Sugammadex for reversal of neuromuscular blockade: a retrospective analysis of clinical outcomes and cost-effectiveness in a single center

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Objective: The aim of the study is to evaluate the clinical and economic impact of introducing a rocuronium–neostigmine–sugammadex strategy into a cisatracurium–neostigmine regimen for neuromuscular block (NMB) management.

Methods: We conducted a retrospective analysis of clinical outcomes and cost-effectiveness in five operating rooms at University Hospital of Padova. A clinical outcome evaluation after sugammadex administration as first-choice reversal drug in selected patients (rocuronium–sugammadex) and as rescue therapy after neostigmine reversal (rocuronium–neostigmine–sugammadex) compared to control was performed. A cost-analysis of NMB management accompanying the introduction of a rocuronium–neostigmine–sugammadex strategy into a cisatracurium–neostigmine regimen was carried out. To such purpose, two periods were compared: 2011–2012, without sugammadex available; 2013–2014, with sugammadex available. A subsequent analysis was performed to evaluate if sugammadex replacing neostigmine as first choice reversal drug is cost-effective.

Results: The introduction of a rocuronium–neostigmine–sugammadex strategy into a cisatracurium–neostigmine regimen reduced the average cost of NMB management by 36%, from €20.8/case to €13.3/case. Patients receiving sugammadex as a first-choice reversal drug (3%) exhibited significantly better train-of-four ratios at extubation (P<0.001) and were discharged to the surgical ward (P<0.001) more rapidly than controls. The cost-saving of sugammadex as first-choice reversal drug has been estimated to be €2.9/case. Patients receiving sugammadex as rescue therapy after neostigmine reversal (3.2%) showed no difference in time to discharge to the surgical ward (P=0.44) compared to controls. No unplanned intensive care unit (ICU) admissions with rocuronium–neostigmine–sugammadex strategy were observed. The potential economic benefit in avoiding postoperative residual curarization (PORC)-related ICU admission in the 2013–2014 period was estimated at an average value of €13,548 (€9,316–€23,845).

Conclusion: Sugammadex eliminated PORC and associated morbidities. In our center, sugammadex reduced the costs of NMB management and promoted rapid turnover of patients in operating rooms, with total cost-effectiveness that counteracts the disadvantages of its high cost.

Keywords: neuromuscular blockade; neuromuscular blocking agents; rocuronium; sugammadex; postoperative residual curarization; cost-benefit analysis.

Introduction

Neuromuscular blocking agents (NMBAs) are routinely used worldwide as part of a modern concept of balanced anesthesia. Rocuronium, an aminosteroid NMA, and cisatracurium, a NMA of the benzylisoquinoline family, are two common intermediate-duration NMBAs whose pharmacokinetic properties make them suitable for administration by either bolus or continuous infusion.1 Rocuronium features a rapid
onset of action.\textsuperscript{2} When a rapid induction of NMB is required, rocuronium 1–1.2 mg/kg may be substitutive of succinylcholine, which is effective, but has a wide range of potentially dangerous adverse effects, including death.\textsuperscript{3} Cisatracurium has an organ-independent metabolism since it is (at physiological pH and temperature) rapidly degraded by Hoffmann elimination in plasma and tissues.\textsuperscript{4} This allows to limit the variability in duration of effect of cisatracurium,\textsuperscript{2} particularly in the presence of kidney or liver disease, and after continuous infusion in case of prolonged surgical procedure.\textsuperscript{1}

Acetylcholinesterase inhibitors, such as neostigmine, are generally administered to hasten recovery from NMB and reduce the likelihood of postoperative residual curarization (PORC).\textsuperscript{5,6} that may occur with any NMBAs.\textsuperscript{1,5} PORC can result in potentially fatal adverse respiratory events (AREs), and, therefore, represents a clinically relevant problem.\textsuperscript{5,6} Administering sugammadex, a modified \(\gamma\)-cyclodextrin that encapsulates and inactivates unbound aminosteroid NMBAs, but not benzylisoquinoline NMBAs, is emerging as a more favorable approach to achieving full reversal of NMB than neostigmine.\textsuperscript{5,7} Sugammadex has been approved for a quick and predictable reversal of moderate and profound NMB at doses of 2 and 4 mg/kg, respectively,\textsuperscript{5,9} and for immediate reversal at a dose of 16 mg/kg after the administration of 1.2 mg/kg rocuronium.\textsuperscript{10} However, the cost of sugammadex has so far hindered its progress of becoming a widely used alternative to neostigmine.\textsuperscript{11} The potential advantage for the health system associated with the routine use of sugammadex has been demonstrated through cost-effectiveness analyses.\textsuperscript{12–14} However, there are no reports of a cost analysis of sugammadex use in clinical practice that considered the outcomes of treated patients, the real costs, and the potential benefits for the health system.\textsuperscript{5}

Therefore, we performed a retrospective analysis of NMB management that examined the clinical and economic impact of introducing a rocuronium plus neostigmine and sugammadex strategy into a regimen based mainly on cisatracurium plus neostigmine.

