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Original Contribution

Operating room discharge after deep neuromuscular block reversed with sugammadex compared with shallow block reversed with neostigmine: a randomized controlled trial☆

Laurie Putz MD[a,*], Christophe Dransart MD[a], Jacques Jamart MD, MSc (Associate Professor)[b], Maria-Laura Marotta MD[c], Geraldine Delnooz MD[a], Philippe E. Dubois MD (Associate Professor)[a]

[a] *Anesthesiology Department, Université Catholique de Louvain, CHU UCL Namur, 1, Avenue Gaston Thérasse, B-5530 Yvoir, Belgium*
[b] *Scientific Support Unit, Université Catholique de Louvain, CHU UCL Namur, 1, Avenue Gaston Thérasse, B-5530 Yvoir, Belgium*
[c] *Gynecology Department, Université Catholique de Louvain, CHU UCL Namur, 1, Avenue Gaston Thérasse, B-5530 Yvoir, Belgium*

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Abstract
Objective: To determine if reversing a deep or moderate block with sugammadex, compared with a shallow block reversed with neostigmine, reduces the time to operating room discharge after surgery and the time spent in the postanesthesia care unit.
Design: A randomized controlled trial.
Setting: Monocentric study performed from February 2011 until May 2012.
Patients: One hundred consenting women with American Society of Anesthesiologists grade I or II were randomized into 2 groups.
Intervention: Laparoscopic hysterectomy was performed under desflurane general anesthesia. For the neostigmine (N) group, 0.45 mg · kg^{-1} rocuronium was followed by spontaneous recovery. A 5-mg rescue bolus was administered only if surgical evaluation was unacceptable. At the end of surgery, 50 µg · kg^{-1} neostigmine with glycopyrrolate was administered. For the sugammadex (S) group, a higher intubating rocuronium dose (0.6 mg · kg^{-1}) was followed by 5-mg boluses each time the train-of-four count exceeded 2. Sugammadex (2-4 mg · kg^{-1}) was administered to reverse the block. All patients were extubated after obtaining a train-of-four ratio of 0.9.
Measurements: The duration between the end of surgery and operating room discharge and the time spent in the postanesthesia care unit.
Main results: The time till operating room discharge was shorter and more predictable in group S (9.15 ± 4.28 minutes vs 13.87 ± 11.43 minutes in group N; *P* = .005). The maximal duration in group S

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* Corresponding author at: Department of Anesthesiology, CHU UCL Namur, Avenue Gaston Thérasse, 1, B-5530 Yvoir, Belgium. Tel.: +32 81 42 39 35; fax: +32 81 42 39 20.
E-mail address: laurie.putz@uclouvain.be (L. Putz).

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was 22 minutes, compared with 72 minutes in group N. The time spent in the postanesthesia care unit was not significantly different (group S: 47.75 ± 31.77 minutes and group N: 53.43 ± 40.57 minutes; $P = .543$).
Conclusion: Maintaining a deep neuromuscular block during laparoscopic hysterectomy reversed at the end of the procedure with sugammadex enabled a faster and more predictable time till operating room discharge than did the classical combination of a shallower block reversed with neostigmine.

1. Introduction

Increasing recent evidence suggests that inducing a deep neuromuscular block (NMB) contributes to improving surgical laparoscopic conditions [1-3]. At the end of such procedures, sugammadex allows for fast and predictable reversal of deep degrees of NMB induced by rocuronium [4,5]. Where available, this new practice is challenging the classical management of intraoperative NMB and the limited reversal of moderate levels of blockade with neostigmine [6,7]. However, the cost-effectiveness of the combination of deep NMB and sugammadex in daily clinical practice has not been determined [8].

To test the hypothesis that intraoperative deep NMB combined with sugammadex reversal reduces the time spent in the operating room (OR) and improves patient recovery in the postanesthesia care unit (PACU), we performed a randomized controlled study to compare this combination with shallow NMB reversed with neostigmine and glycopyrrolate in patients undergoing gynecologic laparoscopic surgery.

