Journal of Anesthesia (2024) 38:631–641
https://doi.org/10.1007/s00540-024-03365-x

ORIGINAL ARTICLE

Effect of nociception level-directed analgesic management on opioid usage in robot-assisted laparoscopic radical prostatectomy: a single-center, single-blinded, randomized controlled trial

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Received: 12 April 2024 / Accepted: 14 June 2024 / Published online: 27 June 2024

Abstract

Purpose To assess the importance of appropriate opioid administration methods according to nociceptive monitoring.

Methods We conducted a randomized controlled trial involving 54 patients who underwent robot-assisted laparoscopic radical prostatectomy at our hospital. Patients were randomly allocated to either receive nociception level (NOL)-directed intraoperative opioid management with a minimum flow of remifentanil (NOL group) or conventional intraoperative analgesic management (control group). The primary outcome was the mean intraoperative remifentanil infusion flow rate (intraoperative remifentanil usage [μg]/ideal body weight [kg]/operation time [min]). The main secondary outcomes were plasma concentrations of three perioperative inflammatory biomarkers (interleukin-6, C-reactive protein [CRP], and cortisol levels) and postoperative pain (Numeric Rating Scale [NRS]) scores 2 h postoperatively and on postoperative days 1, 2, 3, and 7.

Results Compared with standard analgesia management, NOL-directed analgesic management reduced remifentanil consumption by 20% (– 0.038; 95% confidence interval, – 0.059 to – 0.017; $p = 0.0007$). NOL-directed management did not lead to an increase in IL-6, CRP, or cortisol levels compared with conventional analgesic management. Furthermore, this protocol led to improvements in the NRS scores at rest 2 h postoperatively and upon movement up to postoperative day 3.

Conclusion NOL-directed analgesic management reduced remifentanil consumption by 20% and the NRS scores at rest 2 h postoperatively and upon movement up to postoperative day 3 without an increase in inflammatory marker levels.

Registry number Japan Registry of Clinical Trials, JRCTs052220034.

Keywords Anesthesia and analgesia · Analgesics · Nociception · Opioid · Pain measurement · Prostatectomy

Introduction

Anesthetic management is advancing into an era where all three components—hypnosis, analgesia, and muscle relaxation—can be objectively monitored with the availability of nociception monitoring tools [1]. Inappropriate analgesia, involving an opioid underdose, can be harmful; however, an opioid overdose can exacerbate opioid-induced hyperalgesia or acute postoperative pain [2, 3]. Nociception monitoring may allow for optimizing opioid dosage by objectively displaying the balance between nociceptive stimuli and analgesics.

The PMD-200™ (Medasense Biometrics Ltd., Ramat-Gan, Israel) provides the nociception level (NOL) index during surgery [4]. Previous studies have shown that NOL-guided opioid administration decreased remifentanil doses, postoperative pain scores, and hypotensive events [5–7].

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However, one study reported an elevated stress response in the group using the NOL index, despite a decrease in intraoperative remifentanil consumption [6]. These results revealed that an average remifentanil dose of < 0.1 μg/kg/min might result in an inadvertent increase in inflammatory hormone levels and that opioid management guided only by the nociception monitor might not minimize invasive stress for patients [6]. There is also a growing skepticism concerning the excessive restriction of opioid use, as exemplified by the concept of "opioid-free anesthesia."[8, 9] Therefore, we hypothesized that a minimum flow rate of remifentanil of ≥ 0.1 μg/kg/min should be established when planning the NOL-directed opioid administration protocol. We evaluated actual invasive stress using cortisol, which was frequently used in previous studies, [5, 6] as well as the more relevant invasive stress markers, interleukin (IL)-6 and C-reactive protein (CRP).

We hypothesized that a NOL-directed opioid administration protocol ensuring a minimum infusion rate would decrease intraoperative remifentanil consumption without increasing inflammatory marker levels, including IL-6, compared with conventional anesthesia management. Therefore, we aimed to examine the importance of appropriate opioid administration methods according to nociceptive monitoring. Accordingly, we set intraoperative remifentanil consumption as the primary endpoint, with postoperative pain and inflammatory marker levels identified as the secondary endpoints.

Methods

Ethics approval and registration

This single-center, randomized study was conducted at Nara Medical University Hospital, Japan. Ethical approval was received from the Nara Medical University Certified Review Board on May 11, 2022 (identifier: nara0039). This study was registered prior to patient enrollment at the Japan Registry of Clinical Trials (https://jrct.niph.go.jp; identifier: JRCTs052220034; principal investigator: Nobuhiro Tanaka; date of registration: May 27, 2022). Written informed consent was obtained from all participants preoperatively. The protocol of this trial has been previously published [11]. There were no deviations from the methods described in the previously published study protocol. This study was conducted in accordance with the tenets of the Declaration of Helsinki.

Inclusion criteria

We included male patients (age: 20–85 years) with American Society of Anesthesiologists Physical Status 1–3 who were scheduled for robot-assisted laparoscopic radical prostatectomy (RARP).

Exclusion criteria

The exclusion criteria were as follows: preoperative chronic pain; regular intake of beta-blockers, oral steroids, or opioids; cardiac arrhythmia or an implanted pacemaker; and not having a suitable finger for measurements. Preoperative chronic pain was defined as continuous or intermittent pain over the previous 3 months or longer [12]. As there was only one measuring device (PMD-200™) at our institution, we also excluded patients with later entry times to the operating theater for cases where multiple operations were performed at the same time of day.

Allocation

Participants were randomly assigned to two groups in a 1:1 ratio using a web-based service (QuickCals, GraphPad, https://www.graphpad.com/quickcalcs/randomize1/; accessed on June 30, 2022) as follows: the NOL-directed analgesia management group (NOL group) or the conventional analgesia management group (control group). Information regarding the allocated group was concealed in a sealed envelope until the anesthesiologist opened the envelope on the day of surgery.

