REVIEW PAPER

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The efficacy and safety of adamgammadex for reversing rocuronium-induced deep neuromuscular blockage. A systematic review and network meta-analysis

Abdallah Abunamoos
School of Medicine, University of Jordan, Amman, Jordan
https://orcid.org/0000-0001-8147-4985

Amr Elrosasy
Faculty of Medicine, Cairo University, Cairo, Egypt
https://orcid.org/0000-0002-5592-3908

Nada Ibrahim Hendi
Faculty of Medicine, Ain Shams University, Cairo, Egypt
https://orcid.org/0000-0003-1201-0487

Obai Yousef
Faculty of Medicine, Tartous University, Tartous, Syria
https://orcid.org/0009-0001-5832-3780

Ahmad Alzawahreh
Faculty of Medicine, The Hashemite University, Zarqa, Jordan
https://orcid.org/0009-0007-7672-1073

Thoria Ibrahim Essa Ghanm
Faculty of Medicine Mansoura University, Mansoura, Egypt
—

Zina Otmani
Faculty of Medicine, Mouloud Mammeri University, Tizi Ouzou, Algeria
https://orcid.org/0009-0005-4665-2500

Mohamed Abouzid
Department of Physical Pharmacy and Pharmacokinetics, Faculty of Pharmacy, Poznan University of Medical Sciences, Poland
Doctoral School, Poznan University of Medical Sciences, Poland
https://orcid.org/0000-0002-8917-671X
Corresponding author: mmahmoud@ump.edu.pl

Yehia Nabil
Faculty of Medicine, Zagazig University, Zagazig, Egypt
https://orcid.org/0000-0002-1349-2978

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ABSTRACT

Aim. We aim to evaluate the efficacy and safety of adamgammadex, a new modified γ-cyclodextrin, in reversing rocuronium-induced neuromuscular blockade compared with sugammadex or placebo.
Material and methods. We comprehensively searched three electronic databases (PubMed, Scopus, and ScienceDirect) from inception until February 2024 to detect all randomised controlled trials comparing adam-

gammadex versus sugammadex or placebo. STATA software 17 and RevMan version 5.4 were used for network and pairwise meta-analyses, respectively. The study protocol was prospectively registered in PROSPERO (CRD42024516623).
Results. Five randomised controlled trials comprising 530 patients were included in our study. There was a statistically significant difference between adamgammadex and sugammadex compared to placebo in the recovery time of neuromuscular function. A dose-response relationship was observed except for adamgammadex 7 mg/kg, which ranked first. Sugammadex was found to be more effective than a similar dose of adamgammadex. There was a non-significant difference between adamgammadex and sugammadex compared to placebo in the incidence of adverse events.
Conclusions. Adamgammadex or sugammadex can be a safe and effective therapeutic option in reversing rocuronium-induced neuromuscular blockade. More clinical trials with larger sample sizes should be conducted to obtain better evidence regarding these two drugs' most effective and safe doses.

Introduction

Neuromuscular blocking agents (NMBAs) were introduced in anesthesia in 1942 [1]. Their use facilitates tracheal intubation and mechanical ventilation, enhancing surgical intervention quality [2,3]. However, a residual persistence in the neuromuscular blocking effect beyond the end of surgery is a common problem. This may prolong the recovery time and lead to various adverse events, including respiratory complications, airway obstruction, and upper airway dysfunction [4,5]. Therefore, postoperative neuromuscular monitoring is recommended. Additionally, novel therapeutic agents were suggested to ensure adequate recovery of neuromuscular function and the early detection of the need to administer relaxant binding agents such as adamgammadex sodium or sugammadex [6,7].

The traditional neuromuscular block antagonists (neostigmine and edrophonium) are anticholinesterase drugs and have limited efficacy in reversing profound levels of NMB. Moreover, their non-selective action on the muscarinic acetylcholine receptors can lead to various adverse effects due to the interaction of the drug with the muscarinic receptors in other tissues [8]. Consequently, these medications are usually administered with atropine, which may cause untoward events, such as tachycardia, dry mouth, and blurred vision [9]. Thus, more research was directed toward other selective relaxant medications such as adamgammadex sodium and sugammadex.

Sugammadex, the selective relaxant binding agent (SRBA), effectively and quickly restores neuromuscular function from NMBA [10]. However, the concerns about sugammadex associated with hypersensitivity reactions and anaphylaxis restrict its approval in some countries [11]. Furthermore, this SRBA increases the risk of postoperative bleeding [12].

The new medication Adamgammadex sodium, a modified γ-cyclodextrin derivative, has a similar mechanism of action to sugammadex and shows, in pre-clinical animal studies, a similar efficacy to sugammadex but with fewer potential side effects [13,14]. New clinical trials have been done that evaluate the safety and efficacy of Adamgammadex in humans by comparing it with sugammadex or a placebo.

Aim

In this systematic review and network meta-analysis (NMA), we aim to evaluate the efficacy and safety of Adamgammadex or Sugammadex in reversing rocuronium-induced deep neuromuscular blockade in patients undergoing surgery.

Material and methods

We conducted our systematic review and network meta-analysis strictly adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline and the extension statement for network meta-analysis [16]. The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42024516623.

Eligibility criteria

Our inclusion criteria were randomised controlled trials that evaluated the efficacy or safety of Adamgammadex or Sugammadex in reversing rocuronium-induced neuromuscular blockage in healthy adults or patients undergoing surgery with 1–3 American Society of Anesthesiologists (ASA) physical status. We excluded review articles, case reports, conference abstracts, animal studies, observational studies, case series, and data analysis based on these publications. Additionally, we excluded articles if there was no available English full-text version.

Literature search

A comprehensive search was conducted across PubMed, Scopus, and Science Direct to find pertinent published RCTs from inception until February 22, 2024. This date reflects when the literature search was conducted and completed, ensuring consistency and reproducibility. The following search terms were used:

((Adamgammadex) OR (cyclodextrin-based selective reversal agent) OR cyclodextrin)) AND ((rocuronium) OR (neuromuscular blockade) OR (caused deep neuromuscular blockade)).

Manual research was carried out using backward citation analysis on Google Scholar to find all pertinent papers, and the studies' references were screened for possible articles to include.

Screening of the literature

Titles and abstracts from retrieved citations were imported into Rayyan, a web-based tool designed to help researchers organise and manage systematic reviews [17]. EndNote, a reference management software, was used to identify and exclude duplicate citations. Then, two independent authors blindly assessed the retrieved citations in two stages: the first involved checking all extracted publication titles and abstracts, and the second involved examining full-text screening of all eligible abstracts and assessing their suitability for conducting meta-analysis. A third author helped to resolve any conflict.

