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Effects of sugammadex on coagulation: a systematic review and meta-analysis

Yu-Hsun Tsai[1], Ming-Chang Kao[1*] and Hsi-Ning Kao[2]

Abstract

Background Sugammadex, an innovative agent that rapidly and completely reverses rocuronium-induced neuromuscular blockade, may prolong coagulation time and influence postoperative bleeding. This study aimed to investigate the effects of sugammadex on coagulation parameters.

Methods Cochrane Central Register of Controlled Trials, Embase, and PubMed were searched on September 25, 2024, for randomized control trials (RCTs) examining the impact of sugammadex on coagulation time.

Results Five RCTs involving 1328 participants were included. Four RCTs with 1302 participants provided data for the meta-analysis. Sugammadex was found to prolong prothrombin time (PT) without affecting activated partial thromboplastin time (APTT).

Conclusions Sugammadex administration may transiently increase PT values without affecting the APTT. Routine coagulation monitoring is not required in healthy individuals; however, individualized assessment should be conducted in high-risk patients. Further studies are warranted to evaluate the coagulation effects of sugammadex in patients with coagulopathies or those receiving anticoagulant therapy.

Trial registration This study is registered in the PROSPERO database under the ID CRD42024604567.

Keywords Sugammadex, Hemorrhage, Hemostasis, Meta-analysis, Systematic review, Neuromuscular Blockade, Rocuronium, Neostigmine, Surgery

Background

Sugammadex, a modified γ-cyclodextrin, is highly effective in reversing the muscle relaxant effects of rocuronium by binding with steroidal nondepolarizing neuromuscular blocking agents. This result in a faster and more predictable block reversal compared with traditional acetylcholinesterase inhibitors, such as neostigmine and pyridostigmine, and causes fewer unpleasant side effects [1–3]. Common adverse events associated with sugammadex include vomiting, tachycardia, hypotension, and anaphylaxis [4].

A notable concern with sugammadex is its potential interference with hemostasis. While sugammadex has been shown to transiently prolong prothrombin time as measured by the international normalized ratio (PT[INR]) and activated partial thromboplastin time (APTT), these changes typically resolve quickly and are not considered clinically significant [5, 6]. De Kam et al. demonstrated that sugammadex induces a dose-dependent but limited and transient increase in APTT and PT(INR), possibly due to its phospholipid-binding properties, which are primarily observed in vitro [7]. However, conflicting evidence exists; for instance, Nilay et al.

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[8] found no significant effect on coagulation time but reported a notable increase in postoperative bleeding.

Given the growing use of sugammadex in general anesthesia, it is critical to evaluate its potential impact on coagulation, as such effects could increase the risk of bleeding. This study aimed to systematically review and analyze existing evidence on the effects of sugammadex on coagulation.

Methods

This systematic review and meta-analysis focused on randomized controlled trials (RCTs) investigating the effects of sugammadex on coagulation. The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9] and was preregistered in the PROSPERO database (registration no. CRD42024604567).

A comprehensive search of the Cochrane Central Register of Controlled Trials, Embase, and PubMed databases was conducted on September 25, 2024. The search strategy is summarized in Supplementary information file.

We included RCTs that compared the effects of sugammadex with either anticholinesterase agents or placebos on coagulation parameters in adults. Exclusion criteria included non-English trials, non-RCTs, observational or retrospective studies, patients with pre-existing coagulation disorders or bleeding diathesis, and pregnant individuals. Studies examining the effects of different doses of sugammadex without a control group were also excluded.

The primary outcomes were changes in APTT and PT(INR), while secondary outcomes included postoperative bleeding events, bleeding volume, and thromboelastography (TEG) parameter changes.

Two authors (Y.T. and H.K.) independently screened studies and abstracts to identify eligible trials. Full texts were reviewed to ensure inclusion criteria were met. One author (Y.T.) independently extracted data from the included trials. The maximum changes in PT(INR) and APTT were analyzed for all studies, irrespective of the duration elapsed following drug administration.