Materials and methods

The study was approved by the Ethics Committee for Clinical Research of Padova, which waived the requirement to obtain patient’s written informed consent. It was performed in five operating rooms (ORs) at University Hospital of Padova. These ORs have more than 8 hours of cases each workday. Abdominal surgery was the most frequently performed procedure.

Introduction of sugammadex in our center

Given its cost, the Hospital Pharmacy approved (January 1, 2013) the use of sugammadex for reversal of rocuronium-induced NMB under quantitative neuromuscular monitoring only in select patients who were judged to have an increased risk of complications with reversal of NMB by neostigmine (“preventive” use): elderly patients; patients with morbid obesity; patients presenting neurologic impairment, neuromuscular, respiratory, cardiac, kidney (with creatinine clearance [CrCl] >30 mL/min), and liver disease; patients with difficult airway management; and patients with contraindications to neostigmine plus atropine.\textsuperscript{3,15}

Sugammadex was also approved for use as rescue therapy in two situations: “emergency use”, for rapid reversal of high dose rocuronium-induced NMB in case of “cannot ventilate, cannot intubate” (CVCI) situation and “curative” use, for treatment of any PORC-related AREs after reversal of rocuronium-induced NMB with neostigmine,\textsuperscript{16,17} with PORC defined as a train-of-four (TOF) ratio <0.9.\textsuperscript{5} PORC-related AREs were defined as difficult weaning from mechanical ventilation after general anesthesia with NMB and, after tracheal extubation, any critical respiratory event during the early postoperative period.\textsuperscript{6}

Outcome evaluation

An evaluation of outcomes of sugammadex use in the 2013–2014 period was carried out. All treated patients in both the “preventive” and “curative” group were matched with controls for comparison. The controls were chosen from patients with similar clinical characteristics in whom rocuronium-induced NMB was reversed with neostigmine and who did not receive sugammadex. Both cases and controls were chosen from patients who underwent surgery, between 8 am and 8 pm, Monday through Friday, from January 1, 2013 to December 31, 2014.

All patients received inhalational or intravenous anesthesia and NMB with quantitative neuromuscular monitoring. At the time of tracheal extubation, the TOF ratio was measured and recorded. Patients were categorized into one of three groups based on the TOF ratio: acceptable neuromuscular recovery, TOF ratio ≥0.9; mild-to-moderate NMB, TOF ratio 0.7 and 0.9; and severe NMB, TOF ratio <0.7.\textsuperscript{5}

In “curative” use patients, sugammadex was administered to treat PORC-related AREs occurring after the reversal of rocuronium-induced NMB with neostigmine and for which muscle relaxant antagonism was judged necessary. All PORC-related AREs were identified by an anesthetist in
the OR or a nurse in the recovery room (RR). For those that occurred in the RR, an anesthetist examined the patient to confirm a PORC-related ARE.6

Reports sent to the Hospital Pharmacy to justify sugammadex use, the anesthesia records, and our information system’s computer database were used to retrieve data about patients and controls.

The pharmacoeconomic evaluation of sugammadex use
The pharmacoeconomic evaluation involved two aspects: cost-analysis of NMB management accompanying the introduction of a rocuronium–neostigmine–sugammadex strategy into a cisatracurium–neostigmine regimen and estimation of the economic benefits of using sugammadex as first choice reversal drug.

Costs analysis of NMB management
For the cost-analysis of NMB management, two periods were considered: January 1, 2011 to December 31, 2012 (before the introduction of sugammadex) and January 1, 2013 to December 31, 2014 (after the introduction of sugammadex).

Data about the type of anesthesia were collected from the surgical information system’s computer database and classified as general anesthesia with NMB, general anesthesia without NMB, and regional anesthesia (without NMB).

Data about the cost of drugs used for NMB management were retrieved from the Hospital Pharmacy, whose personnel tracked drug costs electronically. As the ORs at University Hospital of Padova are allocated a specific cost center number, we were able to retrieve data on the costs of drugs used exclusively in the ORs involved in this study. For each drug, the unit price was considered. The total costs of drugs used for NMB management were calculated by multiplying each drug cost by the number of vials used. The total costs were also compared for the two time periods.