Data extraction

Two independent reviewers extracted data from the eligible studies into a data extraction Google sheet. Discrepancies were cross-checked and addressed. For each included randomised controlled trial, the following data were extracted if present: population characteristics (age, sex, BMI, weight, and height), study characteristics (Study design, country, number of centers, total participants, follow-up duration, main inclusion criteria, primary outcomes, and conclusion), primary outcomes which assessed the start of adamgammadex drug to the recovery of Train-of-Four ratio (TOFr) 0.9 and the percentage (%) of patients with TOFr ≥0.9.In addition to secondary outcomes, which summarised TOFr 0.7, TOFr 0.8, and percentage (%) of patients with (TOFr ≥0.7 and ≥0.8) and adverse effects, which included (drug-related severe adverse effects, serious adverse effects, anaphylactic reaction, bradycardia, and urinary tract infection).

Quality assessment

Using the Cochrane Collaboration's Risk of Bias tool (version 2, RoB2) [18], two blinded authors assessed the quality of the included studies. The randomisation process, deviation from the intended interventions, missing outcome data, outcome assessment, and choice of the reported result are the five primary categories that make up the composite score used by this tool. The investigators' conclusions are classified as "low risk," "some concerns," or "high risk" of bias for each of these topics. A third investigator reanalysed the disagreements and resolved them. The RoB2 tool summary and graph were produced using the Robvis [19].

Synthesis of results

Network meta-analysis was performed using STATA software 17 for Mac (StataCorp, 2021) [20], and pairwise meta-analyses were conducted using ReviewManager software (RevMan version 5.4) [21]. The network plots were used to represent the different interventions included in each outcome. Each intervention is represented as a circle, and the lines connecting them represent the randomised comparisons between these interventions. The nodal size represents the sample size included in each intervention group. The TOFr (0.9,0.7,0.8) outcomes were used to evaluate the efficacy outcomes, which were then presented as mean difference and 95% confidence interval. Dichotomous outcomes, such as adverse events, were pooled as risk ratio (RR) with its confidence interval.

Continuous data were pooled as Cohen's d with its 95% CI, whereas dichotomous data were pooled as odds ratio (OR) with its 95% confidence interval (CI). The Wan et al. approach was used to transform data from the median (or interquartile range) to the mean and standard deviation (SD) in any study that reported the data. The pooled effect size for all outcomes was determined using the Der Simonian Laird random effects model, which gives weight to a small number of studies at the expense of larger studies. This allowed for the provision of pooled estimates with a wider standard error to account for any inconsistent effect sizes.

Assessment of heterogeneity

Visual inspection of the forest plots was used to assess statistical heterogeneity between trials. Higgins and Thompson I^2 and a chi-square test (CoPlotse Q test) were used to measure it. The equation used is $I^2 = ((Q - df)/Q) \times 100\%$ [23]. Heterogeneity was classified as low, moderate, or high if the I^2 was less than 25%, between 25% and 75%, or greater than 75%. It was considered significant if the p-value of the chi-square test was less than 0.1, as noted in [23].

Publication bias and funnel plots

For the reporting bias assessment, we arranged to assess the publication bias using the funnel plot method. However, the evaluation was not statistically feasible due to the limited number of included studies. According to Egger et al., bias assessment requires at least ten pooled studies [24].

Results

Characteristics of the included studies

Our literature search retrieved a total of 2031 records from online medical databases. We removed 67 duplicates, and the remaining studies underwent title and abstract screening. One thousand nine hundred fifty-three papers were

Table 1. Summary of the studies evaluating adamgammadex in reversing neuromuscular blockage.

Study ID	Follow up (days)	Main inclusion criteria	Primary outcomes	Conclusion
Zhao et al. 2024 (RCT, China, 7 centers) n = 80 [26]	2	18–64-year-old patients, grade 1 or 2 ASA, underwent elective surgery under general anesthesia with rocuronium	ToF 0.9 ratio.	Adamgammadex 7, 8, 9 mg/kg > sugammadex in TOF recovery, tolerance, and low incidence of adverse events
Jiang et al. 2022 (RCT, China, multicenter) n = 52 [27]	1	Patients aged 18–64 years with grade 1 or 2 (ASA), if muscle relaxation was necessary to be used in surgery more than for intubation	ToF 0.9 ratio.	Adamgammadex was safe, effective, and tolerable
Zhao et al 2021 (RCT, China, 1 center) n = 36 [28]	7	Patients aged 18–64 years, ASA 1–2, (BMI) <30 kg m^2, weight 50 kg for men and 45 kg for women underwent elective surgery under general anesthesia using rocuronium to facilitate tracheal intubation and maintain muscle relaxation	ToF 0.9 ratio.	Adamgammadex enabled rapid TOF recovery and good tolerance
Jiang et al. 2020† (RCT, China, 1 center) n = 52 [29]	8	Male and female subjects aged 18–40 with (BMI) of 19–26 kg/m^2 and weight of 50–90 kg for males and 45–85 kg for females	Adverse events.	Adamgammadex may be a novel and safe option
Zhang et al. 2023 (RCT, China, 15 centers) n = 326 [25]	1	Patients aged 18-65 years had an ASA physical status 1-3, had freely given written informed consent, were scheduled to undergo elective surgery with a tracheal tube or laryngeal mask airway, and were expected to receive rocuronium during the surgical procedure	The proportion of subjects with a ToF ratio returning to 0.9 within 5 min. Recovery time to ToF 0.9.	Adamgammadex was non-inferior to sugammadex with a possible lower incidence of adverse drug reactions compared with sugammadex

TOF 0.9 – Recovery time of the TOF ratio to 0.9; ASA – American Society of Anesthesiologists; TOF – Train-Of-Four; BMI – Body Mass Index
† Shown in figures as Jiang et al. 2019

excluded in title and abstract screening. The remaining studies underwent full-text screening, after which we included five records. A detailed description of the selection process is shown in **Supplementary Figure 1.**

Five randomised controlled trials comprising 530 patients were included in our study, [25–29]. Most of the studies included patients scheduled for elective surgery and expected to receive rocuronium during the surgical procedure to facilitate intubation and muscle relaxation. It is worth noting that the Jiang et al. 2020 study was conducted on healthy volunteers, and the Jiang et al. 2022 study included patients if rocuronium was necessary for the surgery rather than the intubation. Among the included studies, four intervention groups were included with rocuronium doses of 4 mg/kg and 8 mg/kg. Three studies included a rocuronium dose of 2 mg/kg, and two included a rocuronium dose of 6 mg/kg. Rocuronium doses of 7, 9, 16, 24, or 32 were only used in one study. Moreover, some studies used sugammadex as an intervention with a 2 or 4 mg/kg dose. A detailed description of the baseline characteristics and a summary of the included studies are shown in **Tables 1** and **2**, respectively.

Risk of bias assessment

Based on the Cochrane risk of bias assessment tool 2 (ROB-2), all included papers had a low risk of bias. The risk of bias graph and summary of the quality assessment domains are shown in **Figure 1**. The network plots are shown in the **Supplementary Figures 2** and **3**.

