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Recovery from deep neuromuscular blockade using different sugammadex doses in elderly patients undergoing laparoscopic robot-assisted prostatectomy

A prospective, randomised, double-blind, phase III trial

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Editor,

Robot-assisted laparoscopic radical prostatectomy (RALP) is performed under deep neuromuscular block (NMB) mainly to allow the use of low pneumoperitoneum pressure.[1,2]

Neuromuscular recovery after rocuronium-induced NMB, even when antagonised with sugammadex, may be slower in the elderly due to differences in pharmacokinetics.[3,4] In elderly patients, adequate recovery from deep NMB within 2 min may be achieved with an estimated sugammadex 95% effective dose (ED95) (95% CI) of 5.4 (4.9 to 5.5) mg kg^{-1}, which is approximately a 50% increased dose compared with the standard dose.[5] However, the ED95 was obtained by isotonic regression analysis and the results have not been confirmed by a randomised trial.

The aim of this prospective, double-blind, single-centre, randomised, superiority, phase III study was to evaluate the effects of a dose of sugammadex increased by 50% compared to the standard dose on the neuromuscular recovery time from deep NMB in elderly patients undergoing RALP. Clinical advantages were also assessed.

This trial was approved by the Ethics Committee of Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy (Study ID: 3764; date of approval 14 Jan 2021; chairperson Prof. Gigliola Sica) and registered at ClinicalTrials.gov (NCT04854993, principal investigator: PA; date of registration: 14 Apr 2021). Patients were enrolled between July 2021 and September 2022 if they were at least 65 years old and were scheduled for RALP. Exclusion criteria were inability to obtain written informed consent; significant liver, renal or pulmonary diseases; current smoking; chronic or acute alcoholism; known or suspected neuromuscular disorders; a family history of malignant hyperthermia; any pre-existing coagulopathy, abnormal blood coagulation tests or pre-operative anticoagulant therapies; BMI at least 30 kg m^{-2}; known allergy or hypersensitivity to the drugs used in the study (propofol, fentanyl, rocuronium bromide, sevoflurane, remifentanil, tramadol, ropivacaine, paracetamol, ketorolac, morphine, sugammadex); planned postoperative admission to ICU; or train-of-four (TOF) count of 1 to 3 at the end of surgery (moderate NMB).

After signed informed consent, patients were randomly assigned to one of the two following treatments to reverse deep NMB at the end of the surgery: 6 mg kg^{-1} sugammadex (Experimental: E group); 4 mg kg^{-1} sugammadex (Control: C group). The un-blinded staff of the hospital experimental pharmacy performed the randomisation and drug preparation. The randomisation was performed with concealed allocation using a computer-generated allocation sequence. The drug was prepared in a shielded prefilled syringe to maintain blindness. The anesthesiologists who administered the different drug doses and collected data were blinded to the group allocation.

The primary endpoint was neuromuscular recovery time: time from the end of sugammadex administration to normalised TOF ratio (TOFr) at least equal to 1 (complete reversal).[6]

Secondary endpoints were time from complete reversal to extubation, time from complete reversal to exit from the operating room, postanaesthesia care unit (PACU) length of stay, haemodynamic parameters and respiratory function (oxygen saturation and respiratory rate) after sugammadex administration.

Study procedures were standardised (Supplementary Text, http://links.lww.com/EJA/B140). Neuromuscular monitoring (TOF-watch-SX, MSD BV, Haarlem, The Netherlands) was applied by placing two electrodes along

the course of the ulnar nerve. The arm was positioned to ensure unencumbered thumb adduction and an elastic preload (Hand Adapter, Organon) was fixed to the distal portion of the thumb. TOF-watch-SX calibration was performed in unconscious patients before the administration of rocuronium. A TOFr measured at the end of calibration was regarded as a baseline value. The post-tetanic count (PTC) was assessed every 15 min during surgery, after rocuronium administration, to ensure deep NMB (PTC 1 to 2 twitches ≤ 2). At the end of surgery, patients randomly received 6 or 4 mg kg^{-1} sugammadex, after ascertaining the presence of a PTC 1 to 2. After sugammadex administration, a normalised TOFr of at least 1 was targeted using a TOF stimulation (four successive pulses of 0.2 ms duration, at a frequency of 2 Hz) and was accomplished by dividing the postoperative measurement by the baseline value.

