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Clinical Research

Propacetamol as an alternative of ketorolac for postoperative pain management using patient-controlled analgesia

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Background: The objective of this study was to examine effect of propacetamol in comparison with ketorolac in intravenous patient-controlled analgesia after gynecologic surgeries.

Methods: Patients aged 18 to 70 years and undergoing laparoscopic gynecologic surgeries were selected. They were randomly allocated to either group K (180 mg of ketorolac with fentanyl and ramosetron) or group P (10 g of propacetamol with fentanyl and ramosetron). Their vital signs and visual analogue scale (VAS) were examined six times (0 min, 15 min, 30 min, 60 min, 12 h, and 24 h) and laboratory workup was done 48 hours after PCA application. Development of side effects was examined 15 minutes after the PCA application. Data from 111 patients were used for the final analysis.

Results: There were no significant differences in changes of systolic and diastolic blood pressures, heart rate, body temperature, and VAS between the groups (P = 0.325, 0.835, 0.346, 0.524, and 0.382, respectively). There were significant differences in the levels of hemoglobin, hematocrit, blood urea nitrogen, and international normalized ratio but it was not clinically meaningful. The development of vomiting, dizziness, and headache were not significantly different between the groups and no patient developed pruritus. Although the overall number of patients with nausea was higher in group P with statistical significance (P = 0.002), there were no significant differences between the groups when examined at each detection time.

Conclusions: The present study suggested propacetamol as a possible alternative of ketorolac in postoperative care after laparoscopic gynecologic surgeries.

Key Words: Analgesia, Ketorolac, Patient-controlled, Propacetamol.

INTRODUCTION

Postoperative pain is not avoidable but can be controlled. Appropriate and rapid management of postoperative pain not only influences the patient's condition but also reduces medical costs. Intravenous patient controlled analgesia (PCA) compensates limitations of traditional pro re nata analgesics, including intra-patient variability in analgesic needs, administrative delays, and variability in serum drug levels. PCA delivers analgesic opioids in an optimal manner and minimizes the effects of pharmacokinetic and pharmacodynamic variability in each patient, providing improved patient satisfaction and superior postoperative pain control [1].

Opioids are used to control postoperative pain by interacting with opioid receptors in the central nervous system to interrupt delivery of pain impulses [2]. The effect of opioids

is tremendous in management of postoperative pain and not only patients but also anesthesiologists prefer its use; however, the use of parenteral opioids often induces side effects such as postoperative nausea and vomiting (PONV), undesirable sedation, dependency, constipation, and paralytic ileus. Application of limited amount of opioid in patient-controlled analgesia (PCA) is necessary to prevent the development of opioid-related side effects; therefore, additive pain controllers such as ketorolac are often used [3-6].

Ketorolac, a nonsteroidal anti-inflammatory drug (NSAID) often used with opioids, controls pain by inhibiting synthesis of prostaglandins [3]. It is reported that ketorolac reduces opioid dose by 36% and development of PONV or sedation is observed less with use of ketorolac [6]. However, use of ketorolac showed higher risk of postoperative bleeding and anastomotic leakage after colorectal surgery due to gastrointestinal and antiplatelet effects [7,8], slowed wound healing, and reduced kidney function [9,10]. Therefore, use of opioid with ketorolac in PCA to vulnerable patients, especially ones with kidney problems or unstable hemodynamic states, is limited. In addition, a prolonged onset of the analgesic action (30–60 min) is another weakness of ketorolac in control of acute pain [11].

In contrast, propacetamol, a prodrug of acetaminophen, is also known to reduce opioid dose by 37% [12] and presents a safer pharmacological profile. A gram of propacetamol infused intravenously hydrolyzes into 0.5 g of acetaminophen and pharmacologically inactive N,N-diethylglycine within 7 min [13-15]. Acetaminophen is widely used to control mild to moderate pain in clinical conditions and is well known for its inhibitory effect on central cyclooxygenase. Analgesic effects of acetaminophen can be explained by its interaction with multiple other neurotransmitters which involve serotonergic, opioidergic, noradrenergic, cholinergic, and nitric acid-synthase systems. Its interaction with the serotonergic system, in particular, is known to be associated with production of the analgesic effects [16].