The recovery time (minutes) of the TOF ratio to 0.9 (Tof 0.9)

A summary of the characteristics of the network meta-analysis is shown in **Supplementary Table 1**. Our network meta-analysis found that TOF 0.9 was significantly faster in adamgammadex 2 mg/kg (MD = -36.25, 95% CI = [-44.54: -27.95]), 4 mg/

Table 2. Baseline characteristics of patients.

Study ID	Groups	Dose (mg/kg)	Age (Years), Mean (SD)	Sex (male) N (%)	Weight (kg), Mean (SD)	Height (cm), Mean (SD)	BMI (kg/m^2), Mean (SD)
Zhao et al. 2024 [26]	Adamgammadex	7	41.8 (11.17)	5 (25%)	66.28 (12.08)	165 (10.10)	24.28 (3.12)
		8	43.6 (11.36)	9 (45%)	65.23 (8.91)	166.2 (8.92)	23.61 (2.35)
		9	40.3 (13.73)	9 (45%)	62.88 (12.96)	165.3 (10.06)	22.88 (3.55)
	Sugammadex	4	49.7 (11.34)	10 (50%)	62.75 (8.93)	163.6 (7.63)	23.38 (1.94)
Jiang et al. 2022 [27]	Adamgammadex	2	38.5 (10.9)	5 (50%)	63 (12)	161 (9)	24.4 (4)
		4	46.4 (10.6)	6 (55%)	68 (11)	162 (8)	25.8 (3)
		6	41.7 (11.1)	4 (33%)	61 (6)	162 (5)	23.1 (2.7)
		8	38.9 (10.1)	3 (30%)	64 (11)	161 (10)	24.8 (3.1)
	Placebo	NA	32.7 (7.7)	6 (67%)	60 (16)	164 (9)	22 (3.6)
Zhao et al. 2021 [28]	Adamgammadex	2	47.5 (13.63)	3 (50%)	64 (10)	163.3 (8.76)	23.8 (2.32)
		4	45 (13.45)	1 (16.6%)	64.17 (11.37)	163.2 (6.31)	24 (2.61)
		6	40.2 (14.47)	3 (50%)	66.5 (11.91)	168.3 (6.38)	23.5 (3.21)
		8	35.8 (11.82)	3 (50%)	67.67 (13.49)	166.3 (9.85)	24.5 (2.81)
		10	39.5 (11.67)	4 (66.6%)	69 (17.7)	168.2 (9.45)	23.8 (3.87)
	Sugammadex	4	52.2 (10.4)	5 (83.3%)	67.75 (5.19)	166.2 (6.52)	24.8 (2.04)
Jiang et al. 2020† [29]	Adamgammadex	0.5	27 (2.5)	2 (50%)	59 (5.9)	166 (3)	NA
		2	21.6 (1.5)	4 (50%)	57 (8.3)	164 (6)	NA
		4	23.1 (3.6)	4 (50%)	55.9 (10.8)	161 (8)	NA
		8	25.4 (3.9)	4 (50%)	59.4 (9.9)	165 (11)	NA
		16	24.9 (1.7)	4 (50%)	60.8 (13.1)	165 (10)	NA
		24	25 (1.5)	4 (50%)	61.6 (8.6)	166 (9)	NA
		32	23.9 (2.6)	4 (50%)	60.6 (9.4)	164 (9)	NA
	NA	NA	NA	NA	NA	NA	NA
Zhang et al. 2023 [25]	Adamgammadex	4	42 (3)	60 (38.7%)	65 (10)	163 (8)	24 (3)
	Sugammadex	4	37 (3.33)	46 (29.7%)	62 (10)	162 (8)	24 (3)

BMI – Body Mass Index; SD – standard deviation; N – number; NA – not available
† Shown in figures as Jiang et al. 2019

Figure 1. Risk of bias graph and Summary of the Rob-2 domains.

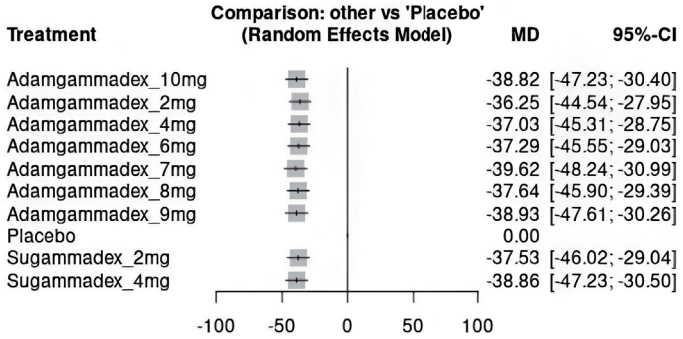

Figure 2. Train-of-Four ratio 0.9 comparison with placebo.

kg (MD = -37.03, 95% CI = [-45.31: -28.75]), 6 mg/kg (MD = -37.29, 95% CI = [-45.55: -29.03]), 7 mg/kg (MD = -39.62, 95% CI = [-48.24: -30.99]), 8 mg/kg (MD = -37.64, 95% CI = [-45.90: -29.39]), 9 mg/kg (MD = -38.93, 95% CI = [-47.61: -30.26]), 10 mg/kg (MD = -38.82, 95% CI = [-47.23: -30.40]) compared to placebo. Moreover, both included Sugammadex doses (2 mg/kg, 4 mg/kg), which led to significantly faster Tof recovery than placebo (see **Figure 2**). The pairwise comparison revealed that sugammadex 2 mg/kg led to a quicker recovery of ToF when compared to adamgammadex 4 mg/kg (MD = -0.50, 95% CI = [-0.53: -0.47]). Moreover, there was a significant difference in favor of sugammadex 4 mg/kg when compared to adamgammadex 6 mg/kg (MD = 0.88, 95% CI = [0.15: 1.61]) and adamgammadex 8 mg/kg (MD = -4.87, 95% CI = [-8.16: -1.58]). Adamgammadex 4 mg/kg, 8 mg/kg, and 10 mg/kg had a significantly faster recovery of ToF when compared to adamgammadex 2 mg/kg (see **Figure 3**).

To confirm the effectiveness of these interventions on ToF 0.9, a cumulative ranking curve was used to rank the different interventions. The ranking showed a dose-response relationship, except for adamgammadex 7 mg/kg, which achieved the highest ranking. Regarding sugammadex, the 2 mg/kg dose was positioned between the adamgammadex 6 mg/kg and 8 mg/kg groups. In contrast, the sugammadex 4 mg/kg dose was positioned between the adamgammadex 10 mg/kg and 7 mg/kg groups, as shown in **Supplementary Figure 4**.

