Original Contribution

Comparison of sugammadex and conventional reversal on postoperative nausea and vomiting: a randomized, blinded trial☆,☆☆,★

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Abstract

Study Objective: To determine whether the new selective binding agent sugammadex causes less postoperative nausea and vomiting (PONV) than the cholinesterase inhibitor neostigmine.

Design: Prospective, randomized, double-blinded study.

Setting: University-affiliated hospital.

Patients: One hundred American Society of Anesthesiologists physical status 1 and 2 patients scheduled for extremity surgery.

Interventions: Patients were randomly assigned to neostigmine (70 μg/kg) and atropine (0.4 mg per mg neostigmine) or sugammadex 2 mg/kg for neuromuscular antagonism at the end of anesthesia, when 4 twitches in response to train-of-four stimulation were visible with fade.
1. Introduction

The cholinesterase inhibitor neostigmine remains the most commonly used neuromuscular blocking agent antagonist. Neostigmine causes bradycardia, gastrointestinal motility, and gastric secretions. Furthermore, neostigmine is thought to increase the risk of postoperative nausea and vomiting (PONV) [1,2], possibly by provoking gastric spasms, which lower barrier pressure and increasing afferent input to central vomiting centers. The combination of neostigmine and atropine may be emetogenic [3]. Neostigmine in doses ≥ 2.5 mg increases the incidence of PONV [4]. Neostigmine does not increase the risk of postoperative vomiting, and there is insufficient evidence to conclude that neostigmine leads to a clinically important increase in the risk of PONV [5].

Sugammadex is a new selective relaxant binding agent, which has a different mechanism of action from anticholinesterase neuromuscular antagonists. Specifically, sugammadex encapsulates steroidal neuromuscular blocking agents, leading to rapid movement of free neuromuscular agent from the tissues into plasma.

Sugammadex has various side effects, including mild headache, nausea, the injection site irritation, dry mouth, fatigue, a cold sensation at the injection site, and oral discomfort [6-9]. Furthermore, the most common adverse effect of sugammadex is nausea [10]. McDonagh et al [11] also reported that 30% of patients given 2 mg/kg sugammadex for antagonism experienced nausea, whereas others report that the drug is well tolerated [12,13]. However, none of these studies was primarily designed to evaluate the effect of sugammadex on PONV. Therefore, the primary hypothesis that there is less PONV when neuromuscular block is antagonized with sugammadex than neostigmine was tested.

2. Materials and methods

This single-center, randomized, double-blind study was conducted at Mustafa Kemal University Hospital. Ethics committee approval (April 2012, approval number 154) was obtained, and written consent was obtained from all patients.

One hundred American Society of Anesthesiologists (ASA) physical status 1 and 2 patients scheduled for extremity surgery (tendon repair and skin graft surgery) during general anesthesia over the course of a year, starting April 2012, were enrolled. Patients were excluded if they had any contraindication to sugammadex or neostigmine administration; were having emergency or urgent procedures; and had a body mass index ≥ 27 kg/m², hepatic impairment (alanine aminotransferase or aspartate aminotransferase or aspartate aminotransferase > 2 times normal), or renal impairment (serum creatinine > 2 mg/dL).

2.1. Protocol

Patients were premedicated with 1-3 mg intravenous midazolam. Qualifying patients were randomly assigned 1:1 without stratification to neuromuscular antagonism with (1) sugammadex 2 mg/kg or (2) neostigmine 70 μg/kg and atropine 0.4 mg atropine per mg neostigmine. Randomization was Web based.

Anesthesia was induced with propofol 2-2.5 mg/kg and fentanyl 1 μg/kg and maintained with 5%-6% desflurane in 66% nitrous oxide in oxygen. Rocuronium 0.6 mg/kg was given intravenously to facilitate tracheal intubation; additional boluses of rocuronium, 0.15 mg/kg, were given to maintain 2 twitches in response to supramaximal electrical stimulation of the ulnar nerve as determined by a TOF-Watch-SX (Schering-Plough Ireland, Dublin, Ireland). Meperidine 0.5 mg/kg was given intravenously when skin closure began. At the end of anesthesia, when 4 twitches of TOF were visible with fade, participants were given the designated neuromuscular antagonist. All patients were extubated when the TOF ratio is ≥ 90%. Antiemetic medications were not given intraoperatively.