For one study that did not report standard deviations (*SD*s) for changes in continuous variables from baseline, correlation coefficients were calculated and used to derive the *SD*s. The following equation was applied:

$$SD_{change} = \sqrt{[(SD_{Baseline})^2 + (SD_{Endpoint})^2 - 2 \cdot r \cdot SD_{Baseline} \cdot SD_{Endpoint}]},$$

We used a correlation coefficient of 0.5 as the default value as the actual correlation (r) between the baseline and endpoint is unknown. This value indicates a moderate correlation and is commonly recommended in the Cochrane Handbook when the true correlation is not reported [10].

The risk of bias (RoB) for each included study was assessed by two authors (Y.T. and H.K.) using the Cochrane Collaboration tool (RoB2), with verification by a third author (M.K.). RoB was evaluated across six domains and categorized as "low," "some," or "high" RoB: (a) selection bias (random sequence generation and allocation concealment), (b) performance bias (blinding of participants and personnel), (c) detection bias (blinding of outcome assessment), (d) attrition bias (incomplete outcome data), (e) reporting bias (selective reporting), and (f) other bias (additional sources of bias).

Meta-analysis was conducted using Comprehensive Meta-analysis Software (version 4). A random-effects model was adopted due to expected clinical heterogeneity. Continuous outcomes were presented as either mean differences or standardized mean differences when different measurement scales were used. Statistical heterogeneity was evaluated using the I^2 statistic, where an I^2 value > 50% was considered indicative of substantial heterogeneity, and > 75% represented very high heterogeneity.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [11] was employed to assess the overall certainty of evidence for primary and secondary outcomes. Outcomes were classified as "high," "moderate," "low," or "very low" certainty.

Results

The PRISMA flowchart (Fig. 1) details the study selection process. Initial screening identified 404 records of which five RCTs comprising 1328 participants met the inclusion criteria [5, 6, 12–14]. All participants provided written informed consent before study enrollment. Sugammadex was administered at a dose of 4 mg/kg in four studies [5, 6, 12, 13] and 2 mg/kg in one study [14]. A summary of study characteristics is presented in Table 1.

Three of the included RCTs [5, 6, 12] reported that sugammadex prolonged coagulation parameters, while the remaining two RCTs [13, 14] found no significant effects. For the meta-analysis, four RCTs [5, 6, 13, 14], including 1302 participants, provided usable data.

The RoB assessment is illustrated in Fig. 2. Among the five RCTs, one was categorized as having a low RoB [13], while the others were classified as having some RoB [5, 6, 12, 14]. Specific biases identified included: selection bias in two studies [6, 12], performance bias and reporting bias in two studies [5, 14], and an additional selection bias in one study [5].

Considerable heterogeneity was observed, attributed to variations in sugammadex dosing (2–4 mg/kg) and the timing of blood sample collection (ranging from 10 min to 24 h postadministration).

