ORIGINAL CLINICAL REPORT

OPEN

Efficacy and Safety of Sugammadex to Shorten Time-to-Extubation Following Cardiac Surgery: A Single-Center Randomized Placebo-Controlled Trial

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OBJECTIVES: Residual neuromuscular blockade (NMB) is an important and modifiable factor associated with prolonged mechanical ventilation after cardiac surgery. Studies evaluating the use of sugammadex for residual NMB reversal in the post-cardiac surgery ICU setting are lacking. We conducted a randomized trial to determine the efficacy of sugammadex in reducing time to extubation in patients admitted to the ICU after cardiac surgery.

DESIGN: Single-center, randomized, double-blind, placebo-controlled trial.

SETTING: University-based cardiothoracic ICU.

SUBJECTS: Patients (n = 90) undergoing elective aortic valve replacement (AVR) and/or coronary artery bypass grafting (CABG) surgery.

INTERVENTIONS: Participants were randomized to receive either sugammadex (2 mg/kg) or placebo after arrival to the ICU.

MEASUREMENTS AND MAIN RESULTS: The primary study endpoint was time from study drug administration to extubation. Of the 90 patients included in the study (45 in each group), a total of 68 patients underwent CABG, 13 AVR, and nine combined AVR and CABG. Baseline characteristics and intraoperative anesthetic medications were comparable between groups. Patients in sugammadex group had reduced time to extubation compared with the placebo group (median [interquartile range (IQR)]–sugammadex group: 126.0 min [84.0–274.0 min] vs placebo: 219.0 min [121.0–323.0 min]; difference in means [95% CI], 72.8 [1.5-144.1 min]; $p = 0.01$. There were no differences in negative inspiratory force (mean [SD]–sugammadex group: 33.79 cm H_2O [8.39 cm H_2O] vs placebo: –31.11 cm H_2O [7.17 cm H_2O]) and vital capacity (median [IQR]–sugammadex group: 1.1 L [0.9–1.3 L] vs placebo: 1.0 L [0.9–1.2 L]). There were no differences between groups in postoperative blood product requirement, dysrhythmias, length of ICU, or hospital stay. There were no serious adverse events in either group.

CONCLUSIONS: This randomized trial showed that the administration of sugammadex after cardiac surgery decreased time to extubation by approximately 1 hour. Larger trials may be required to confirm these findings and determine the clinical implications.

KEY WORDS: cardiac surgery; fast-track extubation

Prolonged intubation after cardiac surgery continues to be a common clinical challenge and is associated with significant risks and costs (1–6). Despite a class I recommendation by the American College of Cardiology supporting care directed toward early postoperative extubation after low to medium risk coronary artery bypass grafting (CABG) surgeries, a sizable proportion of patients continue to have a prolonged course of postoperative intubation

DOI: 10.1097/CCE.0000000000000821

KEY POINTS

Question: Does postoperative administration of sugammadex help shorten the time to extubation among patients who undergo elective cardiac surgery?

Findings: In this single-center double-blind randomized clinical trial of patients who underwent elective coronary artery bypass grafting and/or aortic valve replacement, the time to extubation was significantly shorter in the sugammadex group compared with the placebo group by 78 minutes.

Meaning: These findings support the intraoperative use of sugammadex for early extubation among patients undergoing elective cardiac surgery.

(7). Residual neuromuscular blockade (NMB) is likely one of the key factors leading to prolonged intubation after cardiac surgery (8). It is also a significant contributor to postoperative pulmonary and respiratory complications including hypoxia, hypoventilation, and upper airway obstruction that may require reintubation (9, 10). Due to the profound effects that neuromuscular reversal agents (other than sugammadex) have when used in combination with muscarinic acetylcholine receptor antagonists on the autonomic nervous system and patient hemodynamics, these traditional reversal drugs are not widely used in the postoperative cardiac surgery patient population (11).

Sugammadex, a gamma-cyclodextrin drug, rapidly reverses NMB by encapsulating the nondepolarizing aminosteroid agents rocuronium and vecuronium (12). Reversal of NMB with sugammadex is not associated with cardiovascular effects that are commonly seen with traditional NMB reversal agents (13). However, there have been sporadic reports of hypotension, anaphylaxis, and prolonged activated partial thromboplastin time with the use of sugammadex (14–16). Additionally, although the Food and Drug Administration currently lists sugammadex as indicated for reversal of NMB induced by rocuronium and vecuronium in adults undergoing surgery, its use in the ICU setting post-cardiac surgery is limited due to lack of supportive data (17). In this context, the present study was designed to determine the efficacy of reversing NMB with sugammadex for shortening time to extubation among patients in the cardiothoracic ICU who have undergone aortic valve replacement (AVR), CABG, or a combination AVR/CABG procedure.

