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REPORTS OF ORIGINAL INVESTIGATIONS

Effects of neuromuscular block reversal with sugammadex *versus* neostigmine on postoperative respiratory outcomes after major abdominal surgery: a randomized-controlled trial

Effets du renversement du bloc neuromusculaire à l'aide de sugammadex *vs* de la néostigmine sur l'évolution respiratoire postopératoire après une chirurgie abdominale majeure: une étude randomisée contrôlée

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Abstract

Purpose *Postoperative pulmonary complications may be better reduced by reversal of neuromuscular block with sugammadex than by reversal with neostigmine because the incidence of residual block after sugammadex application is lower and diaphragm function is less impaired than after neostigmine administration. The aim of the study was to compare the effect of reversal of neuromuscular block with sugammadex or neostigmine on lung function after major abdominal surgery.*

Methods *One hundred and thirty adults scheduled for major abdominal surgery under combined general and epidural anesthesia were randomly allocated to receive 40 μg of neostigmine or 4 mg·kg^{-1} of sugammadex to reverse neuromuscular block. Two blinded researchers performed spirometry and lung ultrasound before the surgery, as well as 1 hr and 24 hr postoperatively. Differences in mean changes from baseline were analyzed with repeated measures analysis of variance. Forced vital capacity (FVC) loss one hour after surgery was the main outcome. Secondary outcomes were differences in rate and size of atelectasis one hour and 24 hr after surgery.*

Results *One hundred twenty-six patients were included in the main analysis. In the neostigmine group (n = 64), mean (95% confidence interval [95% CI]) reduction in FVC after one hour was 0.5 (0.4 to 0.6) L. In the sugammadex group (n = 62), the mean (95% CI) reduction in FVC during the first hour was 0.5 (95% CI, 0.3 to 0.6) L. Thirty-nine percent of patients in the neostigmine group and 29% in the sugammadex group had visible atelectasis. Median [interquartile range (IQR)] atelectasis area was 9.7 [4.7–13.1] cm^2 and 6.8 [3.6–12.5] cm^2, respectively.*

Conclusion *We found no differences in pulmonary function in patients reversed with sugammadex or neostigmine in a high-risk population.*

Trial registration *EudraCT 2014-005156-26; registered 27 May, 2015.*

Résumé

Objectif *Les complications pulmonaires postopératoires pourraient être mieux contrôlées en neutralisant le bloc neuromusculaire avec du sugammadex plutôt qu'avec de la néostigmine; en effet, l'incidence de bloc résiduel après l'administration de sugammadex est plus faible et la fonction du diaphragme moins affectée qu'après l'administration de néostigmine. L'objectif de cette étude était de comparer l'effet d'une neutralisation du bloc neuromusculaire réalisée à l'aide de sugammadex vs de la néostigmine sur la fonction pulmonaire après une chirurgie abdominale majeure.*

Méthode *Cent trente adultes devant subir une chirurgie abdominale majeure sous anesthésie générale et péridurale combinée ont été randomisés à recevoir 40 μg de néostigmine ou 4 mg·kg^1 de sugammadex afin de neutraliser le bloc neuromusculaire. Deux chercheurs en*

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aveugle ont réalisé une spirométrie et une échographie pulmonaire avant la chirurgie, ainsi que 1 h et 24 h après l'opération. Les différences de changements moyens par rapport aux mesures de départ ont été analysées à l'aide de mesures répétées d'analyse de la variance. La perte de capacité vitale forcée (CVF) une heure après la chirurgie était notre critère d'évaluation principal. Les critères secondaires comprenaient les différences des taux et de taille de l'atélectasie une heure et 24 h après la chirurgie.

Résultats *Cent vingt-six patients ont été inclus dans l'analyse principale. Dans le groupe néostigmine (n = 64), la réduction moyenne (intervalle de confiance 95 % [IC 95 %]) de CVF après une heure était de 0,5 (0,4 à 0,6) L. Dans le groupe sugammadex (n = 62), la réduction moyenne (IC 95 %) de CVF au cours de la première heure était de 0,5 (IC 95 %, 0,3 à 0,6) L. On a observé une atélectasie visible chez 39 % des patients du groupe néostigmine et 29 % des patients du groupe sugammadex. La surface médiane [écart interquartile (EIQ)] d'atélectasie était de 9,7 [4,7–13,1] cm^2 et 6,8 [3,6–12,5] cm^2, respectivement.*

Conclusion *Nous n'avons découvert aucune différence en ce qui touche à la fonction pulmonaire chez les patients neutralisés au sugammadex ou à la néostigmine dans une population à risque élevé.*

Enregistrement de l'étude *EudraCT 2014-005156-26; enregistrée le 27 mai 2015.*

Respiratory muscle weakness and atelectasis secondary to abdominal surgery are major factors contributing to the development of postoperative pulmonary complications (PPCs).[1] Residual neuromuscular block may increase the risk of PPCs.[2-4] Reversal with sugammadex is associated with a lower incidence of residual paralysis at postanesthesia care unit (PACU) admission than reversal with neostigmine.[5] Moreover, recent studies suggest that electromyographic activity of the diaphragm may be impaired after the use of neostigmine compared with sugammadex.[6]

Our hypothesis was that reversal of neuromuscular block with sugammadex would result in less postoperative pulmonary dysfunction than reversal with neostigmine. The primary objective of this study was to compare the change in forced vital capacity (FVC) one hour after reversal with neostigmine or sugammadex among patients undergoing major abdominal surgery. A secondary objective was to compare area of atelectasis size as assessed by planimetry in postoperative lung ultrasound images.