Economic benefits of using sugammadex as first-choice reversal drug
Two factors were considered for estimation of economic benefits: the difference in minutes between sugammadex and neostigmine with respect to the time until a complete recovery from NMB (TOF ratio ≥0.9) and the estimated costs of OR, and OR and RR staffs per minute using a validated model.13,14

With regard to the first factor, two previous randomized controlled trials comparing sugammadex to neostigmine for reversing moderate and deep NMB were considered for evaluating the time of complete recovery from NMB.18,19

With regard to the second factor, the estimated OR cost was based on the average cost of an OR (comprehensive of OR staff and material costs) at the University Hospital of Padova. The estimated OR staff cost was calculated assuming that the OR staff comprised two consultant surgeons, a consultant anesthetist, and three nurses. The estimated RR staff cost was calculated by assuming that the RR staff comprised one nurse. All costs were expressed in Euros 2015 (€). The potential gain in using sugammadex instead of neostigmine as first choice reversal drug was obtained by multiplying the time difference in minutes for the costs of OR, and OR and RR staffs. Costs of using sugammadex as rescue therapy and cost of neostigmine avoided were excluded in this analysis.

A cost-saving analysis was then performed considering the cost of drugs used and the economic benefits.

Patients transferred from ORs to the intensive care unit (ICU) in the two periods (2011–2012 vs 2013–2014) were screened for the cause of ICU admission. Only patients admitted because of a PORC were considered for the economic assessment of the impact on unplanned ICU admissions by the introduction of sugammadex. The estimated cost of ICU admission was obtained from previously published data20,21 and adjusted to 2015 using the coefficient of conversion produced by ISTAT.22 This value corresponds to the average cost of a 1 day of ICU stay at University Hospital of Padova.23

Statistical analysis
Data regarding surgery and costs are presented as totals and analyzed with chi-square test. For “preventive” and “curative” use of sugammadex, continuous data are reported as means (± standard deviation) and compared using the Student’s t-test. Categorical data are reported as the absolute number with percentages and compared with the chi-square test or Fisher’s exact test. Linear correlation analysis was used to estimate the association between the NMBA administered and presence of PORC-related AREs. Kaplan–Meier estimate-of-survival curves were used to determine the cumulative probability of delayed discharge from the OR to the surgical ward after 1 hour. Curves for the two groups were compared using the log-rank test. A P-value <0.05 was considered statistically significant.

Results
Outcome
Patients undergoing general anesthesia with NMB who received sugammadex for “preventive” use were 3% of the...
Patients undergoing general anesthesia with rocuronium-induced NMB who received sugammadex for treatment of PORC-related AREs (“curative” use) were 3.2% of the cases (96 of 3,017 [cases treated with rocuronium]) (Table 2). PORC-related AREs included both difficult weaning (2% of cases) and postextubation AREs (1.2% of cases). The treated group showed a worse TOF ratio at the end of surgery than controls (Table 2). In the treated group, the occurrence of an ARE was significantly associated with longer surgical procedures (P<0.001), higher dosage of rocuronium (P<0.001), repeated doses of rocuronium (P<0.001), and shorter time between the last dose of rocuronium and tracheal extubation (P<0.001). The most frequent PORC-related AREs were difficult weaning from mechanical ventilation (60.4%), postextubation severe hypoxemia (19.8%), inability to breathe deeply (9.4%), upper airway obstruction (5.2%), signs of respiratory distress (3.1%), and respiratory failure requiring mask ventilation (2%). In the treated group, the PORC-related AREs did not prolong the RR stay, as the time to discharge from the RR was similar in the treated and control groups (Table 2). Sugammadex administration showed not only reduction of the probability of delayed discharge to the surgical ward after 1 hour (Figure 1A and B) but also reduction in PORC-related ICU admissions. Ten PORC-related unplanned ICU admissions were registered in the 2011–2012 period and one in the 2013–2014 period. No unplanned ICU admissions with rocuronium–neostigmine–sugammadex strategy were observed. No adverse drug reactions related to drugs used for NMB management were registered.

