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LETTER

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Optimal dosage of adamgammadex for reversal of rocuronium-induced neuromuscular block: a preliminary meta-analysis

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Dear Editor,

Adamgammadex is a novel reversal agent developed to rapidly reverse rocuronium-induced neuromuscular blockade [1]. It encapsulates rocuronium molecules, rendering them unavailable for binding to nicotinic acetylcholine receptors at the neuromuscular junction. The speed of neuromuscular blockade reversal is an important consideration in anesthetic management, as it can affect operating room efficiency and patient safety. However, the optimal dosage of adamgammadex for reversal of rocuronium-induced neuromuscular block remains unknown. Some studies have reported that the recovery times of the train-of-four (TOF) ratio to 0.9 induced by adamgammadex at a dose of 6 mg/kg are faster than those at a dose of 4 mg/kg [2, 3]. However, one study did not find a significant difference in recovery times between these two doses [4]. Given the limited number of studies currently available in the literature, there is a need to further evaluate whether there is a difference in the speed of reversal of rocuronium-induced neuromuscular blockade between adamgammadex doses of 6 and 4 mg/kg. A meta-analysis of existing studies can provide a more comprehensive and robust assessment of the available evidence.

We conducted a comprehensive literature search using the Medline, Embase, and Cochrane Library electronic databases. The search was performed using a combination of keywords and MeSH terms, including "adamgammadex," "rocuronium," "sugammadex," "neuromuscular blockade," "reversal," "dosage," and "train-of-four ratio." The reference lists of the retrieved articles were manually screened to identify any additional relevant studies. Studies were considered eligible for inclusion in this meta-analysis if they met the following criteria: 1. studies involving adult patients (aged 18 years or older) undergoing surgical procedures requiring general anesthesia and neuromuscular blockade with rocuronium; 2. randomized controlled trials (RCTs) comparing the efficacy of adamgammadex (at doses of 6 mg/kg or 4 mg/kg) with sugammadex for the reversal of rocuronium-induced neuromuscular blockade, and 3. Studies reporting the time to recovery of the TOF ratio to 0.9 as an outcome measure. Non-randomized observational studies, case reports, editorials, or review articles were excluded. Studies that did not report the time to recovery of the TOF ratio to 0.9 or did not compare the specified doses of adamgammadex were also excluded. The primary

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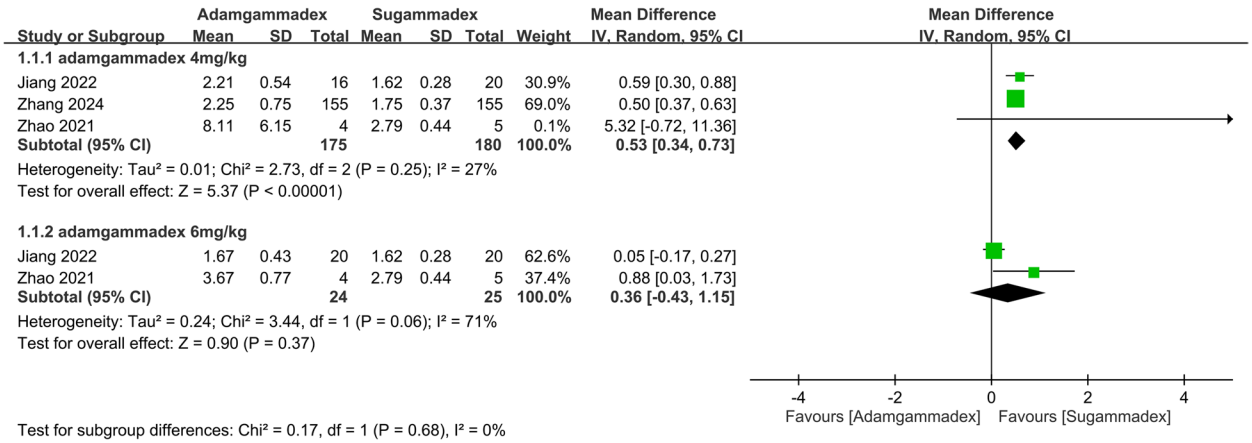