Methods

We carried out a randomized-controlled trial at Hospital Universitario La Princesa, a tertiary care university hospital in Madrid, Spain. The study was approved by the Human Research Ethics Committee (Chairperson Prof. Francisco Abad) on 19 November, 2014 and registered in the EU clinical trials register (EudraCT: 2014-005156-26). The trial was conducted from July 2015 to July 2016.

All patients scheduled for major abdominal surgery (liver resection, pancreatectomy, gastrectomy, or any type of colectomy) were included. Use of postoperative epidural analgesia was also an inclusion criterion. Exclusion criteria included: refusal to participate, admission to postoperative recovery unit under mechanical ventilation, hypersensitivity to any of the drugs, severe asthma or mild asthma under treatment, myocardial infarction or coronary occlusion three months prior to surgery, myasthenia gravis, emergency surgery, pulmonary fibrosis, or very severe chronic obstructive lung disease (GOLD IV). Informed consent was obtained by the residents on duty, the night before surgery.

Study interventions

Before entering the operating room, basal spirometry (KoKo® Legend, nSpire™) and lung ultrasound (LUS) (Sonosite M Turbo with a P21x Phased Array Probe, Sonosite, Bothell, WA, USA) were performed by an independent researcher. Spirometry was performed following international recommendations[7] but with patients in a semi recumbent position (40°) as recommended for postoperative position. Forced vital capacity, forced expiratory volume in the first second (FEV_1), and forced expiratory flow 25–75% were measured. Changes in lung aeration were studied by LUS with the patients in the same position. Sagittal sections were performed at three areas in each lung: ventral, medial, and posterior, corresponding to three predefined locations (parasternal, medial axillary line, posterior axillary line).[8] One to two complete respiratory cycles were recorded in each location for offline analysis. Collapsed areas were defined by sonography as the presence of a condensation "tissue-like" (hepatization) ultrasound pattern. For the offline analysis, a single frame corresponding to end expiration was selected from the video file. Brightness was adjusted setting the brightest level in the bony surface of ribs and the brightness level in the acoustic shadow behind ribs. After this adjustment, the scale in cm^2 was set according to image resolution in pixels. Collapsed areas were then outlined and measured by planimetry. The sum of the six explored lung areas was considered the total collapsed area for the study. We used the software ImageJ

(ImageJ, U. S. National Institutes of Health, Bethesda, MD, USA) for LUS image analysis.[9]

Combined epidural and general anesthesia were carried out by anesthesiologists as routine clinical practice. Neuromuscular block was performed with rocuronium and monitored by train-of-four (TOF) kinetomyography with Datex-Ohmeda MechanoSensor™. Anesthesiologists were free to maintain TOF level according to usual criteria. After the surgical resection was completed, patients were randomly assigned to receive either sugammadex 4 $mg \cdot kg^{-1}$ or neostigmine 40 $\mu g \cdot kg^{-1}$ in combination with atropine 10 $\mu g \cdot kg^{-1}$ using sealed opaque envelopes. An extra dose of reversal was permitted by protocol, when needed, at the discretion of the attending anesthesiologist. Unrestricted blocked randomization was previously carried out by an independent contract research organization with the program M.A.S (sampling and scheduled randomizations) Glaxo SmithKline version 2.1.

Reversal medications were unblinded to the anesthesiologist in the operating room but blinded for the patient and the researcher testing pulmonary function. Separated case report forms and databases were used for clinical and pulmonary data.

One hour after the patient was extubated, new spirometry and lung ultrasound explorations were performed in the postoperative recovery room with the same procedure and position used in the preoperative determinations. Postoperative clinical management was conducted according to clinical preferences. The day after surgery, prior to ward discharge from the postoperative recovery unit, or 24 hr after extubation, additional pulmonary tests were performed.

Outcomes and data collection

Clinical data

Patient variables including age, height, weight, American Society of Anesthesiologists score, history of chronic obstructive pulmonary disease, congestive heart failure, basal peripheral capillary oxygen saturation (SpO_2), smoking, weight loss $> 10\%$, functional class, and respiratory infection in the last month were collected at baseline.

Surgical variables such as duration of surgery (skin-to-skin), open *vs* laparoscopic approach, type of surgery, and anesthetic variables including tidal volume, positive end-expiratory pressure (PEEP), fraction of inspired oxygen (F_iO_2), need for alveolar recruitment (under anesthesiologist criteria), epidural analgesia, and amount of fluids administered were recorded during surgery.