It has been reported that the combined administration of opioids and NSAID increases efficacy and prevents postoperative central sensitization [17,18]. This combination also reduces opioids dose [19]. With this regard, the objective of this study was to examine effect of propacetamol in comparison with ketorolac in intravenous patient controlled analgesia (IV PCA) after gynecologic surgeries.

MATERIALS AND METHODS

The present study was approved by the hospital's Institutional Review Board. All participants gave written, informed consent before the study procedures.

Study subjects

Power and Sample Calculators (Available from http://powerandsamplesize.com/Calculators/) was used for sample size calculation. The suggested minimum sample size was 53 per group at the level of power = 0.8, $\alpha = 0.05$, and effect size of 1.2, which was estimated from a previous study [20]. Considering dropouts and failures, 60 subjects (14% was added) were recruited for each group. A total of 120 patients aged 18 to 70 years and scheduled to undergo laparoscopic gynecologic surgeries between January and June 2016 and whose American Society of Anesthesiologists physical status were either I or II were enrolled in the present study. The types of laparoscopic gynecologic operations included myomectomy, total hysterectomy, ovary cystectomy, and salpingo-oophorectomy. The patients were excluded if they had any kind of severe hepatic, renal, or gastric diseases; if they were given additional analgesics, anti-inflammatory drugs, or antipyretic drugs during the study; or if ketorolac, propacetamol, or fentanyl were contraindicated. The total number of study subjects was 111 and they were randomly allocated to two different intervention groups using a computer-generated randomized table.

Preparations and measurements

Within a month before their scheduled surgeries, preoperative laboratory workup was done. When patients arrived at the hospital for administration, each subject's body weight and height were measured. All patients were administered 0.2 mg of glycopyrrolate and 2 mg of midazolam intramuscularly, and 20 mg of famotidine intravenously as premedication. During the operation, the vital signs were monitored using an electrocardiogram, blood pressure cuff, pulse oximeter, and a bispectral index monitor (Model A 3000, Aspect Medical Systems, Inc., USA).

Moreover, 2 mg/kg of propofol, 0.6–0.8 mg/kg of rocuronium, and remifentanil were used for induction. During the

operation, 3.5 μg/ml propofol in Schnider mode and remifentanil were used in target controlled infusion with total intravenous anesthesia (Orchestra® Base Primea, Fresenius Kabi, France).

The subjects allocated to group K were given 180 mg of ketorolac, 0.3 mg of ramosetron, and 1,000 μg of fentanyl (n = 57) while patients in group P were administered 10 g of propacetamol, 0.3 mg of ramosetron, and 1,000 μg of fentanyl (n = 54). All patients were administered 0.3 mg of ramosetron in order to prevent PONV and all agents were mixed in saline so that the total volume of PCA added up to 100 ml (Automed AM3400, ACE medical, Korea). The PCA was loaded 1 ml/h with 3 ml of bolus and with 15 minutes lock-out intervals. For rescue analgesia, 50 to 100 μg of fentanyl was infused intravenously. Vital signs (systolic and diastolic blood pressure, heart rate, and body temperature [tympanic membrane ^{TM}], bilateral) and visual analogue scale (VAS) were checked right after PCA application. After durations of 15, 30, 60 minutes, and 12 and 24 hours after PCA application, vital signs, VAS, as well as any development of side effects (nausea, vomiting, dizziness, headache, or pruritus) were examined. The total PCA infusion time and amount of PCA infused for 24 hours were recorded. For the study subjects who complained of severe nausea, 5–10 mg of metoclopramide was administered intravenously as needed. Forty-eight hours after the surgeries, postoperative laboratory workup was done. The levels of hemoglobin (Hb), hematocrit (Hct), platelet (plt), prothrombin time (PT), activated partial thromboplastin time (aPTT), aspartate aminotransferase (AST), alanine aminotransaminase (ALT), blood urea nitrogen (BUN), creatinine (Cr), and international normalized ratio (INR) were tested in the workup.

