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Effect of the Combination of Ketorolac and Bupivacaine on Transversus Abdominis Plane Block for Postoperative Analgesia After Gynecological Laparoscopic Surgery

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Background: This study assessed the additional benefits of bupivacaine when combined with ketorolac for transversus abdominis plane (TAP) block after gynecological laparoscopic surgery.





Material/Methods: This randomized, observer-blind trial recruited 153 patients who underwent gynecological laparoscopic surgery. Patients were randomly assigned to receive bupivacaine combined with ketorolac 15 mg/side for TAP block (TK group), bupivacaine for TAP block and 30 mg postoperative intravenous ketorolac (T group), or 30 mg postoperative intravenous ketorolac alone (C group). The primary endpoints included consumption of sufentanil for 24 h postoperatively, actual press times of the patient-controlled analgesia (PCA) pump, and effective press times of the PCA pump, whereas the secondary endpoints included numerical rating scale (NRS) pain scores at rest and during activity, satisfaction with analgesia, episodes of nausea and vomiting and length of hospital stay.

Results: Sufentanil consumption, actual press times of the PCA pump, and effective press times of the PCA pump were lower in the TK and T groups than in the C group. NRS scores at rest and during activity at 1, 2, 4, 6, and 24 hours were significantly lower in the TK and T groups than in the C group. The TK and T groups showed greater satisfaction with analgesia than the C group, while the TK group showed greater overall satisfaction than the C group. Lengths of stay, rates of nausea and vomiting, and venting times did not differ significantly among the three groups.

Conclusions: Combined ketorolac and bupivacaine as TAP block improved the effectiveness of analgesia without increasing adverse events. Trial registration number: ChiCTR1900022577.

MeSH Keywords: **Bupivacaine • Gynecologic Surgical Procedures • Ketorolac**

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Background

Because it is minimally invasive, laparoscopic surgery has several advantages over open surgery, including reduced trauma and postoperative pain, and shorter hospital stay. Advances in laparoscopic surgical instruments and techniques have enabled laparoscopic surgery to be performed in most surgical fields, including gynecology [1]. Although the incidence of postoperative discomfort was found to be lower in patients who underwent laparoscopic than traditional gynecologic surgery, 35–80% of patients who underwent laparoscopic surgery experienced postoperative pain, with the pain lasting up to 72 hours [2,3]. Effective analgesic strategies are therefore needed to reduce discomfort after gynecological laparoscopic surgery.

The delivery of local anesthetic to the transversus abdominis plane (TAP) has shown promise in reducing pain, with ultrasound-guided TAP block associated with better pain control after lower abdominal surgery [4–6]. Moreover, TAP block could reduce postoperative nausea and vomiting induced by intravenous analgesics [7]. The mixture of ketorolac with lidocaine or bupivacaine has been associated with longer local anesthetic time and reduced postoperative pain [8]. However, it is unclear whether TAP block with the mixture of bupivacaine plus ketorolac is more effective than ketorolac alone in controlling postoperative pain after gynecologic laparoscopic surgery. This randomized, observer-blinded trial therefore assessed the efficacy and safety of combined bupivacaine and ketorolac as TAP block for patients after gynecologic laparoscopic surgery.

Material and Methods

Trial design and oversight

This study was a randomized, observer-blinded, 3-armed, single center clinical trial. The protocol and amendments were approved by the ethics committee of our hospital, and the sponsor was responsible for data collection. The first draft of the manuscript was completed by the first author, with the coauthors contributing to revisions of the manuscript. Submission of the manuscript for publication and responsibility for the accuracy and completeness of the data and analyses were per protocol and at the sponsor's discretion.

Trial population

The study included women aged 18–60.0 years, classified as ASA I–III who underwent elective gynecologic laparoscopic surgery and were indicated for postoperative intravenous analgesia. Enrolled patients were instructed on use of the patient-controlled analgesia (PCA) device, and all patients provided written informed consent. Patients were excluded if they

(1) were users of narcotic analgesics or sedatives or long-term users of non-steroidal anti-inflammatory drugs; (2) experienced allergic reactions to the study drugs; (3) had a history of disorders of the neuromuscular, cardiovascular, or endocrine system or allergic or mental illnesses; (4) had a body mass index >30 kg/m² or <18 kg/m²; (5) had a history of peptic ulcer or bleeding; (6) had a blood-clotting disorder; (7) were pregnant or lactating; (8) were addicted to drugs of abuse or alcohol; and (9) were deemed unsuitable for the study by the researcher.