Characteristics of the neuromuscular block including neuromuscular blocking drug, depth of block prior to reversal, reversal drug used, and last TOF percentage registered immediately before awakening were noted. Oxygenation was assessed by the pO_2/F_iO_2 ratio at the first hour after surgery and before discharge while SpO_2 with ambient air was documented after spirometry. Hospital length of stay, Clavien–Dindo classification for postoperative complications, pneumonia, need for mechanical ventilation (invasive or non-invasive), and death were documented.

Variables confounding assessment of FVC such as body mass index, ARISCAT scale for postoperative risk of pulmonary complications, basal FVC and FEV_1, residual neuromuscular block, and postoperative pain visual analogue scale (VAS) before and after spirometry were recorded.

Outcomes

Difference in reduction of FVC in the first hour between groups was the primary outcome. Other spirometry values were analyzed one hour and 24 hr after surgery. Lung atelectasis size was measured by planimetry on ultrasound images as a secondary outcome. Differences in the incidence of hypoxemia (defined as $SpO_2 \leq 92\%$ with F_iO_2 21% after spirometry, or partial pressure of oxygen $[pO_2]/F_iO_2 < 300$ with an F_iO_2 28–31%) were also included in the secondary analysis. Incidence of nausea and vomiting in both groups was included as an exploratory analysis.

Statistical analysis

Sample size

In a previous unpublished study developed in our institution (2013) we found a mean loss of 18.1% and a standard deviation of 14.2% for the difference between basal FVC and FVC 30 min after surgery. We could not find data of previous studies in these settings reporting the clinical relevance of changes in FVC. For these reasons we estimated this relevance based on studies which analyzed changes in FVC and FEV_1 after treatment with bronchodilators.[10,11] According to these studies, we considered as relevant a difference of 7% between groups. For a power of 80% with an α level (probability of a type I error) of 5%, the sample size needed was 64 patients per group.

Variable analysis

Continuous variables were described by their measures of central tendency (mean or median) and dispersion (standard deviation or interquartile range).

