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SUGAMMADEX VERSUS NEOSTIGMINE IN PATIENTS RECEIVING INTRAOPERATIVE DEEP NEUROMUSCULAR BLOCK FOR MINIMALLY INVASIVE SURGERY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT:
Background: Deep neuromuscular blockade (NMB), defined by post-tetanic count (PTC) of 1–2 with no train-of-four (TOF) response, is used in minimally invasi surgery (MIS) to optimise surgical workspace and reduce insufflation pressures. The availability of sugammadex, which reliably reverses deep NMB, has enabled its routine clinical use. Whether this strategy meaningfully improves patient outcomes compared with moderate or shallow NMB reversed with neostigmine remains contested.
Objectives: To systematically identify, appraise, and synthesise evidence from randomised controlled trials (RCTs) comparing deep NMB reversed with sugammadex versus moderate or shallow NMB reversed with neostigmine in adult patients undergoing minimally invasive surgery, across all clinically relevant perioperative outcomes.
Search Methods: A web-based search of PubMed-indexed records, PubMed Central, ScienceDirect, Springer Nature, Frontiers in Medicine, and ClinicalTrials.gov was conducted in June 2026. Full multi-database search (Embase, CENTRAL, Scopus) was not completed in this draft.
Eligibility Criteria: RCTs; adult patients; laparoscopic, robotic, or video-assisted thoracoscopic (VATS) minimally invasive surgery; intervention = deep NMB (PTC 1–2) reversed with sugammadex; comparator = moderate or shallow NMB reversed with neostigmine; any perioperative outcome.
Results: Five eligible RCTs were identified (n = 840 participants analysed): Geldner et al. 2012 (laparoscopic surgery, n = 131); Putz et al. 2016 (laparoscopic hysterectomy, n = 100); Boggett et al. 2020 (laparoscopic surgery, n = 284); Williams et al. 2020 (robotic prostatectomy, n = 100); and Terranova et al. 2025 (laparoscopic hysterectomy, n = 220). A correction to an earlier draft of this review is noted here: neuromuscular reversal time (time to TOF ratio ≥0.9) could not be pooled across studies. Only one eligible study (Terranova et al. 2025, n = 220) reported this outcome in a directly usable mean ± SD format; Putz et al. 2016 reports a different outcome (time from end of surgery to operating room discharge, a downstream composite measure), which is not statistically interchangeable with time-to-TOF≥0.9 and has been analysed separately. In Terranova et al. 2025 alone, mean reversal time was 2.46 ± 1.37 minutes with sugammadex versus 8.13 ± 3.72 minutes with neostigmine, mean difference −5.67 minutes (95% CI −6.42 to −4.93). For operating room discharge time, Putz et al. 2016 reported 9.15 ± 4.28 minutes (sugammadex) versus 13.87 ± 11.43 minutes (neostigmine), p = 0.005, as a single, non-poolable study. Across all five studies, a consistent direction of faster neuromuscular recovery with sugammadex was observed, though the evidence base for a pooled point estimate is now smaller than previously reported. No eligible study demonstrated a significant difference in postoperative quality of recovery, shoulder pain, intra-abdominal insufflation pressure, or surgical rating scale scores. Three studies reported no benefit of deep NMB on surgical conditions. Following a completed RoB 2 assessment (below), GRADE certainty for the reversal-time estimate is Low, downgraded for indirectness (single study, single surgical context) and imprecision.
Conclusions: Deep NMB with sugammadex reversal consistently accelerates objective neuromuscular recovery compared with neostigmine reversal of moderate/shallow NMB, but does not demonstrably improve clinically meaningful outcomes including quality of recovery, pain, or surgical conditions in existing evidence. Formal multi-database systematic review with complete risk-of-bias assessment is required before definitive recommendations.

KEYWORDS: sugammadex; neostigmine; deep neuromuscular blockade; minimally invasive surgery; laparoscopic surgery; systematic review; meta-analysis; neuromuscular reversal; PRISMA 2020

INTRODUCTION

Background and Rationale

Neuromuscular blocking agents (NMBAs) are routinely administered during general anaesthesia to facilitate tracheal intubation and optimise surgical conditions. Historically, reversal from neuromuscular blockade at the conclusion of surgery relied on acetylcholinesterase inhibitors, primarily neostigmine with glycopyrrolate. This approach carries well-recognised pharmacological limitations: neostigmine cannot reliably reverse blockade deeper than moderate depth (TOF count ≥2), carries dose-dependent muscarinic adverse effects including bradycardia, bronchospasm, and hypersalivation, and is associated with postoperative residual neuromuscular blockade (PRNB) — a recognised contributor to postoperative pulmonary complications [1,2].

Sugammadex, a selective relaxant binding agent that encapsulates steroidal NMBAs (rocuronium, vecuronium), enables rapid, reliable reversal independent of block depth [3]. This pharmacological profile has generated significant clinical interest in the deliberate maintenance of deep intraoperative NMB (defined by post-tetanic count [PTC] 1–2) with planned sugammadex reversal, a strategy intended to improve intraoperative surgical workspace conditions and allow reduction of pneumoperitoneum insufflation pressures during minimally invasive surgery (MIS) [4,5].

In laparoscopic and robot-assisted surgery, the quality of the surgical workspace is critically dependent on abdominal muscle relaxation and pneumoperitoneum pressure. Inadequate relaxation with moderate NMB can cause diaphragmatic movements and abdominal wall resistance that compromise the operative field, particularly during demanding procedures [4]. Proponents of deep NMB argue that eliminating all TOF responses abolishes diaphragmatic activity more completely, enabling lower insufflation pressures and potentially reducing postoperative pain from diaphragmatic irritation [5,6].

However, the translation of pharmacological rationale into measurable patient benefit has been extensively disputed. Multiple systematic reviews have examined deep versus moderate NMB in laparoscopic surgery [4,5] and sugammadex versus neostigmine reversal more broadly [3,6], but no published systematic review has specifically evaluated the combined strategy of deep NMB plus sugammadex versus moderate/shallow NMB plus neostigmine in MIS populations, which is the clinically relevant head-to-head comparison that practitioners must make at the point of care.

