Rocuronium Continuous Infusion for Profound Neuromuscular Blockade: A Systematic Review and Meta-analysis

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Objectives: Rocuronium is a muscle relaxant with increased use, because of the binding relation with the reversal agent sugammadex. Its continuous infusion benefits the maintenance of deeper levels of neuromuscular blockade (NMB) ensuring an improved and stable solution for daily surgical anesthesia. This is systematic review on current approaches on rocuronium infusion and monitoring parameters when using rocuronium continuous infusion for profound muscle relaxation (0–2 posttetanic count).

Methods: Database search included publications worldwide until February 28, 2019. Main outcomes studied were the amount of rocuronium used, surgical conditions, and time of recovery after standard sugammadex dose. Secondary assessments include methodological features of rocuronium administration and blockade monitoring. Meta-analysis was conducted to assess the effect means difference of surgical conditions, followed by heterogeneity and sensitive analysis.

Results: Eight randomized trials were identified as eligible. Three studies allowed to account that maintenance of profound muscle relaxation a mean difference of 0.251 mg/kg per hour (95% confidence interval = 0.169–0.334) of rocuronium is required, in relation to moderate NMB, significantly improving surgical conditions (mean difference = 0.653, 95% confidence interval = 0.451–0.856, in a 5-point scale, including data from 6 trials). Only 2 studies presented results on reversal after sugammadex; therefore, no significant results were yielded regarding the time required to complete NMB recovery.

Conclusions: Rocuronium continuous infusion for profound neuromuscular blockade presents inherent advantages in terms of maintenance and stability of the paralysis. Further studies should address the methodological approaches and benefits/drawbacks of this approach.

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Key Words: rocuronium infusion, neuromuscular blockade, NMB monitoring, general anesthesia, posttetanic count

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During general anesthesia, the use of neuromuscular blockade agents (NMBAs) is essential for intubation quality, complete immobilization, and easier/lenient muscle incision/operation.[1,2] In daily anesthesia, deeper levels of muscle relaxation are used to ensure these conditions and continuous infusion benefits the blockade stability. The aim of this study is to behold the current approaches on rocuronium infusion and monitoring parameters for the maintenance of profound neuromuscular blockade (NMB).

Rocuronium is an NMBA frequently used and characterized by quick onset action, dose-based duration, no secondary effects known, no active metabolites nor toxins, and hepatic elimination.[3] The reference for dosage potency is based on the effective dose to inhibit muscle function by 95% (ED_{95}) of the drug (0.305 mg/kg), equivalent to the median dose required to produce 95% of the therapeutic effect. Usually, for an effective induction, $2{\times}ED_{95}$ of rocuronium are administered, producing response depression and rapid onset of action (60–90 seconds). Half-life duration is often insufficient for surgical procedures with longer duration (>60 minutes).[4–8] Nevertheless, rocuronium administration should be balanced according to the desired level of NMB, avoiding light dosage that may allow patients movement/coughing and compromise patient care, as well as overdose, that can prolong the effect and result in residual curarization.[9] Often, to maintain muscle relaxation in longer procedures, several boluses are administered resulting in a fluctuating blockade. However, it is complicated to ascertain the NMBA demand, even when relying on NMB monitoring, or the exact length of the operation.[10] Thus, the use of infusion pumps provides an improved solution for ongoing administration of drugs, being able to ensure a balanced and stable muscle relaxation and improve anesthesia quality. To support this practice, Murray et al[11,12] recently published an update of the clinical practice guidelines for sustained NMB, including recommendations for continuous infusion using NMBA. Moreover, in 2017, Smetana et al[13] conducted a review on the use of continuous infusion of NMBA in the adult intensive care unit.

This approach usually comprises an initial bolus for quick onset, followed by the intubation, and after achieving the desired NMB level, the infusion is started and adjusted along the procedure. The recommendations for rocuronium infusion at steady-state block in standard anesthesia can range from 0.24 to 0.96 mg/kg per hour (mean = 0.6 mg/kg per hour).[13–16] Rocuronium has been administered by continuous infusion, considering computer-based pharmacokinetics models paired with target-control infusion systems, as well as closed-loop feedback control systems[14,17–19]; however, research remains on the development of an adequate solution.

