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Preoperative versus postoperative ultrasound-guided rectus sheath block for improving pain, sleep quality and cytokine levels in patients with open midline incisions undergoing transabdominal gynecological surgery: a randomizer controlled trial



Feng Jin, Zhe Li, Wen-fei Tan * D, Hong Ma, Xiao-qian Li and Huang-wei Lu

Abstract

Background: Nerve block is usually performed before sure my because it inhibits reflection of the skin incision and reduces the amount of intraoperative anesthetic used. We have that performing rectus sheath block (RSB) after surgery would result in a longer duration of the analysis effect, and have a subtle influence on sleep time after surgery but that it would not decrease the perioperative cytokine levels of patients undergoing gynecological surgery.

Methods: A randomized, double-blinded, confolled trial case conducted from October 2015 to June 2016. Seventy-seven patients undergoing elective transable on. If gynecological surgery were randomly assigned to the following two groups: a general anesthesia group who received to 6 ropivacaine hydrochloride RSB preoperatively and saline RSB postoperatively, and another group who received the opposite sequence. The objective of the trial was to evaluate the postoperative pain, sleep and change in cytokine levels of patients during the postoperative 48 h.

Results: A total of 61 female patients (mean age: 50 years; range: 24–65 years) were included in the final study sample. There was no significant difference to be pain, consumption of oxycodone, or time to first administration of patient-controlled intravenous and gesia between the two groups. The postoperative sleep stages N2 and N3 were increased by 52.9 and 29.1 mirrorer patient, espectively, in the preoperative RSB group compared with those in the postoperative group. It preoperative IL-6 concentration in the preoperative RSB group was lower than that in the same group at the end of largery and 24 h postoperatively.

Conclusions. We included that preoperative RSB might preserve postoperative sleep by inhibiting the increase of IL-6 without shortening the analgesia time compared with postoperative RSB in female patients undergoing elective midline. Asion transabdominal gynecological surgery.

7... regis tion: ClinicalTrials.gov, NCT02477098, registered on 15 June 2015.

Rectus sheath block, Sleep, Interleukin-6

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Background

Rectus sheath block (RSB) was introduced into clinical practice in 1899 by Schleich, and it involves blocking the ventral rami of the 7th to 12th intercostal nerves by the injection of a local anesthetic into the space between the rectus muscle and posterior rectus sheath to achieve analgesic effects [1, 2]. With the development of longacting local anesthetic agents, such as ropivacaine, and ultrasonic technology, RSB has become safer and more effective [3, 4].

RSB is usually performed before surgery for patients with general anesthesia because it inhibits reflection of the skin incision and reduces the amount of intraoperative anesthetic used [5–8]. Postoperative surgical RSB appears to provide effective postoperative analgesia for patients undergoing major gynecological surgery [9], and the postoperative placement of RSB analgesia does not significantly alter the oxidative stress marker concentrations in patients with benign disease or cancer [10].

The peripheral inflammatory response to surgery may influence patient outcomes, such as postoperative sleep, and we have published two clinical trials on this topic using the bispectral index (BIS) to monitor sleep [11, 12]. Postoperative sleep disturbances after surgery can be caused by factors such as the anesthesia used, pain and sympathetic activation and psychological responses [13]. However, little information is available about the effect of RSB on sleep quality and the inflammator response during the immediate postoperative period. In particular, there is no information about when representative block or postoperative block will enefit patients.

The primary hypothesis is that per ming RSB after surgery would result in a long duration of analgesic effects. The secondary hypothesis that performing RSB after surgery have conger duration of sleep after surgery but that it would not decrease the perioperative cytokine levels of patient undergoing gynecological surgery. The null pothesis is there is no difference between performing. By before surgery and after surgery.

