Neuromuscular Blocking Agents

Subjects: Critical Care Medicine

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The use of neuromuscular blocking agents (NMBAs) is common in the intensive care unit (ICU). NMBAs have been used in critically ill patients with lung diseases to optimize mechanical ventilation, prevent spontaneous respiratory efforts, reduce the work of breathing and oxygen consumption, and avoid patient–ventilator asynchrony.

Keywords: neuromuscular blocking agents ; acute respiratory distress syndrome ; chronic obstructive pulmonary disease

1. Introduction

Neuromuscular blocking agents (NMBAs) represent a landmark in modern anesthesia, acting on the neuromuscular junction by blocking the transmission of nervous impulses in the motor endplate of striated muscles, resulting in skeletal muscle paralysis [1].

The use of NMBAs is common in the intensive care unit (ICU), especially in cases of acute distress respiratory syndrome (ARDS). It is used in 25–45% of cases, with different practices associated with geographic differences [2]. NMBAs are used in pulmonary critical care patients, such as those with ARDS, to optimize mechanical ventilation (MV), prevent spontaneous respiratory efforts, reduce the work of breathing and oxygen consumption, reduce the risk of barotrauma, and avoid patient–ventilator asynchrony [3][4]. NMBAs have many other beneficial effects on lung function, improving alveolar recruitment, and they can reduce the concentration of interleukins and tumor necrosis factor-alpha, leading to anti-inflammatory effects [5].

Patients with severe ARDS, status asthmaticus, and chronic obstructive pulmonary disease (COPD) often need MV support, which is frequently insufficiently controlled with sedative and analgesic drugs [2][6][7]. NMBAs seem to have beneficial effects on airway pressures. In a small trial conducted on mechanically ventilated children with severe acute hypoxemic respiratory failure, NMBAs decreased the mean airway pressure (p = 0.039) and the oxygenation index (OI) (p = 0.039) in all patients [8]. In a recent trial conducted on 30 patients with moderate-to-severe ARDS, neuromuscular blockade treatment did not affect the transpulmonary driving pressure (expressed as inspiratory lung pressure minus expiratory lung pressure and defined as a surrogate of the stress applied to the lungs) at 48 h [9]. NMBAs also seem to play a role in gas exchange. In their study, Gainnier et al. [10] reported a higher PaO_2/FiO_2 ratio at 48, 96, and 120 h in patients randomized to the NMBA group (p = 0.021).

Thus, when deep sedation fails or is not tolerated, NMBAs could be administered to harmonize the respiratory function [4].

Although these beneficial effects, especially in patients with ARDS, the impact of NMBAs on mortality remains controversial [11]. The routine use of NMBAs in ICUs has decreased in the last decade due to potential harmful effects resulting from immobilization such as venous thrombosis, development of critical illness myopathy, ICU-acquired weakness (ICUAW), autonomic interactions, awareness during paralysis, and residual paralysis after cessation of NMBAs [4][12].

2. General Advantages and Disadvantages of Using NMBAs in Critically Ill Patients with Lung Diseases

NMBAs can ameliorate the management of ventilation [13], limiting decruitment, inspiratory effort, and expiratory alveolar collapse [9]. Some studies demonstrated improved oxygenation using NMBAs, possibly related to the effects on reducing the work of breathing [12][14]. In a randomized controlled trial on patients with ARDS receiving conventional therapy plus placebo or NMBAs, treatment with cysatracurium exerted anti-inflammatory effects by reducing the concentration of interleukins and tumor necrosis factor-alpha in serum and bronchoalveolar lavage [5].

Intra-abdominal hypertension (IAH), defined as an intra-abdominal pressure (IAP) above 12 mmHg, is one of the possible conditions in which the use of NMBAs can improve lung function. It is estimated that around 20% of patients present with IAH on admission to the ICU and almost 50% will develop IAH within the first week in the ICU [14][15]. IAH often progresses with an upper shift of the diaphragm and decreased lung volume and chest wall compliance, resulting in increased airway pressures [16] and decreased oxygenation [17]. Although abdominal contractions can falsely increase IAP values, to date, no recommendation on increasing sedation or using NMBAs to accurately measure IAP has been defined [17]. A recent guideline for the management of IAH and abdominal compartment syndrome in critically ill patients highlighted the possibility of considering the use of NMBAs for persistent IAH [18].

