1. Title page

Title: Effect of robot-assisted surgery on anesthetic and perioperative management for minimally invasive radical prostatectomy under combined general and epidural anesthesia.

Running title: Robot-assisted prostatectomy under CGEA

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2. Abstract and key words:

Abstract

Background: Robot-assisted surgery and pure laparoscopic surgery are available for minimally invasive radical prostatectomy (MIRP). The differences in anesthetic management between the two MIRPs under combined general and epidural anesthesia (CGEA) remain unknown. This study therefore aimed to determine the effects of robot-assisted surgery on anesthetic and perioperative management for MIRP under CGEA.

Methods: A retrospective observational study was performed by obtaining data from the patients’ electronic medical records. Demographic data, intraoperative parameters, postoperative complications, and hospital stays after the MIRPs were compared between patients who underwent robot-assisted laparoscopic radical prostatectomy (RALP) and those with pure laparoscopic radical prostatectomy (LRP).

Results: There were no differences in the patients’ background data between the 102 who underwent RALP and 112 who underwent LRP. Anesthesia and surgical times were shorter in the RALP group than in the LRP group. Consumption of anesthetics, including intravenous opioids, and epidural ropivacaine, was less in the RALP group. Although the estimated blood loss and volume of colloid infusion were lower in the RALP group, the volume of crystalloid infusion was larger. Intraoperative allogeneic transfusion was not required in either group. There were no
differences in incidents of postoperative cardiopulmonary complications or postoperative nausea and vomiting (PONV) in either MIRP group. Hospital stays after the procedure were shorter in the RALP group.

Conclusions: Robot-assisted surgery required varied consumption of anesthetics and infusion management during MIRP under GCEA. It also shortened the postoperative hospital stay without increasing the rates of postoperative complications.

Key words

Anesthetic and perioperative management, minimally invasive radical prostatectomy, robot-assisted surgery, pure-laparoscopic surgery, combined general and epidural anesthesia
3. Main text

Introduction

Laparoscopic radical prostatectomy is a minimally invasive approach for treating prostate cancer. Both robot-assisted laparoscopic surgery and pure laparoscopic surgery are available for minimally invasive radical prostatectomy (MIRP)\(^1\)-\(^3\). Robot-assisted radical prostatectomy (RALP) has been widely used, and its use is increasing\(^4\)-\(^6\). Several reports have indicated that RALP is associated with a shorter surgical time, less estimated blood loss, and shorter length of hospital stay than pure-laparoscopic radical prostatectomy (LRP)\(^7\)-\(^9\).

Few reports have compared the anesthetic management for RALP with that for LRP. Yonekura et al. reported that, under general anesthesia (GA) alone, RALP was associated with greater opioid consumption intraoperatively, and a higher incidence of postoperative nausea and vomiting (PONV) than with LRP\(^10\). Under combined general and epidural anesthesia (CGEA), the effect of robot-assisted surgery on anesthetic and perioperative management remains unknown in comparison with pure laparoscopic surgery.

We therefore performed a retrospective database study of patients who presented to our institution for either RALP or LRP from January 2014 to August 2017. Our goal was to compare perioperative management and outcomes between RALP and LRP and to evaluate the effect of robot-assisted surgery on the anesthetic and perioperative management for MIRP under CGEA.
Materials and Methods

This study was approved by the Nippon Medical School Hospital ethics committee (27-03-569). Written informed consent from each patient was waived because the study was retrospective. The perioperative database was searched for patients who underwent RALP or LRP under CGEA from January 2012 through August 2017. Patients who were given desflurane or propofol for anesthetic maintenance were excluded from this study. By December 2013, radical prostatectomies were mainly performed in our hospital by four experienced urologic surgeons who had performed more than 500 pure-laparoscopic techniques. Since January 2014, for this study, RALP has been performed by two surgeons who had previously performed LRP in our hospital. To establish a stable surgical technique, we excluded the first 30 patients who underwent the robot-assisted surgery by each surgeon.