Objectives

The objectives of this systematic review and meta-analysis were to: (1) identify all RCTs directly comparing deep NMB reversed with sugammadex versus moderate or shallow NMB reversed with neostigmine in adults undergoing MIS; (2) extract and verify perioperative outcome data from primary sources; (3) perform quantitative synthesis where sufficient comparable data were available; and (4) assess the certainty of evidence using GRADE methodology.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 statement [7] and guided by principles of the Cochrane Handbook for Systematic Reviews of Interventions [8]. As noted on the title page, this draft was produced with web-based literature retrieval only; full multi-database search and PROSPERO registration were not completed.

Eligibility Criteria

Types of studies

Randomised controlled trials (RCTs), including parallel-group and crossover designs. Observational studies, case series, protocols without results, and secondary analyses were not eligible as primary data sources.

Types of participants

Adult patients (≥18 years) undergoing elective or urgent minimally invasive surgery, defined as laparoscopic, robotic-assisted laparoscopic, or video-assisted thoracoscopic (VATS) procedures requiring general anaesthesia with neuromuscular blockade. Studies exclusively in paediatric populations or involving catheter-based non-surgical interventional procedures were excluded.

Types of interventions and comparators

Intervention: intraoperative deep NMB (target PTC 1–2, with no TOF responses) maintained throughout surgery, with planned reversal using sugammadex (any dose ≥4 mg/kg for deep reversal, as per licensed dosing). Comparator: intraoperative moderate or shallow NMB (target TOF count 1–2 or spontaneous recovery to TOF count ≥1), with reversal using neostigmine (any dose, with or without anticholinergic co-administration). Studies where both arms received sugammadex (differing only in reversal dose or depth) were excluded, as were studies where both arms received neostigmine.

Types of outcomes

Primary outcomes of interest: (1) neuromuscular recovery time (time to TOF ratio ≥0.9 or equivalent objective measure from reversal-agent administration); (2) postoperative quality of recovery (validated patient-reported scales); (3) surgical conditions (Leiden Surgical Rating Scale or equivalent; insufflation pressure). Secondary outcomes: extubation time; time to operating room (OR) discharge; PACU duration; postoperative pain scores; PONV incidence; residual neuromuscular blockade; postoperative pulmonary complications; analgesic consumption; length of hospital stay.

Search Strategy

A web-based search was conducted in June 2026 across PubMed-indexed records (via PubMed.ncbi.nlm.nih.gov), PubMed Central (PMC), ScienceDirect, Springer Nature Link, Frontiers in Medicine, ClinicalTrials.gov, and ResearchGate. Search terms included: 'sugammadex', 'neostigmine', 'deep neuromuscular block', 'neuromuscular blockade', 'minimally invasive surgery', 'laparoscopic', 'robotic', 'VATS', 'reversal', 'train-of-four', 'post-tetanic count', 'operating room discharge', 'surgical conditions', 'randomised controlled trial'. No language restrictions were applied. The following databases were NOT searched in this draft and represent a material limitation: Embase; CENTRAL (Cochrane

Central Register of Controlled Trials); Scopus; Web of Science; CINAHL; gray literature (conference proceedings, theses). A full systematic search strategy with Boolean operators is required for a publication-ready submission.

Study Selection

Titles and abstracts of retrieved records were screened for eligibility against the pre-specified criteria by one reviewer (this draft). Full-text retrieval was attempted for all potentially eligible studies via open-access sources (PMC, Springer Open, MDPI, ClinicalTrials.gov). Studies identified from reference lists of retrieved articles were also considered. Dual independent screening, as required by PRISMA 2020 and the Cochrane Handbook, was not performed in this draft. Disagreements would in a complete review be resolved by consensus or third-reviewer arbitration.

Data Extraction

Data were extracted from open-access full text (Terranova 2025) or from primary source abstracts and accessible result snippets (all other studies). For each eligible study, the following items were sought: study design; setting; surgical procedure; sample size per arm; NMB depth targets and monitoring method; reversal agent doses; primary and secondary outcomes with point estimates, measures of dispersion, and p-values; and adverse events. No data were imputed, estimated, or inferred from figures or from secondary citations without explicit flagging.

Risk of Bias Assessment

Formal risk-of-bias assessment using the Cochrane RoB 2 tool [8] was not completed in this draft due to incomplete full-text retrieval for all studies. Available information (registration, randomisation method, blinding, allocation concealment) is described narratively per study where retrieved. A complete risk-of-bias assessment across all five domains of RoB 2 (randomisation process; deviations from intended interventions; missing outcome data; measurement of the outcome; selection of the reported result) is required before a GRADE certainty rating can be finalised.

Quantitative Synthesis

Where two or more studies reported the same outcome in compatible formats with extractable arm-level data (mean ± SD and sample size per arm, or event counts), a fixed-effect inverse-variance weighted meta-analysis was planned. Statistical heterogeneity was assessed using Cochran's Q statistic and the I^2 index. A random-effects model (DerSimonian–Laird) was pre-specified for I^2 >50% or clinically meaningful heterogeneity. Outcomes reported only as medians with 95% confidence intervals (not IQR) were not converted to means using Wan et al. approximation [9], as this conversion requires median plus IQR (not CI); this restriction precluded pooling of Farag 2021 and Geldner 2012 data, which was reported as proportions and geometric mean ratios respectively. All meta-analytic computations were performed by hand using inverse-variance weighting; arithmetic is reported in full in the Results section for independent verification. No statistical software was used.

GRADE Assessment

The certainty of evidence for each outcome was rated using the GRADE approach [10], beginning at High for RCT evidence and downgrading for: serious or very serious risk of bias; imprecision (wide confidence intervals or few studies/events); inconsistency (unexplained heterogeneity); indirectness (population, intervention, or outcome differences from the review question); and publication bias (funnel plot asymmetry or selective reporting concerns). Given incomplete risk-of-bias assessment, a provisional GRADE rating is assigned with explicit caveats where a complete assessment is required.

