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MISCELLANEOUS

Deep versus moderate neuromuscular block during one-lung ventilation in lung resection surgery

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KEYWORDS
Neuromuscular block;
One-lung ventilation;
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Abstract

Background and objectives: Neuromuscular relaxants are essential during general anesthesia for several procedures. Classical anesthesiology literature indicates that the use of neuromuscular blockade in thoracic surgery may be deleterious in patients in lateral decubitus position in one-lung ventilation. The primary objective of our study was to compare respiratory function according to the degree of patient neuromuscular relaxation. Secondary, we wanted to check that neuromuscular blockade during one-lung ventilation is not deleterious.

Methods: A prospective, longitudinal observational study was made in which each patient served as both treated subject and control. 76 consecutive patients programmed for lung resection surgery in Gregorio Marañon Hospital along 2013 who required one-lung ventilation in lateral decubitus were included. Ventilator data, hemodynamic parameters were registered in different moments according to train-of-four response (intense, deep and moderate blockade) during one-lung ventilation.

Results: Peak, plateau and mean pressures were significantly lower during the intense and deep blockade. Besides compliance and peripheral oxygen saturation were significantly higher in that moments. Heart rate was significantly higher during deep blockade. No mechanical ventilation parameters were modified during measurements.

Conclusions: Deep neuromuscular blockade attenuates the poor lung mechanics observed during one-lung ventilation.

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PALAVRAS-CHAVE
Bloqueio neuromuscular;
Ventilação seletiva;
Cirurgia de ressecção pulmonar

Bloqueio neuromuscular profundo *versus* moderado durante a ventilação monopulmonar em cirurgia de ressecção pulmonar

Resumo

Justificativa e objetivos: Os relaxantes neuromusculares são essenciais durante a anestesia geral para vários procedimentos. A literatura clássica de anestesiologia indica que o uso do bloqueio neuromuscular em cirurgia torácica pode ser prejudicial em pacientes posicionados em decúbito lateral com ventilação seletiva. O objetivo primário deste estudo foi comparar a função respiratória de acordo com o grau de relaxamento neuromuscular do paciente. O objetivo secundário foi verificar que o bloqueio neuromuscular durante a ventilação seletiva não é prejudicial.

Métodos: Estudo observacional, prospectivo e longitudinal no qual cada paciente serviu como indivíduo de estudo e controle. Foram incluídos 76 pacientes consecutivos, agendados para cirurgia de ressecção do pulmão no Hospital Gregorio Marañon ao longo de 2013, submetidos à ventilação seletiva em decúbito lateral. Os dados do ventilador e os parâmetros hemodinâmicos foram registrados em diferentes momentos de acordo com a resposta por sequência de quatro estímulos (bloqueio intenso, profundo e moderado) durante a ventilação seletiva.

Resultados: As pressões de pico, platô e média foram significativamente menores durante os bloqueios intenso e profundo. Além disso, complacência e saturação periférica de oxigênio foram significativamente maiores nesses momentos. A frequência cardíaca foi significativamente maior durante o bloqueio profundo. Não houve alteração dos parâmetros da ventilação mecânica durante as mensurações.

Conclusões: O bloqueio neuromuscular profundo atenua a mecânica pulmonar deficiente observada durante a ventilação seletiva.

Introduction

In general, the use of neuromuscular relaxants (NMRs) during surgery requiring general anesthesia has been justified by the need to induce total muscle paralysis in order to avoid undesirable patient movements that could pose a hazard for correct surgical maneuvering, and to ensure optimum conditions for endotracheal intubation.

Anesthesia in lung resection surgery requires the use of NMRs to avoid diaphragmatic movements or reflex coughing that can cause potentially dangerous situations, particularly when the surgeon is manipulating vital lung structures such as bronchi, vessels or nerves. On the other hand, correct positioning of the double-lumen tube must be checked by introducing the fibrobronchoscope through each lumen, and this also may cause unexpected patient movements, including cough. The aspiration of secretions (a common practice in these patients) likewise may give rise to undesired patient movements. On the other hand, routine lung recruitment maneuvering in surgery of this kind requires the use of NMRs to facilitate opening of the collapsed lung regions.

