Original Article

Feasibility of opioid-free anesthesia in laparoscopic radical prostatectomy: A retrospective, quasi-experimental study

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Abstract

Background and Aims: Opioid□free anesthesia (OFA) provides adequate analgesia minimizing opioids. OFA has not been evaluated in laparoscopic radical prostatectomy (LRP). Our aim was to evaluate OFA feasibility and its effectiveness in LRP.

Material and Methods: A quasi-experimental retrospective study of 55 adult patients undergoing LRP was performed from September 2020 until December 20223. Predefined protocols for either opioid-based anesthesia (OBA; with continuous remifentanil infusion) or OFA (continuous lidocaine, dexmedetomidine, and ketamine infusion) were followed. In both groups, wound infiltration was performed before skin incision. Primary outcome was postoperative pain management (numerical rating scale [NRS]) in the first 24 postoperative hours. Secondary outcomes were opioid consumption, start to sitting and ambulation, postoperative complications, and length of hospital stay.

Results: OFA protocol patients had better median pain scores during movement at 1, 18 and 24 h, that is, 1 (interquartile range [IQR] 0–3) versus 2.5 (IQR 0–4), $P = 0.047$; 0 (IQR 0–1) versus 1 (IQR 0–2), $P = 0.017$; and 0 (IQR 0–0.25) versus 1 (IQR 0–2), $P = 0.013$, respectively. At 6 and 12 h, there were no statistically significant differences, that is, 0.5 (IQR 0–2) versus 1 (IQR 0–2), $P = 0.908$ and 1 (IQR 0–2) versus 0.5 (IQR 0–2), $P = 0.929$, respectively. Lower morphine requirements were recorded in the first 18 and 24 postoperative hours, that is, 0 (IQR 0–0) versus 1 (IQR 0–2.75) mg, $P = 0.028$ and 0 (IQR 0–2) versus 1.5 (IQR 0–3) mg, $P = 0.012$, respectively. Start to sitting and ambulation occurred earlier in the OFA group ($P = 0.030$ and $P = 0.002$, respectively). Linear regression showed that ambulation was independently associated with the analgesic technique ($P = 0.034$). Only one patient had postoperative nausea and vomiting (PONV) and belonged to the OBA group. There was no difference in total complications or the length of stay.

Conclusion: In this study, OFA strategy was found to be safe, feasible, and provided adequate analgesia, minimizing the use of postoperative opioids, and was independently associated with earlier ambulation.

Keywords: Analgesia, enhanced recovery after surgery, laparoscopic prostatectomy, opioid-free, remifentanil, morphine, ketamine, dexmedetomidine, lidocaine, postoperative Pain

Introduction

Pain significantly affects the postoperative outcomes, leading to complications, prolonged hospital stay, and patient discomfort.[1] Effective pain management is crucial for optimal recovery.

The enhanced recovery after surgery (ERAS)[1] guidelines recommend minimally invasive surgical approaches and comprehensive pain relief strategies focused on nonopioid analgesics. These approaches enhance pain control, minimizing both opioid consumption and associated side effects.[2] In addition, the widespread utilization of opioids in surgical care has contributed to "opioid epidemic."[3] Surgery

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often exposes patients to opioids, with an estimated 5%–8% of opioid-naïve individuals transitioning to chronic use following a single prescription.[4]

Although laparoscopic radical prostatectomy (LRP) is a minimally invasive treatment for prostate cancer,[5] patients still experience pain after the procedure, particularly on the first postoperative day.[6]

Opioid-free anesthesia (OFA) strategy aims to provide effective pain relief using nonopioid agents like α2 agonists or local anesthetics, making possible a drastic reduction in perioperative opioid use.[7-9] OFA has been evaluated in various types of surgeries,[10-12] but in LRP, it remains unexplored.

Our aim was to evaluate the analgesic efficacy of OFA in the first 24 h after LRP by analyzing the numeric rate scale (NRS) values and opioid consumption compared to standard opioid-based anesthesia (OBA).

