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## Cost Differences Between Sugammadex and Neostigmine Use in Non-Operating Room Anesthesia Care

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Cost Differences Between Sugammadex and Neostigmine Use in Non-Operating Room  
Anesthesia Care

A Doctor of Nursing Practice Project Defense

Presented in

Partial Fulfillment of the

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By

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*Keywords:* sugammadex, neostigmine, glycopyrrolate, non-operating room anesthesia care

### *Abstract*

Prior to the introduction of sugammadex, the only option to reverse rocuronium-induced neuromuscular blockade (NMB) were cholinesterase inhibitors (i.e. neostigmine) and anticholinergics (i.e. glycopyrrolate). Sugammadex administration has been shown to provide a more effective and complete reversal of rocuronium. However, the higher cost of sugammadex has been cited as a limiting factor to its use.

The medication costs of sugammadex and neostigmine with glycopyrrolate have been studied in the operating room setting. There is a lack of information regarding the usage and medication costs of sugammadex and neostigmine with glycopyrrolate for non-operating room anesthesia care (NORA). A retrospective chart review was conducted over a 12-month period, from January 1, 2017, to December 31, 2017 aimed at examining the cost associated with the administration of neostigmine with glycopyrrolate versus sugammadex for anesthesia in NORA locations. The following information was collected on patients who met the inclusion criteria: type and dose of NMB reversal agent, age, weight, body mass index (BMI), American Society of Anesthesiologist physical status (ASA PS) classification, NORA locations such as cardiac catheterization laboratory (Cath lab), gastrointestinal laboratory (GI lab), magnetic resonance imaging room (MRI), computed tomography room (CT), interventional radiology (IR), obstetrics (OB) unit, and electrophysiology laboratory (EP lab). This study consisted of 526 patient charts that fulfilled inclusion criteria. Correlational data analysis revealed that there was a weak positive correlation between ASA score and use of sugammadex. There was also a statistically significant difference in the administration between NORA departments, notably in the EP lab.

Due to fluctuating costs of sugammadex, neostigmine, and glycopyrrolate, cost analysis did not reveal sugammadex as a cost-effective option for NMB reversal in NORA locations.

## **Introduction**

Neuromuscular blockade agents (NMBA) are often used intraoperatively to facilitate intubation by anesthesia providers and allow the surgeon to complete the intended procedure without movement interference from the patient. Aminosteroidal NMBA, including rocuronium, are commonly used as part of the anesthetic plan. The conventional NMB reversal agents used are cholinesterase inhibitors like neostigmine. Since the Food and Drug Administration approval of sugammadex in 2016, it has been an alternative to cholinesterase inhibitors as an NMB reversal agent. Sugammadex when compared to neostigmine may have a better safety profile; however, the high cost has limited its use.<sup>1</sup> As more healthcare institutions aim to achieve value-based goals while reducing their overhead costs, many surgical procedures are being performed outside of the main operating room (OR). The cost and use of sugammadex in NORA locations has not been evaluated prior to this study. Nagrebetsky et al.<sup>2</sup> found that there was an increase in NORA during 2010 to 2014. Nagrebetsky et al.<sup>2</sup> also found that the average age of NORA patients has increased, in addition to a greater number of patients with ASA PS classifications of III to IV in NORA locations compared to the OR. The findings of the Nagrebetsky et al.<sup>2</sup> suggest that anesthesia providers will continue to encounter more higher acuity patients in NORA locations. The purpose of this retrospective chart review was to examine the cost associated with the administration of neostigmine with glycopyrrolate versus sugammadex for NORA locations.

## **Background**

The results of multiple meta-analyses and randomized controlled trials show that sugammadex is more reliable in reversing NMB than neostigmine as demonstrated by a higher return of train-of-four ratio greater than or equal to 0.9 at extubation and lower risk of recurarization.<sup>1,3,4</sup> Compared to neostigmine, sugammadex use is associated with significantly lower risk of respiratory and cardiac adverse events and postoperative weakness while both are associated with similar risk of postoperative nausea and vomiting, pain, and neurological adverse events.<sup>1</sup> These findings can be attributed to the different mechanisms of action through which neostigmine and sugammadex exert their effects.