Monitoring of NMB is frequently applied to assess neuromuscular transmission, standing out techniques based on acceleromyography or electromyography, often used to reliably measure the adductor pollicis evoked response after ulnar nerve stimulation.[1,2,20,21] This allows to objectively assess muscle relaxation providing insight on dose adjustments and adequate recovery of the neuromuscular transmission.[21] Train-of-Four (TOF) stimulation, which consists of 2-Hz 4-square pulses, is the standard method used, namely, when nondeep NMB is applied, which is the most frequent scenario in clinical practice.[22] In deeper levels of NMB, after all 4 TOF responses are overcome (zero responses), posttetanic

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count (PTC) stimuli assesses the remaining neuromuscular function. The degree of NMB is characterized by means of measuring the number of twitch responses after a tetanic stimulation.[22] Thus, depth of the NMB can be classified in the following: moderate (1–3 TOF count), deep (TOF count of 0 and PTC ≥ 1), and complete NMB (TOF of 0 and PTC of 0).[23] To guarantee the complete immobility of the patient (including abdominal wall musculature and diaphragm) throughout the procedure, very little or no neuromuscular response is required,[24–27] characterized by 2 or less PTC responses (hereinafter referred to as profound NMB).

For NMB reversal, careful evaluation is recommended to avoid postsurgical residual paralysis.[28,29] One of the most important advances in the field is the introduction of the reversal agent sugammadex, which exerts a safe and effective reversal by quickly forming 1:1 ratio complexes with rocuronium and being eliminated via kidneys and liver.[1,30–33] A dose of 4 mg/kg is recommended for reversal of NMB that reaches 1 to 2 PTC and 2 mg/kg if there is recovery to at least 2 TOF counts.[34,35]

Recently, Bruintjes et al[36] conducted a systematic review and meta-analysis regarding the influence of moderate and deep NMB during laparoscopic surgeries, concluding that deep NMB improves the surgical space conditions (mean difference = 0.65 on a scale 1–5, 95% confidence interval [CI] = 0.47–0.83) and reduces postoperative pain. Following literature, it can be concluded that there is a wide variability when continuous administration of rocuronium to maintain deeper NMB levels is applied. This research aims to explore the current approaches on what rocuronium infusion comprises and the monitoring specifications that permit an improved and stable profound NMB in clinical practice.

METHODS

The current review is registered as CRD42018106626 in PROSPERO (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018106626) and was conducted based on PRISMA guidelines.

In the execution of the current review, the scope of search included publications worldwide until February 28, 2019, independently of language or publication status. The rationale addresses studies with human adult participants, classified as ASA I to IV (American Society of Anesthesiologists class), undergoing a surgical procedure that used rocuronium through continuous infusion aiming for profound neuromuscular blockade (PTC of 0–2), as intervention. Moderate NMB, conventional therapies of rocuronium administration (eg, via periodic boluses), and reversal methodologies are the basis of comparison. Randomized clinical trials, controlled trials, and cohort studies are eligible for inclusion. Studies including pediatric or animal participants and studies using other NMBA to maintain profound NMB were excluded. Primary outcomes were the rocuronium consumption, surgical conditions, and time of reversal after 4 mg/kg of sugammadex. Secondary results include methodological features of rocuronium administration and NMB monitoring.

Search Strategy and Selection Criteria

Data Sources

The databases included PubMed, ISI Web of Science, Cochrane Library, and Google Scholar search engines. The search strategy of references is detailed in Supplement 1 (available online as Supplemental Digital Content at http://links.lww.com/CNP/A8). The included studies bibliographies were checked for additional eligible references.

Study Selection and Extraction

From the search results, the duplicate removal was conducted combining EndNote software (X8; Clarivate Analytics, New York, NY) and secondary manual scan. Afterward, titles and abstracts were screened for relevance to the topic. Next, examination of full texts was conducted, and scanning discrepancies and redundancies was conducted. Studies fitting criteria were included in this review (details in Supplement 2, available online as Supplemental Digital Content at http://links.lww.com/CNP/A8).

The extraction of data was conducted independently, including the important features of the studies (author, year, number of a clinical trial [NCT], ASA class, weight, body mass index, participants) and specifics of the interventions to achieve profound NMB. This included the parameters of rocuronium administration (induction dosage, start infusion rate, rocuronium adjustment principles), monitoring specifics (device, PTC target, and interval between evaluations), and duration of the procedure. Results regarding administered rocuronium for maintaining profound NMB, surgical conditions, and time to recover after sugammadex (standard 4 mg/kg) were also included.

