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Sugammadex for reversal of rocuronium-induced neuromuscular blockade in pediatric patients
A systematic review and meta-analysis

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Abstract

Background: Previous studies have shown that sugammadex, a modified γ-cyclodextrin, is a well-tolerated agent for the reversal of neuromuscular blockade (NMB) induced by a steroidal neuromuscular blocking drug in adult patients. However, its use has not been reviewed in pediatric patients. The aim of this meta-analysis was to evaluate the efficacy and safety of sugammadex in the reversal of rocuronium-induced NMB during surgery under general anesthesia in pediatric patients.

Methods: A literature search was performed using the Pubmed, EMBASE: Drugs and pharmacology, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. Analysis was conducted using RevMan 5.3. Data collected from different trials were pooled; the weighted mean difference or the pooled risk ratio and the corresponding 95% confidence interval (CI) were used for analysis, and heterogeneity (I^2) assessment was performed.

Results: Six randomized controlled trials comparing 253 pediatric patients (age range, 2–18 years) were included in the final analysis. The mean time taken to reach a train-of-four ratio of ≥ 0.9 was significantly shorter in the sugammadex groups (2 and 4 mg/kg) than in the control group (neostigmine or placebo), although the heterogeneity was high. The weighted mean differences of the 2 and 4 mg/kg sugammadex groups were -7.15 (95% CI: -10.77 to -3.54; $I^2 = 96\%$; $P = 0.0001$) and -17.32 (95% CI: -29.31 to -5.32; $I^2 = 98\%$; $P = 0.005$), respectively. The extubation time in the sugammadex group was shorter than that in the control group; the weighted mean difference of the sugammadex group was -6.00 (95% CI: -11.46 to -0.53; $I^2 = 99\%$; $P = 0.03$). There was no significant difference between the groups in terms of the incidence of postanesthetic adverse events; the pooled risk ratio was 0.67 (95% CI: 0.27–1.71; $I^2 = 59\%$; $P = 0.41$).

Conclusion: We suggest that sugammadex is fast and effective in reversing rocuronium-induced NMB in pediatric patients. Although there was no evidence of a higher incidence of adverse events with sugammadex compared to that with neostigmine or placebo, much more data regarding the safety of sugammadex in pediatric patients may be still required.

Abbreviations: CI = confidence interval, ERAS = enhanced recovery after surgery, NMB = neuromuscular blockade, RCT = randomized controlled trial, TOF = train-of-four.

Keywords: adolescent, child, neostigmine, neuromuscular blockade, preschool, reversal, sugammadex

1. Introduction

During surgery, muscle relaxation is required for facilitation of the surgical procedure with adequate anesthetic depth; however, after the surgery, this muscle relaxation needs to be completely reversed. If the complete reversal is not performed, postoperative residual neuromuscular blockade (NMB) can result in ventilatory and pulmonary complications such as desaturation and atelectasis as well as blurred vision and delayed recovery.[1,2]

Sugammadex, a modified γ-cyclodextrin, reverses NMB by forming very tight water-soluble complexes in a 1:1 ratio with steroidal neuromuscular blocking drugs, especially rocuronium and vecuronium.[3] There have been numerous studies on sugammadex and several meta-analyses showing its effectiveness, safety, and superiority to cholinesterase inhibitors in NMB reversal in adult patients.[4,5]

Although some randomized controlled trials (RCTs) and case reports regarding the use of sugammadex in pediatric patients have been published,[6–13] no meta-analysis has been reported so far. Unlike adult patients, pediatric patients have shown a high age-dependent variability in their response to muscle relaxants and NMB reversal agents; this variability is attributed to the differences in the pharmacokinetic and pharmacodynamic profiles of the drugs in patients of different age groups.[14,15]

An individual pediatric patient shows approximately 25% standard deviation in the average response for all NMB-related time parameters (onset time, clinical duration, and time to full recovery), irrespective of the muscle relaxant used.[16] Additionally, some concerns regarding critical adverse effects, such as hypersensitivity and allergic reactions, still remain. These facts necessitate confirming the efficacy and safety of sugammadex in preventing unexpected situations such as residual curarization and other adverse events observed in the data derived from extensive literature search.[17–19]

This meta-analysis was performed to assess the clinical efficacy and safety of sugammadex in the reversal of rocuronium-induced neuromuscular blockage in pediatric patients, and to compare it with cholinesterase inhibitors such as neostigmine.