Data analysis

To compare the groups, Student's *t* tests were performed for variables that were normally distributed and Mann-Whitney *U* tests were performed to compare variables that

Table 1. General Characteristics of Study Subjects

Variables	Group K (n = 57)	Group P (n = 54)	P value
Age (yr)	44.3 ± 9.2	45.1 ± 10.5	0.673
Weight (kg)	59.9 ± 9.7	59.5 ± 9.3	0.847
Height (cm)	158.3 ± 5.1	159.9 ± 5.6	0.131
Operation time (min)	64.0 (52.0–80.0)	65.5 (53.0–88.0)	0.743
Total PCA infusion time (h)	66.8 (51.0–69.1)	58.5 (47.3–66.6)	0.208
Amount of PCA infused for 24 h (ml)	45.1 (35.1–58.0)	43.2 (38.2–54.3)	0.790
Amount of bolus PCA infused for 24 h (ml)	18.0 (9.0–30.0)	18.0 (9.0–27.0)	0.722

Values are presented as mean ± SD or median (interquartile range). PCA: patient controlled analgesia, Group K: 180 mg of ketorolac mixed with fentanyl and ramosetron in IV PCA, Group P: 10 g of propacetamol mixed with fentanyl and ramosetron in IV PCA. There was no significant difference between the groups.

Table 2. Characteristics of PCA Infusion according to Type of Operation

Operation	Variables	Group K	Group P	P value
LM	Total PCA infusion time (h)	65.0 (45.3–68.7)	61.1 (47.7–71.7)	0.648
	Amount of PCA infused for 24 h (ml)	47.0 (39.7–58.0)	43.2 (38.2–54.0)	0.582
	Amount of bolus PCA infused for 24 h (ml)	15.0 (12.0–30.0)	18.0 (9.0–27.0)	0.966
TLH	Total PCA infusion time (h)	67.4 (16.0–69.6)	56.0 (45.8–65.7)	0.301
	Amount of PCA infused for 24 h (ml)	47.8 (35.1–61.0)	48.3 (40.0–57.4)	0.402
	Amount of bolus PCA infused for 24 h (ml)	20.3 (9.0–30.2)	18.0 (12.0–33.0)	0.629
OC/SO	Total PCA infusion time (h)	67.0 (60.0–69.1)	63.2 (56.5–65.8)	0.160
	Amount of PCA infused for 24 h (ml)	44.0 (33.6–57.0)	40.8 (37.3–44.0)	0.957
	Amount of bolus PCA infused for 24 h (ml)	15.1 (6.0–27.0)	15.0 (9.0–18.1)	0.845

Values are presented as median (interquartile range). Mann-Whitney *U* tests were performed. PCA: patient controlled analgesia, LM: laparoscopic myomectomy, TLH: total laparoscopic hysterectomy, OC/SO: ovary cystectomy or salpingo-oophorectomy.

were not normally distributed. Fisher's exact chi-square tests were used to examine the development of side effects for 24 hours after PCA application in both groups. Repeated measure analysis of variance was used to examine changes in systolic and diastolic blood pressure, heart rate, body temperature, and VAS for 24 hours after PCA application. In addition, paired *t* tests were performed repetitively to compare changes in vital signs and VAS over time within a group. Analysis of covariance (ANCOVA) was performed to compare postoperative laboratory workup results with pre-assessment results as covariates.

All statistical analyses were performed with SAS software version 9.4 (SAS Institute Inc., USA), and P value < 0.05 was considered to indicate statistical significance.

