Original Article

Short-term safety and effectiveness of sugammadex for surgical patients with end-stage renal disease: a two-centre retrospective study

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Summary

Sugammadex is a novel reversal agent for aminosteroid neuromuscular blocking drugs, especially rocuronium. Given its renal excretion, sugammadex is not recommended for patients with end-stage renal disease; however, reports exist of its use in this group of patients. This two-institutional retrospective observational study aimed to review the safety profile and effectiveness of sugammadex in surgical patients with end-stage renal disease who required pre-operative renal replacement therapy. Adult surgical patients with end-stage renal disease requiring pre-operative renal replacement therapy, who received sugammadex between April 2016 and January 2019, were studied. The primary outcome was the incidence of postoperative tracheal re-intubation within 48 h. The secondary outcome was the incidence of deferred tracheal extubation in the operating theatre. One hundred and fifty-eight patients were identified from 125,653 surgical patients: 48 patients (30%) underwent renal transplantation and 110 (70%) underwent non-renal transplantation procedures. There were 22 instances (14%) of deferred tracheal extubation due to surgical and/or pre-existing medical conditions. Out of the 136 patients who had the tracheal tube removed at the end of the procedure, three patients had their trachea re-intubated within 48 h: two patients developed pulmonary oedema resulting from volume overload; and one patient had worsening sepsis. No incidence of recurrence of neuromuscular blockade was observed. Of note, 24 (18%) patients were found to have incomplete neuromuscular blockade reversal with neostigmine but administration of sugammadex led to successful tracheal extubation. In conclusion, sugammadex appears to be safe and effective in adult patients with end-stage renal disease receiving pre-operative renal replacement therapy.

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Introduction

The first use of intra-operative neuromuscular blockade was reported in 1942 by Griffith and Johnson who utilised curare for muscle paralysis [1]. Since then, the use of non-depolarising neuromuscular blocking (NMB) agents in patients undergoing general anaesthesia is commonplace. Historically, the reversal of neuromuscular blockade involved competitive antagonism of NMB agents by utilising

acetylcholinesterase inhibitors (e.g. neostigmine), often with the co-administration of an anticholinergic agent (e.g. glycopyrronium or atropine) in attempts to mitigate the attendant adverse effects.

Sugammadex (Bridion®; Merck Sharp and Dohme Corp., Kenilworth, NJ, USA) is a modified γ-cyclodextrin molecule and reversal agent of aminosteroid NMB agents, especially rocuronium [2]. Its mechanism of action is novel in that it encapsulates rocuronium (and to a lesser degree vecuronium) rendering it inactive, while also creating a concentration gradient favouring the movement of rocuronium into the plasma from the neuromuscular junction [2–4]. The added benefit of reversal with sugammadex is the lack of cholinergic symptoms; this novel feature obviates the need for an anticholinergic agent. After approval in Europe and Asia (2008 and 2010, respectively), sugammadex quickly gained popularity in clinical practice. In the USA, however, its use has only been approved since December 2015. A Cochrane systematic review that included 41 studies and 4206 participants validated the superior effectiveness and safety profile of sugammadex compared with neostigmine [5]. Currently, according to the Food and Drug Administration (FDA) package insert, sugammadex is not recommended for the use in patients with end-stage renal disease [6]. This is because sugammadex is a renally excreted water-soluble molecule and is not removed with standard forms of dialysis [7]. In addition, the sugammadex–rocuronium complex is renally excreted [8]; therefore, one of the major concerns for the use of sugammadex in patients with end-stage renal disease is the potential for recurrence of postoperative neuromuscular blockade if the two drugs were to disassociate. Data assessing the safety of sugammadex in patients with end-stage renal disease are lacking. Nevertheless, the use of sugammadex in adult surgical patients with end-stage renal disease can be observed in clinical practice. We aimed to assess the safety and effectiveness of sugammadex in surgical patients with end-stage renal disease by determining the incidence of postoperative recurrence of neuromuscular blockade within 48 h.

Methods

This retrospective observational study was approved by the Institutional Review Board at the University of Pittsburgh Medical Center (UPMC) in Pittsburgh, PA and at Memorial Sloan Kettering Cancer Center (MSKCC) in New York, NY, respectively.

Electronic medical records were reviewed from April 2016 to January 2019, to identify all adult (age ≥ 18 years) patients with end-stage renal disease undergoing general anaesthesia who received sugammadex intra-operatively to reverse rocuronium-induced neuromuscular blockade. In this study, end-stage renal disease was defined as requiring renal replacement therapy (RRT) at the time of surgery; for chronic renal failure this was either intermittent haemodialysis or peritoneal dialysis and for acute renal failure this was either continuous veno-venous haemodialysis or continuous RRT. Patients were not studied if they did not yet require RRT at the time of surgery for acute kidney disease, reported renal disease or chronic kidney disease. Baseline characteristics were collected, which included pre-operative serum creatinine levels and comorbidities (history of emphysema/chronic obstructive pulmonary disease (COPD) or liver disease).