Study protocol

Both groups

All patients underwent RARP in the 25° Trendelenburg position using the AirSeal® insufflation system (SurgiQuest, Milford, CT, USA), with 8–10-mmHg pressure. Before anesthesia induction, the finger probe of PMD-200™ was attached to a finger of the arm contralateral to the arm with a non-invasive blood pressure cuff and a train-of-four (TOF) repetition monitor. After anesthesia induction with propofol (0.5–2 mg/kg), rocuronium (0.6–1.2 mg/kg), remifentanil, and fentanyl, all patients were maintained with sevoflurane 1–1.5% with a target of bispectral index of 40–60 and continuous rocuronium to induce deep muscle relaxation (TOF 0) throughout the surgery under the guidance of TOF repetition monitor. The method of opioid administration is described in detail below for each group. Vasopressors were administered in cases of hypotension, which was defined as a mean blood pressure (mBP) ≤ 60 mmHg. Ondansetron (4 mg) and acetaminophen (1000 mg or 15 mg/kg [if body weight < 50 kg]) were intravenously administered at the end of surgery. The use of steroids and beta-blockers was prohibited to avoid effects on inflammatory marker responses [13]. The patients were extubated after sufficient reversal

of sugammadex. Following extubation, all patients were transferred to the general ward and received intravenous fentanyl patient-controlled analgesia by CADD®-Solis PIB (Smiths Medical, St. Paul, MN, USA), with no basal flow, 1-mL bolus on demand, and a 10-min lock-out interval. Fentanyl concentrations were determined using the ideal body weight (IBW), calculated as $22 \times (\text{height in meters})^2$, with adjustments to 25 µg/kg for IBWs of 50–59.9 kg, 30 µg/kg for 60–69.9 kg, and 35 µg/kg for 70–79.9 kg. In addition, all patients received acetaminophen at 6-h intervals until 24 h postoperatively, with further administration on demand; moreover, nonsteroidal anti-inflammatory drugs were administered.

Control group

The administered remifentanil and fentanyl dose and timing were determined by the anesthesiologist in charge of hemodynamic evaluation. The PMD-200 screen was concealed, and the anesthesiologists could not view the NOL index.

NOL group

Figure 1 shows the perioperative flowchart. We determined the baseline remifentanil infusion rate and fentanyl dose using retrospective data on opioid consumption during RARP at our institution over the last 2 years. This was undertaken as the primary study objective was to compare the efficiency of NOL-directed opioid administration with that of conventional management. The mean remifentanil dose was approximately 0.18 µg/kg/min, with tracheal intubation and skin incisions requiring higher remifentanil doses. Therefore, we set the baseline remifentanil infusion rate as 0.2 µg/kg/min. The mean intraoperative fentanyl dose in our institution over the 2-year period was 350 µg. We developed a protocol whereby fentanyl was intermittently administered during periods of high invasiveness and at the time of wound closure.

After a bolus administration of 30 µg remifentanil and continuous baseline remifentanil infusion for 3 min, 0.5–2 mg/kg propofol, 150 µg fentanyl, and 0.6–1.2 mg/kg rocuronium were administered. Following anesthesia induction, the patients' tracheae were intubated, and the remifentanil infusion rate was decreased to 0.05 µg/kg/min. The remifentanil infusion rate increased to 0.2 µg/kg/min prior to skin incision, followed by bolus administration of 30 µg remifentanil and 100 µg fentanyl. Subsequently, the remifentanil dose was determined according to the administration protocol. Specifically, the remifentanil infusion rate was reduced by 0.03 µg/kg/min when the NOL index was ≤ 10 for over 30 s and increased by 0.03 µg/kg/min when the NOL index was ≥ 25 for over 30 s, followed by a bolus administration of 30 µg remifentanil. The infusion rate was maintained above 0.11 µg/kg/min [11]. The NOL index was reassessed 5 min after changing the infusion rate. If there was an unexpected increase in the NOL index during the 5-min interval and the attending anesthesiologist considered it as harmful for the patient, he/she considered deviating from the opioid protocol. An additional 100 µg of fentanyl was administered at the time of robot de-docking to relieve postoperative pain.