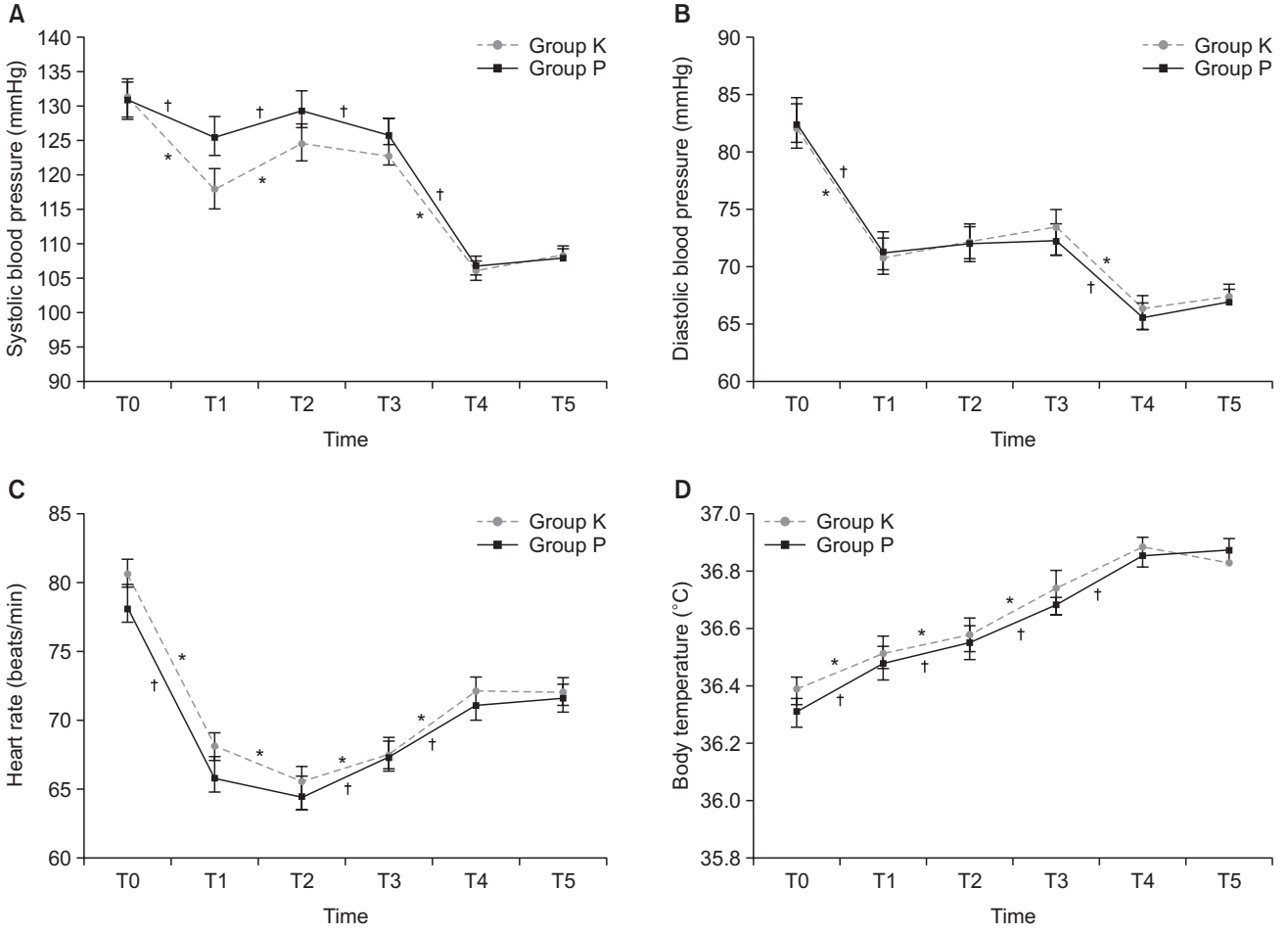

Fig. 1. Values are presented as the mean ± SE. Repeated measures ANOVA were performed. In addition, paired t-tests were performed repetitively for each time segment to compare changes in SBP, DBP, HR, and BT within a group. Group K: 180 mg of ketorolac mixed with fentanyl and ramosetron in the IV PCA, Group P: 10 g of propacetamol mixed with fentanyl and ramosetron in IV PCA. T0, T1, T2, T3, T4, T5: 0 min, 15 min, 30 min, 60 min, 12 h, and 24 h after PCA application. There was significant effect of time (P values are all < 0.001), but no significant difference between the groups (P = 0.325, 0.835, 0.346, and 0.524, respectively). *Indicates significant differences for the time intervals within the group K (P values for SBP changes: T0–T1 < 0.001, T1–T2 < 0.001, T2–T3 = 0.189, T3–T4 < 0.001, T4–T5 = 0.200. P values for DBP changes: T0–T1 < 0.001, T1–T2 = 0.301, T2–T3 = 0.211, T3–T4 < 0.001, T4–T5 = 0.472. P values for HR changes: T0–T1 < 0.001, T1–T2 = 0.008, T2–T3 = 0.045, T3–T4 < 0.001, T4–T5 = 0.952. P values for BT changes: T0–T1 = 0.022, T1–T2 = 0.031, T2–T3 < 0.001, T3–T4 = 0.061, T4–T5 = 0.244). †Indicates significant differences for the time intervals within the group P (P values for SBP changes: T0–T1 = 0.039, T1–T2 = 0.006, T2–T3 = 0.043, T3–T4 < 0.001, T4–T5 = 0.457. P values for DBP changes: T0–T1 < 0.001, T1–T2 = 0.468, T2–T3 = 0.863, T3–T4 < 0.001, T4–T5 = 0.333. P values for HR changes: T0–T1 < 0.001, T1–T2 = 0.152, T2–T3 = 0.005, T3–T4 = 0.013, T4–T5 = 0.615. P values for BT changes: T0–T1 = 0.001, T1–T2 = 0.013, T2–T3 < 0.001, T3–T4 = 0.015, T4–T5 = 0.756).