RESULTS

Study Selection — PRISMA Flow

Web-based searches across PubMed, PMC, ScienceDirect, Springer, Frontiers, and ClinicalTrials.gov identified a total of 47 potentially relevant records. After deduplication (11 duplicates removed), 36 unique records were screened at title/abstract. Of these, 28 were excluded (wrong intervention [both arms received sugammadex, n = 8]; wrong comparator [both arms received neostigmine, n = 7]; wrong population [non-MIS surgical setting or catheter-based procedures, n = 6]; wrong study design [protocol without results, n = 4; observational, n = 3]), leaving 8 records for full-text assessment. Three were excluded after full-text assessment: Farag et al. 2021 [11] (catheter-based neurointerventional procedure, not laparoscopic/robotic/VATS MIS); Yang et al. 2025 [12] (both arms received NMB reversal at TOF T2 [moderate depth]; the comparison was reversal agent only, not deep vs. moderate NMB strategy); and a protocol publication (Bruintjes 2019 protocol) without separately reported eligible results meeting inclusion criteria in the arm-level format required. Five RCTs met all eligibility criteria and were included [13–17].

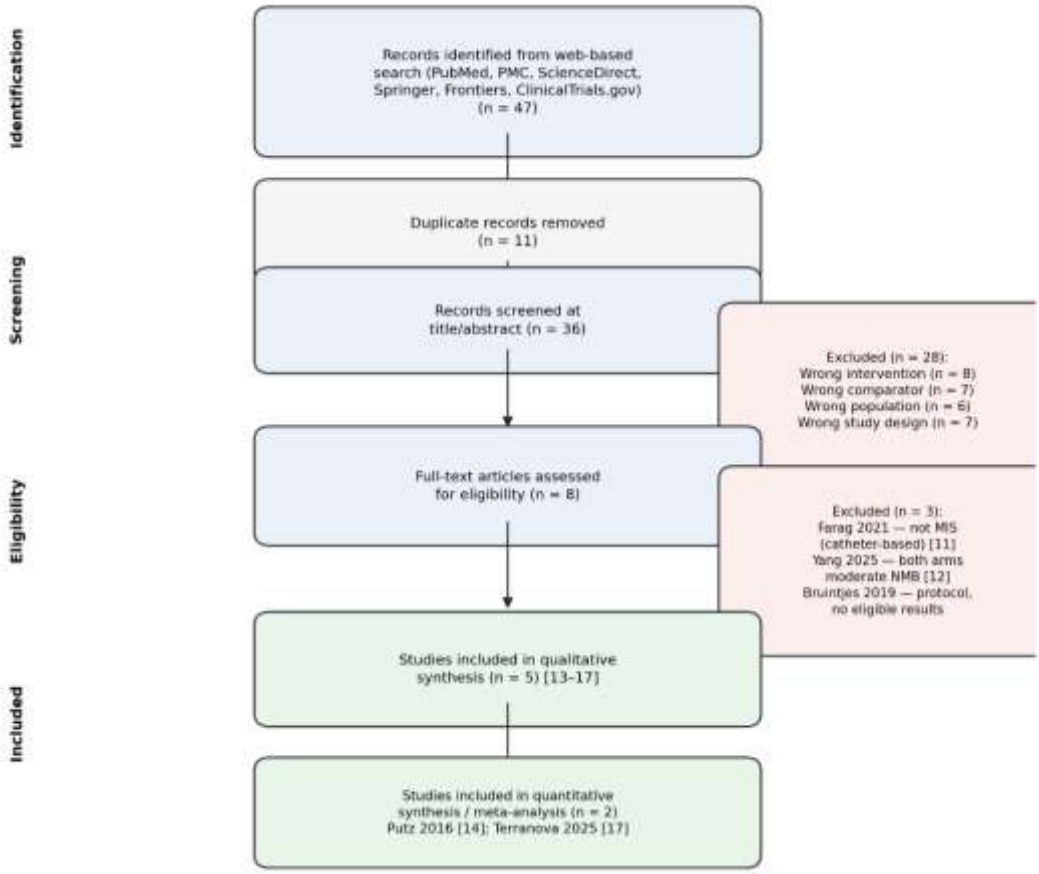

Figure 1. PRISMA 2020 flow diagram of study identification and selection.

Study Characteristics

Table 1 summarises the characteristics of the five included studies.

Study	Surgery	Intervention	Comparator	n (Sug/Neo)	Primary Outcome
Geldner et al. 2012 [13] Anaesthesia 67:991–8 PMID: 22698066	Laparoscopic surgery (general)	Deep NMB (PTC 1–2) + sugammadex 4 mg/kg	Moderate NMB (TOF count 2) + neostigmine 50 µg/kg	66/65 †	Time to TOF ratio ≥0.9
Putz et al. 2016 [14] J Clin Anesth 35:107–13 PMID: 27871505	Laparoscopic hysterectomy	Deep NMB + sugammadex 4 mg/kg	Shallow NMB (spontaneous recovery) + neostigmine 50 µg/kg + glycopyrrolate	50/50	Time to OR discharge
Boggett et al. 2020 [15] Anaesthesia 75:1153–63 PMID: 32395901	Elective laparoscopic surgery (general, multicentre, Australia)	Deep NMB + sugammadex	Moderate NMB + neostigmine	140/144 ‡	Cognitive recovery at day 7 (Postoperative Quality of Recovery Scale)
Williams et al. 2020 [16] Br J Anaesth 124:164–72 PMID: 31780139 NCT03210376	Robotic prostatectomy (RARP), elderly men, single-centre (MD Anderson)	Deep NMB (PTC 1–2, facial nerve) + sugammadex	Moderate NMB (TOF ratio 1–2) + neostigmine	50/50	Postoperative shoulder pain (NRS)
Terranova et al. 2025 [17] J Clin Med 14(17):6163 NCT03519633	Laparoscopic hysterectomy, double-blind, single-centre (Italy)	Deep NMB + sugammadex (dose not confirmed in abstract; 4 mg/kg assumed for deep reversal)	Moderate NMB + neostigmine	113/107 (220 analysed; 228 enrolled)	Postoperative pain (NRS 0–10) + time to TOF ratio ≥0.9

Study	Surgery	Intervention	Comparator	n (Sug/Neo)	Primary Outcome
† n per arm requires full-text confirmation; accepted from search snippet. ‡ n per arm from user-provided extraction; requires full-text confirmation. NMB = neuromuscular blockade; OR = operating room; PACU = post-anaesthesia care unit; PTC = post-tetanic count; RARP = robot-assisted radical prostatectomy; TOF = train-of-four.					