METHODS

Trial Design

The study protocol and statistical analysis plan are posted at ClinicalTrials.gov (NCT03196167) (18). This was a randomized, double-blind, single-center, placebo-controlled trial. The study was approved by the Institutional Review Board (IRB) (Yale University IRB, Approval number: Human Investigations Committee No. 2000021124, approved on June 21, 2017, titled: Efficacy and Safety of Sugammadex [2 mg/kg] to shorten time-to-extubation among postoperative ICU patients following AVR, CABG surgery, or AVR with CABG surgery—a prospective randomized placebo-controlled trial). A written informed consent process was conducted with consent obtained directly from all participants at least 1 day prior to their surgery. All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975.

Study Patients

Adult patients undergoing elective AVR surgeries or CABG with preoperative left ventricular ejection fraction greater than or equal to 45% were eligible for potential inclusion in the study. Exclusion criteria are listed in **Supplement 1A** (http://links.lww.com/CCX/B100). Briefly, patients with moderate to severe left ventricular or right ventricular dysfunction, emergency cases, oxygen requirement at baseline, preexisting renal injury (estimated Glomerular Filtration Rate < 30 mL/min/1.73 m^2), history of chronic opioid use, neuromuscular disorders, or known sensitivity to rocuronium or vecuronium were excluded from the study. Patients were also excluded post-recruitment but pre-randomization if they had untoward intraoperative/immediate postoperative events including anaphylactoid reaction needing treatment, cardiac arrest, postoperative ST changes, postoperative bleeding (> 100 cc/hr for the first 2 hr), or postoperative hypothermia (temperature < 35.5°C on arrival to the ICU). Due to slow recruitment

rates, the protocol was modified during the trial 1) to include patients who underwent isolated AVR surgeries or AVR in addition to CABG and 2) the exclusion criteria for hypothermia on ICU arrival was changed from 36.2 to 35.5 degrees Celsius (**Supplement 4**, http://links.lww.com/CCX/B100).

Study Procedures

For enrolled patients, anesthetic management was left at the discretion of the attending anesthesiology provider. As per the usual clinical practice at our institution, rocuronium or vecuronium were used for NMB. The patients were transferred to the ICU postoperatively intubated and on a propofol and/or dexmedetomidine infusion. No patient received any additional NMB in the ICU.

Upon ICU arrival, criteria for continued eligibility were determined with reference to the post-recruitment, pre-randomization exclusion criteria in the attached protocol (Supplement 1A, http://links.lww.com/CCX/B100). If the decision was made by the clinical team consisting of the surgeon, anesthesiologist and ICU attending to continue a fast-track extubation pathway, eligible patients were randomized, and investigational pharmacy prepared the blinded study drug.

Randomization Assignment and Blinding

The randomization and study drug/placebo preparation were carried out by the investigational pharmacy. Randomization was performed by the investigational pharmacy using a computer-generated algorithm assigning patients in a 1:1 fashion to either sugammadex or placebo, with a block size of four. The research and clinical staff were unaware of the group assignments.

Perioperative Management Per Protocol

Propofol and dexmedetomidine were the only sedatives used postoperatively. Propofol was discontinued 30 minutes after patient's eligibility was confirmed. Dexmedetomidine was allowed to be continued till after extubation based on the judgment of the clinical team. Participants were administered sugammadex (2 mg/kg) or equivalent volume of saline (placebo) by the ICU nurses who received the drugs in a blinded fashion from the research pharmacy. Just prior to the study, drug administration assessment of residual paralysis (defined as < 4/4 twitches or 4/4 with fade during by train of four [TOF] examination) was performed by the study personnel (research nurse) who were blinded to the study arm allocation. The clinical team was unaware of the neuromuscular recovery status. Ten minutes after the drug administration, if the patient was able to lift the head and remained hemodynamically stable, the patient was switched to Continuous Positive Airway Pressure (CPAP) mode of ventilation (pressure support ventilation with 5 cm pressure support and 5 cm positive end-expiratory pressure) for 30 minutes. At the end of the CPAP trial, vital capacity, negative inspiratory force (NIF), rapid shallow breathing index (RSBI), and Arterial Blood Gas were assessed. The patient was ready for extubation if he/she was not hypoxic/hypercarbic, had RSBI less than 100, and had Tidal Volume greater than 300 mL with the final clinical decision to remove the endotracheal tube made by the ICU team.

If a patient failed the 30-minute CPAP trial, the ICU intensivist was immediately notified. Every attempt was made to correct the underlying cause of failure of the spontaneous breathing trial, and a prompt reassessment was made as deemed appropriate by the intensivist to reattempt CPAP trial versus continuing controlled mechanical ventilation.

Primary and Secondary Outcomes

The primary outcome of the study was time from drug administration to extubation. This was calculated from time of end of study drug administration to endotracheal tube removal. In the original protocol, extubation time was initially defined as time from ICU admission to extubation but there were a number of patients who had operating room delays at the conclusion of surgery due to unavailability of ICU beds. To ensure time standardization, the primary endpoint of time to extubation was defined as time from study drug administration, which represents the clinical determination of evaluation for extubation readiness by the clinical care team, to removal of the endotracheal tube. Secondary outcomes were RSBI, NIF, ICU length of stay, and hospital length of stay. Postoperative arrhythmias, change in renal function, and reintubation were recorded during the patients' hospitalization or for 7 days (whichever occurred first). Drug related allergic reaction was recorded for up to 30 minutes after administration. Although reintubation was not mentioned in the a priori protocol, it was recorded as it was deemed as

an important study-related outcome by investigator consensus after protocol development.

