 ; $P < 0.001$), and 3 (2.17 ± 1.13 vs 2.79 ± 1.08 ; $P = 0.011$), and tended to be lower in the PCEA group at PODs 2, 4, and 5. Patient-controlled epidural analgesia provided significantly better pain relief as analyzed by a mixed-effect model. Complications were not significantly different between both groups. There was no significant difference in pain relief between both groups at PODs 4 and 5.

Conclusions: Patient-controlled epidural analgesia was more effective for postoperative pain management compared with PCA from POD 0 to POD 3 in patients with ovarian cancer who underwent cytoreductive surgery, without increasing the morbidity.

Key Words: Ovarian cancer, Epidural analgesia, Patient-controlled analgesia, Postoperative pain

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The incidence of ovarian cancer in Korea is continuously increasing.¹ Patients who undergo abdominal laparotomy usually use patient-controlled analgesia for postoperative pain management, which can be administered as either patient-controlled epidural analgesia (PCEA) or patient-controlled intravenous analgesia (PCA). Many studies have compared different methods of postoperative pain management; however, the conclusions of the studies are inconsistent and controversial. The results of a meta-analysis revealed that PCEA is superior to PCA for pain control after abdominal laparotomy; however, this meta-analysis was not limited to gynecologic oncology patients.^{2,3} A prospective study reported that epidural PCEA is not superior to PCA for postoperative pain control in gynecologic oncology patients,⁴ which contradicts the results of another prospective study reported in 2009.⁵ Moreover, a retrospective study showed that epidural analgesia provided effective postoperative pain relief in gynecologic oncology patients without increasing the duration of hospitalization or complications.⁶

All of the previously mentioned studies included only gynecologic oncology patients. In other words, they were focused on the beneficial effects of PCEA in patients with heterogeneous gynecologic malignancies, including cervical cancer, endometrial cancer, and ovarian cancer. The present study included patients who were definitively diagnosed with ovarian cancer, which is different from previously reported studies; therefore, this study has great clinical significance in terms of reproducibility. Postoperative pain is more severe in patients with ovarian cancer than in other gynecologic oncology patients, due to the long vertical incision for cytoreductive surgery. Effective postoperative analgesia can reduce mortality and morbidity after surgery⁷; as such, an effective and safe method of pain management that does not increase adverse reactions is essential.

For this reason, the aim of the present study was to compare the pain scores and complications of patients who underwent cytoreductive surgery for ovarian cancer and used either PCEA or PCA for postoperative pain management. We hypothesized that PCEA would be superior to PCA for postoperative pain management in ovarian cancer surgery.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board for Health Science Research of the National Cancer Center of Korea (IRB# NCC2015-0100), and included patients who underwent laparotomy for ovarian cancer between January 1 and December 31, 2014. The exclusion criteria were as follows: inability to use PCA, need for emergency operation, history of allergic reaction to local anesthetics or opioid, incomplete electronic medical records, insufficient recovery from anesthesia on postoperative day (POD) 0, and American Society of Anesthesiologists (ASA) score greater than III (which indicates severe systemic disease making the patient unfit to undergo general anesthesia for elective surgery).

In this retrospective cohort study, the electronic medical records of patients with ovarian cancer who underwent cytoreductive surgery were retrospectively analyzed. The

body mass index, recurrence, comorbidities, pathology, operative procedures, estimated blood loss, operative time, and need of blood transfusion were evaluated and compared between the PCEA group and PCA group as clinical variables.

Differences in intensity of pain, measured as pain scores, between the groups receiving PCEA and PCA for 5 PODs, were analyzed and determined as the primary outcome. Pain scores were recorded using a numeric rating scale (NRS). In addition, differences in duration of hospitalization, duration of Foley catheterization, time required for first gas out, use of additional analgesics and antiemetics, urinary tract infection, pulmonary complication, surgical site infections, ileus, and the incidence of complications such as deep vein thrombosis (DVT) were determined as secondary outcomes and analyzed.