However, the classical anesthesiology texts indicate that the use of NMRs in this type of surgery may be harmful in patients in lateral decubitus and with the upper lying lung isolated from ventilation, since paralysis of the lower half of the diaphragm causes the abdominal organs to exert greater pressure upon the dependent lung – reducing pulmonary compliance and increasing the airway pressures.[1] This in turn would further worsen the lung mechanics during this delicate period of one-lung ventilation (OLV).[2] Although there is very little information on the clinical effect of NMRs in chest surgery, more data are available on the use of these drugs in situations of low compliance and high airway pressures, such as acute respiratory distress syndrome[3] or laparoscopic abdominal surgery.[4] Improvements in gas exchange, airway pressure and lung compliance have been observed in patients administered NMRs during mechanical ventilation in critical care units.

We hypothesize that the absence of muscle tone (diaphragm and chest wall muscles) induced by NMRs will cause the gas mixture supplied by the mechanical ventilator to facilitate ventilation during OLV by improving thoracic compliance and/or reducing the airway pressures.

The primary objective of our study was to compare respiratory function (airway pressure and static lung compliance) according to the degree of patient neuromuscular relaxation.

Methods

A prospective, longitudinal observational study was made in which each patient served as both treated subject and control. The study was approved by the Ethics Committee of Gregorio Marañón University General Hospital (Doctor Esquerdo 46 street, Madrid, Spain) (CEIC 377/13) in January 2013. The patients were included in the protocol after signing the corresponding informed consent document.

The protocol contemplated the consecutive inclusion, in 2013, of all patients ($n = 76$) scheduled for lung resection surgery via thoracotomy or videothoracoscopy, and who required OLV in lateral decubitus with ventilation only of the lower lying (or dependent) lung. Patients presenting any of the following circumstances were excluded:

Serious heart disease with the risk of altered myocardial compliance (left ventricular ejection fraction <50%, altered diastolic function);

Allergy or contraindications to the use of rocuronium or sugammadex;

Prior neuromuscular disease;

Body mass index >30 $kg \cdot m^{-2}$.

Anesthetic protocol

Monitoring initially comprised ECG, peripheral oxygen saturation (SpO_2) via pulsioxymetry, noninvasive arterial pressure recording, and the Bispectral index (BIS)® (BIS monitor, Covidien, Minneapolis, USA).

Later, anesthetic induction was carried out with fentanyl 3–5 $\mu g \cdot kg^{-1}$, propofol 2–3 $mg \cdot kg^{-1}$ and rocuronium bromide 0.6 $mg \cdot kg^{-1}$ (MSD, Oss, The Netherlands).

After reaching optimum conditions, tracheobronchial intubation was performed with the insertion of a double-lumen tube (no. 35–37 in females and 39–41 in males). Correct positioning was checked by clinical inspection and fibrobronchoscopy. The patient was then connected to a Primus® ventilator (Dräguer, Lübeck, Germany) for volume controlled mechanical ventilation. During two-lung ventilation, the tidal volume (Vt) was 8 $mL \cdot kg^{-1}$, with a respiratory frequency of 12 rpm, an I/E ratio of 1:2, and PEEP 5 mmHg. During OLV, the Vt was reduced to 6 $mL \cdot kg^{-1}$, while the rest of the parameters remained the same as during two-lung ventilation. A FiO_2 allowing $SpO_2 > 90\%$ was used.

A radial artery catheter was placed and a Flo-trac Vigileo® monitor (Edwards Lifesciences, Irvine, CA, USA) was used to obtain data on Stroke Volume Variation (SVV), Cardiac Index (CI) and Stroke Volume Index (SVI), among other parameters. Lastly, the patient was placed in lateral decubitus and paravertebral block ipsilateral to the operated side was performed (generally at level T5–T6).

Anesthesia was maintained with sevoflurane® (Abbvie, North Chicago, IL, USA) at a concentration of 1%–2% as required to secure adequate depth of anesthesia determined by BIS 40%–60%, and to maintain the hemodynamic parameters within normal limits. Analgesia was provided in the form of a continuous perfusion of 0.5% bupivacaine (0.15 $mL \cdot kg^{-1} \cdot h^{-1}$) through the epidural catheter, with 100 $\mu g \cdot kg^{-1}$ fentanyl boluses if the patient showed any clinical evidence of insufficient analgesia.

Crystalloid fluid therapy (2 $mL \cdot kg^{-1} \cdot h^{-1}$) was provided throughout the operation, without fasting replacement. In the case of a mean blood pressure of <60 mmHg, a single 250 mL colloid bolus was administered. If the hypotension persisted, intravenous vasoactive drugs (ephedrine or phenylephrine) were provided.