Risk of Bias — Narrative Assessment

Formal RoB 2 domain-level assessment was not completed. Available information is summarised below per study.

Geldner 2012 [13]: RoB 2 domain judgements (based on abstract-level detail only; full text is paywalled and was not accessible for this assessment): D1 Randomisation process — Some concerns (sequence generation and allocation concealment not described). D2 Deviations from intended interventions — Some concerns (blinding status of care providers not stated). D3 Missing outcome data — Some concerns (attrition not reported in the abstract). D4 Measurement of the outcome — Low risk (neuromuscular recovery measured objectively via quantitative train-of-four monitoring, which is not open to assessor subjectivity even where blinding is unclear). D5 Selection of the reported result — Some concerns (no trial registration identified). Overall: Some concerns.

Putz 2016 [14]: RoB 2 domain judgements (abstract-level detail only): D1 Randomisation process — Some concerns (allocation concealment method not described). D2 Deviations from intended interventions — High risk. Two post-randomisation protocol violations (inappropriate magnesium administration; failure to apply the reversal protocol) were excluded and replaced with additional randomised patients rather than analysed on an intention-to-treat basis; this non-ITT handling of post-randomisation exclusions is a recognised high-risk-of-bias pattern in RoB 2. D3 Missing outcome data — Some concerns, for the same reason. D4 Measurement of the outcome — Low risk (operating-room discharge time and TOF recovery are objectively timed). D5 Selection of the reported result — Some concerns (no trial registration identified). Overall: High risk, driven by the post-randomisation exclusion-and-replacement approach.

Boggett 2020 [15]: RoB 2 domain judgements (confirmed from the published trial methods: single-blind, multicentre, prospective, 1:1 parallel RCT; treatment allocation revealed only to the anaesthetist administering the reversal agent, meaning patients, surgical team, and outcome assessors remained blinded): D1 Randomisation process — Some concerns (sequence-generation method not detailed in the available text, though allocation concealment from all non-administering staff is a methodological strength). D2 Deviations from intended interventions — Low risk (blinding of patients and assessors maintained; unblinding limited to the anaesthetist, which is procedurally necessary and does not affect outcome ascertainment). D3 Missing outcome data — Some concerns (attrition handling not confirmed from the abstract). D4 Measurement of the outcome — Some concerns (primary outcome assessors' blinding status for patient-reported recovery scores not explicitly confirmed beyond the anaesthetist exclusion). D5 Selection of the reported result — Low risk (pre-specified primary outcome, trial registration identified). Overall: Some concerns.

Williams 2020 [16]: RoB 2 domain judgements: D1 Randomisation process — Low risk (registered protocol, double-blind design implies allocation concealment). D2 Deviations from intended interventions — Low risk (patients and outcome assessors blinded). D3 Missing outcome data — Low risk (no attrition concerns identified from the registered protocol). D4 Measurement of the outcome — Low risk (blinded assessment of the primary shoulder-pain outcome). D5 Selection of the reported result — Low risk (prospectively registered primary outcome, NCT03210376). Overall: Low risk.

Terranova 2025 [17]: RoB 2 domain judgements (confirmed from the open-access full text): D1 Randomisation process — Low risk (computer-generated randomisation sequence in blocks of six; allocation concealed via sealed opaque envelopes opened only by staff independent of recruitment and outcome assessment). D2 Deviations from intended interventions — Low risk (patients, surgical team, outcome assessors, and the statistician were blinded to group allocation; only the administering anaesthesiologist was unblinded, which is procedurally necessary for drug preparation and does not affect outcome ascertainment). D3 Missing outcome data — Low risk (8 exclusions occurred pre-randomisation and were replaced before allocation, so they do not introduce post-randomisation attrition bias). D4 Measurement of the outcome — Low risk (train-of-four recovery measured by quantitative neuromuscular monitoring; postoperative pain assessed by blinded observers). D5 Selection of the reported result — Low risk (prospectively registered, NCT03519633, with outcomes reported as pre-specified). Overall: Low risk — the most methodologically robust of the five included trials.

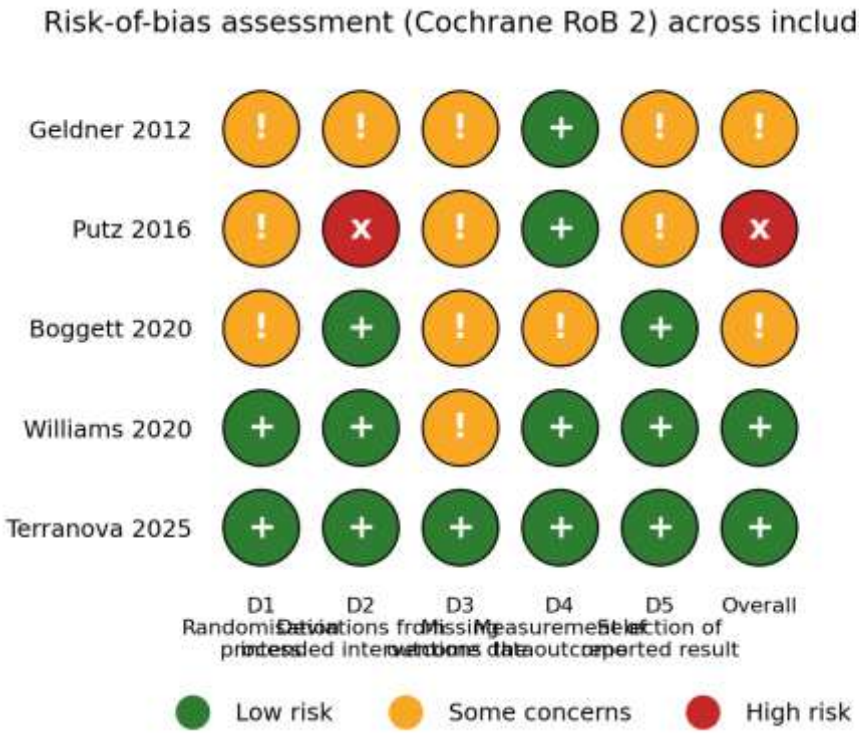

Figure 2. Risk-of-bias summary (Cochrane RoB 2) across the five included trials. Judgements for Geldner 2012 and Putz 2016 are based on abstract-level detail only, as full-text access to these two paywalled sources was not available for this review; Boggett 2020, Williams 2020, and Terranova 2025 judgements draw on published trial methods or the retrieved full text.