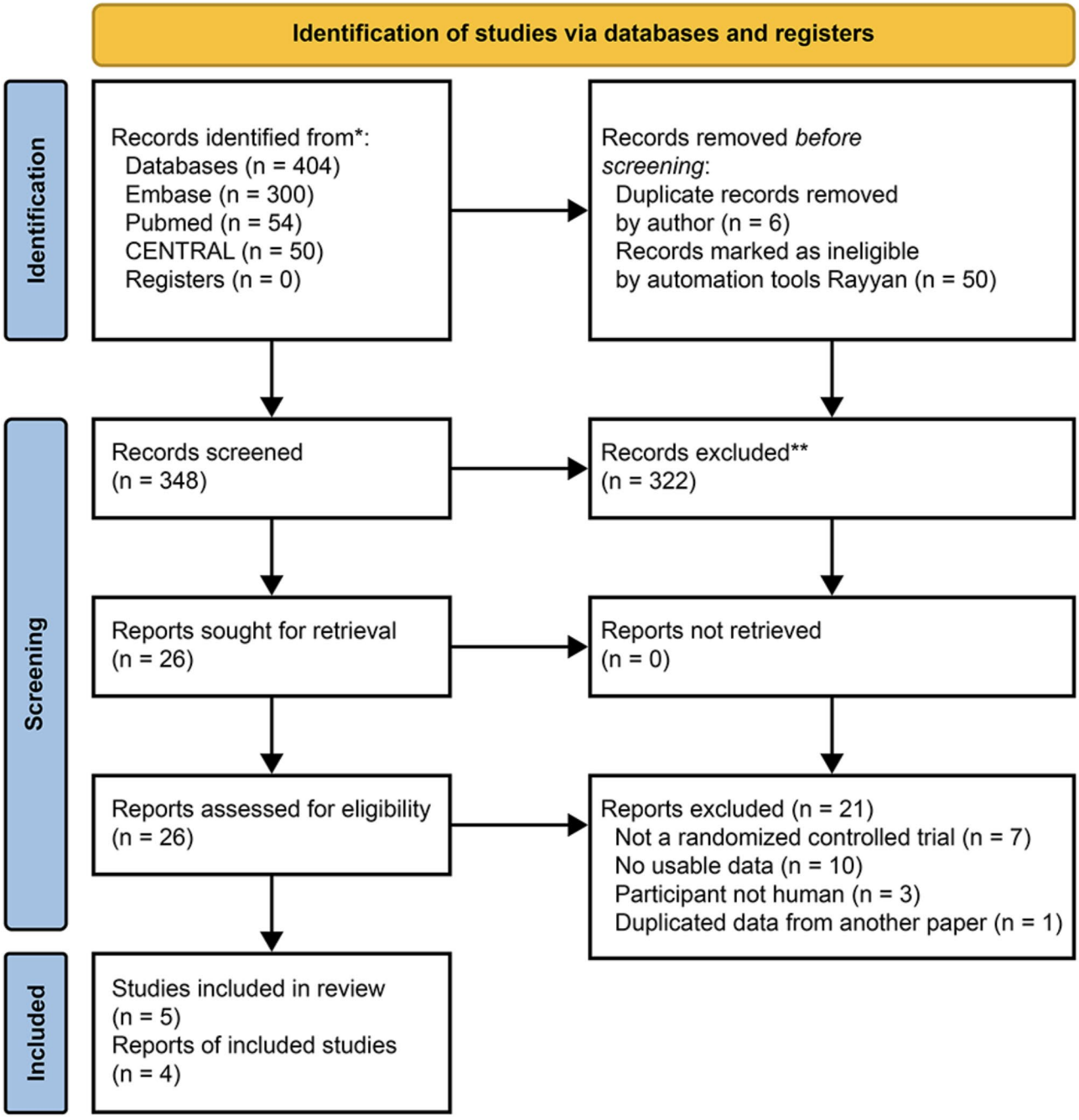

Fig. 1 Flow diagram illustrating the process of literature search, screening, full-text review, and study inclusion, following Preferred Reporting Items for Systematic Review and Meta-Analyses. RCT, randomized controlled trial

The coagulation parameters PT(INR) and APTT measured in these studies reflected this variability in dosing and sampling intervals.

Effect of sugammadex on hemostasis

APTT

Data on APTT were available from four RCTs involving 1302 participants [5, 6, 13, 14]. As shown in Fig. 3, the meta-analysis revealed no significant correlation between sugammadex administration and changes in APTT (standard mean difference: 0.40; 95% confidence interval [95% CI], −0.18 to 0.99; GRADE: moderate quality; Supplemental Table 1). However, substantial statistical heterogeneity was observed across the included studies ($I^2 = 82.5\%$).