Metho

Stuch design

his addy is a prospective, randomized, controlled, and de bie-banded trial. Major assessments were made during a operation and 48 h postoperatively. We followed the Consolidated Standards of Reporting Trials (CONSORT) recommendations in designing and reporting the findings of our study. The trial was approved by the Ethics Committee of the First Hospital of China Medical University (protocol number 2015110901, Chairman Prof. Xing-hua Gao, January 14, 2015, Trial registration: NCT02477098, Principal investigator's name: Wen-fei Tan, Date of registration: 2015–06-15 https://

clinicaltrials.gov/ct2/show/NCT02477098?term=NCT02 477098&rank=1). We changed our published protocol [14] (protocol number 2014071701) from a single-blind to a new double-blind trial with approval from the Ethics Committee. All participants provided written informed consent in accordance with the Declaration of Helsinki.

Patients

Seventy-seven patients undergoing dective ansabdominal gynecological surgery were inrolled in this study from October 2015 to June 2016 the First Hospital of China Medical University. The paties of this trial were visited 24 h and 48 h postop tively by one of the research personnel. Siech quality curing the first postoperative night was assessed ling the BIS data, and venous blood was colleged.

Inclusion a exclusion criteria

The inclusion efferia were as follows: (1) age 18 to 65 years; (2) scheduled to undergo elective midline incision (8–10 cm) transabdominal gynecological surgery for a enign mass (ovarian or uterine); and (3) American enicty of Anesthesiologists (ASA) risk classification I-II. The exclusion criteria were as follows: (1) patient refusal; (2) known hypersensitivity to the study medication (ropivacaine); (3) long-term use of opioids; (4) liver or renal insufficiency; (5) a history of psychiatric or neurological disease; (6) deafness; (7) previous open surgery; (8) regular use of acetaminophen, nonsteroidal anti-inflammatory drugs, corticosteroids, or antiemetics; and (9) a preoperative Pittsburgh Sleep Quality Index (PSQI) global score higher than 6.

Randomization and masking

All patients requiring transabdominal gynecological surgery were randomly assigned via computer-generated sequences placed into sealed envelopes to the following two groups: a general anesthesia group receiving 0.5% ropivacaine hydrochloride RSB (Group PRE) preoperatively and saline RSB postoperatively; and a general anesthesia group receiving preoperative saline RSB and 0.5% ropivacaine hydrochloride RSB postoperatively (group POST). Treatment allocation was revealed by opening the envelope on the morning of surgery. All of the patients, the anesthesiologist performing the block, and the staff involved in postoperative data collection and analyses were blinded to the group allocations. The trial was monitored by an independent data and safety monitoring organization. The group allocations were not revealed until the final statistical analysis was completed.

Interventions

Before anesthesia

All patients were assessed with the PSOI one day before the operation [15]. The PSQI differentiates between good sleepers (PSQI global score < 6) and poor sleepers (PSQI global score ≥ 6) with high sensitivity and specificity. The patients in this study received routine general anesthesia and surgery. No additional requirements or preoperative oral analgesics were permitted. While the patients were in the operating room, standard monitoring was performed, including evaluations of systolic blood pressure, diastolic blood pressure, heart rate, electrocardiography, blood oxygen saturation and the BIS. After venipuncture, 3 ml of venous blood was collected for plasma inflammatory cytokine measurements prior to induction. Plasma samples were used to measure the cytokine concentrations (interleukin-6 [IL-6], tumor necrosis factor-α [TNF-α], IL-1β and interferon-gamma [IFN-y]) in all patients. Commercially available radioimmunoassay kits were used to measure the plasma concentrations of IFN-γ, IL-1β, IL-6, and TNF-α (eBioscience, Bender MedSystems GmbH, Vienna, Austria).