Fig. 1 Forest plot of mean differences in time to recovery of train-of-four (TOF) ratio to 0.9 for adamgammadex versus sugammadex. CI: confidence interval

outcome of interest was the time to recovery of the TOF ratio to 0.9, following the administration of adamgammadex (at doses of 6 mg/kg or 4 mg/kg) or sugammadex. Meta-analysis was performed using a random-effects model to account for potential heterogeneity among the included studies. The effect size was expressed as the mean difference (MD) with 95% confidence interval (CIs). All statistical analyses were performed using Review Manager (RevMan) software version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark). A p-value of less than 0.05 was considered statistically significant.

Three studies met the inclusion criteria and were included in the meta-analysis [2, 3, 5]. All three studies were RCTs that compared various doses of adamgammadex and sugammadex for the reversal of rocuronium-induced neuromuscular block. The studies ranged in size from 35 to 310 patients. Jiang et al. [2] conducted a phase II study comparing adamgammadex doses of 4 mg/kg and 6 mg/kg with sugammadex 2 mg/kg. The study by Zhao et al. [3] was a phase IIa dose-finding study evaluating adamgammadex doses ranging from to 2–10 mg/kg compared to sugammadex 4 mg/kg. The study by Zhang et al. [5] was the largest phase III trial comparing adamgammadex 4 mg/kg to sugammadex 2 mg/kg. The primary efficacy outcome in all studies was the time from the administration of the reversal agent to the recovery of the TOF ratio to 0.9.

Figure 1 shows the mean difference (MD) and 95% confidence intervals (CI) for the time to recovery of TOF ratio to 0.9 for adamgammadex compared to sugammadex in the three included studies. For adamgammadex 4 mg/kg compared to sugammadex, the MD in recovery time ranged from 0.50 min (95% CI: 0.37, 0.63) to 5.32 min (95% CI: -0.72, 11.36). For the comparison of adamgammadex 6 mg/kg to sugammadex, Jiang et al. [2] found no significant difference in recovery times (MD: 0.05 min, 95% CI: -0.17, 0.27). However, Zhao et al. found a faster recovery time with adamgammadex (MD: 0.88 min 95% CI: 0.03, 1.73) [3]. Overall, adamgammadex at a dose of 4 mg/kg tended to have slightly longer recovery times than sugammadex (MD: 0.53 min, 95% CI: 0.34, 0.73, $p<0.00001$), while adamgammadex at 6 mg/kg showed similar recovery times to sugammadex (MD: 0.36 min, 95% CI: -0.43, 1.15, $p=0.37$). However, no subgroup difference was observed between the two dosages ($p=0.68$), indicating that adamgammadex at doses of 4 or 6 mg/kg may be feasible in clinical practice.

This preliminary meta-analysis of three RCTs comparing adamgammadex to sugammadex for the reversal of rocuronium-induced neuromuscular blockade suggests that adamgammadex is an effective reversal agent. The lack of a significant subgroup difference between the 4 mg/kg and 6 mg/kg doses of adamgammadex indicated that both dosages may be clinically feasible. This finding is particularly relevant for anesthesiologists and surgeons, as it suggests flexibility in dosing options while maintaining effective reversal of neuromuscular blockade. However, it is important to note that this meta-analysis was based on a limited number of studies, with sample sizes ranging from 35 to 310 patients. Further large-scale RCTs are needed to confirm these findings and evaluate the safety profile of adamgammadex at different doses.

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Authors' contributions
I-W.C. and K-C.H. wrote the main manuscript text. T-S.Y. prepared Fig. 1. All authors read and approved the final version of the manuscript.

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Availability of data and materials
The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no conflicts of interest.

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