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Effect of injection pain and withdrawal movement of propofol and rocuronium in the induction of anaesthesia on postoperative pain outcomes in gynaecologic laparoscopic surgery: a prospective observational study

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ABSTRACT

INTRODUCTION The pain experience among individuals may differ from each other. This prospective cohort study aimed to determine the impact of injection pain/withdrawal movement of propofol and rocuronium in the induction of anaesthesia on postoperative pain outcomes in gynaecologic laparoscopic surgery.

METHODS A total of 100 patients aged 19–60 years received propofol and rocuronium injections for the induction of anaesthesia. The incidence of propofol injection pain (PIP) and rocuronium-induced withdrawal movement (RIWM), postoperative pain scores and total opioid consumption were evaluated, and the associations between PIP/RIWM and postoperative pain outcomes were determined

RESULTS Visual analog scale (VAS) for pain after surgery and total opioid consumption after surgery in patients with PIP or RIWM were significantly higher than in patients without PIP or RIWM. The correlation between PIP and RIWM, VAS at 1 hour, VAS at 24 hours, total opioid consumption were significant and weakly positive (r = 0.249, r = 0.234, r = 0.22, r = 0.234, respectively). Compared with PIP, RIWM correlated more positively with pain score at 1 hour (r = 0.408 vs. r = 0.234, RIWM vs. PIP) and 24 hours (r = 0.398 vs r = 0.227, RIWM vs. PIP) and total opioid consumption after 48 hours (r = 0.457 vs. r = 0.234, RIWM vs. PIP).

CONCLUSION During anaesthesia induction, the occurrence of PIP and RIWM may predict the severity of postoperative pain and total opioid consumption, with RIWM emerging as a stronger predictor than PIP.

*Keywords**:** anaesthesia, opioids, postoperative pain, propofol, rocuronium*

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INTRODUCTION

Individuals with increased pain processing and/or reduced pain-modulatory capabilities are regarded as pronociceptive, and the reduced pain processing capacity is considered as antinociceptive. The painful experience or perception among individuals may differ from each other.[1]

Propofol and rocuronium, used for induction of general anesthesia, are often associated with pain (in 25%-100% of patients receiving propofol) or withdrawal movement (in 22%-84% of patients receiving rocuronium).[2,3] The characteristics of pain associated with propofol and rocuronium are inconsistent. One study reported that the characteristics of pain associated with the two anesthetic agents are similar in regard to pain during administration, short duration, and intensity decreases with subsequent injection.[4] However, another study reported that the time relationship and the nature of the pain/withdrawal movements induced by rocuronium injection differ from those associated with propofol.[5] Many studies have attempted to reduce the frequency of pain or withdrawal movement after injections of the two drugs.[2-7]

There is evidence that the two anesthetic agents individually may cause injection pain/withdrawal movement during administration.[2-9] However, few studies have studied the impact of pain/withdrawal movement on the severity of postoperative pain and total opioid consumption.

We hypothesized that propofol injection pain (PIP) or rocuronium-induced withdrawal movement (RIWM) during induction of anesthesia might have an impact on postoperative pain scores and opioid consumption. Specifically, we sought to evaluate the incidence of PIP and RIWM during induction and define the association between PIP/RIWM and pain scores at 1h, 24h and 48h as well as total opioid consumption 48h after surgery.

METHODS

All participants provided written informed consent. The study was performed at the University Hospital from June 2020 to October 2020. Ethical approval for this study was provided by the Institutional Review Board of the Wonkwang University School of Medicine Hospital in April 2020 (Registration No. 2020-04-033-002). Patients who were scheduled for laparoscopic gynecological surgery were enrolled in this study. See the consort flow diagram (Fig. 1).

A total of 100 patients, aged 19-60 years and the American Society of Anesthesiologists (ASA) with class I or II who were scheduled for gynecologic laparoscopic surgery were enrolled in this study. Patients with muscular disorders, refusal to participate in this study, difficult venous access on the forearm, history of allergy to propofol or rocuronium, neuromuscular diseases, and patients who received analgesics or sedatives within the previous 24 hours were excluded. Menopausal patients to exclude the hormonal effect on pain.[10]

This study was performed by two attending anesthesiologists. One attending anesthesiologist performed anesthesia induction according to the study protocol. The other attending anesthesiologist measured all outcomes throughout the perioperative period.