Material and Methods

This study was performed according to the Declaration of Helsinki, after receiving Institutional Review Board approval on March 9, 2023, which allowed a waiver of informed consent, given the retrospective nature of the study (Bellvitge University Hospital, protocol no. EOM007/23, March 9, 2023). Results are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.

A previous study showed that LRP can be carried out using general anesthesia combining simple surgical wound infiltration with local anesthetics and continuous intraoperative remifentanil infusion while almost completely avoiding postoperative opioids and optimal acute postoperative pain control can be achieved.[13] In an effort to further reduce opioid use and improve postoperative pain control, we introduced OFA for general and breast surgery procedures in November 2019 and expanded its use to patients undergoing LRP in June 2022 based on a positive experience in other surgeries.[12] All patients undergoing LRP since June 2022 received OFA. All other components of the care management pathway remained unchanged in OFA compared to the standard (OBA) patients.

Exclusion criteria were age below 18 years; anesthesia American Society of Anesthesiologists Physical Status Classification System (ASA) score ≥IV; body mass index (BMI) ≥35 kg/m^2; history of allergy to local anesthetic, opioid, paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), or metamizole; chronic opioid use; conversion to open surgery; and patients who have contraindications to OFA (atrial or auriculoventricular sinus blockade, autonomic system disorders, acute coronary ischemia, or unstable hypovolemic shock).[14]

Baseline demographic and clinical characteristics of the patients and the surgical procedures performed were retrieved from medical records.

The primary endpoint was efficacy of pain control during the first 24 h following surgery using NRS at rest (NRSr) and during movement (NRSm; cough in postanesthesia care unit [PACU]) at 1, 4, 6, 12, 18, and 24 h postoperatively. Patients rated their pain from 0 (indicating no pain) to 10 (indicating worse pain imaginable) according to the previously validated NRS scale. The morphine milligram equivalent (MME) administered during the first 24 h as rescue medication in case of inadequate pain control was also recorded to determine the analgesic efficacy.

Secondary outcomes were technique-related complications and adverse effects, intraoperative hemodynamic events (hypotensive and/or hypertensive events, which were defined as a decrease in systolic blood pressure 20% below the baseline or an increase in systolic blood pressure 20% above the baseline, respectively), length of surgery, postoperative nausea and vomiting (PONV), time to sitting and ambulation, in-hospital postoperative complications according to the Clavien–Dindo classification (CDC)[15] and the Comprehensive Classification Index (CCI),[16] and the length of stay.

Data was obtained through retrospective review of medical records, including anesthesia sheets, operative reports, PACU records, and hospitalization ward daily notes.

All surgical procedures were carried out by the same group of specialized urologists and anesthesiologists. Both the OBA and the OFA anesthetic protocols were predefined. The OBA protocol consisted of induction with intravenous (IV) fentanyl (1.5 μg/kg), propofol (1.5–2 mg/kg), and rocuronium (0.6 mg/kg), and subsequently, IV remifentanil infusion at 0.1 μg/kg/min was started. While the OFA protocol was according to the French protocol by Beloeil *et al.*,[17] which included induction with IV lidocaine (1.5 mg/kg), propofol (1.5–2 mg/kg), ketamine (0.25 mg/kg), and rocuronium (0.6 mg/kg). Before skin incision, IV magnesium sulfate (40 mg/kg) in 100 ml of normal saline solution was administered as a single dose, as well as IV continuous lidocaine (1.5 mg/kg/h), ketamine (0.25 mg/kg/h), and dexmedetomidine (0.7 μg/kg/h) infusions were administered. In both groups, IV continuous infusions were continued until

wound closure. Before skin incision, two syringes containing 40 ml of 0.375% ropivacaine were prepared and given to the urologist, who infiltrated the subcutaneous tissues of the incision sites (15 ml at the mini-laparotomy site and 25 ml distributed at the trocar sites).