Randomization and study agents

Eligible patients were randomly assigned in a 1: 1: 1 ratio to receive bupivacaine combined with ketorolac (Sichuan Medcalo Pharmaceutical Co., Ltd) 15 mg/side for TAP block (TK group), bupivacaine for TAP blocks and 30 mg postoperative intravenous ketorolac (T group), or 30 mg postoperative intravenous ketorolac alone (C group). Randomization was performed out in an observer-blinded manner using a central computerized system and random number table.

Anesthesia

None of the patients was administered drugs preoperatively. After the patient entered the operating room, her right upper limb vein was opened with an 18 G trocar, followed by inhalation of 5 L/min oxygen through the anesthesia mask. Baseline non-invasive blood pressure, electrocardiogram, heart rate and pulse oxygen saturation were recorded by a multi-function monitor. Anesthesia was induced by intravenous injection of a mixture of sufentanil (5 µg/kg), propofol (2 mg/kg), and succinylcholine (1.5 mg/kg), and was maintained at a BIS of 40–60 by administration of remifentanyl (0.2 µg/kg.min) and desflurane. Sufentanil (5 µg/kg) was added if a patient's heart rate or blood pressure increased by at least 20%, with 4 mg ondansetron administered intravenously to prevent postoperative nausea and vomiting.

Postoperative analgesia

Patients in the T and C groups were administered 30 mg ketorolac postoperatively. Patients in the T and TK groups were administered ultrasound-guided bilateral TAP block at the time of postoperative wound coverage. Briefly, patients were placed in the supine position and covered with a sterile towel that had undergone iodine-volt disinfection. Ultrasonic images were obtained with an ultrasonic instrument using a high-frequency probe of 6–13 Hz wrapped in a sterile glove, and the nerve block operation was performed under ultrasound guidance. After the completion on one side, TAP block was performed on the opposite side in the same manner.

Endpoints

The primary endpoints included consumption of sufentanil for 24 hours postoperatively, actual press times of the PCA pump, and effective press times of the PCA pump. Secondary endpoints included numerical rating scale (NRS) pain scores at rest and during activity, satisfaction with analgesia, length of hospital stay, episodes of nausea and vomiting, and venting times. These outcomes were collected and analyzed by investigators who were blinded to the study group assignments.

Statistical analysis

Continuous data are reported as the mean (standard deviation) and median (quartile), depending on the normality of data distribution. Categorical data are reported as the number (percent) of patients and compared among the three groups by CMH or Fisher's exact test. Numerical outcomes in the three study groups were compared by ANOVA, with pairwise comparisons assessed by LSD methods. Satisfaction with analgesia is reported as ranked data, with the Kruskal-Wallis method used for comparisons among the three groups. All analyses were performed on an intention-to-treat basis, with missing data not imputed. The sample size was based on the consumption of sufentanil after laparoscopic surgery of about 22 ± 13 g, an analgesic efficacy ratio of sufentanil to morphine [9], $\alpha=0.05$ and $\beta=0.20$. All reported *P*-values are two-sided, with *P*-values <0.05 considered statistically significant. All statistical analyses were performed using the IBM Statistical Package for the Social Sciences software for Windows, version 19.0.

Results

Patients

From July 2018 to November 2018, 153 patients were randomized, 51 each to the TK, T, and C groups (Figure 1). Two patients in the T group discontinued, resulting in the removal of two patients in the C group (Supplementary Table 1). Table 1 summarizes the baseline characteristics of the patients in the three groups. Their mean age was 40.28 years, their mean body mass index (BMI) was 22.29 kg/m^2 , and the mean duration of the operation was 56.21 minutes. The patient population included 34 with a medical history of diseases, and seven with other diseases and drug use. There were no significant differences among the three groups in mean age, height, weight, BMI, duration of operation, medical history, combination of disease and medication, diastolic blood pressure, heart rate and SpO_2 . However, systolic blood pressure was significantly lower in the T group than in the TK and C groups ($P=0.0377$).

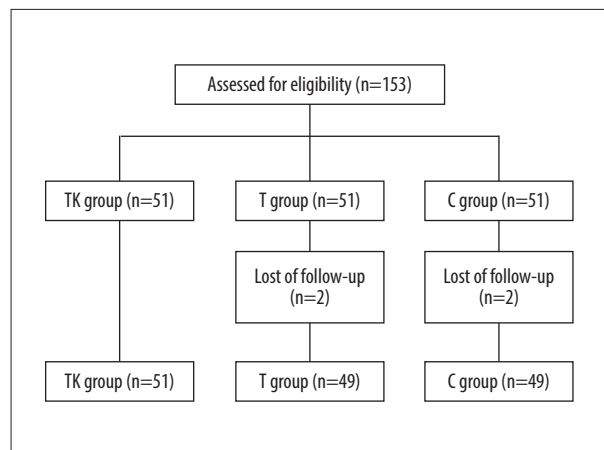


Figure 1. Flow chart of the study population.

