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Review

Sugammadex administration in patients with end-stage renal disease: a narrative review with recommendations

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Due to unknown safety concerns, sugammadex should not be administered to patients with end-stage renal disease (ESRD). However, because the supply of benzylisoquinolinium-type neuromuscular blocking agents (NMBAs) has been discontinued, rocuronium is the only non-depolarizing NMBA that can be used in clinical settings in some countries, including South Korea. The administration of sugammadex cannot be avoided to achieve rapid and complete neuromuscular recovery in patients with ESRD or renal transplantation after rocuronium administration. Although there has been a limited number of clinical studies involving the use of sugammadex in patients with ESRD, studies have shown that sugammadex can effectively and safely reverse rocuronium-induced neuromuscular blockade (NMB) in patients with ESRD, however recovery of neuromuscular function in patients with ESRD is slower than in patients with normal renal function. Nonetheless, safety-concerns are yet to be addressed. Considering the small number of clinical studies, high heterogeneity among studies, and insufficient safety information, more extensive data on the efficacy and safety of sugammadex in patients with ESRD are needed. In particular, it is important to secure data on safety, including residual NMB after surgery, recurarization and cardiorespiratory complications, anaphylactic reactions, and long-term morbidity and mortality. Furthermore, anesthesiologists should remember that performing proper quantitative neuromuscular monitoring and neuromuscular management based on the monitoring signs are the most essential requirements when using sugammadex in patients with ESRD.

Keywords: Chronic kidney failure; Drug-related side effects and adverse reactions; End-stage renal disease; Neuromuscular blockade; Rocuronium; Sugammadex.

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INTRODUCTION

Sugammadex, a neuromuscular blockade (NMB) reversal agent, binds strongly with neuromuscular blocking agents (NMBAs), including rocuronium, by encapsulating them in the blood and is excreted by the kidney in the form of a stable complex, resulting in the rapid and complete reversal of the NMB [1].

Concomitant renal dysfunction in patients with end-stage renal disease (ESRD) affects the pharmacokinetics (PKs) of non-depolarizing NMBAs, making neuromuscular function recovery prolonged or unpredictable. Therefore, when sugammadex is administered to patients with severe renal impairment, sugammadex or sugammadex–rocuronium complex is not excreted by the kidneys, posing a high risk of long-term exposure to the free sugammadex or complex (continuously present in high concentrations in the blood). The use of sugammadex is not currently recommended in

this patient group due to the risk of prolonged NMB state (presence of residual NMB) and recurarization or anaphylactic reactions in the postoperative period [2]. Sugammadex is not recommended by the US Food and Drug Administration for patients with a creatinine clearance of less than 30 ml/min [3]. Furthermore, the Korean Ministry of Food and Drug Safety does not recommend the administration of sugammadex to patients with severe renal impairment (creatinine clearance of less than 30 ml/min) or patients requiring dialysis.

Nevertheless, there are cases where a combination of rocuronium and sugammadex is necessary for proper NMB management under anesthesia in surgical patients with chronic kidney disease in various clinical situations (such as surgery with very short operation time, including laryngeal microsurgery). Additionally, there are problems associated with the supply of benzylisoquinolinium-type NMBAs, their side effects and limitations. For these reasons, recently, it is common for patients with ESRD to be prescribed a combination of rocuronium and sugammadex. Therefore, considering this situation, it is necessary to comprehensively review and analyze studies on the administration of sugammadex in patients with ESRD.

Several prospective case-control studies, retrospective cohort studies, and case reports on the administration of sugammadex in patients with ESRD (or patients undergoing kidney transplantation) have been reported. A systematic review and meta-analysis [4], presented data analysis results on its efficacy and safety by synthesizing and integrating the results of studies reporting the use of sugammadex, and a retrospective study that investigated relatively long-term mortality [5], were reported. Table 1 shows the characteristics and results of the relevant studies.