Anesthesia was maintained using propofol target-controlled infusion to achieve a patient state index (PSI) between 25 and 50, and rocuronium infusion at 0.6 mg/kg/h was administered to ensure muscle relaxation. No additional analgesics were administered during surgery.

All patients received PONV prevention with IV dexamethasone (4 mg) after induction of anesthesia and IV ondansetron (4 mg) 30 min before the end of surgery. After wound closure, residual neuromuscular blockade was antagonized with neostigmine (0.05 mg/kg) and atropine (0.02 mg/kg), and tracheal extubation was performed when patients reached a regular standard of spontaneous breathing. Subsequently, patients were transferred to PACU and were kept in observation for 4 h.

All patients were prescribed a standardized multimodal nonopioid analgesic regimen for the postoperative period, which included IV paracetamol (1 g/8 h), IV NSAIDs (dexketoprofen 50 mg/8 h; not administered in case of renal failure), and IV metamizole (2 g/8 h). IV morphine (2 mg every 20 min as needed for NRS >3) was prescribed as the rescue medication in case of inadequate pain control. After 4 h of observation in PACU, if the clinical parameters permitted, oral intake was started and patients were transferred to the hospital ward, where our hospital's acute pain team carried out the protocol-driven follow-up.

Postoperative complications were considered if they occurred during hospital stay after surgery. PONV was treated with on-demand IV ondansetron (4 mg/8 h as needed) during the entire postoperative period. On the second postoperative day, if oral intake was tolerated, multimodal analgesia was changed to oral medications: paracetamol (1 g/8 h) and metamizole (575 mg/8 h) or dexketoprofen (25 mg/8 h) in all patients (depending on their renal function). If despite this, the patient reported NRS >3 at rest, oral tramadol (50 mg) was administered as needed in both groups. Tramadol consumption was calculated and reported in MME.

Analgesia prescribed at discharge from the hospital was oral paracetamol (1 g/8 h) in all patients.

Statistical analysis

Results are reported as median (interquartile range [IQR]) or mean (standard deviation [SD]) for quantitative data and percentage or rank for qualitative data depending upon the distribution of data. Kolmogorov–Smirnov test was run to evaluate data distribution. The Mann–Whitney U test was used to compare differences in the quantitative data, and the Pearson Chi-square test was used for categorical data. Fisher's exact test was applied in place of the Chi-square test when the cell count was less than 5. A multivariate analysis using linear regression was performed to identify which factors were associated with start to sitting and ambulation. A multivariate P value of less than 0.05 was considered statistically significant and an independent predictor. Measures of effect size were reported as 95% confident intervals (CIs). All P values are two sided. P value <0.05 was considered statistically significant. Statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS) v 22.0 (SPSS Inc, Chicago, IL, USA).

Results

From September 2020 to December 2022, a total of 55 patients were included: 28 (50.9%) patients received OBA and 27 (49.1%) received OFA. No patients were excluded due to conversion to open surgery. Baseline characteristics were similar in both groups, except for age; patients were younger in the OFA group ($P = 0.013$). Patient characteristics are summarized in Table 1. Intraoperative hemodynamic management, surgical features, and length of surgery are detailed in Table 2. No hypotensive events were observed during surgery. No patient experienced complications related to wound infiltration, and there were no intraoperative events attributable to the systemic effects of local anesthetics in the OFA group. Blood products were not administered during surgery in any group.

Pain scores during movement were significantly better in the OFA group than in the OBA group at three time points in the first 24 hours: median NRSm at 1 h was 1 (IQR 0–3) versus 2.5 (IQR 0–4), $P = 0.047$; at 18 h was 0 (IQR 0–1) versus 1 (IQR 0–2), $P = 0.017$; and at 24 h was 0 (IQR 0–0.25) versus 1 (IQR 0–2), $P = 0.013$, respectively. Pain scores at rest and other timepoints during movement were not significantly different between the two groups [Figures 1 and 2, respectively].