The primary outcome measures were the duration of surgery, pharmacologic reversal, OR discharge, OR and PACU occupation times, and the length of hospital stay. The secondary outcome measure was a modified Aldrete recovery score that was collected in the PACU. In addition, we discuss the potentially related economic opportunities.

2. Methods

2.1. Patient selection

After approval from the institutional ethical committee (CHU Dinant Godinne om 050, Chairperson Pr P. Evrard, registered in November 2010 at the Belgian Federal Agency for Medicines and Health products No. B03920109764) and the acquisition of written informed consent, 100 patients were enrolled in the study between February 2011 and May 2012. The results of the first part of the study (ie, evaluations of the intraoperative surgical conditions between the groups) have previously been published [2]. This second part of the study reports completely different data focused on timing and quality of patients' recovery.

The study population included American Society of Anesthesiologists I-II female patients, ranging in age from 18 to 80 years, who were scheduled to undergo a laparoscopic hysterectomy. We excluded patients with renal or hepatic diseases and those with neurologic disorders or allergies to any of the medications used in the study protocol.

2.2. Study groups and randomization

The randomization of the 2 treatment groups was performed with the minimization procedure described by Taves [9] and generalized by Pocock and Simon [10]. We enrolled consecutively the patients and accounted for the following 4 criteria while allocating them to the treatment groups: (1) age (18-40, 41-60, and 61-80 years), (2) body mass index (<20, 20-24, 25-29, 30-34, and 35-39 kg/m^2), (3) type of surgery (laparoscopic hysterectomy, laparoscopic subtotal hysterectomy, or laparoscopic subtotal hysterectomy and cervical sacrofixation), and (4) number of pregnancies (0-5). The randomization was performed with customized software.

2.2.1. Neostigmine group

A low intubating rocuronium dose (0.45 mg $\cdot$ kg^{-1}) induced a short NMB (train-of-four [TOF] count 0 at the time of tracheal intubation) followed by spontaneous recovery unless the surgical condition was unacceptable, as evaluated by the senior experienced surgeon; in such cases, a rescue 5-mg rocuronium bolus dose was administered. If necessary when TOF ratio was <0.9, 50 μg $\cdot$ kg^{-1} neostigmine with glycopyrrolate was administered at the end of surgery to reverse any residual NMB [7]. This study group was designed to correspond to usual clinical practice in numerous hospitals, avoiding deep and most moderate levels of blockade at the end of the procedure to allow for as effective neostigmine reversal as possible [6].

2.3. Sugammadex group

A higher intubating rocuronium dose (0.6 mg $\cdot$ kg^{-1}) induced deeper and longer NMB. In the case of extended procedures, a deep NMB (TOF count <1) was reinduced by repeated 5-mg bolus doses each time the TOF count reached or exceeded 2. Sugammadex at 2 to 4 mg $\cdot$ kg^{-1} was administered after the end of surgery to reverse the moderate or deep NMB accordingly [11].

One senior surgeon in charge of the study and all the clinical care nurses were blinded to the group assignment throughout the study. The senior anesthesiologist in charge of the patient strictly observed the following protocol.

Table 1 Recovery scores.

	0 point	1 point	2 points
Motor activity	Not able to move	Motor weakness	Move arms and legs
Breathing	Bradypnea <6/min	Weak ventilation or dyspnea	Deeply breathing and coughing
Pulse oximetry	<90% with O_2	Need O_2 to maintain >90%	>92% with air
Systolic blood pressure	>50% (+ or −) of baseline	20%-49% baseline	<20% baseline
Consciousness	No response on call or physical stimulation	Wake up with simple physical stimulation	Awake on call and orienting
PONV	Intense	Mild	None
Pain	VAS >7	VAS 3-6	VAS <3

PACU recovery score that included 7 items, each of which was rated on a scale from 0 to 2 points. A minimum of 12 points was mandatory before PACU discharge. PACU = postanesthesia care unit; PONV = postoperative nausea or vomiting' VAS = visual analog score.