Logistically, NORA presents challenges such as less access to emergency personnel, equipment, and/or medications and being at a greater distance from the patient compared to the OR setting. Youn et al.<sup>5</sup> states that the lack of monitoring equipment, emergency equipment and medications, and the unfamiliar location associated with NORA pose risks to the patients and anesthesia providers. Newer and more advanced procedures are performed in NORA locations on patients are otherwise not optimized for surgical interventions which increases the degree of unfamiliarity for anesthesia providers and increases risks to the patient.<sup>5</sup> In reviewing closed claims, Robbertze et al.<sup>6</sup> found patients who received NORA compared to anesthesia care in the traditional OR setting had a higher incidence of mortality and adverse events, which often were preventable.

Some studies indicate that the higher cost of sugammadex factors into the limited use of the newer NMB reversal.<sup>7,8</sup> Despite the higher cost of sugammadex, the benefits of decreased recovery time in the operating room, quicker discharge to the recovery units, and decreased

complications related to postoperative residual curarization may justify and offset medication cost differences.<sup>9</sup>

There is confounding evidence as to the overall costs associated with the two NMB reversal agents. There is no standardized guideline that determines when it is appropriate to use neostigmine and glycopyrrolate versus sugammadex that enhances medication cost savings while still maintaining safe reversal for the patients who received rocuronium. Factors such as ASA PS classification, patient weight, and age are some examples of determining factors for the choice of NMB reversal agent.<sup>4,9,10</sup>

## **Review of Literature**

### *Literature Search*

A search for recent literature regarding cost and sugammadex was performed on PubMed. Search terms “costs” and “sugammadex” yielded 35 results. Literature search was further narrowed with the search terms “costs and cost analysis” and “sugammadex” which yielded nine results.

### *Pharmacology of Cholinesterase Inhibitors*

Cholinesterase inhibitors work by inhibiting the cholinesterase enzyme that breaks down acetylcholine. Cholinesterase inhibitors work indirectly to increase the concentration of acetylcholine which competes with any residual NMBA to bind to the nicotinic receptors at the motor end plates.<sup>11</sup> Neostigmine is normally administered along with glycopyrrolate, an anticholinergic, to decrease the cholinergic side effects of neostigmine. It is important to note that administration of glycopyrrolate also has its own anticholinergic side effects, including vagolytic effects. When neostigmine is administered after full reversal of NMB, dose-dependent



negative effects to the genioglossus and diaphragm muscles can occur, which may lead to upper airway obstruction and respiratory failure.<sup>1</sup> However, recent research conducted by Murphy et al.<sup>4</sup> concluded patients who had a train-of-four (TOF) ratio of 0.9 or greater and received neostigmine had no adverse effects including postoperative obstruction, respiratory function, and no difference in peripheral capillary oxygen saturation (SpO<sub>2</sub>) compared to the control group.

The NMBA can have a duration of action longer than that of the anticholinesterase inhibitor, which can lead to a phenomenon known as recurarization.<sup>7</sup> Recurarization can lead to neuromuscular dysfunction which can contribute to postoperative respiratory complications such as aspiration, airway muscle weakness, airway obstruction, hypoxemia, impaired ventilation, reintubation, prolonged stay in post-anesthesia care unit, and prolonged hospital stay.<sup>7</sup>

### *Pharmacology of Sugammadex*

Sugammadex is a NMB reversal agent with a different mechanism of action than neostigmine. Since sugammadex does not interact with muscarinic or nicotinic receptors and has no effect on acetylcholinesterase, the cholinergic effects observed with neostigmine and anticholinergic effects of glycopyrrolate are avoided with sugammadex administration.

Sugammadex can be used in situations where patients cannot be ventilated or intubated after administration of rocuronium. Sugammadex has also been used as a rescue NMB reversal agent after administration of neostigmine, in cases of recurarization that impacts respiratory function.

Sugammadex has also been used when there is suspicion of anaphylaxis after rocuronium administration.

### **Use of Neostigmine and Sugammadex**

There are many factors affecting the cost of neostigmine and sugammadex such as cost agreed upon between a healthcare system and the pharmaceutical company. Depending on institution and unit preferences for various size and concentration of vials and/or prefilled syringes of sugammadex, neostigmine, and glycopyrrolate, the cost of the medications will vary. The researchers in this study focused on the costs of preferred size and concentrations of sugammadex, neostigmine, and glycopyrrolate used at NSUHS NORA locations since this is where the research was conducted.