Statistical Analysis

Prior to initiation of the study, mean time to extubation based on preliminary data was estimated at 503.40 minutes (± 173.40 min). This duration was based on retrospective data, which was calculated as time from admission to the ICU to endotracheal tube removal. We determined that randomization of 90 subjects (45 subjects in each arm) would provide 90% power to detect a difference of 120 minutes between sugammadex and placebo groups using a two-sided alpha level of 0.05, based on a two-sample *t* test.

Comparisons of baseline for continuous variables were examined graphically and by summary statistics: means (± SD) for normally distributed variables and medians (interquartile range [IQR]) for variables that were not normally distributed. Categorical variables were examined by calculating frequency distributions.

As an a priori determination, the analysis was conducted with the intention-to-treat principle on all randomized subjects regardless of the actual treatment received. Per the posted statistical plan for the primary outcome of time to extubation, a two-sided Student *t* test on the log-transformed data was performed. Given the non-normal distribution of the primary outcome, the median difference and 95% CIs of the outcomes between the sugammadex and placebo was also estimated using the Hodges-Lehman estimator, which was not a part of the a priori statistical plan (**Supplement 2**, http://links.lww.com/CCX/B100). Student *t* test and Mann-Whitney *U* test were used for other continuous outcomes based on distribution characteristics. To compare the frequency of adverse events between the two groups, chi-square test or Fisher exact test was used. All *p* values were two-sided, and *p* values of less than 0.05 were considered significant.

Study Oversight

A data and safety monitoring board consisting of the ICU nurse manager, senior critical care staff and anesthesiologist met regularly to review the study conduct and discuss any serious events. Throughout the study period, no major adverse events were reported. The study was continued without interruptions except from January 3, 2020, to January 7, 2020, due to a mandatory suspension of clinical trials secondary to the COVID-19 pandemic. No interim analysis was performed (**Supplement 5**, http://links.lww.com/CCX/B100).

RESULTS

Baseline Characteristics

During the study period between October 2017 and October 2020, a total of 142 patients were evaluated for eligibility and 90 subjects were randomized with 45 subjects assigned to each group (**Supplementary Fig. 1**, http://links.lww.com/CCX/B100). Seven patients who underwent randomization did not receive the study drug (in a majority of cases due to clinical instability post-randomization precluding fast-track extubation) but were included in the intention-to-treat analysis (**Supplement 1**, http://links.lww.com/CCX/B100). A total of 68 patients underwent CABG, 13 AVR, and nine combined AVR and CABG. Baseline demographic characteristics and preoperative laboratory values were well-balanced between the two groups (**Table 1**). A higher proportion of patients were on beta blockers and statins in the sugammadex group compared with the placebo group (beta blockers—sugammadex group: 33 [73.3%] vs placebo group: 23 [51.1%]; statins—sugammadex group: 40 [88.9%] vs placebo group: 31 [68.9%]). The two groups had a similar preoperative risk score (Society of Thoracic Surgeons [STS] score (19) mean [± SD]—sugammadex group: 1.58 [± 0.80] vs placebo group: 1.34 [± 0.49]).

Except for fentanyl dosing, the groups were well matched with respect to anesthetic medications received intraoperatively (**Table 2**). The median dose of fentanyl group is higher in the sugammadex group 400.0 μg (0.0–750.0 μg) compared with the placebo group 150.0 μg (0.0–750.0 μg). Intraoperative NMB dosing was also similar in the two groups as was the qualitative TOF response prior to study drug/placebo administration. The two groups were also not different with respect to cardiopulmonary bypass time and the cross-clamp time. The two arms were similar with respect to residual paralysis on TOF monitoring prior to drug administration (sugammadex: 18.4% vs placebo 27.5%). The time from ICU arrival to study drug administration (median [IQR]) for the cohort was 91 minutes (75–110 min) and was similar between the two arms (median [IQR]—sugammadex 93 min [80–107 min] vs placebo 90 min [73–110 min]; $p = 0.48$).