The patients in the OFA group required less use of rescue MME during the first 24 postoperative hours [Table 3]. There were no postoperative systemic side effects related to the systemic effects of local anesthetics in the OFA group.

Five patients showed postoperative complications during the entire hospitalization period. The observed complications were mild (Clavien–Dindo grade 2), and the difference

in the incidence of overall complications between the two groups was not statistically significant ($P = 0.352$). CCI was also similar between groups: 0 (IQR 0–0) in the OBA group versus 0 (IQR 0–0) in the OFA group ($P = 0.171$). In the OBA group, there were three cases of hemorrhage requiring transfusion of blood products and one case of bladder perforation, which did not require surgical intervention. PONV was very rare in both groups, with only one patient in the OBA group experiencing PONV. In the OFA group, one patient had an intra-abdominal infection, which was managed conservatively with antibiotics.

The analysis of secondary outcomes is shown in Table 4 When multivariate analysis was performed, analgesic technique was independently associated with start to ambulation (95% IC: -14.2 (-27.3 to -1.1), $P = 0.034$), while the time of surgery ($P = 0.504$), MME requirement in the first 18 postoperative hours ($P = 0.574$), and age ($P = 0.875$) were not independently associated. When start to sitting was analyzed, the analgesic technique ($P = 0.145$), as well as the time of surgery ($P = 0.817$), MME requirement in the first 18 postoperative hours ($P = 0.429$), and age ($P = 0.750$) were not independently associated.

Discussion

In our study, the OFA regimen was associated with better analgesia during movement in the first 24 postoperative hours (1, 18, and 24 h postoperatively) in comparison to the OBA protocol, leading to earlier mobilization and less rescue opioid consumption. OFA has recently been gaining recognition as a valuable strategy in different types of surgery;[10-12] however, it has not been formally evaluated in laparoscopic prostate surgery.

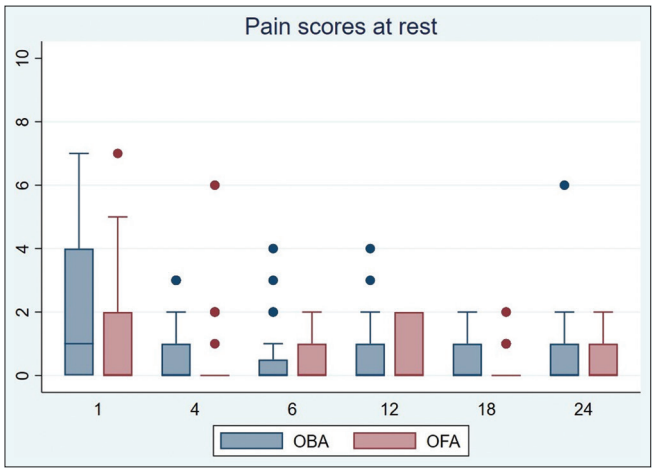

Figure 1: NRS scores at rest in the first 24 postoperative hours in the opioid‐free and opioid‐based anesthesia groups. The horizontal axis shows the time (postoperative hours), and the vertical axis shows the NRS scores. Median (line within box), interquartile range (box), and range (error bars) are shown. NRS = numeric rate scale, OBA = opioid-based anesthesia, OFA = opioid-free anesthesia

Table 1: Demographic and clinical characteristics

	OBA (*n*=28)	OFA (*n*=27)	*P*
ASA			
I	1 (3.6%)	1 (3.7%)	0.558
II	26 (92.9%)	1 (385.2%)	
III	1 (3.6%)	3 (11.1%)	
Dyslipidemia	5 (17.9%)	3 (11.1%)	0.705
Heart diseases	3 (10.7%)	0	0.236
COPD	4 (14.3%)	4 (14.8%)	1
CKD	3 (10.7%)	5 (18.5%)	0.469
Stroke	1 (3.6%)	0	1
HTA	16 (57.1%)	12 (44.4%)	0.346
DM	9 (31.1%)	6 (22.2%)	0.409
Smoking status	7 (25%)	6 (22.2%)	0.808
Age (years)	66 (IQR 63.3–68)	62 (IQR 58–68)	**0.013**
BMI (kg/m^2)	27.2 (IQR 24.5–30)	26.8 (IQR 25.3–29.7)	0.893