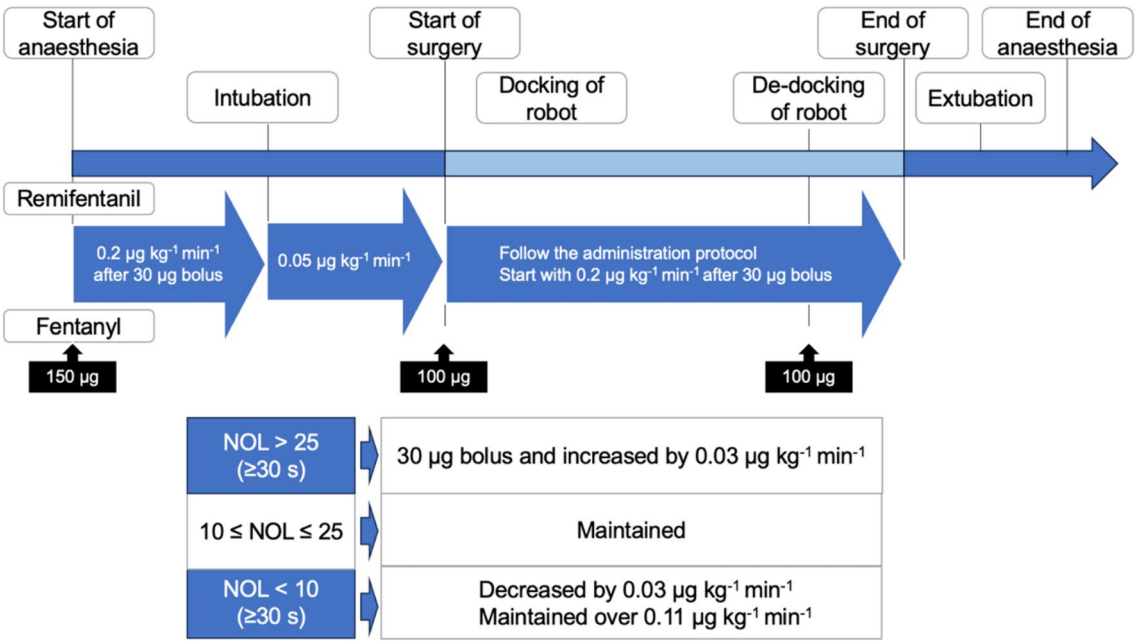

Fig. 1 The flowchart of the protocol for the NOL group. NOL, nociception level

Primary and secondary endpoints and data collection

The primary endpoint was the mean intraoperative remifentanil infusion rate per IBW. The secondary endpoints were as follows: (1) total amount of fentanyl consumption during anesthesia and postoperatively; (2) perioperative IL-6, CRP, and cortisol levels; (3) postoperative pain score (Numeric Rating Scale [NRS]; ranging from 0 [no pain] to 10 [the most intense pain imaginable]) at 2 h postoperatively and on postoperative days (PODs) 1, 2, 3, and 7; (4) incidence of postoperative nausea and vomiting (PONV) at 2 h postoperatively and on PODs 1, 2, and 3; (5) occurrence of chronic pain at 3 months postoperatively; (6) dose of vasoactive agents (phenylephrine, ephedrine, norepinephrine, atropine); and (7) duration of hypotension (mBP ≤ 60 mmHg), hypertension (systolic blood pressure ≥ 160 mmHg), bradycardia (heart rate < 40 beats/min), and tachycardia (hear rate > 100 beats/min).

Blood samples for measuring IL-6 and cortisol levels were collected by investigators and assessed using an electrochemiluminescence immunoassay. Data on preoperative baseline IL-6 and cortisol levels were collected before intubation. We collected blood samples to measure IL-6 levels immediately after the operation and on POD 1, while those to measure cortisol levels were collected immediately after the operation. Cortisol was not measured on POD 1 because it peaks at 0–4 h postoperatively [10]. Data on preoperative CRP levels were retrieved from electronic records, while CRP levels on POD 1 were determined using morning blood samples collected under the supervision of an urologist.

The pain NRS scores and PONV were evaluated via face-to-face interviews. Data regarding the consumption of opioids and other agents, details of surgery, results of routine blood tests, and complications were collected from electronic medical records. Patients completed the Japanese version of three questionnaires (Pain Catastrophizing Scale [PCS], Hospital Anxiety and Depression Scale [HADS], and World Health Organization Disability Assessment Schedule 2.0 [WHODAS 2.0]) on the day before the surgery [14–16]. The HADS, WHODAS 2.0, and NRS scores as occurrence of chronic pain were also completed 3 months postoperatively by mail. The PCS is a 13-item self-reported scale designed to assess catastrophic thinking related to pain. Each item has five responses with assigned values ranging from 0 to 4, with a total score of ≥ 30 points representing a clinically relevant level of catastrophizing [17]. The HADS is a 14-item self-administered questionnaire designed to screen hospital patients for anxiety and depression, with seven questions each addressing anxiety and depression. Each item has four responses with assigned values ranging from 0 to 3 in either ascending or descending order. The responses to all the questions pertaining to each mood were subsequently summated (total score: 0–21 points). The total WHODAS 2.0 score ranged from 0 to 48 points. It was converted into a percentage (0%, no disability; 100%, complete disability).

Sample size calculation

The sample size was calculated with reference to a previous meta-analysis, in which NOL-guided analgesia protocols reduced intraoperative remifentanil consumption (standardized mean difference [SMD]: -0.68; 95% confidence interval [CI]: – 1.13 to – 0.24; $p = 0.003$) [18]. In this study, we expected lower variability because we focused on one disease and procedure and solely used the NOL index. The estimated SMD was -0.8, and a sample size of 25 patients for each group was required to achieve a power of 80% with a significance level of 0.05. Considering a dropout rate of 10%, we enrolled 27 patients in each group. Moreover, the appropriateness of this SMD setting was found to be -0.87 in a recent meta-analysis on NOL [19].

Statistical analyses

Baseline characteristics are presented as means with standard deviations (SD) for continuous variables and as frequencies and proportions for categorical variables.

The mean intraoperative remifentanil infusion rates were calculated by dividing the total amount of intraoperative remifentanil usage by the duration of surgery and IBW. These infusion rates are presented as the mean with 95% CI and was assessed using Welch's *t* test since remifentanil consumption varies substantially depending on the anesthesiologist. The occurrence of PONV and chronic pain and hospitalization duration were evaluated using the Chi-square test. Other variables were evaluated using Student's *t* test. Changes in IL-6, cortisol, and CRP levels were evaluated using a mixed model for repeated measures (MMRM) considering the fixed effects of study group and time point (treated as a categorical variable). All statistical analyses were performed using SAS software (v9.4; SAS Institute Japan Ltd., Tokyo, Japan). The level of significance was set at $p < 0.05$.