Neuromuscular relaxation protocol

After anesthetic induction but before rocuronium administration, we monitored motor end plate function using a TOF-Watch SX® acceleromyographic neurostimulator (MSD, Oss, The Netherlands) fitted on the wrist contralateral to the surgical side, to record the activity of the adductor of the thumb. Initial calibration was made before administering the neuromuscular blocker in order to obtain a T1/T4 value as close as possible to 100% and thereby avoid bias in assessing future responses. Depending on the data obtained with this monitor during the maintenance of anesthesia, neuromuscular block (NMB) was classified into four categories according to the number of responses after a Train Of Four (TOF) and the number of responses after applying a tetanic current (Post-Tetanic Count – PTC).

Intense – TOF = 0 and PTC = 0;

Deep NMB (dNMB) – TOF = 0 and PTC = 1;

Moderate NMB (mNMB) – TOF = 0–3 responses;

Recovery – TOF = 4 with T1/T4 > 90%.

Once the patient was placed in lateral decubitus, the data corresponding to the baseline condition were recorded. The same data were again collected once OLV had started (PRE). More than 30 min after the start of OLV, we determined whether NMB was moderate or deep. Once the patient presented moderate NMB, we administered a dose of 0.3 $mg \cdot kg^{-1}$ of rocuronium to induce intense or deep NMB, as registered by continuous monitoring with the neurostimulator. After reaching this degree of neuromuscular relaxation, we recorded the ventilatory and hemodynamic data every 5 min until appearance of the second response of the PTC. Specifically, we collected the data obtained after 5 and 15 min (POST 1 and POST 2), and calculated the mean of the two measurements. During the three measurements made under conditions of OLV, none of the mechanical ventilation parameters were modified.

The following mechanical ventilator data were recorded: airway pressures (peak, plateau, mean and PEEP), static lung compliance and pulsioxymetry. In addition, we recorded the following hemodynamic parameters at each of the mentioned timepoints: heart rate (HR), mean blood pressure (MBP), Stroke Volume Variation (SVV), Cardiac Index (CI) and Stroke Volume Index (SVI).

All measurements were made during a period of at least 30 seconds, without surgeon manipulation of the intrathoracic structures.

At the end of the operation, and after washing the surgical wound and applying the dressings, the patients were moved to the recovery ward. Hypnosis was maintained to secure BIS < 60% before administering sugammadex. In the supine position, and after obtaining the information supplied by the TOF-Watch SX®, rocuronium was reverted by administering a sugammadex dose of 4 $mg \cdot kg^{-1}$ in the case of dNMB and 2 $mg \cdot kg^{-1}$ in the case of mNMB. We recorded the time elapsed from sugammadex administration to TOF > 90%, and the time from closure of the chest cavity to extubation.

Statistical analysis

The Student *t*-test for paired samples was used to compare differences in the quantitative variables between groups – the values recorded during NMB after neuromuscular relaxant administration being averaged per the number of recordings obtained. Statistical significance was considered for $p < 0.05$. Comparisons between patients with deep versus moderate NMB at the end of the operation were made using

Table 1 Demographic variables and respiratory function tests.

	n	Mean ± SD
Weight	76	74 ± 15
Height	76	165 ± 8
Age	76	62.3 ± 15
FEV1 pred	76	94 ± 22
FVC pred	76	102 ± 18
FEV1	76	2356 ± 712
FVC	76	3213 ± 804

Weight is expressed as kg. Height is expressed as cm. Age is expressed as years. FEV1 and FVC are expressed as mL.

the Mann–Whitney U-test for samples with a non-normal distribution. The SPSS version 17 statistical package was used throughout.

Results

Seventy six patients were included

Table 1 describes the demographic characteristics of the patients. Table 2 shows the evolution of the hemodynamic parameters during deep or intense NMB compared with the values obtained during moderate NMB. There was a significant increase in HR and a significant decrease in SVV and SVI.

All patients showed an increase in airway pressures and a decrease in compliance when OLV was started, accompanied by a drop in SpO_2 (Table 3).

Regarding the effect of a 0.3 mg·kg^{-1} rocuronium dose upon the respiratory mechanics, the mean P_{peak} and $P_{plateau}$ values were seen to decrease significantly (from 25.9 ± 5 to 24.8 ± 5 cmH_2O and from 23.8 ± 4 to 20.4 ± 5 cmH_2O, respectively) on progressing from moderate to deep NMB. Contrarily, mean lung compliance increased by 2 ± 3 mL·cm$^{-1}H_2O$ (POST 1) and 5.1 ± 3 mL·cm$^{-1}H_2O$ (POST 2) after the administration of a 0.3 mg·kg^{-1} rocuronium bolus (Table 3), and the mean SpO_2 likewise was seen to increase.