Table 1 Characteristic of the included studies

Reference	Study design	Participant	Differential Interventions in the Study Groups	Control	Blood Sample Time(After the Drug Was Administered)	*N*	Number of Men	Mean Age (Years)	Outcome of Interest
Pieter-Jan [12]	Single center RCT	Healthy male volunteers	Sugammadex 4 mg/kg with or without aspirin	Placebo with or without aspirin	3, 15, 30 min; 1, 3, 6 h	26	26 (100%)	25.7	GMR for platelet aggregation, APTT, PT, bleeding time
Pieter-Jan [6]	Single center RCT	Healthy subject	Sugammadex 4 mg/kg and, 16 mg/kg	Placebo	2, 3, 5, 15, 30 min; 1, 5, 12 h	8	7 (87.5%)	34.8	APTT/PT(INR)
Niels [5]	Multiple center RCT	The patient received thromboprophylaxis while undergoing hip/knee surgery	Sugammadex 4 mg/kg	Neostigmine or spontaneous recovery	10, 60 min	1184	518 (43.7%)	67	Bleeding events; APTT/PT
Nilay [14]	Single center RCT	Patients who received septoplasty	Sugammadex 2 mg/kg	Neostigmine 0.05 mg/kg	120 min	50	31 (62%)	34.6	Postoperative blood loss PT/APTT
Hae [13]	Single center RCT	Patients received abdominal laparoscopic surgery	Sugammadex 4 mg/kg	Pyridostigmine 0.15 mg/kg	10, 60 min; 24 h	60	31 (51.6%)	45	Thromboelastography; PT/APTT/blood loss

GMR Geometric mean ratio, APTT Activated partial thromboplastin time, PT Prothrombin time

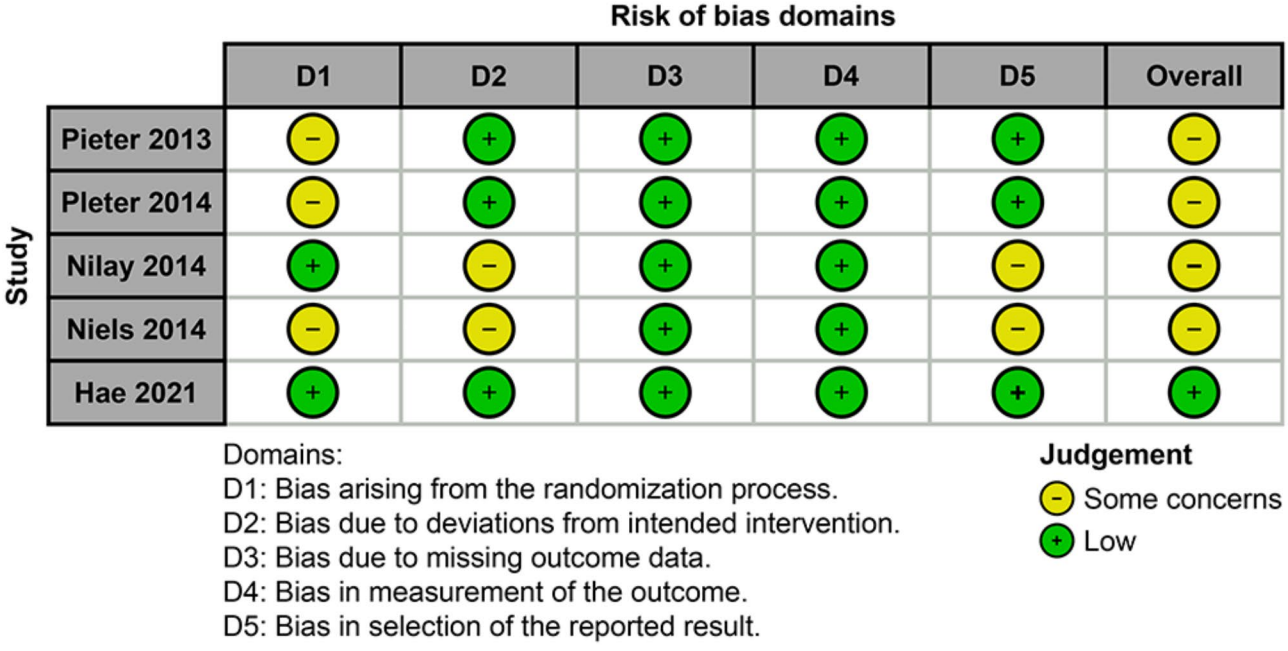

Fig. 2 Assessment of the risk of bias in the included studies

PT and international normalized ratio

Four RCTs [5, 6, 13, 14] also provided data on PT/INR. The meta-analysis indicated that sugammadex may increase PT(INR) (mean difference: 1.42; 95% CI, 0.28–2.56; GRADE: low quality; Supplemental Table 1). Statistical heterogeneity was notably high ($I^2 = 94\%$).

