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La funzione diaframmatica in Anestesia e Terapia Intensiva: ruolo della ultrasonografia nella curarizzazione residua postoperatoria

Diaphragmatic function in Anesthesia and Intensive Care Unit: role of ultrasonography in assessing postoperative residual curarization

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Abstract

Background The extensive use of neuromuscular blocking agents (NMBAs) during surgical procedures has increased the concern of residual paralyzing effect in the post-operative period. In order to avoid residual effects neuromuscular monitoring is advocated in intra-operative setting to improve patient safety. For many years Acetyl Cholinesterase inhibitors (AChEi), has been used to reverse muscle block but their short half-life can cause a partial recurarization in ward setting especially if intermediate-long acting agents are administered. Sugammadex is the first selective reversal drug for steroidal neuromuscular blocking agents, and it has been proved to give full and rapid recovery of muscle strength, thus minimizing the occurrence of residual curarization. Acceleromyography of the adductor of pollicis is the gold standard to detect residual curarization but is not affordable in awake patients. Diaphragm is the major respiratory muscle and its dysfunction is associated with the occurrence of respiratory failure. Introduction of ultrasonography made studying the diaphragm thickness more reliable and a good tool individuate residual effect of NMBAs in awake patients.

Methods/Design A prospective, double-blind, single centre randomized study enrolling patients with ASA physical status I-II, between 18-80 years old, undergoing deep neuromuscular block with rocuronium during ear nose throat surgery. Primary objective of the study was to compare the effect of Neostigmine (NEO group) versus Sugammadex (SUG group) on post-operative residual curarization by using of two different tools: diaphragm ultrasonography and acceleromyography. Neuromuscular monitoring was performed by using the adductor of pollicis by means of train of four stimulation with ratio between the last and the first twitch. Patients were extubated when the ratio was greater than 0.9. Diaphragm ultrasound has evaluated thickening fraction (TF), which is the ratio between the end expiratory thickness and the end inspiratory one normalized on the expiratory one. Ultrasonography was carried out before the initiation of general anesthesia, before

extubation, 10 and 30 minutes after discharging from the operating room. The secondary objective was the reduction of the incidence of post-operative complications related to residual neuromuscular block. The statistical analysis has been carried out by using Generalized Estimating Equations (GEE) multiple linear regression model adjusting for time of the measurement and baseline TF whilst association between drug and collateral effect have been evaluated using logistic regression model. P-values smaller than 0.05 have been considered statistically significant.

Results The difference between basal TF and 30 minutes TF called ΔTF30 was significantly lower in participants who have received sugammadex than in whom has received neostigmine as reversal drug ($p < 0.0001$). Any postoperative respiratory complications were recorded in patients enrolled independently to group allocation. The incidence of postoperative nausea and vomiting (PONV) was on a major extent in the NEO group (27.59%) than in the SUG group (6.67%) with an overall adjusted odds ratio of 5.333 (p value=0.0467).

Discussion Post-operative residual curarization is a topic of paramount importance because its occurrence can cause complications related, increasing of length of stay in the hospital and costs. In our study sugammadex has guaranteed a complete recovery of diaphragm thickening 30 minutes after extubation; by contrast the administration of neostigmine/atropine did not ensure a full recovery of basal TF. Moreover, PONV has occurred more frequently with the AChEi than with the γ-cyclodextrin. Diaphragm ultrasound assessment could become a bedside evaluation tool in future in the context of perioperative medicine in the interest of speeding up the discharge from the hospital.

Trial Registration: EudraCT 2013-004787-62, registered on June 18th 2014 as "Evaluation of muscle function recovery after deep neuromuscular blockade by acceleromyography of the

adductor pollicis or diaphragmatic echography: comparison between sugammadex and neostigmine".

https://www.clinicaltrialsregister.eu/ctr-search/search?query=2013-004787-62

NCT02698969 registered on Clinicaltrials.gov on February 15th 2016 as "Recovery of Muscle Function After Deep Neuromuscular Block by Means of Diaphragm Ultrasonography and Adductor Pollicis Acceleromyography: Comparison of Neostigmine vs. Sugammadex as Reversal Drugs"

https://clinicaltrials.gov/ct2/show/NCT02698969?term=adembri&rank=1

Keywords: Diaphragm ultrasonography, Sugammadex, Post-operative residual curarization, neuromuscular monitoring

Ultrasonography in Intensive Care Unit (ICU) and in Operating Room (OR)

Ultrasonography has become a precious tool to better manage critically ill patients. On the one hand its safety and a bedside use allow clinicians to obtain important information about cardiovascular, respiratory, gastrointestinal, urogenital and nervous systems that complete physical examination. Besides, an ultrasound machine is of outstanding importance to carry out procedures formerly not possible in ICU such as placements of guided central venous lines, ultrasound-guided pleural, peritoneal and pericardial drainages [1-3]. On the other hand, ultrasonography is an imaging technique that is extremely operator-dependent and intensivists needs to be skilled to perform reliable exams [4]. Indeed, medical personnel who operate in a critical care environment must be educated for the purposes of acquiring and maintaining competences in different fields in which ultrasonography can be applied. That is why there is a growing interest in developing different tiers of competency and certification [5].