2.4. Intraoperative care

The patient's premedication involved the administration of 0.5 mg of lorazepam 60 minutes before arrival in the operating theater. The anesthesia equipment consisted of a 3-lead electrocardiogram, a noninvasive blood pressure measurement device, and finger pulse oximetry. An intravenous line containing Ringer's lactate solution was inserted into a major left forearm vein.

We used a quantitative neuromuscular transmission (NMT) monitor to guide rocuronium administration continuously in every patient, from NMB induction to tracheal extubation. Using electromyography, the adductor pollicis responses were recorded after ulnar nerve stimulation (NeuroMuscular Transmission module; GE Healthcare, Buckinghamshire, UK) according to good clinical research guidelines [12]. TOF stimulations were applied every 20 seconds. When the TOF count was 0, a posttetanic count was determined every 5 minutes.

Anesthesia was induced with intravenous sufentanil at 0.15 $\mu g \cdot kg^{-1}$, ketamine at 0.5 $mg \cdot kg^{-1}$, and propofol at 2 to 3 $mg \cdot kg^{-1}$ and immediately maintained with a minimum of 6% desflurane to a target minimal alveolar concentration of 1 to 1.2 according to need (Zeus Infinity–empowered anesthesia machine; Drägerwerk AG and Co, Lübeck, Germany). After the patient lost consciousness, the ventilation was manually controlled. The randomized dose of rocuronium was then administered, and tracheal intubation was performed once the evoked muscular responses ceased (TOF count 0). Controlled mechanical ventilation was initiated (semiclosed circuit, 40%-45% oxygen in air) and adjusted to produce an end-tidal carbon dioxide concentration within the range of 30 to 35 mm Hg. After the patient had been placed in the lithotomic position, we determined the hemodynamic baseline before the surgical procedure began. During the study period, the oropharyngeal and right-hand temperatures were maintained above 36°C and 32°C, respectively. The intraperitoneal CO_2 insufflation pressure was set and monitored at 13 mm Hg throughout the procedure. The patient was placed in the maximal Trendelenburg position at 45° for the duration of the surgery (Maquet, Ardon, France). Postoperative pain and nausea were prevented via the administration of 1 g of paracetamol, 1 $mg \cdot kg^{-1}$ of tramadol, 50 mg of alizapride, and 0.625 mg of dehydrobenzperidol 30 minutes before the end of surgery. We added 10 mg of butylhyoscine to prevent spasms on the urinary catheter. At the end of the surgery, the abdominal cavity was completely exsufflated, and the abdominal ports were removed. No further rocuronium bolus was administered. The patient was placed flat, the laparoscopic incisions were sutured, and the skin was dressed. The NMB reversal agent was administered depending on the group and the level of NMB recovery. The effects of pharmacologic reversal were monitored until a TOF ratio greater than 0.9 was obtained; then the administration of desflurane was interrupted, and the vapor was washed out rapidly (Zeus 1-minute wash-out during mechanical ventilation followed by fresh gas flow >10 L/min O_2 95% in air in spontaneous breathing mode) [13]. All patients were extubated after the recovery of spontaneous breathing, swallowing, and airway protection reflexes. The monitors were removed, and the patients were transferred to the PACU with oxygen.

We recorded the duration of the surgery (T1), the duration of NMB reversal—from the injection of the reversal agent until a TOF ratio of 0.9 was achieved—(T2), the time between the end of surgery and OR discharge (T3), and the total time spent in the OR (T4).

2.5. Postanesthesia care unit

In the PACU, nurses who were blinded to the study group evaluated the patients' recoveries on arrival and every 15 minutes, using a modified Aldrete score that included 7 items, each of which counted for 2 points, as described in Table 1 [14-16]. When needed (ie, when the visual analog score was >3), intravenous morphine (1 mg) was administered every 5 minutes to alleviate pain. Ondansetron (4 mg) was added in cases of mild postoperative nausea or vomiting. After a minimum of 30 minutes, the patients were declared ready for discharge if their recovery score was >12 and every item was under control.

Table 2 Characteristics of patient groups according to each minimization criterion.