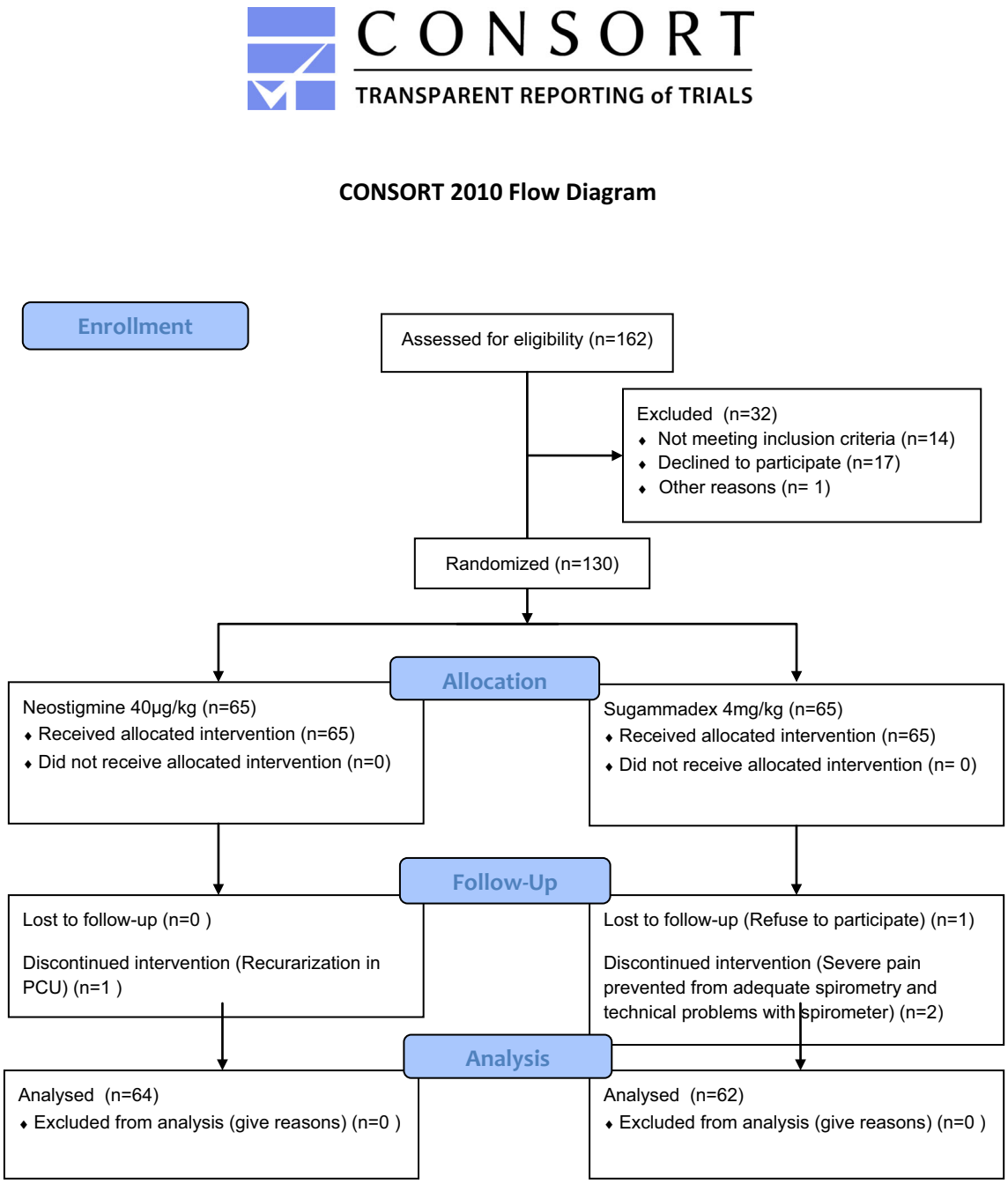

Fig. 1 Consort statement

Homoscedasticity was tested with Levene's test and normality with Shapiro–Wilk test. Differences in confounding factors between groups were analyzed with t-test in case of quantitative variables and χ^2 test for categorical variables. Corresponding non-parametric tests were used when needed. Differences in mean changes from baseline were analyzed with repeated measures analysis of variance (ANOVA) with treatment as a principal factor. Bonferroni post hoc test was used when $P \leq 0.05$ in ANOVA. If significant deviations from normality or the assumption of homoscedasticity were observed, a nonparametric test was used.

Results

One hundred and thirty patients were randomized 1:1 to receive either neostigmine 40 $\mu g \cdot kg^{-1}$ + atropine 10 $\mu g \cdot kg^{-1}$ or sugammadex 4 $mg \cdot kg^{-1}$. One patient was excluded from analysis in the neostigmine group because

Table 1 Characteristics of participants

	Neostigmine ($n = 64$)	Sugammadex ($n = 62$)
Age (yr), mean (SD)	69.9 (13.0)	65.9 (12.0)
BMI ($kg \cdot cm^{-2}$), mean (SD)	26.05 (4.9)	26.2 (4.8)
Gender, men *n* (%)	32 (50%)	32 (52%)
ASA		
I	0 (0)	4 (6)
II	38 (59)	35 (56)
III	25 (39)	21 (34)
IV	1 (2)	2 (3)
History of COPD, *n* (%)	4 (6)	4 (6)
ARISCAT scale		
Low	24 (37)	25 (40)
Medium	28 (44)	26 (42)
High	12 (19)	11 (18)
Basal spirometry		
FVC (L), mean (SD)	3.0 (1.0)	3.0 (1.0)
(% predicted), mean (SD)	80.7 (19.9)	75.1 (18.3)
FEV_1 (L), mean (SD)	2.2 (0.8)	2.4 (0.9)
(% predicted), mean (SD)	80.9 (20.8)	79.8 (19.7)
FEV_1/FVC (%), mean (SD)	74 (8)	79 (14)

ARISCAT = Canet´s preoperative pulmonary risk index; ASA = American Society of Anesthesiologists physical status classification; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in first second; FVC = forced vital capacity; SD = standard deviation

of probable recurarization. This patient had one count in the TOF at reversal and four counts with a TOF ratio of 96% immediately after extubation. Twenty minutes after arrival to PACU he suffered dyspnea, severe hypoxemia, and muscular weakness, which was treated with 200 mg of sugammadex without monitoring muscular status. He was excluded from analysis because of protocol violation. In the sugammadex group one patient refused to participate before the one-hour spirometry, another patient could not have an adequate spirometry because of postoperative pain, and in one patient spirometry was not performed on time because of spirometer failure. Figure 1 shows the study flow chart.

Baseline and clinical characteristics

Demographic and clinical baseline characteristics were similar in both groups (Table 1). Surgical and anesthetic management are described in Table 2. At the moment of neuromuscular block reversal, the proportion of patients with deep neuromuscular block (TOF count equal to 0) was three of 64 (5%) in the neostigmine group compared with 13 of 62 (21%) in the sugammadex group ($P = 0.007$). Nevertheless, only 19 of 62 (31%) of those reversed with sugammadex had TOF < 90% measured immediately after extubation compared with 45 of 64 (71%) of those in the neostigmine group ($P < 0.001$).

Spirometry outcomes

Values of FVC at baseline, one, and 24 hr following surgery, expressed in litres, are shown in Table 3. The decrease in FVC one hour after surgery, expressed as a percent of baseline, was 16% (95% CI, 12 to 20) in the neostigmine group and 13% (95% CI, 9 to 18) in the sugammadex group ($P = 0.40$). The day after surgery, decreases in FVC, expressed as a percent of baseline, were 24 (95% CI, 20 to 29)% and 24 (95% CI, 20 to 29)%, respectively ($P = 0.94$). Therefore, decreases in FVC one hour and one day after surgery were similar in both groups. FEV_1 values in litres (not shown) decreased proportionally to FVC; relative differences were 15% one hour (95% CI, 11 to 18) and 25% (95% CI, 21 to 29) one day after surgery. Again, there were no differences were between groups.