Anyhow, over the last decades, the various ultrasound probes available have become the "visual stethoscope" in evaluating patients [6]. Therefore, the approach to study lungs, heart and cardiovascular system and the abdomen has completely changed. Thanks to a whole body ultrasonography, clinicians may early recognize the causes of instabilities of the patient admitted to ICU [7]. Nowadays, ultrasound-guided vascular accesses are advocated because the occurrence of complications is less than with the "blind" technique. Likewise, critical care doctors are requested to be trained in diagnosing deep venous thrombosis (DVT), studying aorta and inferior vena cava (IVC) [8, 9]. Transthoracic Echocardiography (TTE), performed with square surface probe, is a mainstay scan for patients who present hemodynamic instability of unknown origin not responsive to standard fluid resuscitation. A basic TTE should be performed utilizing the main acoustic windows (parasternal long axis view, parasternal short axis view, apical four and five chamber view, subcostal view)

identifying hypovolemia, left and right ventricular dysfunction and cardiac tamponade. A more advanced approach should emphasize the assessment of valvular apparatus in the left and the right heart and a further deepening with transesophageal study (TEE) [10]. Chest ultrasonography, performed by a skilled intensivist, is helpful to diagnose causes of respiratory failure and dyspnea such as lung consolidations, pleural effusions, pneumothorax, pulmonary edema. Moreover, clinicians can safely perform bedside procedures ultrasound-guided including thoracentesis and chest tube placements [11]. Abdomen is a challenging field because 20 organs are contained inside. Usually ultrasonography is complementary to a CT scan but rapid evaluation of kidney and bladder is important to rule out obstruction to urinary catheter. Besides, a quick scan of liver, gallbladder and Douglas' pouch provides information including presence of stones and ascites with the possibility of ultrasound guided tube placements and paracentesis alike [12].

Between the abdomen and the thorax there is the diaphragm, the main respiratory muscle. Studying its function with ultrasonography has been practicing since 1989 but only recently, due to improvement of technologies, has widespread in the critical care context [13, 14]. Medical personnel, who has an adequate training, could use diaphragm echography to assess whether patients are weanable from mechanical ventilation or to detect residual curarization in the operating room after deep neuromuscular blockade.

Diaphragm Ultrasonography

The diaphragm is the main inspiratory muscle and among imaging techniques useful for studying it, ultrasonography is a portable, non-invasive and ionizing radiation-free device which might represent a good tool for functional analysis [15].

Wait et al. used M-mode ultrasonography to measure diaphragm thickening in 1989, showing a linear relationship between diaphragm thickening and lung volumes [14]. From these initial observations, diaphragmatic ultrasonography has been applied to different fields of daily clinical practice.

Other more recent studies have focused on amplitude of excursion of the diaphragmatic dome using M-mode ultrasonography. This method has seemed to be reproducible and suitable to show postoperative diaphragmatic dysfunction after major abdominal surgery [16, 17]. A variant of this method has been applied after cardiac surgery, in patients who required prolonged mechanical ventilation [18]. Furthermore, sequential two-dimensional (B-mode) analysis of the zone of apposition (ZOA) to the rib cage has been shown to provide a useful tool to asses and determine subsequent recovery from diaphragmatic paralysis, in a cohort of medical patient with unexplained dyspnea [19].

Currently, other interesting fields of application include weaning patients from mechanical ventilation (MV) and evaluation of the work of breathing during non-invasive ventilation (NIV). In the ICU setting, ultrasonography of the diaphragm may be used to identify patients difficult to wean from MV and to assess the rate of diaphragmatic dysfunction [20].

Although sonography has become a widely used tool, capable of providing a non-invasive, bedside evaluation of diaphragmatic function, a significant limitation lies on the intrinsic operator-dependency of the technique. Recently, a study showing the relationship between diaphragm thickening, assessed by M-mode scanning of the ZOA, and respiratory

muscle efforts, exhibited low intraobserver variability [13]. However, all measures have been carried out by two equally experienced physicians. Moreover, the interobserver variability remains to be established [21].

Some concerns remain, in our opinion, about the real reproducibility and repeatability when this tool is used to study the diaphragm. We have observed (unpublished observations) that the reproducibility and repeatability of diaphragm ultrasonography was moderate when the test has been performed by three different operators with different levels of experience with sonography.

Operating theatre should be the next setting in which diaphragmatic function should be assessed through ultrasonography. The main area of interest may be diagnosing residual curarization but there also studies that have evaluated the thickening during intravenous administration of hypnotic drugs [22].

Deep neuromuscular block (dNMB) and Postoperative residual curarization (PORC)

Non-depolarizing neuromuscular blocking agents (NMBAs) are extensively used by anesthesiologists to keep deep neuromuscular block (dNMB) during surgical operations. To avoid postoperative residual effects of NMBAs, muscle relaxants should be fully catabolized to inactive metabolites prior to extubation. Nevertheless, when a patient is waking from general anesthesia, it is possible that some of the administered paralyzing agent is not completely transformed to its inactive form at the level of neuromuscular junction, provoking residual effects that can be burdensome to clinically diagnose [23].

The use of intra-operative neuromuscular monitoring, when NMBAs are administered, has been encouraged to decrease postoperative residual curarization (PORC) [24, 25] because any clinical exams is able to exclude residual effect of muscle relaxants [26].

Acceleromyography, the most commonly used method of quantitative monitoring, appraises muscle acceleration responding to nerve stimulation by train of four (TOF) and post-tetanic count (PTC) methods [27, 28]. TOF consists in four short 2 Hz stimulations. For many years, a TOF ratio between the amplitude of the last stimulation and that of the first one inferior than 0.9 was used to define PORC. Instead, PTC consists of a 5-second 50 Hz tetanic stimulation followed by a 20-second 1 Hz stimulation. The elicitation of fewer than five twitches indicates dNMB [29]. Even though these types of monitoring are strongly recommended, they are not regularly performed in the operating room scenario. Furthermore, the TOF test may be bothersome to awake patients.

The incidence of PORC ranges from 9% to 47% when no reversal drug is administered [30]. For many years, reversing the NMBA effect has been done using an acetylcholinesterase inhibitor (AChEi) such as neostigmine. These inhibitors, which increase acetylcholine levels in the neuromuscular junction, antagonize the paralyzing agent but do

not hasten its metabolism. Therefore, as a result of the unpredictable metabolism of blocking drugs, a partial recurarization may occur when the AChEi effect has elapsed [31]. Indeed, an observational study showed that, 20 minutes after administration of neostigmine, 18% of patients had a TOF ratio <0.9 [32]. Moreover, as shown in an animal study, when neostigmine is administered in the setting of full recovery from a muscle relaxant, the drug can cause weakness of the diaphragm and genioglossus muscle even if this effect is not seen when residual paralysis is still present [33].