The 18-gauge intravenous lines in all patients were secured at the forearm by skilled nurses. The patients were not premedicated. In the operating room, all patients were assessed using the bispectral (BIS) monitor, electrocardiography (ECG), noninvasive arterial blood pressure (BP) measurement, and pulse oximetry. Anesthesia in all patients was induced using 2 mg/kg of 1% propofol (long chain triglyceride (LCT) emulsion) over 15 seconds. When BIS score arrived at 60, 0.6 mg/kg of 1% rocuronium was injected over 10 seconds. All patients didn't receive any analgesics (including opioids) before propofol and rocuronium administration.

The patients were assessed using the numeric rating scale (NRS) score for pain severity

after half-dose and full-dose propofol injection, when considering one arm-brain circulation time (15–20 seconds). The attending anesthesiologist asked the patients how they felt pain to evaluate pain severity of PIP while half -dose of propofol was administered, which took 7 to 8 seconds. After the rest of the propofol was administered, the attending anesthesiologists asked the same question. If a patient could not respond to verbal questions following full-dose administration, the NRS score for pain after half-dose administration was recorded. The greater NRS related with PIP at half-dose or full-dose was recorded as pain severity.

The withdrawal responses associated with rocuronium during administration were graded by the investigating anesthesiologist according to the following scales: 1 (none) = no response; 2 (mild) = movement at the wrist only; 3 (moderate) = movement involving the upper arm or shoulder; 4 (severe) = movement in more than one extremity or a generalized response**.**

Anesthesia was maintained with sevoflurane and an oxygen/air mixture (fraction of oxygen, 50%). When sevoflurane was required, its administration was started at the end-tidal concentration of 1 minimum alveolar concentration (MAC), and the concentration was adjusted by stepwise titration according to acceptable hemodynamic limits (mean arterial blood pressure between -20% and +20 % and heart rate between -20% and +20 %) and to a target bispectral index (BIS) between 40 and 60. When surgery was completed, the pyridostigmine and glycopyrrolate were administered to reverse neuromuscular blockade.

A PCA pump included fentanyl (800 μg), ketorolac (150 mg), and ramosetron (0.6 mg) in 150 mL of saline for the postoperative analgesia during 48 hours. It was prepared to deliver a basal infusion of 2 mL/h, bolus doses of 0.5 mL, and 15 minutes lockout period. The pain severity during the postoperative period was measured using a 100-mm linear VAS. When patients complained of pain, an attending anesthesiologist checked the VAS score for pain. After that, analgesics were given to patients on demand. When patients complained of pain corresponding

to 50 mm or more, they were treated with intravenous 100 mcg fentanyl. Intravenous Ketorolac15-30 mg was administered if the pain score was less than 40 mm on the VAS score.

The primary outcome was the correlations between PIP, the grade of RIWM, and postoperative pain outcomes. Secondary outcomes included incidence of PIP and RIWM (by grade), use of rescue analgesic agents, complications on cannulated venin, recall for PIP or respiratory difficulty, VAS score at 1h, 24h and 48h, and PCA opioid consumption at 24h and 48h.

The sample size was calculated with PASS 2008 (NCSS, LLC. Kaysville, Utah, USA). The proportions of patients with PIP and RIWM in preliminary investigation were 0.312 and 0.590, respectively. Thus, a sample size of 100 patients would be enable for the detection of a significant difference with a power of 80% and an α-coefficient of 0.05. SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Demographic data is presented as mean ± SD or number of patients (percentage). Postoperative pain scores and opioid consumption at different time points were compared between patients with and without PIP and those with and without RIWM, using the independent t-test or Mann-Whitney U test for continuous variable (where applicable) and the χ^2 test or Fisher's exact test for categorical variables, as appropriate. The correlation between parameters was analysed with the Kendal tau-b test. Statistical significance was defined as $p \leq 0.05$ for all analyses.

RESULTS

100 patients were enrolled in this study but five patients were withdrawn after enrolment due to conversion to open surgery, loss of follow-up, and re-exploration for postoperative bleeding (Fig. 1). Frequency of occurrence of grade I/II/III/IV of RIWM were 43.2%, 0%, 42.1% and 14.7%, respectively. Complications on vein postoperatively included tenderness (4.2%), redness (6.3%), hardness (1.1%), tenderness and hardness (1.1%) recall of pain or respiratory

difficulty (9.5% or 0%) (Table I).

Compared with patients without PIP, those with PIP had significantly higher pain scores at 1 h ($p = 0.017$) and 24h ($p = 0.024$) (Table II). Patients with PIP also had higher opioid consumption at 24h ($p = 0.014$), 48h ($p = 0.047$) and for 48 hours postoperatively ($p = 0.017$). Similarly, postoperative pain scores and opioid consumption were significantly higher in patients with RIWM, compared with those without RIWM ($p < 0.001$) (Table III).