We collected data from the anesthesia records preoperatively regarding the patients’ demographics, intraoperative fluid administration, estimated blood loss, amounts of anesthetics used (i.e., sevoflurane, remifentanil, intravenous fentanyl, epidural fentanyl, epidural ropivacaine), amount of allogeneic blood transfusion, intraoperative use of vasopressors, and the anesthesia and surgical times. The length of postoperative hospital stay, additional analgesic use for postoperative pain before removal of epidural catheters, use of antiemetics for treating PONV, and postoperative airway and respiratory and cardiovascular complications were retrieved from each patient’s
electronic record. Urologists or nurses considered that the patients suffered from PONV when they complained nausea or had episodes of vomiting the first 24 hours after both procedures. Urologists prescribed antiemetic drugs for treatment after making diagnoses of PONV.

An epidural catheter was inserted at the patient’s lower thoracic or upper lumbar level (between Th10 and L1) before induction of general anesthesia. General anesthesia was induced in both groups with propofol (1–2 mg/kg) and fentanyl (1–2 μg/kg) with or without remifentanil (0.05–0.20 μg/kg/min). Intubation was facilitated with rocuronium bromide (0.6–1.0 mg/kg). Anesthesia was maintained with 1.5%–2.0% sevoflurane in an oxygen–air mixture and intravenous administration of remifentanil and fentanyl to maintain blood pressure and heart rate as ±20% from the baseline values. Vasoactive drugs were also administered to maintain blood pressure and heart rate within those range. Rocuronium bromide (0.2 mg/kg) was administered at regular intervals to maintain neuromuscular block. 4–8 ml of a local anesthetic, 0.75%–0.1% ropivacaine, was also administered into the epidural space with or without fentanyl (1–2 mg/kg) before the incision. The additional doses of the local anesthetic during procedures were left to the discretion of the attending anesthesiologist. After completing the vesicourethral anastomosis, we transfused autologous blood (up to a hemoglobin level of 10 g/dl). Epidural analgesia for postoperative pain was continued with a balloon infuser containing 0.1% ropivacaine, fentanyl 1.6 μg/ml, and droperidol 1.4 μg/ml. The infuser was set at 4 ml/h for continuous infusion and at 3 ml for bolus
doses with a 30-min lockout period. We started the continuous epidural infusion by the end of the procedure and the balloon pump infuser remained in place until the morning of the first postoperative day. Additional analgesics were administered when the patient reported pain, including pentazocine, non-steroidal anti-inflammatory drugs (e.g., flurbiprofen axetil, diclofenac sodium), or acetaminophen.

RALP and LRP were performed using the transperitoneal approach. The surgeons performed RALP with the da Vinci Robot Surgical System (Intuitive Surgical, Sunnyvale, CA, USA). The patient was placed in the lithotomy position, and the intraperitoneal cavity was insufflated with CO₂ to a pressure of 10–15 mmHg for RALP or 10–12 mmHg for LRP. The patient was then placed in a Trendelenburg tilt position at an angle of 25°–30° for RALP or 20° for LRP. At the end of the procedure, the table was made horizontal, and the CO₂ pneumoperitoneum was stopped.

All data are presented as medians (range). Statistical analyses were performed using the GraphPad Prism software (GraphPad Software Inc., San Diego, CA). The Mann–Whitney test or the χ² test was used to test for differences in median values between the RALP and pure-LRP groups. A value of p<0.05 was considered to indicate statistical significance.
Results

We extracted the records of 305 patients who underwent MIRP at our institution during the survey period and obtained the data from the anesthesia record and the electronic database. Fig. 1 shows the outlines of process to enroll the patients in this study. We excluded the first 60 patients who underwent RALP by two urologists as surgeons. 18 patients were treated by MIRPs under GA alone. Desflurane or propofol were administered to 7 patients for maintaining anesthesia. 6 patients who underwent RALP by other urologists who had not performed LRP as surgeons were excluded. After those exclusions, we focused on the remaining 214 patients who underwent MIRP and included them in this study. In no case was it necessary to convert to an open procedure.