Sugammadex is a γ-ciclodextrin and the first selective reversal agent for steroidal NMBAs. It has been shown to give full and rapid recovery of muscle strength, thus minimizing the occurrence of PORC [32, 34]. It is composed of an internal hydrophobic part, which chelates aminosteroid NMBAs forming a stable complex 1:1, and an external hydrophilic part, which increases its solubility in the bloodstream. The low dissociation rate of the complex and its unmetabolized urinary excretion allows to guarantee a rapid and long-lasting recovery from dNMB [35-37].

The diaphragm, the major respiratory muscle in humans, is a great septum between the thoracic and abdominal cavities. The movement of the diaphragm accounts for 60%–70% of the total tidal volume of respiration. Failure of diaphragmatic function is believed to play a central role in the pathophysiology of the clinical syndrome known as “pump respiratory failure” [38-40]. Although a TOF ratio >0.9 in the adductor pollicis rules out residual curarization, the diaphragm is often not evaluated in the operating room. The diaphragm is the most highly resistant muscle to NMBAs as well as the first to recover [41], but the occurrence of its dysfunction has been implicated in postoperative respiratory failure, especially when mechanical ventilation is prolonged [42]. Therefore, it is of paramount importance to study diaphragmatic function in the perioperative context.

Since 1989, ultrasonography has been used to evaluate diaphragm function by measuring thickness variations in the apposition zone, which reflect the extent of contraction of the muscle [14]. Vivier et al. recently demonstrated that the thickening fraction (TF), namely the difference between the thickness at the end of inspiration (TEI) and that at the end of expiration (TEE), normalized for TEE (TEI-TEE/TEE), is directly related to respiratory workload, and suggested that TF could be used as an index to select those patients ready to be weaned from noninvasive ventilation [13]. Their data also suggested that ultrasound TF could be used to assess diaphragm recovery after dNMB and may be more comfortable for awake patients than acceleromyography.

We therefore hypothesized that diaphragmatic ultrasonography is a reliable tool for detecting residual curarization in patients who receive sugammadex or neostigmine as reversal drugs.

Aim of the study

The present study aims to detect diaphragmatic dysfunction by means of ultrasonography for the purpose of assessing PORC after deep neuromuscular blockade with an aminosteroid muscle relaxant drug and two different drugs administered as reversal after dNMB.

Methods

Study Design and Eligibility

This study was a prospective, double-blind, randomized controlled trial involving 60 patients with ASA physical status I-II and age between 18 and 80 years, who underwent dNMB with rocuronium during ear, nose or throat (ENT) surgery in a single academic hospital. The Institutional Review Board of Tuscany Region approved the protocol with registration number CE SPE 13.068. Exclusion criteria were: a history of hepatic or renal disease; chronic or acute alcoholism; allergy or hypersensitivity to sugammadex or neostigmine; current medications with effects on the central nervous system; a history of neurologic disease; and diaphragmatic palsy, pregnancy, or nursing arrhythmias.

Randomization

Written informed consent was obtained during the pre-operative evaluation by an anesthesiologist working in the anesthesia unit of the hospital. Afterwards, each patient was randomly allocated to either the sugammadex (SUG) group or the neostigmine (NEO) group. Randomization has been performed using a table created at www.randomization.com. The allocation plan has been carried out using a block randomization method 1:1 to distribute the patients equally to each group. Table assignment to one group or the other has been managed by a pharmacist with limited involvement in the study; this person has also performed the allocation plan and prepared the drugs.

Intervention Plan

In order to standardize the anesthetic technique, no premedication has been administered. All patients underwent neuromuscular monitoring with ulnar nerve stimulation using the TOF-Watch (Organon, Oss, Netherlands). The device has been calibrated pre-operatively, and the parameters has been set using standard TOF methodology after administration of a hypnotic drug, prior to muscle relaxation. General anesthesia has been

induced by intravenous injection of fentanyl (2 µg/kg body weight), propofol (2 mg/kg), and rocuronium (0.6 mg/kg). Tracheal intubation has been performed after the patient failed to register signals with TOF. To maintain dNMB, rocuronium (0.15 mg/kg) has been re-administered when PTC elicited more than five twitches. Sevoflurane has been supplied at an age-adjusted end-tidal concentration of 1.0 MAC in an air/oxygen mixture. Fentanyl has been titrated with a bolus of 0.5 µg/kg every 30 minutes, to keep an adequate level of analgesia.

Prior to induction of anesthesia, baseline TF has been evaluated by one operator skilled in ultrasonography using an Esaote MyLab 40 ultrasound instrument (Esaote, Genoa, Italy). Patients have been placed on the bed in a semi-recumbent (45°) position, assessed with a goniometer. The operator used a 10–12 MHz high-frequency linear probe to individuate the diaphragm in the midaxillary line in the apposition zone between the lung and liver on the right and between the lung and spleen on the left, in the intercostal spaces between the ninth, tenth and eleventh ribs, 0.5–2 cm above the costophrenic sinus. TF has been calculated as the TEI-TEE/TEE ratio, recorded in time-motion mode. The muscle has been located utilizing the hyperechoic pleural and peritoneal layers. Three assessments have been performed in consecutive breaths and averaged [13].