Results

Participant characteristics

We recruited 73 patients between July 2022 and June 2023 (Fig. 2). Among them, we excluded 12 patients owing to failure to meet the inclusion criteria, six owing to conflicting surgical schedules, and one owing to the absence of a researcher. Accordingly, 54 patients were randomized and allocated to each group. Two patients in each group were

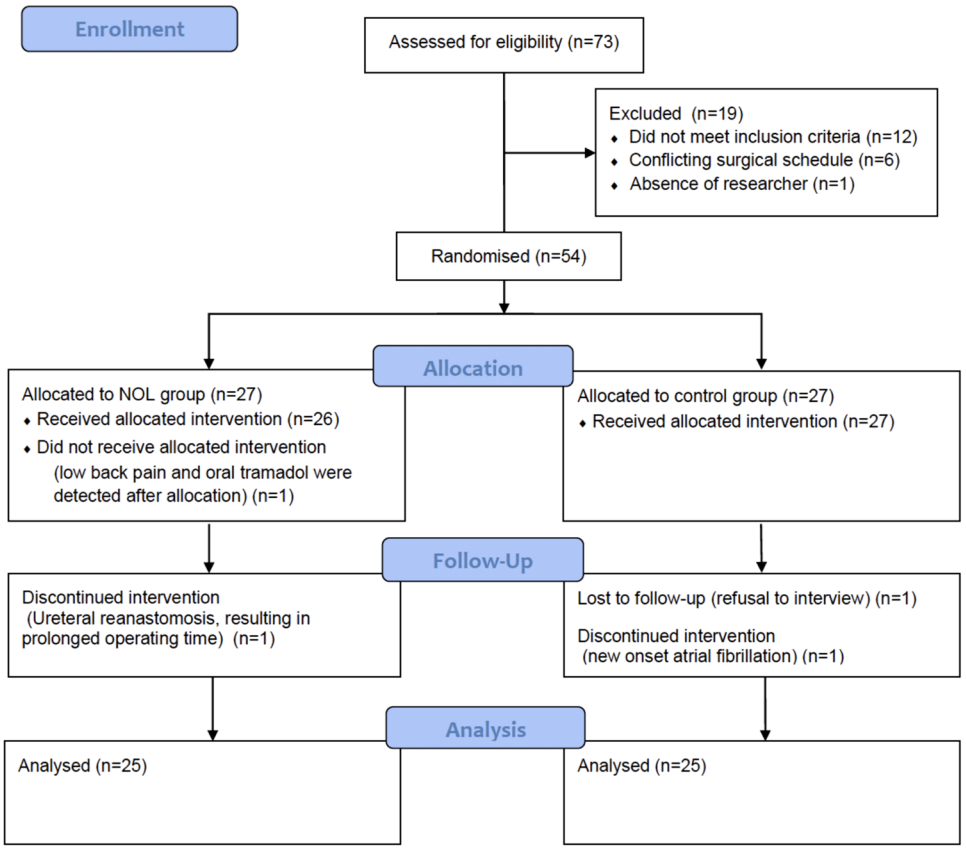

Fig. 2 Study enrollment. CONSORT diagram illustrating flow of participants enrolled, detailing numbers of participants included. *NOL* nociception level

excluded after allocation because of the reasons shown in Fig. 2. Finally, the data of 50 patients were analyzed. Patient characteristics and surgical data are shown in Table 1. No adverse events, such as intraoperative body movements or intraoperative arousal due to strict remifentanil titration, were observed. The NOL values accumulated every 5 s were divided into the categories "NOL < 10," "10 ≤ NOL ≤ 25," and "NOL > 25." The distribution of the intraoperative NOL values was subsequently averaged by group and displayed.

Primary outcome

The mean intraoperative remifentanil infusion rates were 0.13 (SD: 0.017) and 0.16 (SD: 0.049) μg/kg/min for the NOL and control groups, respectively, indicating a decrease of – 0.038 μg/kg/min (95% CI: -0.059 to – 0.017, $p = 0.001$) in the NOL group (Table 2, Fig. 3).

Secondary outcomes

All results regarding the secondary outcomes are shown in Table 2. The mean IL-6 levels at the end of surgery were 66.24 (SD: 58.2) and 72.05 (SD: 60.2) pg/mL for the NOL and control groups, respectively (mean difference: – 5.8, 95% CI: – 38.39 to 26.75). The mean IL-6 levels on POD 1 were 49.29 (SD: 24.76) and 67.14 (SD: 51.73) pg/mL, respectively (mean difference: – 17.85, 95% CI: – 40.16 to 4.46; Fig. 4A). MMRM also revealed no significant differences between both the groups with respect to cortisol and CRP levels (Fig. 4B, C). Online Resource 1 displays the association between the individual remifentanil dose during surgery and levels of serum inflammatory markers. Regarding intraoperative events, the frequency of ephedrine use was lower in the NOL group than in the control group; however, there were no significant between-group differences in the time of events, including hypotension. Regarding the pain NRS scores, the NOL group had significantly lower pain at rest 2 h postoperatively and on movement at all time points up to POD 3 (Fig. 4D, E). There were no significant between-group differences in the incidence of PONV, the postoperative amount of fentanyl used or requested, and the incidence of post-surgical pain at 3 months postoperatively.