Table I Data for “preventive” use of sugammadex in high-risk patients and comparison with a control group

<table>
<thead>
<tr>
<th></th>
<th>Treated groupa</th>
<th>Control groupb</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female), n (%)</td>
<td>60 (46.8)/68 (53.2)</td>
<td>57 (44.5)/71 (55.5)</td>
<td>0.8</td>
</tr>
<tr>
<td>Age, years, mean ± SD</td>
<td>64±15</td>
<td>62±14</td>
<td>0.58</td>
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<tr>
<td>Weight, kg, mean ± SD</td>
<td>88±25</td>
<td>84±22</td>
<td>0.18</td>
</tr>
<tr>
<td>Height, cm, mean ± SD</td>
<td>174±8</td>
<td>172±9</td>
<td>0.14</td>
</tr>
<tr>
<td>Reversal in patients with difficult airways, n (%)</td>
<td>8 (6.2)</td>
<td>4 (3.1)</td>
<td>0.37</td>
</tr>
<tr>
<td>Elderly subjects (≥75 yr), n (%)</td>
<td>27 (21)</td>
<td>27 (21)</td>
<td>1.0</td>
</tr>
<tr>
<td>Morbid obesity (BMI &gt;35), n (%)</td>
<td>36 (28.1)</td>
<td>36 (28.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Respiratory disease, n (%)</td>
<td>10 (7.8)</td>
<td>15 (11.7)</td>
<td>0.4</td>
</tr>
<tr>
<td>Cardiac disease, n (%)</td>
<td>14 (10.9)</td>
<td>19 (14.8)</td>
<td>0.45</td>
</tr>
<tr>
<td>Kidney disease, n (%)</td>
<td>22 (17.1)</td>
<td>16 (12.5)</td>
<td>0.38</td>
</tr>
<tr>
<td>Cirrhosis, n (%)</td>
<td>4 (3.1)</td>
<td>7 (5.4)</td>
<td>0.54</td>
</tr>
<tr>
<td>Neuromuscular disease, n (%)</td>
<td>3 (2.3)</td>
<td>4 (3.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Contraindications to neostigmine/atropine, n (%)</td>
<td>4 (3.1)</td>
<td>0 (0)</td>
<td>0.12</td>
</tr>
<tr>
<td>Duration of surgery, min, mean ± SD</td>
<td>153±92</td>
<td>162±111</td>
<td>0.45</td>
</tr>
<tr>
<td>Duration of anesthesia, min, mean ± SD</td>
<td>174±98</td>
<td>192±121</td>
<td>0.17</td>
</tr>
<tr>
<td>Inhalational anesthesia/TIVA, n (%)</td>
<td>102 (79.6)/26 (20.4)</td>
<td>96 (75)/32 (25)</td>
<td>0.45</td>
</tr>
<tr>
<td>Intraoperative analgesia (remifentanil/fentanyl), n (%)</td>
<td>91 (71.1)/37 (28.9)</td>
<td>84 (65.6)/44 (34.4)</td>
<td>0.42</td>
</tr>
<tr>
<td>Degree of NMB at extubation, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acceptable, n (%)</td>
<td>128 (100)</td>
<td>71 (55.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mild-to-moderate, n (%)</td>
<td>0 (0)</td>
<td>41 (32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe, n (%)</td>
<td>0 (0)</td>
<td>16 (12.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RR length of stay, min, mean ± SD</td>
<td>56±29</td>
<td>103±52</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Notes: aAdministration of sugammadex for reversal of rocuronium-induced NMB. bAdministration of neostigmine for reversal of rocuronium-induced NMB. cReversal of NMB at the end of surgery in patients with difficult mask ventilation or endotracheal intubation observed at induction of anesthesia. dModerate-to-severe chronic obstructive pulmonary disease or asthma. eIschemic heart disease, chronic heart failure. fMild-to-moderate renal impairment (CrCl > 30 mL/min) or kidney transplantation. gDuchenne muscular dystrophy, dermatomyositis, multiple sclerosis, myasthenia gravis. hDesflurane or sevoflurane anesthesia. iAt the time of tracheal extubation and after reversal drugs administered (sugammadex in treated group and neostigmine in control group). Degree of NMB was rated as acceptable if recovery of the TOF ratio was 0.90, mild-to-moderate if the TOF ratio was 0.7–0.90, or severe if the TOF ratio was <0.70. Student’s t-test and chi-square test or Fisher’s exact test were performed when appropriate. P<0.05 was considered statistically significant.

