Original Article

# Decrease in heart rate following the administration of sugammadex in adults

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## Abstract

**Background and Aims:** Sugammadex is a novel agent for reversal of steroidal neuromuscular blocking agents (NMBAs) with potential advantages over acetylcholinesterase inhibitors. In preclinical trials, there have been rare instances of bradycardia with progression to cardiac arrest. To better define this issue, its incidence and mitigating factors, we prospectively evaluated the incidence of bradycardia after sugammadex administration in adults.

**Material and Methods:** Patients ≥ 18 years of age who received sugammadex were included in this prospective, open label trial. After administration, heart rate (HR) was continuously monitored. HR was recorded every minute for 15 minutes and then every five minutes for the next 15 minutes or until patient was transferred out of the operating room. Bradycardia was defined as HR less than 60 beats/minute (bpm) or decrease in HR by ≥ 10 beats per minute (bpm) if the baseline HR was <70 bpm.

**Results:** The study cohort included 200 patients. Bradycardia was observed in 13 cases (7%; 95% confidence interval: 4, 11), occurring a median of 4 minutes after sugammadex administration (IQR: 4, 9, range: 2-25). Among patients developing bradycardia, two (15%) had cardiac comorbid conditions. One patient received treatment for bradycardia with ephedrine. No clinically significant blood pressure changes were noted. On bivariate analysis, patients receiving a higher initial sugammadex dose were more likely to develop bradycardia. On multivariable logistic regression, initial sugammadex dose was not associated with the risk of bradycardia.

**Conclusion:** The incidence of bradycardia after administration of sugammadex in our study was low and not associated with significant hemodynamic changes.

**Keywords:** Anesthesia, neuromuscular blockade reversal, perioperative management

## Introduction

Pharmacologic agents to reverse neuromuscular blockade are commonly administered at the conclusion of surgical procedures to allow return of normal neuromuscular function with resumption of spontaneous ventilation, and to facilitate tracheal extubation.[1-3] Until recently, acetylcholinesterase inhibitors such as neostigmine were the agents of choice. In 2015, the United States Food & Drug Administration (FDA) approved the clinical use of sugammadex, a novel pharmacologic agent to reverse neuromuscular blockade in adults. Sugammadex is the first non-competitive antagonist for the reversal of steroidal NMBAs, including rocuronium and vecuronium.[4-8] In preclinical trials, sugammadex administration has been shown

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to be relatively safe, with the majority of adverse effects being minor and self-limiting. However, the package insert notes rare episodes of marked bradycardia with occasional progression to cardiac arrest within minutes of administration.[1] Although adult studies have reported a 2% incidence of bradycardia, which is lower than with neostigmine,[9-11] specific clinical information regarding bradycardia episodes potentially related to sugammadex administration is limited. There are limited data regarding the impact on hemodynamic status, the need for interventions to treat clinical compromise, and patient risk factors for bradycardia related to sugammadex. Furthermore, despite concerns regarding the possibility of bradycardia, the causal relationship between sugammadex and bradycardia remains speculative, as no mechanism has been postulated for this response.

Based on our growing clinical experience with sugammadex for reversal of NMBAs in adults, we prospectively evaluated the incidence of bradycardia after sugammadex administration in this population. Our primary aim was to describe the incidence of bradycardia in adults receiving sugammadex. Secondarily, we aimed to characterize patient and procedure characteristics associated with bradycardia after sugammadex administration and to determine if treatment for the bradycardia was necessary due to clinically significant hemodynamic concerns, including hypotension or clinical compromise.

## Material and Methods

After Institutional Review Board approval requiring written patient consent (IRB ID: MOD00016723 approved March 12, 2018), we enrolled patients scheduled for surgery requiring the administration of sugammadex to reverse neuromuscular blockade with rocuronium or vecuronium into this prospective, observational study. The study was conducted at the University of Kansas Medical Center (Kansas City, Kansas). The study was registered at clinicaltrials.gov (NCT03294018). Patients with a known allergy to sugammadex or those less than 18 years of age were excluded. The decision to use sugammadex was based on the clinical judgment of the anesthesia team. After sugammadex administration, heart rate (HR) was continuously monitored and prospectively recorded every minute for 15 minutes and then every 5 minutes for the next 15 minutes or until the patient was transferred from the operating room. During this time, any bradycardic event was noted. Bradycardia was defined as HR below 60 beats/minute (bpm) or a decrease in HR by ≥10 beats per minute (bpm) if the baseline HR was <70 bpm. The occurrence of bradycardia-associated hemodynamic compromise, including hypotension, the decision to treat bradycardia, and the medications used to treat it were prospectively recorded. Additionally, demographic information was prospectively collected for each subject, including age, weight, gender, comorbid conditions, type of surgery, and concomitant medications.