2. Materials and methods

We searched multiple comprehensive databases to find literature regarding sugammadex use in pediatric patients. This study was based on the Cochrane Review Methods.[20]

2.1. Database and literature sources

We searched the MEDLINE (January 1, 1950–August 3, 2015), Embase (January 1, 1980–August 3, 2015), Cochrane Library (January 1, 1987–August 3, 2015), and KoreaMed (June 1, 1958–August 3, 2015) databases using the Medical Subject Headings (MeSH) and free text terms. Our search was not restricted by language or year of publication.

The following keywords and MeSH terms were searched in MEDLINE: sugammadex, selective relaxant binding agent, bridion, gamma-Cyclodextrins, and Org 25969. To identify unpublished or ongoing studies, we searched the World Health Organization International Clinical Trials Registry Platform and the ClinicalTrials.gov websites. After the original electronic search, we checked the bibliographies from identified studies. The identified articles were assessed individually for inclusion in the analysis.

2.2. Study selection

Decision regarding the inclusion of the studies in the analysis was made independently by 2 reviewers (BGL and YJW), and was based on predefined inclusion criteria. Studies were selected after being subjected to 2 levels of screening. At the 1st level, we screened the titles and abstracts of the identified studies. At the 2nd level, we screened the full texts. Discrepancies between the reviewers were resolved by discussion. The following studies were included in our meta-analysis: RCTs involving pediatric patients who were administered sugammadex; studies that evaluated the time taken for the train-of-four (TOF) ratio to recover to ≥0.9; and studies that evaluated the prevalence of drug-related adverse events.

2.3. Data extraction

The 2 reviewers independently extracted data from each study using a predefined data extraction form. Any disagreement unresolved by discussion was analyzed by a 3rd reviewer (IOL).

The following variables were extracted from the studies: mean and standard deviation of the time taken for a TOF ratio to reach ≥0.9, extubation time, and dichotomous data regarding the incidence of postanesthetic adverse events in the intervention and control groups; demographic, clinical, and treatment characteristics (e.g., age range of the patients, type of operation, use of anesthetic drugs such as a volatile agent or propofol, and the number of patients in the intervention and control groups); type of the intervention protocol; 1st author and the year of publication; and method of assessment.

If the above variables were not mentioned in the articles, we gathered the data from the authors via email.

2.4. Assessment of methodological quality

The 2 reviewers (BGL and YJW) independently assessed the methodological quality of each study using the Cochrane Collaboration tool for assessing risk of bias. This tool is widely used to assess the methodological quality of RCTs and consists of the following 7 items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. The risk of bias was classified into 3 categories: high, low, or unclear. Any unresolved disagreements between the reviewers were resolved through discussion or by a 3rd reviewer (IOL).

2.5. Statistical analysis

The primary outcome of our review was the time taken to reach a TOF ratio of ≥0.9. It was defined as the time from the start of administration of sugammadex/control medication to recovery of the TOF ratio to ≥0.9. Secondary outcomes were extubation time and the incidence of postanesthetic adverse events. Extubation time was defined as the time from the discontinuation of the anesthetic agents (time=0 minute) to tracheal extubation.

Continuous variables, including the time to reach a TOF ratio of ≥0.9 and extubation time, were analyzed using the weighted mean difference with 95% confidence interval (CI). A weighted mean difference with a 95% CI < 0 would indicate that the time taken was shorter in the sugammadex group than that in the control group. The incidence of postanesthetic adverse events, a dichotomous variable, was analyzed using the risk ratio with 95% CI.

We used RevMan, version 5.3, for these analyses.

Each analysis was assessed for statistical heterogeneity using the Cochrane Q test and I^2 statistics. For the I^2 statistics, the proportion of between-study inconsistency due to true differences between the studies rather than differences due to random error or chance, with values >50%, were considered to have a significant heterogeneity. $P < 0.1$ for Cochrane Q test was considered statistically significant. If P was >0.1 and the I^2 was <50%, the fixed-effects model was used, otherwise, the random effects model was used.[20]

Since we included a small number of studies, a subgroup or sensitivity analysis could not be performed except the effect of the different TOF criteria at giving sugammadex on the time to reach a TOF ratio of ≥0.9.

The analysis of publication bias (used for at least 10 studies) was not assessable for this meta-analysis considering the small number of included studies.