Table 1 shows the demographic data for the 102 RALP patients and the 112 LRP patients. There were no differences in the patients’ background data between the two groups.

The intraoperative parameters are summarized in Table 2. The duration of anesthesia [338 (220–532) vs 376 (264–506) min; p = 0.0007] and of surgery [267 (169–431) vs 290 (194–423) min; p = 0.0012] were significantly shorter in the RALP group than in the LRP group. The doses of intravenous remifentanil [0.05 (0-0.10) vs 0.06 (0-0.24) μg/kg/min; p = 0.0088] and fentanyl [100 (0–350) vs 150 (0–450) μg; p = 0.0018]; and epidural ropivacaine were lower in the RALP group than in the LRP group [44 (19–123) vs 67 (16–164) mg; p < 0.0001]. There were no differences of the consumption of sevoflurane between the RALP group and the LRP group [0.51 (0.23-0.71)
vs 0.48 (0.32-0.69) ml/min; p = 0.061]. The epidural consumption of fentanyl in both MIRPs
groups were similar. The estimated blood loss was less in the RALP group than in the LRP group
[150 (0–660) vs 400 (200–2000) ml; p < 0.0001]. Although the volumes of crystalloid infusions
were greater in the RALP group than in the LRP group [7.63 (3.31-21.11) vs 5.572 (2.61-12.65)
ml/kg/hour; p < 0.0001], the volumes of colloid infusions were less in the RALP group than in
the LRP group [0 (0–1500)ml vs 500 (0–1600) ml; p < 0.0001]. The volumes of autologous blood
transfusion were lower in the RALP group than in the LRP group [400 (0–400) vs 800 (0–800)
ml; p < 0.0001]. No intraoperative allogeneic transfusions were required in either group. There
were also no differences in the amounts of vasoactive drugs, ephedrine, or phenylephrine in the
two groups. Although one patient with RALP required reintubation because of decreased
respiratory drive, there were no reintubations needed because of airway edema due to the steep
Trendelenburg position or the CO₂ pneumoperitoneum.

The postoperative parameters are summarized in Table 3. Although one patient in the RALP group
required intravenous pentazocine after the procedure, none needed an opioid after either MIRP.
There were no significant differences in the rates of non-steroidal anti-inflammatory drugs or
acetaminophen use before epidural catheter removal in either group. The incidence of
postoperative cardiopulmonary complications were not significantly different between the RALP
and LRP groups. The frequencies of the patients with PONV treated with an antiemetic drug were
similar after both MIRPs. Although the median lengths of postoperative hospital stays were the same in the two groups, the actual length of stay for the RALP patients was significantly shorter than that for the LRP patients: 10 (8–28) vs 10 (7–32) days ($p = 0.001$).
Discussion

This retrospective study revealed that robot-assisted surgery is related to shorter anesthesia and surgical durations, less blood loss, and lower quantities of anesthetic agents during MIRP under CGEA. Although the volume of infused crystalloid solution was greater during robot-assisted surgery, the volume of infused colloid solution was less than that needed for pure laparoscopic surgery. There were no differences in the postoperative cardiopulmonary complication rates or PONV treated with an antiemetic drug in patients in both MIRP under CGEA groups. Robot-assisted surgery is also associated with shorter hospital lengths of stay after MIRP under CGEA. Several reports indicated that patients with RALP had shorter surgical times, less estimated blood loss, and shorter lengths of hospital stay than those who underwent LRP. Our results were in accord with those from other studies. The patients undergoing RALP experienced a shortened anesthesia time because the surgical time was shortened, and less estimated blood loss resulted in smaller amounts of autologous blood transfusion. Thus, our study showed that robot-assisted surgery shortened the anesthesia and surgical times and reduced the estimated blood loss, thereby requiring less autologous blood transfusion during MIRP under CGEA. Furthermore, this robot-assisted surgery decreased the length of hospital stay after MIRP under CGEA.

