# Potentiation by sevoflurane of rocuronium-induced neuromuscular block is greater in older than younger adult patients: a randomised controlled trial

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**Keywords:** acetylcholine; elderly; geriatric pharmacology; neuromuscular junction; post-tetanic count; propofol; rocuronium; sevoflurane

Editor—Sevoflurane prolongs the duration of action of non-depolarising neuromuscular blocking agents[1] by presynaptic inhibition of repetitive motor nerve firing[2] and reducing acetylcholine release,[3] and thereby reduced activation of the postsynaptic acetylcholine receptor.[4] Age-related denervation occurs at motor neurones in spinal and peripheral nerves, contributing to skeletal muscle atrophy.[5] After partial muscle denervation, reinnervation by neighbouring motor units appears critical in regeneration of the neuromuscular junction. There is also age-related reduction in the density of synaptic vesicles containing acetylcholine[6] and of the active zones from which quanta of acetylcholine are released.[7] It is likely that neuromuscular junctions having these conformational changes because of advanced age are more sensitive to sevoflurane. We evaluated the hypothesis that prolongation of the effect of sevoflurane on the duration of action of rocuronium-induced neuromuscular block is greater in older than in younger adult patients.

The protocol was approved by the Hospital Ethics Committee on Human Rights in Research. After registration with the University Hospital Medical Information Network (ID:UMIN000031153), 34 younger adults (20–45 yr) and 34 older patients (70–91 yr) consented to participate in this study, and were equally randomised to the group anaesthetised with sevoflurane (S-group) or to the group anaesthetised with propofol (P-group). For patients in the S-group, anaesthesia was induced with fentanyl, continuous infusion of remifentanil, and propofol i.v. After insertion of a supraglottic airway device without the aid of neuromuscular blocking agents, anaesthesia was maintained with an end-tidal sevoflurane concentration of 1.5–2.0 vol%, and remifentanil and fentanyl, as required. For patients in the P-group, anaesthesia was induced with fentanyl, remifentanil, and a target-controlled infusion of propofol i.v., and maintained with a target-controlled infusion of propofol of 2–3 μg $ml^{-1}$, and remifentanil and fentanyl, as required. The ulnar nerve was stimulated with 0.2-ms square-wave stimuli, which were delivered in a train-of-four (TOF) mode at 2 Hz every 15 s. Contraction of the ipsilateral adductor pollicis muscle was measured using TOF-Watch SX™ (Organon Ltd., Dublin, Ireland). After ensuring calibration and stable baseline TOF responses for at least 5 min, all patients received rocuronium 1 mg $kg^{-1}$ i.v. Post-tetanic count (PTC) was assessed every 6 min during repetitive TOF stimulation. Once the first PTC had been detected, TOF stimulation was repeated until recovery of the first twitch (T1) of TOF. Times from administration of rocuronium to recovery of the first PTC and T1 were compared between groups. Before emergence from anaesthesia, a TOF ratio of 1.0 normalised to baseline TOF ratio was observed in all patients. Data are presented as mean (standard deviation). For comparison of the times, two-way analysis of variance and Fisher's least significant difference *post hoc* test were used. A $P$-value of <0.05 was considered statistically significant.

Data from all patients could be analysed. The patients' characteristics were not different between P- and S-groups in both adults and older patients (Supplementary Table S1). The duration until recovery of the first PTC was longer in older patients, particularly in the S-group (P-group: 30.5 [8.6] min, S-group: 64.6 [18.2] min, $P$<0.001), than younger adults (P-group: 23.3 [7.4] min, S-group: 32.5 [7.1] min, $P$<0.001, Supplementary Table S2). In younger adults, intervals between recovery of the first PTC and T1 were similar regardless of anaesthetic used (P-group: 13.4 [5.4] min, S-group: 17.2 [6.2] min). However, in older adults, the interval was prolonged in the S-group (30.6 [9.1] min, $P$<0.001) compared with the P-group (15.5 [7.6] min). Sevoflurane caused a marked shift to the right of the correlation line expressing the relationship between time to recovery of PTC and T1, indicating prolonged time to recovery from neuromuscular block with sevoflurane anaesthesia in older adults (Fig 1).