3. Results

3.1. Identification of studies

The databases search yielded 1843 articles (Fig. 1). Of these, 1832 publications were excluded because it was clear from the title and abstract that they did not fulfill the selection criteria. For the remaining 11 articles, we obtained the full manuscripts and
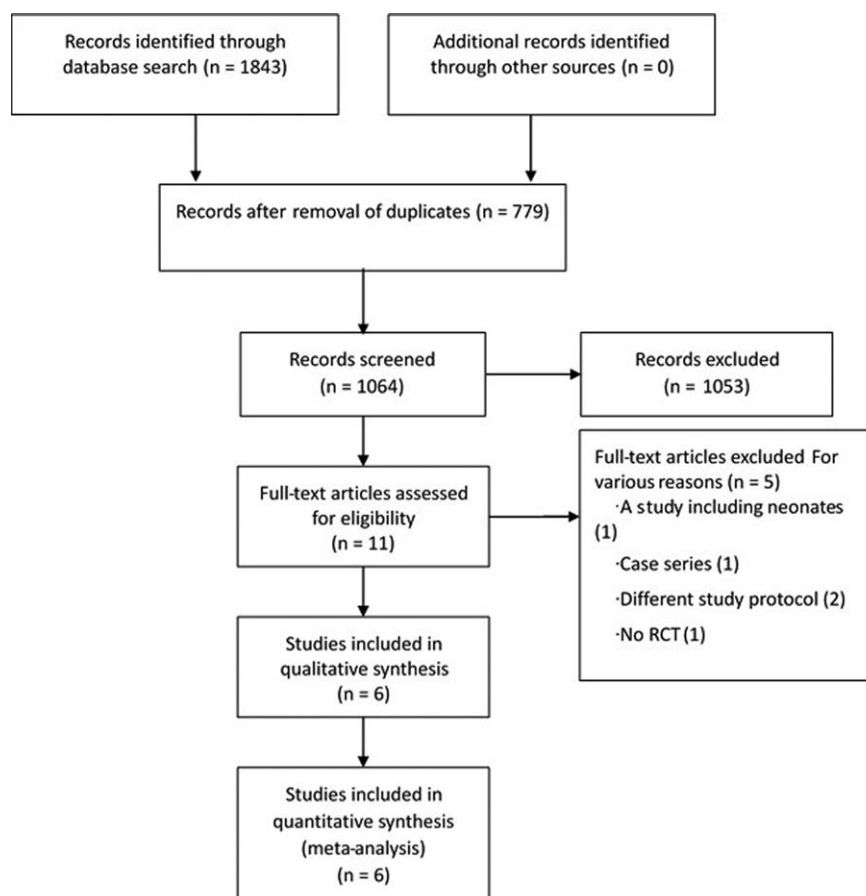
Figure 1. Meta-analysis flowchart. RCT = randomized controlled trial.

evaluated them. We identified 6 potentially relevant studies and excluded 5 publications for the following reasons: they included neonatal patients; they were case reports; they included 2 sugammadex bolus administration doses within a short time interval; they were not randomized studies; and the control group was also treated with sugammadex. Hence, 6 studies were finally included in our analysis (Fig. 1).

3.2. Study characteristics and patient demographics

Details of the selected studies are summarized in Table 1. Six trials including 253 pediatric patients (age range, 2–18 years) were included in the final analysis. Of the 253 patients, 129 patients were in the intervention group and were treated with sugammadex (2 or 4 mg/kg), while 124 patients were in the control group and were treated with placebo or neostigmine. Five studies were conducted in Europe and 1 in Egypt. The treatment regimens for the intervention group were sugammadex 2 mg/kg (4 studies) or 4 mg/ kg (3 studies). The treatment regimens for the control group were as follows: neostigmine 0.05 mg/kg with atropine 0.025 mg/kg in 2 studies and neostigmine 0.04 mg with atropine 0.02 mg/kg, neostigmine 0.03 mg with atropine 0.01 mg/kg, neostigmine 0.06 mg with atropine 0.02 mg/kg, and placebo, each in 1 study.

3.3. Quality of the included studies (risk of bias in the included studies)

See Table 2.

3.4. Allocation

All the 6 studies reported that they were randomized; however, allocation concealment was adequately reported only in 3 studies (50%) (Table 2). The method of random sequence generation was reported in 5 studies (83%).