Primary efficacy outcomes

Table 2 shows the primary efficacy outcomes in the TK, T, and C groups. Significant differences were observed among the three groups in the consumption of sufentanil over 24 hours, actual press times of the PCA pump, and effective press times of the PCA pump ($P<0.001$ each). Sufentanil consumption was lower in the TK (10.49 ± 5.36 ml) and T (13.42 ± 6.39 ml) groups than in the C group (25.26 ± 11.19 ml); whereas there was no significant difference between the TK and T groups. The actual press times of the PCA pump were also significantly lower in the TK (4.39 ± 2.81 min) and T (5.53 ± 2.78 min) groups than in the C group (10.41 ± 4.72 min), but did not differ significantly in the TK and T groups. In addition, the effective press times of the PCA pump were significantly lower in the TK (4.20 ± 2.14 min) and T (5.37 ± 2.56 min) groups than in the C group (10.10 ± 4.48 min), with no significant difference between the TK and T groups.

Secondary outcomes

Table 3 shows NRS pain scores in the three groups at rest and during activity measured 1, 2, 4, 6, and 24 hours after surgery. Mean NRS pain scores at rest and during activity were lower in the TK and T groups than in the C group at 1 and 2 hours. Although there were no significant differences between the TK and T groups at 1 hour, NRS pain scores at rest were lower in the TK group than in the T group (1.75 ± 0.89) at 2 hours. At 4 hours, NRS pain scores at rest and during activity were lower in the TK group than in the T and C groups, and NRS pain scores during activity, but not at rest, were lower in the T group than in the C group. At both 6 and 24 hours, NRS pain scores at rest and during activity were lower in the TK group than in the T and C groups, with no significant differences between the T and C groups.

There were no significant differences among the three groups in the incidence of nausea and vomiting at all

Table 1. Characteristics of the patients at baseline.

Variable	TK group (n=51)	T group (n=49)	C group (n=49)	P value
Mean age (years)	39.86 (10.07)	39.76 (9.59)	41.22 (9.92)	0.7127
Height (m)	1.61 (0.06)	1.60 (0.04)	1.60 (0.05)	0.8279
Weight (Kg)	57.21 (7.30)	56.75 (6.63)	57.92 (7.67)	0.7204
BMI	22.18 (2.57)	22.08 (2.47)	22.62 (2.74)	0.5536
Duration of operative (min)	54.04 (17.34)	56.98 (18.68)	57.61 (18.35)	0.5743
Medical history				
None	37.00 (72.55)	39.00 (79.59)	39.00 (79.59)	0.6235
Yes	14.00 (27.45)	10.00 (20.41)	10.00 (20.41)	
Combination of disease and medication				
None	48.00 (94.12)	48.00 (97.96)	46.00 (93.88)	0.9647
Yes	3.00 (5.88)	1.00 (2.04)	3.00 (6.12)	
DBP	75.12 (9.13)	73.90 (8.51)	74.00 (8.98)	0.7470
SBP	122.53 (11.43)	116.96 (11.94)	122.67 (14.01)	0.0377
Heart rate	83.29 (8.72)	82.67 (9.38)	82.80 (7.94)	0.9307
SpO ₂	98.84 (0.64)	98.80 (0.50)	98.76 (0.60)	0.7525

BMI – body mass index; DBP – diastolic blood pressure; SBP – systolic blood pressure.

Table 2. Primary end points.

Group	Consumption of sufentanil (ml)	The actual press times of PCA pump	Effective press times of PCA pump
TK group	10.49±5.36*	4.39±2.81*	4.20±2.14*
T group	13.42±6.39***	5.53±2.78***	5.37±2.56***
C group	25.26±11.19	10.41±4.72	10.10±4.48
F value	46.98	40.28	46.98
P value	<0.001	<0.001	<0.001

* P value for TK versus C <0.05; *** P value for T versus C <0.05.

time points (Supplementary Table 2), mean venting times (Supplementary Table 3), and duration of hospital stay (Table 4). Satisfaction with analgesia ($P=0.0006$) and overall satisfaction ($P=0.0031$) differed significantly among the three groups (Table 4), with pairwise comparisons showing higher levels of satisfaction with analgesia and overall satisfaction in the TK group than in the C group, and higher levels of satisfaction with analgesia in the T group than in the C group (Supplementary Table 4).