Atelectasis on lung ultrasound

Examples of ultrasound technique and measurements are shown in Figs 2-4. Three patients were excluded from the

Table 2 Surgical and anesthetic management

	Neostigmine (n=64)	Sugammadex (n=62)
Surgery procedure, *n* (%)		
Gastric/small bowel, *n* (%)	7 (11)	6 (10)
Liver resection, *n* (%)	7 (11)	8 (13)
Pancreatic resection, *n* (%)	6 (9)	4 (6)
Colorectal, *n* (%)	41 (64)	39 (63)
Others, *n* (%)	3 (5)	5 (8)
Surgical approach		
Laparoscopic, *n* (%)	39 (61)	30 (48)
Open surgery, *n* (%)	25 (39)	32 (52)
Anesthetic management		
Vt mL·kg^{-1}, mean (SD)	8.1 (1.1)	8.1 (1.2)
PEEP, mean (SD)	7.7 (5.6)	7.7 (2.5)
F_iO_2 (mmHg), mean (SD)	0.5 (0.7)	0.5 (0.9)
Alveolar recruitment, *n* (%)	15 (23.4)	27 (43.6)
Rocuronium dose (mg), mean (SD)	113 (41)	126 (39)
Reversal drug dose (μg·kg^{-1} or mg·kg^{-1}), mean (SD)	39. (2.7)	4.0 (0.4)
Intraoperative balance (mL·kg^{-1}·hr^{-1}), mean (SD)	5.9 (4.2)	5.2 (2.8)
Surgery duration (min), median [IQR]	192.5 [155–240]	210 [165–280]
TOF=0 before reversal, *n* (%)	3 (5) *	13 (21) *
Residual NMB (TOF < 90%), *n* (%)	45 (71) **	19 (31) **
Residual NMB (TOF < 70%), *n* (%)	11 (17)	4 (6)

F_iO_2 = fraction of inspired oxygen; Intraoperative balance = (crystalloids (mL) + colloids (mL) + hemoderivatives (mL) − urine output (mL) − bleeding (mL))/(surgery duration (hr)) × (weight (kg)); IQR = interquartile range; NMB = neuromuscular block defined immediately after extubating; PEEP = positive end expiratory pressure, TOF = train-of-four; Vt = tidal volume adjusted to ideal weight. *P value = 0.007; **P value < 0.001

Table 3 Forced vital capacity at baseline, and one hour and 24 hr following surgery

	Neostigmine n = 64	Sugammadex n = 62
Basal FVC	3.0 (0.1)	3.0 (0.1)
1st hour FVC	2.5 (0.1)	2.6 (0.1)
Difference 1st hour *vs* basal**	0.5 (0.6)*	0.4 (0.6)*
	(0.4 to 0.6)	(0.3 to 0.6)
24 hr FVC	2.2 (0.1)	2.2 (0.1)
Difference 24 hr *vs* basal**	0.8 (0.6)*	0.8 (0.6)*
	(0.6 to 0.9)	(0.6 to 0.9)

Data expressed in liters. Mean (SD) . 95% CI = 95% confidence interval; FVC = forced vital capacity, l. SD = standard deviation. *P value (time factor) ≤ 0.001. **P value (treatment factor) > 0.20

lung ultrasound analysis after one hour in the neostigmine group because of basal abnormalities (consolidation or pleural effusion). Forty-two patients had visible new consolidations in the first hour (Table 4). Twenty-four of them (39%) were in the neostigmine group and 18 (30%) were in the sugammadex group. Median atelectasis size was 9.7 cm^2 in those patients who received neostigmine and 6.7 cm^2 when sugammadex was employed for neuromuscular block reversal (Table 4).

The number of patients with lung consolidations at the first day after surgery increased to 43 (74%) in the neostigmine group and to 39 (66%) in the sugammadex group. Median atelectasis size was 17.0 cm^2 and 13.6 cm^2, respectively. No statistically significant differences were found during the early postoperative period.

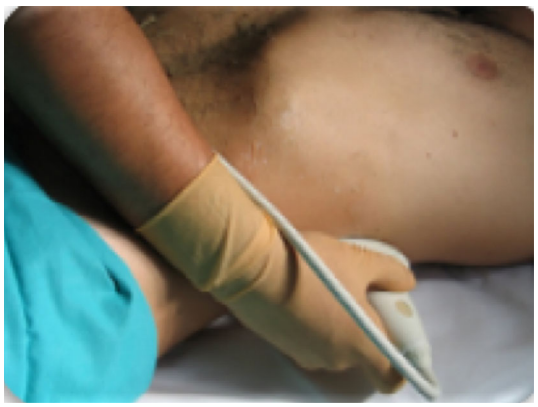

Fig. 2 Probe located in last intercostal space, posterior axillary line in a sagittal orientation