When postoperative visual analog scale exceeded 5 cm, diclofenac sodium 75 mg was given intravenously; tramadol (1 mg/kg) intramuscularly was used as rescue analgesic. PONV was treated with ondansetron 4 mg intravenously and, if persistent, with metoclopramide 10 mg intravenously.

2.2. Measurements

Baseline risk of PONV was assessed using the Apfel score. According to this preoperative risk assessment tool, there are 4
predictors. These are female gender, history of motion sickness or PONV, nonsmoking, and postoperative opioids. Predictive PONV risk (%) score and correlated PONV risk: 0, 10%; 1, 21%; 2, 39%; 3, 61%; 4, 79% [14]. The following times were recorded: duration of anesthesia, neuromuscular antagonism, extubation, first eye opening, and head lift. These times were all started at the administration of the reversal agent. The neuromuscular response of the adductor pollicis to supramaximal stimulation of the ulnar nerve at the wrist was recorded by a TOF-Watch-SX (Schering-Plough Ireland). The system was calibrated before muscle relaxation was given.

An anesthetist blinded to treatment queried patients about postoperative pain using visual analog scale (0-10 cm) at the moment and 30 minutes after admission to the postanesthesia care unit and 1, 2, 6, 12, 18, and 24 hours after anesthesia. PONV was evaluated as follows: 0, no nausea; 1, mild nausea, duration ≤15 minutes; 2, nausea ≥15 minutes; 3, retching or vomiting [15]. Any nonzero response to either nausea or vomiting queries was considered to be positive for postoperative PONV. Nausea, vomiting, pain, heart rate, noninvasive blood pressure, and oxygen saturation as measured by pulse oximetry were evaluated after 30 minutes in the postanesthesia care unit and 1, 2, 6, 12, 18, and 24 hours after anesthesia.

Side effects including bradycardia (heart rate <60 beats per minute), hypotension (decrease in systolic arterial pressure of >10 mm Hg from baseline), itching, headache, respiratory depression (respiratory rate <10), cough, bronchospasm, irritation at injection site, and abnormally increased oral secretions were recorded. First oral intake, gastrointestinal motility (first flatus time), and ambulation times were recorded.

### 2.3. Statistics

The results of a pilot study were used to calculate the sample size. α Was set at .05, β was set at .8. In the pilot study, the SD was 0.8 for both groups, and true difference of means was 0.5 points on our 4-point PONV scale. The sample size for each group was calculated at least 44 patients for our planned 1-tailed analysis. We, therefore, enrolled 50 patients in each group to allow for some patients dropping out and technical failures.

Unless otherwise specified, data were summarized using median and range for continuous variables and percentages for categorical variables. Categorical variables were compared using 1-sided χ² tests, and continuous variables were compared using 1-sided Mann-Whitney U test. Time depended variables were compared using repeated-measures analysis of variance with post hoc Scheffé’s F. P < .05 was statistically significant. SPSS 19.0 for Windows software was used for statistical analysis.

### 3. Results

One hundred consenting patients who fulfilled the entry criteria were enrolled; all completed the entire study and were included in the final analysis. Patients assigned to each medication were comparable with respect to age, height, body weight, ASA physical status, Apfel score, duration of surgery, and duration of anesthesia (Table 1).

Fig. 1 represents the proportion (numbers of the patients in each group) of the patients according to the PONV scale. The nausea and vomiting scores were significantly lower with sugammadex than neostigmine upon arrival in the postanesthesia care unit (med: 0 [min-max, 0-3] vs med: 0 [min-max, 0-3]; P < .05). However, there were subsequently no significant differences during the remaining initial 24 postoperative hours (P > .05).

Extubation, first eye opening, and head lift times were shorter in sugammadex patients than in those given neostigmine (P ≤ .001 for each). In contrast, there were no significant differences between the groups in first flatus, oral intake, or time to ambulation (Table 2). The incidence of postoperative complications was also similar in each group (Table 3). Patients given neostigmine were more often bradycardic, and patients in sugammadex group had more coughing. One patient in the sugammadex group had respiratory depression, not requiring reintubation, which was deemed a serious adverse event.

Heart rates were significantly lower with neostigmine than sugammadex throughout the first 24 postoperative hours (Fig. 2). In contrast, systolic and diastolic arterial blood pressures were similar except at 24 hours where systolic arterial pressure was significantly lower in patients given neostigmine.

Postoperative ondansetrone (45 vs 41 patients) and metoclopramide (16 vs 10 patients) were similar in each group, as were analgesic consumption (Table 4) and pain scores (Fig. 2).