Discussion

Although laparoscopic surgery can shorten recovery time, controlling pain caused by port-site wounds remains a challenge [10]. The use of bupivacaine as a TAP block after laparoscopic surgery was found to significantly reduce pain score at discharge [11,12]. The combination of TAP block and ketorolac 30 mg was associated with less variable dynamic pain than TAP block or ketorolac 30 mg alone in patients undergoing total abdominal hysterectomy, whereas pain at rest, opioid consumption, and rates of nausea, vomiting, and rescue antiemetics did not differ significantly among these three groups [13]. However, it was not clear whether TAP block with combined ketorolac and bupivacaine could provide additional benefits.

Table 3. NRS scores at rest and activity after surgery.

Group	1 h	2 h	4 h	6 h	24 h
Rest					
TK group	2.10±1.19*	1.75±0.89***	1.65±1.05***	1.59±1.06***	1.43±0.94***
T group	2.31±1.23***	2.33±1.20***	2.41±1.19	2.20±1.15	2.00±1.02
C group	3.39±1.55	3.10±1.25	2.86±1.38	2.61±1.29	2.13±1.10
F value	13.40	18.45	12.71	9.72	6.53
P value	<0.001	<0.001	<0.001	<0.001	0.002
Activity					
TK group	3.51±1.60*	3.27±1.17*	3.08±1.32***	3.02±1.19***	2.88±1.19***
T group	3.76±1.45***	3.76±1.16***	3.92±1.26***	3.78±1.07	3.53±0.98
C group	5.12±1.75	4.73±1.50	4.53±1.60	4.20±1.47	3.71±1.13
F value	14.47	16.71	13.61	11.48	7.72
P value	<0.001	<0.001	<0.001	<0.001	<0.001

* P value for TK versus C <0.05; ** P value for TK versus T <0.05; *** P value for T versus C <0.05.

Table 4. Analgesic satisfaction and length of stay.

Outcomes	TK group	T group	C group	P value
Length of stay (days)				
2.5	3 (5.88)	1 (2.04)	1 (2.04)	0.3280
3	48 (94.12)	48 (97.96)	47 (95.92)	
4	0 (0.00)	0 (0.00)	1 (2.04)	
Analgesic satisfaction				
Very dissatisfied	0 (0.00)	0 (0.00)	0 (0.00)	0.0006
Dissatisfied	0 (0.00)	0 (0.00)	0 (0.00)	
General	0 (0.00)	1 (2.04)	1 (2.04)	
Satisfied	18 (35.29)	22 (44.90)	35 (71.43)	
Very satisfied	33 (64.71)	26 (53.06)	13 (26.53)	
Overall satisfaction				
Very dissatisfied	0 (0.00)	0 (0.00)	0 (0.00)	0.0031
Dissatisfied	0 (0.00)	0 (0.00)	0 (0.00)	
General	0 (0.00)	0 (0.00)	1 (2.04)	
Satisfied	17 (33.33)	21 (42.86)	31 (63.27)	
Very satisfied	34 (66.67)	28 (57.14)	17 (34.69)	

The present study found that sufentanil consumption and actual and effective press times of the PCA pump were significantly lower in the TK and T groups than in the C group. Moreover, NRS pain scores at rest and during activity were lower in the TK than in the C group at various postoperative timepoints. Furthermore, satisfaction with analgesia and overall satisfaction were greater in the TK group. In contrast, the incidence of nausea and vomiting at various timepoints, along with venting

time and duration of hospital stay, did not differ significantly in the three groups of patients.

This study found TAP blocks could reduce sufentanil consumption and actual and effective press times of the PCA pump, regardless of whether TK or T was used as TAP blocks. This finding could be explained by the reduced vascular supply at the application site and the residual effects of local anesthetic in

the neural sheaths [14,15]. Moreover, our finding, that the TK group achieved better pain control at rest and during activity than the T and C groups at 6 and 24 hours, suggests that analgesic effects were longer in patients administered ketorolac and bupivacaine for TAP block than in those administered bupivacaine alone and those without TAP blocks. Ketorolac inhibits the biosynthesis of prostaglandins, suggesting that the combination of ketorolac and opioids could reduce the consumption of opioids and provide greater analgesic effects. Ketorolac delivered at the subarachnoid level could act directly on the spine, blocking hyperalgesia caused by activation of spinal glutamate and substance P receptors, suggesting that delivery of ketorolac to a more proximal site of the nerve would have greater effect than its delivery to the nerve terminal [16–18].