BMI=body mass index, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, DM=diabetes mellitus, HTA=hypertension, IQR=interquartile range, OBA=opioid-based anesthesia, OFA=opioid-free anesthesia Data are expressed as median (IQR) or number (%). Statistically significant differences shown in bold (P-value) <0.05

Table 2: Intraoperative characteristics

	OBA (*n*=28)	OFA (*n*=27)	*P*
Time of surgery (min)	220 (IQR 197.5–243.75)	240 (IQR 170–260)	0.442
Time of anesthesia (min)	290 (IQR 250–313.75)	285 (IQR 230–330)	0.893
Hypertensive episode (number of patients)	6 (21.4%)	9 (33.3%)	0.322
Lymphadenectomy	7 (25%)	8 (29.6%)	0.700

IQR=interquartile range, OBA=opioid-based anesthesia, OFA=opioid-free anesthesia Data expressed as median (IQR) or number (n)

Table 3: MME requirement in the first 24 postoperative hours

	OBA (*n*=28)	OFA (*n*=27)	*P*
One postoperative hour (mg)	0 (IQR 0–2)	0 (IQR 0–0)	0.316
Four postoperative hours (mg)	0 (IQR 0–2)	0 (IQR 0–0)	0.264
Six postoperative hours (mg)	0 (IQR 0–2)	0 (IQR 0–0)	0.264
12 postoperative hours (mg)	0 (IQR 0–0)	0 (IQR 0–0)	0.326
18 postoperative hours (mg)	1 (IQR 0–2.75)	0 (IQR 0–0)	**0.028**
24 postoperative hours (mg)	1.5 (IQR 0–3)	0 (IQR 0–2)	**0.012**

Data expressed as median (IQR). Statistically significant differences shown in bold (P-value) <0.05. MME=morphine milligram equivalent, OBA=opioid-based anesthesia, OFA=opioid-free anesthesia

Table 4: Secondary outcomes

	OBA (*n*=28)	OFA (*n*=27)	*P*
Time to sitting (hours)	20 (IQR 18–20)	18 (IQR 17–20)	**0.030**
Time to ambulation (hours)	24 (IQR 20–42)	20 (IQR 18–22)	**0.002**
Length of stay (days)	3 (IQR 2–4)	2 (IQR 2–4)	0.307

Data expressed as median (IQR). Statistically significant differences shown in bold (P-value) <0.05. OBA=opioid-based anesthesia, OFA=opioid-free anesthesia

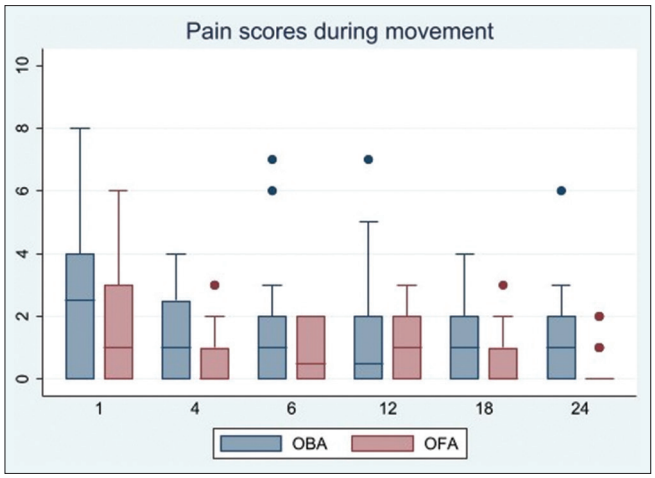

Figure 2: NRS scores during movement in the first 24 postoperative hours in the opioid‐free and opioid‐based anesthesia groups. The horizontal axis shows the time. The horizontal axis shows the time (postoperative hours), and the vertical axis shows the NRS scores. Median (line within box), interquartile range (box), and range (error bars) are shown. NRS = numeric rate scale, OBA = opioid-based anesthesia, OFA = opioid-free anesthesia

