Meta Analysis

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Appropriate dosing of sugammadex for reversal of rocuronium-/vecuronium-induced muscle relaxation in morbidly obese patients: a meta-analysis of randomized controlled trials

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Abstract

Objective: To conduct a meta-analysis to compare different dosing scalars of sugammadex in a morbidly obese population for reversal of neuromuscular blockade (NMB).

Methods: PubMed®, ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL) and Google Scholar were searched for relevant randomized controlled trials (RCTs) comparing lower-dose sugammadex using ideal body weight (IBW) or corrected body weight (CBW) as dosing scalars with standard-dose sugammadex based on total body weight (TBW) among morbidly obese people after NMB. Mean difference with SD was used to estimate the results.

Results: The analysis included five RCT with a total of 444 morbidly obese patients. The reversal time was significantly longer in patients receiving sugammadex with dosing scalar based on IBW than in patients receiving sugammadex with dosing scalar based on TBW (mean difference 55.77 s, 95% confidence interval [CI] 32.01, 79.53 s), but it was not significantly different between patients receiving sugammadex with dosing scalars based on CBW versus TBW (mean difference 2.28 s, 95% CI −10.34, 14.89 s).

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Conclusion: Compared with standard-dose sugammadex based on TBW, lower-dose sugammadex based on IBW had 56 s longer reversal time whereas lower-dose sugammadex based on CBW had a comparable reversal time.

Keywords
Sugammadex, morbidly obese, total body weight, ideal body weight, corrected body weight, lean body weight

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Introduction

Sugammadex is a selective reversal agent for neuromuscular blockade (NMB) induced by aminosteroid neuromuscular blocking agents.[1] An increasing number of studies have demonstrated its superior efficacy over anticholinesterases in general surgical populations.[2–4] Sugammadex reverses NMB more rapidly with fewer adverse events than neostigmine in morbidly obese patients undergoing surgery.[5] Trials from the clinical development phase of sugammadex have suggested dosing by total body weight (TBW) to provide a consistent molar ratio of sugammadex to NMB agents to limit residual block.[6,7] For reversal agents, under-dosing can cause prolonged recovery, residual NMB or recurarization.[8,9]

Sugammadex is an expensive drug the cost of which can cause financial burden, especially when used in morbidly obese individuals that require a high dose. Before lower-dose sugammadex can be considered as a cost-saving strategy for the reversal of NMB, it is crucial to clarify whether lower-dose sugammadex using ideal body weight (IBW) or corrected body weight (CBW) as dosing scalars has comparable reversal time as standard-dose sugammadex based on TBW. Therefore, a systematic review and meta-analysis of randomized controlled trials (RCTs) was undertaken to compare the effect of lower-dose sugammadex using IBW or CBW as dosing scalars with that of standard-dose sugammadex based on TBW. The reversal time, defined as the time to recovery of train of four ratio (TOFR), was set at $\geq$0.9 among morbidly obese people after moderate or deep NMB with either rocuronium or vecuronium.

Materials and methods

Data sources and search strategy

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[10] Approval from the institutional review board or ethics committee was waived as this research was a meta-analysis of published RCTs. This systematic review was not prospectively registered, but was registered retrospectively at INPLASY (registration no. 202240130).

Electronic databases, including PubMed®, ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL) and Google Scholar were searched from 1966 to 31 December 2021, utilizing the keywords and database-specific subjects (MESH terms) "sugammadex", "obesity" and "body weight". The full search strategies were as follows (i) for

PubMed®, ("Sugammadex"[Mesh]) AND ("Obesity"[Mesh]); (ii) for ClinicalTrials.gov, condition or disease: obesity (automatically including synonyms: obese, adiposity), other terms: sugammadex (automatically including synonyms: Bridion, Org 25969); (iii) for the Cochrane Central Register of Controlled Trials (CENTRAL), #1 MeSH descriptor: [Sugammadex] explode all trees, #2 MeSH descriptor: [Obesity] explode all trees; #3 = #1 and #2; (iv) for Google Scholar, with all of the words: sugammadex morbid obesity, with the exact phrase: body weight.