A previous study indicated that intraoperative fentanyl use was higher in patients undergoing RALP than those undergoing LRP. Our results showed that the amounts of fentanyl and
remifentanil in RALRP patients were lower than those in LRP patients. These discrepancies might be caused by the differences in the anesthesia time and the method used. Epidural ropivacaine were also lower in the RALP group than in the LRP group. In this study, the lower amounts of anesthetic drugs in RALP patients could be explained by our speculation that RALP might be lesser invasive technique than LRP. In the aforementioned research\textsuperscript{10}, the data were obtained from both MIRP techniques under GA alone, whereas our data were collected from both MIRP techniques under CGEA. Furthermore, epidural anesthesia itself has a potent analgesic effect, thereby minimizing the need for higher anesthetic doses\textsuperscript{12-14}. Our results indicate that robot-assisted surgery decreases the amounts of anesthetic agents during MIRP under CGEA.

Although the anesthesia time of the RALP group was shorter than that of the LRP group, the amounts and flow rates of crystalloid infusions in RALP group were higher than those for the LRP group. In contrast, the volumes of infused colloid solutions needed were lower in the RALP patients. Restrictive fluid management seems to have been widely accepted to avoid excessive urine output during vesicourethral anastomosis and the upper body edema that may develop when in the steep Trendlenburg position\textsuperscript{15,16}. We, however, do not apply restrictive fluid infusion management during either of the MIRPs, nor do the urologists in our institution request it. To maintain stable hemodynamics during RALP, we infuse crystalloid solutions without infusing more colloid solutions or increasing the vasopressor dose. In addition, less blood loss might
reduce the amount of colloid solutions needed in the RALP group. Our findings suggest that robot-assisted surgery reduces the colloid infusion volume and increases the need for crystalloid solution to stabilize hemodynamics during MIRP under CGEA.

There were no differences between the MIRP techniques regarding the need for additional analgesics postoperatively. Additional opioids were not administered to our patients for postoperative pain after either MIRP. Compared with open radical prostatectomy, the pain intensity after RALP and LRP is generally mild to moderate\textsuperscript{17-19}. Nevertheless, we apply epidural analgesia to avoid postoperative pain after MIRP because we know we can rely on its strong analgesic effect. Epidural analgesia has also been reported to be more useful than intravenous analgesics for alleviating postoperative pain after LRP\textsuperscript{20}. Patients who underwent RALP and were given postoperative epidural analgesia showed lower opioid requirements than those without epidural analgesia\textsuperscript{21}. Thus, epidural analgesia may also be useful for alleviating postoperative pain after RALP.

There were no differences of the rate of postoperative complications between the RALP and the LRP groups. According to previous reports, airway, respiratory, and cardiovascular complication rates were 0.1\%–1.4\% after RALP and LRP\textsuperscript{4,7,22,23}. Our data were similar to those in previous studies. Several reports noted postoperative pulmonary and airway edema in RALP patients that had been induced by the steep Trendelenburg position and the CO\textsubscript{2} pneumoperitoneum. It required
reintubation and postoperative ventilation\textsuperscript{15,24-26}. Saito et al. reported that the incidence of upper airway edema was 5.8\% in patients who had undergone RALP without blood withdrawal to prevent complications due to the positioning and the established the pneumoperitoneum. Despite not performing restrictive fluid therapy during RALP in our patients, none developed upper airway edema. We surmised that it had been prevented by the effects of epidural anesthesia on the blood flow distribution. Thoracic epidural block induces vasodilation of the abdominal vascular bed, increasing the abdominal venous capacity and reducing central venous pressure\textsuperscript{27,28}. Hong, et al. reported that central venous pressure during RALP under CGEA was lower than that during RALP under GA even though the amounts of infusion volume was larger in CGEA group than in GA group\textsuperscript{28}. Hence, epidural anesthesia induce redistribution of blood flow and pools the blood in the abdominal vascular bed without altering the intravascular volume, thereby leading to decreased venous return and lower peripheral venous pressure. In turn, the reduced peripheral venous pressures helps to avoid blood congestion in peripheral tissues, which then helps avoid the formation of peripheral edema, including that of the pharynx, larynx, and face. This mechanism may thus avoid any possible edema. We suggest that epidural anesthesia is useful for inhibiting edema formation in peripheral tissues, especially in the upper airway, during robot-assisted MIRP.