Enrolment was set at 30 patients (34 to allow for any) considering a 30% decrease in the recovery time to be clinically relevant, from 177.6 s using 4 mg kg^{-1} sugammadex [4] to 124.3 s (6 mg kg^{-1} sugammadex), given a standard deviation of 42.8 s, to obtain a power of 0.90 with $\alpha = 0.05$ using two-tailed Student's *t*-test. Nonparametric Mann–Whitney and Chi-squared tests were used for continuous and categorical variables. Statistical analyses were performed using STATA software (version 14.0) (Stata Corp LLC, College Station, Texas, USA).

A total of 33 patients (16 in the C group and 17 in the E group) were included in the final analysis (Supplemental Figure I, http://links.lww.com/EJA/B141). Pre-operative characteristics are reported in the Supplemental Table (http://links.lww.com/EJA/B142). There were no statistically significant differences between the two groups in the recovery time from deep NMB, 384.0 (277.5 to 495.0) s (C group; $n = 16$) vs. 286.0 (210.0 to 420.0) s (E group; $n = 17$) (Fig. 1a, Table 1). Secondary end-points did not differ between groups (see Fig. 1b–d and Table 1). Likewise, the occurrence of nonserious (12.5% in C vs. 35.3% E group, $P = 0.13$) and serious adverse events (12.5 vs. 17.7%, $P = 0.68$) were similar in the two groups (Table 1).

Among SAEs, one patient from group C had a recurrence of paralysis and required an additional dose of sugammadex upon arrival in PACU. During the respiratory arrest, oxygenation was delivered via the laryngeal mask. The subsequent postoperative course was uneventful. Four cases of increased drain output during the postoperative ward stay without the need for transfusion were reported (two from the E group and two from the C group), with one patient from C group also showing asymptomatic COVID-19 infection. The most frequent nonserious adverse event was abdominal postoperative pain (four from E group and one from C group), followed by hyperpyrexia (one from E group and one from C group) and one case of self-resolving oral swelling in E group.