EFFICACY OF SUGAMMADEX IN PATIENTS WITH ESRD

Several prospective case-control studies on the administration of sugammadex in patients with ESRD have been reported, with some administrating sugammadex 2.0 mg/kg for reversal of moderate NMB [6,7], while others administered sugammadex 4.0 mg/kg for reversal of deep NMB [8,9]. Staals et al. [6,7] reported the results of a phase III trial conducted to determine the efficacy, safety, and PKs of sugammadex in patients with ESRD by dividing them into pharmacodynamic and safety findings [6] and PK findings [7], respectively.

Table 1. Characteristics of the Main Studies Investigating the Use of Sugammadex in Patients with End-stage Renal Disease

Study	Study design	Patients with ESRD (sample size)	Patients in control (sample size)	SGX dose	Primary outcome/main secondary outcomes	Main results and conclusion	Side effects
Staals et al., 2008 [6]	Prospective clinical trial.	ClCr < 30 ml/min (15)	ClCr ≥ 80 ml/min (15)	2 mg/kg	Time from SGX to recovery to TOF ratio 0.9/reoccurrence of NMB	SGX was well tolerated by all patients	No SGX-related serious adverse events
Staals et al., 2010 [7]	Prospective clinical trial.	ClCr < 30 ml/min (15)	ClCr ≥ 80 ml/min (15)	2 mg/kg	Pharmacokinetic data of SGX and rocuronium including plasma clearance	Pharmacokinetics in renal failure were largely different to healthy patients. Urinary excretion was reduced	
de Souza et al., 2015 [8]	Prospective clinical trial.	ClCr < 30 ml/min undergoing KT (20)	ClCr > 90 ml/min (20)	4 mg/kg	Time from SGX to recovery TOF ratio of 0.9/time to TOF ratio of 0.7 and 0.8.	SGX effectively and safely reversed profound NMB; however, recovery to a TOF ratio 0.9 was prolonged in renal failure	No adverse events or evidence of recurrence of NMB
Panhuizen et al., 2015 [9]	Case control comparative study	ClCr < 30 ml/min (35)	ClCr ≥ 80 ml/min (35)	4 mg/kg	Time from SGX to recovery to TOF ratio 0.9/pharmacokinetic data	SGX rapidly reverse deep NMB in renal impairment, but clearance is reduced	No NMB recurrence. Nine of 35 patients reported serious adverse events, but none were related to SGX
Min et al., 2017 [10]	Open label, two parts, phase 1 study	ClCr 30–50 (8 and 6) and < 30 ml/min (8 and 6)	ClCr ≥ 80 ml/min (8 and 6)	4 mg/kg	Pharmacokinetic data including SGX exposure	SGX exposure is increased, and clearance is decreased with increasing renal dysfunction. SGX was well tolerated with renal impairment	Drug-related adverse events including dizziness, headache, infusion site reaction, pain in extremity and oral paresthesia, which were each reported by 1 (4%)

(Continued to the next page)