Data were extracted if the mean, standard deviation (SD), and number of patients (n) were reported or could be estimated. Unadjusted values were calculated and normalized. For studies reporting median and range values, mean and SD calculation were based on the formulas presented by Hozo et al[37] and Higgins and Green.[38] Parametrization of surgical condition scales was also conducted for equipotent comparisons of the results (5-point scale). Moreover, if the information on rocuronium used was not directly provided, the assessment of the total amount of drug administered to maintain profound NMB was calculated and standardized for analysis (stipulated in administered rocuronium per weight per hour). The interval between NMB monitoring, total procedure, and recovery duration was measured in minutes. In addition, authors were contacted for a follow-up on absent data.

Risk of bias assessment was performed at study design level including the Cochrane Collaboration tool.[38]

Data Analysis

OpenMetaAnalyst Version 10.10 (Center for Evidence based Medicine, Brown University, Providence) was used to conduct meta-analyses and calculate the effect size, expressed as means difference with 95% CI, if data were available from minimum 3 studies. The difference in means was computed using the random effects model. Heterogeneity was analyzed and reported as the I^2 test, considering more than 50% statistically significant heterogeneity. To investigate findings robustness, a sensitivity analyses examined the following: (*a*) studies with the lowest risk of other bias, (*b*) studies with 1 to 2 PTC targets, and (*c*) studies with shorter interval of PTC measurements (≤15 minutes). To explore possible causes of heterogeneity and the influence of certain variables, subgroup analysis can be included if necessary data are available. Moreover, if at least 10 comparisons are accessible, publication bias examination through subgroup analysis and asymmetry of the funnel plot is considered.

RESULTS

Study Selection and Description

Initial duplicate and redundancy screen resulted in a total of 151 admissible references. From first-hand title/abstract analysis, 23 publications were eligible for full-text review. Three clinical trials have yet not reported results (NCT02454504, NCT01539044, and NCT02320734). A total of 8 researches met PICO criteria and

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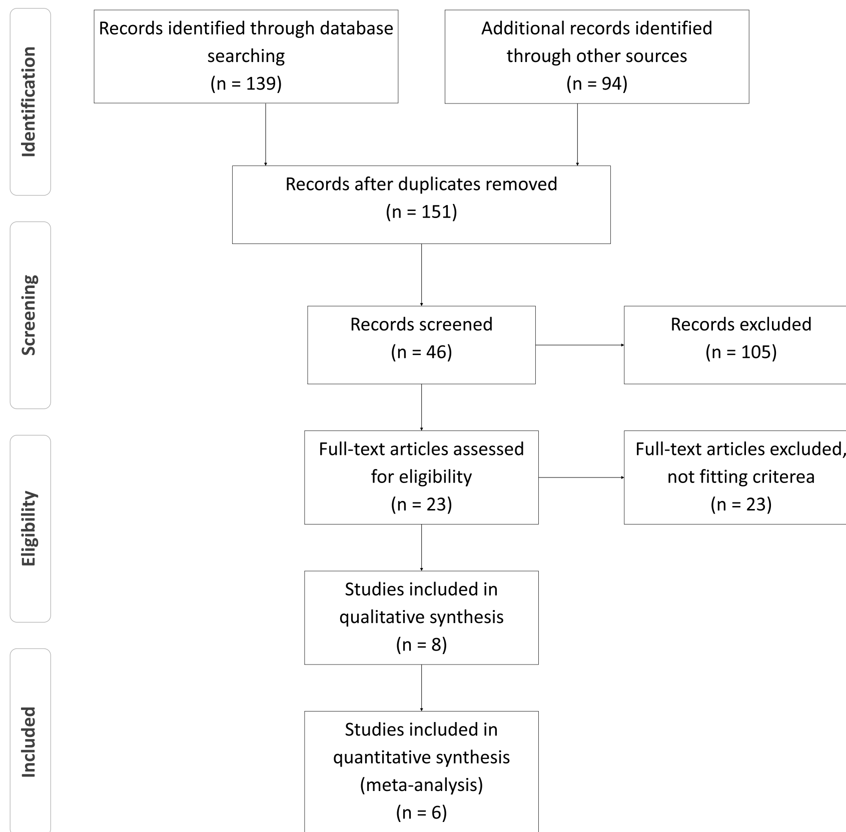

FIGURE 1. The PRISMA flowchart diagram of study selection process.

were eligible for applicability (Fig. 1), resulting in a total of 483 participants. The exclusion justifications of remaining articles are presented in Supplement 3 (available online as Supplemental Digital Content at http://links.lww.com/CNP/A8), stressing unadjusted target of NMB degree as the most common reason. The characteristics of the included studies are briefly summarized in Table 1 (detailed in Supplement 4, available online as Supplemental Digital Content at http://links.lww.com/CNP/A8). Authors were contacted for a follow-up and however were unable to provide additional information.