TABLE 1.
Baseline Demographic and Preoperative Characteristics of the Two Groups

Variable	Placebo ($n = 45$)	Sugammadex ($n = 45$)
Demographic characteristics		
Age (yr)[a]	66.0 (59.0–71.0)	67.0 (62.0–72.0)
Female sex, *n* (%)	5 (11.1)	8 (17.8)
Body mass index, mean (± SD)	29.55 (4.8)	29.39 (4.6)
Smoking, *n* (%)		
Current (within 1 yr)	8 (17.8)	7 (15.6)
Never	19 (42.2)	21 (46.7)
Prior (> 1 yr)	18 (40.0)	17 (37.8)
Coexisting medical conditions, *n* (%)		
Hypertension	32 (71.1)	37 (82.2)
Chronic obstructive pulmonary disease	1 (2.2)	1 (2.2)
Transient ischemic attack/stroke	1 (2.2)	2 (4.4)
Preoperative laboratory values		
Hemoglobin A1c[a]	6.2 (5.8–7.2)	6.9 (6.3–7.4)
Preoperative hemoglobin (g/dL)[a]	14.6 (13.6–15.3)	13.9 (12.8–14.7)
Creatinine (mg/dL)[a]	0.9 (0.8–1.0)	1.0 (0.9–1.1)
Preoperative medications, *n* (%)		
ASA	33 (73.3)	37 (82.2)
Plavix	02 (4.4)	2 (4.4)
Angotensin-converting enzyme/angiotensin receptor blockers	23 (51.1)	30 (66.7)
Beta blockers	23 (51.1)	33 (73.3)
Statins	31 (68.9)	40 (88.9)
Other antihyperlipidemics	5 (11.1)	7 (15.6)
Risk scores		
ASA class		
≤ 3, *n* (%)	13 (28.9)	14 (31.1)
4, *n* (%)	32 (71.1)	31 (68.9)
Society of Thoracic Surgeons surgery Risk Score, mean (± SD)	1.34 (0.5)	1.58 (0.8)

[a]Median (interquartile range).

Primary Outcome

Time from study drug administration to extubation was shorter in the sugammadex group compared with the placebo group (median [IQR]—sugammadex group: 126.0 min [84.0–274.0 min] vs placebo: 219.0 min [121.0–323.0 min]; difference in means [95% CI]: 72.8 min [1.5–144.1 min]; $p = 0.01$ [**Fig. 1** and **Table 3**]). The Kaplan-Meier curve depicting time to extubation shows early separation of the two arms (Gehan-Wilcoxon statistic $p = 0.03$) (**Fig. 2**) (**Supplement 6**, http://links.lww.com/CCX/B100).

Secondary Outcomes

Respiratory Characteristics. The vital capacity (median [IQR]—sugammadex group: 1.1 L [0.9–1.3 L] vs placebo: 1.0 L [0.9–1.2 L]) and NIF (mean [± SD]—sugammadex group: –33.79 cm H_2O [± 8.39 cm H_2O] vs placebo: –31.11 cm H_2O [± 7.17 cm H_2O]) were not different between the two groups. Similarly, the RSBI between the two groups was similar (Table 3). No subject in either arm required reintubation or support by Bilevel Positive Airway Pressure or high-flow nasal cannula.

Length of Stay. The two groups did not differ with respect to ICU length of stay (median [IQR]—sugammadex group: 2.0 d [2.0–3.0 d] vs placebo: 2.0 d [2.0–3.0 d]; $p = 0.65$) and length of hospitalization (mean [± SD]—sugammadex group: 5.0 d [4.0–6.0 d] vs 5.0 d [4.0–6.0 d]; $p = 0.77$).

Safety Outcomes

There were no serious adverse events in either group. One patient in the placebo group developed postoperative congestive heart failure deemed unrelated to study participation. Five patients (11.11%) in the sugammadex group and three (6.67%) in the placebo group had a postoperative creatinine increase by greater than 0.5 mg/dL, a difference that was not statistically significant ($p = 0.71$). No patient needed new dialysis.

Atrial fibrillation was the most common arrhythmia. Three patients (6.67%) in the sugammadex group developed postoperative atrial fibrillation and six (13.33%) in the placebo group ($p = 0.48$). None of the patients had a stroke postoperatively. No patient had sudden tachycardia, hypotension or brisk bleeding post drug/placebo administration as evaluated by the study personnel at the

TABLE 2.
Intraoperative and Immediate Postoperative Characteristics of the Two Groups