General anesthesia

All operations performed in the study were completed between 08:00 am and 12:00 noon by the same group of surgeons. General anesthesia was induced with 2 intravenous (IV) propofol, 2 mg of IV milazon 0.4 μg/kg IV sufentanil, and 0.2 mg/kg IV cit racurium The tidal volume was adjusted to 6-8 ml/kg, and the ventilator rate was adjusted to maintain end-tidal Q₂ at 35-45 mmHg. For the maintenance of anesthesia, sevoflurane (Baxter Healthcare of Puer Rico Guayama, Puerto Rico) was used at an entitled concentration of 2-2.5%, and an air-oxygen (FiC): mixture was adjusted for the maintenant of aresthesia with the intraoperative titration of W fentanil after intubation in both groups. An additical cisatracurium dose (0.05 mg/ kg) was applied needed. It the end of surgery, the trachea was extubate fter the return of spontaneous respiration and neuron uscular function, and the patient was the transferred to the post-anesthesia care unit (PACU). e patients received pain relief (visual halo ue scale (VAS) score of less than 3) using 5–10 μg race sufentanil. Three milliliters of venous blood was liected for plasma inflammatory cytokine measurements at the PACU.

RSB technique

Before and at the end of surgery, a bilateral single-shot RSB of 15 ml of solution was performed under ultrasound guidance by the same anesthesiologist. The rectus muscle was imaged with an ultrasound probe in the transverse orientation at the level of the umbilicus. A broadband (5-12 MHz) linear array ultrasound probe (S-Nerve Ultrasound System, SonoSite, Bothell, Washington, USA) was used with an imaging depth of 4-6 cm. A PAJUNK (PAJUNK, GmbH, Medizintechnologie, Geisingen, Germany) insulated needle (50 mm, 21 gauge) was introduced a few millimeters from the probe using an in-plane technique at an angle of approximately 45 degrees to the skin 1 cm to the side and do from the navel. The ultrasound imaging allowed for the tification of the rectus muscle and hype ecnoic railway-like lines deep in this muscle (the terior rectus sheath and the peritoneum). I nder direct vision, the needle tip was advanced to the crired position, where 15 ml of solution was inject. cat. , nydrodissection of the rectus muscle away free the posterior rectus sheath on each side. The echnique was repeated on the opposite side. The proces to was performed by one completely aseptic technique. In investigator using group PRE, 13 ml 55% ropivacaine hydrochloride RSB before surge, and 15 ml of saline RSB at the end of surger administered on each side. An opposite block sequence as performed in group POST.

Posperative analgesia: Patient-controlled intravenous analges. (PCIA)

the patients, irrespective of the group allocation, received PCIA with oxycodone. A PCIA pump (AponZZB-I50, Nantong, China) was set up with a bolus injection of 2 mg every 5 min for a maximum of 10 mg every 4 h without basal infusion. The PCIA pump was stopped 48 h postoperatively, and postoperative nausea and vomiting were treated with 5 mg IV tropisetron (in the ward).

Postoperative nocturnal sleep: The BIS-vista monitor

Postoperative nocturnal sleep was evaluated with the BIS-Vista monitor (Aspect Medical Systems, Norwood, MA, USA), and three outcome measures were used in this study: the area under the curve (AUC) and sleep stages N2 and N3 [16]. A cutoff of BIS < 55, with a sensitivity of 87% and specificity of 93%, was identified as stage N3 in this trial. The BIS threshold that identified stage N2 was < 73 [17]. The observation period included 11 h of monitoring (from 19:00 pm to 06:00 am). The BIS-AUC was calculated using the trapezoidal rule, which uses trapeziums to approximate the region under a curve and to calculate its area (GraphPad Prism version 5.01). Each night, the AUC values were set to missing if the recordings were less than 11 h in duration.

Study outcomes

The primary objective was to compare the interval between leaving the PACU and receiving the first PCIA bolus injection on the first postoperative night between patients who received preoperative RSB and those who received postoperative RSB. The secondary objectives were to compare the following: (1) cumulative oxycodone consumption at 48 h after surgery between patients who received preoperative versus postoperative RSB; (2) postoperative sleep status, which was measured using a BIS-Vista monitor during the first night after surgery; and (3) cytokine levels (IFN- γ , IL-1 β , IL-6, and TNF- α), which were compared during the operation and at 24 and 48 h postoperatively.