Postoperative bleeding events

Only one RCT [5] reported on postoperative bleeding events. According to Niels et al., the incidence of postoperative bleeding was comparable between the sugammadex group (17 treatments, $N = 596$) and the usual care group (24 events, $N = 588$).

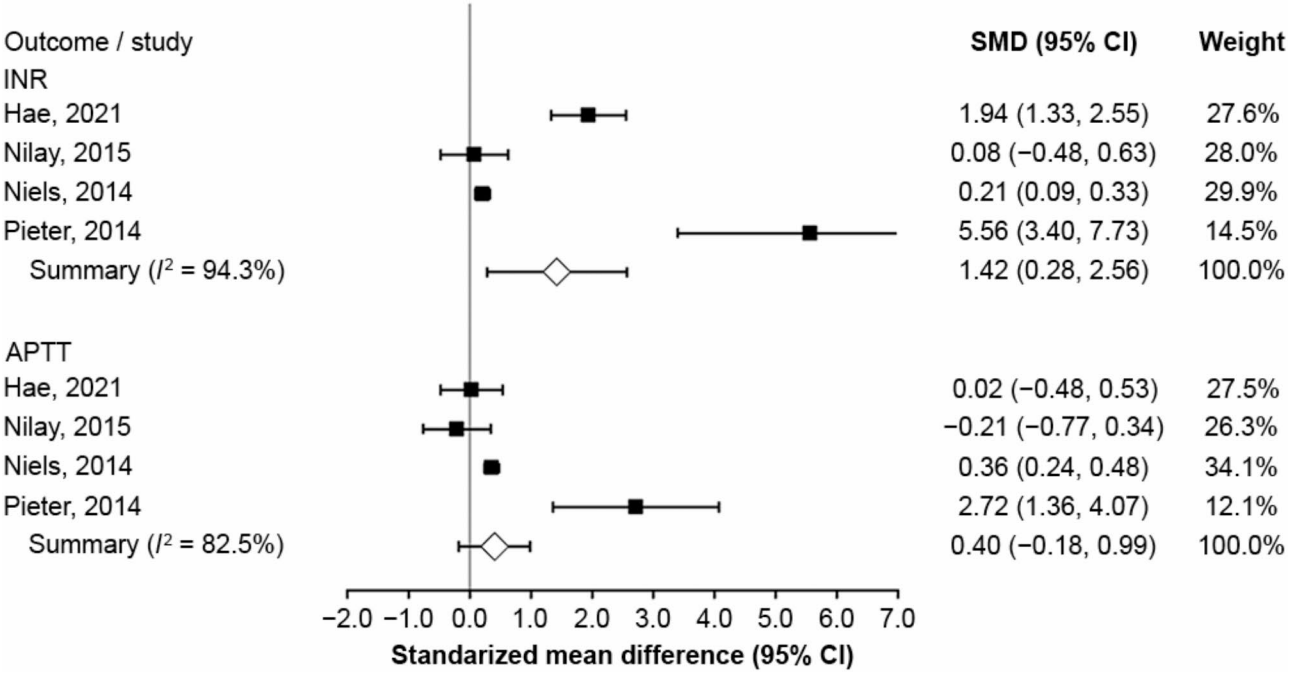

Fig. 3 Results of the meta-analysis evaluating the effects of sugammadex on coagulation time

Postoperative bleeding amount

Two RCTs [13, 14] contributed data on postoperative bleeding volume. Hae et al. reported no significant differences in 24-h postoperative bleeding volume between the sugammadex group (36 mL, $N = 30$) and the control group (40 mL, $N = 30$). In contrast, Nilay et al. observed significantly greater bleeding in the sugammadex group (4.1 mL, *SD*: 2.7, $N = 24$) compared with the control group (2.5 mL, *SD*: 2.7, $N = 26$).