Variable	Placebo ($n = 45$)	Sugammadex ($n = 45$)
Surgical factors		
Type of surgery		
AVR, *n* (%)	8 (17.8)	5 (11.1)
CABG, *n* (%)	34 (75.6)	34 (75.6)
CABG/AVR, *n* (%)	3 (6.7)	6 (13.3)
Redo sternotomy, *n* (%)	1 (2.2)	0 (0.00)
Off-pump surgery, *n* (%)	0 (0.00)	1 (2.2)
Cardiopulmonary bypass time (min)[a]	85.0 (68.8–95.2)	89.2 (74.4–110.1)
Cross-clamp time (min)[a]	63.6 (54.2–78.9)	68.7 (54.0–84.0)
Intraoperative anesthetic variables		
Total intraoperative fentanyl (μg)[a]	150.0 (0.0–750.0)	400.0 (0.0–750.0)
Total intraoperative sufentanil (μg)[a]	250.5 (0.0–495.7)	145.6 (0.0–370.4)
Total intraoperative midazolam (mg)[a]	7.0 (5.0–10.3)	7.0 (5.0–8.0)
Total intraoperative propofol (mg)[a]	185.0 (93.0–281.0)	204.0 (120.0–501.0)
Total intraoperative rocuronium (mg)[a]	150.0 (100.0–200.0)	150.0 (100.0–200.0)
Total intraoperative vecuronium (mg)[a]	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Intraoperative crystalloids (mL)[a]	1,900.0 (1,400.0–2,208.0)	1,950.0 (1,400.0–2,450.0)
Intraoperative colloids (mL)[a]	0.0 (0.0–0.0)	0.0 (0.0–500.0)
RBC, *n* (%)		
0	44 (97.8)	43 (95.6)
1	01 (2.2)	1 (2.2)
3	0 (0.00)	1 (2.2)
Platelets, *n* (%)		
0	35 (77.8)	34 (75.6)
1	10 (22.2)	11 (024.4)
Fresh frozen plasma, *n* (%)		
0	42 (93.3)	44 (97.8)
1	1 (2.2)	1 (2.2)
2	2 (4.4)	00 (0.0)
Ventilatory parameters		
Intraoperative tidal volume (mL/kg)[a]	5.7 (4.6–6.8)	5.3 (4.3–6.5)
Pao_2/Fio_2 on first arterial blood gas in the ICU[a]	210.0 (180.0–276.7)	224.6 (188.3–281.7)
Residual paralysis		
Residual paralysis on train of four monitoring prior to drug administration, *n* (%)	29 (72.5)	31 (81.6)
Dexmedetomidine use in ICU		
Subjects who received dexmedetomidine, *n* (%)	35 (77.8)	35 (77.8)
Maximum dose (μg/kg/hr)[a]	0.40 (0.3–0.7)	0.60 (0.3–0.7)
Minimum dose (μg/kg/hr)[a]	0.0 (0.0–0.2)	0.0 (0.0–0.2)

AVR = aortic valve replacement, CABG = coronary artery bypass grafting.
[a]Median (interquartile range).