Table 1. Continued

Study	Study design	Patients with ESRD (sample size)	Patients in control (sample size)	SGX dose	Primary outcome/main secondary outcomes	Main results and conclusion	Side effects
Adams et al., 2020 [15]	Two centers retrospective study	ESRD which is mandatory renal replacement therapy (158)	None	Median 200 mg	Tracheal re-intubation within 48 h/deferred tracheal extubation in the operating theatre	SGX appears to be safe and effective	Three reintubation within 48 h, no residual NMB
Paredes et al., 2020 [16]	Historical cohort study, three-distinct geographic locations	eGFR < 15 ml/min (219)	None	Mean 217 mg (2.7 mg/kg)	Any complication possibly related to SGX/patient mortality within 30 days	None of the outcomes appeared to be related to SGX use. SGX could be considered in patients with ESRD	Three reintubation, two hypoxemia not requiring reintubation, one pneumonia, nine mortality within 30 days, but none of these related to SGX use
Ono et al., 2018 [19]	Retrospective study	Severe renal failure, median eGFR 8 ml/min, underwent KT (99)	None	Median 200 mg	Efficacy (creatinine at postoperative day 1)/complications related to recurarization	Serum creatinine was 2.4 mg/dl at postoperative day 1, SGX was efficacious and safe in renal transplantation	No adverse events were observed
Song et al., 2022 [5]	Retrospective propensity-score-matched study	ESRD dependent on hemodialysis using SGX (797 matched out of 806)	ESRD on hemodialysis using non-SGX (797 matched out of 1,233)	2–4 mg/kg	30-day and 1-year mortality	No significant difference in the 30-day or 1-year mortality rate between SGX and non-SGX before or after matching. SGX did not increase the mortality rate in ESRD	
Valente, 2020 [17]	Case report	A patient with acute renal failure ClCr 28.4 ml/min (1)	Same patient after 18 months with no renal impairment (1)	1,000 mg (15.5 mg/kg) vs. 200 mg		High dose SGX was used over 20 min to obtain TOF ratio 0.99 in renal failure, but normal need and response to the same patient with no renal impairment	No adverse events clearly related to SGX were observed
Arslantas and Cevik, 2019 [20]	Retrospective study	KT recipients reversed with SGX (14)	KT recipients reversed with neostigmine (28)	2–4 mg/kg	Serum creatinine/acute rejection, graft failure, length of stay, and mortality	SGX may be safely used in KT. Serum creatinine and graft survival rates at 28 days were not affected by SGX	No difference in risk of serious adverse effects. 7% rejection and 7% mortality
Vargas et al., 2021 [21]	Retrospective, case-control study	KT recipients with rocuronium-SGX (30)	KT recipients with cisatracurium- neostigmine (36)	2 mg/kg	Transplanted kidney function including serum creatinine, urea, and electrolyte	No differences in creatinine urea, and electrolyte. SGX during KT did not affect relevant kidney recovery outcomes in the first week	
Carron et al., 2022 [22]	Retrospective cohort case-control study	KT recipients with rocuronium-SGX (175)	KT recipients with cisatracurium- neostigmine (175)	2–4 mg/kg	Serum creatinine/urea and eGFR	SGX for reversal of NMB showed a better recovery in KT than neostigmine with lower creatinine/urea and higher eGFR	Lower incidence of hypoxemia with SGX, no major postoperative complications

ESRD: end-stage renal disease, SGX: sugammadex, ClCr: creatinine clearance, KT: kidney transplant, eGFR: estimated glomerular filtration ratio, TOF: train-of-four, NMB: neuromuscular blockade.

Administration of sugammadex 2.0 mg/kg for reversal of rocuronium-induced moderate NMB

Staals et al. [6] reported that the mean time of recovery of the train-of-four (TOF) ratio to 0.9 was not significantly different between patients with ESRD and healthy patients with normal renal function. However, reversal of NMB using sugammadex tended to be slower in patients with ESRD (a mean value of 2.0 min for recovery of the TOF ratio to 0.9 in patients with ESRD vs. 1.65 min in controls). They suggested that sugammadex 2.0 mg/kg rapidly and effectively reverses rocuronium-induced moderate NMB in patients with ESRD and healthy controls; thus, sugammadex was well tolerated by all patients.

Administration of sugammadex 4.0 mg/kg for reversal of rocuronium-induced deep NMB

First, de Souza et al. [8] reported that the mean time of recovery of the TOF ratio to 0.9 after sugammadex (4.0 mg/kg) administration was significantly prolonged in the ESRD group (5.6 ± 3.6 min) than in the control group (2.7 ± 1.3 min), and they suggested that sugammadex 4.0 mg/kg effectively and safely reversed rocuronium-induced deep NMB in patients with ESRD, although the recovery was slower than in healthy controls. Panhuizen et al. [9] reported median (95% confidence interval) time from sugammadex 4.0 mg/kg to recovery to TOF ratio of 0.9 was 3.1 (2.4–4.6) and 1.9 (1.6–2.8) min for ESRD versus control group and suggested that sugammadex 4 mg/kg provided rapid reversal of rocuronium-induced deep NMB in patients with ESRD and control patients. However, the recovery time was significantly different between patients with ESRD and healthy controls.