All included records are randomized trials published in English between 2012 and 2019, reporting the maintenance of profound NMB (PTC < 2) throughout the infusion of rocuronium. Seven studies compared moderate with profound NMB and one study evaluated the reversal effect comparing sugammadex to neostigmine. At induction, the intubation dose differed between 0.3 and 1 mg/kg and initial infusion records show a variance of rate between 0.3 and 0.9 mg/kg per hour. Regarding the NMB monitoring, reported time interval between consecutive stimuli measurements range from 3 to 15 minutes. The applied level of NMB target was 1 to 2 PTC (75%) or 0 to 1 PTC (25%). The different ranges of PTC target adopted can generate different dose adjustments and total amounts of rocuronium administered. The measurement of 0 PTC responses, which can be caused by overdosing, is unadvisable because it cancels the tracking of NMB and limits the measurement below it, blinding the anesthesiologist to the cumulative effect and the expected time to recover positive values.

From the inclusive outcome measurements for meta-analysis, 6 studies reported on the surgical space conditions (75%); 7 presented the amount of rocuronium required during the procedure in which only 3 quantified the data for both moderate/profound groups (38%); 2 studies presented results on reversal time after standard sugammadex dose of 4 mg/kg (25%).

Figure 2 presents the results of risk of bias assessment (detailed in Supplement 5, available online as Supplemental Digital Content at http://links.lww.com/CNP/A8). All publications were randomized, 25% allocation was unclear, 63% show low bias in participants and personnel blinding, and 88% of the studies blinded the outcome assessment. None reported unclear or high risk of attrition or reporting bias. Because of uncertainty of preserving the allocated NMB level, other unclear bias was identified in 1 study attributed to absent information on monitoring interval and 2 studies with high risk of other bias as result of lack mentioning calibration of the monitoring device and unreliable rocuronium infusion and adjustments methods.

Because of the reduced number of studies included, data were insufficient to conduct subgroup analysis or a reliable funnel plot asymmetry evaluation.

Rocuronium Administration

Only Baete et al,[39] Kim et al,[42] and Kim et al[44] quantified the amount of rocuronium used for each group, including a total of 177 participants. Data were standardized for analysis. Meta-analysis of amount of rocuronium administered to maintain profound versus moderate NMB showed a mean difference of 0.251 mg/kg per hour (95% CI = 0.169–0.334) (Fig. 3) with a I^2 value of 54.81%, proving a significant heterogeneity between studies. Specifically, the mean (SD) amount of rocuronium for profound NMB was 0.743 (0.167) mg/kg per hour and 0.475 (0.088) mg/kg per hour for moderate NMB.

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TABLE 1. Data Abstraction of Studies Continuous Infusion of Rocuronium for Deep or Intense NMB

			Intervention					
			Rocuronium Administration		Monitoring			
Author (Year)	Trial Reference	Sample Size	Induction Dose, mg/kg	Infusion Start Rate, mg/kg per h	PTC Target	Stimuli Interval, min	Comparison	Inclusive Outcome
Baete et al[39] (2017)	NCT01748643	60	0.6	0.6	1–2	5	Moderate versus deep NMB	Administered rocuronium (mg/kg); surgical conditions (SRS)
Yoo et al[40] (2015)	NCT02109133	66	1	0.6	1–2	15	Moderate versus deep NMB	Administered rocuronium (mg); surgical conditions (SRS)
Madsen et al[41] (2017)	NCT02140593	128	0.6	N/A	0–1	3–5	Moderate versus deep NMB	Surgical conditions (SRS)
Kim et al[42] (2016)	NCT02266056	61	0.6	N/A	1–2	N/A	Moderate versus deep NMB	Administered rocuronium (mg); surgical conditions (5-stage satisfaction scale)
Martini et al[25] (2014)	NCT01361149	24	1	0.6	1–2	15	Moderate versus deep NMB	Administered rocuronium (mg); surgical conditions (SRS); reversal recovery time (min)
Staehr-Rye et al[43] (2014)	NCT01523886	48	0.3 + 0.7	3–4	0–1	3–4	Moderate versus deep NMB	Administered rocuronium (mg); surgical conditions (4-point scale)
Kim et al[44] (2019)	NCT02762890	56	1	0.3	1–2	10	Moderate versus deep NMB	Administered rocuronium (mg)
Mekawy and Fouad Ali[45] (2012)	N/A	40	0.6	0.6–0.9	1–2	N/A	Recovery neostigmine versus sugammadex	Administered rocuronium (mg); reversal recovery time (min)