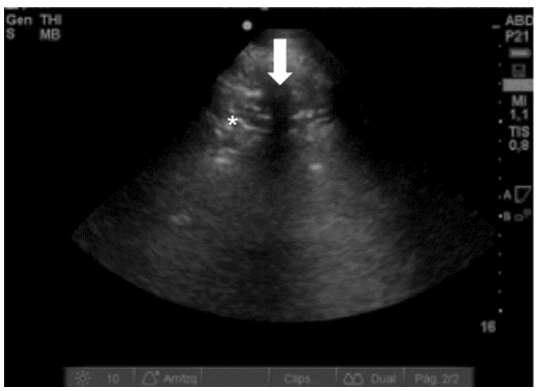

Fig. 3 Arrow = border of the rib with acoustic shadowing beneath it. Asterisk = lung consolidation

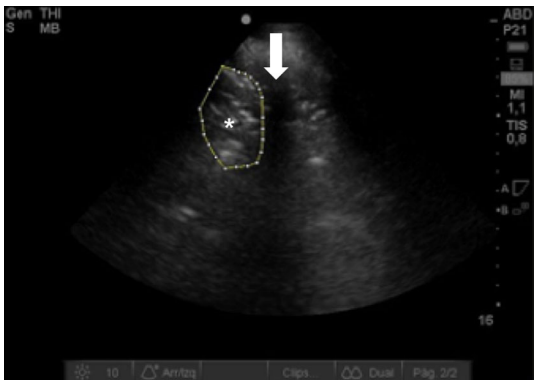

Fig. 4 Arrow = border of the rib with acoustic shadowing beneath it. Asterisk = lung consolidation. Consolidation area is outline using manual tracing tools in ImageJ software. Area is calculated after adjusting scale with the same software

Postoperative complications

Incidence of postoperative hypoxemia ($SpO_2 \leq 92$), measured without oxygen after a spontaneous recruitment maneuver (spirometry) or with oxygen when pO_2/F_IO_2 rate was lower than 300, was similar in both groups (Table 5). The day after surgery, one (1%) patient in the neostigmine group and 10 (16%) patients in the sugammadex group had a SpO_2 with ambient air after spirometry of less than 92%. There were no differences between groups in respiratory complications, other postoperative complications, need for mechanical ventilation, or death (Table 5).

Discussion

We found no differences in postoperative spirometry at one and 24 hr after surgery in patients who received sugammadex or neostigmine to reverse neuromuscular block. FVC decreased by approximately 15% compared with baseline one hour postoperatively in both study groups, an amount lower than expected for upper abdominal surgery.[4,12,13] Previous data describing FVC loss after surgery are heterogeneous and were published many years ago. After upper abdominal surgery, a loss of at least 30% of FVC is expected.[14] We believe that good postoperative analgesia and patient cooperation was responsible for the reported preservation of FVC.[15]

Atelectasis may occur in up to 90% of anesthetized patients[16] and is suspected when oxygenation is impaired after surgery. The rate of postoperative atelectasis, especially one hour after general anesthesia is not well documented. In our population, incidence of atelectasis measured by LUS one hour after surgery was lower than expected. Intraoperative low tidal volume (Vt) ventilation with PEEP may reduce the incidence of atelectasis and pulmonary complications.[17-19] In our patients, the mean Vt was 8 $mL \cdot kg^{-1}$ ideal body weight with very low dispersion and PEEP above 4 cmH_2O was applied in every patient. Lung ultrasound is a novel and accurate technique for postoperative lung collapse diagnosis,[20] but may be less sensitive than computed tomography.

Although there is not a unanimous definition for PPCs, clinically relevant pulmonary complications after elective major abdominal surgery are uncommon.[1] Such was the case in our study with only four patients requiring mechanical ventilation and two developing pneumonia. Our study focused on process markers like changes in FVC and atelectasis that might be a starting point for clinically relevant pulmonary complications. Surprisingly, both FVC loss and incidence and size of atelectasis were higher the day after surgery. Protective mechanical ventilation may have influenced the benefit found in the first hour. Lack of early mobilization, positive fluid balance, or inconsistent chest physiotherapy may have increased atelectasis as time passed.[21] It is unlikely to be related to the agent used for neuromuscular block reversal.

Table 4 Atelectasis on lung ultrasound

	Neostigmine	Sugammadex
1st hour atelectasis rate (%)*	24/61 (39)	18/61 (30)
24 hr atelectasis rate (%)*	42/58 (74)	39/59 (66)
1st hour atelectasis size (cm^2) Median [IQR]*	9.7	6.8
	[4.7–13.0]	[3.6–12.5]
24 hr atelectasis size (cm^2) Median [IQR]*	16.98	13.54
	[8.3–24.3]	[6.7–25.5]