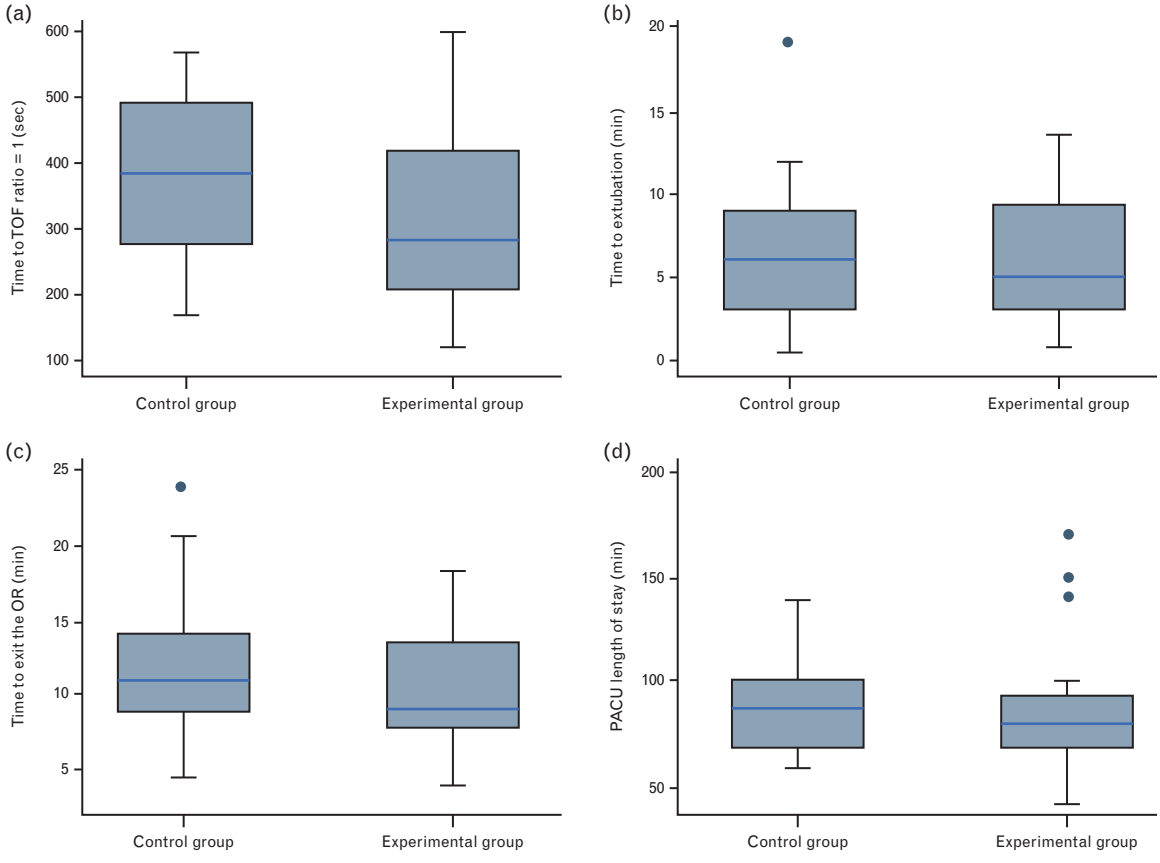
These findings suggest that increasing the dose of sugammadex by 50% does not meaningfully reduce the recovery time from the rocuronium-induced deep NMB in elderly patients undergoing RALP. Sugammadex is the only therapeutic option to reverse deep NMB and also provides the advantage of adjusting the dose based on neuromuscular monitoring to achieve the optimal effect.[6,7] Notably, we observed the recurrence of neuromuscular block in a patient from the experimental group. Therefore, even a higher dose of sugammadex does not

Table 1 Intra-operative and outcome data

	C Group, $n = 16$	E Group, $n = 17$	Z or Chi-square	*P*
Starting RcBr (mg)	76.0 [70.0 to 81.5]	78.0 [65.0 to 80.0]	-0.07	0.94
I.o. RcBr (mg)	49.0 [12.3 to 63.4]	29.2 [12.0 to 48.7]	0.50	0.61
Total RcBr (mg)	125.2 [94.6 to 134.5]	106.6 [92.0 to 139.6]	0.40	0.69
MAP[a] (mmHg)	94.0 [90.0 to 100.0]	92.0 [82.0 to 95.0]	1.30	0.19
SAP[a] (mmHg)	131.5 [120.0 to 140.5]	130.0 [120.0 to 140.0]	0.32	0.74
DAP[a] (mmHg)	77.0 [69.0 to 80.0]	74.0 [67.0 to 78.0]	1.01	0.31
HR[a]	71.5 [59.5 to 81.0]	73.0 [70.0 to 83.0]	-0.76	0.45
SpO_2[a] (%)	98.0 [97.0 to 99.0]	98.0 [97.0 to 99.0]	-0.26	0.79
RR[a]	14 [13 to 14]	14 [13 to 14]	0.66	0.51
Anaesthesia duration (min)	231.0 [207.0 to 281.0]	226.0 [195.0 to 260.0]	0.11	0.91
Surgery duration (min)	190.0 [168.5 to 229.0]	193.0 [146.0 to 205.0]	0.13	0.90
Neuromuscular recovery time (s)	384.0 [277.5 to 495.0]	286.0 [210.0 to 420.0]	1.17	0.24
Reversal (normalised TOFr)	1.05 [1.02 to 1.13]	1.03 [1.01 to 1.09]	1.31	0.19
Time from reversal to extubation (min)	6.1 [3.0 to 8.9]	5.0 [3.0 to 9.5]	0.50	0.61
Time from reversal to exit the OR (min)	11.0 [8.9 to 14.2]	9.0 [7.8 to 13.5]	0.88	0.37
PACU LoS (min)	89.0 [68.5 to 101.0]	80.0 [67.0 to 95.0]	0.31	0.76
PACU SpO_2 on arrival	96.0 [94.5 to 98.5]	97 [96.0 to 98.0]	-0.61	0.54
PACU SpO_2 at discharge	97.5 [96.0 to 98.0]	98 [98.0 to 99.0]	-1.73	0.08
Total AEs	4 [25.0]	9 [52.9]	2.69	0.10
Nonserious AEs	2 [12.5]	6 [35.3]	2.33	0.13
Serious AEs	2 [12.5]	3 [17.7]	0.17	0.68
Duration of hospitalisation (days)	3.0 [3.0 to 3.0]	3.0 [3.0 to 6.0]	-1.59	0.11