N/A, not available or no answer; SRS, surgical rating scale (1–5).

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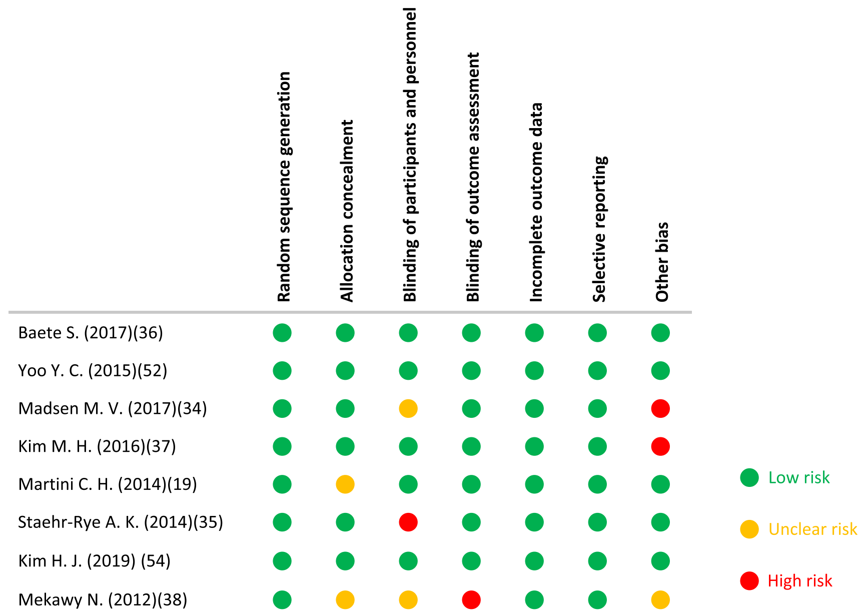

FIGURE 2. Diagram for studies risk of bias per domain.

Surgical Conditions

Surgical condition assessment was performed in 6 studies (with 397 participants), recorded in a 5-point scale (83%) or 4-point scale (17%) and were included in the meta-analysis. On a scale of 1 to 5, the surgical conditions are improved with profound NMB by an estimate mean difference of 0.653 (95% CI = 0.451–0.856) (Fig. 4). The outcome of calculation resulted in a I^2 value of 48.4%, showing a moderate level of heterogeneity between studies. Specifically, a mean (SD) score was 3.673 (0.261) for moderate and 4.239 (0.383) for profound NMB, improving surgical conditions from good to optimal.

Sensitive Analysis

The uncertainty in maintaining the allocated NMB level, generated by the nonrobust monitoring and dose adjustment methods, was recognized as other bias. By removing these studies from the meta-analysis, results did not significantly alter the estimated mean difference and showed very low heterogeneity (6.7%, Supplement 6.A, available online as Supplemental Digital Content at http://links.lww.com/CNP/A8). On the other hand, both Madsen et al[41] and Staehr-Rye et al[43] considered a lower-range target of PTC 0 to 1. Though not statistically significant, the subtraction of these studies from the meta-analysis resulted in a mean difference of 0.694 (95% CI = 0.525–0.863) with 0% between-study heterogeneity (Supplement 6.B, available online as Supplemental Digital Content at http://links.lww.com/CNP/A8). Moreover, often in NMB studies, the blockade degree is measured very sporadically during surgeries, aiming to relate it with surgical conditions assessment in specific stages of the procedure. Studies with shorter interval between PTC measurements are expected to provide more information and have a direct impact on rocuronium adjustments. However, sensitive analysis including studies with PTC measurements done every 15 minutes or less showed no significant difference (0.609 [0.352–0.866] mg/kg per hour, I^2 = 57.8%, Supplement 6.C, available online as Supplemental Digital Content at http://links.lww.com/CNP/A8).