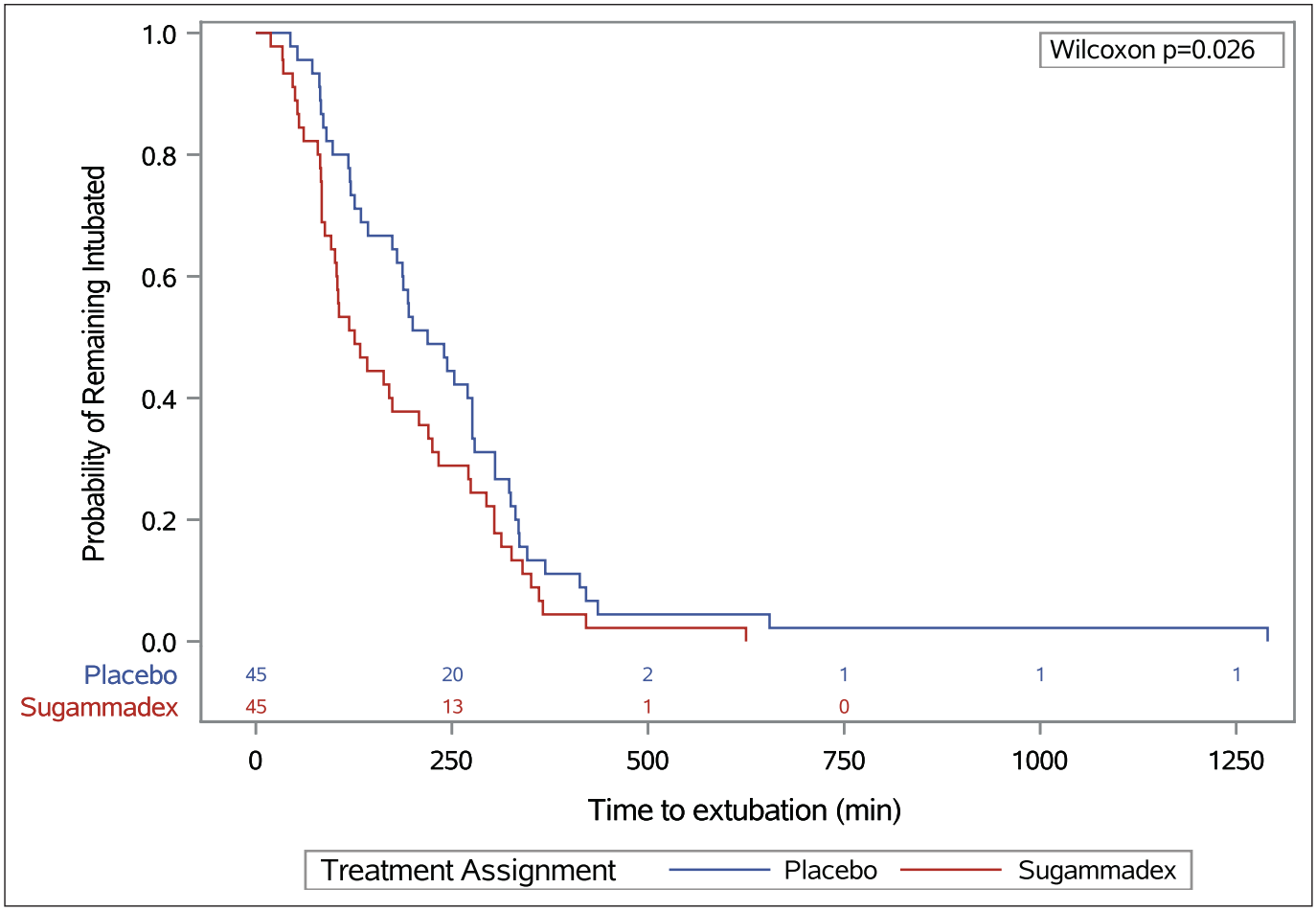

Figure 1. Median time to extubation: *Notched box plots* depicting median (*horizontal line*) and 95% CI (*notch*) of time from study drug administration to extubation in the sugammadex and placebo group. The *boxes* depict the range from the first to third quartile of extubation time in each group. Patients in the sugammadex group had a significantly shorter median time to extubation compared with placebo group (median [interquartile range]—sugammadex group: 126.0 min [84.0–274.0 min] vs placebo: 219.0 min [121.0–323.0 min]; $p = 0.01$). *One point (representing extubation time of 1,290 min in the placebo arm) was clipped as it went beyond the scale on the *y*-axis.

patient's bedside. No patient had to be taken back to the operating room emergently for bleeding.

DISCUSSION

Among patients undergoing elective CABG, AVR, or combined CABG/AVR surgeries use of sugammadex shorten mean time to extubation by approximately 73 minutes, corresponding to a 33.24% reduction in the time from drug administration to extubation. The time-to-event analysis curve suggested a stronger effect earlier after administration. This observation would be expected as the benefit of NMB reversal for extubation readiness occurs shortly after sugammadex administration, while in the absence of pharmacological reversal, the NMB agents wear off over time. At that point, other etiologies such as hypoxia, residual sedation may be the primary reasons delaying extubation (rather than residual NMB).

There were no differences with respect to adverse events or secondary endpoints between the sugammadex and placebo groups. The respiratory characteristics were measured just prior to extubation. It is plausible that the patients in the placebo arm, albeit later compared with sugammadex arm, recovered from the NMB at the time of extubation and hence no differences in the respiratory characteristics were observed.

A majority of the patients had no residual paralysis at the time of study drug administration. On a sensitivity analysis (**Supplement 3**, http://links.lww.com/CCX/B100) including only patients with residual NMB at the time of study drug administration, the difference

TABLE 3.
Primary and Secondary Outcomes by Study Arm

Variable	Placebo	Sugammadex	*p*
Primary outcome			
Time to extubation (min)[a]	219.0 (121.0–323.0)	126.0 (84.0–274.0)	**0.01**[d]
Secondary outcomes			
Negative inspiratory force (cm per H_2O)[b]	−31.0 (−37.0 to −24.0)	−33.0 (−40.0 to −27.0)	0.32
Vital capacity (L)[a]	1.0 (0.9–1.2)	1.1 (0.9–1.3)	0.29
Rapid shallow breathing index (breaths/min/L)[a]	32.7 (24.6–46.4)	40.0 (28.9–60.6)	0.89
Length of ICU stay (d)[a]	2.0 (2.0–3.0)	2.0 (2.0–3.0)	0.42
Length of hospital stay (d)[a]	5.0 (4.0–6.0)	5.0 (4.0–6.0)	0.31
Safety outcomes			
New dysrhythmia[c]	6 (13.3%)	3 (6.7%)	0.48
Change in renal function[c,e]	3 (6.7%)	5 (11.1%)	0.71
Postoperative congestive heart failure[c]	1 (2.2%)	0 (0%)	1.00

[a]Median (interquartile range).
[b]Mean (± SD).
[c]*n* (%).
[d]Statistically significant ($p < 0.05$).
[e]Change in renal function was defined as creatinine elevation > 0.5 mg/dL.

in median time to extubation was even more pronounced favoring sugammadex (time to extubation—median [IQR]: sugammadex 105 min [84–361 min] vs placebo 244 min [98–346 min]; $p = 0.53$) compared with subjects who had full recovery from NMB (time to extubation—median [IQR]: sugammadex 142 min [84–304 min] vs placebo 194 min [120–305 min]; $p = 0.26$). It is to be noted that none of these, however, reached statistical significance, probably because the trial was not powered for this sensitivity analysis.

Given improved postoperative outcomes, the Enhanced Recovery After Surgery (ERAS) and the American Heart Association guidelines recommend extubation of patients undergoing cardiac surgery within 6 hours postoperatively for mild to moderate risk patients (1, 7). Various interventions have been attempted to decrease time to extubation in this patient population including limiting opioids, avoiding benzodiazepines, and implementing multidisciplinary protocols (20–23). However, given the complexity of surgery and multitude of patient comorbidities, the 6-hour extubation goal is often difficult to achieve consistently. Not surprisingly, rates of early extubation have ranged from 12% to 55% (22, 24, 25) in the published literature. While reversal of NMB may be one factor for delayed extubation, other factors such as residual effect of opioids, operational delays in the ICU, and patient factors such as pulmonary edema, acidosis, and pain management may have affected extubation times. Not surprisingly, the median (IQR) time to extubation time (time from study drug administration to endotracheal tube removal) even in the sugammadex arm was 126 minutes (84.0–274.0 min). However, given our observed difference in time to extubation with sugammadex in our cohort, the inclusion of sugammadex in extubation protocols may help with realizing these quality metrics.