Minimization criteria	Neostigmine group	Sugammadex group
Age (y)	51.7 ± 10.9	49.9 ± 9.8
Body mass index (kg/m^2)	25.9 ± 4.9	26.7 ± 5.3
Type of surgery		
LH	43	43
LASH	2	3
LASH + sacrofixation	5	4
No. of pregnancies		
0/1/2/3/4/5 or more	7/5/24/6/7/1	2/10/19/11/6/2

LH = laparoscopic hysterectomy; LASH = laparoscopic subtotal hysterectomy; LASH + sacrofixation = laparoscopic subtotal hysterectomy and cervix sacrofixation.

For each patient, we recorded the initial recovery score, the best recovery score, the discharge readiness time, and the morphine consumption. The reasons for all nonoptimal scores (<14) were determined.

2.6. Sample size and statistics

The sample size established for the first part of the study with an α error rate of 0.05 and a power of 0.90 was calculated to be 86 patients with the G*Power 3 software [2,17]. We randomized 100 patients into 2 groups. This patient number is higher than recently published trials that were specifically designed with similar aims [3,18].

The data were compared between the 2 groups using the Wilcoxon rank sum test. *P* values <.05 were considered statistically significant.

The economic considerations were based on a multifactorial evaluation of the OR costs. In our university training institution (400 beds, most of the staff are composed of salaried employees), accounting for physician, trainee, nurse, and technical staff compensation, as well as building and medical equipment amortization, we concluded that the cost of one opened OR was approximately $20 per minute. This value is within the range of published data [19].

According to the study location in Belgium, a 200-mg vial of sugammadex costs $85, whereas a 2.5-mg vial of neostigmine with 0.5 mg of glycopyrrolate costs $4. Accounting for OR and drug costs, a reduction of 4.25 minutes (85/20) in OR occupation time per sugammadex vial was taken as the significant threshold for sugammadex cost-effectiveness that would warrant further discussion.

3. Results

Of the 100 initially enrolled patients, 2 were excluded after randomization due to intraoperative violations of the protocol (ie, an inappropriate magnesium administration at induction in one case and a failure apply the protocol in the other case) and were prospectively replaced by 2 other patients who were also randomized. The final analysis included 100 patients (50 in neostigmine group and 50 in sugammadex group). The details of the patients' characteristics, which were similar due to the randomization criteria, are provided in Table 2.

The patients included in the neostigmine and sugammadex groups received a total rocuronium dose of 33.4 ± 6.9 mg and 57.0 ± 15.4 mg, including 19 and 131 additional 5 mg boluses, respectively. The NMB reversal agents were administered according to the actual level of NMB recovery at the end of skin dressing, as detailed in Fig. 1.

The results are presented in Table 3. Neither the potential benefit of reducing the duration of surgery with deep NMB nor the overall time spent in the OR and PACU reached statistical significance.

In contrast, Wilcoxon rank sum tests revealed highly significant differences in the NMB reversal times (T2) and OR discharge times (T3; Fig. 2). The latter difference between groups was 4.72 minutes on average. Moreover, the range of values at T3 (the maximal duration in the neostigmine group was 72 minutes and that in the sugammadex group was 22 minutes) was clinically relevant because the interindividual variability in the reversal time with neostigmine resulted in unpredictably delayed discharges from the OR.

In the PACU, the recovery scores, incidences of adverse effects, and morphine consumptions did not differ significantly between the groups. The hospital discharge times were also not different.

4. Discussion

This study demonstrated that shorter and more predictable OR discharges occur after the administration of sugammadex to patients at moderate or deep levels of NMB than after the administration of neostigmine to patients at moderate or even much shallower levels of blockade. Similar to the results of Geldner et al. [4], we confirmed a clinically significant benefit in the time spent by the patient in the OR after the end of surgery. The use of sugammadex allowed the anesthesiologist to reverse moderate or deep NMB that was maintained until the end of surgery while reducing the times required for safe extubation and OR discharge.