RESULTS

Table 1 displays the general characteristics of study subjects. There were no statistical differences between the groups regarding age, weight, and height (P = 0.673, 0.847, and 0.131, respectively). For both the groups, the operation took about one hour. The median values for PCA infusion time and amount of PCA infused for 24 hours was lower for group P than for group K; however, there were no significant differences (P = 0.208 and 0.790).

The number of patients who underwent laparoscopic myomectomy (LM) was 31. A total of 46 patients received total laparoscopic hysterectomy (TLH). Ovary cystectomy or salpingo-oophorectomy (OC/SO) was performed for 34 patients. For group K, 17, 23, and 17 patients received LM, TLH, and OC/SO, respectively. For group P, 14, 23, and 17 patients underwent LM, TLH, and OC/SO, respectively. There were no significant differences in the total PCA infusion time, amount of PCA infused for 24 hours, and amount of bolus PCA infused for 24 hours between the groups (Table 2).

Fig. 1 illustrates the changes in systolic and diastolic blood pressures, heart rate, and body temperature for 24 hours after PCA application. The change patterns for group P are quite similar to that for group K; there were no significant differences between the groups (P = 0.325, 0.835, 0.346, and 0.524, respectively).

The changes in VAS after PCA application are illustrated in Fig. 2. For both groups, there were gradual decreases in VAS with time. The changes in VAS after PCA application were not significantly different between the groups (P = 0.382).