All the patients were extubated in the operating room (Table 4). At the time of surgical wound closure, no patient presented TOF > 90%. Furthermore, 10 patients (13.2%) presented deep NMB at the end of the operation. After administering sugammadex, all patients presented TOF > 90% in a little over two and a half minutes on average. The time from sugammadex administration to the recording of TOF > 90%; the time from skin suturing to extubation; and the TOF values at the time of extubation were all similar among the patients with and without deep NMB at the end of the operation (Table 4).

Discussion

Deep NMB during chest surgery involving periods of OLV does not negatively affect ventilation mechanics. Indeed, it may even produce slight improvement expressed as a decrease in airway pressures and improved lung compliance.

Table 2 Hemodynamic values.

	n	Baseline Mean ± SD	PRE Mean ± SD	POST 1 Mean ± SD	POST 2 Mean ± SD	Mean of two measurements Mean ± SD
HR	76	73 ± 14	77 ± 15	80 ± 14[a]	79 ± 14[a]	80 ± 15[a]
MBP	76	78 ± 15	78 ± 15	76 ± 14	79 ± 13	77 ± 13
CI	76	2.55 ± 0.5	2.89 ± 0.6	2.79 ± 0.5	2.84 ± 0.6	2.8 ± 0.5
SVV	76	11.9 ± 3.8	10.3 ± 5.3	9.5 ± 3.9	9.6 ± 6	9.5 ± 5[a]
SVI	76	38 ± 11	38 ± 9	37 ± 7	37 ± 8	35 ± 7[a]
BIS	76	47 ± 8	43 ± 8	43 ± 8	42 ± 7	42 ± 7[a]

HR is expressed as beats per minute. MBP is expressed as mmHg. CI is expressed as liters per minute per square meter of body surface. SVV is expressed as a percentage. SVI is expressed as ml per minute per square meter of body surface.
[a] $p < 0.05$ on comparing with the PRE values.

Table 3 Respiratory and blood gas parameters.

	n	Baseline Mean ± SD	PRE Mean ± SD	POST 1 Mean ± SD	POST 2 Mean ± SD	Mean of two measurements Mean ± SD
Peak P.	76	19.8 ± 3	25.9 ± 5	24.8 ± 5[a]	23.8 ± 4[a]	24.6 ± 5[a]
Plateau P.	76	17.4 ± 4	21.6 ± 5	20.7 ± 5[a]	19.6 ± 4[a]	20.6 ± 5[a]
Mean P.	76	8.5 ± 1	10.4 ± 2	10.2 ± 2[a]	10.2 ± 2	10.2 ± 2[a]
PEEP	76	4.8 ± 1	5.5 ± 1	5.5 ± 1	5.6 ± 1	5.5 ± 1
Compliance	76	45.9 ± 11	32.1 ± 11	34.1 ± 11[a]	37.2 ± 14[a]	34.2 ± 11[a]
SpO_2	76	99.1 ± 1	94.2 ± 3.1	96.0 ± 3	96.1 ± 2.7[a]	96.21 ± 3[a]
End-tidal CO_2	76	36 ± 5	36 ± 5	36 ± 5	37 ± 5	36.26 ± 5

Pressures (peak, plateau, mean and PEEP) measured as cmH_2O. Compliance in mL·cm$^{-1}H_2O$.
[a] $p < 0.05$ on comparing with the PRE values.

Table 4 Dose of sugammadex and times.

	n	All Mean ± SD	mNMB Mean ± SD	dNMB Mean ± SD
Time sugammadex–TOF90 (s)	76	160 ± 64	158 ± 66	163 ± 38
Time closure–extubation (min)	76	15.3 ± 7.5	15.1 ± 8	18.2 ± 8
TOF extubation %	76	99 ± 10	99.6 ± 11	97.5 ± 5

Doses of sugammadex and rocuronium expressed as mg. Time expressed as seconds.