Sugammadex has been found to induce much faster reversals even from the deepest levels of blockade compared with neostigmine in randomized controlled trials and in clinical practice [4,5,20]. However, sugammadex reversal is not always as rapid as expected in every patient. The maximal reversal time provided by the literature when reversing deep NMB with sugammadex is up to 20 minutes [20,21]. Moreover, inappropriate (ie, lower than recommended) sugammadex dosing can lead to uncertain effects [20,21]. Thus, sugammadex clearly cannot replace good clinical practice and the systematic use of NMT monitoring to manage each stage of NMB in every patient [6,22,23].

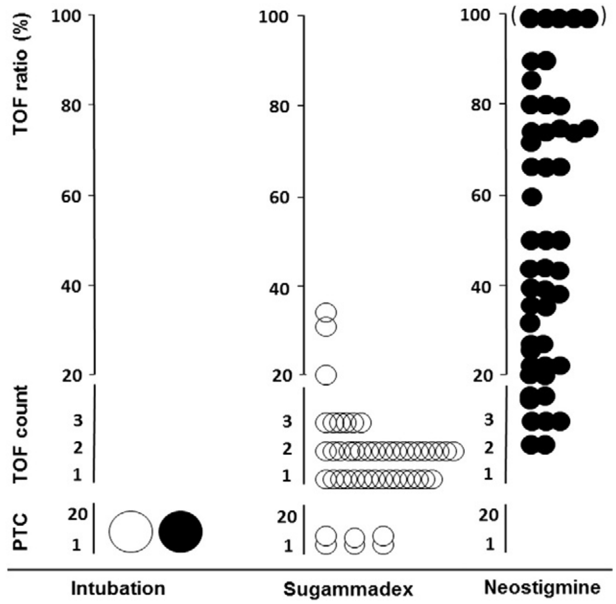

Fig. 1 NMT monitoring. The actual level of neuromuscular blockade measured by electromyography at the time of intubation (TOF count 0 in all cases) and sugammadex or neostigmine administration (except if TOF ratio > 0.9). The patients from sugammadex group are represented as white dots, and those from neostigmine group are represented as black dots. See the Methods section for details. NMT = neuromuscular transmission; TOF = train-of-four; PTC = post tetanic count.

To limit the cost in the sugammadex group, the block recovered a moderate level before being deepened by rocuronium boluses, except after the abdominal ports have been removed (few patients reached a TOF count of 3 or 4). On the other hand, to minimize the duration of reversal, our study design let the NMB recover shallow levels of blockade in most patients in the neostigmine group (TOF count 4 with fade; Fig. 1). Despite this, the proper reversal of moderate to deep NMB with sugammadex (2-4 mg · kg^{-1}) was not only faster than reversal with neostigmine (at moderate or much higher NMB levels) but also more predictable, as demonstrated by a much lower standard deviation (1.15 vs 15.43 minutes). This benefit was reflected in more rapid OR discharges. The time spent in the OR between the end of surgery and discharge was shorter on average, as has been previously published [4], and also more predictable when sugammadex was used (Fig. 2). The interindividual variability was more important in the neostigmine group, which included several challenging outliers. Such delayed and unpredictable discharges are a threat to the efficient organizations of the OR programs—this issue is discussed later.

A deep NMB is defined as a posttetanic count of 1 or more, but a TOF count of 0; on the other hand, a moderate NMB gets a TOF count of 1 to 3 [6,12]. Compared with moderate NMB, there is good evidence that the maintenance of deep NMB optimizes the surgical conditions during abdominal and gynecologic surgeries, especially during lower abdominal laparoscopies [1]. Specifically, in the first part of our study, only the deep NMB was found to prevent sudden abdominal wall contractions that can induce unacceptable surgical conditions (occurring in 28% of cases in the shallow block group) and disrupt the course of the procedure [2]. Blobner et al [3] recently demonstrated that deep neuromuscular blockade improves surgical laparoscopic conditions during cholecystectomy but does not reduce surgical time. Our study confirmed this finding and was unable to demonstrate a significant reduction in the duration of surgery under optimal conditions with deep NMB. Neither of these studies was designed to evaluate the intraoperative patient safety.

