

Reviewer 2

Major comment.

1. It has been widely known that anesthetics affect the sensitivity of neuromuscular blocker pharmacologic actions. For example, inhaled anesthetics may act synergistically with neuromuscular blockers. Also, deep anesthesia may reduce the required dose of neuromuscular blockers. Are there any differences in anesthetics (intravenous vs inhaled anesthetics) selection for each group in this study? Also, are there differences in depth of anesthesia between groups?

Response: we totally agree with your opinion that inhaled anesthetics may act synergistically with neuromuscular blockers. As described in the study procedures, all the patients in this study were under total intravenous anesthesia. The opioid analgesics (fentanyl, remifentanyl, or sufentanil) and propofol (target controlled infusion) was used for pain control and sedation depending on the experience of the researcher. During the surgery, rocuronium at dose of 0.1 - 0.2 mg kg⁻¹ was administered when the T₁ or T₂ of TOF occurred. When the surgery finished, adamgammadex or sugammadex was injected by the researcher when the T₂ of the TOF reappeared. The opioid analgesics and propofol were stopped when the surgery finished. Thus, we considered that there are not significant differences in depth of anesthesia between groups.

2. From this study, it looks that low dose of adamgammadex group had a lower incidence of adverse effects (AEs) (mainly TEAEs), and the high dose group showed a higher number of AEs (mainly TEAEs). But there is no description of the difference of AEs between the groups except the basic vital sign and ECG variables. Are there any differences of AEs between groups? In addition, it remains unclear as to whether any of the described AEs are due to surgical/anesthetic factors or the effects of drugs alone. For example, how can we confirm that emesis described as one of treatment emergent adverse events (TEAEs) is related to the use of neuromuscular reversal agents?

Response: the result of TEAEs was presented in Figure 4.

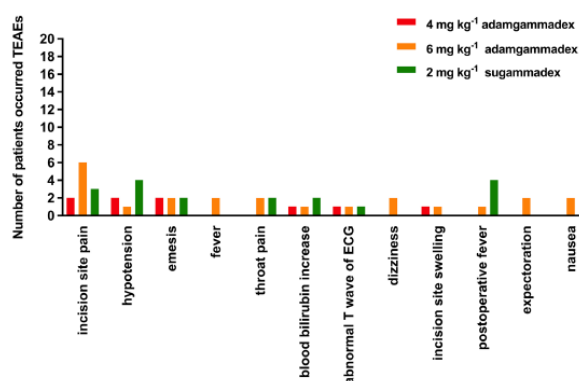


Figure 4 The number of treatment emergent adverse events (TEAEs) in patients.

Then, the drug-related AEs was presented in the Table 3:

Table 3 Adverse events by dose group: safety population set

	adamgammadex (4 mg kg ⁻¹ , n =16)		adamgammadex (6 mg kg ⁻¹ , n =20)		sugammadex (2 mg kg ⁻¹ , n = 20)	
	events	patients	events	patients	events	patients
PTE, n	0	0	1	1	0	0
TEAEs, n	10	6	43	11	29	14
SAEs, n	0	0	0	0	0	0
drug-related AEs, n *	0	0	2 [#]	2	0	0
drug-related SAEs, n *	0	0	0	0	0	0
anaphylactic reaction, n	0	0	0	0	0	0

* Considered to be possibly, probably, or definitely related to treatment.

[#] one case of increased urine acetone bodies and one case of first-degree atrioventricular block.

PTE, pretreatment event; TEAE, treatment emergent adverse events; AE, adverse event; SAE, serious adverse event.

In result section:

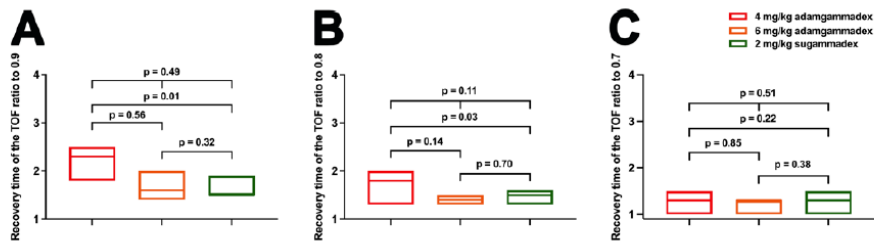
For drug-related AEs, the increased urine acetone bodies and first-degree atrioventricular block were observed in two patients from 2 mg kg⁻¹ sugammadex group. According to CTCAE guidance, the grade of those drug-related AEs was 1, and they recovered back to normal without any treatment.

3. The authors classified the AEs of neuromuscular reversal agents into six categories. However, although the severity of AEs is clearly described in the manuscript, how these categories are defined is somewhat confusing. How did the authors classify the AEs of neuromuscular reversal agents?

Response: AEs were categorized into five grades according to the Common Terminology Criteria for AEs (CTCAE) version 4.03: grade 1 (mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated); grade 2 (moderate; minimal, minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living); grade 3 (severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living); grade 4 (life-threatening consequences; urgent intervention indicated.); grade 5 (death related to AEs). Grades 4 and 5 were classified as serious adverse events (SAEs).

4. In terms of selecting dose of adamgammadex, the authors described that adamgammadex requires a higher dose than sugammadex to produce a similar effect. 4mg/kg or 6mg/kg adamgammadex is equipotent to 2mg/kg sugammadex from a pharmacological point of view? If the dose is not equipotent, this may lead to the bias of efficacy and safety outcomes in this study?

Response: we further compared among groups by post hoc test, and the result was presented as followed:



Then, the conclusion was rewrote as following:

For rocuronium-induced moderate neuromuscular block, the median time of the TOF_{ratio} recovery to 0.9 in the 6 mg kg⁻¹ adamgammax groups showed no significant difference compared with the 2 mg kg⁻¹ sugammax group. The 6 mg kg⁻¹ adamgammax is equipotent to 2mg/kg sugammax from a pharmacological point of view. Thus, we considered that it may not lead to the bias of efficacy and safety outcomes in this study