Efficacy of sugammadex in patients with ESRD in a systematic review and meta-analysis

A recently published systematic review found that the time required to reach a TOF ratio ≥ 0.9, 0.8, or 0.7 was significantly longer in patients with ESRD. The plasma clearance of sugammadex in patients with ESRD was significantly lower than that in healthy controls, based on meta-analysis of six prospective observational studies [4]. However, given that the difference in the recovery time is not long enough to cause a clinically significant difference (e.g., the mean difference of the time to reach a TOF ratio of 0.9:1.14 min), it is believed that the NMB reversal time in patients with ESRD is slightly longer than that in patients with normal renal function.

PHARMACOKINETIC ASSESSMENT OF SUGAMMADEX IN PATIENTS WITH ESRD

Staals et al. [7] investigated the effect of ESRD on the PKs of sugammadex and rocuronium, and on the elimination of rocuronium encapsulated by sugammadex in patients with ESRD and controls using plasma and urine sampling at various times up to 48–72 h after sugammadex administration. Panhuizen et al. [9] collected blood samples from patients with ESRD and controls to assess rocuronium and sugammadex concentrations at various times up to 24–48 h after sugammadex injection. Min et al. [10] compared PKs of a single IV dose of sugammadex in patients with moderate and severe renal impairment to healthy patients.

Total plasma clearance of sugammadex in patients with ESRD was significantly lower than that in healthy controls [7,10]. Total plasma clearance of rocuronium in patients with ESRD was significantly lower than that in healthy controls [4]. Additionally, the effect of renal impairment on total plasma clearance was found to be greater with sugammadex than with rocuronium [7].

Staals et al. [7] reported significant differences in the PKs of sugammadex and rocuronium between patients with ESRD and healthy controls, with ESRD having a greater effect on sugammadex PK variables than those of rocuronium. The reason is that extrarenal clearance of rocuronium can occur in patients with ESRD, and even after encapsulating rocuronium with sugammadex, unbound rocuronium undergoes hepatic metabolism and elimination. Therefore, the total plasma clearance of rocuronium is less affected by renal impairment than sugammadex. The greater effect of renal impairment on total plasma clearance of sugammadex compared to rocuronium suggests that plasma concentrations of sugammadex remain relatively high in patients with ESRD during the postoperative period. Therefore, the possibility of the existence of unbound rocuronium is reduced, and in this situation, if the stability of the sugammadex–rocuronium complex is guaranteed, the risk of recurarization with free rocuronium may be low [4].

In addition, the plasma concentration of rocuronium 12 h after sugammadex injection was significantly higher in patients with ESRD [7,9]; however, this was due to the limitations of liquid chromatography–mass spectrometry to mea-

sure the plasma concentration of sugammadex and rocuronium. Because this assay cannot distinguish between encapsulated rocuronium (sugammadex–rocuronium complex) and free rocuronium, high plasma concentrations of rocuronium in patients with ESRD measured after sugammadex administration do not represent plasma concentrations of pure unbound (free) rocuronium [7,9,11,12]. Fortunately, a sugammadex–rocuronium complex may exist in equilibrium with a low dissociation constant because of strong binding [13]. However, it is unknown how long sugammadex–rocuronium complexes stably exist in the blood and whether changes in the binding force occur in patients with ESRD. If the internal environment in which the binding force of the sugammadex–rocuronium complex is reduced in these patients, the risk of fatal complications, including recurarization, still exists. Furthermore, given that the sugammadex–rocuronium complex was found in the body for a longer period in patients with ESRD (when considering the report for prolonged sugammadex– rocuronium complex exposure in patients with ESRD [9]), and there are no reported clinical data for the long-term distribution and elimination of this complex in their body, further PK studies with longer follow-up periods should be conducted.