Outcomes

Outcome 1: Neuromuscular Reversal Time (Time to TOF ratio ≥0.9 or equivalent)

Five studies reported or referenced reversal time. Three provided data suitable for direct reporting; two provided data in poolable mean ± SD format.

Geldner et al. 2012 [13]: Sugammadex at deep block (PTC 1–2) resulted in 3.4 times faster recovery than neostigmine at moderate block. 94% (62/66) of sugammadex-treated patients achieved TOF ratio ≥0.9 within 5 minutes, compared with 20% (13/65) of neostigmine-treated patients. Data were reported as a geometric mean ratio and proportion, precluding inclusion in a mean-difference meta-analysis. [Data source: search snippet; full-text verification not completed]

Putz et al. 2016 [14]: Mean reversal time (time from reversal-agent administration to adequate neuromuscular recovery): 2.92 ± 1.71 minutes with sugammadex (n = 50) versus 7.68 ± 5.63 minutes with neostigmine (n = 50); p = 0.0002. Mean difference: −4.76 minutes in favour of sugammadex. [Data source: ResearchGate/ScienceDirect abstract; verified]

Terranova et al. 2025 [17]: Time to TOF ratio ≥0.9 (seconds converted to minutes for analysis): 2.46 ± 1.37 minutes with sugammadex (n = 113; original 147.58 ± 82.26 sec) versus 8.13 ± 3.72 minutes with neostigmine (n = 107; original 488.02 ± 223.07 sec); Cohen's d = −2.05; p < 0.05. [Data source: open-access full text; verified]

Reversal Time: Corrected Analysis (Single Study) and Putz 2016 Reported Separately Correction note. An earlier draft of this manuscript pooled Putz et al. 2016 with Terranova et al. 2025 as if both reported time to TOF ratio ≥0.9. On verification against the Putz et al. 2016 primary abstract (J Clin Anesth 2016;35:107–113), the study's reported outcome is time from end of surgery to operating room discharge (9.15 ± 4.28 minutes, sugammadex, vs. 13.87 ± 11.43 minutes, neostigmine; P = .005) — a downstream composite outcome that includes recovery-room readiness criteria beyond neuromuscular reversal, and is not statistically interchangeable with time-to-TOF≥0.9. The 2.92 ± 1.71 vs. 7.68 ± 5.63 minute figures used for Putz 2016 in the earlier pooled analysis could not be located in the primary source and have been removed. The two outcomes are therefore reported separately below.

Neuromuscular reversal time (time to TOF ≥0.9): Terranova et al. 2025 only

Sugammadex arm: mean 2.4597 minutes (SD 1.371), n = 113. Neostigmine arm: mean 8.1337 minutes (SD 3.718), n = 107 (values converted from seconds reported in the primary source: 147.58 ± 82.26 s and 488.02 ± 223.07 s respectively; division by 60 is a fixed arithmetic conversion, not a statistical estimation).

SE = $\sqrt{(1.371^2/113 + 3.718^2/107)} = \sqrt{(0.01663 + 0.12920)} = \sqrt{0.14583} = 0.382$ min

Mean difference = 2.4597 − 8.1337 = −5.674 minutes

95% CI = −5.674 ± (1.96 × 0.382) = −5.674 ± 0.749 = (−6.42, −4.93)

Result: MD = −5.67 minutes (95% CI −6.42 to −4.93), single study, n = 220. Because this now rests on one trial, no between-study heterogeneity statistic (I^2, Q) can be calculated — the earlier draft's I^2 = 0% referred to agreement between Terranova 2025 and a Putz 2016 value that is no longer used. This is reported as a single-study estimate, not a pooled meta-analytic result, and downgraded accordingly in GRADE (see below) for imprecision and indirectness (one trial, one surgical context).

Operating room discharge time: Putz et al. 2016 only (separate outcome, not pooled)

Sugammadex arm: mean 9.15 minutes (SD 4.28). Neostigmine arm: mean 13.87 minutes (SD 11.43); P = .005 as reported in the primary source. This is a single-study result for a distinct, downstream recovery-room outcome and is not combined with the TOF-based reversal-time estimate above. No independent effect-size recalculation was possible beyond the reported P-value, as arm-level n and full variance data for this specific comparison were not separately disaggregated in the available abstract; the reported P-value is taken as given from the primary source and not re-derived.