Criteria for removal from the study

During the study, patients found to have the following were removed from the study: (1) a loss of over 500 ml of blood during surgery; (2) an operation time of longer than 3 h; (3) a violation of the trial protocol; or (4) a desire to withdraw from the study.

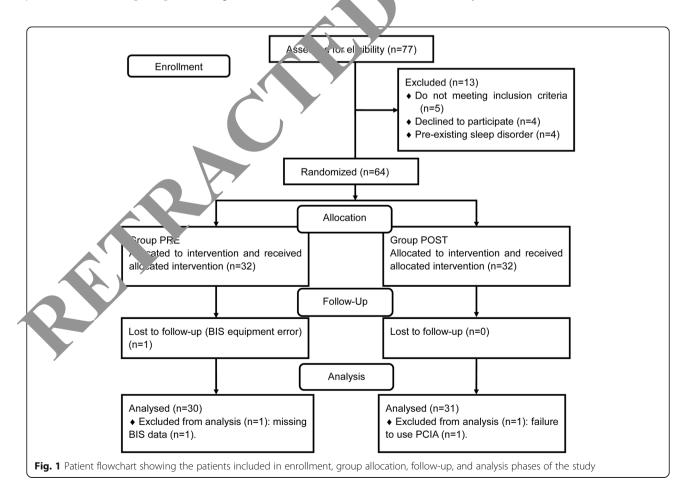
Sample size

Sample size was calculated on the basis of the average (mean \pm standard deviation [SD]) interval between leaving the PACU and the receipt of the first PCIA bolus injection on the first postoperative night calculated, which

was calculated in the pilot study (group PRE: 203.2 ± 21.5 min; and group POST: 258.2 ± 98.7 min). The formula for determining sample size [18] was $n = 15.7/\text{ES}^2 + 1$, where ES is the effect size, defined as the difference between the groups divided by the mean of the SD between the groups, with $\alpha = 0.05$ and power = 0.8 The study was adequately powered, with n = 32 in each group.

Statistical analysis

Statistical analysis was performed using SPS's software, version 22 for Windows (IBM, Arnonk, NY, USA). A fully specified statist of analysis protocol was written in an independ to mean. Before statistical testing, each continuous viable was analyzed to determine whether it is a normal distribution using the Kolmogorov-Smirnov est. Continuous data are described as the man (SD) or median (25% and 75% percentiles) and we had alyzed with the independent test or the Man Whitney U test, respectively. Categorical construction as a frequency or percentage and were analyzed by the chi-square test. Repeated-measures ANOVA was used to determine dimensions in the cytokine levels within and between



the groups. For intervals between leaving PACU and the first PCIA trigger, we analyzed data using the Kaplan-Meier survival method and compared groups using the log-rank test. A P value < 0.05 was considered statistically significant.

Results

Patient characteristics

Of the 77 potential patients assessed for eligibility, 13 patients were excluded; thus, 64 patients were randomly assigned to two groups. One patient was lost to followup because of a BIS equipment error, and one patient in group PRE was excluded from the analysis because of missing BIS data. One patient in group POST was excluded from the analysis because of failure to use PCIA. A total of 61 female patients (mean age: 50 years; range: 24-65 years) were included in the final study sample (Fig. 1). Group sample sizes of 30 and 31 achieve 85% power with a significance level (alpha) of 0.05 using a one-sided two-sample t-test with PASS11 software (NCSS LLC, Utah, USA). Table 1 presents the results of the demographic and preoperative characteristics of the two groups. There was no significant difference in these characteristics between the two groups.

VAS and PCIA data

The interval between leaving the PACU and region of the first PCIA bolus injection on the first postoperate night was 211.5 min and 229.1 min in group PRE an POST respectively (Table 2). The Kaplar-Meier urvival analysis of the interval between leaving the PAC and receiving the first PCIA bolus injection for the two

groups is shown in Fig. 2a. The log-rank test also suggested no detectable difference between the two groups (P = 0.736). There was no significant difference in the VAS, consumption of oxycodone, or time to first PCIA trigger between the two groups.