Study selection and data abstraction

Criteria for trial inclusion were as follows: (i) the study had an RCT design; (ii) patients included those >18 years of age with a body mass index $\geq 40\,kg/m^2$ that underwent general anaesthesia with any degree of NMB induced by either rocuronium or vecuronium; (iii) studies that compared TBW with IBW or CBW as dosing scalars for sugammadex; and (iv) outcomes were presented as mean ± SD, standard errors (SEs) or 95% confidence intervals (CI). CBW was defined as IBW + 0.4 × (TBW–IBW). Studies were excluded if : (i) they were not published in a full-text article; (ii) they were published in any language other than English; (iii) they did not include a dosing scalar based on TBW in any arm. The data regarding baseline characteristics, including age, sex and number of patients in each group, were extracted. Data on the primary and secondary outcomes of each trial were also extracted. Two reviewers (J.Q.L. and D.S.) independently screened and selected studies from the search results and extracted data using standardized forms in Microsoft® Excel® (Microsoft, Redmond, WA, USA). Any disagreements between reviewers were resolved by consensus. If not resolved, the final decision was made by a third reviewer (C.W.L.).

Quality assessment

Studies were independently reviewed by J.Q.L. and D.S. to assess their respective risks of bias. The Risk of Bias (RoB 2) tool was used for RCTs as proposed previously to assess the different domains of bias.[11] Discrepancies were resolved by discussion and by adjudication with a third reviewer (C.W.L.) if necessary.

Statistical analyses

Data were analysed based on the per-protocol principle. The primary outcome was the time to reach TOFR ≥ 0.9 from administration of sugammadex (reversal time). The secondary outcomes were the rate of postoperative respiratory complications and any adverse events (AEs) occurring after administration of sugammadex. Meta-analyses were performed using the RevMan 5.4 software (Cochrane Collaboration, Oxford, UK). The mean difference with SD was used to estimate the results between the active and control groups. The random-effects model was used to calculate the pooled estimate when two or more trials provided sufficient data for a given outcome. Statistical heterogeneity was assessed with the I^2 statistic, with values of 30–60% and 50–90% considered to indicate moderate and substantial heterogeneity, respectively.[12] A two-sided P-value <0.05 was considered statistically significant. Publication bias was assessed using funnel plots when ≥10 studies were included in the meta-analysis.

Results

A total of 978 records were identified during the search (Figure 1). All were screened and of these 11 candidate reports were retrieved. After assessing the full texts

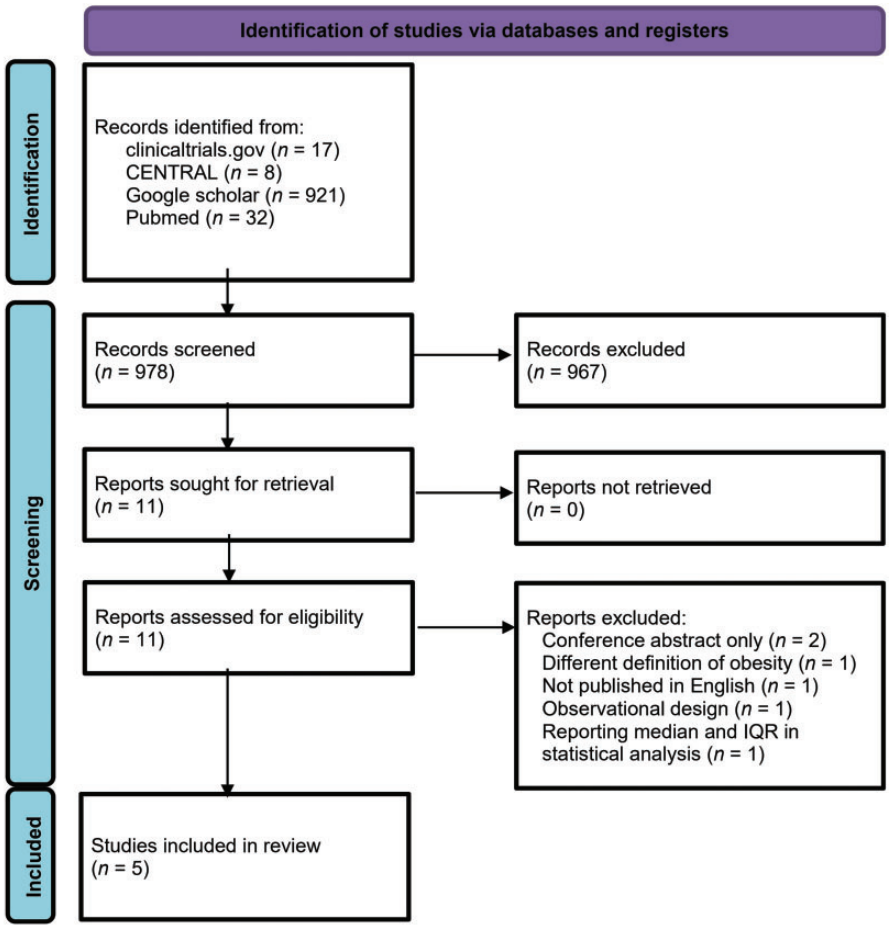

Figure 1. Flow diagram of eligible studies showing the number of citations identified, retrieved and included in the final meta-analysis.