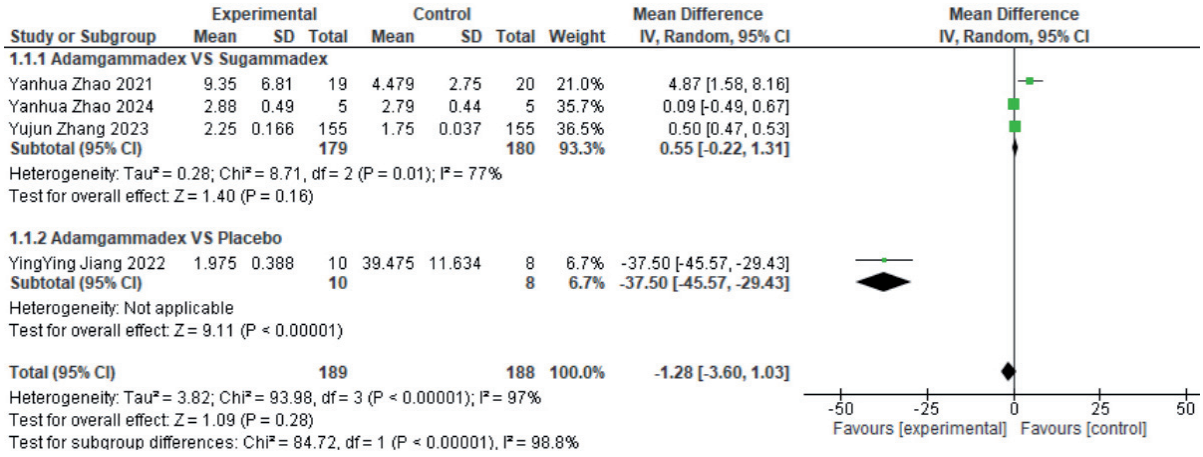

Figure 3. Train-of-Four ratio 0.9, individual study result.

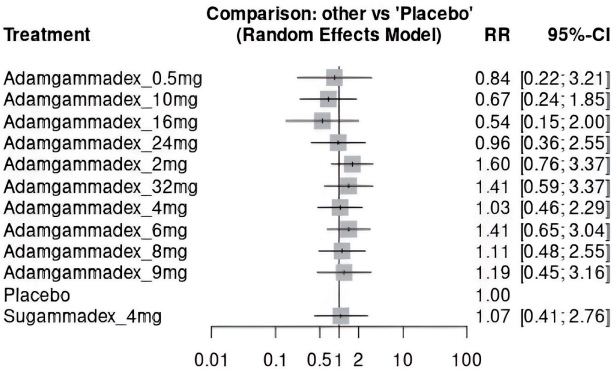

Figure 4. Adverse events comparison with placebo.

Direct pairwise meta-analysis showed no significant difference between adamgammadex and sugammadex (see **Supplementary Figure 5**).

The recovery time (minutes) of the TOF ratio to 0.7 (ToF 0.7)

Our direct pairwise meta-analysis showed a non-significant difference regarding ToF 0.7. Based on the intervention time, subgrouping showed a statistically significant difference between adamgammadex and placebo in favour of adamgammadex (MD = -23.85, 95% CI = -28.40: -19.30). However, there was no statistically significant difference between adamgammadex and sugammadex (MD = -3.53, 95% CI = -11.59: 4.52). The test for subgroup differences showed substantial results (I^2 = 94.6%, P < 0.0001) (see **Supplementary Figure 6**).

Adverse events

The network meta-analysis showed a non-significant difference in adverse effects among any intervention group compared to placebo, indicating that adamgammadex or sugammadex could be a safe intervention for inducing muscle relaxation in elective surgeries (see **Figure 4**). A summary of the individual study results is shown in **Supplementary Figure 7**. The ranking of risk ratios of the different intervention groups and placebo is shown in **Supplementary Table 3**. Our direct pairwise comparison showed no significant difference between adamgammadex and sugammadex in the incidence of adverse events. No heterogeneity was observed in any of the subgroups (see **Supplementary Figure 8**).

Discussion

Significance of the study

Our findings indicate that adamgammadex and sugammadex significantly expedite the recovery of neuromuscular function, as measured by ToF 0.9. The analysis revealed that higher doses

generally resulted in faster recovery of muscular function, except for the adamgammadex 7 mg/kg dose, which exhibited the highest efficacy. Furthermore, our study determined that the 4 mg/kg dose of sugammadex did not show a statistically significant difference in efficacy compared to the 7 mg/kg dose of adamgammadex. Additionally, the 2 mg/kg dose of sugammadex was associated with a significantly faster recovery of neuromuscular function compared to an equivalent dose of adamgammadex.

Explanation of our findings

Neuromuscular blocking agents such as rocuronium are widely used during surgical procedures to facilitate tracheal intubation and mechanical ventilation and optimise surgical conditions [30]. However, a high percentage of patients may experience persistent residual neuromuscular blockade postoperatively, which may put the patients at an increased risk of postoperative complications such as hypoxia, airway obstruction, aspiration, or prolonged hospital stay [31,32]. Thus, selective relaxant binding agents such as Sugammadex and Adamgammadex were suggested as a therapeutic option to reverse the rocuronium-induced neuromuscular blockade [10]. Literature indicates that sugammadex can be safe and effective. However, it was reported that it may be associated with a risk of bleeding due to its anticoagulant effect and a risk of hypersensitivity reaction, up to anaphylaxis [33,34].

On the other hand, adamgammadex is a newly synthesised selective relaxant-binding agent. Structural modifications of the core of sugammadex were synthesised. Pores studies found that adamgammadex reverses the neuromuscular blocking effect of rocuronium in a concentration-dependent manner. Moreover, it was suggested to have a lower risk of bleeding or hypersensitivity [9,13]. We conducted this network meta-analysis to assess the difference in efficacy and safety of different doses of adamgammadex or sugammadex in reversing the rocuronium-induced neuromuscular blockade.

All of the included studies assessed neuromuscular function recovery using the train of four measure, which is the simple count of muscle twitches resulting from neuromuscular stimulation. The ToF ratio is the ratio between the amplitude of the fourth and the first twitch. Adequate recovery is considered when the TOF ratio is ≥0.9 [13].

Our study found that adamgammadex and sugammadex significantly accelerated recovery from neuromuscular blockade compared to placebo. The cumulative ranking curve revealed a dose-response relationship consistent across all included clinical trials [35]. This dose-response effect may be attributed to the competitive inhibition mechanism of adamgammadex and sugammadex against rocuronium. Although the cumulative ranking curve indicated a dose-response relationship, the 7 mg/kg dose of adamgammadex ranked higher than the 8, 9, and 10 mg/kg doses. However, a statistically significant difference was only observed between the 7 mg/kg and 8 mg/kg doses of adamgammadex. No statistically significant difference was found between the 7 mg/kg dose of adamgammadex and the 4 mg/kg of sugammadex. The lack of significance in many cases could be due to the small number of included trials, which might have limited the ability to detect significant differences between the interventions. Zhao et al. supported our findings by reporting no intergroup differences between the 7, 8, and 9 mg/kg doses of adamgammadex. They also noted that adamgammadex led to a slightly longer recovery time than sugammadex, although the results did not reach statistical significance [29].