Among the most common complications after cardiac surgery are respiratory complications. The presence of residual paralysis has been considered one of the important risk factors for postoperative respiratory events (9, 26, 27). However, despite the universal use NMB blockade for cardiac surgery, NMB reversal is not routinely used after cardiac surgeries (11). One of the key potential reasons behind this practice may be the associated tachycardia/bradycardia and the possibility of potentiating atrial fibrillation associated with use of neostigmine and glycopyrrolate for NMB reversal (28). Compared with neostigmine/glycopyrrolate, NMB reversal with sugammadex has been associated

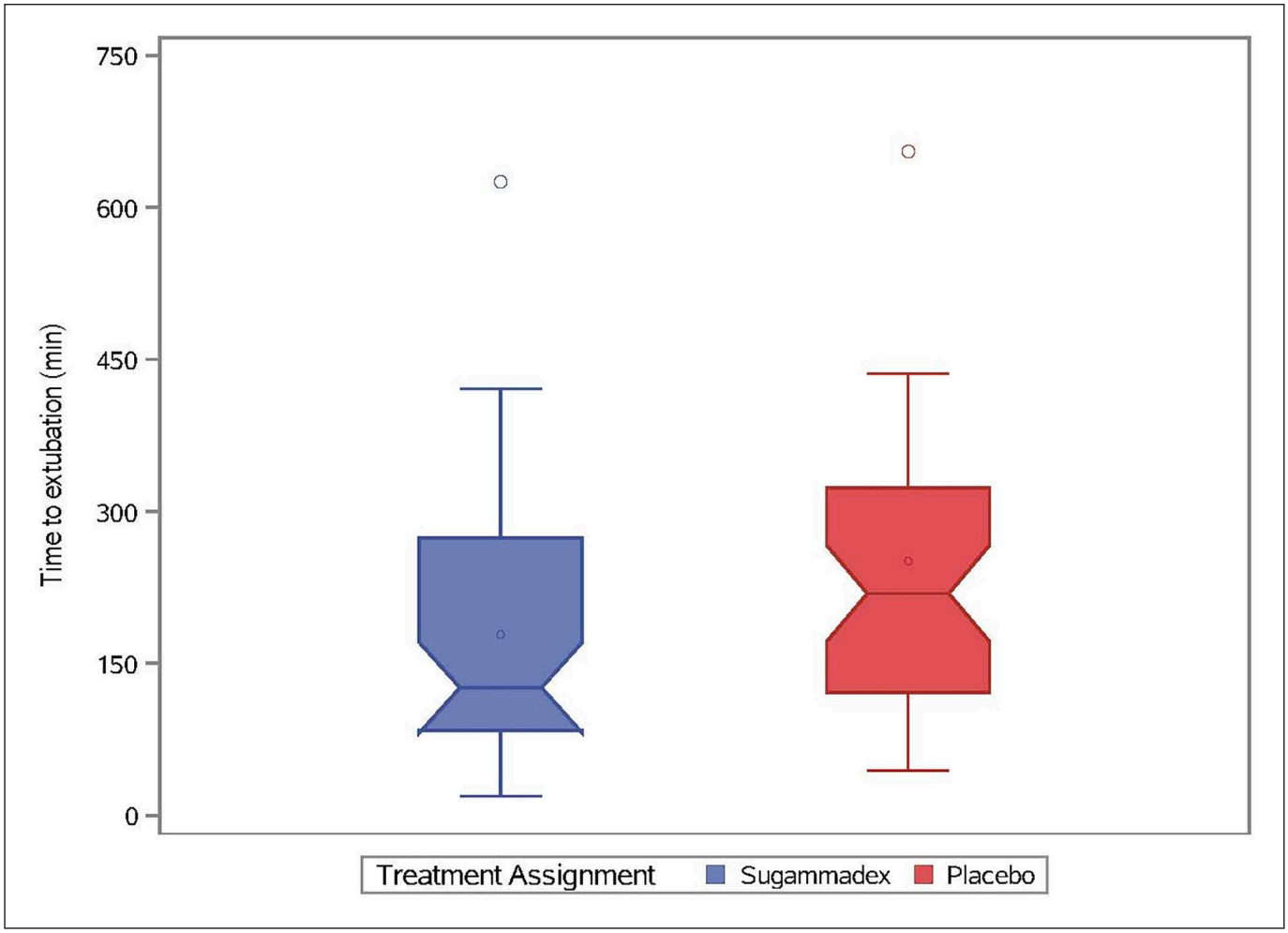

Figure 2. Kaplan-Meier curves for time to extubation: Time from study drug administration to extubation.

with a lower frequency of tachycardia of tachycardia, more effective NMB reversal, and improved postoperative pulmonary outcomes (29–31). However, sugammadex use has been associated with rare instances of bradycardia, hypotension, and anaphylaxis (30–32). These side effects were not seen in our study. We thus leveraged these advantages of sugammadex to reverse NMB blockade in the cardiac surgical population. In our limited sample size, we did not see any drug related adverse effects compared with placebo. However, it should also be noted that although patients in the sugammadex arm were extubated significantly quicker than the placebo arm, this did not translate to improvement in any downstream outcomes or length of ICU stay.