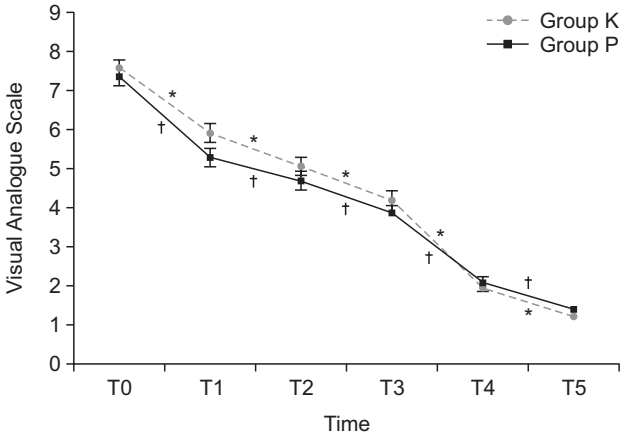

Fig. 2. Values are presented as the mean ± SE. Repeated measures ANOVA was performed. Group K: 180 mg of ketorolac mixed with fentanyl and ramosetron in IV PCA, Group P: 10 g of propacetamol mixed with fentanyl and ramosetron in IV PCA. T0, T1, T2, T3, T4, T5: 0 min, 15 min, 30 min, 60 min, 12 h, and 48 h after PCA application. There was significant effect of time (P < 0.001) but no significant difference between the groups (P = 0.382). *Indicates significant differences for the time intervals within the group K (P values for VAS changes: T0–T1 < 0.001, T1–T2 < 0.001, T2–T3 < 0.001, T3–T4 < 0.001, T4–T5 < 0.001). †Indicates significant differences for the time intervals within the group P (P values for VAS changes: T0–T1 < 0.001, T1–T2 = 0.002, T2–T3 < 0.001, T3–T4 < 0.001, T4–T5 < 0.001).

Table 3. Comparison of Laboratory Workup Results

Variable	Group K (n = 57)		Group P (n = 52)		P value
	Baseline	48 h	Baseline	48 h	
Hb	11.79 ± 1.52	10.56 ± 1.40	12.29 ± 1.50	11.30 ± 1.27	0.023
Hct	35.43 ± 3.84	31.78 ± 3.68	36.53 ± 3.46	33.60 ± 3.19	0.027
plt	275.61 ± 73.76	213.86 ± 53.43	270.35 ± 57.72	230.83 ± 54.54	0.758
BUN	12.01 ± 3.69	6.26 ± 2.69	12.18 ± 4.00	5.00 ± 2.65	0.005
Cr	0.67 ± 0.10	0.61 ± 0.10	0.68 ± 0.10	0.62 ± 0.11	0.955
AST	19.42 ± 9.42	17.33 ± 5.96	19.42 ± 5.51	19.17 ± 9.14	0.197
ALT	16.47 ± 14.21	12.40 ± 6.35	16.13 ± 9.75	14.17 ± 9.21	0.135
PT	11.77 ± 0.71	12.72 ± 2.69	11.57 ± 0.61	11.93 ± 0.64	0.079
aPTT	29.20 ± 3.52	30.94 ± 3.78	34.30 ± 39.41	30.38 ± 4.20	0.400
INR	1.03 ± 0.06	1.09 ± 0.09	1.02 ± 0.05	1.05 ± 0.05	0.017

Values are presented as mean ± SD. Analysis of covariance was performed with pre-assessment as a covariate. Postoperative levels of Hb, Hct, BUN, and INR were significantly different between the groups (P = 0.026, 0.027, 0.005, 0.017). Hb: hemoglobin, Hct: hematocrit, plt: platelet, BUN: blood urea nitrogen, Cr: creatinine, AST: aminotransferase, ALT: aminotransaminase, PT: prothrombin time, aPTT: activated partial thromboplastin, INR: international normalized ratio.

Except for two patients who were discharged before 48 hours past PCA application, postoperative laboratory workup was established for every study subject. The mean values of Hb, Hct, plt, BUN, Cr, AST, ALT, PT, aPTT, and INR and results of ANCOVA with pre-assessment as a covariate are presented in Table 3. The mean levels of Hb, Hct, plt were decreased in both groups. There were dramatic decreases in the mean value of BUN while the level of Cr remained quite stable. The differences in mean AST levels were 2.09 in group K and 0.25 in group P and that of ALT levels were 4.07 and 1.96, respectively. Mean PT was elongated in both groups. The mean levels of aPTT were increased in group K but were decreased in group P. Postoperative levels of Hb, Hct, BUN, and INR were significantly different between the groups (P = 0.026, 0.027, 0.005, 0.017).