Implications of these findings for clinical practice

The development of adamgammadex appears mainly targeted toward the Chinese market, and it remains unclear whether this drug will become popular enough globally to replace sugammadex [36]. Clinically, adamgammadex was expected to perform similarly to sugammadex [36]. Our study supports this idea, showing that adamgammadex and sugammadex are safe therapeutic options for reversing rocuronium-induced neuromuscular blockade during surgery. Both drugs provided rapid recovery of neuromuscular function, with no significant difference in adverse events compared to placebo.

Strengths and limitations

This is the first meta-analysis to investigate the efficacy and safety of adamgammadex and sugammadex for reversing neuromuscular blockade, primarily during surgery. However, this study is not without limitations. First, the limited number of included studies may lead to imprecision

and an inability to detect statistically significant differences among the various doses. Second, there was heterogeneity in the study populations; four included patients undergoing elective surgery, while one involved healthy volunteers. This variability could affect patient characteristics or baseline neuromuscular function, influencing the efficacy and risk of adverse events. Third, most included studies focused on elective surgery patients, introducing variability in surgery duration, potential complications, and anaesthetic techniques, which could impact the efficacy and timing of adamgammadex or sugammadex administration. This also limits the generalizability of our results to emergency surgeries or other types of elective surgeries not assessed in our study. Fourth, all included studies were conducted in China, which may limit the generalizability of our findings to populations with different demographics and health conditions. Finally, due to the limited number of included studies, we could not perform a publication bias assessment, potentially affecting the robustness of our meta-analysis.

Recommendations for future research and clinical practice

Further well-conducted clinical trials are needed to establish the evidence regarding the use of Adamgammadex or Sugammadex for rocuronium-induced neuromuscular blockade. This will lead to a deeper understanding of these patients' most effective and safe doses.

Conclusion

Our study indicates that Adamgammadex/Sugammadex can be a safe and effective intervention in reversing the neuromuscular blockade caused by rocuronium during surgical procedures. Although a dose-response relationship is noted, few studies have drawn a solid conclusion. Further studies using multiple doses should be conducted to establish this effect.

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Authors' contributions
AA: conceptualisation and methodology. AA, OY, AZ, and TIEG: investigation and data curation. AE: formal analysis. AA, NIH, AZ, and TIEG: Writing – Original Draft. NIH and MA: Supervision. AA and MA: Project administration. ZO, MA, and YN: Writing – Review & Editing. All authors read and approved the final content.

Ethical consideration
This article is based on previously conducted studies and contains no new studies with human participants.

Consent to participate
Not applicable.

Consent for publication
Not applicable.

Data Availability
All data will be available from the first or corresponding author upon reasonable request.

Conflict of interest statement
The authors declare no conflict of interest.

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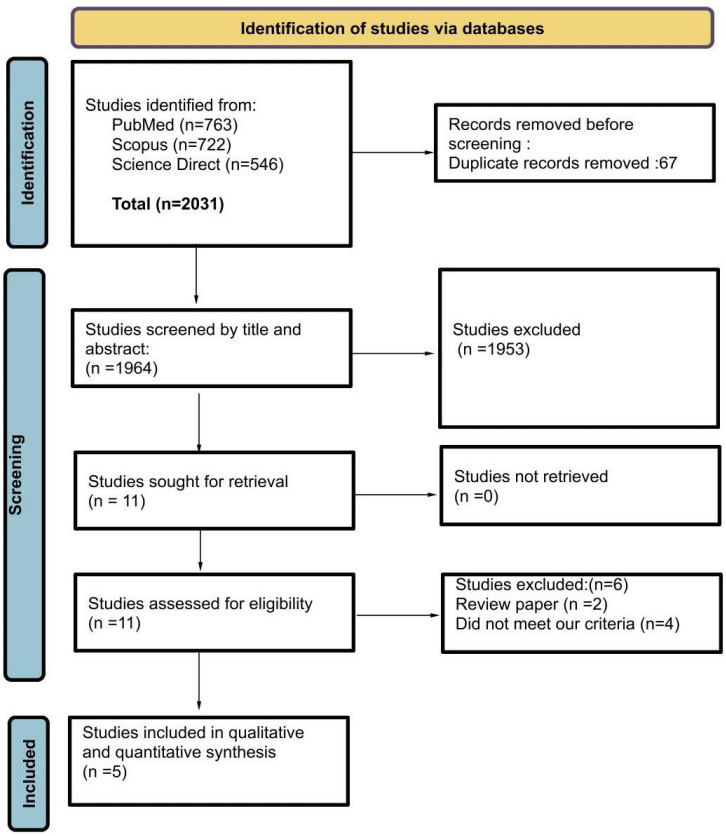
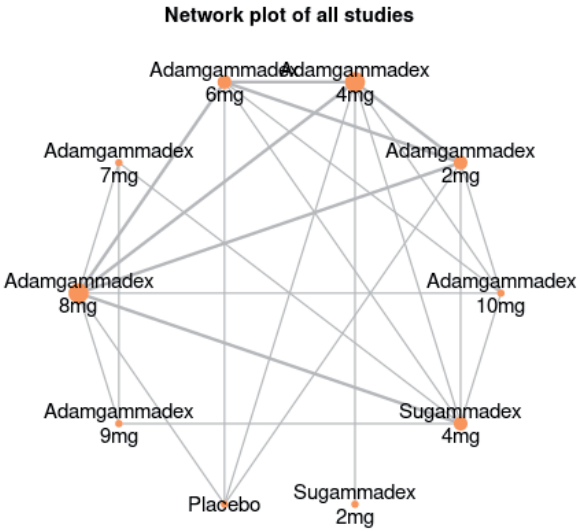
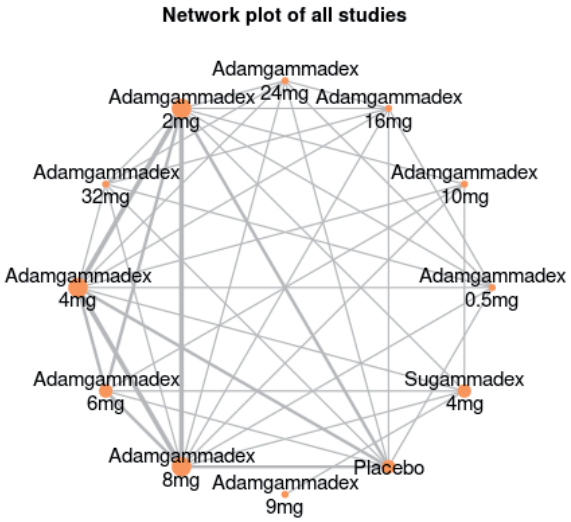