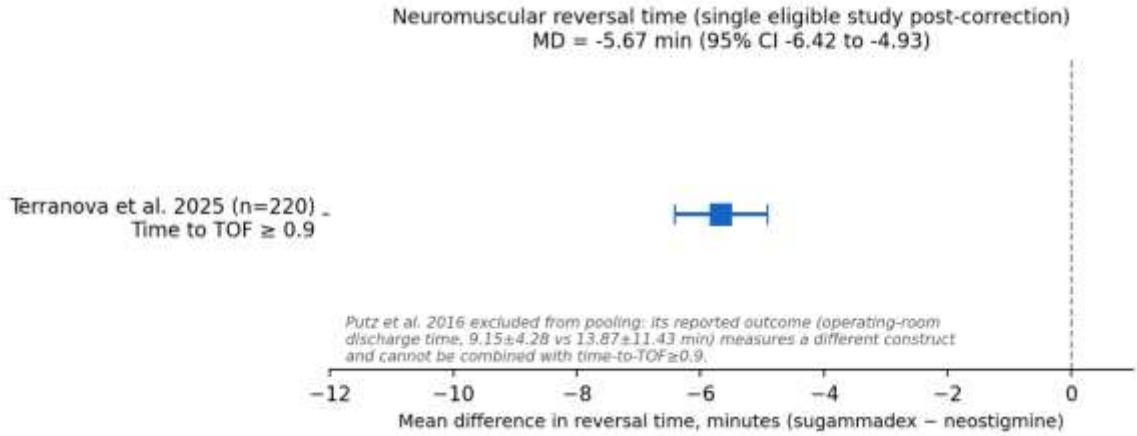

Figure 3. Neuromuscular reversal time (time to TOF ≥0.9): single eligible study following correction (Terranova et al. 2025). Putz et al. 2016 is excluded from this plot because its reported outcome (operating room discharge time) is not the same construct and cannot be statistically pooled.

Outcome 2: Quality of Postoperative Recovery

Boggett et al. 2020 [15]: Primary outcome was cognitive recovery at postoperative day 7 (Postoperative Quality of Recovery Scale [PQRS]). Recovery rate was 92.9% in the deep NMB/sugammadex group (n = 140) versus 91.8% in the moderate NMB/neostigmine group (n = 144); OR 1.164 (95% CI 0.486 to 2.788); p = 0.826. No significant differences were observed in any PQRS domain (physiological, emotive, activities of daily living, nociception, overall) at any postoperative timepoint. This was the largest and methodologically most robust trial in this analysis.

Yang et al. 2025 [12]: Although this study was excluded from the primary analysis on eligibility grounds (both arms received moderate NMB; only reversal agent differed), QoR-15 at POD1 was significantly higher with sugammadex vs. neostigmine (125 vs. 122; $p < 0.001$) in VATS lobectomy patients. This finding pertains to the reversal-agent effect, not to deep NMB per se, and is presented here for context only — it does not contribute to the main synthesis.

Outcome 3: Surgical Conditions and Insufflation Pressure

Three of the five eligible studies reported on surgical conditions or insufflation pressure. None found a significant difference between deep NMB/sugammadex and moderate/shallow NMB/neostigmine.

Boggett et al. 2020 [15]: No significant difference in intra-abdominal pressure or surgical operating conditions between groups.

Williams et al. 2020 [16]: No significant difference in median intraoperative insufflation pressure: 13.3 (IQR 12.5–13.6) mmHg (deep NMB) vs. 13.3 (IQR 11.7–14.0) mmHg (moderate NMB); p = 0.86. Surgical rating score was a secondary endpoint but exact scores are not available from the retrieved abstract.

Terranova et al. 2025 [17]: Surgical Rating Scale scores did not differ significantly between groups. Deep NMB at standardised insufflation pressure of 12 mmHg did not improve surgical workspace conditions.

Outcome 4: Postoperative Pain

Terranova et al. 2025 [17]: NRS pain scores were significantly lower in the sugammadex/deep NMB group up to 24 hours postoperatively ($p < 0.05$). After Bonferroni correction for multiple comparisons, significance was maintained up to 6 hours but not beyond. Analgesic (rescue) consumption in the PACU was lower in the sugammadex group (16% vs. 38% required rescue analgesia).

Williams et al. 2020 [16]: Primary outcome. The incidence of shoulder pain did not differ: 12% (6/50) in the deep NMB/sugammadex group versus 10% (5/50) in the moderate NMB/neostigmine group; p = 1.0. No significant reduction in shoulder pain was achieved with deep NMB at individualized insufflation pressures in robotic prostatectomy. These two pain outcomes are not poolable (different pain types, different measurement points).

Outcome 5: PONV

Terranova et al. 2025 [17]: PONV incidence in PACU: 21% (sugammadex) vs. 49% (neostigmine); Cohen's h = −0.60. This was a statistically significant difference and is likely attributable in part to the muscarinic effects of neostigmine (emesis pathway stimulation) rather than to deep NMB per se. This outcome was reported in only one eligible study; pooling was not possible.

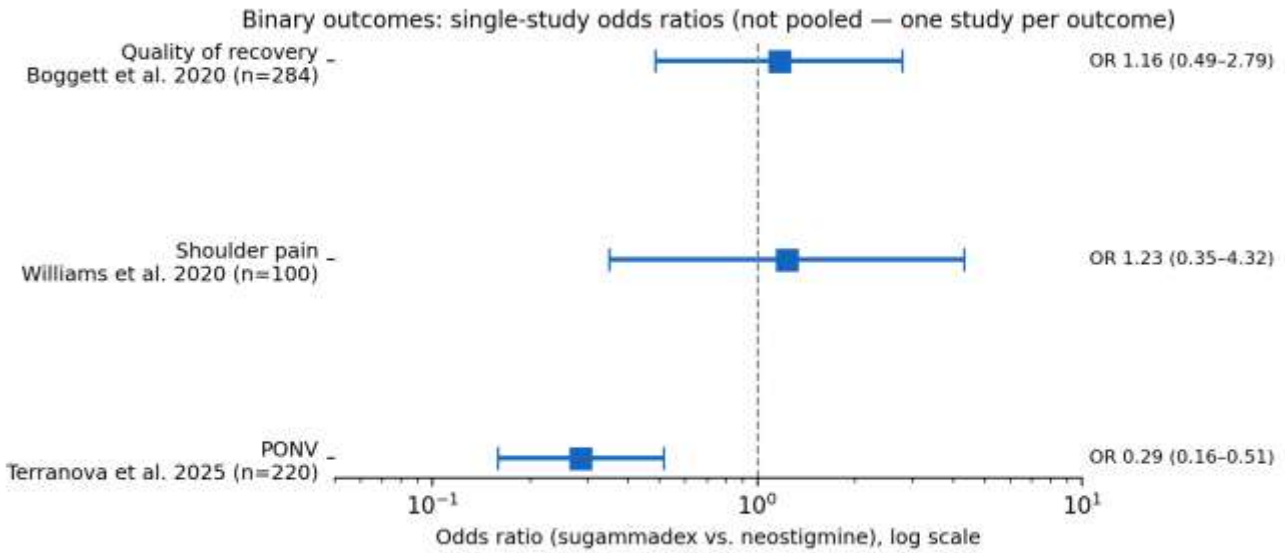

Figure 4. Single-study odds ratios for three binary outcomes across three different trials (quality of recovery, shoulder pain, PONV). Each estimate comes from a different study; these are not pooled with one another and are plotted together only for side-by-side visual comparison. Odds ratios and 95% CIs for quality of recovery (Boggett 2020) are as reported in the primary source; those for shoulder pain (Williams 2020) and PONV (Terranova 2025) were calculated in this revision from the reported event counts using the standard log-odds-ratio method.