3.5. Blinding

Only 1 study (Ozgün et al, 2014),[11] which reported blinding of the outcome assessors, was assessed as having a low risk of bias and the other studies were assessed as having unclear or high risk of bias (Table 2).

3.6. Incomplete outcome data

The 3 studies (50%) that reported the completeness of outcome data for each main outcome were assessed as having low risk of bias (Table 2).

3.7. Selective reporting and other potential sources of bias

All the studies were assessed as having unclear risk of bias related to selective reporting, and 4 studies (67%) were assessed as having low risk of other potential source of bias (Table 2).

3.7.1. Effect of intervention. Primary outcome was the mean time taken to reach a TOF ratio of ≥0.9, which indicated the rate

Table 1

Details of the studies included in the meta-analysis.

Study ID	Journal	Patient age (years)	Setting/country	Type of surgery	TOF ratio at NMB reversal	Anesthetic agent at NMB reversal	Sugammadex	Reversal agent of control group
Gaona et al, 2012 (abstract for poster presentation)	British Journal of Anaesthesia (supplement)	2–11	Children's & University Hospital/Spain	Short length surgery	PTC <2–3 (intervention), PTC >2–3 (control)	Not mentioned	4 mg/kg	Neostigmine 0.05 mg/kg+ atropine 0.025mg/kg
Ghoneim and El Beltagy, 2015	Saudi Journal of Anesthesia	7–18	University Hospital/Egypt	Undergoing, elective craniotomy for posterior fossa tumor excision	TOF 2 count	After termination of sevoflurane	4 mg/kg	Neostigmine 0.04 mg/kg+ atropine 0.02mg/kg
Kara et al, 2014	Revista Brasileira de Anestesiologia	2–12	General Hospital/Turkey	Outpatient surgery as elective lower abdominal or urogenital procedures	TOF 2 count	After termination of sevoflurane	2 mg/kg	Neostigmine 0.03 mg/kg+ atropine 0.01 mg/kg
Ozgün et al, 2014	Journal of Research in Medical Sciences	2–12	General Hospital/Turkey	General anesthesia in the supine position for ear nose and throat surgery	TOF 2 count	Sevoflurane sustained	2 mg/kg	Neostigmine 0.06 mg/kg+ atropine 0.02mg/kg
Plaud et al, 2009	Anesthesiology	2–17	University Hospital/6 European centers	General of <60 minutes, scheduled for surgery in a supine position	TOF 2 count	Propofol	2 mg/kg and 4 mg/kg	Placebo
Veiga et al, 2011 (abstract for poster presentation)	Eur J Anaesthesiol (supplement)	2–9	University Hospital/Spain	Scheduled for general anesthesia	TOF 2 count	70% nitrous oxide	2 mg/kg	Neostigmine 0.05 mg/kg+ atropine 0.025mg/kg

NMB=neuromuscular blockade, PTC=posttetanic count, TOF=train-of-four.

Table 2

Risk of bias assessment for all the 6 randomized controlled trials.

