

# Sugammadex, the Guardian of Deep Muscle Relaxation During Conventional and Robot-Assisted Laparoscopic Surgery: A Narrative Review

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**Abstract:** High intra-abdominal pressure induced by artificial pneumoperitoneum can obviously impair respiratory and circulatory functions and has a negative effect on the prognosis of patients undergoing conventional and robot-assisted laparoscopic surgery. The application of deep neuromuscular blockade during the operation is reported to lower the intra-abdominal pressure and improve patients' outcome. However, concern lies in the risks of postoperative residual muscular paralysis with the use of deep neuromuscular blockade. Sugammadex, a specific antagonist for aminosteroids muscle relaxants, can effectively and rapidly reverse rocuronium and vecuronium induced neuromuscular blockade of different depths. Thus, sugammadex allows the ability to safeguard the application of deep neuromuscular blockade in laparoscopic operations and helps to alleviate the adverse complications associated with pneumoperitoneum. Here, we review the application of deep neuromuscular blockade in different laparoscopic surgeries and discuss the benefits and possible risks of sugammadex administration in the reversal of deep neuromuscular blockade in these operations.

**Keywords:** deep neuromuscular blockade, laparoscopic surgery, muscle relaxation remnants, sugammadex

## Introduction

Laparoscopic surgeries, including conventional and robotic-assisted surgeries, are becoming increasingly popular worldwide.<sup>1,2</sup> However, creation and maintenance of artificial pneumoperitoneum during the operation can result in a variety of adverse intraoperative and postoperative complications, especially hemodynamic impairment and poor ventilation.<sup>3–5</sup> Studies have shown that application of deep neuromuscular blockade (NMB) in laparoscopic surgery can effectively allow a lower intra-abdominal pressure and improve the prognosis of patients undergoing laparoscopic surgeries.<sup>6,7</sup>

Postoperative residual curarization, with an incidence up to over 50%, is one of the most severe complications and the biggest concern for the application of deep NMB application in laparoscopic surgeries.<sup>8–10</sup> Sugammadex is a potent and specific antagonist of rocuronium, which can quickly reverse any degree of rocuronium-induced muscle relaxation with minimal side effects, thereby significantly reducing the occurrence of complications caused by incomplete neuromuscular recovery.<sup>11,12</sup>

The aim of this narrative review is to provide up-to-date evidence regarding the advantages of the application of deep NMB in different laparoscopic surgeries, and

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it also aims to discuss the benefits and possible risks of sugammadex administration in the reversal of deep NMB in these operations.

## Definition of Deep Neuromuscular Blockade

The depth of NMB in general anesthesia is divided into four levels: mild, moderate, deep and intense. Train of four stimulation count (TOF-C) and post-tetanic stimulation count (PTC) have been widely used to define the depths of NMB in clinical studies on muscle relaxation presently. Generally speaking, TOF-C of 4 is defined as mild NMB, and TOF-C from 1 to 3 as moderate NMB, PTC of 2 or less as deep NMB and PTC of zero is as intense NMB.<sup>13</sup>

## Application of Deep Neuromuscular Blockade in Laparoscopic Surgery

Laparoscopic surgery has been acknowledged to be a meaningful milestone since ether anaesthesia.<sup>14</sup> Compared with conventional laparotomy, laparoscopic surgery is minimally invasive with smaller incision, milder postoperative pain, less intraoperative blood loss, faster recovery, shorter hospital stay, as well as more cosmetic surgical wound. Laparoscopic surgery becomes more and more popular and is accepted worldwide.<sup>15,16</sup> In recent years, owing to several technological improvements, robot-assisted laparoscopic surgery is being applied in a wide variety of specialties and achieves even better outcomes.<sup>17,18</sup> However, for patients undergoing laparoscopic surgeries, artificial pneumoperitoneum should be established and maintained during the operation to facilitate laparoscopic surgical maneuver. High intra-abdominal pressure from carbon dioxide insufflation could result in hemodynamic impairment and adverse ventilation consequences.<sup>19,20</sup> Hemodynamic impairments secondary to elevated intra-abdominal pressure include increased afterload and preload, decreased cardiac output, sometimes accompanied by arrhythmia and intraoperative hypertension, whereas ventilatory consequences include increased airway pressure, hypercarbia, atelectasis and reduced thoracic compliance.<sup>15</sup> For those patients who have very poor cardiopulmonary reserve functions and could not tolerate the high-pressure pneumoperitoneum-related physiological changes, laparoscopic surgery becomes even more risky.<sup>16,21</sup>

Over the years, the ability to ensure the laparoscopic surgery field and operating space, while at the same time reducing the pressure of pneumoperitoneum and minimizing the adverse effects, has been of utmost importance.