Sugammadex Reversal

In contrast, only Martini et al[25] and Mekawy and Fouad Ali[45] evaluated the reversal recovery time after 4 mg/kg of sugammadex after profound NMB, showing a mean (SD) of 5.1 (2.4) and 2.47 (0.51) minutes, respectively. Meta-analysis was not possible to be conducted because of insufficient study reports.

DISCUSSION

One important strength this study entails is related to the pioneer review aiming to assess the evidence on specific parameters and outcomes of continuous infusion of rocuronium for profound NMB. Cammu[46] considers that to maintain a constant dose-effect relation along the procedure, continuous infusion stands out as the most appropriate technique by means of optimizing dose requirement over time, NMB monitoring, and selectively antagonizing the NMB. The current work aimed to study these characteristics, conducting a systematic review on current available researches.

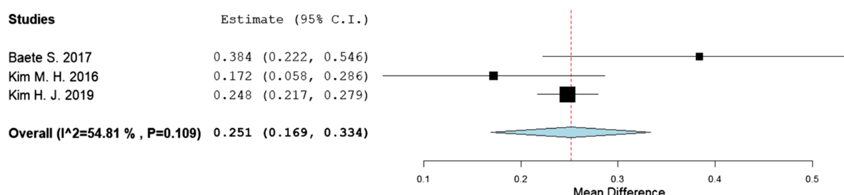

FIGURE 3. Meta-analysis and forest plot of rocuronium administration of included studies (milligram per kilogram per hour), with a mean (SD) amount of rocuronium for profound NMB of 0.743 (0.167) mg/kg per hour and 0.475 (0.088) mg/kg per hour for moderate NMB.

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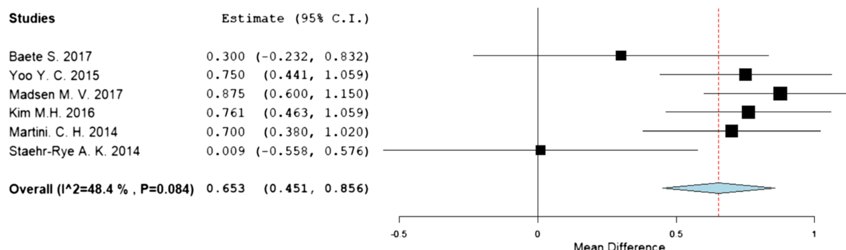

FIGURE 4. Meta-analysis and forest plot of surgical conditions of included studies, with a mean (SD) of 4.239 (0.383) surgical conditions score for profound NMB and 3.673 (0.261) for moderate NMB.

For that purpose, to achieve a safe and stable profound NMB is critical to understand the association between NMBAs over time and its effect on the NMB level.

The NMBA producers provide a dosage recommendation based on ED_{95}, relying on the experience of professionals to individualize the dosage.[13] However, there are different approaches taken, depending on different criteria (eg, patient features, duration of surgery, method of sedation), which may result in different outcomes when aiming to maintain a certain NMB level.[1,2] Results show that the mean amount of rocuronium required to maintain profound NMB with respect to moderate NMB is equivalent to $0.82 \times ED_{95}$ of additional rocuronium per hour (95% CI = $0.554–1.09 \times ED_{95}$). Nevertheless, these results cannot provide a decisive conclusion on the adequate amount of rocuronium to be used. The quantity of rocuronium required to maintain the NMB level can vary significantly for each patient and the intended doses mentioned in the studies anesthetic procedures can be misleading. Neuromuscular blockade maintenance must be individualized for each patient and guided by NMB monitoring. Other studies[40,47] reported similar amounts of required rocuronium to maintain the 1 to 2 PTC relaxation level (0.689 [0.162] and 0.72 [0.39] mg/kg per hour). Although these values are within the range of infusion requirements, these also show a significant dosage increase over the recommendation of 0.6 mg/kg per hour

There have been investigations comparing intermittent boluses with continuous infusion of rocuronium.[16,48–50] Although no comparative studies to profound NMB via bolus administration were found, it is reliable to conclude that continuous infusion presents inherent advantages in terms of maintenance and stability of the muscle relaxation.