### **Cost savings**

Sugammadex has the potential to have a cost-effective benefit for the reversal of moderate to deep steroidal-induced NMB as long as the time savings is directed towards another income producing activity, towards scheduling more operations as a result of reduced emergence time, or towards freeing up staff to take care of another patient.<sup>9</sup> In a study by Chambers et al.<sup>12</sup>, sugammadex is likely to be cost-effective when shorten recovery time occurs in the OR rather than the recovery room. However, the shortened recovery room time can be cost-effective when if its use results in decreased mortality. In a systematic review by Paton et al.<sup>13</sup> the use of sugammadex estimated the time saved in the OR has a value of £4.44 per minute and £0.33 per minute in recovery room. Interestingly, Paton et al.<sup>13</sup> predicted the cost of reversal agents would increase if sugammadex use is to be recommended for reversal of NMBAs.

Aouad et al.<sup>14</sup> acknowledged the higher cost of sugammadex compared to neostigmine and found that half dose sugammadex (2 mg/kg) in combination with neostigmine is non-inferior to full dose sugammadex (4 mg/kg) for rocuronium-induced deep NMB.

It is likely that if there were no cost-restrictions with the use of sugammadex, anesthesia providers will be more prone to administer sugammadex due to its limited adverse effects and more complete reversal of rocuronium and/or vecuronium. In a study by Watts et al.<sup>15</sup>, the cost-limitations and use restrictions of NMB reversal agents were lifted and the use of sugammadex, neostigmine, and rocuronium was analyzed. Watts et al.<sup>15</sup> found that use of sugammadex increased from 7.1% to 65.3% while use of neostigmine decreased from 59.6% to 12.5%. The authors concluded that there will be an increase in sugammadex use due to its safety profile and efficacy if cost-restrictions were lessened or alleviated.<sup>16</sup>

In summary, cost-savings studies comparing neostigmine and sugammadex are limited and many variables could play significant effect on cost-savings on either drug as shown in Table 2. This study examined data on the cost-savings of sugammadex in the population that NSUHS served in 2017.

### **Project Design**

After receiving IRB approval from DePaul University and NSUHS, a retrospective chart review of using EPIC, NSUHS's EMR software, was conducted at NSUHS's four hospitals (Evanston Hospital, Glenbrook Hospital, Highland Park Hospital, and Skokie Hospital). Data was accessed from January 1, 2017 to December 31, 2017 to analyze the usage of sugammadex, neostigmine, and glycopyrrolate in NORA locations such as Cath lab, GI laboratory, MRI, CT, IR, OB unit, and EP lab.

This methodology avoided any impact on routine anesthetic care of the patient. Adult patients over the age of 18 who received rocuronium for surgical paralysis and did not require mechanical ventilation postoperatively were included. Patients who required sugammadex for

rescue NMB reversal after administration of neostigmine, patients under the age of 18, and patients requiring mechanical ventilation postoperatively were excluded. The following information was collected and grouped accordingly (Appendix A) on patients who met the inclusion criteria: dosage of the NMB reversal agent, age, weight, body mass index (BMI), ASA PS classification, and NORA.

The dependent variable was the dose and type of NMB reversal agent used. In the NSUHS Anesthesia Department, neostigmine is supplied as 3 mL prefilled syringes. Glycopyrrolate is supplied as 0.4 mg/2 mL vials. Sugammadex is supplied as 200 mg/2mL vials and 500 mg/5 mL vials. According to department policy, these syringes and vials are single patient use only. The number of vials and/or syringes of NMB reversal agents were deduced from the the dose administered to the patient during the procedure.

Age divided into the following groups to look for any trends related to the documented uses of NMB reversal agent: 18-35 years old, 36-50 years old, 51-65 years of old, 66-80 years old, and equal to or greater than 81 years old. The patients were divided into the following groups based on weight: less than or equal to 50 kg, 51-60 kg, 61-70 kg, 71-80 kg, 81-90 kg, 91-100 kg, and greater than 100 kg. It was necessary to analyze the data based on weight since weight based dosing is recommended for the NMB reversals. This weight-based dosing determines how many vials and/or syringes are necessary for adequate reversal. For example, a 60 kg patient will only require one 3 mL syringe of neostigmine (3 mg/3 mL concentration) while a 70 kg patient will require two syringes (one entire 3 mL syringe in addition to 0.5 mL of a second syringe). Partial doses must be wasted after a procedure and are not reused or shared with another patient. BMI was divided into five groups: less than 18.5 (underweight), 18.5-24.9

(normal weight), 25 - 29.9 (overweight), 30.0-34.9 (obesity I), 35-39.9 (obesity II), and equal to or greater than 40 (extreme obesity). ASA PS classification was divided according to the patient's ASA PS classifications assigned preoperatively by anesthesia provider: ASA I, ASA II, ASA III, ASA IV, and ASA V. NORA locations were divided by their locations such as Cath lab, GI lab, MRI, CT, IR, OB unit, and EP lab.