Development of side effects including nausea, vomiting, dizziness, headache, and pruritus was examined five times for 24 hours after PCA application (15 min, 30 min, 60 min,

Detection time	Group	Nausea						Vomiting					
		Patients with S/E				N (%)	P value	Patients with S/E				N (%)	P value
T1	Group K					0 (0.0)	0.487					0 (0.0)	–
	Group P	1				1 (1.9)						0 (0.0)	
T2	Group K					0 (0.0)	0.234					0 (0.0)	–
	Group P	1	2			2 (3.7)						0 (0.0)	
T3	Group K					0 (0.0)	0.118					0 (0.0)	0.234
	Group P	2	3	4		3 (5.6)		2	3			2 (3.7)	
T4	Group K					0 (0.0)	0.053					0 (0.0)	0.487
	Group P	2	4	5	6	4 (7.4)		2				1 (1.9)	
T5	Group K					0 (0.0)	0.053					0 (0.0)	–
	Group P	3	6	7	8	4 (7.4)						0 (0.0)	
Total number of patients with S/E	**Group K**					**0 (0.0)**	***0.002***					**0 (0.0)**	0.234
	Group P					**8 (14.8)**						**2 (3.7)**	

Detection time	Group	Dizziness						Headache					
		Patients with S/E				N (%)	P value	Patients with S/E				N (%)	P value
T1	Group K	1'				1 (1.8)	1.000					0 (0.0)	–
	Group P	1				1 (1.9)						0 (0.0)	
T2	Group K	1'				1 (1.8)	1.000					0 (0.0)	–
	Group P	1				1 (1.9)						0 (0.0)	
T3	Group K					0 (0.0)	0.487					0 (0.0)	–
	Group P	1				1 (1.9)						0 (0.0)	
T4	Group K	2'				1 (1.8)	0.612					0 (0.0)	0.487
	Group P	5	6			2 (3.7)		6				1 (1.9)	
T5	Group K	2'	3'			2 (3.5)	0.673					0 (0.0)	0.112
	Group P	5	6	9		3 (5.6)		6	7	10		3 (5.6)	
Total number of patients with S/E	**Group K**					**3 (5.3)**	0.712					**0 (0.0)**	0.112
	Group P					**4 (7.4)**						**3 (5.6)**	

Fig. 3. Values are presented as number (%). Each colored-square represents a study subject and a square with the same color and number represents an identical individual. Fisher's exact chi-square tests were performed. Group K: 180 mg of ketorolac mixed with fentanyl and ramosetron in IV PCA, Group P: 10 g of propacetamol mixed with fentanyl and ramosetron in IV PCA. T1, T2, T3, T4, T5: 15 min, 30 min, 60 min, 12 h, and 24 h after surgery. S/E: side effect. A total of 13 patients experienced side effects, three from group K and 10 from group P (five patients experienced more than one type of side effects). There were no significant differences in the development of nausea, vomiting, dizziness, and headache between the groups at each time segments. However, the overall development of nausea for 24 hours was significantly different between the groups (P = 0.002).

12 h, and 24 h). Fig. 3 illustrates detailed development of side effects at each time segment and compares overall development of side effects between the groups. The total number of patients who experienced any type of side effects was 13, three from the group K and ten from the group P, within 24 hours after surgery. All three patients in group K experienced dizziness. Most of the patients in group P experienced nausea and five patients experienced more than one type of side effect. No patients in group K suffered any side effects at 60 minutes. None of the patients from both groups developed pruritus. There were no significant differences in the development of nausea, vomiting, dizziness, and headache between the groups at each detection time. However, the overall number of patients who experienced nausea within 24 hours after surgery was significantly different between the groups (P = 0.002).

DISCUSSION

The present study findings showed gradual stabilization of vital signs after PCA application. The systolic and diastolic blood pressures and heart rate were consistently decreased within the normal ranges and there were no significant differences between the groups. The systolic and diastolic blood pressures gradually stabilized with appropriate pain control [21]. The heart rate decreased within 15 minutes since the PCA application and did not show any significant change afterwards [22]. The body temperature drops during the operation was recovered as well. None of the study subjects were administered with any additional antipyretics in the recovery room and the wards since none of them developed fever. The development of postoperative fever was prevented by ketorolac and propacetamol mixed in PCA [23-25].