Abbreviations: BMI, body mass index; TIVA, total intravenous anesthesia with propofol; NMB, neuromuscular blockade; CrCl, creatinine clearance; TOF, train-of-four; RR, recovery room; yr, year; min, minute; SD, standard deviation.
Table 2 Data for “curative” use of sugammadex for adverse respiratory events and comparison with control group

<table>
<thead>
<tr>
<th>AREs group (96 patients)</th>
<th>Control group (96 patients)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female), n (%)</td>
<td>61 (63.6)/35 (36.4)</td>
<td>58 (60.4)/38 (39.6)</td>
</tr>
<tr>
<td>Age, years, mean ± SD</td>
<td>67±9</td>
<td>66±11</td>
</tr>
<tr>
<td>Weight, kg, mean ± SD</td>
<td>71±10</td>
<td>73±9</td>
</tr>
<tr>
<td>Height, cm, mean ± SD</td>
<td>175±8</td>
<td>177±8</td>
</tr>
<tr>
<td>ASA physical status II/III/IV, n</td>
<td>39 (40.6)/47 (49)/10 (10.4)</td>
<td>46 (47.9)/43 (44.8)/7 (7.3)</td>
</tr>
<tr>
<td>Duration of surgery, min, mean ± SD</td>
<td>159±97</td>
<td>146±85</td>
</tr>
<tr>
<td>Duration of anesthesia, min, mean ± SD</td>
<td>190±106</td>
<td>174±92</td>
</tr>
<tr>
<td>Long-standing surgery (&gt;2 hours), n (%)</td>
<td>55 (57.3)/41 (42.7)</td>
<td>47 (49)/49 (51)</td>
</tr>
<tr>
<td>Inhalational anesthesia/TIVA, n (%)</td>
<td>71 (74)/25 (26)</td>
<td>76 (79.1)/20 (20.9)</td>
</tr>
<tr>
<td>Intraoperative analgesia (remifentanil/fentanyl), n (%)</td>
<td>64 (66.6)/32 (33.4)</td>
<td>55 (57.3)/41 (42.7)</td>
</tr>
</tbody>
</table>

NMB-related data
- Rocuronium total dose, mg: 108±35 vs 102±37 (P=0.21)
- Dose repeated, n (%): 75 (78.1) vs 71 (74.0) (P=0.61)
- Time from last dose, min, mean ± SD: 54±19 vs 59±21 (P=0.1)
- Neostigmine, mg, mean ± SD: 3±0.6 vs 3.2±0.9 (P=0.12)
- Degree of NMB at evaluation, n (%): Acceptable, n (%): 8 (8.3) vs 73 (76) (P<0.001), Mild-to-moderate, n (%): 27 (28.1) vs 14 (14.6) (P=0.034), Severe, n (%): 61 (63.6) vs 9 (9.4) (P<0.001)
- RR length of stay, min, mean ± SD: 66±27 vs 70±25 (P=0.44)

Notes: *Patients with AREs after reversal of NMB with neostigmine. †Patients without AREs after reversal of NMB with neostigmine. ‡Inhalational anesthesia: desflurane or sevoflurane anesthesia; TIVA. §Degree of NMB at evaluation: at the time of tracheal extubation (before sugammadex administration in treated group). Degree of NMB rated as acceptable if recovery of the TOF ratio was ≥0.90, mild-to-moderate if the TOF ratio was 0.7–0.90, or severe if the TOF ratio was <0.70. TOF ratio was measured using acceleromyography (TOF-WatchSX, Organon Teknik, Ireland). Student’s t-test and chi-square test or Fisher’s exact test were performed when appropriate. P<0.05 was considered statistically significant.

Abbreviations: ARE, adverse respiratory events; ASA, American Society of Anesthesiologists; NMB, neuromuscular blockade; RR, recovery room; TIVA, total intravenous anesthesia with propofol; TOF, train-of-four; yr, year; min, minute; sD, standard deviation.

Costs analysis of NMB management

Despite the overall number of procedures involving general anesthesia with NMB increasing significantly (P<0.0001) (Figure 2), the introduction of rocuronium–neostigmine–sugammadex into a regimen based on cisatracurium–neostigmine as the main strategy for NMB management decreased the total costs of NMB management by 25% from 2011–2012 to 2013–2014 (Figure 3). Although the costs per vial remained constant, the total costs for succinylcholine (P=0.0026) and cistracurium (P<0.0001) significantly decreased, whereas the costs for rocuronium (P<0.0001), sugammadex (P<0.0001), and neostigmine (P=0.0164) significantly increased over the

Figure 1 Comparison of postoperative course between treated and control groups in 2013–2014 period.

Notes: Cumulative probability of delayed discharge to the surgical ward after reversal of NMB at the end of general anesthesia with sugammadex for “preventive” use (A) and “curative” use (B) vs control. Control group: reversal of NMB with neostigmine. Treated group: reversal of NMB with sugammadex. Kaplan–Meier estimate-of-survival curves were obtained using GraphPad Software, Inc., La Jolla, CA, USA. P<0.05 was considered statistically significant.