PIP was weakly correlated with RIWM ($r = 0.25$, $p = 0.012$). The correlation of PIP /RIWM with postoperative pain scores and opioid consumption is shown in Table V. There was a significant but weakly positive correlation of PIP and RIWM with VAS pain scores at 1h and 24h, as well as total opioid consumption in the 48h postoperative period. However, RIWM emerged as the stronger predictor and was also positively correlated with VAS pain scores at 48h (Table IV). Patients with RIWM had a higher VAS for pain and PCA cumulative opioid consumption compared to patients without RIWM in patients with or without PIP (Table V).

DISCUSSION

The present study demonstrated that PIP and RIWM had significant correlations with postoperative pain outcomes, including pain scores and opioid consumption. This observation is consistent with those reported by previous studies.[3-5] This study showed that the pain severity with NRS and opioid consumption in patients with PIP or RIWM were significantly higher than patients without PIP or RIWM. The observation of PIP and RIWM suggests that preoperative pain perception may be used to predict pain outcomes after surgery.

One study reported that preoperative pain induced by venous cannulation and propofol infusion predicted postoperative pain after laparoscopic cholecystectomy.[10] Patients with venous cannulation-induced pain intensity with VAS score ≥ 2.0 was associated with greater

postoperative pain, and earlier and higher consumption of opioids compared to those < 2.0 VAS score. For the differences between the present study and the previous study,[10] the present study had included both subjective and objective measures of pain for PIP and RIWM.

This study had also included a more uniform population of premenopausal female adults to mitigate the confounding effects caused by gender. The experience or perceptions of pain may differ from age and sex, owing to biological or psychosocial mechanisms; they may even differ for individuals of the same age or sex because of their experience of pain.[11-14] Propofol and rocuronium used in the present study have a very large range of incidence of injection pain or withdrawal movement. Therefore, these may result from the above-mentioned reasons.

The incidence of venous complications and recall after propofol or rocuronium injection in the present study were similar to those reported in previous studies.[15,16] The characteristics PIP in the present study were mild, transient, acceptable and low frequency of recall.

The present study has several limitations. First, age and sex can affect pain experience or perception.[13,17] We performed gynaecologic surgery in women without menopause to reduce selection bias. We should have considered the hormonal state according to the stages of their menstrual cycles, and this may have affected the results in this study. The findings in this study could not be extrapolated to male patients as it was conducted primarily in females. More research in gender specific surgery (e.g. men-prostate surgery) is required to establish preoperative pain sensitivity and its correlation with postoperative pain and analgesic consumption and to evaluate the effect of sex differences on these correlations. Second, different formulations of propofol may affect PIP severity.[16] In the present study, lipid based-long chain triglyceride (LCT) propofol was used to determine the impact of injection

pain/withdrawal movement of propofol and rocuronium in induction of anesthesia on postoperative pain outcomes. The results associated with LCT propofol used in the present study may differ from other different formulations [medium chained triglyceride (MCT)/LCT propofol or triglyceride-free microemulsion propofol].

In conclusion, the perception of PIP and RIWM at anaesthesia induction has significant and positive correlations with postoperative pain outcomes, with RIWM emerging as the stronger predictor for postoperative pain severity and total opioid consumption. PIP and RIWM may be used to identify patients who will require more intensive pain management postoperatively.