The incisions were made from the pelvis to the xiphoid process with a midline incision during laparotomy, according to the protocol of the Center for Uterine Cancer in the National Cancer Center of Korea. The surgical procedures were described in detail in a previous publication.⁸

Each patient was allowed to choose between PCEA and PCA after receiving an explanation of the advantages and disadvantages of each method during the preanesthetic evaluation. Induction and maintenance of general anesthesia and thoracic epidural catheterization were performed by the same anesthesiologist. Epidural catheterization was performed at the T9–T11 levels after general anesthesia induction in the operating room, and its appropriate catheterization was tested with a test dose bolus injection with an epidural catheter. Twenty minutes before performing the incision, 6 to 8 mL of 0.375% ropivacaine was injected via epidural catheter, and the anesthesia was maintained by an inhalation agent and local anesthetics which were injected via an epidural catheter for 3 hours.

In each group, all of the patients were administered a regimen of the same drug at the same concentration for 1 year. The PCEA regimen was 0.125% of ropivacaine and 2.5 μ g/mL of fentanyl. The background continuous rate was 3 mL/h, and the bolus dose was 2 mL with a 15-minute lockout time. The PCA regimen was a combination of 15 μ g/mL and 0.5 mg/mL of morphine. The background continuous rate was 0.3 mL/h, and the bolus dose was 1 mL with a 10-minute lockout time. The total PCEA and PCA dose was 600 and 200 mL, respectively, which was enough for pain control for a week. After the total dose of PCEA was finished, the epidural catheter was removed immediately.

To quantify postoperative pain intensity, the patients were asked to use an NRS to grade their pain from 0 (no pain) to 10 (most severe pain). These pain scores were recorded by nurses in the patients' medical records. The NRS scores were recorded every 6 hours (4 times a day), and the mean scores were used for analysis. An NRS score of 0 (lowest score) indicated mild pain, and 10 (highest score) indicated severe pain.

Duration of hospitalization, length of urinary catheterization, and time to gas out after surgery were analyzed using a day scale beginning on the day of surgery. The occurrence of ileus, DVT, pulmonary complications, and surgical site infection was studied by reviewing the patients' medical charts. When the NRS scores were greater than or equal to 5 points, the patients were asked if they needed

additional analgesics, and a nonsteroidal anti-inflammatory drug such as ketorolac (Trolac, 30 mg/mL, Shinpoong Co, Ansan, Korea) was administered accordingly, per the protocol of the Center for Uterine Cancer in the National Cancer Center of Korea. Patients who received additional analgesics at least once were classified as the extra analgesic use group. Ramosetron was administered intravenously as an antiemetic to all of the patients in both the PCEA and PCA groups. When a patient experienced nausea or vomiting, additional antiemetics were used, according to the protocol. Patients who received additional antiemetics at least once after the initial administration of ramosetron were considered part of the extra antiemetic use group.

To avoid bias, all of the electronic medical records were collected by a neutral researcher who did not have any conflict with our study. All of the researchers were blinded until the statistical analysis results were concluded by a statistician.

Statistical Analysis

Statistical analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, NC). Means were compared using an independent sample *t* test or Wilcoxon rank sum test, and proportions were compared using Fisher exact test or a χ^2 test at each time point. To take into account correlations among repeated measurements, a mixed-effects model was applied. Odds ratios and 95% confidence intervals (CIs) were analyzed using SPSS version 21. A *P* value of less than 0.05 was considered significant.

RESULTS

A total of 109 patients with ovarian cancer underwent laparotomy between January 1 and December 31, 2014. Four patients were excluded, including 3 with an ASA score of III, and 1 who was unable to use PCA; therefore, 105 patients were analyzed in the present study. However, 18 patients were excluded on POD 0 because of inadequate recovery from anesthesia, and 4 patients (1 on POD 3, 1 on POD 4, and 2 on POD 5) were excluded because of incomplete medical records. Although electronic medical records were used in the analysis, no definite criteria were used to define inadequate recovery; this can be a potential confounder in this study.

Thirty-eight patients received PCEA, and 67 patients received PCA. The patients' demographic and clinical characteristics are presented in Table 1. There were no statistically significant differences between the 2 groups with respect to age, body mass index, recurrence rate, comorbidities, or pathology of ovarian cancer.

Surgical Outcome

Comparative data related to surgery between the 2 patient groups are presented in Table 2. There was no statistically significant difference in mean surgical time between the PCEA and PCA groups (380.3 vs 332.8 minutes, respectively). The mean estimated blood loss values were 740.8 and 641.8 mL in the PCEA and PCA groups, respectively; the difference was not statistically significant. The rate of blood transfusion was significantly higher in the PCEA group than in the PCA group (47% vs 27%, *P* = 0.033). The number of

bowel resections was also significantly higher in the PCEA group than in the PCA group (68% vs 46%, *P* = 0.029).