Abbreviation: NMB, neuromuscular blockade; min, minutes.
The overall incidence of AREs (3.2%) observed in our study is within the range of 1.3%–6.9% reported in the literature. Residual effects of NMBAs are common in the postoperative period, with rates ranging from 26% to 64%. The economic benefit in speeding the complete recovery from NMB and the discharge to surgical ward was estimated to be €6.6/min based on OR cost, and €3.72/min and €0.35/min based on OR and RR staffs, respectively (Table 3).

Considering that in the University Hospital of Padova the OR cost (€6.6/min) includes also the OR staff cost (€3.72/min), the gain in shorter OR stay based on OR cost was estimated to be €18,064 as obtained by calculating the difference between the loss of gain associated to neostigmine (€19,727) and sugammadex (€1,663) (Table 4 and Figure 4). Based on RR staff cost, the gain in shorter RR stay was estimated to be €2,105.6, considering the mean difference time of RR stay (Table 2). The total gain was then €20,169.6 which is derived from the sum of estimated gains in OR (€18,064) and in RR (€2,105.6). The final analysis, in which the cost of neostigmine for “preventive” use (€94) was excluded, showed a cost of €154.7/case and an estimated gain of €157.6/case, with a net cost-saving of €2.9/case.

The average cost of ICU stay was estimated to be €1,354.8/day (range from €931.6/day to €2384.5/day). Based on estimated cost of ICU stay, the economic benefit in avoiding PORC-related ICU admission was estimated at €13,548 (€9,316–€23,845).

**Discussion**

An NMB management based on rocuronium–neostigmine–sugammadex strategy is less expensive than that based on cisatracurium–neostigmine regimen. Sugammadex was demonstrated to increase safety in patients receiving a rocuronium-induced NMB, avoiding PORC if given as the first-reversal drug in high-risk patients and allowing prompt treatment of PORC-related AREs occurring after administration of standard reversal drugs. Despite its cost, sugammadex showed resource savings to the hospital by speeding the recovery from NMB in the OR. It was also shown to potentially produce resource savings by reducing the rate of PORC, time spent in the RR, and rate of unplanned ICU admissions.

PORC following intraoperative NMBAs administration is common in the postoperative period, with rates ranging from 26% to 64%. Residual effects of NMBAs are associated with an increased risk of AREs. The overall incidence of AREs (3.2%) observed in our study is within the range of 1.3%–6.9% reported in the literature.
incidence of postextubation AREs is greater than the 0.8% reported by Murphy et al., but close to the 1.3% that Rose et al.26 reported in their study. Postoperative AREs are associated with increased postoperative morbidity and mortality, prolonged postanesthesia care unit (PACU) stay, or unanticipated admissions to the ICU.5,26,28 Strategies to reduce PORC include the use of short- or intermediate-duration NMBAs, neuromuscular monitoring, and reversal agents.5

The use of intermediate-duration NMBAs has been shown to reduce (albeit not eliminate) the risk of AREs.28,29 Cisatracurium is purported to be advantageous over rocuronium because of its organ-independent metabolism.4,30,31 However, a regimen based on cisatracurium for NMB does not completely eliminate the risk of PORC.5 In a randomized, controlled, double-blind, multicenter trial of 338 patients, the incidence of PORC in patients receiving cisatracurium was 57%, which was significantly \( P<0.05 \) higher than the 44% incidence in those receiving rocuronium.4 A wide variability in the rate of spontaneous recovery has been observed after a single dose of an intermediate-duration NMBA, which can be prolonged by such factors as hypothermia, interactions with halogenated agents, and underlying diseases, and which may extend even longer than 2 hours.32 Furthermore, both a continuous infusion and repeated doses of these NMBAs are associated with an increased risk of PORC.1,4,33

The routine use of neuromuscular function monitoring has been previously shown to reduce the incidence of PORC.5,29,34 However, quantitative monitoring of neuromuscular transmission does not entirely abolish the risk of PORC.28 Furthermore, it is not always used in clinical practice.35