## **Methods**

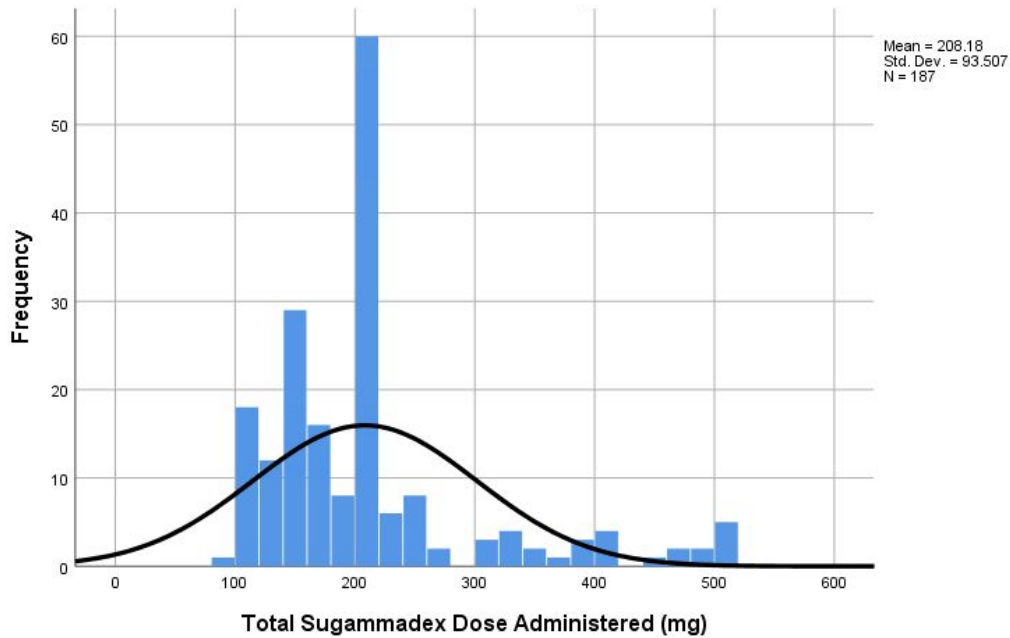
### *Statistical analysis*

After removal of 31 patient charts that fulfilled at least one exclusion criteria, 526 charts were included in this study. Data analysis was conducted using IBM Statistical Package for the Social Sciences for Windows (version 25). Descriptive statistics were conducted for numerical variables which included ASA PS classification, BMI, and patient weight. Correlational analyses were conducted between separate independent variables and anesthesia provider choice of administering sugammadex.

## **Results**

The study was completed with 526 charts which all fulfilled the inclusion criteria. The average ASA score was  $2.76 \pm 0.028$ . The mean weight was found to be  $85.15 \pm 1.00$  kg and mean BMI was  $28.68 \pm 0.27$  kg/m<sup>2</sup>. Of the 526 patient charts reviewed, sugammadex was administered to 187 patients as NMB reversal agent. Analysis of the dosage of sugammadex administered revealed that there was a non-normal distribution with a large number of patients receiving 200 mg of sugammadex (Figure 1).

Figure 1.- Frequency of Sugammadex Dose



Analysis of the correlation between ASA score and administration of sugammadex revealed a statistically significant Spearman’s rho of 0.0117 ( $p = .007$ ,  $\alpha = 0.05$ ), indicating a weak positive correlation. There was no statistically significant correlation noted between age category, BMI category, and weight category compared to administration of sugammadex using Spearman’s test. There was also no statistically significant correlation between actual BMI and actual weight compared to administration of sugammadex using Pearson’s test. A cross-tabulation was created to compare use of sugammadex in various NORA departments. As shown in Table 1, the administration of neostigmine was more frequent than the administration of sugammadex in NORA departments, except in the EP lab with 27 patients having received neostigmine and 41 patients having received sugammadex.