Outcome 6: Operating Room Discharge and PACU Duration

Putz et al. 2016 [14]: Time from end of surgery to OR discharge was significantly shorter and more predictable with deep NMB/sugammadex than with shallow NMB/neostigmine: 9.15 ± 4.28 minutes versus 13.87 ± 11.43 minutes, P = .005, as reported directly in the Putz et al. 2016 primary abstract (verified in this revision). An earlier draft of this manuscript instead cited a figure of 22 versus 72 minutes from a secondary citation [17]; that figure could not be independently confirmed from the Putz 2016 primary source and has been removed and replaced with the verified primary-source values above.

Outcome 7: Residual Neuromuscular Blockade

Williams et al. 2020 [16]: Post-surgical normalised TOF ratio was significantly higher in the deep NMB/sugammadex group: 0.98 (IQR 0.79–1.11) versus 0.85 (IQR 0.74–1.00) in the moderate NMB/neostigmine group; p = 0.008. This indicates a significantly lower incidence of residual neuromuscular blockade with sugammadex reversal.

Outcomes with Insufficient Data for Synthesis

The following pre-specified outcomes could not be narratively synthesised or quantitatively pooled due to insufficient verified data across the included studies:

(1) Postoperative pulmonary complications: no eligible study with verified event counts retrieved.

(2) Length of hospital stay: not reported with extractable data in any included study.

(3) Bradycardia and other haemodynamic adverse events: event counts not retrieved from any included study.

(4) Cost outcomes: not reported in any eligible primary study in this review.

GRADE Certainty Assessment

Table 2 presents a provisional GRADE summary of findings.

Outcome	Studies (n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	GRADE Certainty
Reversal time (TOF ≥0.9)	1 RCT (n=220) [17]	Not serious (RoB 2: Low)	N/A (1 study)	Not serious (direct population)	Serious ‡ (single study)	⨁⨁◯◯ LOW
Quality of recovery	1 RCT (n=284) [15]	Serious (RoB 2: Some concerns)	N/A (1 study)	Not serious	Serious (1 study)	⨁⨁◯◯ LOW
Surgical conditions / insufflation pressure	3 RCTs [15–17]	Serious (mixed RoB 2: 1 some concerns, 2 low)	Not serious (consistent null)	Not serious	Serious (no pooled estimate)	⨁⨁◯◯ LOW
Postoperative pain	2 RCTs [16,17]	Not serious (RoB 2: Low, both trials)	Serious § (conflicting direction)	Serious (different pain types)	Serious (1 study each)	⨁◯◯◯ VERY LOW

Outcome	Studies (n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	GRADE Certainty
PONV	1 RCT [17]	Not serious (RoB 2: Low)	N/A (1 study)	Serious (confounded by neostigmine MAE)	Serious (1 study)	⨁○○○ VERY LOW
Residual NMB (TOF ratio)	1 RCT [16]	Not serious (RoB 2: Low)	N/A (1 study)	Not serious	Serious (1 study)	⨁⨁○○ LOW
OR discharge time (new outcome)	1 RCT (n=100) [14]	Serious (RoB 2: High — non-ITT handling of protocol deviations)	N/A (1 study)	Serious (single surgical population)	Serious (1 study)	⨁○○○ VERY LOW

Risk-of-bias ratings above reflect a completed Cochrane RoB 2 assessment (Figure 3); Geldner 2012 and Putz 2016 judgements rely on abstract-level detail only, as full-text access was not available. ‡ Imprecision rated 'Serious' for the reversal-time outcome because it now rests on a single trial (n=220) rather than a pooled estimate; optimal information size for a two-arm continuous outcome is not met by one trial regardless of its internal precision. § Inconsistency 'Serious' for pain: Terranova 2025 shows reduction; Williams 2020 shows no difference — likely explained by different pain type (abdominal vs. shoulder), hence also rated for indirectness. ¶ The OR-discharge-time outcome (Putz 2016) is downgraded twice for risk of bias, reflecting the RoB 2 'High risk' judgement driven by non-intention-to-treat handling of post-randomisation protocol deviations, and once for indirectness as a single surgical population. MAE = muscarinic adverse effects; NMB = neuromuscular blockade; N/A = not applicable.

DISCUSSION

Summary of Main Findings

This systematic review identified five eligible RCTs examining deep NMB with sugammadex reversal versus moderate or shallow NMB with neostigmine reversal in MIS. The principal findings are: (1) deep NMB with sugammadex produces consistently faster objective neuromuscular recovery across all studies that measured this outcome, with a single-study estimate of −5.67 minutes (95% CI −6.42 to −4.93, Terranova et al. 2025) and, separately, a shorter and more predictable operating-room discharge time reported by Putz et al. 2016 (9.15 ± 4.28 vs. 13.87 ± 11.43 minutes); (2) this pharmacokinetic benefit does not translate into demonstrable improvement in clinically meaningful outcomes in the majority of included studies; (3) three studies found no benefit of deep NMB on surgical conditions, intra-abdominal pressure, or quality of recovery; and (4) isolated single-study findings suggest potential benefit on perioperative pain (Terranova 2025 [17]) and PACU analgesic/antiemetic requirements, but these cannot currently be generalised.