Discussion

In this study, we developed a protocol ensuring a minimum flow of remifentanil, used NOL for the first time in RARP, and evaluated invasive stress using multiple inflammatory markers. Our findings demonstrate that NOL-directed analgesic management reduced remifentanil consumption by 20%, NRS scores at rest 2 h postoperatively, and NRS

Table 1 Patient characteristics

	NOL group ($n=25$)	Control group ($n=25$)
Patient characteristics		
Age (years)	68 (6.6)	68 (5.8)
Weight (kg)	69.9 (9.7)	64.7 (8.6)
Height (cm)	169.8 (7.4)	166.5 (4.6)
BMI (kg/m^2)	24.2 (3.2)	23.3 (2.8)
ASA-PS, *n* (%)		
I	3 (12.0)	3 (12.0)
II	21 (84.0)	22 (88.0)
III	1 (4.0)	0 (0.0)
Comorbidity, *n* (%)		
Hypertension	15 (60.0)	12 (48.0)
Diabetes	4 (16.0)	4 (16.0)
Chronic kidney disease	2 (8.0)	3 (12.0)
Preoperative assessments		
WHODAS 2.0 (%)	4.3 (7.1)	5.0 (5.2)
PCS	22.6 (9.8)	20.9 (11.5)
HADS-total	10.0 (4.3)	10.3 (5.9)
HADS-A	4.8 (2.9)	4.8 (3.6)
HADS-D	5.2 (2.7)	5.5 (3.4)
Surgical data		
Procedure, *n* (%)		
Standard RARP	11 (44.0)	14 (56.0)
RS-RARP	14 (56.0)	11 (44.0)
Lymph node dissection, *n* (%)		
Yes	12 (48.0)	14 (56.0)
No	13 (52.0)	11 (44.0)
Duration of surgery (min)	261 (78)	259 (63)
Duration of anesthesia (min)	317 (79)	315 (64)
NOL data		
NOL < 10 (%)	78.0	69.0
10 ≤ NOL ≤ 25 (%)	18.9	25.1
NOL > 25 (%)	3.1	5.9

Data are presented as means (standard deviations) or counts with proportions (occupancy)

ASA-PS American Society of Anesthesiologists physical status; *HADS* Hospital Anxiety and Depression Scale; *IL-6* interleukin-6; *NOL* nociception level; *PCS* Pain Catastrophizing Scale; *RARP* robot-assisted radical prostatectomy; *RS-RARP* Retzius space-sparing robot-assisted radical prostatectomy; *SD* standard deviation, *WHO-DAS2.0* World Health Organization Disability Assessment Schedule 2.0

scores on movement up to POD 3 without an increase in stress marker levels.

Funcke et al. reported that while the use of NOL and pupillometry could decrease the amount of intraoperative remifentanil compared with the use of conventional management, they observed increased cortisol levels at intraoperative remifentanil flow rates of ≤ 0.2 μg/kg/min, particularly at ≤ 0.1 μg/kg/min [6]. We considered that a minimum flow rate should be ensured for the proper use of NOL and developed a protocol to maintain a minimum flow rate of > 0.11 μg/kg/min, which was inspired by a previously reported protocol that had allowed zero-remifentanil and led to increased cortisol levels. Our NOL-directed strategy led to a 20% reduction in remifentanil use and still did not increase the levels of stress hormones or inflammatory cytokines; however, the difference in dosage was only 0.038 μg/kg/min. It remains unclear whether this difference is clinically significant. Furthermore, numerous studies using nociceptive monitoring to control intraoperative remifentanil administration have been successful in reducing remifentanil consumption by 28–45%; however, there have been no reported improvements in early postoperative NRS scores [6, 20, 21]. Contrastingly, we observed an improvement in postoperative pain NRS scores. This could be attributed to the protocol involving a mixture of intraoperative fentanyl and remifentanil. Many centers in our country, including ours,

Table 2 Primary and secondary outcomes

	NOL group ($n=25$)	Control group ($n=25$)	Mean difference (95% CI)	P value
Intraoperative opioid amount				
Remifentanil (μg/kg/min)	0.125 (0.017)	0.162 (0.049)	– 0.038 (– 0.059 to – 0.017)	0.001
Fentanyl (μg/kg)	5.548 (0.481)	5.768 (0.623)	– 0.220 (– 0.537 to 0.097)	0.17
Laboratory data				
IL-6 (pg/mL)				
Preoperative	1.5 (2.05)	1.14 (0.69)		
The end of surgery	66.24 (58.2)	72.05 (60.2)	– 5.8 (– 38.39 to 26.75)	0.72
POD 1	49.29 (24.76)	67.14 (51.73)	– 17.85 (– 40.16 to 4.46)	0.12
CRP (mg/dL)				
Preoperative	0.09 (0.09)	0.14 (0.35)		
The end of surgery	4.45 (1.27)	5.38 (1.98)	– 0.94 (– 1.88 to 0.01)	0.053
POD 1	4.23 (2.59)	4.94 (2.45)	– 0.71 (– 2.14 to 0.72)	0.32
Cortisol (μg/dL)				
Preoperative	11.83 (5.01)	10.96 (3.38)		
At end of surgery	9.12 (7.38)	6.33 (5.36)	2.79 (– 0.87 to 6.46)	0.13
Postoperative data				
NRS scores at rest				
2 h postoperatively	2.4 (1.9)	4.0 (1.9)	– 1.6 (– 2.7 to – 0.5)	0.005
POD 1	1.2 (1.2)	1.4 (1.2)	– 0.2 (– 0.9 to 0.5)	0.492
POD 2	1.2 (0.8)	1.4 (1.2)	– 0.2 (– 0.8 to 0.4)	0.482
POD 3	0.6 (0.9)	1.0 (1.0)	– 0.3 (– 0.9 to 0.2)	0.247
POD 7	0.4 (1.2)	0.4 (0.6)	0.0 (– 0.6 to 0.5)	0.878
NRS scores on movement				
2 h postoperatively	3.8 (1.9)	5.8 (1.9)	– 2.0 (– 3.1 to – 0.9)	0.001
POD 1	3.4 (0.3)	4.6 (0.3)	– 1.2 (– 2.1 to – 0.3)	0.014
POD 2	3.2 (1.3)	4.6 (2.0)	– 1.4 (– 2.3 to – 0.4)	0.007
POD 3	2.4 (1.2)	4.1 (1.5)	– 1.7 (– 2.5 to – 0.9)	<0.001
POD 7	1.2 (1.5)	1.7 (1.4)	– 0.5 (– 1.3 to 0.3)	0.245
PONV				
2 h postoperatively	4 (16%)	7 (28%)		0.496
POD 1	3 (12%)	4 (16%)		1.000
POD 2	1 (4%)	2 (8%)		1.0
POD 3	0 (0%)	0 (0%)		N/A
Postoperative request for Fentanyl PCA (times)	16.2 (17.0)	25.9 (25.3)	– 9.7 (– 21.9 to 2.6)	0.119
POD 0	4.7 (5.3)	5.7 (5.9)	– 0.96 (– 4.1 to 2.2)	0.546
POD 1	5.8 (5.9)	9.4 (11.2)	– 2.5 (– 8.8 to 1.4)	0.152
POD 2	4.6 (0.9)	8.9 (1.8)	– 3.1 (– 7.1 to 0.9)	0.129
Postoperative fentanyl (μg/kg)	7.9 (7.9)	12.0 (11.6)	– 4.1 (– 9.8 to 1.5)	0.147
Duration of hospitalization (days)	9 (9–9)	9 (9–9)		0.470
Three months later				
Chronic pain, n (%)	2 (8%)	5 (20%)		0.417
WHODAS 2.0 (%)	9.3 (11.8)	9.8 (10.0)	– 0.5 (– 6.7 to 5.7)	0.872
HADS				
HADS-total	8.0 (5.9)	9.1 (5.7)	– 1.0 (– 4.4 to 2.2)	0.514
HADS-A	3.1 (3.2)	4.0 (3.1)	– 0.9 (– 2.7 to 0.9)	0.305
HADS-D	4.9 (3.4)	5.0 (3.4)	– 0.2 (– 2.1 to 1.8)	0.868
Intraoperative data				
Tachycardia (min)	0.0 (0.0)	0.1 (0.4)	– 0.1 (– 0.3 to 0.1)	0.179
Bradycardia (min)	0.4 (1.8)	0.0 (0.2)	0.4 (– 0.4 to 1.1)	0.326