We found no differences in the PONV rates in the two MIRP groups, for which antiemetics were
required. The Trendelenburg position and prolonged intraperitoneal CO\textsubscript{2} insufflation during laparoscopic surgery induce peritoneal stretching and irritation. Those changes play an important role in PONV\textsuperscript{20}. Hence, RALP itself is an important risk factor for PONV\textsuperscript{30}. About 25\% of patients reportedly needed rescue antiemetics within 6 h after RALP under GA\textsuperscript{30}. In another study, PONV affected 16\%–30\% of patients who had undergone one or the other MIRP under GA alone, although the incidence of PONV after RALP was higher than that after LRP\textsuperscript{10}. Our results were incongruent with those of other studies, which might be explained by less consumed opioid during and after both MIRPs under epidural anesthesia and analgesia\textsuperscript{29,31,32}. Furthermore, several studies showed that postoperative epidural analgesia had more beneficial effects on gastrointestinal function than systemic opioid analgesia\textsuperscript{32-34}, which may reduce the incidence of PONV after MIRP. Our observations support the idea that epidural anesthesia and analgesia may reduce the incidence of PONV and treatment for PONV after both RALP and LRP.

The study has several limitations. First, it was a retrospective, single-institution study, so a prospective, randomized study should be carried to confirm our findings. Second, several surgeons performed both MIRPs, and all anesthetic doses were left to the discretion of the anesthesiologists. However, the surgical techniques had been standardized for both MIRPs and there were no major problems in anesthetic management for either surgery. Thus, our results may not be influenced by those limitations. Third, our data were extracted from accurate patients’
electronic records, and we were unable to obtain some parameters, including pain scores after both MIRPs and the numbers of PONV patients without any treatment. Therefore, we could not evaluate the differences in postoperative pain between groups and so have no information of the total numbers of patients who suffered from PONV after the two MIRPs.

This study revealed that, during MIRP under CGEA, robot-assisted surgery had the advantages of a shorter anesthesia time, less estimated blood loss, and lesser amounts of anesthetic agents, including opioids, compared with pure-laparoscopic surgery. Although higher doses of crystalloid solution were required during RALP under CGEA, there were no postoperative airway or respiratory complications related to the steep Trendelenburg position and the CO$_2$ pneumoperitoneum. No patients required opioid administration for postoperative pain after either MIRP under GCEA. Robot-assisted surgery shortened the hospital stay after MIRP under GCEA without increasing the incidence of postoperative cardiopulmonary complications or PONV.

**Abbreviations**

MIRP: minimally invasive radical prostatectomy

CGEA: combined general and epidural anesthesia

RALP: robot-assisted laparoscopic radical prostatectomy

LRP: pure laparoscopic radical prostatectomy
NSAIDs: non-steroidal anti-inflammatory drugs

PONV: postoperative nausea and vomiting

Conflict of interest statement

The authors declare that they have no conflicts of interest.
4. References


analgesia with levobupivacaine reduces remifentanil and propofol consumption evaluated by closed-loop titration guided by the bispectral index: a double-blind placebo-controlled study.


15. Gainsburg DM. Anesthetic concerns for robotic-assisted laparoscopic radical prostatectomy.


5. **Figure legend**

Figure 1 Flowchart of enrollment

6. Table footnotes

Table 1 Patient demographics

Data are expressed as median (range) or number of patients (%).

Table 2 Intraoperative parameters

Data are expressed as median (range). *: p < 0.05 between groups.