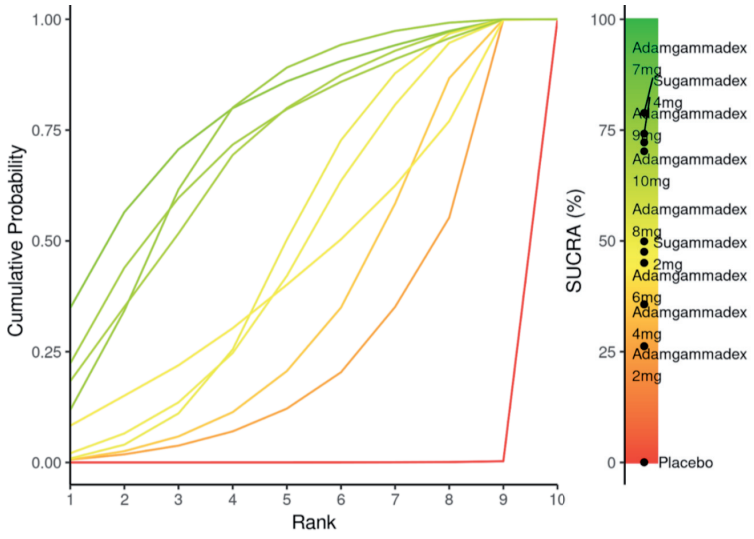
Supplementary Figure 1. Prisma.



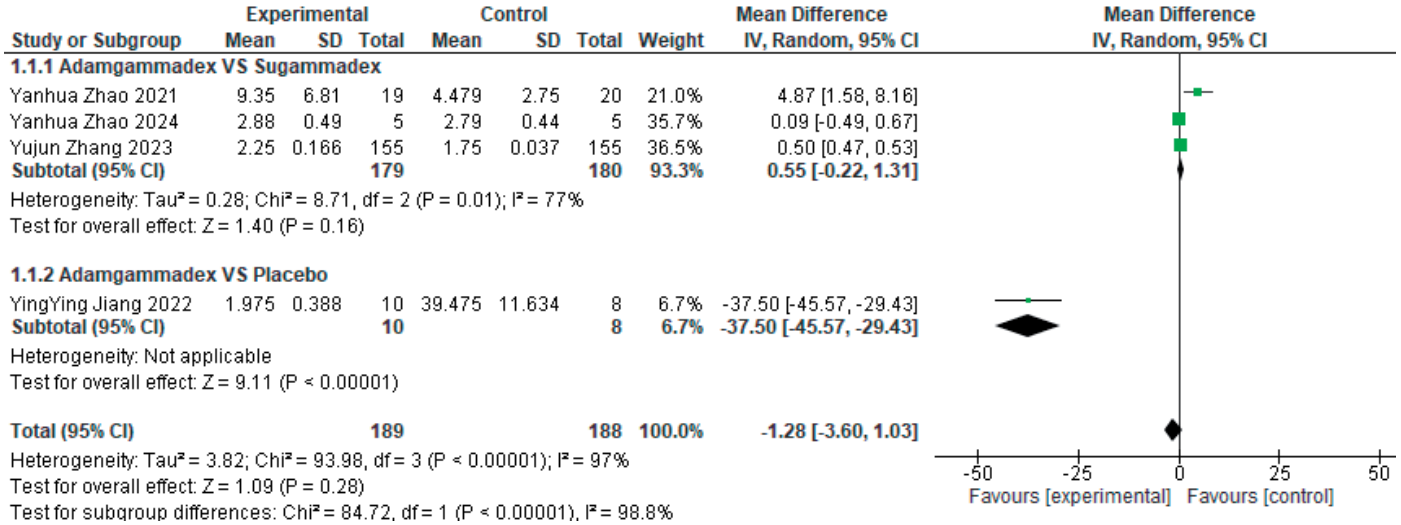
Supplementary Figure 2. Network plot of all studies reporting ToF 0.9.



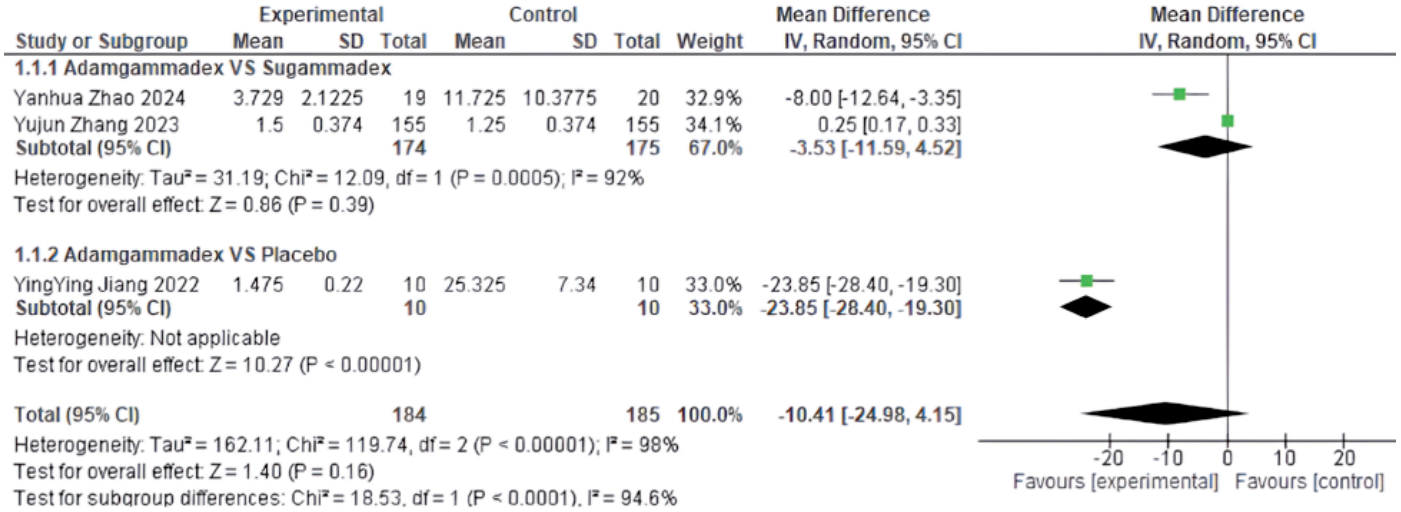
Supplementary Figure 3. Network plot of all studies reporting Adverse events.