Table 2 (continued)

	NOL group ($n=25$)	Control group ($n=25$)	Mean difference (95% CI)	P value
Hypertension (min)	1.4 (2.7)	1.7 (3.0)	– 0.3 (– 1.9 to 1.3)	0.692
Hypotension (min)	8.9 (17.6)	11.9 (25.8)	– 2.2 (– 14.7 to 10.3)	0.726
Phenylephrine (μg)	32.0 (130.6)	118.0 (233.5)	– 86.0 (– 193.5 to 21.6)	0.115
Ephedrine (mg)	8.2 (6.6)	19.1 (3.7)	– 10.9 (– 18.8 to 3.0)	0.008
Nicardipine (mg)	0.2 (0.5)	0.1 (0.4)	0.0 (– 0.1 to 0.3)	0.737
Atropine (mg)	0.0 (0.0)	0.0 (0.0)	0.0	N/A
Deviation from protocol	0 (0%)			

Values are presented as means (standard deviations), medians (interquartile ranges), and mean differences (95% confidence intervals [CIs]) with P values. Tachycardia and bradycardia are defined as a heart rate > 100 beats/min and < 40 beats/min, respectively. Hypertension and hypotension are defined as a systolic blood pressure > 160 mmHg and mean blood pressure < 60 mmHg, respectively

CRP C-reactive protein; *HADS* Hospital Anxiety and Depression Scale; *IL-6* interleukin-6; *N/A* not available; *NOL* nociception level; *NRS* Numerical Rating Scale; *PCA* patient-controlled analgesia; *POD* postoperative day; *PONV* postoperative nausea and vomiting; *WHO-DAS2.0* World Health Organization Disability Assessment Schedule 2.0