BIS-AUC and sleep stages N2 and N3 during the intire nocturnal sleep period

The BIS-AUC in group PRE was lower than the in group POST, indicating "better" sleep in the PRE group [16] (Table 3). Furthermore, the time s_F at in sleep stages N2 and N3 was significantly increased by 52.9 min and 29.1 min, respective in group PRE compared to group POST. One a map in the first postoperative night BIS data of the two roups is shown in Fig. 2b.

Cytokine levels and eir correlation with the BIS data

There was a spain difference in the all cytokine levels between the wo groups (Fig. 3). In group POST, the concentions of four cytokines were higher compared to those of group PRE (P < 0.05; Fig. 3a-d). IL-6 concentration increased during the postoperative 48 h concentration in group PRE was lower than that in group entry ion in group PRE was lower than that in group ST at the end of surgery and 24 h postoperatively (P < 0.001; Fig. 3b).

Discussion

The results of this study suggest that there is no difference in the first PCIA remedy trigger between patients who undergo elective transabdominal gynecological

Table 1 Patient demographic data haracteristics

Variable	Group PRE $(n = 30)$	Group POST $(n = 31)$	95% Confidence interval	Р
Body mass index (kg 32)	24.8 ± 2.9	22.9 ± 2.6		0.625 ^b
ASA (I/II)	19/11	18/13		0.674 ^c
Pittsburgh sleeo Quality Index global score I traop ation	3.0[2.0,3.5]	3.0[2.0,4]		0.518 ^a
auon anesthesia (min)	131.1 ± 20.4	133.9 ± 28.8	(- 15.6,10.0)	0.663 ^b
Duk on of surgery (min)	79.7 ± 17.1	76.8 ± 21.7	(-7.1,12.9)	0.570 ^b
Volume loading (ml)	1413.3 ± 351.1	1441.9 ± 354.8	(- 9.5,352.3)	0.763 ^b
Bleed amount (ml)	150[120,205]	150[130,230]		0.930 ^a
Length of skin incision (cm)	9.0[8.0,9.5]	9.0[8.0,10.0]		0.951 ^a
Sufentanil (µg)	47.3 ± 4.1	47.1 ± 4.8	(-2.1,2.5)	0.837 ^b

 $Values \ represent \ the \ mean \pm SD, \ the \ number \ of \ patients, \ or \ the \ median \ [25th \ percentile]$

^aMann–Whitney U test

^bStudent's *t* test ^cchi-square test

Table 2 Visual analogue scale and patients control intravenous analgesia data

Variable	Group PRE	Group POST	95% Confidence	Р
	(n = 30)	(n = 31)	interval	
Visual analogue scale (24 h)	2.0 [0.5,3.0]	2.0 [1.0,3.0]		0.534 ^a
Visual analogue scale (48 h)	1.0 [1.0,2.0]	1.0 [0,2.0]		0.685 ^a
Time to first PCIA trigger (min)	211.5 ± 35.3	229.1 ± 42.1	(- 126.3,91.3)	0.523
Consumption of oxycodone during 24 h (mg)	32 [24,52]	32 [16,56]		0.7-
Consumption of oxycodone from 24 h to 48 h (mg)	4 [0,4]	4 [0,20]		0.443³

Values represent the mean \pm SD, or the median [25th percentile, 75th percentile]

surgery with preoperative RSB or postoperative RSB. Patients with preoperative RSB may have better sleep preservation than patients treated with postoperative RSB. Compared to the postoperative RSB group, the concentrations of all cytokines tested were lower in the preoperative RSB group. IL-6 in the postoperative RSB group increased compared to the preoperative group at the end of surgery and 24 h postoperatively.