In a situation where the stability of the sugammadex–rocuronium complex and the PK process in the body are unclear in patients with ESRD, the following study results related to the dialysability of this complex by high-flux dialysis in patients with severe renal impairment are encouraging. Cammu et al. [14] evaluated the dialysability of sugammadex and the sugammadex–rocuronium complex in six patients with acute severe renal impairment in the intensive care unit (ICU). All patients received rocuronium 0.6 mg/kg, followed by sugammadex 4.0 mg/kg 15 min later. Rocuronium and sugammadex concentrations in the plasma and dialysate were measured before, during, and after high-flux dialysis. The reduction ratio (the reduction extent of the plasma concentration at the end of a dialysis episode compared to that before dialysis) and dialysis clearance in plasma and dialysate were calculated for each dialysis episode. They reported that the mean plasma concentrations of sugammadex and rocuronium were reduced by 69% and 75% during the first dialysis episode, respectively, with reductions of approximately 50% during subsequent dialysis episodes. The mean dialysis clearance of sugammadex and rocuronium in the blood were 78 and 89 ml/min, respectively. Therefore, they concluded that in patients with severe renal impairment, hemodialysis using high-flux dialysis could be effective in removing sugammadex and sugammadex–rocuronium complex. According to the findings of this study, in patients with ESRD who have been receiving renal replacement therapy, including hemodialysis before surgery, if hemodialysis using a high-flux dialysis method is performed in the patients within 24–48 h after surgery, the sugammadex–rocuronium complex can be effectively removed, which further reduces the risk of postoperative complications, such as recurarization [4].

SAFETY-RELATED RESULTS OF SUGAMMADEX IN PATIENTS WITH ESRD

Safety outcomes of sugammadex in patients with ESRD in prospective case-control studies

In prospective trials by Staals et al. [6] and de Souza et al. [8], no sugammadex-related serious adverse events (AEs) were reported in the small samples of 15 and 20 patients, respectively. A relatively larger sample of 35 patients in a prospective case-control trial by Panhuizen et al. [9] reported at least one serious AE in nine renal patients and three patients in the healthy control group; however, none were considered to be related to sugammadex, and no clinical evidence (e.g., respiratory problems) of residual NMB or recurrence of NMB was reported after extubation for any patient. As a phase 1 PK study of sugammadex performed in two parts, Min et al. [10] closely monitored the side effects of sugammadex in two parts. Drug-related AEs, including dizziness, headache, infusion site reaction, pain in the extremities, and oral paresthesia, were reported in 1 (4.2%) of the 24 patients in their part 1 study, and no drug-related AEs were reported in the part 2 study with 18 patients. No hypersensitivity was reported in either part of this study.

Short-term safety outcomes of sugammadex in patients with ESRD in retrospective cohort studies

The short-term safety outcomes of sugammadex in surgical patients with ESRD were assessed in a retrospective study by Adams et al. [15]. The main outcomes of the study were the incidence of deferred tracheal extubation in the operating room and tracheal reintubation within 48 h of surgery in patients whose trachea was extubated at the end of surgery. Of the 158 patients with ESRD, 22 (13.9%) underwent deferred tracheal extubation due to surgical and/or

pre-existing medical conditions. Of the 136 patients who had the tracheal tube removed at the end of the surgery, three patients had tracheal reintubation within 48 h; however, two of these cases were because of pulmonary edema due to volume overload, and one case was due to deterioration of sepsis. None of the patients showed any evidence of NMB recurrence. They concluded that sugammadex is safe and effective. Paredes et al. [16] reported a cohort study of 219 patients with stage 5 chronic kidney disease who received sugammadex. No hypersensitivity reaction was observed, and reintubation was required in three patients; two patients developed hypoxemia that did not require reintubation, and one patient developed pneumonia, 9 (4.1%) patients died within 30 days of surgery. None of these events was related to the administration of sugammadex.