At the end of the operation and when TOF neuromuscular monitoring showed a minimum of two twitches, patients have received the reversal drug according to the group to which they have been randomized. Patients in NEO Group has received 50 µg/kg neostigmine and 15 µg/kg atropine, while those in SUG Group 2 mg/kg sugammadex [43]. The drugs have been prepared for intravenous injection in identical volumes in undistinguishable syringes so that the anesthesiologist has been blinded to the treatments that patients received. Extubation has been performed when all the following criteria were met: (i) the patient has been awake and has executed simple commands; (ii) the patient's respiratory pattern has been regular with a tidal volume of 6–7 mL/kg referred to ideal body weight; and

(iii) the TOF ratio was >0.9. Immediately prior to extubation, bilateral diaphragm ultrasonography has been performed to assess muscle recovery in spontaneously breathing patients; these measurements have been compared with the baseline muscle assessment. Two additional diaphragm ultrasound scans have been accomplished 10 and 30 minutes after discharge from the operating theater. Follow-up has been undertaken to document adverse events and complications until discharge from the hospital. The physician who has realized the ultrasound scan was different from the one who has administered the reversal drug and has been blinded to the treatment that patients received (Figure 1).

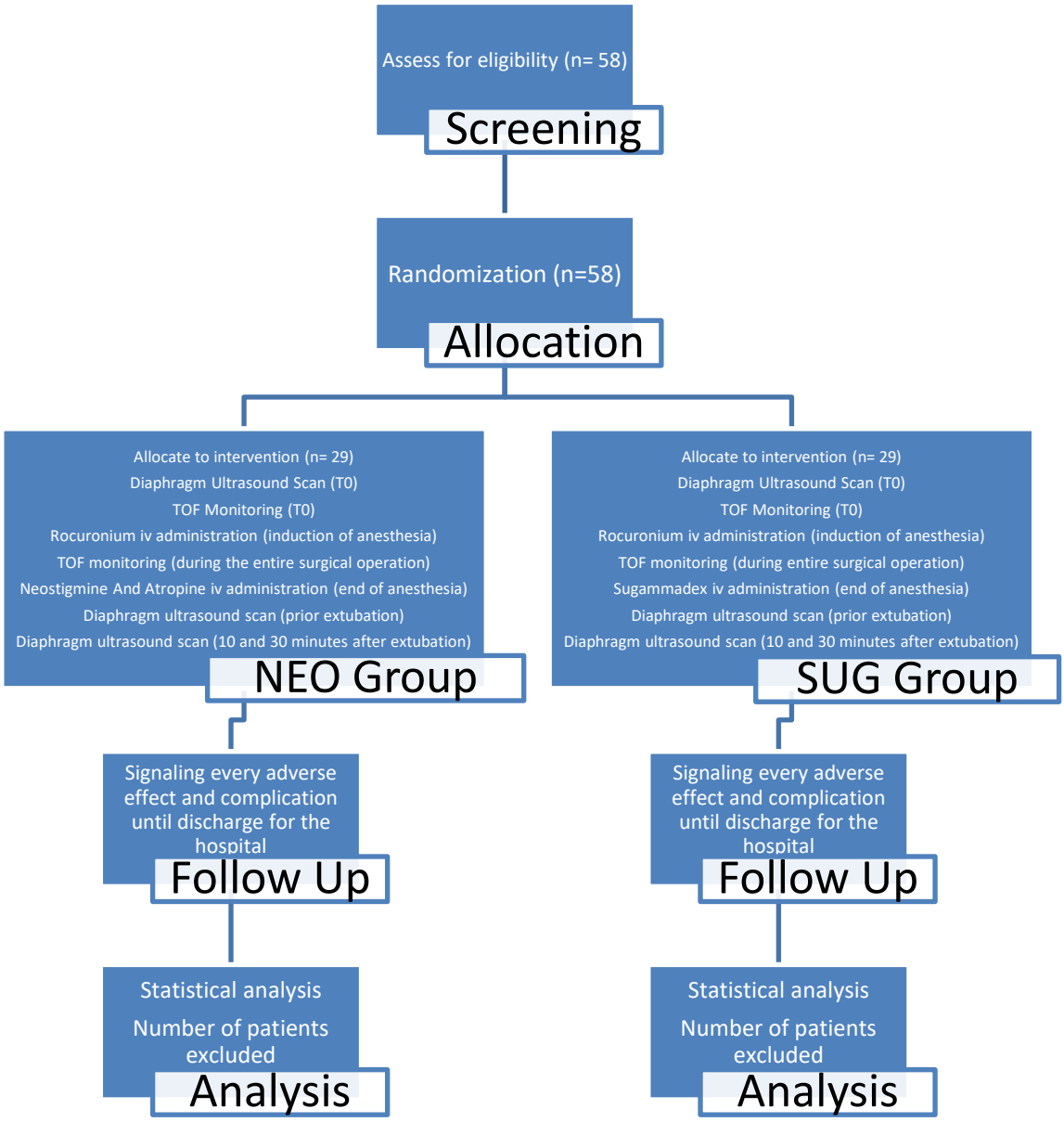

Figure 1. Flowchart of the protocol

In the case of unexpected events, such as a change in drug dose or a participant's request to withdraw from the study, the protocol has been stopped and this fact was recorded on the case report form (CRF). To ensure participants' adherence, no further tests have performed except those necessary to finalize the protocol. Required medical care and interventions have been allowed during the trial unless they interfered with the correct conduct of the study.

The primary endpoint has been a 30% reduction in the incidence of recurarization in patients who received sugammadex compared with neostigmine 30 minutes after drug administration. The primary endpoint has been assessed at 30 minutes because the effects of neostigmine start to fade after this time has elapsed [44]. Recurarization has been determined from the percentage TF compared to baseline TF. It has not been known which percentage TF indicates recurarization, but from our unpublished observations, values of 40% or less could be considered to indicate residual muscle paralysis. However, we did not know what percentage of patients have a TF <40% when neostigmine is administered.