As sugammadex was introduced into clinical practice, some anesthesiologists noticed surprisingly fast arousals from

Table 3 Results.

	Neostigmine group	Sugammadex group	*P*
T1 surgery	1:14:03 ± 0:22:39	1:09:25 ± 0:22:19	.278
T2 reversal	0:09:56 ± 0:15:26	0:02:37 ± 0:01:09	.001
T3 OR discharge	0:13:52 ± 0:11:26	0:09:09 ± 0:04:17	.005
T4 OR time	2:01:08 ± 0:28:08	1:51:20 ± 0:24:58	.103
Initial recovery score	12.29 ± 1.25	12.04 ± 1.47	.410
Best recovery score	13.73 ± 0.45	13.84 ± 0.37	.201
Time PACU discharge	0:53:26 ± 0:40:34	0:47:45 ± 0:31:46	.543
Total time OR + PACU	3:02:52 ± 0:41:36	2:49:20 ± 0:38:30	.064
Hospital stay (d)	3.34 ± 0.74	3.38 ± 1.41	.457
In PACU, patients experimented troubles with (n)			
Pain (VAS >3)	29	25	.352
Morphine (mg)	4.52 ± 3.97	3.69 ± 4.29	.199
PONV	4	4	.976
$SpO_2 + O_2$	10	9	.760
Consciousness	4	5	.751
Blood pressure	3	5	.479

The results are expressed as the mean ± SD. Time is expressed as h:mm:ss. See the methods section for details. OR = operating room; PACU = postanesthesia care unit; PONV = postoperative nausea or vomiting.

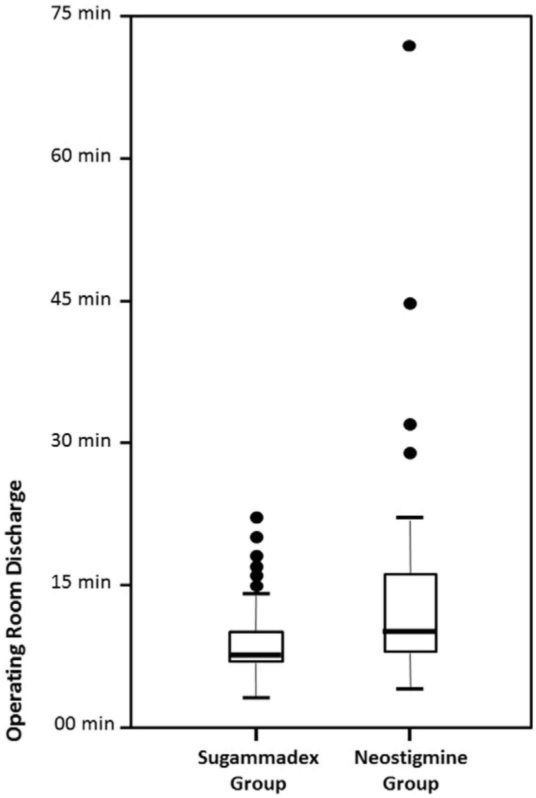

Fig. 2 OR discharge. The time between the end of surgery and OR discharge is expressed in minutes comparing the neostigmine group (shallow neuromuscular block reversed with neostigmine) and sugammadex group (deep to moderate neuromuscular block reversed with sugammadex). Boxes represent 25-75th percentiles, with the median as bold line. Dots are values more than 1.5 box lengths from 75th percentile (outliers), and whiskers are the smallest or largest observed values that are not outliers. OR = operating room.

anesthesia. Among these anesthesiologists, Chazot and colleagues [24] described sudden electroencephalographic modifications and clinical signs of recovery that occurred 30 seconds after the administration of a sugammadex bolus. These authors proposed a "spindle theory" to explain the acute recovery. Even earlier, Vasella and colleagues [25] explained similar results observed after the administration of neostigmine with the "afferentation theory," which was based on the observation that the arousal effect appeared to correspond with a sudden increase in afferent signals from muscle stretch receptors. In contrast, when Illman and colleagues [26] conducted a study that was specifically designed to examine the possible effects of sugammadex on the level of anesthesia as defined by BIS and spectral entropy levels, they found no effect.