### Table 3 Estimated costs associated with the operating room, operating room staff, and recovery room staff

<table>
<thead>
<tr>
<th></th>
<th>Annual salary (€)</th>
<th>Working(^a) time</th>
<th>OR,(^b) cost/min (€)</th>
<th>OR staff, cost/min (€)</th>
<th>RR staff, cost/min (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultant surgeon senior</td>
<td>98,234</td>
<td>45 wk/38 h</td>
<td>–</td>
<td>0.96</td>
<td>–</td>
</tr>
<tr>
<td>Consultant surgeon junior</td>
<td>82,116</td>
<td>45 wk/38 h</td>
<td>–</td>
<td>0.80</td>
<td>–</td>
</tr>
<tr>
<td>Consultant anesthetist</td>
<td>98,234</td>
<td>44 wk/38 h</td>
<td>–</td>
<td>0.98</td>
<td>–</td>
</tr>
<tr>
<td>Nurse D-level</td>
<td>36,186</td>
<td>45 wk/38 h</td>
<td>–</td>
<td>0.35</td>
<td>–</td>
</tr>
<tr>
<td>Nurse B2-level</td>
<td>29,370</td>
<td>45 wk/38 h</td>
<td>–</td>
<td>0.35</td>
<td>0.35</td>
</tr>
<tr>
<td>OR cost for hour</td>
<td>400</td>
<td>–</td>
<td>6.6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Total cost for minute (€)</td>
<td>6.6</td>
<td>3.72</td>
<td>0.35</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:** \(^a\)Working time: effective working time of staff at Padova Hospital. \(^b\)OR cost: all comprehensive average cost for hour of an OR in Padova Hospital. \(^c\)Surgeon with \( >15 \) years of National Health Service activity. \(^d\)Surgeon with \( 6-15 \) years of National Health Service activity. Personnel costs were based on annual salaries provided by the Personal Administration of Padova Hospital according with National Health Service.

**Abbreviations:** OR, operating room; RR, recovery room; wk, week; h, hours.

### Table 4 Comparison of productivity loss according to reversal strategy

<table>
<thead>
<tr>
<th>Reversal time (min)</th>
<th>Cases (n)</th>
<th>Overall time (min)</th>
<th>Staff costs (€)</th>
<th>OR costs (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sugammadex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate NMB</td>
<td>1.7(^a)</td>
<td>93</td>
<td>158</td>
<td>588</td>
</tr>
<tr>
<td>Deep NMB</td>
<td>2.7(^a)</td>
<td>35</td>
<td>94</td>
<td>350</td>
</tr>
<tr>
<td>Total</td>
<td>128</td>
<td>252</td>
<td>938</td>
<td>1,663</td>
</tr>
<tr>
<td><strong>Neostigmine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate NMB</td>
<td>13.7(^a)</td>
<td>93</td>
<td>1,274</td>
<td>4,740</td>
</tr>
<tr>
<td>Deep NMB</td>
<td>49(^a)</td>
<td>35</td>
<td>1,715</td>
<td>6,380</td>
</tr>
<tr>
<td>Total</td>
<td>128</td>
<td>2,989</td>
<td>11,120</td>
<td>19,727</td>
</tr>
</tbody>
</table>

**Notes:** The reversal times to recovery to TOF ratio \( \geq 0.9 \) multiplied by number of patients were used for estimation of overall time loss. The overall time loss multiplied by costs of OR staff and OR in Padova Hospital was used for calculation of productivity (gain) loss. The mean time to recovery to TOF ratio \( \geq 0.9 \) (sugammadex vs neostigmine) were taken from Illman et al.\(^b\) for moderate NMB (1.7 vs 13.7 minutes) and from Jones et al.\(^b\) for deep NMB (2.7 vs 49 minutes). Moderate NMB was observed in 93 patients, while deep NMB was observed in 35 patients.

**Abbreviations:** OR, operating room; NMB, neuromuscular blockade; TOF, train-of-four.

### Figure 4 Estimation in euro (€) of productivity (gain) loss with reversal of rocuronium-induced NMB by sugammadex administered for “preventive use” compared to neostigmine

**Notes:** Chi-square tests were performed. Significance (*) was taken at \( P<0.05 \).

**Abbreviation:** NMB, neuromuscular blockade.
The administration of reversal agents plays, then, an important role in reducing the risk of PORC.\textsuperscript{5,29,34} Traditionally, acetylcholinesterase inhibitors, such as neostigmine, are used to hasten recovery from NMB. However, their efficacy is limited because of a ceiling effect, which limits their effectiveness when the NMB is profound.\textsuperscript{5,29} Moreover, using higher or repeated doses of neostigmine to improve neuromuscular recovery and reduce the rate of PORC may also be associated with increased postoperative respiratory morbidity.\textsuperscript{36} Because of its mechanism of action, sugammadex improves the quality and safety of NMB reversal in clinical practice.\textsuperscript{1,4,14,37} Sugammadex has been shown to reduce the incidence of PORC and AREs, and to shorten the time for discharge from the OR.\textsuperscript{7,29,38} The usefulness of sugammadex for treatment of AREs after neostigmine reversal has also been reported.\textsuperscript{17,39} Our data provide evidence supporting the benefit of sugammadex in preventing PORC and associated morbidities,\textsuperscript{38} particularly in high-risk patients, such as those who are elderly or obese and those who have respiratory, cardiac, kidney, liver, or neuromuscular disease.\textsuperscript{5,40–43}