Interestingly, the application of deep NMB in laparoscopic surgery makes the use of a low pneumoperitoneum pressure possible and offers great benefits, which include improvement of surgical field, mitigation of high pneumoperitoneum pressure related postoperative pain (deep abdominal pain and shoulder pain), inhibition of stress responses and alleviation of the post-operative impairment of cardiopulmonary function.<sup>22–25</sup> Studies have indicated that deep NMB, in comparison to moderate NMB, significantly enlarges the abdominal space after artificial pneumoperitoneum establishment for laparoscopic cholecystectomy or gynecological laparoscopy.<sup>26–29</sup> It also helps to optimize surgical conditions for the abdominal fascia suturing.<sup>30,31</sup> A systematic review and meta-analysis revealed that deep NMB block was more frequently associated with excellent or good surgical exposure than moderate NMB.<sup>32</sup> Sustained deep NMB could also facilitate robot-assisted laparoscopic radical prostatectomy at a low intra-abdominal pressure and provide acceptable surgical conditions.<sup>33</sup> It is worth noting that a Trendelenburg (head down tilt) position is always taken in this surgery and the abdominal viscera is pulled away from the operative field by gravity. The Trendelenburg (head down tilt) position has been demonstrated to decrease intra-abdominal pressure compared with supine position.<sup>34,35</sup> But it is nonphysiologic and potentially deteriorates pneumoperitoneum-induced adverse physiologic effects when maintained for extended periods.<sup>36,37</sup> Combined with body positioning, deep NMB is more effective at paralyzing abdominal muscles and lowering intra-abdominal pressure, creating a superior surgical condition, being accompanied with less complications and better prognosis, thus we speculate that there will be a promising prospect for the application of the strategy of deep NMB in laparoscopic surgeries.<sup>28,38</sup>

## Disadvantages of the Application of Deep Neuromuscular Blockade

Nevertheless, due to the significantly high incidence of postoperative residual curarization, the clinical benefits of maintaining deep NMB for various laparoscopic surgeries are still in debate.<sup>39</sup> To acquire deep NMB, anesthesiologists usually administer more sedatives and analgesics to increase the depth of anesthesia or use fast acting muscle relaxants as an alternative.<sup>40–42</sup> Generally speaking, residual muscle relaxation means that the patient's motor function has not fully recovered after surgery. Residual muscle relaxation may cause airway obstruction, respiratory depression and hypoxemia. When muscles

responsible for deglutition are involved, life-threatening aspiration pneumonia may occur.<sup>43</sup> Postoperative residual curarization is a safety hazard to surgical patients and strongly affects the prognosis.<sup>44,45</sup> Special attention needs to be paid to it. A large prospective observational multicenter study conducted by Kirmeier et al described that the total dose of neuromuscular blocking medicine during the operation was directly associated with an increased risk of post-anaesthetic pulmonary complications.<sup>46</sup> Madsen et al reported that forty percent of patients who were maintained under deep NMB still had an inadequate surgical field, and an intense NMB was needed to improve the conditions.<sup>47</sup> In addition, residual muscle relaxation significantly extends the time required for extubation and postoperative monitoring, thereby increasing the medical expenses.

In clinical practice, the depth of NMB is measured with a neuromuscular monitor. However, due to the complexity of operations, tedious connection of monitoring devices, easy interference of external factors and unfamiliarity of anesthetists with objective techniques, neuromuscular monitoring is often difficult to be performed routinely.<sup>48–50</sup> Moreover, it can trigger an unpleasant experience in awake patients.<sup>51,52</sup> The adverse consequences caused by residual muscle relaxation often make anesthesiologists reluctant to use deep NMB in clinical work, despite its many advantages.<sup>53,54</sup> Therefore, in order to effectively decrease or even avoid the occurrence of various complications associated with profound blockade, a definite and effective NMB reversal is indeed imperative. The development and application of sugammadex makes it possible to introduce deep NMB in clinical practices while allowing for subsequent safe reversal of motor blockade. As a more potent and specific antagonist than neostigmine, sugammadex is designated as the best candidate to reverse different depths of rocuronium-induced muscle relaxation, thereby circumventing the occurrence of various complications associated with profound blockade.