Pain Outcome

The pain scores of the PCEA group were significantly lower on the day of surgery (POD 0) and on PODs 1 and 3 (Table 3). The relative risks with 95% CIs on PODs 0, 1, and 3 were 7.108 (2.688–18.796, *P* < 0.001), 6.570 (1.794–24.068, *P* = 0.005), and 2.882 (0.954–8.703, *P* = 0.048), respectively (Table 4). There were no statistically significant differences between the pain scores and relative risks with 95% CIs of the 2 groups at PODs 2, 4, and 5; however, the pain scores tended to be lower in the PCEA group.

Because of the repeatedly measured data, a mixed-effects model was used to analyze the correlations at each time point in the same patients, which resulted in an overall significant difference in the rate of change (slope) between the 2 groups (Table 5). In other words, PCEA provided better pain relief than PCA.

TABLE 1. Patient demographic and clinical characteristics

Variables	PCEA (n = 38)	PCA (n = 67)	<i>P</i>
Age, y			
Mean ± SD	53.8 ± 8.1	53.3 ± 11.3	0.768
BMI, kg/m ²			
Mean ± SD	22.7 ± 2.8	30.2 ± 54.2	0.126
Recurrent, n (%)			
No	29 (76)	48 (72)	0.603
Yes	9 (24)	19 (28)	
Comorbidities, n (%)			
Hypertension	5 (13)	20 (30)	0.060
Thyroid disease	5 (13)	3 (4)	0.135
Pulmonary disease	2 (5)	0 (0)	0.129
Diabetes mellitus	1 (3)	7 (10)	0.253
Coronary artery disease	1 (3)	0 (0)	0.362
Congestive heart failure	0 (0)	0 (0)	
Chronic kidney disease	0 (0)	0 (0)	
Pathology, n (%)			
Serous	31 (82)	43 (64)	0.206
Endometrioid	4 (11)	11 (16)	
Sarcoma	1 (3)	2 (3)	
Clear cell	1 (3)	0 (0)	
Krukenberg	1 (3)	0 (0)	
Mucinous	0 (0)	3 (4)	
Granulosa	0 (0)	2 (3)	
Teratoma	0 (0)	2 (3)	
Others	0 (0)	4 (6)	
BMI, Body mass index.			

TABLE 2. Surgery-related characteristics

Variables	PCEA (n = 38)	PCA (n = 67)	P
Operative procedure performed, n (%)			
Tumor debulking	37 (97)	65 (97)	1.000
Para-aortic lymph node dissection	30 (79)	45 (67)	0.199
Pelvic lymph node dissection	29 (76)	46 (69)	0.404
Omentectomy	28 (74)	48 (72)	0.822
Bowel resection	26 (68)	31 (46)	0.029
Salpingo-oophorectomy	24 (63)	45 (67)	0.678
Hysterectomy	23 (61)	42 (63)	0.827
Required blood transfusion	18 (47)	18 (27)	0.033
Splenectomy	8 (21)	12 (18)	0.694
Cholecystectomy	8 (21)	5 (7)	0.063
Liver resection	5 (13)	6 (9)	0.522
Pancreatectomy	4 (11)	3 (4)	0.251
VATs	2 (5)	2 (3)	0.619
Breast excision	1 (3)	1 (1)	1.000
Neck dissection	1 (3)	1 (1)	1.000
Gastrectomy	1 (3)	0 (0)	0.362
EBL, mL			
Mean ± SD	740.8 ± 557.4	641.8 ± 617.5	0.192
Operative time, min			
Mean ± SD	380.3 ± 141.1	332.8 ± 130.7	0.085
Require blood transfusion pRBC, U	18 (47%)	18 (27%)	0.033
Mean ± SD	1.3 ± 1.6	1.0 ± 1.9	0.091

EBL, Estimated blood loss; pRBC, packed red blood cells; VATs, video-assisted thoracic surgery.