of the 11 reports, seven reports were excluded for the following reasons: published as a conference abstract, published in a language other than English, non-compliant definitions of morbid obesity, observational design and reporting data as only medians and interquartile ranges. The final analysis included 444 patients with morbid obesity from five RCTs.[13–17]

The characteristics of the five RCTs are summarized in Table 1.[13–17] Four trials reported a comparison between TBW and IBW as the dosing scalar.[13–16] Four trials reported a comparison between TBW and CBW, calculated as $\text{IBW} + 0.4 \times (\text{TBW}–\text{IBW})$, as the dosing scalar.[13–15,17] One trial also included a group of patients receiving no reversal agent and another trial included a group in which $\text{IBW} + 0.2 \times (\text{TBW}–\text{IBW})$ had been used as the dosing scalar; the patients from these groups were not incorporated into the pooled analysis.[13,17] The mean $\pm$ SD age was 40.82 ± 10.71 years.

Table 1. Characteristics of the five studies included in a meta-analysis of randomized controlled trials to evaluate the effect on reversal time of lower-dose sugammadex using ideal body weight (IBW) or corrected body weight (CBW) as dosing scalars with that of standard-dose sugammadex based on total body weight (TBW).[13–17]

Studies	*n*	Participants	Surgery	Groups	Depth of NMB at reversal	Dosage	Maintenance	Other outcomes
Van Lancker et al., 2011[13]	103	F:M = 71:32 Age: 43.9 ± 11.35 years BMI: 43.15 ± 3.66 kg/m^2	Laparoscopic bariatric surgery	TBW, IBW, CBW-20%, CBW-40%	T1–T2 recovery	2 mg/kg	Propofol, N_2O	Extubation time; time to eye opening; independent or assisted transfer from the theatre-table to bed; clinical signs of residual paralysis upon arrival to the PACU; incidence of nausea or vomiting; visual analogue scale pain scores; recovery scores
Elfawy et al., 2019[14]	58	F:M = 37:21 Age: 30.25 ± 4.2 years BMI: 49.23 ± 4.13 kg/m^2	Laparoscopic bariatric surgery (gastric sleeve or bypass)	TBW, IBW, CBW-40%	T2 recovery	2 mg/kg	Isoflurane	Extubation time; duration of PACU stay
Ornek et al., 2020[15]	60	F:M = 48:12 Age: 42.23 ± 11.4 years BMI: 47.17 ± 8.37 kg/m^2	Laparoscopic sleeve gastrectomy	TBW, IBW, CBW-40%	No information	2 mg/kg	Propofol, remifentanil	Extubation time; time to reach a BIS > 80 (cortical recovery time); time to eye opening; time to first verbal answer; time to orientation; delayed discharge from PACU secondary to respiratory complications
Horrow et al., 2021[16]	150	F:M = 110:40 Age: 47.99 ± 13.11 years BMI: 46.22 ± 5.24 kg/m^2	Not specified	TBW, IBW	T2 recovery or PTC 1	2 mg/kg or 4 mg/kg	Not specified	Treatment-related arrhythmias; hypersensitivity; anaphylaxis; clinically-rele arrhythmias; unspecified adverse events and events of clinical interest 14 days after surgery
Li et al., 2021[17]	96	F:M = 65:31 Age: 31.2 ± 7.06 years BMI: median (IQR): 44.8 kg/m^2 (41.9–49.1) in CBW group; 45.7 kg/m^2 (42.8–48.8) in TBW group	Laparoscopic bariatric surgery	TBW, CBW-40%, control (no reversal agent)	PTC 1–2?	4 mg/kg	Sevoflurane	Time to TOFR > 0.7; any AEs at PACU and at follow-up at 10 h post-operation and on day 8; MAP and HR at 1, 5, 10 and 30 min after administration of sugammadex

Data presented as mean ± SD for age and BMI unless otherwise stated.