Long-term safety outcomes of sugammadex in patients with ESRD in a retrospective cohort study

Long-term safety outcomes were assessed in a recent retrospective propensity-score-matched study. Song et al. [5] analyzed the mortality associated with sugammadex in 2,039 surgical patients with ESRD who required hemodialysis (806 in the sugammadex group and 1,233 in the non-sugammadex group). After propensity score matching, 1,594 patients were analyzed (797 in the sugammadex group and 797 in the non-sugammadex group). No significant differences were observed in the 30-day or 1-year mortality rate between the sugammadex group and the non-sugammadex group before or after matching. They concluded that the use of sugammadex did not increase the 30-day and 1-year mortality rates after surgery in patients with ESRD. This study recommends the safe use of sugammadex in patients with ESRD with respect to long-term safety outcomes.

Safety of sugammadex in patients with ESRD in a case report

Valente et al. [17] reported a case of a 78-year-old man who weighed 66 kg with acute renal failure (estimated glomerular filtration rate [eGFR] of 28.4 ml/min) requiring a high dose of sugammadex for rocuronium reversal during general anesthesia. Sugammadex at a dose of 1,000 mg (15.5 mg/kg) was administered over 20 min to achieve NMB reversal from TOF count 1 to TOF ratio of 0.99. The patient was then extubated and transferred to the general ward. No weakness or respiratory complications were observed during the remaining hospital stays. The patient underwent another surgery with normal renal function after 18 months, and at that time, sugammadex 200 mg rapidly reversed the NMB from a TOF count of 0–2 to a TOF ratio of 0.95. In this case, no AEs related to sugammadex were observed, despite the high dose of sugammadex. This may contribute to expanding the safety profile of sugammadex and its use in patients with renal failure. In addition, this case suggests that dose modification of sugammadex may be necessary for patients with ESRD.

Taken together, although serious AEs directly related to sugammadex use were rarely observed in the abovementioned trials and case report, safety-related issues of sugammadex in patients with ESRD have not yet been resolved due to insufficient safety data.

Safety of sugammadex in patients with ESRD in a systematic review and meta-analysis

Kim et al. [4] reported that there were no significant differences between patients with ESRD and patients with normal renal function in the incidence of NMB recurrence, delayed recovery to a TOF ratio of 0.9, or other clinical signs of inappropriate neuromuscular recovery. Furthermore, in retrospective cohort studies [15,16], the possibility of residual NMB related to sugammadex was found to be insignificant. These findings suggest that sugammadex can effectively and safely reverse rocuronium-induced NMB in patients with ESRD. However, further studies are needed given the small number of included studies and the high heterogeneity of some results.

THE USE OF SUGAMMADEX IN RENAL TRANSPLANTATION PATIENTS

Reliable and sufficient reversal of NMB is important in patients with ESRD undergoing renal transplantation, to prevent microaspiration because of their perioperative immunosuppressed status. Therefore, there is no doubt about selecting a more effective and safer NMB reversal agent and providing proper NMB management using quantitative neuromuscular monitoring to measure neuromuscular function during anesthesia and to reduce postoperative residual NMB or recurarization [18].

Ono et al. [19] studied 99 consecutive patients who had undergone living renal transplantation. They investigated the efficacy and complications of sugammadex in the first

48–72 h in the surgical ICU and during 6 months follow-up period. In their study, no AEs, including recurarization, were recorded during the observation period following sugammadex administration. Although 14 (14.3%) patients had severe renal impairment (eGFR < 30 ml/min) on postoperative day 5, there were no signs of recurarization. Therefore, they concluded that the sugammadex–rocuronium complex may be excreted without detachment in their setting after renal transplantation and may remain stable for a long time in patients with renal transplants. In addition, considering that no patients required additional sugammadex injection at a dose of more than 4 mg/kg in their study, they recommended a dose of sugammadex 4 mg/kg to achieve complete recovery from deep NMB in patients with ESRD. Moreover, they emphasized that anesthesiologists should pay attention to the titrating amount of sugammadex while avoiding unnecessary overdoses, although no allergic reaction was observed in their study.