Study demographics were re/ported as a count for categorical variables and a mean ± standard deviation for continuous variables. In the descriptive analysis, we compared patient and procedural characteristics by occurrence of bradycardia. Characteristics were compared between groups using Chi-square tests or Fisher's exact tests for categorical measures, and rank-sum tests for continuous measures. As a previous review reported a 2% incidence rate of bradycardia in adults receiving sugammadex, we aimed to test the hypothesis that the incidence of bradycardia will be no higher than 2% in the adults receiving sugammadex in our institution, allowing for a 3% margin of error.[9,10] To assess this hypothesis, we performed a one-sided, one-sample test of proportion. Testing our hypothesis with 80% power required the recruitment of 191 patients. To account for potential attrition from the study or missing data, we planned to recruit 200 patients.

In addition to estimating the incidence of bradycardia, we performed multivariable logistic regression analysis to assess the independent association of patient and procedural characteristics with the onset of bradycardia. Characteristics included in the model were gender, age, weight, and initial sugammadex dose. To construct the multivariable analysis, we used a forward selection model, and controlled for presence of cardiac comorbidity rather than procedure type (abdominal, head and neck, orthopedic, cardiac, other), due to collinearity between these variables. Analysis was performed using Stata/IC 14.2 (College Station, TX: StataCorp, LP), and two-tailed $P < 0.05$ was considered statistically significant.

## Results

The study cohort included 200 patients (60% female). The median age of the patients was 60 years (interquartile range [IQR]: 44, 68 years) and the median weight was 84 kg (IQR: 69, 99 kg). The initial sugammadex doses ranged from 1.7 to 15.1 mg/kg (median 2.0 mg/kg, IQR 2.0, 4.0 mg/kg). A second sugammadex dose was administered to one patient. Procedures included abdominal surgery (62%), orthopedic

**Table 1: Cardiac comorbid conditions in the study cohort**

| Cardiac comorbid condition | Number of patients |
|---|---|
| Coronary artery disease | 24 |
| Congestive heart failure | 1 |
| Sinus bradycardia | 1 |
| Tachyarrhythmia* | 8 |
| Total | 34 |

**Supraventricular tachycardia, Wolf-Parkinson-White syndrome, atrial fibrillation*

surgery (11%), and other surgery types (28%). A cardiac comorbidity was noted in 34 patients (17%) [Table 1]. Average HR over the study period is shown in Figure 1. In 146 patients, the lowest HR recorded after sugammadex was lower than the baseline HR while in 54 cases, the lowest HR was the same as or higher than the baseline HR. Using the study definition, bradycardia was observed in 13 cases (7%; 95% confidence interval: 4, 11), occurring a median of 4 minutes after sugammadex administration (IQR: 4, 9 minutes, range: 2-25 minutes). The absolute and percentage decrease in HR (median, range and IQR) in the entire study cohort and patients who experienced bradycardia are listed in Table 2. Among patients developing bradycardia after sugammadex administration, 2 (15%) had documented cardiac comorbidities. One patient required treatment with ephedrine for bradycardia 31 minutes following the administration of sugammadex. On bivariate analysis [Table 3], only patients receiving a higher initial sugammadex doses were more likely to experience bradycardia. Other patient characteristics, including age, gender, cardiac comorbidities and procedure type, were not associated with an increased risk of bradycardia. Multivariable logistic regression [Table 4] confirmed that initial sugammadex dose was not associated with the risk of bradycardia.