IQR = interquartile range. Atelectasis size: data from patients with atelectasis

*P value (treatment factor) > 0.25

Table 5 Postoperative events

	Neostigmine (n=64)	Sugammadex (n=62)
PO hypoxemia ($SpO_2 \leq 92\%$; F_iO_2 0.21)		
1st hour, n (%)	14 (21)	17 (27)
24 hr, n (%)	1 (1) *	10 (16) *
PO hypoxemia ($pO_2/F_iO_2 < 300$)		
1 hr, n (%)	8 (12)	7 (11)
24 hr, n (%)	3 (4)	8 (12)
Assisted ventilation		
Use of NIV, n (%)	0 (0)	2 (3)
Use of postoperative MV, n (%)	2 (3)	2 (3)
Pneumonia, n (%)	1 (1)	1 (1)
Postoperative analgesia		
VAS 1st hour median [IQR]	0 [0–3]	0 [0–3]
VAS 24 hr median [IQR]	0 [0–2]	1 [0–3]
Surgical complications[a]		
Type I, n (%)	8 (12)	8 (13)
Type II, n (%)	12 (19)	8 (13)
Type IIIa, n (%)	5 (8)	4 (6)
Type IIIb, n (%)	0 (0)	2 (3)
Type Iva, n (%)	1 (2)	5 (8)
Type IVb, n (%)	4 (6)	3 (5)
Type V (death), n (%)	1 (2)	1 (2)
Length of stay (days), mean (SD)	11.4 (8.4)	12.9 (10.6)

a = Clavien–Dindo classification; F_iO_2 = fraction of inspired oxygen; IQR = interquartile range; MV = mechanical ventilation; NIV = noninvasive ventilation; PO = postoperative; pO_2 = partial pressure of oxygen; VAS = visual analogue scale. *P = 0.013

Residual neuromuscular paralysis is a frequent complication of general anesthesia with an incidence of up to 30%[3,22] reported in the literature. Our study, despite the open use of quantitative neuromuscular monitoring, was no different. Despite protocolized monitoring of neuromuscular block, and the possibility of using rescue doses of neostigmine, none of the clinical researchers used more than 40 $\mu g \cdot kg^{-1}$. More than two thirds of patients in the neostigmine group and nearly one third of those in the sugammadex group had a TOF ratio $\leq$ 90% immediately after extubation. Although we determined TOF ratio immediately after extubation instead of in the PACU, as commonly done,[23] the proportion of patients with an inadequate reversal was high. Previous research showed an association between residual neuromuscular block and PPCs.[3] Our study was not designed to evaluate this association.

A recently published multicentre prospective observational study including 22,803 patients did not show any advantage of sugammadex over neostigmine with respect to preventing pulmonary complications.[24] Moreover, extubation with a TOF ratio > 90% was not associated with a lower risk of postoperative respiratory complications. Authors concluded that using neuromuscular agents during anesthesia is associated with an increased risk of postoperative pulmonary complications irrespective of dose. Diaphragm impairment after surgery, immobilization, and inflammatory response may have a more relevant influence in postoperative pulmonary outcomes than reversal agents.

There are limitations to our study. Use of recruitment maneuvers was not controlled and 27 (44%) patients in the sugammadex group received this intervention during surgery compared with 15 (23%) in the neostigmine group. The PROVHILO trial did not show differences in pulmonary outcomes when a recruitment maneuver followed by a PEEP of 12 cmH_2O was performed.[25] The iPROVE trial also failed to prove better oxygenation three hours after surgery or a lower rate of atelectasis during the first day with an intraoperative open lung strategy with individual PEEP assessment.[26] We believe this had little impact on our results. Secondly, anesthesiologists in the operation room were not blinded to the study drug and managed neuromuscular block under their own criteria. This could have biased results because of different rocuronium dose regimens. Total rocuronium dose was

10% higher in the sugammadex group but time of surgery was also slightly higher for these patients. The rate of TOF = 0 before reversal was significantly higher in the sugammadex group. We did not record post tetanic count before reversal when TOF = 0. These patients might have been at risk of symptomatic residual neuromuscular block but with respect to our findings and the main point of our results, none of these factors influenced postoperative lung function one hour after surgery.

In conclusion, we found no differences in spirometry after reversal with sugammadex or neostigmine in a high-risk population with intraoperative lung-protective ventilation, neuromuscular block monitoring, and epidural analgesia. No difference in the incidence of atelectasis, area of atelectasis, or pulmonary complications was noted. The benefit of sugammadex might be related to the reduction of infrequent critical respiratory events during the immediate postoperative period due to severe residual neuromuscular block.