Our data shows that both protocols offer optimal analgesia, but patients in the OFA group achieved lower NRSm at 1, 18, and 24 postoperative hours ($P = 0.047$, $P = 0.017$, and $P = 0.013$, respectively). These results are in agreement with other studies in abdominal surgery.[12,18] Hublet *et al.*[18] compared OFA and OBA groups in patients undergoing pancreatic surgery and showed that the NRS values in the OBA group were almost systematically above the cutoff for opioid administration (>4), while an NRS pain score lower than 4 was the standard in the OFA group. Our group previously compared OFA versus OBA strategies in patients undergoing cytoreductive surgery/hyperthermic intraperitoneal chemotherapy[12] and also found lower NRS scores in the OFA group. However, at 4 and 12 h postoperatively, the differences were not statistically significant. We think that the lower NRS scores in the OFA group, especially during movement at 18 and 24 h postoperatively, could be due to the initiation of sitting and/or ambulation during these time points. This fact might be explained by the antihyperalgesic techniques included in the OFA regimen, such as magnesium sulfate,[19] dexmedetomidine[20] and ketamine, and/or by the avoidance of opioid-induced hyperalgesia (OIH).[21] Both these hypotheses are supported by the fact that movement-related pain (dynamic pain) is more intense than pain at rest and seems to be more closely associated with pain-related functional impairment.[22] Dynamic pain seems to be associated with OIH,[23] which may cause patient's discomfort with higher pain scores and greater use of analgesics as in our study.[18,23] OIH is characterized by a paradoxical response in patients receiving high dose or long-duration opioids for treating pain. As a result, patients become more sensitive to certain painful stimuli.[23] Fletcher and Martinez[21] carried out a meta-analysis, which revealed that high intraoperative doses of remifentanil (doses of remifentanil oscillated between 0.05 and 0.9 μg/kg/min) may slightly increase pain intensity at rest during the first 24 postoperative hours and moderately increase morphine use after surgery with no increase in morphine-related side effects; however, no significant difference was found for pain on movement, but this may have been a consequence of the heterogeneity of the data and lack of statistical power.

On the other hand, despite the fact that the total MME administered in the postoperative period for breakthrough pain in or study was very low in both groups, opioid consumption during the first 24 postoperative hours was lower in the OFA group: MME 1.5 (3) mg versus 0 (2) mg, $P = 0.012$. Indeed, we also analyzed MME consumed in the first 18 postoperative hours because initial mobilization typically occurs around this timepoint, and also found that opioid requirements in the OFA group were lower. The very low MME requirements may be explained not only by OIH, but also because we used a standardized hospital protocol based on scheduled nonopioid analgesics such as paracetamol, NSAIDs, and metamizole. Several studies have demonstrated decreased opioid use with this approach.[24] In fact, we observed that opioid requirements were extremely low in both groups. Horodyski *et al.*[25] compared in robotic-assisted laparoscopic prostatectomy an opioid-free strategy based on transversus abdominis plane (TAP) block plus posterior rectus sheath of the midline supraumbilical and postoperative analgesia relied on paracetamol, and opioids/ibuprofen as initial breakthrough medication versus postoperative standard care relied on opioid administration primarily. They observed better pain scores and less morphine requirements in the opioid-free pathway. However, in their study, the average pain scores were higher than ours (45.9% of the patients showed NRS >3 on the first day) and the oral (excluding IV) mean MME consumption was 37.9 mg in the standard group versus 12.5 mg in the opioid-free group. Despite the use of TAP block in this previous study[25], which has been shown in a systematic review to provide long-lasting analgesia up to 24–48 postoperative hours[26] compared to the short effect of wound infiltration (approximately 8 h)[27] used in our study, we hypothesize that these extremely different results rely primarily on our standardized hospital protocol based on scheduled nonopioid medications in the postoperative period and they were further improved in the OFA group by the complete avoidance of opioids intraoperatively. Furthermore, minimizing the use of postoperative opioids is a major advantage for controlling opioid-related side effects such as PONV. All these would be compatible with our findings, in which only one patient had PONV and belonged to the OBA group. Another reason for the low incidence of PONV is that LRP