Our study has some limitations. First, this was a single-center study that may lack generalizability to other institutions with differing care patterns. However, our baseline extubation times are comparable to others reported in the literature (22, 33). Second, we excluded patients undergoing mitral valve surgeries or those with moderate to severe left ventricular dysfunction, as these patients often have preexisting pulmonary edema. Although this further limited the generalizability of our findings, including this patient population would have increased heterogeneity and potentially confounded the effect of our treatment on the primary outcome in the context of a relatively small sample size. Third, seven patients in the study were randomized but did not receive the study drug or placebo. These patients were included in the intention-to-treat analysis. We did not perform a per protocol analysis. Extubation time was defined from study drug administration to extubation. This definition was different from our a priori planned protocol, which included time from the end of surgery to extubation. It is unlikely that this change would have caused different outcomes, as unexpected operating room delays provided

justification for the change, and the clinical team (which administered the study drug and performed extubation) were blinded to the study arm allocation. It should be noted that the sample size was calculated by measuring the time from ICU arrival to extubation. On a post hoc analysis, we found that the time from ICU arrival to extubation for the study cohort: (median [IQR], 281 [192–418]) was faster than the time used for sample size calculation. One possible reason behind this could be that the trial included patients that were not very critical at the time of randomization as we excluded hemodynamically unstable patients (as listed in the exclusion criteria) while we used our entire cardiac surgical cohort for sample size analysis. The key implication is that sugammadex may help in faster extubation in patients who can be "fast tracked," where NMB is possibly the underlying cause keeping patients from being extubated.

It is possible that the subjects in the sugammadex group could potentially be sicker as they had a higher STS score (although not statistically significant) and a higher percentage of them were on cardiac medications (beta blocker and statins). This could have potentially adversely affected extubation times of patients in the sugammadex group because of negative confounding. Next, anesthetic management was left to the discretion of the attending anesthesiologist. It is possible that heterogeneity in the anesthetic management could have affected the study results. In this context, there were some differences in the intraoperative opioid dosing (especially fentanyl) in the two arms as noted in Table 2. The reason behind allowing anesthesiologists use their clinical discretion to guide opioid dosing was to allow for individual titration as there are substantial differences in dose response to opioids, and this would also allow them to tailor the management to patient's hemodynamics. The reason behind differences in fentanyl dosing between the two groups are unclear. Given the randomization and blinded nature of the trial, the likelihood that subjects in a particular arm selectively got different management is low. Another important limitation was that the dose of sugammadex was not titrated, and all patients received a fixed dose of 2 mg/kg. This was done because in our experience, most patients by the time of extubation readiness for extubation, no longer have a deep block. Furthermore, allowing for titration to twitches after deciding patient readiness would have potentially delayed extubation as the study drug/placebo were prepared offsite by the investigational pharmacy and was delivered to the bedside nurse for administration. We also did not use quantitative NMB monitoring to assess NM blockade, although increasing evidence suggests that the former is superior to qualitative methods. We did not formally test for delirium in the patients. Although given the Randomized Control Trial design, we would expect that both the groups would have similar rates of delirium. However, in the absence of formal testing, we are unable to make that adjudication. It is also important to note that since the study included one subject who underwent off-pump surgery and one patient who underwent redo sternotomy, generalization of the effect of sugammadex to this patient population cannot be made based on the findings of this study. Our study did not show any difference in length of ICU stay between the two arms (**Table 3**; and **Supplement 7,** http://links.lww.com/CCX/B100). While the ICU at our tertiary care center has standard criteria for ICU discharge, other extraneous factors such as bed availability, surgeon preference and nursing staffing on the floors could also have affected the length of ICU stay.

CONCLUSIONS

In this prospective randomized, double-blind, placebo-controlled trial, we found that in patients undergoing cardiac surgery, sugammadex administration prior to extubation in the ICU setting decreased time to extubation by approximately 1 hour. No adverse events were observed. Incorporation of NMB reversal by sugammadex to ERAS protocols for cardiac surgery may decrease time to extubation postoperatively in patients who qualify for fast-track extubation. No benefit on patient outcomes or ICU length of stay was observed in the study. Larger trials may be required to confirm these findings and to determine if this practice may also reduce postoperative pulmonary complications.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccejournal).

Supported, in part, by a research grant from Investigator-Initiated Studies Program of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Kenilworth, NJ. Merck & Co. owns and sells sugammadex.

The authors have disclosed that they do not have any potential conflicts of interest.

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The opinions expressed in this article are those of the authors and do not necessarily represent those of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Kenilworth, NJ.

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