Data are presented as medians (IQR) or *n* (%). AEs, adverse events; DAP, diastolic arterial pressure; HR, heart rate; I.o., intra-operative; LoS, length of stay; MAP, mean arterial pressure; PACU: postanaesthesia care unit; RcBr, rocuronium bromide; RR, respiratory rate; SAP, systolic arterial pressure; SpO_2, oxygen saturation; TOFr, train-of-four ratio. [a] Haemodynamic and/or respiratory parameters after sugammadex administration (secondary outcomes).

Fig. 1 Box plots of time from the end of sugammadex administration to a normalised train-of-four ratio (TOFr) at least equal to 1 measured in seconds (a), time from neuromuscular reversal (TOFr = 1) to extubation measured in minutes (b), time from neuromuscular reversal (TOFr = 1) to exit from the operating room (OR) measured in minutes (c) and postoperative anaesthesia care unit (PACU) length of stay measured in minutes (d). The y-axis is numerical and primary outcome, whereas the x-axis is categorical and represents patients belonging to the two groups. The box is the interquartile range, which represents the 25th to the 75th percentile. The whiskers represent the lower and the higher adjacent values. The middle line in the box represents the median value.



completely abate the re-onset of the block. We hypothesised that the recurrence of paralysis, despite the use of neuromuscular monitoring and the administration of a high dose of sugammadex (6 mg kg^{-1}), could be linked to pharmacogenomic factors responsible for variability in rocuronium pharmacokinetics, dose requirement and efficacy.[8]

Regarding limitations, we found a median neuromuscular recovery time in the experimental group about 25% shorter than the control group. However, the variability was much larger than expected, so the power was too low to show a statistically significant difference between groups. This large variability may reflect the slower reversal of rocuronium-induced NMB by sugammadex in some elderly patients.[3,4] In line with this hypothesis, a recent study demonstrated that when given in TOF-driven mode, the sugammadex administered dose is usually lower than the recommended one.[9]

In our study, the recovery time from the neuromuscular block obtained with a similar dose of sugammadex was almost trebled compared to that reported by previous authors [5] (about 6 vs. 2 min), probably due to the different methodology used. In the cited study,[5] adequate neuromuscular reversal was defined as a TOFr equal to 0.9. In contrast, in our current study, complete reversal was defined as a TOFr at least equal to 1 using normalised acceleromyography.[3] A TOFr = 0.9 measured by mechanography of the adductor thumb muscle is frequently considered an adequate reversal value.[10] However, a TOFr more than 0.9 may guarantee a more adequate reversal of NMB, as acceleromyography shows higher TOFr values of about 10% compared to mechanomyography.[6,10]

In conclusion, if the administered dose of sugammadex is adequate, further increasing the dose will not accelerate the extubation time.

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VISUAL ABSTRACT