Two secondary endpoints have been assessed. One secondary endpoint has been a 10% reduction in respiratory complications related to recurarization obtained with sugammadex compared with neostigmine. Respiratory complications taken into consideration have been new cough and sputum production, abnormal breath sounds not present at baseline, temperature more than 38°C, chest radiography documentation of atelectasis or new infiltrates, and physician documentation of atelectasis or pneumonia [45]. The other secondary endpoint has been a 30% decrease in postoperative nausea or vomiting (PONV) in patients who received sugammadex compared with those who received neostigmine.

Data have been collected on paper CRFs. All personal information have been registered in an environment limited to medical personnel so as to maintain absolute confidentiality. Data entry have been performed at one central site that maintains the overall

database and have been carried out the data analysis. All the compiled CRFs have been archived in a locker where only clinicians involved in the study had the access. With the aim of eliminating possible data entry errors, individual data have been compared to a range of plausible values. After data entry, automated checks, which have been defined a priori, have been performed to search for internal inconsistencies, range errors, or missing data. For each atypical, out-of-range or missing datum, a query has been automatically sent to the investigator. Once all the queries are solved, the database have been locked and used for statistical analysis.

Statistical Analyses and Sample Size Calculation

The statistical analysis has been carried out by an independent statistician by means of SAS 9.3 (SAS Institute, Inc., Cary, NC, USA). For the primary endpoint, the effect of drug on ΔTF have been estimated by using Generalized Estimating Equations (GEE) multiple linear regression model adjusting for time of the measurement and baseline TF. For the secondary endpoint, association between drug and collateral effect have been evaluated using logistic regression model. P-values smaller than 0.05 have been considered statistically significant.
Finally, descriptive statistics of all variables describing the characteristics of the patients enrolled in the study and those excluded from the study have been. Continuous variables have been expressed as Mean (± standard deviation - SD) and Median (ranging from 25th to 75th percentiles). Percentages have been calculated for dichotomous data. For categorical variables, frequency counts and percentages have been calculated.

Because this is the first clinical trial that proposes, as its primary endpoint, a relative reduction of 30% in the incidence of recurarization, the needed sample size has been calculated using the statistical software Epi Info (version 7). With a 95% confidence intervals (CI) and a power of 80%, and assuming equal variance between the two groups, this

analysis has showed that at least 28 patients per group were required. For the secondary outcome, the number needed to treat has been calculated with a CI of 95%.

Results

From October 2016 to May 2017 a total of 59 consecutive patients underwent to ear, nose or throat (ENT) procedures of microlaryngeal surgery have been enrolled and randomly allocated into two groups (figure 2).

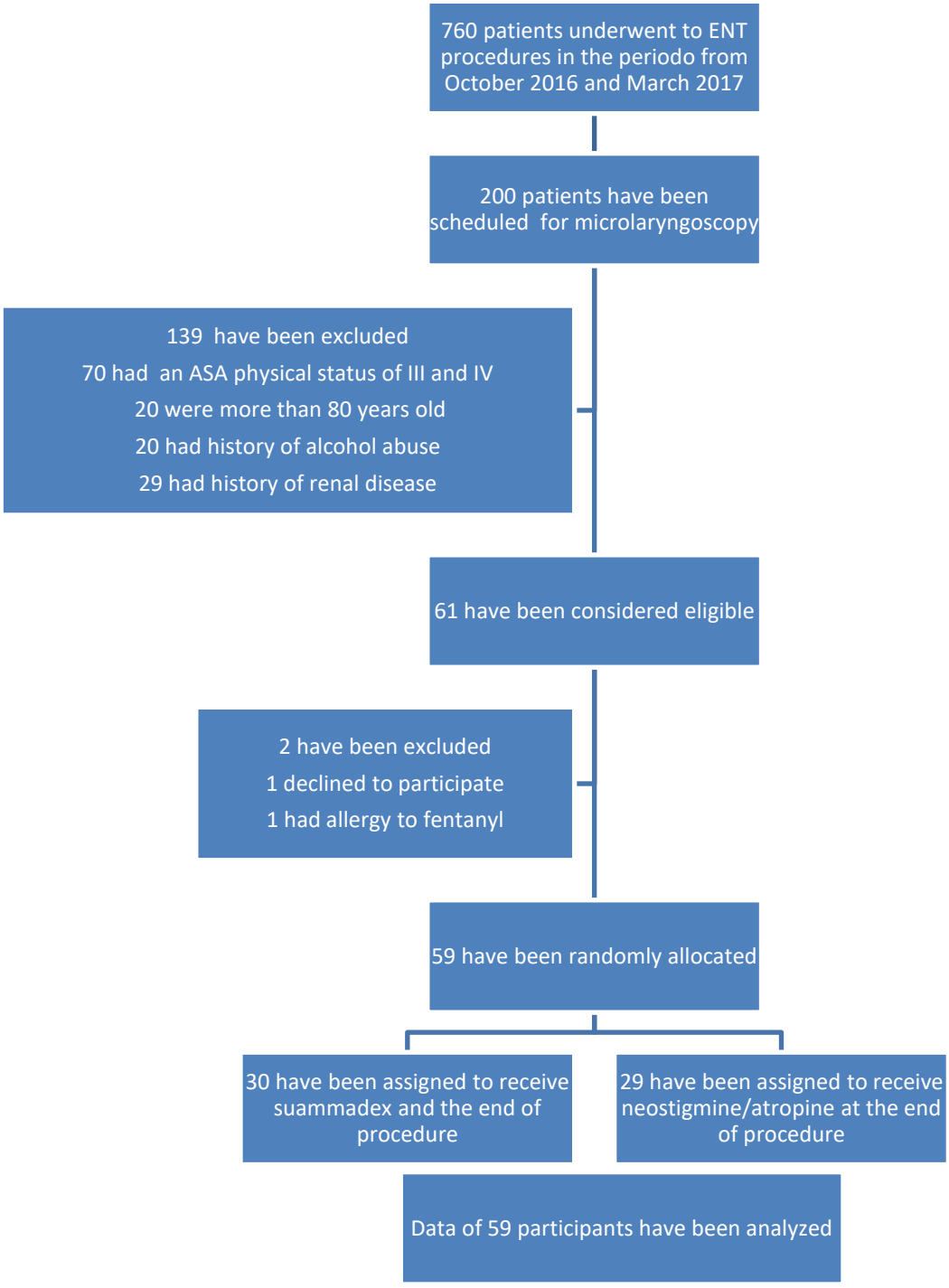

Figure 2 Number of individuals who has been screened, enrolled, allocated and included in statistical analysis. CNS = Central Nervous System

Each participant has signed an informed consent both for enrolling and publication of their individual details and accompanying images in this manuscript. The authors hold all the consent forms. Patients are equally distributed in both groups and main characteristic are shown on table I.