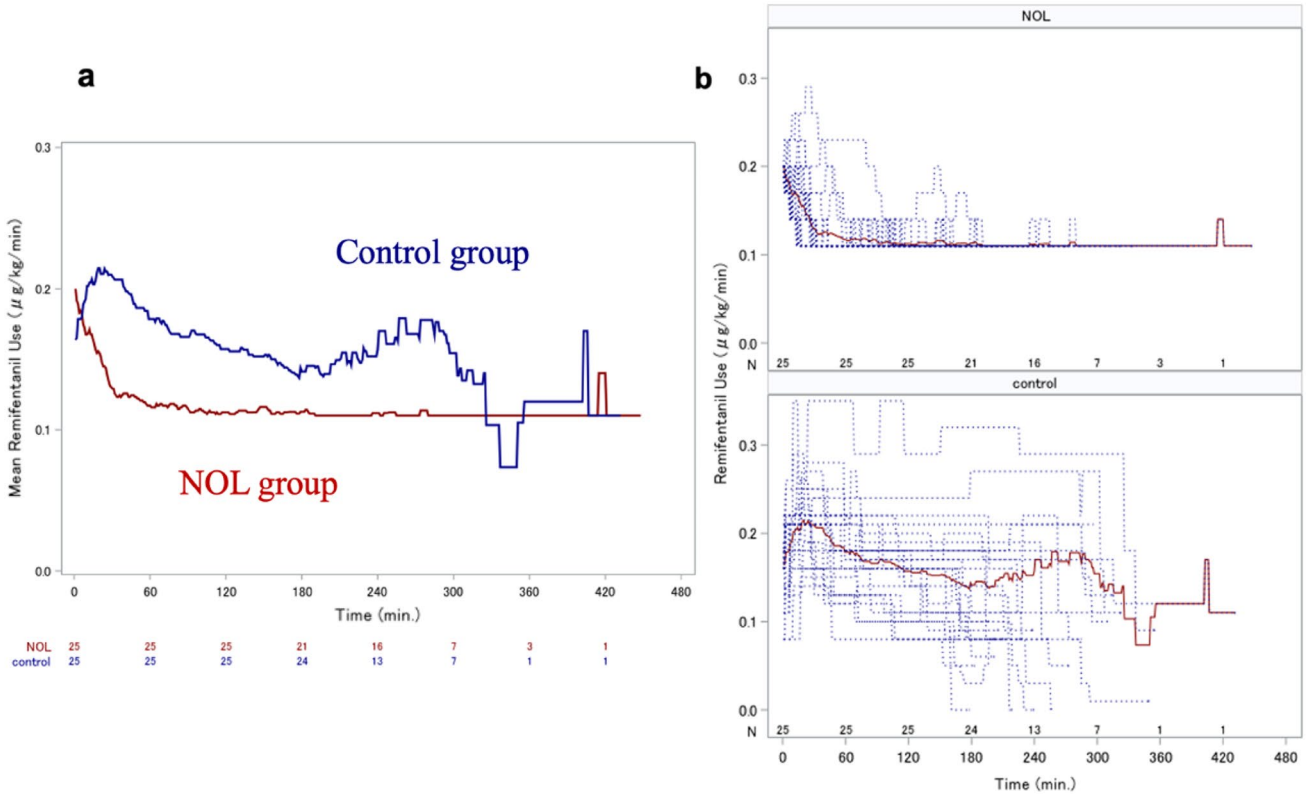

Fig. 3 Trends in remifentanil flow rates. **A** The mean remifentanil flow rate in the NOL and control groups. **B** Spaghetti plot graph representing the change in remifentanil flow rate by individual patient in both groups. The vertical axis represents the mean remifentanil flow rate and the horizontal axis represents the operation time. The blue dotted line shows the change in remifentanil dose flow rate for each patient and the red line shows the mean. In the NOL group, a flow rate of 0.11 μg/kg/min was reached in all the cases. The total number of remifentanil flow rate changes (median [interquartile range]) in the NOL and control groups was 5 [3–7.5] and 5 [4–8] times, respectively. No significant differences were observed ($P=0.271$). The number of times (median [interquartile range]) the remifentanil flow rate was increased according to increasing NOL (median [interquartile range]) was 1 [0–3] in the NOL group. *NOL* nociception level

do not have a post-anesthetic care unit [22]. Accordingly, we had to use fentanyl in combination to ensure a sufficient opioid effect-site concentration without causing respiratory depression and intense pain to return the patient to the ward immediately after extubation. We initially considered this to be a major limitation that impeded the interpretation of

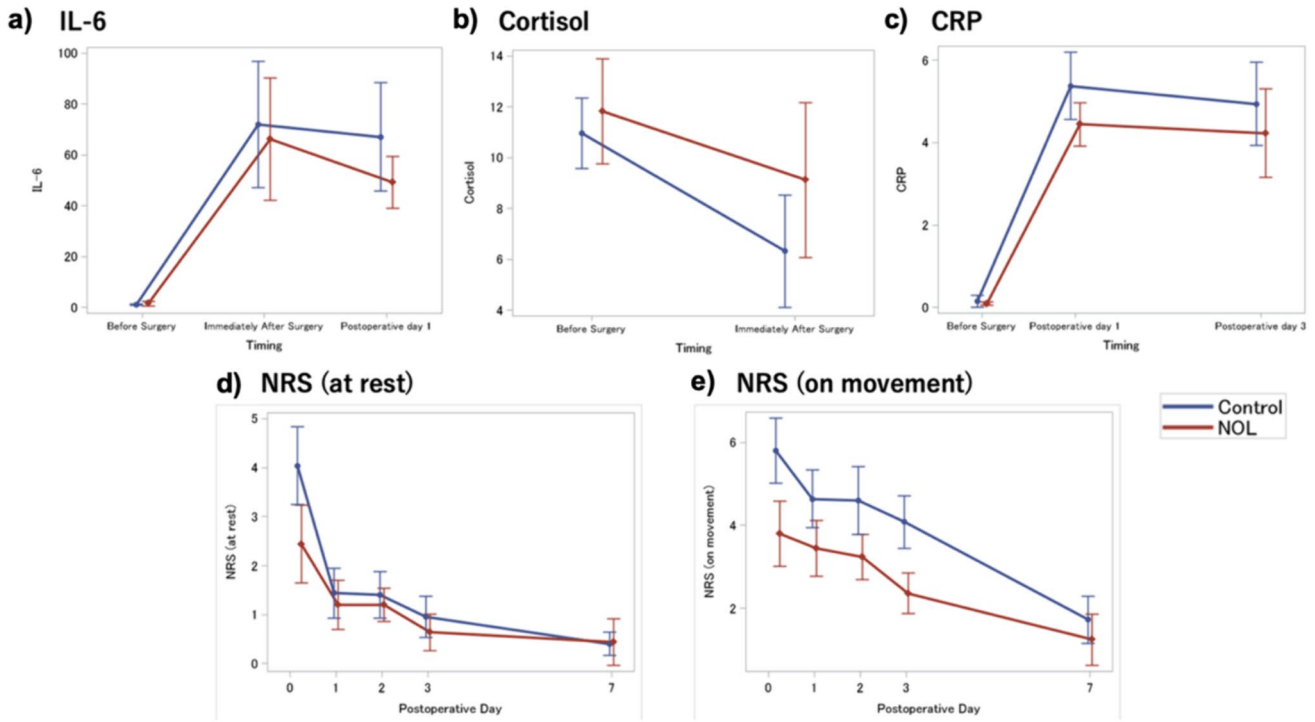

Fig. 4 Trends in serum inflammatory markers level and in the NRS pain scores. **A** Interleukin-6, **B** cortisol, **C** C-reactive protein, **D** NRS pain scores at rest, and **E** NRS scores on movement. *CRP* C-reactive protein; *IL-6* interleukin-6; *NRS* Numerical Rating Scale