Sugammadex's effect on grafted (transplanted) kidney function is important and warrants further investigation, in addition to its efficacy and safety in patients undergoing renal transplantation. Given that sugammadex can interact with corticosteroids, which play an important role in immunosuppression in patients undergoing renal transplantation, Arslantas et al. [20] retrospectively investigated whether there are any differences in grafted kidney function in recipients of renal transplantation when sugammadex or neostigmine is administered to the recipient. They reported no significant differences in serum creatinine values, the incidence of acute rejection episodes, graft failure, length of hospital stay, mortality, and graft survival rates until postoperative day 28 between recipients reversed with sugammadex and those reversed with neostigmine. Nevertheless, they suggested that considering the sugammadex–corticosteroid interaction and its long-term effects on immunosuppression and grafted kidney function, current safety data are insufficient to support the recommendation of routine sugammadex use in patients undergoing renal transplantation.

Vargas et al. [21] compared the effects of rocuronium and sugammadex on transplanted kidney function to cisatracurium and neostigmine. They reported that blood creatinine levels at 6, 12, and 24 h were significantly lower in the rocuronium– sugammadex group than in the cisatracurium–neostigmine group and that there were no significant differences between the two groups in blood sodium and potassium, diuresis, urinary sodium, and potassium levels before and after transplantation. They concluded that the administration of rocuronium and sugammadex during renal transplantation did not affect the grafted kidney function in the first week after transplantation.

Recently, Carron et al. [22] reported a single-center, 2014–2017 retrospective cohort case-control study that compared the impact of rocuronium–sugammadex versus cisatracurium–neostigmine on grafted kidney function in patients with renal transplants. The study included 350 patients who underwent renal transplantation and were equally divided into a sugammadex group (175 patients) and a neostigmine group (175 patients). The study showed that serum creatinine and serum urea levels were lower, while eGFR was higher in the sugammadex group than in the neostigmine group after transplantation. The sugammadex group showed a significantly lower incidence of severe postoperative hypoxemia, shorter post-anesthesia care unit stay, and reduced ICU admissions. They concluded that the rocuronium–sugammadex combination for NMB management showed a better-grafted kidney function and recovery profile and fewer AEs than cisatracurium–neostigmine in patients undergoing kidney transplantation.

LIMITATIONS AND FUTURE CHALLENGES

A few prospective observational studies using sugammadex in patients with ESRD have been reported [6-10]. Regarding the method of evaluating safety-related results, each study had various reporting outcomes and observation periods related to adverse reactions. In some studies, there was insufficiently detailed mention of safety results. Thus, more prospective observational studies are needed to evaluate sugammadex-related efficacy and safety in patients with ESRD. Although several high-quality retrospective cohort studies have been reported recently [15,16,19], additional large-scale retrospective studies, including more robust safety-related data, such as, data associated with recurarization, anaphylactic reactions, long-term morbidity and mortality, and sugammadex-related cardiovascular complications, including bradycardia associated with hyperkalemia, which can occur frequently in patients with ESRD, are needed.

Magoon et al. [23] hypothesized that sources of concern with sugammadex in patients with ESRD include the possible instability of rocuronium-sugammadex binding, prolonged clearance times for rocuronium and sugammadex, difficult dosing of sugammadex for deep NMB, and sugammadex-related bradycardia. The cardiovascular adverse ef-

fects of sugammadex include corrected QT interval prolongation, atrioventricular block, atrial fibrillation, hypotension, and asystole associated with sugammadex warrant caution and further studies to examine its safety [24]. Most importantly, when administering rocuronium and sugammadex to patients with ESRD, it is essential to determine the depth of NMB during surgery using a quantitative neuromuscular monitoring device and to determine the appropriate dose of sugammadex accordingly. If such quantitative neuromuscular monitoring is not performed, it is difficult to rule out the possibility of residual NMB [23].