Two questions that motivated his clinical trial can be answered. First, surgeon always ound "water" in their incision when the RSB was performed preoperatively (white arrow, Fig. 1). They suggested performing RSB postoperatively he the leakage of drugs would attenuate the enact. However, the stability of preoperative of her odynamics (data not shown) encouraged the a esthesiologists to finish the block as

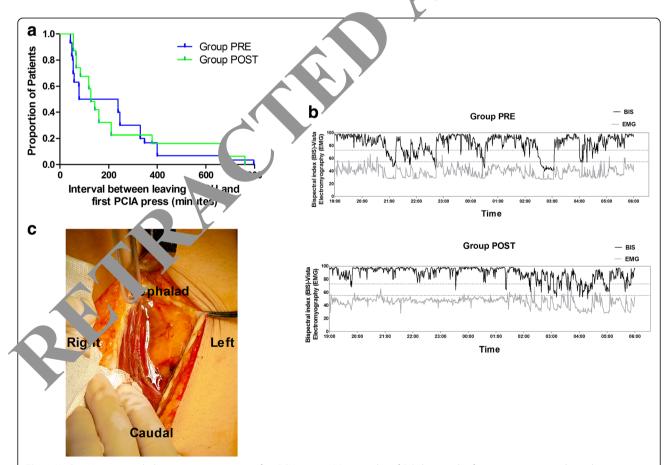


Fig. 2 Kaplan-Meier survival plot representing time to first PCIA trigger (**a**), examples of BIS data on the first postoperative night in the two groups (**b**), and a picture of one incision (**c**). **a** The log-rank test suggested no detectable difference between the two groups (P = 0.736). **c** The white arrow shows fluid in the rectus sheath

^aMann–Whitney U test ^bStudent's t test

Table 3 BIS data of patients in the two groups on the first postoperative night

BIS data	Group PRE	Group POST	95% Confidence	Р
	(n = 30)	(n = 31)	interval	
BIS-AUC (%)	82.5 [81.8, 84.7]	86.5 [86.4.7, 86.9] ^a		< 0.001
Stage N2 sleep (min)	134.0 ± 10.7	81.1 ± 10.6 ^b	(42.9,62.9)	< 0.001
Stage N3 sleep (min)	54.5 ± 12.4	25.4 ± 7.9^{b}	(19.2,39.2)	< 0.001

Values represent the median [25th percentile, 75th percentile] and the mean $\pm\,\text{SD}$ bispectral index, SEI sleep efficiency index, AUC, area under the curve

early as possible. In the postoperative period the anesthesiologists were concerned about the changes in the local anatomy and distortion of nerve elements. However, a block after surgery will theoretically prolong the effective time of the local anesthetic. For elective transabdominal gynecological surgery lasting no more than 3 h, there is no difference in the opioid consumption and the first remedy trigger time between preoperative and postoperative RSB. In one study, Wulf et al. [19] reported that the arterial ropivacaine level after the block (ilioinguinal iliohypogastric block, 20 ml of 0.5% ropivacaine) peaked at 30 min. The onset time of the local anesthetic in the

nerve terminal may be less that the peak concentration time [20]. The interval between a completed RSB procedure and the incision new 30 min in our center, which is usually enough time for 0.5% ropivacaine to work on the cerve terminal. Although the surgeons will find "water in the incision, the nerve block will be complete. The change in the local anatomy and the social anesthetic as expected.

Second, surgery-related postoperative release of the proinflam for IL-6 cytokine is increased in patients after spinal and general anesthesia [21]. Increased IL levels may be associated with alterations in sleep in