## An Overview of Sugammadex

With its unique antagonistic mechanism and metabolic pathway, sugammadex is superior in terms of its reversal speed and efficacy as opposed to minimal side effects.<sup>55</sup> Specifically, sugammadex is a modified gamma-cyclodextrin that can selectively encapsulate rocuronium and other aminosteroid neuromuscular blocking agents and promptly form a one-to-one complex, which is eliminated through the kidney. Since the free non-depolarizing neuromuscular

blocking agent is encapsulated by sugammadex, its ability to bind to and block acetylcholine receptors is neutralized. Its concentration in circulation decreases rapidly.<sup>56</sup> The interaction of muscle relaxants and nicotinic cholinergic receptors at the neuromuscular junction is disrupted, and NMB induced by rocuronium or vecuronium is reversed. It would be interesting to note that the affinity and selectivity of sugammadex for rocuronium was 2.5 times higher than that for vecuronium in a dose-dependent manner.<sup>57</sup> The reversal effect of NMB is achieved in about three minutes after sugammadex administration, which is not affected by blood pH value and temperature.<sup>58</sup> Alongside its high efficiency and impressive advantage in reversing NMB of any depths at any time,<sup>59</sup> sugammadex also plays an important role in some other special conditions. For instance, sugammadex has widened the performance of general anesthesia in pregnancy and<sup>60</sup> children,<sup>61–63</sup> as well as lung, hepatic and renal insufficiency patients,<sup>64–68</sup> the management of difficult airway,<sup>69,70</sup> and in patients with myasthenia gravis.<sup>71,72</sup> In addition, sugammadex has also been proposed as a useful adjunct to treat anaphylaxis induced by rocuronium. It was reported that the anaphylaxis cascade was reversed almost immediately when sugammadex was administered.<sup>73,74</sup> With its favourable tolerance and great safety, the cardiovascular, digestive, and respiratory adverse effects associated with anticholinesterases may be eliminated with the administration of sugammadex. Sugammadex is currently marketed for use in more than seventy countries around the world, but only an estimated 10% of the surgical population have received sugammadex from 2010 to 2018.<sup>75</sup> Except for hypersensitivity, bleeding, bradycardia, effect on coagulation parameters and risk of recurarization, there are a number of potential adverse events that remain of concern.<sup>76–80</sup> In Japan, sugammadex is now the leading cause of perioperative anaphylaxis since it has been approved for clinical use.<sup>59</sup> A case was also reported that deep residual NMB reoccurred in a 74-year-old woman who received a single dose of sugammadex (4 mg/kg).<sup>81</sup>

Given its distinguishing antagonistic effect on NMB at any depth and its potential risks, the dosage of sugammadex has been further investigated by researchers. Routinely, 4 mg/kg is recommended for deep NMB (PTC 1–2) and 2 mg/kg for train-of-four Count (TOFC)  $\geq 2$ .<sup>82</sup> In addition, an injection of 16 mg/kg is indicated only when patients receive a large single dose of rocuronium above 1.2 mg/kg or when NMB is required to be reversed within

3 minutes. All recommended doses of sugammadex should be based on the actual body weight of patients.<sup>57,83</sup>

## The Effect of Sugammadex on Deep Neuromuscular Blockade Used for Various Laparoscopic Surgeries

Deep NMB during laparoscopic surgery makes favorable exposure under low-pressure pneumoperitoneum (intra-abdominal pressure 8–10 mm Hg) possible.<sup>84</sup> Consequently, low pneumoperitoneum pressure helps to alleviate internal organs ischemia-reperfusion injury, systemic inflammation, as well as pressure-related injury to the abdominal wall. As described, exposure to the surgical field is facilitated, which can optimize the surgical field of vision, provide ideal conditions for abdominal surgery, shorten the operation time, reduce the risk of intraoperative adverse events and complications and improve early prognosis. Therefore, the technique of “deep NMB combined with low pneumoperitoneum pressure” has been widely accepted in laparoscopic surgeries in recent years. However, the adverse consequences caused by residual muscle relaxation often discourage anesthesiologists from using deep NMB. An editorial by Murphy et al emphasized that the harm of postoperative residual NMB was clear and an appropriate dose of reversal agents should be routinely administered after surgery.<sup>85</sup> In contrast to neostigmine, sugammadex has greater potential to achieve a reliable, accurate and rapid reversal of deep NMB induced by rocuronium or vecuronium.<sup>86–89</sup> Thus we hypothesized that sugammadex could be the “guardian” of deep muscle relaxation during laparoscopic surgery. Patients undergoing laparoscopic gastrectomy have a shorter hospital stay and a lower incidence of postoperative complications after receiving subgammadex at the end of surgery.<sup>90</sup> For extremely obese and high risk cardiac patients who are scheduled for laparoscopic sleeve gastrectomy and abdominoplasty, it was highlighted by Carron et al that the ideal combination of rocuronium and sugammadex should be applied, which would achieve the purpose of desirable muscle relaxation condition through rocuronium-induced deep NMB coupled with a fast recovery with sugammadex reversal after surgery.<sup>91</sup> Sugammadex administration against profound blockade in laparoscopic cholecystectomy or appendectomy had positive effects on the recovery of gastrointestinal motility compared with the use of a mixture of glycopyrrolate and pyridostigmine.<sup>92</sup> Concerning patients who underwent laparoscopic hysterectomy, a series of randomized controlled trials have proved the superiority of sugammadex administration in effectively reversing deep block at the end of the procedure