| Study	Sequence generation	Allocation concealment	Blinding of participants, personnel, and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other source of bias	Overall risk of bias
Gaona et al, 2012	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Ghoneim and El Beltagy, 2015	Low	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Kara et al, 2014	Low	Low	High	Low	Unclear	Low	High
Ozgün et al, 2014	Low	Low	Low	Low	Unclear	Low	Unclear
Plaud et al, 2009	Low	Low	Unclear	Low	Unclear	Low	Unclear
Veiga et al, 2011	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
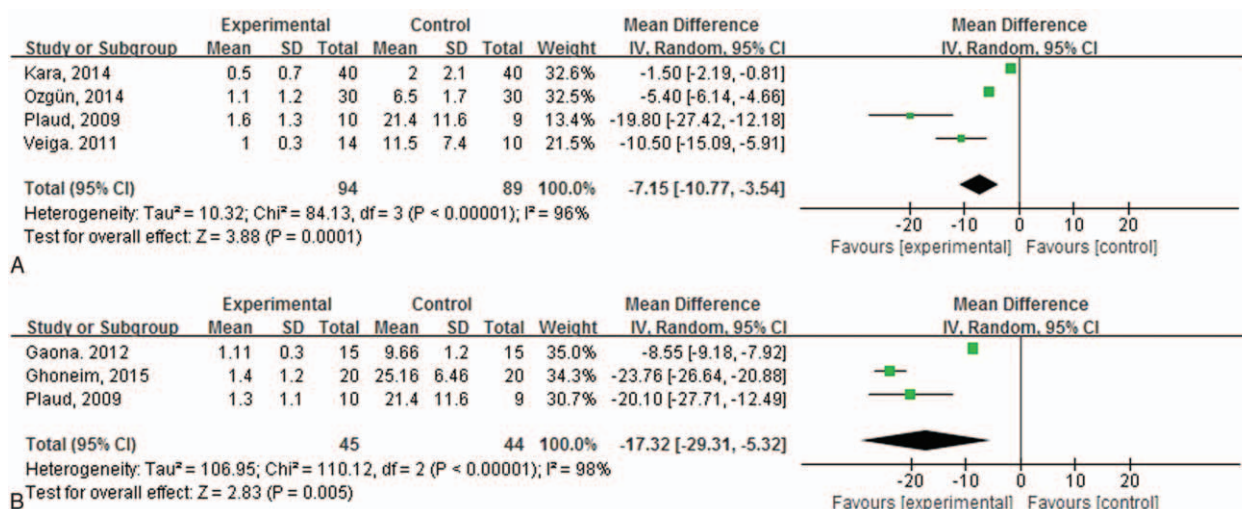
Figure 2. Time to reach a TOF ratio of ≥0.9 (minute) measured from the time of administration of (A) 2 mg/kg or (B) 4 mg/kg of sugammadex and a control drug (neostigmine or placebo). The experimental group was administered 2 mg/kg or 4 mg/kg of sugammadex. The control group was administered neostigmine or placebo. CI = confidence interval, IV = inverse variance, SD = standard deviation, TOF = train-of-four.

of NMB reversal after the administration of sugammadex or neostigmine/placebo. For comparing this outcome between the 2 mg/kg sugammadex group and the control group, 4 studies were analyzed; the mean time (95% CI) to reach a TOF ratio of ≥0.9 was significantly shorter in the 2 mg/kg sugammadex group than that in the control group using neostigmine or placebo (the weighted mean difference: −7.15; 95% CI: −10.77 to −3.54; $P = 0.0001$), although the heterogeneity was high ($I^2 = 96\%$) (Fig. 2A). For comparing this outcome between the 4 mg/kg sugammadex group and the control group, 3 studies were analyzed; the mean time (95% CI) taken to reach a TOF ratio of ≥0.9 was also significantly shorter in the 4 mg/kg sugammadex group than that in the control group using neostigmine or placebo (the weighted mean difference: −17.32; 95% CI: −29.31 to −5.32; $P = 0.005$), although the heterogeneity was high ($I^2 = 98\%$) (Fig. 2B).

As we can see in the Table 1, in the 4 studies included in the sugammadex 2 mg/kg group, the TOF before giving sugammadex was all same as a TOF count 2. But, in the 3 studies included in the sugammadex 4 mg/kg group, the TOF before giving sugammadex was not same in all studies. In 1 study (Gaona et al, 2012),[8] 4 mg/kg of sugammadex was administered at a posttetanic count (PTC) of <2–3, while in the other 2 studies (Ghoneim and El Beltagy, 2015, Plaud et al, 2009),[9,12] it was administered at a TOF count 2. Therefore, to investigate the effect of the different TOF criteria at giving sugammadex on the time to

reach a TOF ratio of ≥0.9, we performed sensitivity analysis with the exclusion of the study of Gaona et al, 2012.[8] Consequently, we found that the time taken to reach a TOF ratio of ≥0.9 was still significantly shorter in the 4 mg/kg sugammadex group than that in the control group using neostigmine or placebo (the weighted mean difference: −23.30; 95% CI: −25.99 to −20.61, $P < 0.001$), but the heterogeneity became very low ($I^2 = 0\%$).

The secondary outcomes were extubation time and the incidence of postanesthetic adverse events. For evaluating the difference in extubation time between the 2 and 4 mg/kg sugammadex intervention group and the neostigmine control group, 3 studies were analyzed. Extubation time was significantly shorter in the sugammadex group than that in the control group; the weighted mean difference was −6.00 (95% CI: −11.46 to −0.53; $I^2 = 99\%$; $P = 0.03$) (Fig. 3).