	SUG		NEO		
Total	30		29		
Male	16		14		
Female	14		15		
	Mean	**SD**	**Mean**	**SD**	**p value**
Age (yo)	55,66	14,06	49,20	17,76	0,1198
Weight (Kg)	72,94	13,60	66,30	15,39	0,0779
Height (cm)	170,63	8,78	167,83	11,00	0,2761
BMI ($Kg*m^{-2}$)	25,01	4,03	23,37	3,87	0,1078
Fentanyl (mcg)	151,56	36,82	147,33	39,82	0,6663
Fentanyl ($mcg*kg^{-1}$)	2,08		2,22		
Propofol (mg)	166,88	32,17	155,67	32,66	0,1789
Propofol ($mg*kg^{-1}$)	2,29		2,35		
Rocuronium (mg)	46,31	7,47	42,57	8,42	0,0696
Rocuronium ($mg*kg^{-1}$)	0,63		0,64		
Neostigmine (mg)			3,08	0,67	
Neostigmine ($mcg*kg^{-1}$)			46,51		
Atropine (mg)			1,23	0,43	
Atropine ($mcg*kg^{-1}$)			18,51		
Sugammadex (mg)	180	36,37			
Sugammadex ($mg*kg^{-1}$)	2,47				
TOF ratio > 0.9 (min)	3,07	1,22	11,67	4,28	< 0.0001

Table I Patients characteristic. Data are shown as mean and standard deviation (SD). P value has been calculated through a student t test.

In the NEO group mean (±SD) and median (25th to 75th percentiles) of basal TF were 1.31 (±0.75) and 1.07 (0.81 to 1.50) respectively. In the SUG group mean and median of basal TF were 1.02 (±0.35) and 1.00 (0.77 to 1.21) respectively. The GEE multiple linear regression model has been used to analyze the difference between basal TF and 30 minutes TF (thickening fractioning measured 30 minutes after the extubation) called ΔTF30 in both

groups. ΔTF30 was significantly lower in participants who have received sugammadex than in whom has received neostigmine as reversal drug (p value < 0.0001) (Figure 3 and 4).

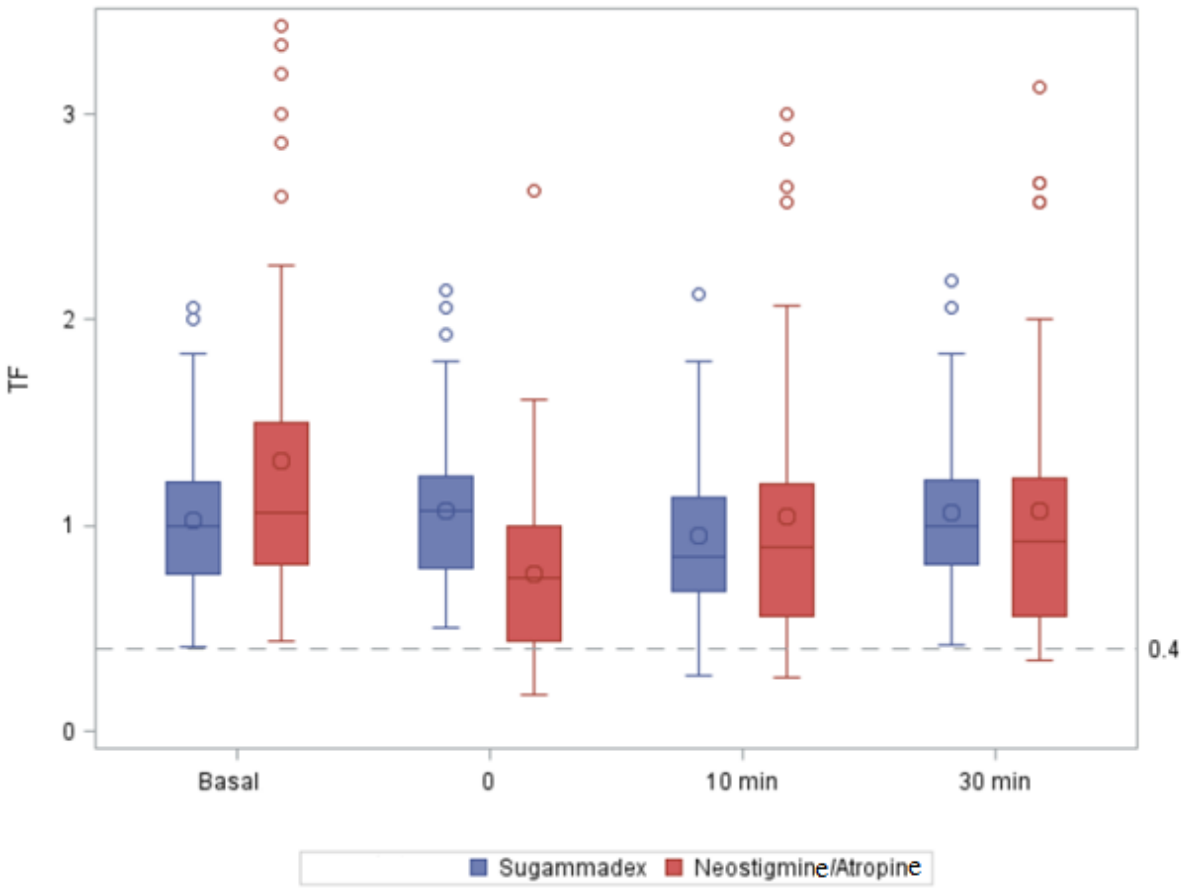

Fig 3. TF calculated before anesthesia (basal), at the moment of extubation (0) and 10 and 30 minutes after extubation in both groups