When paralyzing the patient, it is always important to consider the possibility of the development of complications associated with the administration of NMBAs, such as corneal abrasions [4] and venous thrombosis [19], and complications associated with prolonged immobilization such as ICUAW and myopathy. The relationship between ICUAW and NMBAs is controversial [4]. Although a recent meta-analysis did not show an association between NMBAs and neuromuscular dysfunction acquired in critical illness (odds ratio (OR), 1.21; 95% confidence interval (CI), 0.67–2.19), merged data from all the included studies suggested a modest association (OR, 1.25; 95% CI, 1.06–1.48; I = 16%) between NMBA use and ICUAW [20]. Many other studies have confirmed the association [21][22] or the potential risk [23] of the development of ICUAW with the use of NMBAs, but with a weak study design and high risk of bias because of the multi-factorial causes of ICUAW and heterogeneous outcomes [24]. In this uncertainty, the association between the use of NMBAs and critical weakness does not seem to be reasonable. Thus, recent SCCM guidelines did not relate the use of NMBAs with the risk of ICUAW, rather associating it with prolonged immobility and muscle disuse [25]. In addition, NMBAs impaired airway protective reflexes [26] and increased the risk of upper airway obstruction and pneumonia. Moreover, these patients needed deep sedation due to prolonged treatment with NMBAs [27].

Critically ill patients often have multi-organ-system disorders and receive treatments for longer periods; thus, the elimination of NMBAs and metabolites can be delayed, resulting in greater accumulation [4][28] and adverse events, difficulty in weaning from the ventilator [29], and the risk of venous thrombosis [19].

3. Patient–Ventilator Asynchrony

Patient–ventilator asynchrony is frequently observed during MV and is associated with worse outcomes and higher mortality [30].

Ventilatory under-assistance or over-assistance translates to different types of asynchronies [31]. Under-assistance could lead to an increased load on respiratory muscles, air hunger, and lung injury caused by excessive tidal volumes (V_T). Over-assistance could yield decreased inspiratory drive, which may result in reverse triggering, thus worsening lung injury. In addition, asynchronies may increase intrathoracic pressure, thus modifying cardiac output and hemodynamic status [32].

Yoshida et al. [33] demonstrated that an increase in distending pressure, caused by spontaneous effort in mechanically ventilated patients, could worsen a pre-existing lung injury through a pendelluft effect from non-dependent lung areas toward dependent areas because the diaphragm contraction is poorly transmitted across the pleural surface in an injured lung. Therefore, management of patient–ventilator asynchrony with neuromuscular blockade may be considered to minimize the lung and diaphragm injury associated with spontaneous breathing [34], especially in patients with ARDS [35].

The use of NMBAs in the critical care setting is frequently guided by personal experience and local practice, more than validated guidelines and recommendations [25]. NMBAs minimize the risk of ventilator-induced lung injury (VILI). However, the use of NMBAs requires adequate sedation to prevent VILI and may lead to extended time on MV, longer ICU stays, and increased risk of ventilator-associated pneumonia (VAP) [36][37]. NMBAs should be administrated with adequate sedation. Nevertheless, the sedation level is a factor that could affect the incidence of asynchrony. Observational studies showed an association between deep sedation and a higher incidence of patient–ventilator asynchronies [30][38].

A multi-center study showed a lower incidence of asynchronies with lighter sedation with dexmedetomidine compared with deeper sedation with propofol [39]. So, increasing sedation does not always represent an effective strategy to reduce asynchrony. When asynchrony is related to double triggering, deeper sedation associated with neuromuscular blockade could be taken into consideration. In contrast, in the case of reverse triggering, muscle effort could result in inflation so that a reduced sedation and NMBA strategy could be considered [40].

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