NMB, neuromuscular blockade; F, female; M, male; BMI, body mass index; N_2O, nitrous oxide; PACU, post-anaesthesia care unit; BIS, bispectral index; PTC, post-tetanic count; TOFR, train-of-four ratio; AE, adverse event; MAP, mean arterial pressure; HR, heart rate.

According to the descriptions of the RoB 2 tool, three of five (60%) studies had a low risk of bias in all five domains (see supplementary materials, Figure 1).[14,16,17] In the other two studies, some concerns of bias arose from domain 1 (randomization) and/or domain 4 (measurement of outcome).[13,15] No domain in any study was considered to have a high risk of bias.

The pooled results from four included trials using a random-effects model showed that in patients treated with NMB using either rocuronium or vecuronium, the reversal time was significantly longer in those receiving sugammadex with a dosing scalar based on IBW than in those receiving sugammadex with a dosing scalar based on TBW (mean difference 55.77 s, 95% CI 32.01, 79.53 s, $P < 0.00001$) (Figure 2). In contrast, the reversal time was not significantly different between patients receiving sugammadex with a dosing scalar based on CBW versus TBW (mean difference 2.28 s, 95% CI –10.34, 14.89 s). Using TBW versus IBW or CBW as the dosing scalar resulted in a shorter reversal time (mean difference 27.59 s, 95% CI 10.01, 45.17 s, $P = 0.002$).

All five studies reported some outcomes related to safety and AEs, such as residual paralysis and delayed discharge from the post-anaesthesia care unit (PACU) due to respiratory complications. However, there was considerable heterogeneity in the outcome measures used so a pooled analysis was not conducted. The adverse events in each RCTs are summarized in Table 2.

Discussion

To the best of our knowledge, this is the first meta-analysis of RCTs to explore the association between different dosing scalars on the reversal times for sugammadex among morbidly obese patients undergoing elective surgery under NMB induced by rocuronium or vecuronium. When IBW was used as the dosing scalar of

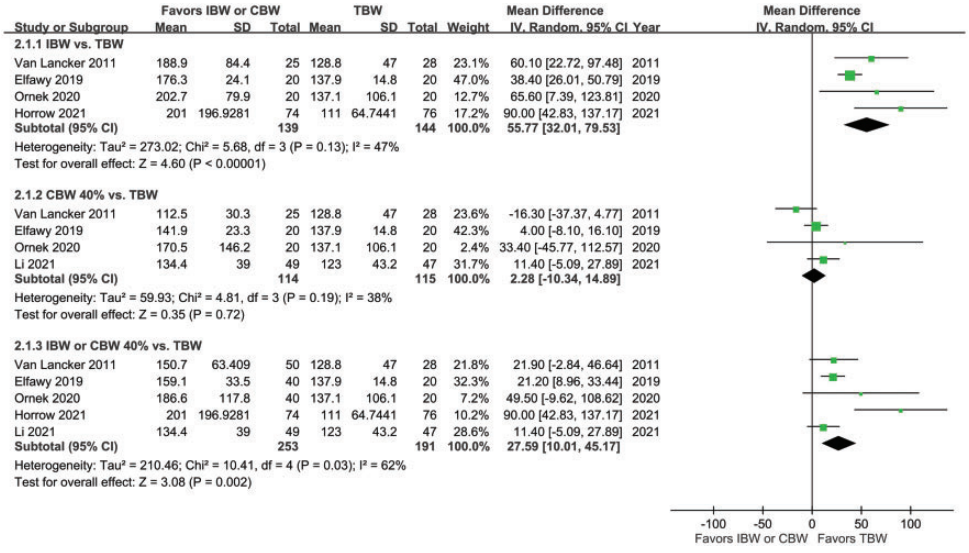

Figure 2. Forest plot of a meta-analysis of randomized controlled trials to evaluate the effect on reversal time of lower-dose sugammadex using ideal body weight (IBW) or corrected body weight (CBW) as dosing scalars with that of standard-dose sugammadex based on total body weight (TBW). The colour version of this figure is available at: http://imr.sagepub.com.