The primary outcome measure was the incidence of re-institution of mechanical ventilation within 48 h of surgery in patients whose trachea was extubated at the end of surgery. The reason for re-institution of mechanical ventilation was extensively sought using the electronic chart and special attention was paid to identify any description of signs or symptoms of muscle weakness that could indicate recurrence of neuromuscular blockade. The secondary outcome was the incidence of deferred tracheal extubation at the end of surgery, despite the administration of sugammadex.

Results

During the 34-month study period, 125,653 cases of general anaesthesia were performed (55,859 at UPMC and 69,794 at MSKCC). Overall, sugammadex was used in 26,650 (21%) cases (12,161 (22%) at UPMC and 14,489 (21%) at MSKCC) (Fig. 1). The need to utilise reversal agent and choice of reversal agents were at the discretion of the care provider of each case.

A total of 158 patients met the inclusion criteria and their medical records underwent further review. The mean (SD) age of patients was 56.0 (14.6) years and 105 (66.5%) patients were men. Mean (SD) body mass index was 28.8 (7.1) $kg.m^{-2}$. Of these 158 patients, the mode of pre-operative RRT was intermittent haemodialysis in 135 (85%) patients and peritoneal dialysis in 23 (15%). No patients were identified as having acute renal failure requiring RRT. There were 19 (12%) patients with COPD/emphysema and 10 (6%) with liver disease. Forty-eight (30%) patients underwent kidney transplantation surgery: 42 had isolated kidney transplantation and 6 had combined kidney and pancreas transplantation. The remaining 110 (70%) patients underwent non-renal transplant procedures (Fig. 1).

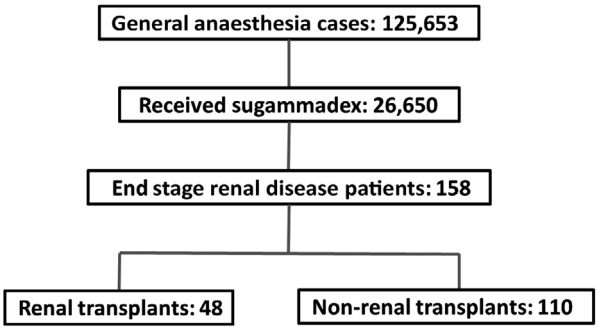

Figure 1 Flow chart of anaesthetic cases identified from electronic patient records.

There were 22 (14%) cases of deferred tracheal extubation at the end of the surgical procedure. The reasons listed for deferred tracheal extubation included: pre-existing or new tracheostomy procedure (n = 10); pre-operative medical comorbidities (n = 7); and intra-operative events that precluded tracheal extubation at the end of surgery (n = 5).

Of the remaining 136 cases where the tracheal tube was removed at the end of surgery, 3 cases (2%) of tracheal re-intubation occurred within 48 h. Baseline characteristic details of the three patients and the doses of rocuronium and sugammadex, alongside drug timings and train of four recordings are outlined in Tables 1 and 2, respectively. The first patient had an isolated kidney transplant and failed tracheal extubation due to pulmonary oedema due to volume overload. The patient suffered a peri-operative non-ST segment elevation myocardial infarction and their trachea was extubated on postoperative day 0 in the intensive care unit (ICU). The second patient underwent a combined kidney–pancreas transplant, and required tracheal re-intubation on the first postoperative day. This was due to desaturation resulting from pulmonary oedema secondary to volume overload following delayed kidney graft function which necessitated urgent haemodialysis. The third patient underwent irrigation and debridement of a mid-sternal chest wound for osteomyelitis after a prior coronary artery bypass procedure. Tracheal re-intubation occurred on the second postoperative day in the ICU after hypoxia and hypercarbia associated with worsening sepsis, with an elevated blood lactate level (8.9 $mmol.l^{-1}$) and an increasing white blood cell count (from 6000 to 13,000. μl^{-1} over the prior 48 h). There was no evidence of recurrence of neuromuscular blockade in any of these patients.

Interestingly, 24 (18%) patients were initially reversed with a standard dose of neostigmine (0.7 $mg.kg^{-1}$ up to a maximum dose of 5 mg). Due to signs and symptoms of residual muscle weakness, sugammadex median (IQR [range]) dose of 200 (163–200 [80–400]) mg was administered. This yielded immediate and full reversal of muscle strength and led to successful removal of the tracheal tube at the end of surgery.

Discussion

We identified a total of 158 adult surgical end-stage renal disease patients requiring pre-operative RRT who underwent general anaesthesia and received sugammadex as the reversal agent for rocuronium. Not including 22 patients in whom tracheal extubation was deferred due to medical and surgical reasons, 136 patients had their trachea extubated at the end of surgery. Of these, three patients required tracheal re-intubation within 48 h; however, none of these tracheal re-intubations were due to recurrence of neuromuscular blockade. Of note, there were 24 patients in whom sugammadex was effective as a rescue agent for an incomplete reversal of rocuronium with a standard dosage of neostigmine.