Out of the 6 trials, 5 compared postanesthetic adverse events in the sugammadex group with those in the control group (neostigmine or placebo). Each adverse event such as vomiting, airway spasm, desaturation, cardiovascular complication, or Q-T prolongation was clearly reported in all the trials regardless of the publication type (full-text or abstract). There was no significant difference between the sugammadex group and the control group in terms of the overall incidence of postanesthetic adverse events; the risk ratio was 0.67 (95% CI: 0.27–1.71; $I^2 = 59\%$, $P = 0.41$) (Fig. 4). The incidence of adverse respiratory events such as airway spasm and desaturation in the sugammadex group (2.4%,
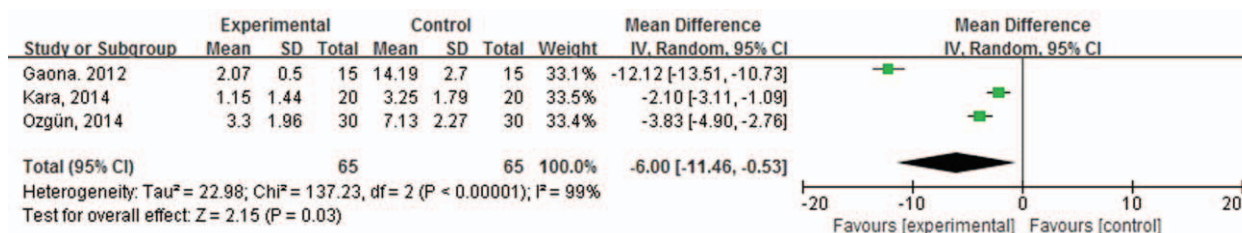

Figure 3. Extubation time (minute). The experimental group was administered 2 mg/kg or 4 mg/kg of sugammadex. The control group was administered neostigmine or placebo. CI = confidence interval, IV = Inverse variance, SD = standard deviation.
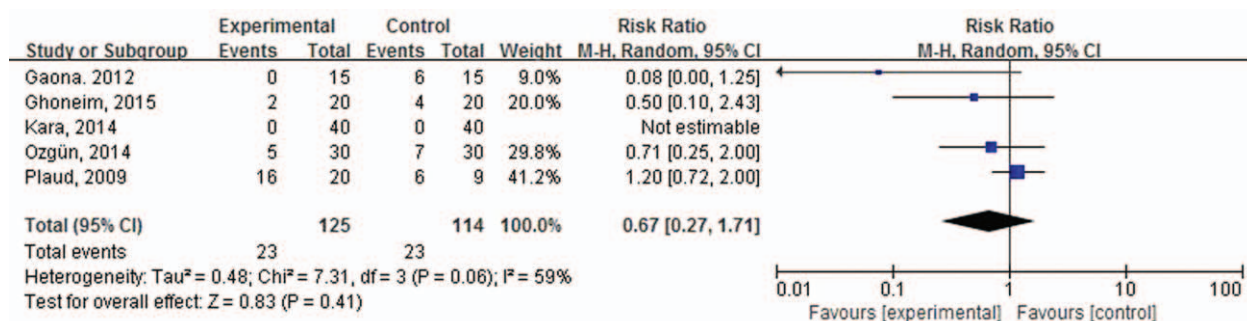
Figure 4. Incidence of postanesthetic adverse events (number of patients). The experimental group was administered 2 mg/kg or 4 mg/kg of sugammadex. The control group was administered neostigmine or placebo. CI = confidence interval, M-H = Mantel–Haenszel.

3 out of 125 patients) was comparable to that in the control group (1.8%, 2 out of 114 patients). The incidence of vomiting in the sugammadex group (10.4%, 13 out of 125 patients) was also comparable to that in the control group (12.3%, 14 out of 114 patients).

4. Discussion

The results of this meta-analysis suggest that sugammadex shortens the rocuronium-induced NMB reversal time and the extubation time compared to neostigmine or placebo, with similar postanesthetic adverse events, in pediatric patients undergoing surgery under general anesthesia.

Sugammadex has been administered to pediatric patients for off-label use in many countries, although its use was accepted by the European registration authorities in July 2008, resulting in restriction of pediatric studies.[16] Furthermore, the US Food and Drug Administration has asked for additional data for the resolution of some concerns regarding hypersensitivity and allergic reactions, and it also has stated that more pediatric studies will be organized to acquire valid pediatric documentation on the effectiveness of sugammadex in different clinical scenarios.[15] Considering these points, reviewing data of extensive literature on RCTs and other articles regarding sugammadex use in pediatric patients can be very significant.