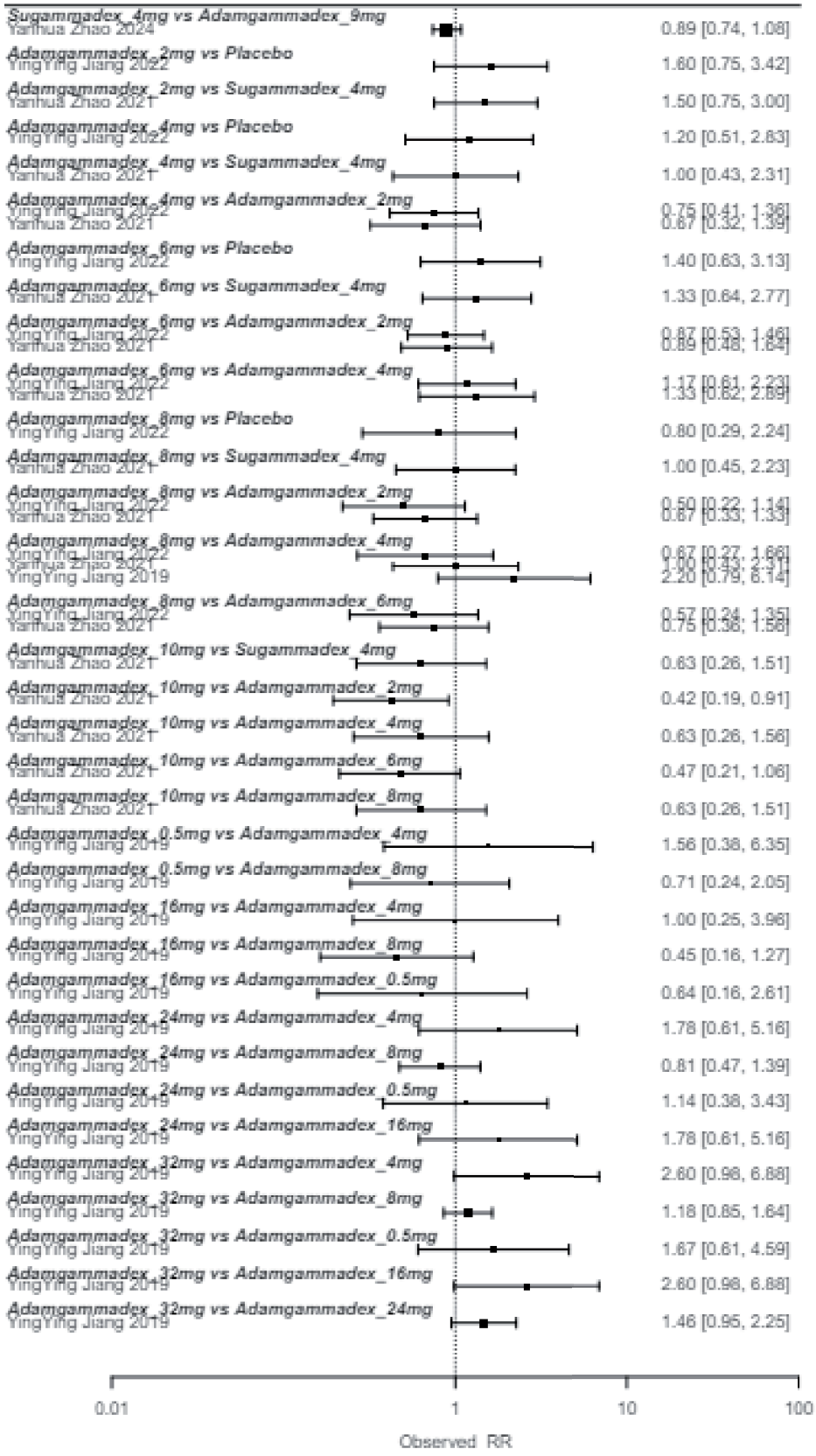
Supplementary Figure 4. Cumulative ranking of ToF 0.9.



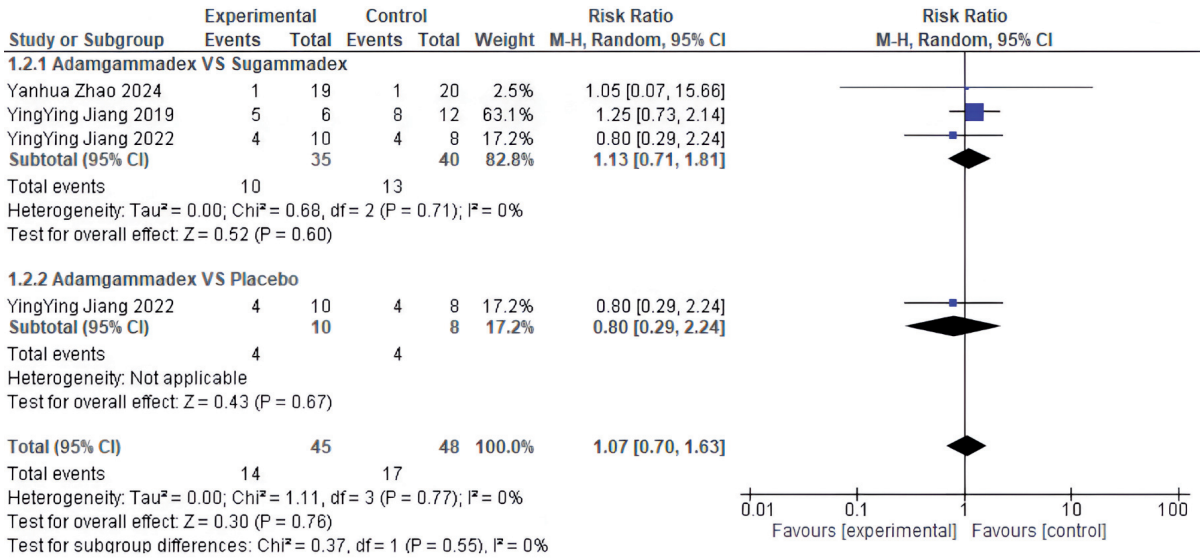
Supplementary Figure 5. Direct pairwise meta-analysis of ToF 0.9.



Supplementary Figure 6. Forest plot of ToF 0.7.



Supplementary Figure 7. Individual study results for adverse events.



Supplementary Figure 8. Direct pairwise meta analysis adverse events.

Supplementary Table 1. Summary characteristics of all studies reporting ToF 0.9.

Characteristic	Value
Number of Interventions	10
Number of Studies	4
Total Number of Patients in Network	464
Total Possible Pairwise Comparisons	45
Total Number of Pairwise Comparisons With Direct Data	25
Is the network connected?	TRUE
Number of Two-arm Studies	1
Number of Multi-Arms Studies	3
Average Outcome	3.498

Supplementary Table 2. Ranking Tof 0.9.