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References

1. *Ball L*, *Battaglini D*, *Pelosi P*. Postoperative respiratory disorders. Curr Opin Crit Care 2016; 22: 379-85.
2. *Fuchs-Buder T*, *Nemes R*, *Schmartz D*. Residual neuromuscular blockade: management and impact on postoperative pulmonary outcome. Curr Opin Anaesthesiol 2016; 29: 662-7.
3. *Martinez-Ubieto J*, *Ortega-Lucea S*, *Pascual-Bellosta A*, *et al*. Prospective study of residual neuromuscular block and postoperative respiratory complications in patients reversed with neostigmine versus sugammadex. Minerva Anestesiol 2016; 82: 735-42.
4. *Kumar GV*, *Nair AP*, *Murthy HS*, *Jalaja KR*, *Ramachandra K*, *Parameshwara G*. Residual neuromuscular blockade affects postoperative pulmonary function. Anesthesiology 2012; 117: 1234-44.
5. *Brueckmann B*, *Sasaki N*, *Grobara P*, *et al*. Effects of sugammadex on incidence of postoperative residual neuromuscular blockade: a randomized, controlled study. Br J Anaesth 2015; 115: 743-51.
6. *Cammu G*, *Schepens T*, *De Neve N*, *Wildemeersch D*, *Foubert L*, *Jorens PG*. Diaphragmatic and intercostal electromyographic activity during neostigmine, sugammadex and neostigmine-sugammadex-enhanced recovery after neuromuscular blockade: a randomised controlled volunteer study. Eur J Anaesthesiol 2016; 33: 8-15.
7. *Anonymous*. Standardization of spirometry, 1994 update. American Thoracic Society. Am J Respir Crit Care Med 1995; 152: 1107-36.
8. *Lichtenstein DA*. Lung ultrasound in the critically ill. Ann Intensive Care 2014; 4: 1.
9. *Rueden CT, Eliceiri KW*. Visualization approaches for multidimensional biological image data. Biotechniques 2007; 43(1 Suppl): 31, 33-6.
10. *Rennard S*, *Fogarty C*, *Reisner C*, *et al*. Randomized study of the safety, pharmacokinetics, and bronchodilatory efficacy of a proprietary glycopyrronium metered-dose inhaler in study patients with chronic obstructive pulmonary disease. BMC Pulm Med 2014; 14: 118.
11. *Beeh KM*, *Moroni-Zentgraf P*, *Ablinger O*, *et al*. Tiotropium Respimat® in asthma: a double-blind, randomised, dose-ranging study in adult patients with moderate asthma. Respir Res 2014; 15: 61.
12. *Treschan TA*, *Kaisers W*, *Schaefer MS*, *et al*. Ventilation with low tidal volumes during upper abdominal surgery does not improve postoperative lung function. Br J Anaesth 2012; 109: 263-71.
13. *Joris J*, *Kaba A*, *Lamy M*. Postoperative spirometry after laparoscopy for lower abdominal or upper abdominal surgical procedures. Br J Anaesth 1997; 79: 422-6.
14. *Treschan TA*, *Schaefer M*, *Kemper J*, *et al*. Ventilation with high versus low peep levels during general anaesthesia for open abdominal surgery does not affect postoperative spirometry: a randomised clinical trial. Eur J Anaesthesiol 2017; 34: 534-43.
15. *Kimball WR*, *Carwood CM*, *Chang Y*, *McKenna JM*, *Peters LE*, *Ballantyne JC*. Effect of effort pain after upper abdominal surgery on two independent measures of respiratory function. J Clin Anesth 2008; 20: 200-5.
16. *Duggan M*, *Kavanagh BP*. Atelectasis in the perioperative patient. Curr Opin Anaesthesiol 2007; 20: 37-42.
17. *Severgnini P*, *Selmo G*, *Lanza C*, *et al*. Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function. Anesthesiology 2013; 118: 1307-21.
18. *Yang D*, *Grant MC*, *Stone A*, *Wu CL*, *Wick EC*. A meta-analysis of intraoperative ventilation strategies to prevent pulmonary

complications: is low tidal volume alone sufficient to protect healthy lungs? Ann Surg 2016; 263: 881-7.
19. *Guay J, Ochroch EA*. Intraoperative use of low volume ventilation to decrease postoperative mortality, mechanical ventilation, lengths of stay and lung injury in patients without acute lung injury. Cochrane Database Syst Rev 2015; 12: CD011151.
20. *Acosta CM*, *Maidana GA*, *Jacovitti D*, *et al*. Accuracy of transthoracic lung ultrasound for diagnosing anesthesia-induced atelectasis in children. Anesthesiology 2014; 120: 1370-9.
21. *Greco M*, *Capretti G*, *Beretta L*, *Gemma M*, *Pecorelli N*, *Braga M*. Enhanced recovery program in colorectal surgery: a meta-analysis of randomized controlled trials. World J Surg 2014; 6: 1531-41.
22. *Murphy GS*, *Szokol JW*, *Marymont JH*, *Greenberg SB*, *Avram MJ*, *Vender JS*. Residual neuromuscular blockade and critical respiratory events in the postanesthesia care unit. Anesth Analg 2008; 107: 130-7.
23. *Abrishami A, Ho J, Wong J, Yin L, Chung F*. Sugammadex, a selective reversal medication for preventing postoperative residual neuromuscular blockade. Cochrane Database Syst Rev 2009; 4: CD007362.
24. *Kirmeier E*, *Eriksson LI*, *Lewald H*, *et al*. Post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR): a multicentre, prospective observational study. Lancet Respir Med 2019; 7: 129-40.
25. *PROVE Network Investigators, for the Clinical Network of the European Society of Anaesthesiology; Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJ*. High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. Lancet 2014; 384: 495-503.
26. *Ferrando C*, *Soro M*, *Unzueta C*, *et al*. Individualised perioperative open-lung approach versus standard protective ventilation in abdominal Surgery (iPROVE): a randomised controlled trial. Lancet Respir Med 2018; 6: 193-203.