The benefits associated with sugammadex have a cost, which is primarily related to the direct cost of the drug itself. However, in our economic evaluation, sugammadex may contribute to overall cost-savings for the hospital in several ways. First, it reduced the cost of NMB management by requiring the use of rocuronium, which is three times less expensive than cisatracurium at the current list price in our hospital. Second, sugammadex allowed a rapid, safe, and complete recovery from NMB in high-risk patients.\textsuperscript{15,40–44} Third, sugammadex as rescue therapy after neostigmine reversal quickly resolved PORC-related AREs. Both these latter two aspects have clinical and economic implications. Prolonged time to extubation at the end of general anesthesia delays OR exit and slows OR workflow.\textsuperscript{45} Different surgical and anaesthesiological factors may concur to a prolonged extubation that is regarded unfavorably by both anaesthesiologists and surgeons.\textsuperscript{45,46} To such purpose, residual curarization showed to increase significantly the risk of delayed OR exit and PACU discharge.\textsuperscript{46} A proper NMB management may then play an important role in helping to avoid prolonged extubation time and delayed OR exit.\textsuperscript{52,47} Sugammadex has been shown to reduce the anesthesia time,\textsuperscript{47} and time for OR exit and PACU discharge.\textsuperscript{38,48} The economic benefits have been estimated to have a value of £6.6/min gained in OR (£3.72/min considering only the OR staff cost) and £0.35/min gained in the RR, with a net saving of £2.9/case. A recent pharmaco-economic evaluation estimated that time saved in the OR has a value of £4.44/min, whereas time saved in the PACU has a value of £0.33/min, confirming that sugammadex 2 mg/kg (or 4 mg/kg) is cost-effective for reversal of moderate (or deep) NMB induced by rocuronium\textsuperscript{13,14} and has the potential to increase the OR productivity with an associated economic benefit.\textsuperscript{21} However, the effort to reduce extubation time from the end of surgery has an economical advantage only if the OR represents a variable cost and not a fixed cost.\textsuperscript{45,49} This may be the case in which all (eg, >90\%) ORs at a hospital have more than 8 hours of cases each workday. In such situations, there is a rationale to reduce the chance that tracheal extubation times will be prolonged.\textsuperscript{45,49}

Another suggested benefit of sugammadex that was not investigated in this study is that scheduled surgical procedures may not be delayed or suspended because of unanticipated problems with the preceding surgery, such as prolonged reversal of NMB or PORC-related AREs requiring postoperative care or unplanned ICU admission.\textsuperscript{13,14} The economic benefit may reach an average value of €1,354.8 for each avoided day of ICU stay. Finally, by reducing morbidity and mortality associated with PORC or being unable to quickly reverse profound NMB with standard reversal drugs in a CVCI situation, sugammadex promotes improved quality and safety of anesthetic management that may not be quantifiable from an economic viewpoint, but is nevertheless highly desired.

The study has some limitations. First, it was performed in a single national center. The cost of drug use may be subject to variations among national hospitals. Furthermore, some aspects of the cost-analysis may not apply to other countries and different health-care systems.\textsuperscript{14} Second, the benefit of reduction in OR time may depend on the day of the week and the hours of cases in the OR in which the intervention is applied and may be lost in case of emergency room or ORs scheduled relatively empty in which ORs represent a fixed cost.\textsuperscript{45,50} Third, it is possible that sugammadex produces further resource savings than those considered; however, there are no suitable data to provide a basis for such modeling, so these were not considered.\textsuperscript{14} Finally, an evaluation of the outcomes of patients undergoing general anesthesia with cisatracurium-induced NMB was not performed.\textsuperscript{14}

Conclusion

In conclusion, sugammadex promotes a rapid turnover of patients in the OR, which is cost-effective and limits the disadvantage of its high cost. Through a rapid, predictable, and safe reversal of rocuronium-induced NMB, sugammadex minimizes the risk of PORC and its consequences.
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Author contributions
MC has made contributions to conception and design of the study, acquisition of data, analysis and interpretation of data, and drafting and revising the manuscript.

FB has made contributions to conception and design of the study, acquisition and interpretation of data, and revising the manuscript.

FZ has made contributions to acquisition and interpretation of data, and revising the manuscript.

CO has made contributions to conception and design of the study, analysis and interpretation of data, and revising the manuscript.

All authors agree on all aspects of the work, and read and approved the final paper.

Disclosure
MC, FB, and CO have received payments for lectures from Merck Sharp and Dohme (MSD), Italy. The authors report no other conflicts of interest in this work.

References