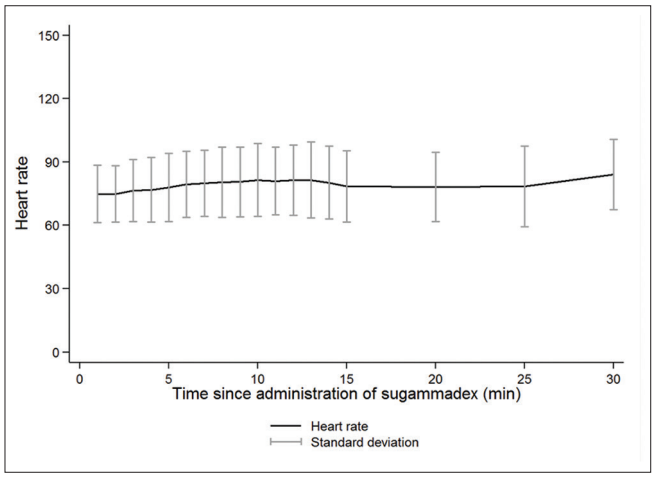


**Figure 1:** Heart rate for the initial 30 minutes following the administration of sugammadex

## Discussion

NMB is often reversed at the completion of surgery to achieve spontaneous ventilation and to facilitate tracheal extubation. Failure to reverse NMB or inadequate reversal of NMB has been shown to be associated with increased morbidity and mortality.[12,13] Acetylcholinesterase inhibitors have been the mainstay of NMB reversal since the 1950s. Acetylcholinesterase inhibitors reverse NMB through competitive antagonism of NMBAs, by increasing acetylcholine at the neuromuscular junction. However, increased acetylcholine at muscarinic receptors away from the neuromuscular junction may result in unwanted parasympathomimetic side effects, such as hypersalivation, bronchospasm, and bradycardia. As such, co-administration of an anticholinergic agent is required.[1,14,15] There is also a relative pharmacologic ceiling effect with the inhibition of acetylcholinesterase which requires partial recovery of neuromuscular function before an acetylcholinesterase inhibitor can be administered and be efficacious.[12,15] Even with the presence of residual neuromuscular function, residual blockade is common in the post-anesthesia care unit and may lead to respiratory insufficiency or respiratory failure.

**Table 2: Absolute and percent change of heart rate from baseline**

| | Absolute decrease of HR from baseline: bradycardia cases (*n*=13) | % decrease of HR from baseline: bradycardia cases (*n*=13) | Absolute decrease of HR from baseline: all cases with a decrease in HR (*n*=146) | % decrease in HR from baseline - all cases with a decrease in HR (*n*=146) |
|---|---|---|---|---|
| Median (IQR) | 13 (11, 17) | 19% (18%, 24%) | 6 (3, 10) | 8% (4%, 13%) |
| Range | 10-33 | 15% - 41% | 1-33 | 1% - 41% |

*HR=Heart rate; n=Number: IQR=Interquartile range. Fifty-four cases where the lowest HR was the same as or higher than the baseline HR are not included in the data*

**Table 3: Patient and procedural characteristics according to the occurrence of bradycardia**

| Characteristics | *n* (%) or Median (IQR) | | *P* |
|---|---|---|---|
| | Bradycardia (*n*=13) | No Bradycardia (*n*=187) | |
| Female | 7 (54%) | 112 (60%) | 0.668 |
| Age (years) | 55 (30, 68) | 60 (44, 68) | 0.394 |
| Weight (kg) | 84 (65, 92) | 84 (69, 100) | 0.581 |
| Cardiac comorbidity | 2 (15%) | 32 (17%) | 0.873 |
| Procedure type | | | |
| Abdominal | 9 (69%) | 114 (61%) | 0.423 |
| Orthopedic | 0 | 22 (12%) | |
| Other | 4 (31%) | 51 (27%) | |
| Initial sugammadex dose (mg/kg) | 2.0 (2.0, 4.0) | 2.0 (2.0, 2.1) | 0.033 |

*IQR=Interquartile range*

**Table 4: Multivariable regression of characteristics associated with bradycardia**

| Characteristics | OR | 95% CI | *P* |
|---|---|---|---|
| Female | 0.7 | (0.2, 2.5) | 0.601 |
| Age (years) | 1.0 | (0.9, 1.0) | 0.208 |
| Weight (kg) | 1.0 | (1.0, 1.0) | 0.512 |
| Cardiac comorbidity | 0.8 | (0.1, 5.6) | 0.852 |
| Initial sugammadex dose (mg/kg) | 1.3 | (1.0, 1.8) | 0.083 |

*CI=Confidence interval, OR=Odds ratio*

Sugammadex, a synthetically modified γ-cyclodextrin, is a novel NMB reversal agent that does not interact with cholinergic mechanisms to revere NMB. Its chemical structure consists of a hydrophilic exterior and a hydrophobic core which acts by forming a 1:1 complex with the steroidal non-depolarizing NMB agents, rocuronium and vecuronium, in the plasma thereby lowering the effective concentration available at the neuromuscular junction.[1,4,14,15] In contrast to acetylcholinesterase inhibitors, sugammadex is efficacious even when administered during profound neuromuscular blockade, has a lower incidence of residual blockade, and does not require the co-administration of an anticholinergic agent.