Comparing and observing the sugammadex-administered group and the neostigmine-administered control group in patients with ESRD would be a more efficacious for identifying sugammadex-related complications.

The use of several types of sugammadex, including many generic sugammadex, will gradually increase as only rocuronium is available in the supply of NMBAs worldwide. Considering the current limitations in terms of the effectiveness and safety of sugammadex in patients with ESRD, close patient monitoring through quantitative neuromuscular monitoring is more important. In addition, various international societies of anesthesiologists and pharmaceutical companies need to solve the supply problem of benzylisoquinolinium-type NMBAs (e.g., mivacurium, atracurium, and cisatracurium).

Recently, an experimental study showed the histochemically detectable nephroprotective effect of sugammadex in an ischemia-reperfusion rat model [25]. Considering the effect of sugammadex on renal function in patients with reduced renal function or in those undergoing renal transplantation, experimental and clinical studies on the renal protective effect of sugammadex will be valuable in the future.

RECOMMENDATIONS REGARDING THE USE OF SUGAMMADEX APPLICABLE IN PATIENTS WITH ESRD

Based on this review, we intend to present the minimum recommendations applicable to actual clinical settings for patients with ESRD undergoing general anesthesia as follows:

1. Quantitative NMB monitoring is mandatory for patients with ESRD because their responses to rocuronium and sugammadex may be more unpredictable and incomplete than those of healthy patients.
2. Considering the unresolved issue of sugammadex dosing, especially for deep NMB, moderate NMB and the corresponding sugammadex dose are recommended.
3. In patients with ESRD who have undergone hemodialysis before surgery, hemodialysis using a high-flux dialysis method within 24–48 h after surgery may be helpful. Patients who do not undergo hemodialysis require closer monitoring for a longer period to prevent postoperative complications.
4. Considering the potential risk of cardiopulmonary complications in patients with ESRD, close monitoring, including electrocardiogram, oxygen saturation, blood pressure, and blood tests for electrolytes, are required during the perioperative period.
5. A rocuronium-sugammadex combination is feasible for NMB management in patients undergoing renal transplantation. Nevertheless, routine sugammadex use is not yet recommended because of the unresolved issues of sugammadex-corticosteroid interaction and its long-term effects on immunosuppression and grafted kidney function.

CONCLUSION

Considering real clinical situations, including the discontinuation of the benzylisoquinolinium-type NMBAs, the use of sugammadex in clinical practice for NMB management cannot be avoided to achieve safe and complete neuromuscular recovery in patients with ESRD or patients with renal transplants after rocuronium administration.

Sugammadex can effectively and safely reverse rocuronium-induced NMB in patients with ESRD; however, the recovery of neuromuscular function in these patients is significantly slower than that in patients with normal renal function. However, the difference in the recovery rate was insufficient to be clinically significant. Considering the insufficient amount of reported data to date, more extensive data are required on the efficacy and safety of administration of sugammadex in patients with ESRD, especially safety-related results, including postoperative residual NMB, recurarization, and incidence of cardiopulmonary complications, and a problem in the dosing for reversal of deep NMB. Furthermore, it is important to perform appropriate quantitative neuromuscular monitoring during general anesthesia of patients with ESRD in actual clinical settings. Anesthesiologists should remember that it is essential to confirm the depth of perioperative NMB through neuromuscular monitoring, ad-

minister an appropriate dose of sugammadex, and closely monitor the recovery of neuromuscular function.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

AUTHOR CONTRIBUTIONS

Conceptualization: Byung Gun Lim. Data curation: Seok Kyeong Oh, Byung Gun Lim. Methodology: Byung Gun Lim. Visualization: Seok Kyeong Oh. Writing - original draft: Seok Kyeong Oh, Byung Gun Lim. Writing - review & editing: Seok Kyeong Oh, Byung Gun Lim. Investigation: Seok Kyeong Oh. Supervision: Byung Gun Lim. Validation: Byung Gun Lim.

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