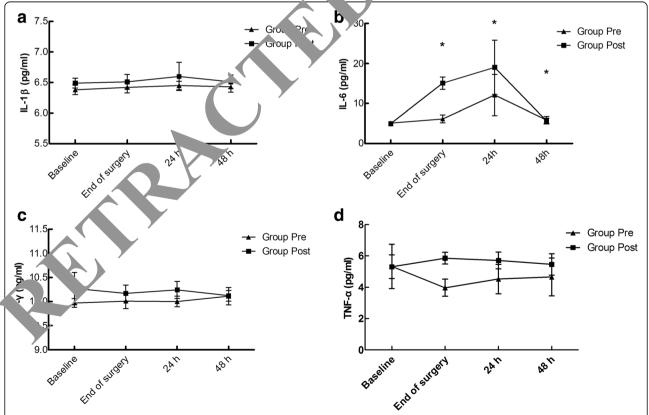


Fig. 3 Comparison of the plasma concentrations of IL-1β (a), IL-6 (b), IFN- γ (c), and TNF- α (d) between the two groups. a $P_{group} = 0.048$, $P_{time} = 0.285$, and $P_{group-time\ interaction} = 0.865$. b P_{group} , P_{time} , and $P_{group-time\ interaction} < 0.001$. #P < 0.001 vs. baseline. c $P_{group} < 0.001$, $P_{time} = 0.949$, and $P_{group-time\ interaction} = 0.120$. d $P_{group} = 0.003$, $P_{time} = 0.325$, and $P_{group-time\ interaction} = 0.298$

^aMann–Whitney U test ^bStudent's t test

the context of pathological or other conditions [22]. In our previous study, we found that patients receiving epidural analgesia may have preserved sleep quality on the first night after surgery due to better pain management and inhibition of increasing IL-6 levels [11]. The upregulation of IL-6 at central sites is an important component of the surgery-induced inflammatory response in patients and may influence postoperative sleep [23]. Plasma IL-6 levels are correlated with non-rapid eye movement sleep, rapid eye movement sleep and fatigue [24]. In this trial, the preoperative RSB not only exhibited stable hemodynamics, as shown by the monitoring data, but also inhibited the upregulation of all cytokines tested, specifically IL-6. Inhibition of the upregulation of cytokines may thus influence postoperative sleep as recorded by a BIS monitor.

This trial produced an interesting result. No complaints were reported regarding the presence of the urethral catheter in our female patients undergoing a transabdominal gynecological operation before the use of RSB. However, in the pilot study of this trial, more patients complained about the presence of the urethral catheter and preferred the pain of an incision. This phenomenon suggested that the somatic pain of the incision masked the visceral pain of the urethral catheter in our previous technique. Covering the urethral catheter in local anesthetic cream, RSB and PCIA with codone is a potentially better multimodal analysis to nique patients undergoing tran bdomina for gynecological surgery with an open midline incl.

This study has several limitations. The main deficiency was the lack of validation of a full polysomrogram. We also need to observe the postoperative leep disturbance for more days after the operator. Finally, our study included only female patients and the conserved several polysomrogram.

Conclusions

There is no din once in the first PCIA remedy trigger or opioid consumption between the two groups. Patients with preoperative R\$B may have better sleep preservation that present treated with postoperative R\$B. Compared to the postoperative R\$B group, the once trations of all cytokines tested were lower in the preparative R\$B group. We conclude that preoperative R\$B ight preserve the first postoperative sleep by inhibiting the increase in IL-6 without shortening of analgesic time compared with postoperative R\$B in female patients undergoing elective midline incision transabdominal gynecological surgery.

Abbreviations

PACU: Postanesthesia care unit; PCIA: Patient-controlled intravenous analgesia; PSQI: Pittsburgh Sleep Quality Index; RSB: Rectus sheath block; VAS: Visual analogue scales

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Availability of data and materials

The datasets used and/or analyzed in the current study available from the corresponding author upon reasonable request.

Authors' contributions

FJ, ZL and WFT made substantial contributions to the st. design. These authors conducted the study, collected and analyzed data, the propared the manuscript. HM, XQL and HWL helped to analyze and interpret the data. All authors read and approved the final manuscript.

Ethics approval and consent to partic

This trial was approved by the Ethics Commune of the First Hospital of China Medical University (protoccumber 2015, 19901, Chairman Prof. Xing-hua Gao, January 14, 2015 (Trial registration, NCT02477098, Principal investigator's name: Wen-fei Tan, Date of registration, 15-06-15 https://clinicaltrials.gov/ct2/show/NCT02477098/te/m=, 102477098 rank=1). All participants provided written informed countries in proceedings with the Declaration of Helsinki.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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