During pre-clinical trials, bradycardia was been reported by the manufacturers of sugammadex (Merck Sharp & Dohme Ltd). In the company's package insert and data sheet on sugammadex, it is stated that "Cases of marked bradycardia, some of which have resulted in cardiac arrest, have been observed within minutes after the administration of [sugammadex]". It also states that the incidence of bradycardia is approximately 1% (https://www.merck.com/product/usa/pi_circulars/b/bridion/bridionpi.pdf). Following its introduction for clinical use, there have also been anecdotal reports of bradycardia, which were temporally linked to the administration of sugammadex. Some of these reports describe bradycardia with progression to cardiac arrest in patients with co-morbid cardiac conditions such as variant angina, baseline sinus bradycardia, and atrial fibrillation.[16,17] However, it has been difficult to prove a causal relationship between the bradycardia and the administration of sugammadex, as other medications may have been administered at the same time. For example, although King *et al.* reported severe bradycardia following the administration of sugammadex in a pediatric patient with a denervated, transplanted heart, the patient had also received dexmedetomidine.[18] There have also been reports of sugammadex-induced bradycardia and cardiac arrest in previously healthy patients with no co-morbid cardiac features. In 2014, Bilgi and colleagues reported severe bradycardia that progressed to cardiac arrest in a previously healthy adult male who received 200 mg of sugammadex.[19] Sanoja *et al.* reported severe, treatment-resistant bradycardia that progressed to cardiac arrest within 1 minute of the administration of sugammadex.[20]

Our study prospectively evaluated the incidence of bradycardia after sugammadex administration adults undergoing various surgical procedures. We noted an incidence of bradycardia of 7% (13 of 200 patients) when using fairly liberal inclusion criteria for bradycardia: defined as HR below 60 beats/minute (bpm) or HR decrease ≥10 beats per minute (bpm) if the baseline HR was less than 70 bpm. Despite the bradycardia in these 13 patients, no hemodynamic compromise was noted and only 1 patient (0.5%) received pharmacologic treatment for what was deemed to be clinically significant bradycardia.

The overall incidence of bradycardia seen in our study (7%) is higher when compared to a 2% incidence noted in a previous meta-analysis of adult trials.[9] However, the definition of bradycardia in the studies included in this meta-analysis varied, and was different from the criteria used in our study. One study by Shaller and colleagues defined a heart rate of lower than 40 beats per minute as bradycardia.[21] Another study by Jones and colleagues defined bradycardia as heart rate ≤50 bpm and a decrease of at least 15 beats/min from baseline.[22] Additionally, meta-analyses in adults have shown that the risk of bradycardia is reduced in patients treated with sugammadex versus neostigmine.[9,11]

Although our study showed a higher incidence of bradycardia when compared to other adult studies, the bradycardia in these patients did not result in a clinically significant outcome. Overall, in our study and similar studies, the incidence of bradycardia after administration of sugammadex is low. Despite this potential side effect, there are many benefits to using sugammadex for NMB reversal. Sugammadex avoids the adverse effects caused by acetylcholinesterase inhibitors and muscarinic agonists. Sugammadex has also been shown to have the ability to reverse profound neuromuscular blockade as well as result in a faster return to spontaneous ventilation and tracheal extubation, when compared to traditional agents.[1,2,12,15,23]

Life-threatening adverse reactions such as bradycardia and cardiac arrest are infrequent, but they represent a potentially serious health risk. As a definitive mechanism by which sugammadex induces bradycardia has not been proposed, we would suggest that continuous ECG monitoring should be continued following its administration. Our data suggest that the incidence of bradycardia may be dose-related, while anecdotal experience suggests bradycardia may occur in patients with pre-existing conduction issues or when sugammadex is administered with other medications that have negative chronotropic and dromotropic effects.

Limitations of the current study include the fact that we did not include a comparative group of patients receiving neostigmine so a direct comparison of the incidence of bradycardia between the two groups could not be made. Furthermore, we did not

rigorously control the dosing of sugammadex, leaving it to the discretion of the anesthesia team. Lastly, although our results do not suggest a statistically significant correlation between comorbid cardiac disease and the incidence of bradycardia, the study cohort included only 34 patients (17%) with comorbid cardiac disease, thereby limiting further analysis of this risk factor.

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## Conflicts of interest

There are no conflicts of interest.

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