Thromboelastography

One RCT [13] investigated the effects of sugammadex on TEG. Hae et al. found that the mean value of the K parameter was significantly prolonged 10 min after sugammadex administration (treatment group: 1.5 min, $N = 28$; control group: 1.3 min, $N = 29$).

§ platelet

Based on the available RCT evidence, sugammadex does not substantially impair platelet function. In two RCTs included in this meta-analysis, de Kam et al. [12] found no clinically significant reduction in platelet aggregation in healthy volunteers after sugammadex administration, whereas Chang et al. [13] reported no difference in maximum amplitude—an indicator of clot strength primarily influenced by platelet function and fibrinogen levels—on TEG compared with pyridostigmine. Thus, sugammadex does not appear to compromise platelet-related hemostasis.

Discussion

This systematic review and meta-analysis evaluated the effects of sugammadex on hemostasis, comparing it with anticholinesterase agents or placebos in adult patients. Our findings suggest that sugammadex transiently increases PT but does not affect the APTT. No included studies reported an increased risk of postoperative bleeding, suggesting that these coagulation changes may not be clinically significant. Pieter et al.'s [6] study, despite having a small sample size ($N = 8$), reported a substantially larger effect size for PT prolongation than other included studies. This may have disproportionately influenced the pooled estimate in our meta-analysis. However, as Pieter et al.'s study used a rigorous randomized design and its findings aligned with the overall trend, we retained this study in our analysis and acknowledged its potential impact on our interpretation.

As our meta-analysis excluded patients with coagulation disorders, with hepatic dysfunction, and receiving anticoagulants, the applicability of the findings to high-risk populations remains uncertain. Future studies should examine the coagulation effects of sugammadex in these patients. Until then, individualized assessment is advised for patients at an increased risk of bleeding.

To explore potential sources of heterogeneity, we conducted a subgroup analysis comparing sugammadex doses of 2 and 4 mg/kg (Supplemental Table 2). Reportedly, the PT values increased in both subgroups, whereas the APTT remained unaffected, which was consistent with the overall findings. However, the strength of this

analysis is limited by the fact that only one RCT used the dose of 2 mg/kg.

Basic coagulation tests, including PT and APTT, are essential for assessing coagulation status and estimating the risk of bleeding or thrombosis [15]. APTT measures fibrin generation through the intrinsic pathway, while PT(INR) evaluates fibrin generation via the extrinsic and common pathways.

The mechanism underlying sugammadex-induced coagulation changes has been partially elucidated in previous studies. Dirkmann et al. [7] demonstrated, in an in vitro ROTEM study, a significant reduction in the activity of intrinsic pathway factors (VIII, IX, XI, and XII) and increased clotting times, possibly due to sugammadex's phospholipid-binding properties. De Kam et al. [12] proposed that sugammadex's anticoagulant effects may result from factor Xa inhibition, either alone or in combination with inhibition of the intrinsic pathway.

The results of previous studies on the effects of sugammadex on coagulation parameters have been inconsistent. Moon et al. [16] investigated postoperative coagulation in patients undergoing hepatectomy, comparing two groups who received either sugammadex (4 mg/kg) or pyridostigmine (0.25 mg/kg) following surgery. The authors found no significant differences between the groups in terms of PT(INR) and APTT. Additionally, both groups exhibited comparable blood loss volumes and similar incidences of relaparotomy for bleeding control within 24 h.

In contrast, Carron et al. [17] assessed the effects of sugammadex on coagulation in obese patients undergoing bariatric surgery. This study divided 60 patients into two groups receiving sugammadex at doses of either 2 or 4 mg/kg. Their findings revealed a significant prolongation in APTT, while PT(INR) remained unaffected.