This pooled meta-analysis suggested several important points about sugammadex use in pediatric patients. First, it showed the superior efficacy of sugammadex at clinically standard dosages including a dose of 4 mg/kg as well as the dose of 2 mg/kg, which has only been approved in children for reversal of moderate NMB (TOF count 2). Its clinical efficacy in pediatric patients was not grossly different from that in adults.

Second, the shorter time required to reach a TOF ratio of ≥0.9 and for extubation in the sugammadex group of this meta-analysis may allow faster recovery of patients and better operating room turnover, resulting in better prognosis in terms of overall patient outcomes. Enhanced recovery after surgery (ERAS) has recently gained increasing attention; the ERAS protocols for perioperative care have been proven to reduce the complications after surgery, improve overall outcomes, and shorten the hospital stay.[21] Thus, guidelines for specific fields are being formulated and published worldwide.[22,23] According to the ERAS protocol, the use of short-acting anesthetic agents is one of the elements comprising the intraoperative component of the protocol.[24] Use of sugammadex after rocuronium administration can reduce the anesthesia time, recovery time, and length of hospital stay in adult patients, making it eligible to be included

in the territory of short-acting anesthetic agents in the ERAS protocol.[18,25] Taken together, further studies regarding the effectiveness of sugammadex as a new element in the ERAS protocol for pediatric patients may be necessary.

Third, the overall incidence of postanesthetic adverse events was comparable between the sugammadex group and the control group. Especially, there was no evidence of a higher incidence of severe adverse events such as airway spasm and desaturation with sugammadex compared to that with neostigmine or placebo. However, the overall incidence of vomiting in both the groups was higher than that reported in adult studies, which might be characteristic of pediatric anesthesia.[4] In addition, abnormal urinalysis results, such as increased urinary levels of N-acetylglucosaminidase, were not reported in the studies included in this meta-analysis, although they have been reported as a rare drug-related adverse event of sugammadex in adults in previous studies.[26,27]

There are some limitations of this meta-analysis and the major one is its high heterogeneity. The reason for high heterogeneity in the data regarding the time required to achieve a TOF ratio of ≥0.9 could be related to the fact that volatile anesthetics, including sevoflurane, can enhance the effect of rocuronium, thus affecting the reversal of rocuronium-induced NMB.[28] Although administration of volatile anesthetics was terminated at the time of administration of the reversal agent in 4 studies, sevoflurane administration was continued in 1 study (Ozgün et al, 2014),[11] and 1 study did not mention anything regarding this point (Gaona et al, 2012).[8] In addition, the high heterogeneity may be due to interage differences among the study participants. Although this meta-analysis excluded infants, 2 studies (Ghoneim and El Beltagy, 2015, Plaud et al, 2009)[9,12] included adolescents, while 4 excluded these patients.

Another limitation of this meta-analysis is that we could not assess the publication bias because of the small sample size. Tests for funnel plot asymmetry are usually performed when at least 10 studies are included in a meta-analysis. As our analysis included only 6 studies, the tests for asymmetry were ineffective in differentiating chance from asymmetry.

"Third, only 1 study (Ozgün et al, 2014)[11] was properly blinded during the research process and the other studies included in the meta-analysis did not make mention of blinding adequately. Blinding is a critical methodological feature of RCTs to maximize the validity of the results and minimize the bias.[29] Although the objective data including the time taken to reach a TOF ratio of ≥0.9 may be less influenced by blinding, further well-designed RCTs with proper blinding methods are needed to assess the effectiveness of sugammadex in pediatric patients."

In conclusion, we suggest that sugammadex is fast, effective, and relatively tolerable in reversing rocuronium-induced NMB in pediatric patients. However, considering the high heterogeneity in the results about the efficacy of sugammadex, suggested by the time required to reach a TOF ratio of ≥ 0.9 and the extubation time, further RCTs about sugammadex use in pediatric patients may be needed. As for the issue of safety, although there was no evidence of a higher incidence of adverse events with sugammadex compared to that with neostigmine or placebo, much more data and evidence to support the safety of sugammadex in pediatric patients may be still required.

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