and shortening the length of hospital stay.<sup>93,94</sup> Many studies showed that the robotic approach had longer operative time compared with conventional laparoscopic surgery.<sup>95–99</sup> And prolonged operative time combined with elevated intra-abdominal compartment pressure could incur more cardiopulmonary complications.<sup>100</sup> A retrospective study concluded that in comparison with neostigmine, the reversal of rocuronium in robot-assisted laparoscopic prostatectomy surgery with sugammadex represented its superiority in a shorter hospital stay and post-anaesthetic recovery time.<sup>101</sup> Moreover, it was found that patients with deep NMB during laparoscopic operations recovered 3.4 times faster when NMB was antagonized with sugammadex than with neostigmine.<sup>102</sup>

## Possible Risks After the Administration of Sugammadex for Reversing Deep Neuromuscular Blockade

Muscle relaxant antagonist sugammadex certainly has a variety of proven benefits, especially in the reversal of deep rocuronium or vecuronium-induced NMB, a feature that neostigmine does not have. However, till now, the study of sugammadex has been involved only in a relatively small fraction of surgical population, and there may be other potential drawbacks yet to be known. This is especially true when sugammadex is used in specific populations, such as children, elderly patients and pregnant women.<sup>60,103,104</sup> The most common adverse reactions to sugammadex include dysgeusia, transient hypotension, movement before the end of anesthesia, nausea and vomiting.<sup>105</sup> Apart from these side effects, a possible link between sugammadex administration and QT interval prolongation was also reported.<sup>106–109</sup> However, in the latest literature, this possible side-effect was debated, and the authors argued that the arrhythmia was not related to sugammadex.<sup>78</sup> The risk of recurarization even after sugammadex administration should not be negligible, especially in patients with prolonged elimination of rocuronium and sugammadex caused by severe renal impairment.<sup>110–112</sup> In addition to the patient's poor metabolism of muscle relaxants, there are some other factors that can cause recurarization. For instance, when the provider chooses to use lower-than-recommended doses of sugammadex, re-NMB can recur, even if initial NMB has been reversed.<sup>113,114</sup> Toremifene, a selective estrogen receptor modulator, has a high binding affinity for sugammadex. When the medicine is given, it is able to displace the steroidal neuromuscular blockade agents from sugammadex and re-paralysis may

occur.<sup>115</sup> The recurrence of paralysis may also be caused by drugs that can potentiate neuromuscular blockade.<sup>115</sup> With the expanding use and further research of sugammadex in the reversal of deep NMB in clinical anesthesia, the possible mechanism will hopefully be elucidated to the maximum extent in the future.

Due to the risks described above, the decision to use a lower-than-recommended dose of sugammadex is often taken, which leads to an increased event of residual NMB or recurrence of NMB and pulmonary outcomes. Consequently, based on the objective determination of NMB depth, an appropriate dose of sugammadex should be administered.<sup>113,116</sup> In addition, it is worth noting that sugammadex is a selective antagonist exclusively to aminosteroid non-depolarizing muscle relaxants.<sup>117</sup> Deep muscle relaxation induced by atracurium or cisatracurium can only be reversed by neostigmine.<sup>118</sup>

## Conclusion

Although the definite effect of deep NMB in laparoscopic application is yet to be identified, it undoubtedly provides a new scope for reducing pneumoperitoneum pressure, promoting ideal operation conditions and improving patients' outcomes. Sugammadex is a major breakthrough and innovation in the field of anesthesia. When administered with an appropriate dose, sugammadex offers anesthesiologists greater flexibility and better control over different depths of NMB, especially deep NMB and intense NMB. However, a clear and comprehensive understanding of the adverse effects of sugammadex has yet to be obtained and more large-scale multi-center studies on sugammadex are urgently needed. We believe that sugammadex-rocuronium combined deep NMB and the resulting low pneumoperitoneal pressure will be a routine practice during laparoscopic surgery in the near future.

## Abbreviations

NMB, neuromuscular blockade; TOF-C, train of four stimulation count; PTC, post-tetanic stimulation count.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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