Table 2. Adverse events (AEs) reported in the five studies included in a meta-analysis of randomized controlled trials to evaluate the effect on reversal time of lower-dose sugammadex using ideal body weight (IBW) or corrected body weight (CBW) as dosing scalars with that of standard-dose sugammadex based on total body weight (TBW).[13–17]

Study	Adverse events
Van Lancker et al., 2011[13]	None reported
Elfawy et al., 2019[14]	Did not record adverse events
Ornek et al., 2020[15]	None reported
Horrow et al., 2021[16]	TBW group
	Treatment-emergent events
	Sinus tachycardia ($n = 4$), sinus bradycardia ($n = 9$)
	Events of clinical interest
	Clinically relevant arrhythmia ($n = 1$)
	Other AEs
	Serious AEs ($n = 1$)
	IBW group
	Treatment-emergent events
	Sinus tachycardia ($n = 3$), sinus bradycardia ($n = 4$), other arrhythmias ($n = 1$)
	Events of clinical interest
	Hypersensitivity ($n = 1$), clinically relevant arrhythmia ($n = 1$)
	Other AEs
	Drug-related AEs ($n = 2$), serious AEs ($n = 5$)
Li et al., 2021[17]	TBW group
	Bradycardia ($n = 3$), muscle weakness ($n = 1$) and drug hypersensitivity ($n = 1$)
	CBW group
	Bradycardia ($n = 5$)

sugammadex, compared with the dosing scalar of sugammadex based on TBW, it was associated with an increase in reversal time of 56 s. The reversal time was not different when CBW or TBW were used as the dosing scalar of sugammadex.

As sugammadex is expensive, there have been several reports investigating the use of reduced doses in otherwise healthy adult patients with favourable clinical outcomes.[18,19] In contrast, studies on the appropriate dosing in patients with morbid obesity are scarce. Although a guideline published in 2020 suggested using IBW or CBW for obese patients, the evidence level was low, and the strength of the recommendation had limited support.[20] An observational study suggested that the dosing scalars of sugammadex based on IBW were insufficient to reverse deep NMB in morbidly obese patients.[21] This current meta-analysis of RCTs further suggests that patients receiving sugammadex with the dosing scalars based on IBW had a reversal time approximately 1 min longer than patients receiving sugammadex with the dosing scalars based on TBW among patients with morbid obesity. Therefore, sugammadex dosage based on IBW may not be appropriate for morbidly obese patients.

This current meta-analysis found that dosing by CBW (calculated as $\text{IBW} + 0.4 \times [\text{TBW}–\text{IBW}]$) was not associated with a significant difference in the reversal time compared with dosing by TBW.

This finding supports the argument of dose reduction formerly proposed in an observational study.[22] In this study, a subgroup analysis was performed to compare various clinical effects of dosing by IBW plus <35%, 35–50%, and >50%, which found no significant differences in reversal time and time to extubation.[22] Because the included trials used CBW (calculated as $IBW + 0.4 \times [TBW–IBW]$) as the dosing scalar, and only one trial additionally reported the effects of using CBW calculated as $IBW + 0.2 \times (TBW–IBW)$ as the dosing scalar,[13] thus the dosage of sugammadex using dosing scalars less than $IBW + 0.4 \times (TBW–IBW)$ could not be suggested based on the currently available evidence.

The results of this current meta-analysis revealed that the dosing scalars of sugammadex based on body weights other than TBW (IBW or CBW in this study) were associated with a prolonged reversal time, but the weighted mean difference was approximately 20 s. However, the clinical significance of this small difference was undetermined. The analysis of outcomes related to the safety of different dosing scalars was unsatisfactory because of the high heterogeneity among the included studies and low event rates. Although this current meta-analysis is insufficient to provide meaningful recommendations, it nevertheless indicates the importance of incorporating outcomes that reflect both risks and benefits into future research on this poorly understood topic.

Sugammadex is the only direct reversal agent for NMB induced by rocuronium or vecuronium that is in clinical use. It may help speed up post-operative discharge in addition to allowing reversal of neuromuscular blockade.[23] An RCT found that sugammadex resulted in a higher tidal volume ($P = 0.013$), arterial oxygenation ($P = 0.03$) and diaphragmatic electromyographic activity ($P < 0.001$) after tracheal extubation than neostigmine, indicating better diaphragm-driven inspiration after sugammadex administration.[24] Two separate meta-analyses have found that sugammadex may decrease the incidence of postoperative residual curarization compared with neostigmine.[25,26] Sugammadex is unlikely to encapsulate propofol or remifentanil because of its low affinity for these medications;[27] however, reports suggest that it may trigger awakening from intravenous anaesthesia.[28] According to two trials,[3,29] patients receiving sugammadex were more alert and better oriented before being transferred to the recovery room following general anaesthesia than those receiving neostigmine. The afferentation theory, often known as the muscle spindle theory, proposes that active muscular action in light-anaesthetized subjects affects the brain through muscle afferent receptors. In one animal study,[30] light-anaesthetized canines showed increased cerebral blood flow, vascular resistance and electroencephalogram responses following noxious stimulation, but decreased responses after NMB administration. However, higher anaesthetic depth monitoring values after sugammadex or neostigmine[31,32] may be due to the electromyography frequency (30–300 Hz) coinciding with that of the electroencephalography (0–50 Hz). A recent meta-analysis comparing sugammadex with neostigmine revealed a significantly faster discharge from the operating room (OR) to the PACU ($P = 0.00001$) and from the PACU to the surgical ward ($P = 0.0469$).[23] A subgroup analysis of morbidly obese patients revealed a significantly faster discharge from the PACU to the surgical ward ($P = 0.0001$).[23] These findings suggest that sugammadex may result in time savings in the OR and PACU.