### 4. Discussion

The incidence of PONV is nearly 30% in unselected inpatients and 70%-80% in high-risk populations [16,17].
PONV is among the complications patients most fear [18] and may delay discharge [19], thus increasing hospital costs [20]. Mechanisms behind PONV are multifactorial, but the incidence is distinctly affected by choice of anesthetic medications [17].

Sugammadex had lower nausea and vomiting scores upon arrival to the postanesthesia care unite (PACU), a difference perhaps related to speedy recovery of neuromuscular strength. For example, muscle weakness may lead to hypoventilation and hypoxia, which may, in turn, contribute to PONV [4]. Consistent with this theory and as reported in previous studies [21], clinical measures of muscular strength including time to extubation, first eye opening, and head lift were all significantly shorter in sugammadex patients. Another potential explanation for the initial reduction in PONV is an emetic effect of neostigmine, although the most recent meta-analysis identifies no such complication [5]. Anticholinergic drugs administered with neostigmine may reduce PONV, although there is little support for this theory [15,22].

Lower PONV scores in the sugammadex patients did not persist. Nausea and vomiting were observed in 60% of the patients randomized to sugammadex and 58% of those assigned to neostigmine during the initial 24 postoperative hours. Incidence of PONV seems to be relatively high when compared to other studies done in similar patient populations; however, we believe this difference results from anesthetic technique and choice of analgesic drug. Nitrous oxide given intraoperatively and tramadol given postoperatively may have contributed significantly to the current results. PONV severity and antiemetic use were also comparable in the 2 groups. The benefit of sugammadex on PONV was thus limited and transient. Time to oral intake, recovery of gastrointestinal function, and ambulation were also similar in the 2 groups.

Adverse events were rare, and the incidence was similar in each group. Bradycardia was more common with neostigmine (14% vs 2%). In contrast, coughing was more common with sugammadex (18% vs 2%), although it is possible that coughing was simply more apparent in patients given sugammadex because muscular strength was enhanced [23]. In a clinical study with 77 patients, 2.6% of the patients had bronchospasm after sugammadex of a dose of 4 mg/kg. The mechanism is not clear, but hyperresponsiveness of bronchial smooth muscles was the suggested reason.

We found significantly lower heart rates in neostigmine group. It is well known that bradycardia is a consequence of

**Table 2** Clinical recovery parameters

<table>
<thead>
<tr>
<th></th>
<th>Neostigmine (n = 50), median (interquartile range)</th>
<th>Sugammadex (n = 50), median (interquartile range)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extubation (min)</td>
<td>4 (1-3.25)</td>
<td>3 (1-3.25)</td>
<td>.001</td>
</tr>
<tr>
<td>First eye opening (min)</td>
<td>7 (5-11)</td>
<td>4 (3-7.25)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Head lift time (min)</td>
<td>8 (11-25)</td>
<td>4 (2-7.25)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>First flatus (h)</td>
<td>9.5 (6-13)</td>
<td>9 (6-13.25)</td>
<td>.983</td>
</tr>
<tr>
<td>First oral intake (h)</td>
<td>7 (4-7.25)</td>
<td>7 (5-8)</td>
<td>.24</td>
</tr>
<tr>
<td>Ambulation (h)</td>
<td>6 (4-11)</td>
<td>6 (5-10.5)</td>
<td>.689</td>
</tr>
</tbody>
</table>

Results presented as numbers or median and interquartile range.
neostigmine administration. We also found that heart rates were significantly greater in patients given sugammadex during the initial hour of recovery; thereafter, differences were small and presumably of little clinical importance. Meretoja [24] reported an increase in heart rate with sugammadex. It is difficult to know exactly the reason but, presumably, the initial difference resulted from a bradycardic effect of neostigmine [25].

The doses of sugammadex, neostigmine, and atropine are the ones most commonly described and used [4]. Obviously, results might differ with other doses. Patients who experience PONV during the initial 24 hours often continue to experience symptoms during the subsequent 48 hours. The occasional patient initially experiences PONV after 24 hours. However, it seems unlikely that choice of neuromuscular antagonist would influence PONV so long after administration especially given the PONV scores were essentially zero in each group at 24 hours.

In summary, selective relaxant binding agent antagonism with sugammadex speeds recovery of neuromuscular strength but only slightly and transiently reduces PONV compared with neostigmine and atropine. There was also no benefit in terms of time to oral intake, recovery of gastrointestinal function, or ambulation.

References