Table 1. Sugammadex usage within various NORA departments

		DEPARTMENT					
		Cardiac catherization lab	GI lab	MRI	IR	Electrophysiol ogy lab	Total
Received sugammadex	No	182	47	24	59	27	339
	Yes	59	41	14	32	41	187
Total		241	88	38	91	68	526

A Pearson Chi-square analysis was performed and found that there was statistically significant difference in the administration of sugammadex within NORA departments ( $p = 0.000$ ,  $\alpha = 0.05$ ).

Cost analysis

The primary investigators found that there was a large discrepancy between the 2018 and 2019 costs of sugammadex, neostigmine, and glycopyrrolate. While exact acquisition costs of these three medications cannot be obtained, the primary investigators found pricing through Lexicomp. The following chart reflects pricing of sugammadex, neostigmine, and glycopyrrolate in 2018 and 2019.

Table 2. 2018 and 2019 Lexicomp Costs of NMB Reversal Agents

	Prices as of October 14, 2018	Prices as of February 9, 2019
Sugammadex (200 mg/2 mL vial)	\$114.00 <sup>16</sup>	\$119.68 <sup>19</sup>
Sugammadex (500 mg/5 mL vial)	\$208.80 <sup>16</sup>	\$219.35 <sup>19</sup>
Neostigmine (3 mg/3 mL prefilled syringe)	\$37.62 <sup>17</sup>	\$6.12 - \$16.20 <sup>20</sup>
Glycopyrrolate (0.4 mg/2 mL vial)	\$16.78 <sup>18</sup>	\$6.72 - \$28.76 <sup>21</sup>

Calculations of the vials of sugammadex and glycopyrrolate and syringes of neostigmine were determined by the dosage of medication administered to the patient. Based on 2018 prices, these three medications used in NORA locations accounted for \$51,128.82. Based on 2019 prices with neostigmine and glycopyrrolate listed with a price range, the cost of the three medications ranged from \$33,466.41 to \$48,683.61. There was a notable drop in the price of neostigmine and a slight increase in the price of sugammadex in 2019.

### **Discussion**

The weak positive correlation between ASA PS classification and use of sugammadex aligns with the increased safety profile of sugammadex and usage on higher acuity patients. Based on the lack of correlation between age, BMI, and weight, NSUHS anesthesia providers did not preferentially use sugammadex based on these independent variables. Statistically significant difference in the use of sugammadex by department may be related to the nature of anesthesia cases in the EP lab, such as cardiac ablation that requires deep paralysis. While no other NORA departments preferentially used more sugammadex than neostigmine, there was an evident preference in the choice of sugammadex in the EP lab.

There were notable limitations to the cost analysis for this study. While 2017 prices of sugammadex, neostigmine, and glycopyrrolate could not be obtained, 2018 and 2019 prices were available to the principal investigators. Due to the fluctuating prices, wide price ranges of neostigmine and glycopyrrolate, and varying acquisition costs for healthcare facilities of the three medications, it is difficult to determine whether sugammadex or neostigmine and glycopyrrolate would have been more cost-effective as a NMB reversal agent.

### **Conclusion**



With higher risks associated with performing surgical procedures in NORA locations, there was a slight correlation between use of sugammadex and ASA PS classification. EP lab was the only department where sugammadex was administered more frequently than neostigmine. Cost-analysis could not be performed to determine if the choice of NMB reversal agent would lead to cost savings. The inability to perform cost-analysis was due to the constant fluctuating costs of sugammadex, neostigmine, and glycopyrrolate and a large range of acquisition costs of these medications. A potential explanation of the frequency of neostigmine and sugammadex use observed in this study may be due to the anesthesia provider preference of NMB reversal agent. Neostigmine has been the traditional NMB reversal agent until Food and Drug Administration approval of sugammadex. It may be valuable for future studies to observe use of these NMB reversal agents in NORA locations at a later time and determine if there is a notable difference in the usage of sugammadex and neostigmine.

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Appendix

Appendix A- Data Classification

<u>Age (years)</u>	<u>Weight (kg)</u>	<u>BMI</u>	<u>ASA PS Classification</u>	<u>Non-operating room location</u>
18-35	≤ 50	< 18.5	I	Cardiac catheterization lab
36-50	51-60	18.5-24.9	II	GI lab
51-65	61-70	25-29.9	III	MRI
66-80	71-80	30-34.9	IV	CT
≥ 81	81-90	35-39.9	V	IR
	91-100	≥ 40		OB
	> 100			EP lab