Although the medication cost of sugammadex is not inexpensive and a certain dose is more beneficial in obese individuals, the cost may be saved elsewhere. Since a greater

dose of sugammadex (CBW as a dosing scalar compared with IBW) is related to a shorter reversal time, it may assist in saving time and money in clinical practice. Sugammadex is cost-effective for the routine reversal of rocuronium-induced moderate or profound block, according to a model analysis, if all reductions in recovery time associated with sugammadex are achieved in the operating room and the value of each minute saved exceeds the total cost of the drug itself.[33] Sugammadex has been shown to allow a decreased risk of prolonged tracheal extubation compared with neostigmine, which may result in delayed OR exit, cancellation of future operation schedules or forcing personnel to work overtime.[34] Using anaesthetic drugs that limit the variability in tracheal extubation time may reduce the OR turnover time,[35] thus increasing productivity. According to previous studies, minimizing turnover time may lead to improved OR occupancy, the number of cases finished within similar working hours,[36–38] and hence, a lower cost. Sugammadex decreased OR occupancy and personnel costs and potentially boosted the workflow in morbidly obese patients undergoing laparoscopic sleeve gastrectomy.[40] Sugammadex, compared with neostigmine, was shown to save money by lowering postoperative respiratory problems.[40] Individuals reversed by sugammadex that underwent surgery for obstructive sleep apnoea, a certain number of whom may have been obese, had lower treatment costs and total expenses according to a prospective randomized study.[40] With so many elements influencing cost, calculating the exact amount of money saved by using sugammadex is difficult. However, a cost analysis revealed that if the operating room time was estimated to be more than $8.60/min, sugammadex reversal was recommended above neostigmine or no reversal drug.[41] Sugammadex was less expensive than no reversal or neostigmine treatment when the odds of unplanned postoperative ventilation exceeded 0.019 and 0.036, respectively.[41] In addition, the dose reduction of sugammadex from TBW to CBW in morbidly obese patients can further decrease the total costs directly from the reduction of drug costs.[41]

Since obesity is characterized by excessive fat accumulation in adipose tissue and a number of associated physiological derangements, defining morbid obesity according to body mass index can mistakenly include patients with increased body weight that are not actually 'obese'.[42] Heterogeneous body composition profiles have been shown to affect drug pharmacokinetics among individuals under chemotherapy.[43] Based on the pharmacological principles, it can be assumed that body composition, in addition to body weight, can also have an effect on the pharmacokinetics of sugammadex. Further studies are expected to investigate the intricate relationships between body weight, body composition and the pharmacokinetics of sugammadex.

This current meta-analysis had several limitations. First, it did not search for grey literature. However, as there are so few studies on this subject in the mainstream databases, it is doubtful that the grey literature could provide a significant contribution. Secondly, only RCTs directly comparing sugammadex dosing scalars based on TBW versus IBW or CBW were included. During the screening stage, several studies were excluded because they only investigated the effect of using other body weights as dosing scalars.

In conclusion, lower-dose sugammadex based on IBW had a reversal time 56 s longer than standard-dose sugammadex based on TBW among patients with morbid obesity that received rocuronium- or vecuronium-induced NMB. Conversely, lower-dose sugammadex based on CBW (calculated as $\text{IBW} + 0.4 \times [\text{TBW–IBW}]$) had a similar reversal time as standard-dose

sugammadex based on TBW among patients with morbid obesity. Therefore, it could be a viable alternative dosing scalar of sugammadex if dose reduction is considered. Further large RCTs are warranted to clarify the safety and cost-effectiveness of different dosing scalars of sugammadex for patients with morbid obesity.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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Supplemental material

Supplemental material for this article is available online.

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