the results. However, most studies on intraoperative fentanyl use with nociceptive monitoring have reported improvement in postoperative pain scores rather than opioid reduction [5, 23, 24]. Furthermore, precise control of intraoperative nociception using opioids may enhance medium- and long-term outcomes [9]. We believe that our results were achieved by a combination of remifentanil with fentanyl and adjusting the opioid dose by NOL monitoring to not only reduce remifentanil but also control nociception sufficiently. In fact, the percentage of time with NOL > 25 relative to operative time was 5.9% in the intervention group with higher intraoperative remifentanil use, compared to 3.1% in the NOL group.

Previous studies have used cortisol levels as the stress-related endpoint in NOL-directed opioid management [6]. In this study, we also measured the IL-6 levels to assess invasiveness as cortisol levels exhibit diurnal variations and are less accurate than IL-6 or CRP levels [10]. We consider this to be another strength of the study. Elevated IL-6 levels on POD1 are reportedly associated with complications in abdominal surgery [25]. However, in our study, there were no statistically significant between-group differences in the levels of these markers. The clinical importance of the approximately 25% reduction in the IL-6 levels in the NOL group may warrant further investigation.

There has been increasing interest in chronic post-surgical pain (CPSP) [26, 27]. A previous study reported that the mean NRS value at 12 weeks after RARP was 0.48, [28] consistent with our findings (0.48 and 0.16 in the control and NOL groups, respectively). The prevalence of CPSP was not mentioned in the previous study; however, it was 14% in our study. Future studies are needed to determine whether nociceptive monitoring can be used to prevent CPSP.

Limitations

The study had some limitations. First, our focus was solely on RARP conducted at a single institution, and we did not assess the effectiveness of nociceptive monitors other than NOL. Second, there is no accepted gold standard for anesthetic management in the control group [6, 29]. Third, it is important to consider the appropriateness of the minimum flow rate of remifentanil. While Funcke et al. used NOL for radical retropubic prostatectomy, [6] we applied it to RARP, which may have been less invasive [30]. Our protocol uses fentanyl in combination, and a flow rate of remifentanil of 0.11 μg/kg/min was reached in all cases in the NOL group. The percentage of time showing NOL < 10 in the NOL group was 78%, compared with 69% in the control group. This suggests that the minimum remifentanil flow rate could have been further reduced. Thus, the remifentanil sparing effect may have been underestimated. However, we were unable to examine the minimum flow rate that was truly necessary in RARP from an ethical and safety standpoint. Even if the NOL suggests a "relative overdose of opioid," a minimum

flow rate setting to prepare for abrupt changes in invasiveness should be considered for each surgical procedure in the future.

Conclusion

Our findings demonstrated that NOL-directed analgesic management reduced remifentanil consumption by 20% compared with conventional analgesia management. Moreover, NOL-directed management did not increase the levels of IL-6, CRP, or cortisol when compared with the levels in the control group. This protocol also resulted in an improvement in the NRS scores at rest 2 h postoperatively and in the NRS scores on movement up to POD 3. Utilizing NOL as an indicator, it is suggested that adjusting opioid dosage on a moment-to-moment basis while ensuring a minimal flow rate of remifentanil may help mitigate patient invasiveness.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00540-024-03365-x.

Acknowledgements We would like to thank Dr. Keiko Uemura (Department of Anesthesiology, Nara Medical University, Kashihara, Japan), Ms. Miki Uyama, and Dr. Takumi Hirata (Institute for Clinical and Translational Science, Nara Medical University, Kashihara, Japan) for their monitoring in the conduct of this study. We would also like to thank the staff of the Department of Urology, Nara Medical University, and the nursing staff of Ward "C4" of Nara Medical University Hospital for their cooperation in this study. Finally, we are grateful to R. Takashima, M. Taketsuna, M. Kojima, K. Hiro, S. Suzuki, and S. Kasama (Institute for Clinical and Translational Science, Nara Medical University Hospital, Kashihara, Japan) for their support in starting the study.

Authors' contributions Nobuhiro Tanaka: This author helped in study design, data collection, writing of the first draft of the paper, manuscript revision, and critical appraisal and approval of the final version of the manuscript. Yuma Kadoya: This author helped in study design, patient recruitment, data collection, writing of the first draft of the paper, manuscript revision, and critical appraisal and approval of the final version of the manuscript. Takanori Suzuka: This author helped in data collection and critical appraisal and approval of the final version of the manuscript. Takayuki Yamanaka: This author helped in data collection and critical appraisal and approval of the final version of the manuscript. Mitsuru Ida: This author helped in manuscript revision, supervision of the study, and critical appraisal and approval of the final version of the manuscript. Yusuke Naito: This author helped in manuscript revision and critical appraisal and approval of the final version of the manuscript. Naoki Ozu: This author helped in data analysis and critical appraisal and approval of the final version of the manuscript. Shunta Hori: This author helped in patient recruitment, manuscript revision, and critical appraisal and approval of the final version of the manuscript. Masahiko Kawaguchi: This author helped in supervision of the study and critical appraisal and approval of the final version of the manuscript.

Funding This work was supported by a grant from the Japan Society for the Promotion of Science (grant number JP 22K16606); and Nara Medical University Clinical Research Grant Program (grant number 21–003). The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Data availability The data that support the findings of this study is available from the corresponding author upon reasonable request.

Declarations

Conflict of interest None.

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