Our study found that patients in the TK group experienced greater satisfaction with analgesia and greater overall satisfaction than patients without TAP blocks, and that patients in the T group achieved greater satisfaction with analgesia than patients in the C group, findings that may be due to significant improvements in the primary endpoints and pain control provided by TK. However, there were no differences among these groups in the incidence of nausea and vomiting at various timepoints, venting time, and duration of hospital stay. However, the incidence of nausea and vomiting in these groups was low, resulting in insufficient power to detect potential differences among groups [19–21]. In addition, the severity of pain gradually decreased in the three groups, reducing the differences among groups in venting times and duration of hospital stay.

This study has three main strengths. First, this study was designed as a randomized, observer-blinded, 3-armed clinical trial, with the baseline characteristics being generally balanced among the three patient groups, thereby eliminating potential

selection and confounder biases. Second, this study was the first to use TK as a TAP block in patients who underwent gynecological laparoscopic surgery. Third, outcomes evaluating the effectiveness of treatment were thoroughly investigated. Fourth, pain scores and rates of nausea and vomiting were evaluated at various timepoints, enabling a determination of treatment effectiveness over time.

Nevertheless, this study also had several limitations. First, this was a single-center study, which may reduce the ability to generalize from our findings. Second, detailed medical histories and combinations of diseases and medications were not recorded, preventing investigation of the potential impact of these factors. Third analyses of primary efficacy endpoints were not stratified. Fourth, the statistical power of this study was insufficient to detect differences among groups of the incidence of nausea and vomiting.

Conclusions

Combined ketorolac and bupivacaine, or bupivacaine alone as a TAP block reduced the consumption of sufentanil and the actual and effective press times of PCA pumps when compared with ketorolac alone in women undergoing laparoscopic gynecologic surgery. Moreover, combined ketorolac and bupivacaine as a TAP block resulted in better pain control, especially with regard to prolonged analgesic effects, without increasing the incidence of nausea and vomiting. Future studies showed compare the effects of various TAP block strategies.

Conflict of interests

None.

Supplementary Data

Supplementary Table 1. Details regarding the non-inclusion of recruited patients.

	Group	Total patients	Total discontinued	Rate	P value
Discontinued per protocol*	TK group	51	0	100.00	0.3289
	T group	51	0	100.00	.
	C group	51	2	96.08	.
Loss to follow-up**	TK group	51	0	100.00	0.3289
	T group	51	2	96.08	.
	C group	51	0	100.00	.
Total	TK group	51	0	100.00	0.5467
	T group	51	2	96.08	.
	C group	51	2	96.08	.

* Conversion to laparotomy, intraoperative blood loss >1000 ml, or duration of surgery <0.5 or >2.0 hours; ** non-completion of specified follow-up duration.

Supplementary Table 2. Incidence of nausea and vomiting over time among patients in the three groups.

Outcomes	TK group	T group	C group	P value
1 h				
No	51 (100.00)	49 (100.00)	48 (97.96)	0.3604
Nausea	0 (0.00)	0 (0.00)	1 (2.04)	
Nausea and vomiting	0 (0.00)	0 (0.00)	0 (0.00)	
2 h				
No	51 (100.00)	49 (100.00)	49 (100.00)	1.0000
Nausea	0 (0.00)	0 (0.00)	0 (0.00)	
Nausea and vomiting	0 (0.00)	0 (0.00)	0 (0.00)	
4 h				
No	49 (96.08)	48 (97.96)	47 (95.92)	0.8234
Nausea	2 (3.92)	1 (2.04)	2 (4.08)	
Nausea and vomiting	0 (0.00)	0 (0.00)	0 (0.00)	
6 h				
No	49 (96.08)	49 (100.00)	46 (93.88)	0.2350
Nausea	1 (1.96)	0 (0.00)	3 (6.12)	
Nausea and vomiting	1 (1.96)	0 (0.00)	0 (0.00)	
24 h				
No	50 (98.04)	49 (100.00)	49 (100.00)	0.3826
Nausea	0 (0.00)	0 (0.00)	0 (0.00)	
Nausea and vomiting	1 (1.96)	0 (0.00)	0 (0.00)	

Supplementary Table 3. Mean venting time among patients in the three groups.

Group	Venting time (min)
TK group	0.66±0.24
T group	0.64±0.19
C group	0.67±0.21
F value	0.38
P value	0.6823

Supplementary Table 4. Results of pairwise comparisons of satisfaction with analgesia and overall satisfaction.

Outcomes	Statistic	P value
Satisfaction with analgesia		
TK vs. T group	1.242	0.643
TK vs. C group	3.833	<0.001
T vs. C group	2.566	0.031
Overall satisfaction		
TK vs. T group	0.942	1.000
TK vs. C group	3.256	0.003
T vs. C group	2.292	0.066

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