A systematic review encompassing nine studies [18] reported that sugammadex administration resulted in temporary increases in both APTT and PT(INR) when compared with traditional reversal agents. We hypothesize that these discrepancies across studies may stem from differences in the timing of blood sample collection following sugammadex administration. Supporting this hypothesis, Rahe-Mayer et al. [5], in the largest trial included in this review ($N = 1184$), observed that prolonged PT(INR) and APTT values were transient, resolving within 60 min postadministration.

The findings of this systematic review align with those of Kang et al. [19], who compared two groups of patients receiving either 2- or 4-mg/kg sugammadex without the use of a placebo. Both groups exhibited significant increases in PT(INR) after sugammadex administration, but no significant differences were observed between the groups. Additionally, there were no reported changes in APTT.

An important clinical consideration is whether sugammadex-associated prolongation of coagulation times translates into a higher risk of surgical bleeding or increased blood transfusion requirements. Several studies [5, 8, 16] have demonstrated that sugammadex use does not correlate with increased postoperative bleeding. Similarly, Ryan et al. [20] reported no association between intraoperative sugammadex use and an increased risk of bleeding. However, Tae et al. [14] observed a greater postoperative bleeding volume in patients treated with sugammadex compared with those receiving neostigmine (4.1 mL vs. 2.5 mL, respectively, as measured by nasal tip dressings). In a retrospective cohort study of 29,062 patients, Schmidt et al. [21] found no significant differences in the incidence of postoperative blood transfusions between the sugammadex and neostigmine groups.

In addition to APTT and PT, TEG offers a comprehensive assessment of hemostatic function by quantitatively evaluating whole blood clot formation. However, the limited number of studies on this topic has produced mixed results. One study [13] reported that sugammadex significantly prolonged the mean value of the K parameter, while another study [19] noted an increase in the R time, although the value remained within the normal range.

The findings related to bleeding volume and TEG parameters remain inconclusive, necessitating further large-scale studies to clarify these observations.

Limitations

First, all the included patients received sugammadex at a dose of either 4 or 2 mg/kg; 16 mg/kg, the recommended dose for emergency reversal, was not evaluated. Second, our analysis was limited to healthy individuals without pre-existing coagulation disorders or those taking anticoagulants. Third, postoperative bleeding data were limited, with only one RCT explicitly reporting bleeding events, and no standardized assessment methods were employed across studies. Fourth, the statistical heterogeneity was high ($I^2 > 80\%$), potentially due to variability in sugammadex dosing, patient populations, and blood sampling times. Although only four RCTs were included, we conducted a leave-one-out sensitivity analysis to assess the influence of individual studies. Exclusion of Pieter et al.'s [6] study resulted in the loss of statistical significance for PT and substantially reduced heterogeneity in APTT, indicating that this study had a notable impact on the pooled estimates (Supplemental Table 3). Given the small number of included studies, the statistical power of this analysis remains limited, and removing any single trial reduces the evidence base to only three studies, which may compromise interpretability. Therefore, these findings should be interpreted with caution. Future studies should incorporate standardized bleeding outcome

measures, such as TEG or ROTEM, and include high-risk populations to improve generalizability.

Conclusions

Sugammadex transiently increases PT values compared with traditional acetylcholinesterase inhibitors but does not considerably affect APTT. None of the included studies reported increased risk of postoperative bleeding in healthy individuals. Routine coagulation monitoring is not necessary in the general surgical population. However, individualized assessment should be considered for high-risk patients, such as those with coagulopathies or receiving anticoagulant therapy. Future research should evaluate these effects in high-risk populations to determine their clinical relevance.

Abbreviations

APTT	Activated partial thromboplastin time
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PT	Prothrombin time
RCT	Randomized control trials
RoB	Risk of bias
SD	Standard deviations

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-025-03041-x.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Author contributions

Yu-Hsun Tsai conducted the screening of published studies, data extraction, meta-analysis, and risk of bias assessment and authored the manuscript. Hsi-Ning Kao participated in the study screening, data extraction, and risk of bias assessment. Ming-Chang Kao contributed to study screening, data extraction, and confirmation of the meta-analysis, risk of bias assessment, and manuscript revision.

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Data availability

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Clinical trial number

Not applicable.

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