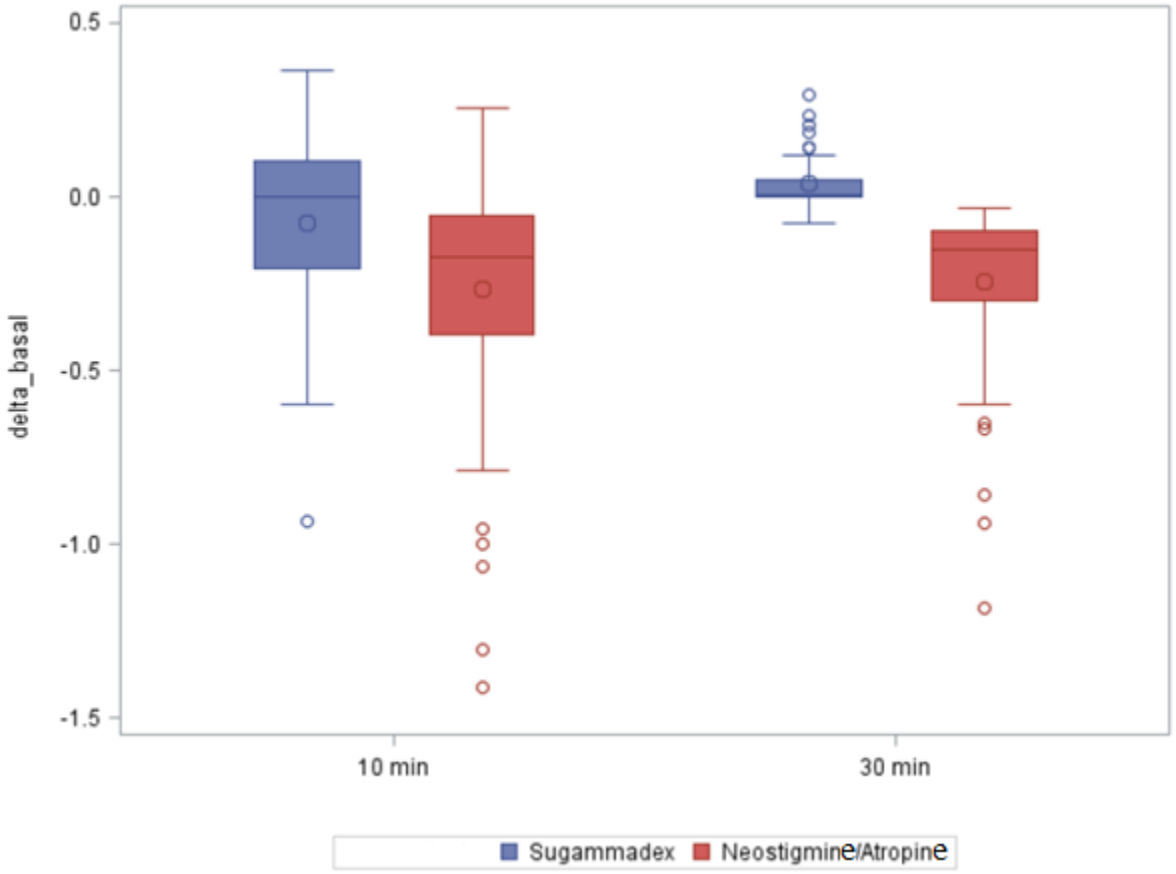

Fig 4 Difference between basal TF and 10 and 30 minutes after orotracheal tube removal in both groups

One patients in the NEO group has developed laryngospasm few seconds after the extubation without any need of reintubation. Anyhow, all the rest of participants enrolled did not developed further postoperative respiratory complications, independently to group allocation. One subject in the NEO group has complained of headache in the postoperative period. Moreover, five people who has received neostigmine has shown drooling in the recovery room. 27.59% of participants in the NEO group has experienced PONV whilst nausea and vomitus accounted for 6.67 of the total percentage in the SUG group (Table II and III). The overall adjusted odds ratio was 5.333 (95% confidence interval 1.025 to 27.758) with a p value of 0.0467 (Fig 5).