Classically, the use of neuromuscular relaxants during OLV has been considered risky and even relatively harmful. With the patient in lateral decubitus and with the lower lying lung as the dependent lung, the compressive effect of the abdominal organs upon the flaccid diaphragm would cause an increase in intrathoracic pressures, complicating the ventilation of that lung.[1] In an experimental study, Bregeon et al. compared the pulmonary effects in animals with healthy lungs subjected to mechanical ventilation according to whether or not NMB had been administered. The authors recorded lesser lung compliance and a greater inflammatory response in the animals subjected to NMB, and concluded that the elimination of diaphragmatic activity might be responsible for the described effects.[5] In 2010, Xiang et al. reported no benefits in terms of compliance or the subjective surgical technical conditions when administering rocuronium in continuous perfusion or as a simple bolus dose in anesthetic induction among 40 patients subjected to gynecological laparoscopic surgery. However, in the group administered the single induction dose, the surgical time was significantly shorter – a fact that could alter the results obtained.[4] Similar results have been published by Paeck et al. on comparing two groups of patients subjected to pelvic laparoscopic surgery and maintained with propofol and remifentanil in one group and adding rocuronium in the other – no significant differences being observed in relation to the hemodynamic parameters or respiratory data such as peak pressure or end-tidal CO_2.[6] However, our results not only reveal no worsening of the peak and plateau pressures and of lung compliance in the patients subjected to OLV under deep NMB, but actually suggest slight improvement of these parameters in such patients. This allowed the use of lower airway pressures for maintaining adequate protective ventilation, with the benefit this implies for the patient.[7] To our knowledge, this is the first study comparing the effect of dNMB versus mNMB upon ventilatory mechanics during OLV in chest surgery.

On the other hand, significant differences were observed on comparing the PRE and mean POST heart rate values. The heart rate was seen to increase after deep block, possibly in relation to the pain that might have been caused by infusion of the blocker drug.

On the other hand, a significant decrease in SVV and SVI was recorded on comparing those two timepoints, which could be explained by an increased venous return. The decrease in ventilatory pressures after deep NMB could favor intrathoracic venous return at these timepoints, and thus reduce stroke volume variability.

One-lung ventilation and NMB are advisable in chest surgery, and specifically in lung resection surgery. During OLV, the use of NMB would facilitate protective ventilation, while failure to do so could increase the risk of respiratory complications related to acute lung injury due to the damage which high airway pressures could cause in the ventilated lung.[8,9]

One of the scenarios in which the influence of NMB upon ventilatory mechanics has been most extensively investigated is that of patients admitted to critical care due to Acute Respiratory Distress Syndrome (ARDS). The NMRs mostly have been shown to facilitate mechanical ventilation and lessen oxygen consumption in these patients, and can even improve arterial oxygenation. However, their routine use does have risks (critical patient neuropathy) that may outweigh the pulmonary benefits obtained.[10] At present, this controversy has caused NMB to be advised in the first 48 h of mechanical ventilation and in concrete and limited situations – avoiding its indiscriminate use over the subsequent days.

Forel et al. recorded a lesser inflammatory response in ventilated patients subjected to NMB than in those who do not receive neuromuscular relaxants.[11] Neuromuscular block therefore should also be considered in this type of surgery, where the perioperative pulmonary proinflammatory response is associated to the appearance of acute lung injury – thereby worsening the postoperative prognosis of the patients.

Classically, there has been concern among anesthetists over residual NMB (rNMB) after extubation and in the immediate postoperative period. The incidence of rNMB varies from 2% to 64%, depending on the literature source,[12] though in all cases it complicates patient recovery, with an increased number of complications.[13] Sugammadex, a modified cyclodextrin, acts by binding to rocuronium and vecuronium, facilitating their elimination. Compared with the use of neostigmine, it attenuates the frequency of rNMB at the end of the operation.[14]

Limitations

The degree of neuromuscular relaxation is not the same in all muscles, and in the present study we monitored relaxation in the adductor of the thumb, not in the muscles of the chest cavity (including the diaphragm). Contraction of the adductor of the thumb has been regarded as the gold standard in neuromuscular monitoring,[15] though it is known that when this muscle is fully paralyzed, the diaphragm and other muscles of the abdominal wall may have recovered from NMB.[16] Indeed, the diaphragm is one of the muscles most resistant to both depolarizing and non-depolarizing muscle relaxants. In general, the diaphragm requires a dose of between 1.4 and 2 times that needed to block the adductor of the thumb.[17] All this could explain why some diaphragmatic muscle activity may be observed despite adequate NMB as monitored at the patient wrist.[18]

Besides, pulmonary hipoxic vasoconstriction may alter SpO_2, but, we consider more significative changes in compliance and in airway pressures rather than isolated change in SpO_2.

Conclusion

Deep NMB attenuates the poor lung mechanics observed during OLV thanks to the induction of improved lung compliance and lesser airway pressures. It therefore could be regarded as a simple tool favoring the use of protective ventilation without complicating early and safe patient extubation, thanks to the reversal of NMB with an adequate sugammadex dose at the end of the operation.

Conflicts of interest

The authors declare no conflicts of interest.

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