Our results revealed that older patients are much more susceptible to the potentiating effects of sevoflurane and show markedly slower recovery of PTC and T1. During deep neuromuscular block, PTC results from a physiologic mechanism of post-tetanic facilitation. Tetanic stimulation effectively induces mobilisation of synaptic vesicles from a reserve pool to an immediately releasable pool in motor nerve terminals. Subsequent stimulations can transiently increase the release of acetylcholine and evoke muscular twitch responses. Sevoflurane has a greater inhibitory effect on exocytosis of acetylcholine from the neuromuscular junction.[8] It has been shown that the prejunctional effects of halothane increase with age.[3] It is therefore conceivable that recovery of PTC from rocuronium-induced neuromuscular block is prolonged in older patients through presynaptic inhibition by sevoflurane.

The interval from recovery of the first PTC to appearance of T1 averaged 13–15 min and was not different between adults and older adults in the P-group. An advantage of propofol may be that the interval from recovery of PTC to subsequent

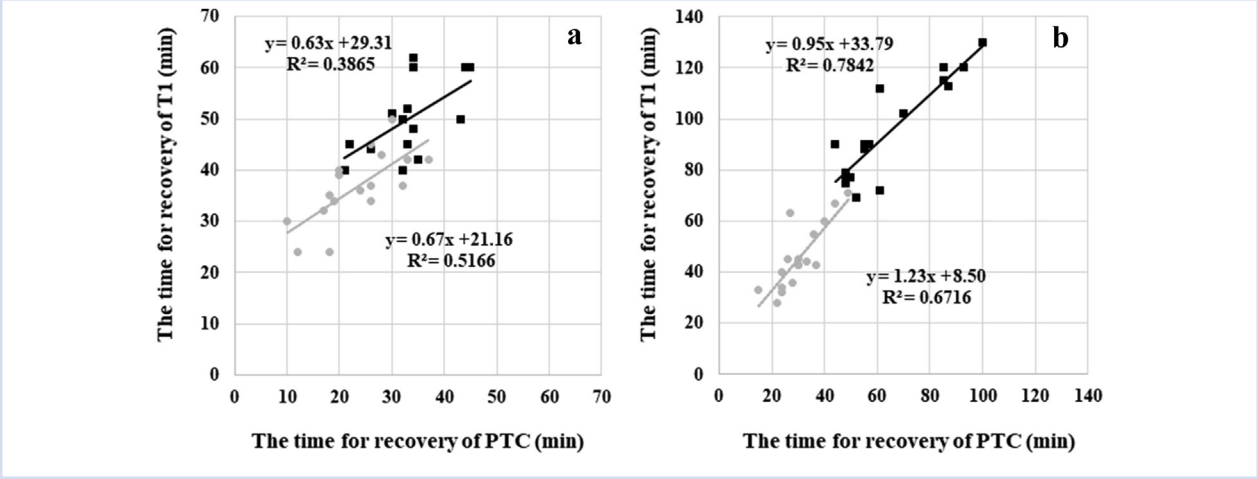


Fig 1. Relationship between time for recovery of the first post-tetanic count (PTC; horizontal axis) and first twitch (T1; vertical axis) in: (a) younger and (b) older adult patients. In the older patients, the correlation obtained during sevoflurane anaesthesia is shifted to right. The results indicate that sevoflurane prolonged times for recovery of the PTC and T1 in older patients. Correlation lines: bold, sevoflurane-group; thin, propofol-group; Y, time for recovery of T1; X, time for recovery of PTC.

recovery of T1 can be similarly estimated in both younger and older adults. Sevoflurane, on the other hand, significantly prolonged the interval between return of the first PTC and T1 only in older adults. The appearance of T1 represents a decrease in the occupancy rate of postsynaptic acetylcholine receptors at the motor endplate for rocuronium. Our results suggest that sevoflurane might also provide postsynaptic potentiation by enhancing binding of rocuronium at the receptor sites.

A limitation of this study is that the total time of sevoflurane inhalation was longer in the older adults. The interaction between sevoflurane and rocuronium seems to be time-dependent and therefore, may be more enhanced in older patients. A 30-min inhalation is sufficient for stabilisation of sevoflurane-induced potentiation of neuromuscular block.[9] Therefore, adequate time for the inhibitory actions of sevoflurane on neuromuscular transmission was provided even in the younger adults. As a second limitation, the inhaled concentration of sevoflurane was not adjusted for age, which might have led to higher relative dosing in the older adults.