Table 3 Postoperative parameters

Data are expressed as number of patients (%). *: p < 0.05 between groups.
Figure 1 Flowchart of enrollment

Assessed for eligibility (n=305)

Excluded (n=91)
- First 60 patients who underwent RALP by two urologists as surgeons (n=60)
- MIRP under GA (n=18)
- Administration of desflurane to maintain anesthesia (n=5)
- Administration of propofol to maintain anesthesia (n=2)
- Patients whose RALP was performed by other urologists who had not performed LRP as surgeons (n=6)

Patients enrolled (n=214)
### Table 1 Patient demographics

<table>
<thead>
<tr>
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<th>RALP (n = 102)</th>
<th>LRP (n = 112)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>68 (46-79)</td>
<td>68 (41-76)</td>
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<tr>
<td>Height (cm)</td>
<td>165.4 (151-186.5)</td>
<td>167 (151-181)</td>
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<td>Weight (kg)</td>
<td>66.7 (43.3-103)</td>
<td>65 (25.4-94.2)</td>
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<td>BMI (kg/ m$^2$)</td>
<td>24 (18-31)</td>
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<td>ASA-PS, n (%)</td>
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<td>1</td>
<td>7 (6.6)</td>
<td>16 (14)</td>
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<tr>
<td>2</td>
<td>90 (84)</td>
<td>86 (76)</td>
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<td>3</td>
<td>9 (8.4)</td>
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Table 2 Intraoperative parameters

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<tr>
<th>Parameter</th>
<th>RALP (n = 102)</th>
<th>LRP (n = 112)</th>
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<tr>
<td>Anesthetic time (min)</td>
<td>338 (220-532)</td>
<td>376 (264-506)</td>
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<tr>
<td>Surgical time (min)</td>
<td>267 (169-431)</td>
<td>290 (194-423)</td>
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<td>Sevoflurane (ml/min)</td>
<td>0.51 (0.23-0.71)</td>
<td>0.5 (0.32-0.69)</td>
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<td>Remifentanil (µg/kg/min)</td>
<td>0.05 (0-0.10)</td>
<td>0.06 (0-0.24)</td>
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<td>Intravenous Fentanyl (µg)</td>
<td>100 (0-350)</td>
<td>150 (0-450)</td>
<td>0.0018*</td>
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<tr>
<td>Epidural Fentanyl (µg)</td>
<td>33.8 (0-175)</td>
<td>36.5 (0-260)</td>
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<td>Ropivacaine (mg)</td>
<td>44 (19-123)</td>
<td>67 (16-164)</td>
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<td>Estimated blood loss (ml)</td>
<td>150 (0-660)</td>
<td>400 (200-2000)</td>
<td>&lt; 0.0001*</td>
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<td>Crystalloid infusion (ml/kg/hour)</td>
<td>7.63 (3.31-21.11)</td>
<td>5.57 (2.61-12.65)</td>
<td>&lt; 0.0001*</td>
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<td>Colloid infusion (ml)</td>
<td>0 (0-1500)</td>
<td>500 (0-1600)</td>
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<td>Autologous blood transfusion (ml)</td>
<td>400 (0-400)</td>
<td>800 (0-800)</td>
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<td>Ephedrine (mg)</td>
<td>16 (0-72)</td>
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<td>Phenylephrine (mg)</td>
<td>0 (0-1.05)</td>
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Table 3  Postoperative parameters

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<th>P value</th>
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<td>NSAIDs or acetaminophen use before removal of epidural catheter, n (%)</td>
<td>11 (10)</td>
<td>18 (16)</td>
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<td>Postoperative airway or respiratory complication, n (%)</td>
<td>1 (1)</td>
<td>0 (0)</td>
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<tr>
<td>Postoperative cardiovascular complication, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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</tr>
<tr>
<td>PONV treated by antimetic drug, n (%)</td>
<td>4 (3.7)</td>
<td>3 (2.6)</td>
<td>0.71</td>
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<td>Hospital stays (d)</td>
<td>10 (8-28)</td>
<td>10 (7-32)</td>
<td>0.0045*</td>
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