The patients' subjective pain perception subsided in both groups after PCA applications. Varrassi et al. [26] reported a similar result by administrating 30 mg of ketorolac and 2 g of propacetamol by IV drip infusion. Heo et al. [20] also reported a similar effect of 8 g of propacetamol mixed with fentanyl and ramosetron compared to 180 mg of ketorolac through PCA. The present study provided similar results with 180 mg of ketorolac and 10 g of propacetamol. Even though there was no statistical significance between the groups, the decrease in VAS was greater in the group P 15 minutes after PCA application. The rapid analgesic onset time of propacetamol compared to delayed onset time of ketorolac [12,14,15] may explain this finding. The amount of remifentanil used during the operation processes was not significantly different between the groups either (remifentanil amount used [median (IQR)]): group K = 348 μg (288–388), group P = 354 μg (290–398), P value = 0.659).

There were no significant differences between the groups in total fluid input volume and estimated blood loss. The median total fluid input volume of group K was 400 ml (interquartile range [IQR]: 250–600) and that of group P was 350 ml (IQR: 25–450). The median estimated blood loss of group K was 40 ml (IQR: 20–70) and that of group P was 30 ml (IQR: 20–50). The laboratory workup results obtained 48 hours after PCA application revealed significant differences in Hb, Hct, BUN, and INR between the groups but the differences were not clinically meaningful since the results were within the normal ranges. No evidence of hepatotoxicity or nephrotoxicity was found either.

There was no significant difference between the groups in development of vomiting, dizziness, and headache within 24 hours after surgery and none of the patients developed pruritus. These findings were also correlated to the findings of the previous study [20]. Although the development of nausea was not significantly different between the groups when analyzed at each detection time, the overall number of patients who experienced nausea was greater in group P than in group K, with statistical significance. A possible explanation of this finding might be the effect of propacetamol as itself or the effect of 0.1 g / 5 ml × 10 ampules of sodium citrate, a solution added to reduce injection pain of propacetamol. It is supported by a previous study result which reported that ingestion of sodium citrate induced nausea [27,28]. Although further studies are required to evaluate the effect of sodium citrate when administered intravenously with the use of propacetamol, it is suggested that the use of alternative solutions, such as normal saline, might prevent the development of the side effects. In addition, further studies with a large sample size are also required for the development of nausea. Until then, the application of propacetamol as indicated in the study should be cautiously performed for sensitive patients or patients who had experienced severe postoperative nausea and vomiting in the past.

The present study has several limitations. First, due to Berksonian bias, generalization of the present study find-

ings is limited. Second, it would be more meaningful if the measurement time intervals were made more frequent and uniform. Third, the effect of PCA was more accurately examined if preoperative laboratory workup was compared with the results acquired right after the surgeries, 24 hours, and 48 hours after the PCA applications. Fourth, the degree of pain was obtained by evaluating resting, moving, and coughing pain (including during defecation) in average. Despite these limitations, the major strengths of this study include the following. The targeted patients were restricted to those with benign gynecologic diseases and only one selected surgeon was mainly involved in the operations so that the possible variabilities due to disease types and surgical processes were limited. In addition, objective physiologic effects were investigated by performing laboratory workup to compensate for subjective pain scores and development of side effects. Also, the developments of side effects were examined thoroughly for 24 hours after the surgery, by comparing the overall number of patients with side effects between the groups and the development of side effects at each measurement time between the groups.

Administration of PCA based on opioid combined with propacetamol showed no significant difference in pain control compared to PCA combined with ketorolac. Although the use of propacetamol was related to unexpected nausea in some incidences, it may be useful in patients with contraindications for ketorolac, including kidney problems, if additional attention is paid to the side effects. It could be an effective pain controller and an alternative of ketorolac in IV PCA after gynecologic surgeries.

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