Regarding surgical conditions assessment, 5 of the 6 studies were conducted for laparoscopic surgeries and 1 study for upper laparotomy. In both procedures, the abdominal wall relaxation is fundamental to provide insight on surgical condition. Although there is no criterion standard, 5-point Leiden surgical rating scale quantification was considered for the analysis.[25] Other studies have compared deep to moderate NMB,[27,36] reporting 99% of good or optimal conditions under deep NMB, justifying the interest in the use of this approach.[51] Meta-analysis results proved that profound NMB improves surgical conditions over moderate NMB, with a mean difference of 0.653 (95% CI = 0.451–0.856). In a 5-point scale, this can be considered significant with relevant applicability in improving surgical conditions; however, results show significant heterogeneity.

In the evaluation of the meta-analysis, it was not possible to reliably perform subgroups, funnel plots, or meta-regression analysis because of the reduced number of studies included. To examine findings robustness, a sensitivity analyses was executed. Within the sensibility analysis context and limitations, it revealed a similar improvement (0.61–0.69) in surgical conditions, supporting the obtained results. From overall analysis, it is possible to notice that the heterogeneity is mostly driven by the studies by Baete et al[39] and Staehr-Rye et al.[43] Both show a smaller effect in the surgical conditions. A possible explanation may be the shorter surgery duration, which implies an inferior sample of the data acquisition instances. This is supported by the report by Park et al[27] that states the frequency of measurements during surgery and multiple assessments of surgical conditions and increase sensitivity to detect a difference between 2 levels of NMB.

Several studies have been conducted to investigate the response instigated by different doses of sugammadex after deep NMB with rocuronium infusion.[47,52–56] The expected time of reversal, after 4 mg/kg of sugammadex, is reported having a duration of 2 to 3 minutes.[47,53,55,56] Only 2 included studies evaluated the reversal with standard dosing of sugammadex, reporting significant different results. This can be justified by the instant of reversal infusion. Although Martini et al[25] administered sugammadex at the end of the surgery (regardless of the NMB degree) resulting in a reversal time of 5.1 (2.4) minutes, Mekawy and Fouad Ali[45] waited until T2 recovery to infuse the reversal agent taking 2.47 (0.51) minutes long to recover.

Limitations

Often, studies' description of detailed information on NMB monitoring and rocuronium administration parameters is very narrow and unreliable on several aspects. The findings of this study may show a conditioned evidence strength and should be interpreted in the limited setting of the investigations included, as is expressed in the significant heterogeneity of the results. Regarding rocuronium administration, some studies consider additional bolus as NMB adjustment method, as high as 0.6 mg/kg.[43] This dose leads to a significant depression of the neuromuscular activity and may compromise the stability of NMB level. Considering that rocuronium has a quick rate of therapeutic effect, large intervals between consecutive NMB measurements may blind the anesthesiologist to any deviation from NMB target that may occur in between evaluations. Thus, the accuracy in ensuring the NMB level continuously rises doubt, making it difficult to consistently adjust the dosing. Sugammadex time reversal is dependent on the administered dose and NMB degree when given. Although it enables a rapid and effective reversal,[57] the introduction and appropriate use of this drug are expensive and not always available.

The 2 main features with direct impact in ensuring the accuracy of preserving the allocated NMB level are rocuronium administration and monitoring parameters. These features were also important in the bias assessment, revealing "unclear" in one study and "high" other risk of bias in 25% of the publications. Although the impact of this source of bias remains uncertain, because of the complexity of defining and adopting an ideal methodological protocol for maintaining profound NMB, it can be admitted that the quality of studies was high and risk of bias did not compromise the results.

The main objective of this review was to study the methodological approaches regarding rocuronium administration, NMB

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monitoring, and reversal, when applying continuous infusion for profound NMB (PTC > 2). A total of 8 clinical trials were included in the analysis. Outcome assessment of rocuronium consumption and surgical conditions was performed comparing to moderate NMB level. Time of reversal after 4 mg/kg of sugammadex was assessed as opposed to conventional approaches. Findings suggest that the maintenance of profound NMB with 0 to 2 PTC >target comparatively to moderate NMB level requires a mean difference of 0.251 mg/kg per hour (95% CI = 0.169–0.334) of rocuronium and provides significant benefit to surgical conditions (mean difference = 0.653 in a 5-point scale). No significant conclusions were admitted regarding the time required to complete sugammadex reversal. In conclusion, continuous infusion provides a more practical way to maintain the NMBA administration rate and pared with appropriate monitoring is able to promote a stable paralysis depth. Nonetheless, the methodology for maintenance of profound NMB degree must be further investigated and establish.

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