The fate of the sugammadex–rocuronium complex and sugammadex is uncertain in patients with end-stage renal disease since the complex is renally excreted and not removed with a standard form of dialysis [7]. There is concern for potential recurrence of postoperative neuromuscular blockade in patients with end-stage renal disease if the sugammadex–rocuronium complex disassociates and a free form of rocuronium is released to cause muscle weakness or paralysis. This persists as the primary impetus for the FDA package insert language that discourages the use of sugammadex in patients with end-stage renal disease. Fortunately, such a recurrence of potential neuromuscular blockade is highly unlikely since the association constant (Ka) of sugammadex and rocuronium is relatively high at 17,000–20,400 M^{-1} [2]. Even if such a disassociation could occur, it most likely re-associates immediately given the high K_a value. In the event dissociation occurs, the concentration of free rocuronium would be very small and unlikely to demonstrate any clinical effect. Furthermore, this free rocuronium would eventually undergo normal biliary excretion. Although the clinical experience of the usage of sugammadex with end-stage renal disease patients is scarce, two sugammadex pharmacokinetic studies in patients with end-stage renal disease failed to demonstrate any incidence of recurrence of neuromuscular blockade in the first 48 h following its administration [9, 10]. A third pharmacokinetic study did not observe any clinical evidence of residual neuromuscular blockade or recurrence of neuromuscular blockade after tracheal extubation [11]. A prospective trial in patients

Table 1 Baseline characteristics of patients with end-stage renal failure who required postoperative tracheal re-intubation.

	Age; years	Sex	Procedure	RRT type	Serum creatinine; mmol.l^{-1}	Weight; kg	Comorbidities
Patient 1	56	Male	Transplant kidney	Haemodialysis	0.50	95	Ischaemic heart disease Type-2 diabetes mellitus (with diabetic nephropathy, neuropathy and retinopathy)
Patient 2	27	Male	Transplant kidney and pancreas	Haemodialysis	0.39	57	Type-1 diabetes mellitus Previous tracheostomy due to ARDS (decannulated 5 months prior, known subglottic stenosis)
Patient 3	78	Female	Flap graft	Haemodialysis	0.29	69	Recent CABG with sternal osteomyelitis Type-2 diabetes mellitus (with diabetic nephropathy)

RRT, renal replacement therapy; CABG, coronary artery bypass grafts; ARDS, adult respiratory distress syndrome.

Table 2 Doses and timing of rocuronium and sugammadex and train of four recordings for patients with end-stage renal failure who required postoperative tracheal re-intubation.

	Total rocuronium dose; mg	Last dose of rocuronium; mg	Time from final rocuronium dose until sugammadex; min	TOF before sugammadex	Sugammadex dose; mg.kg^{-1}	TOF after sugammadex
Patient 1	140	10	68	4	4.0	Not available
Patient 2	310	10	78	4	3.3	4
Patient 3	40	10	79	4	3.0	Sustained tetanus

TOF, train of four.

undergoing renal transplant procedures in which patients were randomly allocated to receive sugammadex as part of their anaesthetic plan, showed no adverse events in the first 2 h postoperatively [12]. Of note, many of these patients would have adequate renal clearance post renal transplant procedure, so the study result must be interpreted with caution. Our results similarly demonstrate the safety of sugammadex for end-stage renal disease patients without any incidence of recurrence of neuromuscular blockade.

Another long-term concern is that end-stage renal disease patients may continue to have free-sugammadex and the sugammadex–rocuronium complex in their system, and that sugammadex is a known antigen antecedent for anaphylactic reactions. The rates of anaphylaxis due to sugammadex are estimated to be as high as any other drug commonly used during anaesthesia, including NMB agents [13, 14]. Any repeat exposure with sugammadex for these end-stage renal disease patients may need additional consideration. Of note, no documentation of anaphylaxis to sugammadex was found for any patient included in this study.

There are several limitations to this study. First, we fully acknowledge that the use of sugammadex in patients with end-stage renal disease was outside of the FDA recommendations. In the two institutions, there was no institutional protocol on the use of sugammadex during the study period and its usage was under the discretion of anaesthetic care providers. As part of a routine institutional review on sugammadex usage, we noticed patients with end-stage renal disease received sugammadex and therefore we felt obliged to report our observations. The finding that 24 patients were rescued with sugammadex after incomplete reversal of rocuronium with neostigmine could suggest the potential use of sugammadex in this population. Second, the number of patients with end-stage renal disease exposed to sugammadex was small and therefore we were unable to provide a definitive safety profile, despite combining cases from two institutions. Still, this is, to our knowledge, the largest cohort of patients reporting the clinical experiences of the use of sugammadex in patients with end-stage renal disease. Third, we only included patients with end-stage renal

disease necessitating pre-operative RRT. This was due to the technical challenge of accurately identifying all end-stage renal disease patients whose creatinine clearance was < 30 ml.min^{-1}.

In conclusion, none of the investigated adult surgical patients with end-stage renal disease who received reversal of rocuronium paralysis with sugammadex exhibited any evidence of recurrence of neuromuscular blockade. Studies with a longer follow-up of the fate of sugammadex and sugammadex–rocuronium complex and their clinical impact in end-stage renal disease patients are warranted.

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