Based on evaluations of recovery using a modified Aldrete score upon arrival in the PACU, our study demonstrated no significant benefit of sugammadex reversal in terms of quality or speed of recovery after general anesthesia. The patients from both groups who were admitted to the PACU a few minutes after OR discharge presented similar recovery scores. We speculate that we would have observed a different result if the recovery assessments have been performed closer to tracheal extubation, but this would raise the question of the clinical relevance of such a potential transient effect.

Similarly, our study revealed similar PACU stay durations in both groups. Previous studies have demonstrated that residual NMB on arrival to the PACU is associated with delayed discharge [27]. Our protocol imposed the criteria of the recovery of a TOF ratio >0.9 on both groups before awakening and extubating the patients, which ruled out the residual block and its potential influence on PACU initial recovery assessments and stay durations. In these conditions, reversal with sugammadex did not further favor better recovery scores compared with neostigmine. The lack of differences between groups in the PACU could be related to improved management of residual NMB in the OR for every patient, based on quantitative NMT monitoring.

The postoperative factors that most frequently contributed to the time spent in the PACU were the need for supplemental pain management (visual analog score >3 in 54% of the patients), hypoxemia, hypotension, insufficient consciousness recovery, and postoperative nausea or vomiting (see Table 3). However, there was no significant difference between groups. This finding confirms recent studies that have been conducted in the same context and compared recovery from deep NMB + sugammadex vs moderate NMB + neostigmine after laparoscopic surgery [4,18,28].

The translation of the possible benefits of NMB reversed by sugammadex in reducing the hospital stay is controversial. Some studies have demonstrated significant decreases in postoperative pneumonia [29] and hospital discharge time (2.0 vs 2.2 days) [30]. However, as with other studies [31,32], we found no difference between our 2 groups. Further studies should specifically determine whether the intraoperative advantage of deep NMB (ie, improvements in surgical conditions) and reversal with sugammadex (ie, reducing OR discharge time and residual NMB) improve patient outcomes.

Compared with the neostigmine group, the use of sugammadex was associated with a more predictable OR discharge and trend toward shorter stays on average (ie, total OR + PACU time, P = .064; see Table 3 for details). Better predictability and shorter times allow for a better dynamism of the operating theater staff by improving turnover while respecting the OR schedule as closely as possible. However, the economic value of the time saved by improved OR efficiency remains unclear and depends on the ability of the staff to perform other productive activities and the ability of the OR manager to proactively fine-tune the staffing to match the surgical demand [8,33-35].

As with the OR, the PACU is a bottleneck in patient flow. Any delay of admission or discharge, particularly in the late afternoon or evening, might affect the costs of the PACU due to the salaries of the nurses and anesthesiologists (eg, extra hours have higher costs) and should be limited as much as possible [27]. Because it prevents residual NMB, the association between NMT monitoring and sugammadex could reduce the times spent in the OR and PACU and thus the associated costs. However, sugammadex would be cost-effective only if the reduction in recovery time occurs mainly in the operating theater (high-value staff time) rather than in the PACU (relatively lower-value staff time) [8]. For instance, in the conditions of our study, the total excess time spent in OR waiting for neostigmine reversal (220 minutes) could compensate for the cost of one sugammadex vial for every patient, which was sufficient in most cases. The financial consequences of deep NMB management based on sugammadex reversal depend on multiple factors that include the intraoperative advantages in terms of the surgical conditions, the value of the time spared, and who is charged for the drugs (ie, the health care system, the hospital, the department, or the patient). Further studies should precisely define the financial effects of such strategies in the specific conditions of each health care system and hospital cost and for specific surgical procedures.

In conclusion, the maintenance of a moderate to deep NMB during laparoscopic hysterectomy with reversal at the end of the procedure with sugammadex enabled faster and more predictable OR discharges than did the classical combination of shallower NMB reversed with neostigmine.

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