In conclusion, sevoflurane had greater potentiating effects than propofol on rocuronium-induced neuromuscular block, which was more marked in the elderly. Moreover, the degree of potentiation by sevoflurane was greater in older adult patients than in younger adult patients.

## Authors' contributions

Study design: all authors
Patient recruitment: ST, OK, MY, MM
Data collection: ST, OK, TS
Data analysis: all authors
Statistical analysis: TS
Writing manuscript: ST, OK
Review and editing: all authors

## Declarations of interest

TS and ST have received speaker's fees from MSD Inc., Japan.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.05.047.

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doi: 10.1016/j.bja.2020.05.047
Advance Access Publication Date: 3 July 2020


# Perioperative vasoactive drugs in patients undergoing major abdominal surgery. Comment on *Br J Anaesth* 2020; 124: 513–24

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**Keywords:** cardiovascular; goal-directed therapy; haemodynamics; major abdominal surgery; perioperative care; postoperative outcome; vasoconstrictor agents

*Editor*—I read with great interest the article by Deng and colleagues[1] on assessing the effect of *vasoactive drugs* in patients undergoing major abdominal surgery. Their systematic review and meta-analysis claims that perioperative vasoactive drugs reduce postoperative complications and the length of hospital stay. Although the authors openly discuss the limitations of their findings, I would like to point out methodological concerns and the need for some data to be validated and revised.

First, I am concerned about the authors' assertion that missing outcome data are at a low risk of bias (risk-of-bias figure in Supplementary material 2[1]). The authors assumed that no trial included in their meta-analysis had missing outcome data. However, the study by Sandham and colleagues,[2] the largest RCT included, reported that 1 yr mortality rates were 163/910 (17.9%) in the intervention group and 155/941 (16.5%) in the control group. In accordance with the principle of intention-to-treat analysis, the number for each group should be 997 vs 997 not 910 *vs* 941. Patients lost to follow-up (87/997 missing from the intervention group and 56/997 missing from the control group) can result in incomplete outcome data; the high risk of attrition bias is arguably inevitable. As including an appraisal of the risk of bias in studies is an integral part of systematic review methods, the authors should report the reason(s) for these missing data and evaluate whether missingness in the outcome could depend on its true value.[3] In addition, the authors should clearly state any assumptions or imputation methods used to handle the missing data.

Second, there is no equipoise regarding comparison of trials with different study protocols, resulting in important methodological limitations. Although pre-specified eligibility criteria were applied in this systematic review and meta-analysis, the characteristics of protocolised vasoactive support interventions varied. Some trials had different objectives for vasopressor and inotrope support interventions. For example, in the study of Stens and colleagues[4] included in this systematic review, the clinical effectiveness of additional cardiac index (CI) and pulse pressure variation (PPV)-guided haemodynamic therapy and that of conventional MAP-guided fluid therapy were compared. Their study adopted protocolised vasoactive management therapy; however, this study did not mean to compare the vasoactive management strategy. Thus, there are substantial differences in the way vasoactive agents were initiated, titrated, and weaned between trials. In fact, in the study of Stens and colleagues,[4] there were substantial differences amongst groups that received vasopressor or inotropic agents (64–78% in the CI–PPV group *vs* 35–38% in the control group), suggesting that the intervention group did not necessarily receive vasoactive agents and *vice versa*. Therefore, the authors' hypothesis that 'the perioperative administration of vasoactive drug therapy, with or without goal directed therapy, reduced mortality, morbidity'[1] does not seem to be compatible with their protocol for this systematic review and meta-analysis. To explain this major concern regarding heterogeneity, pre-established protocols[5] should be described in detail.

Lastly, I would like to see the overall quality of the evidence assessed via the Grading of Recommendations, Assessment, Development and Evaluations framework for relevant outcomes.[6]

I believe that considering the aforementioned factors would have improved the quality and credibility of this study.

## Declaration of interest

The author declares that they have no conflicts of interest.

## Acknowledgements

Funding Supported by JSPS KAKENHI Grant Number JP20K17834.