is not an intra-abdominal technique, and thus excludes bowel manipulation, decreasing the incidence of ileus.

There were no postoperative systemic side effects related to analgesic technique in any of the patients. Our findings are contradictory to the multicenter study carried out by Beloeil *et al.*[17] comparing OFA with dexmedetomidine versus OBA with remifentanil in major or intermediate noncardiac surgery. They observed that patients who received IV dexmedetomidine infusion had more postoperative hypoxemia, delayed extubation, prolonged PACU stay, and intraoperative bradycardia related to a prolonged sedation. It could be due to their mean dosage of the continuous dexmedetomidine infusion, which was high (1.2 (2) μg/kg/h). Dosing differences may be associated with different effects, sometimes even more important than the medication choice. We probably did not observe side effect of dexmedetomidine due to our fixed dosage (0.7 μg/kg/h), similar to that reported by Hublet *et al.*[18] (0.5 (0.2) μg/kg/h). On the other hand, no adverse events or reports of symptoms of local anesthetic toxicity were recorded related to IV lidocaine infusion in the OFA group. Although local anesthetic systemic toxicity could theoretically lead to even fatal events, the truth is that toxicity from perioperative lidocaine infusion is exceedingly rare.[28] The mean plasma levels obtained with IV lidocaine infusion at the doses used in our study are estimated to be between 1.3 and 4.0 μg/ml, with a mean of 1.9 (0.7) μg/ml, which is well below the levels required to observe systemic toxicity (5–8 μg/ml).[29]

When secondary outcomes were evaluated, start to sitting and ambulation occurred earlier in the OFA group ($P = 0.030$ and $P = 0.002$, respectively). Multivariate analysis showed that analgesic technique was an independent factor associated with the start of ambulation ($P = 0.034$). This outcome is of great interest because early mobilization is one of the core principles of ERAS guidelines, leading to early discharge and lower incidence of complications and readmissions. Optimal pain control is one of the requirements that has to be met to achieve early mobilization.

Our study has some limitations, and the conclusions that can be drawn are influenced by its retrospective nature. One limitation is the small number of patients, considering that it was a pilot study to evaluate OFA in this type of surgery. We have tried to mitigate the possible bias by using predetermined clinical pathways for all aspects of patient management to reduce variability in care among different providers. Furthermore, pain control was excellent in both groups of patients, which makes it more difficult to evaluate the incremental benefit that OFA might bring. Another limitation was intraoperative nociception monitoring devices was not used to compare the analgesic efficacy of OBA and OFA; however, we attempted to provide adequate intraoperative analgesia by monitoring hemodynamic events such as hypertension and tachycardia and we did not observe intraoperative hypertensive episodes, which might occur due to inadequate analgesia.[30] Despite these limitations, we believe that the results of this study suggest that OFA could further enhance multimodal nonopioid-based pain management pathways for LRP patients, in favor of better pain control, less opioid consumption, as well as earlier mobilization. We think that future prospective trials should be performed to test the hypothesis that OFA may improve outcomes and shorten the length of stay in LRP.

In conclusion, OFA may offer an optimal analgesia, with less opioid requirements and earlier mobilization in patients undergoing LRP.

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Conflicts of interest
There are no conflicts of interest.

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