Postoperative Outcome

Secondary outcomes are shown in Table 6. In particular, there were no statistically significant differences in the duration of hospitalization or time to first gas out between the

PCEA and PCA groups. Extra analgesic use tended to be higher in the PCA group than in the PCEA group (33% vs 16%, $P = 0.058$). There was no significant difference in the use of additional antiemetics between the 2 groups.

TABLE 3. Postoperative NRS pain score

Variables	PCEA (n = 38)	PCA (n = 67)	P
	Mean ± SD	Mean ± SD	
POD 0	2.47 ± 1.75	4.39 ± 1.17	<0.001
Missing	6	12	
POD 1	2.65 ± 1.02	3.32 ± 1.09	<0.001
POD 2	2.47 ± 1.19	2.92 ± 1.12	0.086
POD 3	2.17 ± 1.13	2.79 ± 1.08	0.011
Missing		1	
POD 4	2.26 ± 0.99	2.52 ± 0.96	0.249
Missing		1	
POD 5	1.86 ± 1.06	2.15 ± 1.09	0.269
Missing	1	1	

DISCUSSION

In the current study, PCEA provided better management of postoperative pain compared with PCA. In particular, the pain scores of the PCEA group were low without complications, and the relative risk shows a similar tendency.

TABLE 4. The relative risks and 95% CIs of POD 0–5 days

Variable	Mean	Odds Ratio (95% CIs)	P
POD0	3.68	7.108 (2.688–18.796)	<0.001
POD1	3.08	6.570 (1.794–24.068)	0.004
POD2	2.76	1.017 (0.267–2.497)	0.123
POD3	2.56	2.882 (0.954–8.703)	0.048
POD4	2.42	1.110 (0.372–3.309)	0.852
POD5	2.05	0.545 (0.156–1.906)	0.342

TABLE 5. Across time difference between PCEA and PCA

Label	Num DF	Den DF	F Value	Pr > F
Overall treatment difference	1	398	27.21	<0.001

Epidural analgesia was significantly superior for pain relief at PODs 0, 1, and 3, and tended to be better at PODs 2, 4, and 5.

Previous comparative studies on the effects of PCEA and PCA have focused mainly on PODs 1 and 2,^{5,9} whereas the present study analyzed the effects from POD 0 to POD 5. In particular, pain is most severe at POD 0, the day of surgery, thereby necessitating effective pain management. The present study excluded patients who did not recover from anesthesia on the day of surgery. The NRS scores were measured 6 hours after surgery and at other times when postoperative communication was possible, and the scores were averaged to obtain the pain scores for POD 0. Although it was difficult to measure the NRS scores due to missing data, mainly because the patients were unable to communicate or were in surgery for a long time, these difficulties could be overcome using a mixed-effects model. As a result, pain scores that were statistically significant and different with respect to mean values could be obtained, as shown by the NRS score of 2.47 and 4.39 in the PCEA and PCA group, respectively.

In a prospective study conducted by Ferguson et al,⁵ pain control effects of PCA and PCEA were compared until POD 6. Patient-controlled epidural analgesia had superior effects at PODs 1, 2, and 3, and the effects were independently analyzed between PODs 1 and 6 daily. In contrast, in our study, a comparative analysis between the 2 groups across various time points was performed to determine the overall difference. In other words, general trends were analyzed to calculate overall differences through POD 5, including the day of surgery and without excluding days such as PODs 1 and 2. Overall, PCEA was shown to be superior for postoperative pain management compared with PCA, making our study distinct from previous studies.

There were no significant differences in secondary outcomes between the 2 groups. Reports have stated that epidural analgesia in laparoscopic colorectal surgery improved bowel function recovery and decreased the incidence of postoperative colorectal ileus.^{10,11} On the other hand, recent studies of gynecologic oncology patients have reported that epidural analgesia had no specific effects on bowel function recovery or ileus incidence.^{6,9} Consistent with those results, our study found no significant differences in the incidence of complications between the 2 groups; however, the PCEA group had a higher number of bowel resections than the PCA group. According to a previous study, bowel resection in ovarian cancer surgery significantly increased postoperative ileus and delayed bowel function recovery.¹² Although the PCEA group had a higher number of bowel resections in the present study, there was no difference in bowel function recovery between the 2 groups. Therefore, a prospective study is required to confirm the benefits of PCEA in patients with ovarian cancer who undergo extensive cytoreductive surgery, including bowel surgery.