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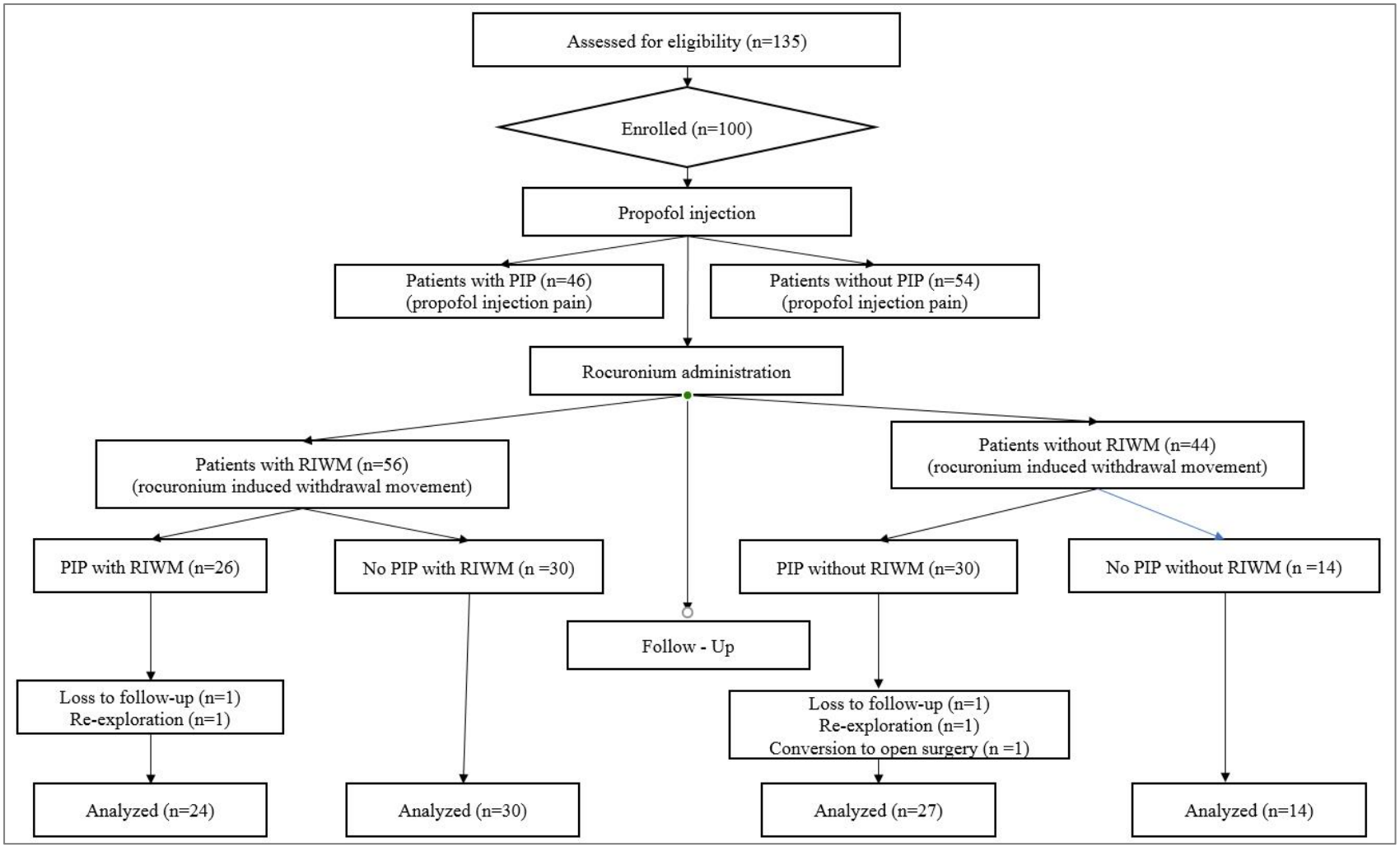

Fig. 1 Consort flow diagram *PIP: propofol injection pain, RIWM: rocuronium induced withdrawal movement*

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Table I. Patient demographic and perioperative data.

	Patients (n = 95)
Age (yr)	38.8 ± 9.0
Height (cm)	160.8 ± 3.7
Weight (kg)	61.1 ± 7.6
ASA	
I	30 (32.6)
II	65 (68.4)
Duration of anesthesia (min)	96.2 ± 29.6
Duration of surgery (min)	66.6 ± 28.9
Type of surgery	
Laparoscopic myomectomy	16 (16.8)
Laparoscopic subtotal hysterectomy	16 (16.8)
Laparoscopic vaginal hysterectomy	32 (33.7)
Laparoscopic vaginal hysterectomy and lymph node dissection	13 (13.7)
Laparoscopic cystectomy	18 (18.9)
Basal BIS	95.1 ± 2.7
BIS immediately after propofol injection	95.0 ± 1.9
Time to get BIS less than 60 (sec)	31.7 ± 6.0
The incidence of PIP	51 (53.7)
NRS for PIP	17.8 ± 20.8
Grade of RIWM	
1 (No withdrawal)	41 (43.2)
2 (Wrist withdrawal)	0 (0)
3 (Arm only)	40 (42.1)
4 (Generalized movement)	14 (14.7)
Rescue analgesics	
Ketorolac	44 (46.3)
Fentanyl	44 (46.3
Complications on vein	
Tenderness	4 (4.2)
Redness	6 (6.3)
Hardness	1 (1.1)
Tenderness and hardness	1 (1.1)
Recall	
Pain	9 (9.5)
Respiratory difficulty	0

Values are expressed as mean ± SD or numbers (%).

ASA: American society of anesthesiologists; BIS: bispectral index; NRS: numeric rating scale; PIP: propofol injection pain, RIWM: rocuronium induced withdrawal movement

Table II. Pain outcomes related with propofol injection pain (PIP).