PONV	Sugammadex	Neostigmine/Atropine	Total
No	28	21	49
Yes	2	8	10
Total	30	29	59

Table II number of cases of PONV in both groups

PONV	Sugammadex (%)	Neostigmine/Atropine (%)
No	93.33	72.41
Yes	6.67	27.59

Table III Percentages of cases of PONV in both groups

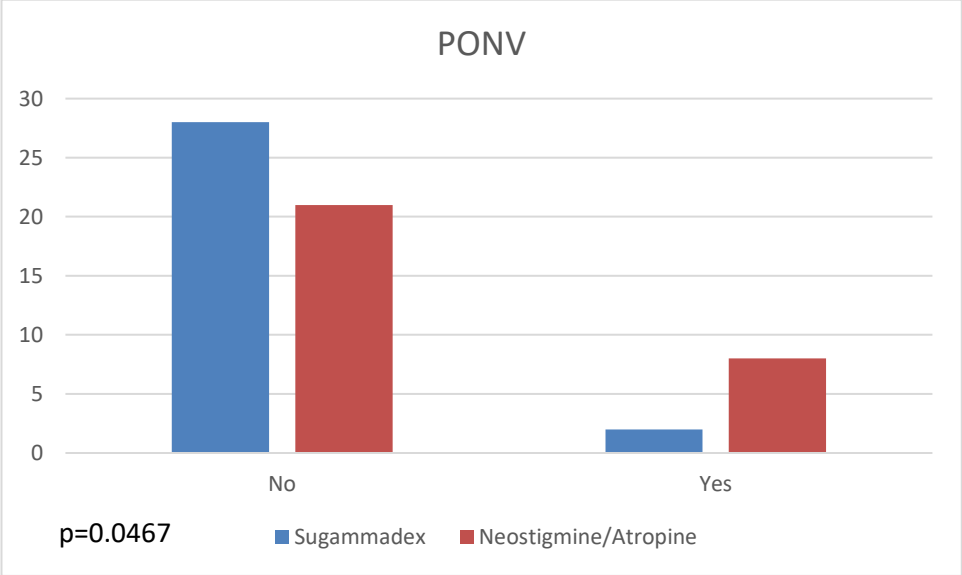

Fig 5 Bar chart for the incidence of PONV

Discussion

Ultrasound technology is a safe, accurate and cost-effective bedside tool, capable of easing physical examination if used by well-trained physicians [46]. In the last decades, ultrasound machines have become very popular in managing critically ill patients, both in emergency departments and in ICUs. The main fields of interest for this technique include point-of-care echocardiography, evaluation of volume status, lung ultrasound (diagnosis of pneumothorax, consolidations, pleural effusions), evaluation of free abdominal fluid accumulation , or assistance in the placement of vascular accesses and other invasive devices such as pleural or abdominal drainages [47]. To the best of our knowledge, one of the first applications of ultrasonography to the diaphragm was in 1989 [14]. Since that moment, there has been an increasing interest in diaphragm echography. The main fields of research have been post-operative paralysis [17-19], assessment of neuromuscular disorders [48-50], weaning from MV [20, 51], management of medical patients with dyspnea [19] and evaluation of diaphragm rupture in trauma patients [52]. A variety of ultrasonographic methods have been used to evaluate diaphragm thickness or excursion: two-dimensional evaluation of the craniocaudal displacement from the renal pelvis [53]; M-mode of the thick echogenic line visualized through the liver acoustic window [16, 17, 54, 55]; two-dimensional and M-mode evaluation of the diaphragm in the ZOA [13, 14, 19, 56, 57].

Ultrasound assessment of the diaphragm is not feasible if the operator is not adequately trained, but when skilled operators are available this tool enables bedside evaluations of the major respiratory muscle. We have observed (unpublished observations) that the reproducibility and repeatability of diaphragm ultrasonography is moderate when the test is performed by three different operators with different levels of experience with sonography.

For the primary endpoint the present study is the first one that has assessed if TF measurements in the operating room has enabled physicians to diagnose and eventually treat recurarization after dNMB. The rational for comparing sugammadex to neostigmine, 30 minutes after the extubation, is that the latter has a pharmacokinetic profile that cannot avoid recurarization, especially when an intermediate or long-lasting muscle relaxant is administered. By contrast, the former avoids recurarization due to its stable binding with steroid NMBA molecules by means of van der Waals and hydrophobic interactions [58]. In our study there was no difference between basal TF and 30 minutes TF in the SUG group; otherwise in the NEO group basal TF was greater than that one measured at thirty minutes with a statistical significant difference of ΔTF30 among the two groups. The occurrence of a weakening of diaphragm thickness during inspiration, in patients who received neostigmine/atropine, has happened even though acceleromyography has showed a TOF ratio greater than 0.9 at the moment of orotracheal tube removal. Considering that this is the first experience that has included diaphragm sonography in evaluating its thickness after dNMB, it is not known if a partial recurarization happens systematically in each individual who receive neostigmine/atropine as reversal drug. However, this AChEI halves it life in a period ranging from 15 to 31 minutes increasing the possibility of a partial residual paralysis when an intermediate-acting blocking agent such as rocuronium has been used [59].

Moreover, 3 patients in the NEO group did not reach a TF of 0.4, a value considered the threshold in order to exclude diaphragmatic dysfunction based on previous study and our unpublished data on heathy volunteers [13]. This scenario cannot be considered irrelevant because potential recurarizations remain unrecognized and, consequently, the incurrence of postoperative respiratory complications.

For the secondary endpoint, as written above, no respiratory complications have been recorded during the length of stay in the hospital of participants. The incidence of

postoperative nausea and vomiting was greater in the NEO than in the SUG group with an odds ratio of 5.33 with a p value < 0.05. Nonetheless, there was no delays in discharging for patients who received neostigmine.

Based on our results, even if a TOF ratio is greater than 0.9 at the moment of extubation regardless of NMBA administered there is a small percentage of individuals in the NEO group who develop diaphragmatic dysfunction thirty minutes after orotracheal tube removal. This dysfunction has not been observed in subjects who has received sugammadex. Therefore, we strongly suggest to assess diaphragmatic thickening by means of ultrasonography for the purpose of detecting residual curarization after deep neuromuscular blockade. Clinicians need to be trained by experienced personnel due to the risk of overestimating or underestimating the thickness of this muscle. Besides, the administration of sugammadex as a reversal drug could be justified to prevent PONV and respiratory complications considering that the more and more outpatients are scheduled to undergo to short procedures such as microlaringoscopy.

Our study has some limitations. Primarily, the study is a single center trial. Secondarily, the protocol has been developed enrolling patients ASA physical status I and II in ENT surgery. It is not known how diaphragm thickening behaves in procedures involving this muscle such as thoracic and abdominal surgery. Moreover, patients ASA physical status III and IV could have underlying condition that affects diaphragmatic function. This is a first experience that assesses diaphragm recovery for the purpose of identifying residual curarization. Indeed, to reinforce this evidence, it is necessary to undertake multicenter randomized controlled trials involving a greater number of participants in different types of surgery.

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