In a recent study by Courtney-Brooks et al,⁹ a group of gynecologic oncology patients receiving continuous epidural infusion had a higher incidence of venous thromboembolism. In contrast, there was no significant difference in DVT incidence between the 2 groups in our study. However, because venous thromboembolism is not a complication with a high incidence level, it might be difficult to draw a statistically significant conclusion from the sample size of 105 patients used in our study. Therefore, a well-designed prospective study with a larger sample size is needed to further analyze the effects of PCEA on the incidence of venous thromboembolism.

Duration of hospitalization was also similar between the 2 groups in our study, which is consistent with the results of

TABLE 6. Postoperative morbidity

Variables	PCEA (n = 38)	PCA (n = 67)	P
Antiemetics, n (%)			
No	23 (61)	35 (52)	0.412
Yes	15 (39)	32 (48)	
Extra analgesia, n (%)			
No	32 (84)	45 (67)	0.058
Yes	6 (16)	22 (33)	
Complication, n (%)			
No	34 (89)	65 (97)	0.124
Yes	4 (11)	2 (3)	
Infection, n (%)			
No	35 (92)	62 (93)	0.606
Yes	3 (8)	5 (7)	
Ileus, n (%)			
No	38 (100)	62 (93)	0.156
Yes	0 (0)	5 (7)	
Pruritus, n (%)			
No	38 (100)	66 (99)	0.638
Yes	0 (0)	1 (1)	
DVT, n (%)			
No	38 (100)	66 (99)	0.638
Yes	0 (0)	1 (1)	
UTI, n (%)			
No	38 (100)	67 (100)	
Yes	0 (0)	0 (0)	
Length of hospital stay			
Mean ± SD	19.29 ± 11.64	16.69 ± 6.05	0.620
Missing		1	
Length of urinary catheterization			
Mean ± SD	4.61 ± 2.41	5.24 ± 3.22	0.487
Time to gas out, d			
Mean ± SD	4.97 ± 1.38	5.69 ± 2.46	0.190

UTI, Urinary tract infection.

preceding studies. Many previous studies were conducted under the assumption that epidural analgesia would reduce the duration of hospitalization by accelerating patient recovery.¹³ However, epidural analgesia was found to have no effect on the duration of hospitalization in a recent study and meta-analysis. Duration of hospitalization was affected not only by pain control, but also by various variables, and a standardized clinical pathway or protocol could reduce the duration of hospitalization.¹⁴

The need of transfusion was significantly higher in the PCEA group, which might be explained in 2 ways. First, because combined general anesthesia with epidural anesthesia was performed in the PCEA group, it is possible that more fluid was injected intravenously during surgery to supplement the volume depletion effect due to epidural anesthesia. In this study, general anesthesia with epidural anesthesia by 0.375% ropivacaine was combined for balanced anesthesia in the PCEA group. It is well known that epidural anesthesia can induce functional hypovolemia, and the need of transfusion increases as the requirement of fluid increases.¹⁵ Therefore, additional transfusion might be requested to supplement diluted hemoglobin. Second, although the patients selected PCEA or PCA, when a more aggressive and higher risk surgery was planned, more severe postoperative pain was expected; hence, PCEA might have been more strongly recommended in some cases by the anesthesiologist who collected the consent forms. Therefore, it is possible that because the surgery itself was invasive and aggressive, there was more blood loss, resulting in greater blood transfusion to supplement it. However, this is only a hypothesis, and the inherent limitations of a retrospective study could be present. Nevertheless, as this is the first study to report the effects of epidural analgesia in patients with ovarian cancer (with long incision and maximal cytoreductive surgery), the results are significant. One of the strengths of the present study is that it included patients with a similar range of incisions, and therefore, a more objective comparison of the pain control methods was conducted.

Selection bias is inevitable because of the retrospective study design, and the patients were allocated arbitrarily. Because of the retrospective design of the present study, precise control of the clinical characteristics in both groups was impossible. In addition, a greater sample size was needed to clearly detect a superior effect with statistical significance on PODs 2, 4, and 5. Therefore, further prospective study is required to confirm the real effects and complications after cytoreductive surgery in patients with ovarian cancer.

In conclusion, in exploratory laparotomy of patients with ovarian cancer, PCEA may be more beneficial in the management of postoperative pain compared with PCA, without increasing the morbidity.

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