	Patients with PIP (n = 44)	Patients without PIP (n = 51)	*P*-value
VAS for pain at 1 h after surgery	45.7 ± 9.3	40.4 ± 11.7	0.017
VAS for pain at 24 h after surgery	36.6 ± 9.6	31.8 ± 10.7	0.024
VAS for pain at 48 h after surgery	23.6 ± 8.1	22.6 ± 9.3	0.549
PCA cumulative opioid consumption during 0-24 h after surgery	51.2 ± 3.7	53.2 ± 3.9	0.014
PCA cumulative opioid consumption during 24-48 h after surgery	50.7 ± 2.7	49.7 ± 2.3	0.047
Total PCA cumulative opioid consumption for 48 h after surgery	103.9 ± 6.1	99.9 ± 9.3	0.017
Rescue analgesics			0.566
No analgesics	2 (4.5)	5 (9.8)	
Ketorolac	20 (45.5)	24 (47.1)	
Fentanyl	22 (50.0)	22 (43.1)	

Values are expressed as mean ± SD or numbers (%). PCA: patient-controlled analgesia; VAS: visual analog scale

Table III. Pain outcomes related with rocuronium induced withdrawal movement (RIWM).

	Patients with RIWM (n = 54)	Patients without RIWM (n = 41)	*P*-value
VAS for pain at 1 h after surgery	46.3±10.5	38.3 ± 9.7	0.000
VAS for pain at 24 h after surgery	37.6 ± 9.5	29.3 ± 9.8	0.000
VAS for pain at 48 h after surgery	25.2 ± 9.5	20.2 ± 6.9	0.006
PCA cumulative opioid consumption during 0-24 h after surgery	53.8 ± 3.9	49.9 ± 2.6	0.000
PCA cumulative opioid consumption during 24-48 h after surgery	51.1 ± 2.7	48.9 ± 1.6	0.000
Total PCA cumulative opioid consumption in 48 h after surgery	104.8 ± 6.0	97.7 ± 8.9	0.000
Rescue analgesics			0.045
No analgesics	3 (5.6)	4 (9.8)	
Ketorolac	20 (37.0)	24 (58.5)	
Fentanyl	31 (57.4)	13 (31.7)	

Values are expressed as mean ± SD or numbers (%). PCA: patient-controlled analgesia; VAS: visual analog scale

Table IV. The correlations between propofol injection pain (PIP), the grade of rocuronium-induced withdrawal movement (RIWM) and pain outcomes.

	VAS score for pain at 1 h after surgery	VAS score for pain at 24 h after surgery	VAS score for pain at 48 h after surgery	Total opioid consumption for 48 h after surgery
The incidence of PIP	r = 0.234	r = 0.227	r = 0.085	r = 0.234
	P = 0.013	P = 0.016	P = 0.375	P = 0.00
The grade of RIWM	r = 0.408	r = 0.398	r = 0.330	r = 0.457
	P = 0.00	P = 0.00	P = 0.04	P =0.00

VAS: visual analog scale

Table V. Pain outcomes related with PIP and RIWM.

	No PIP / No RIWM (n = 14)	No PIP / RIWM (n = 30)	PIP / No RIWM (n = 27)	PIP / RIWM (n = 24)
VAS for pain at 1 h after surgery	39.3 ± 7.3*	48.7 ± 8.6	37.8 ± 10.9*	43.3 ± 12.0
VAS for pain at 24 h after surgery	30.7 ± 8.3*	39.3 ± 9.1	28.5 ± 10.6*	35.4 ± 9.8
VAS for pain at 48 h after surgery	20.0 ± 6.8	25.3 ± 8.2	20.4 ± 7.1	25.0 ± 11.0
PCA cumulative opioid consumption during 0-24 h after surgery	50.4 ± 2.7*	54.5 ± 3.8	49.6 ± 2.6*	53.0 ± 4.0
PCA cumulative opioid consumption during 24-48 h after surgery	48.7 ± 1.3*	51.7 ± 2.7	49.0 ± 1.8*	50.4 ± 2.7
Total PCA cumulative opioid consumption in 48 h after surgery	99.1 ± 3.3*	106.1 ± 5.8	96.9 ± 10.7*	103.3 ± 6.0
Rescue analgesics				
no analgesics	1 (7.1)	1 (3.3)	3 (11.1)	2 (8.3)
ketorolac	10 (71.4)	10 (33.3)	14 (51.9)	10 (41.7)
fentanyl	3 (21.4)	19 (63.3)	10 (37.0)	12 (50.0)

*Values are expressed as mean ± SD or numbers (%). PCA: patient-controlled analgesia; VAS: visual analog scale; PIP: propofol injection pain; RIWM: rocuronium induced withdrawal movement. *P < 0.05 vs no PIP and RIWM.*