Adamgammadex_7mg	0.06 [-2.39; 2.52]	.	-0.68 [-3.22; 1.86]	-4.81 [-8.54; -1.07]	.	.	.	.	.
-0.75 [-3.09; 1.59]	Sugammadex_4mg	0.44 [-1.61; 2.49]	-0.75 [-3.36; 1.87]	-1.10 [-2.84; 0.64]	.	-0.88 [-2.89; 1.13]	-5.32 [-11.64; 1.00]	-10.52 [-21.32; 0.28]	.
-0.80 [-3.75; 2.16]	-0.04 [-2.04; 1.95]	Adamgammadex_10mg	.	-0.53 [-2.59; 1.53]	.	-1.32 [-3.42; 0.78]	-5.76 [-12.11; 0.59]	-10.96 [-21.77; -0.15]	.
-0.68 [-3.22; 1.86]	0.07 [-2.43; 2.57]	0.11 [-2.98; 3.20]	Adamgammadex_9mg	-4.12 [-7.97; -0.28]	.	.	.	.	.
-1.97 [-4.61; 0.66]	-1.22 [-2.86; 0.42]	-1.18 [-3.07; 0.72]	-1.29 [-4.07; 1.49]	Adamgammadex_8mg	.	-0.59 [-1.98; 0.81]	-0.70 [-2.54; 1.15]	-1.40 [-3.35; 0.54]	-37.50 [-45.78; -29.22]
-2.09 [-5.68; 1.50]	-1.34 [-4.25; 1.57]	-1.29 [-4.33; 1.74]	-1.41 [-5.11; 2.29]	-0.12 [-2.69; 2.45]	Sugammadex_2mg	.	-0.50 [-2.37; 1.37]	.	.
-2.33 [-5.10; 0.45]	-1.57 [-3.33; 0.19]	-1.53 [-3.48; 0.42]	-1.64 [-4.56; 1.27]	-0.35 [-1.73; 1.03]	-0.24 [-2.82; 2.35]	Adamgammadex_6mg	-0.27 [-2.15; 1.60]	-1.00 [-2.97; 0.98]	-37.10 [-45.39; -28.81]
-2.59 [-5.65; 0.47]	-1.84 [-4.06; 0.38]	-1.79 [-4.19; 0.60]	-1.91 [-5.10; 1.28]	-0.62 [-2.37; 1.14]	-0.50 [-2.37; 1.37]	-0.26 [-2.04; 1.51]	Adamgammadex_4mg	-0.94 [-2.91; 1.04]	-37.23 [-45.51; -28.94]
-3.37 [-6.49; -0.25]	-2.62 [-4.92; -0.32]	-2.57 [-5.04; -0.11]	-2.69 [-5.93; 0.55]	-1.40 [-3.24; 0.44]	-1.28 [-4.00; 1.44]	-1.04 [-2.90; 0.81]	-0.78 [-2.75; 1.19]	Adamgammadex_2mg	-36.40 [-44.70; -28.10]
-39.62 [-48.24; -30.99]	-38.86 [-47.23; -30.50]	-38.82 [-47.23; -30.40]	-38.93 [-47.61; -30.26]	-37.64 [-45.90; -29.39]	-37.53 [-46.02; -29.04]	-37.29 [-45.55; -29.03]	-37.03 [-45.31; -28.75]	-36.25 [-44.54; -27.95]	Placebo

Supplementary Table 3. Ranking Adverse events.

Adamgammadex_16mg	.	0.64 [0.16; 2.61]	0.56 [0.19; 1.63]	1.00 [0.25; 3.96]	.	.	0.45 [0.16; 1.27]	.	.	0.38 [0.15; 1.02]	.
0.80 [0.22; 2.90]	Adamgammadex_10mg	.	.	0.63 [0.26; 1.56]	.	0.63 [0.26; 1.51]	0.63 [0.26; 1.51]	.	0.47 [0.21; 1.06]	.	0.42 [0.19; 0.91]
0.64 [0.16; 2.61]	0.80 [0.21; 2.96]	Adamgammadex_0.5mg	0.88 [0.29; 2.64]	1.56 [0.38; 6.35]	.	.	0.71 [0.24; 2.05]	.	.	0.60 [0.22; 1.65]	.
0.56 [0.19; 1.63]	0.70 [0.27; 1.79]	0.88 [0.29; 2.64]	Adamgammadex_24mg	1.78 [0.61; 5.16]	.	.	0.81 [0.47; 1.39]	.	.	0.68 [0.44; 1.05]	.
0.53 [0.17; 1.61]	0.65 [0.30; 1.43]	0.82 [0.26; 2.61]	0.93 [0.46; 1.90]	Adamgammadex_4mg	1.20 [0.51; 2.83]	1.00 [0.43; 2.31]	0.93 [0.55; 1.58]	.	0.81 [0.49; 1.33]	0.38 [0.15; 1.02]	0.72 [0.45; 1.14]
0.54 [0.15; 2.00]	0.67 [0.24; 1.85]	0.84 [0.22; 3.21]	0.96 [0.36; 2.55]	1.03 [0.46; 2.29]	Placebo	.	1.25 [0.45; 3.49]	.	0.71 [0.32; 1.59]	.	0.62 [0.29; 1.34]
0.51 [0.15; 1.75]	0.63 [0.26; 1.51]	0.79 [0.22; 2.81]	0.90 [0.38; 2.17]	0.97 [0.48; 1.95]	0.94 [0.36; 2.43]	Sugammadex_4mg	1.00 [0.45; 2.23]	0.89 [0.74; 1.08]	0.75 [0.36; 1.56]	.	0.67 [0.33; 1.33]
0.49 [0.18; 1.36]	0.61 [0.27; 1.35]	0.76 [0.26; 2.20]	0.87 [0.51; 1.49]	0.93 [0.55; 1.57]	0.90 [0.39; 2.08]	0.96 [0.47; 1.97]	Adamgammadex_8mg	.	0.67 [0.38; 1.17]	0.85 [0.61; 1.17]	0.59 [0.35; 1.00]
0.45 [0.13; 1.58]	0.56 [0.23; 1.37]	0.71 [0.20; 2.55]	0.81 [0.33; 1.98]	0.86 [0.42; 1.79]	0.84 [0.32; 2.21]	0.89 [0.74; 1.08]	0.93 [0.44; 1.94]	Adamgammadex_9mg	.	.	.
0.38 [0.12; 1.19]	0.48 [0.23; 1.01]	0.60 [0.19; 1.93]	0.68 [0.33; 1.41]	0.73 [0.45; 1.18]	0.71 [0.33; 1.53]	0.76 [0.39; 1.48]	0.79 [0.47; 1.32]	0.85 [0.42; 1.70]	Adamgammadex_6mg	.	0.88 [0.60; 1.30]
0.38 [0.15; 1.02]	0.48 [0.21; 1.10]	0.60 [0.22; 1.65]	0.68 [0.44; 1.05]	0.73 [0.42; 1.28]	0.71 [0.30; 1.70]	0.76 [0.35; 1.62]	0.79 [0.57; 1.08]	0.85 [0.39; 1.86]	1.00 [0.56; 1.79]	Adamgammadex_32mg	.
0.34 [0.11; 1.04]	0.42 [0.20; 0.88]	0.53 [0.17; 1.67]	0.60 [0.30; 1.22]	0.64 [0.41; 1.00]	0.63 [0.30; 1.32]	0.67 [0.35; 1.28]	0.69 [0.42; 1.13]	0.75 [0.38; 1.47]	0.88 [0.60; 1.30]	0.88 [0.50; 1.53]	Adamgammadex_2mg