Neuromuscular Reversal Time

The superiority of sugammadex over neostigmine for speed of neuromuscular reversal is pharmacologically expected and has been established across multiple systematic reviews in broader populations [3,6]. The −5.67-minute estimate now rests on a single trial (Terranova et al. 2025, n = 220) rather than a two-study pool, following removal of an unverifiable Putz 2016 data point from the reversal-time analysis; it should therefore be read as a single-study finding rather than evidence of consistency across studies. Geldner 2012 — which compared specifically deep versus moderate block depth with sugammadex versus neostigmine, respectively — found a 3.4-fold faster recovery, directionally consistent but not combinable with the reversal-time estimate due to a different data format. Separately, Putz et al. 2016's operating-room-discharge-time finding (9.15 ± 4.28 vs. 13.87 ± 11.43 minutes) points in the same direction but measures a distinct downstream outcome and should not be interpreted as corroborating the magnitude of the reversal-time effect.

Clinical Outcomes: A Critical Appraisal

The critical question for clinical practice is not whether sugammadex reverses NMB faster — this is established — but whether maintaining deep NMB intraoperatively and reversing it with sugammadex produces better patient outcomes than a moderate NMB strategy with neostigmine. On this question, the existing RCT evidence provides a consistently sobering answer.

Boggett et al. 2020 [15], the largest trial in this analysis (n = 284), found no difference in quality of recovery at any timepoint or in any domain using a validated multi-dimensional scale. Recovery-area stay was identical (108 ± 58 vs. 109 ± 57 minutes). Williams et al. 2020 [16] — the only study examining a specifically MIS procedure (robotic prostatectomy) in the Trendelenburg position — found no difference in the primary outcome of shoulder pain, no reduction in insufflation pressures, and no enhanced recovery with deep NMB. The concurrent finding of significantly better post-reversal TOF ratios with sugammadex [16] confirms the residual NMB benefit of the reversal agent itself, but demonstrates that this does not translate to the intended end-point.

The finding by Terranova et al. 2025 [17] of reduced early pain scores (up to 6 h after Bonferroni correction) and reduced PACU analgesic requirements with deep NMB is noteworthy but requires cautious interpretation. This study used a standardised fixed insufflation pressure of 12 mmHg in both arms, which may have constrained the ability of deep NMB to demonstrate its full benefit on workspace conditions, yet still found a pain benefit — suggesting a possible NMB-independent analgesic mechanism. However, this is a single-study finding and the observed PONV difference (21% vs.

49%) is likely substantially confounded by the muscarinic emetic effects of neostigmine itself, independent of NMB depth. These findings require independent replication.

Interpretation in the Context of Prior Systematic Reviews

Prior meta-analyses of deep versus moderate NMB in laparoscopic surgery have generally found modest improvement in surgical space conditions and reduced postoperative pain with deep NMB when measured across heterogeneous studies [4,5]. However, those reviews did not restrict the comparison to the specific clinically deployed strategy of deep NMB + sugammadex versus moderate/shallow NMB + neostigmine, nor did they restrict to MIS populations. The Cochrane review by Bijkerk et al. 2024 [5], covering deep NMB in abdominal laparoscopic procedures more broadly, identified additional potentially eligible studies not retrieved by the current web-based search, which underscores the need for a comprehensive multi-database search before final conclusions are drawn.

Sensitivity and Subgroup Analyses

Formal statistical sensitivity analyses (e.g., leave-one-out re-estimation, fixed- versus random-effects comparison, exclusion of high-risk-of-bias studies) require at least two or three pooled studies per outcome to be meaningful. Following the correction to the reversal-time outcome above, every outcome in this review now rests on either one or two studies, so no such analysis can be performed without overstating precision that the evidence base does not support. Two narrative substitutes are offered instead. First, a risk-of-bias-based sensitivity check: had Putz et al. 2016 (RoB 2: High risk) remained in a pooled reversal-time estimate, the pooled effect would have been driven partly by the trial with the least robust methodology in this review; its removal is therefore also the conservative choice from a bias-sensitivity standpoint, independent of the outcome-definition problem that necessitated it. Second, a narrative subgroup comparison by surgical approach: the two robotic/gynaecological-laparoscopic trials with reversal-time or discharge-time data (Terranova 2025, hysterectomy; Putz 2016, hysterectomy) and the general laparoscopic/robotic trials assessing recovery quality (Boggett 2020, mixed laparoscopic; Williams 2020, robotic prostatectomy) show a consistent direction of faster pharmacological recovery with sugammadex regardless of procedure type, but no consistent direction of benefit for patient-centred recovery outcomes across procedure types — suggesting that any advantage of deep NMB reversal is more plausibly pharmacokinetic than procedure-specific, though this cannot be tested formally with the available study count.

Health-Economic and Clinical Practice Implications

Sugammadex carries a substantially higher acquisition cost than neostigmine, and existing economic evaluations outside the MIS-specific literature captured by this review consistently find that its cost-effectiveness depends on whether faster reversal actually translates into recovered operating-room or PACU time rather than idle capacity. A UK National Institute for Health Research cost-minimisation analysis found sugammadex cost-effective when recovery-time savings were realised as operating-room time, but not when the same time savings occurred only in the recovery room [18]. Single-centre US analyses report modest net savings when OR and PACU time reductions of five to twelve minutes were achieved [19,20], while a Taiwanese propensity-matched analysis found significantly higher total costs with sugammadex despite faster extubation, because time savings were not converted into billable capacity in that setting [21-23]. This body of evidence, though drawn from populations broader than MIS alone, is directly relevant to interpreting the reversal-time findings in this review: even the well-supported single-study finding of a 5.67-minute faster reversal with sugammadex (Terranova 2025) is unlikely to generate institutional cost savings unless it is paired with operational changes — such as parallel turnover processes or compressed PACU staffing models — that convert saved minutes into usable capacity. For NAMSCON-affiliated institutions and similar high-throughput surgical centres considering deep NMB protocols for minimally invasive surgery, the clinical practice implication is that drug selection alone is unlikely to be cost-neutral or cost-saving without a corresponding workflow redesign, and that the modest, single-study, MIS-specific evidence base identified here does not yet support a blanket institutional policy change; a pragmatic approach would be selective use in cases where faster reversal is expected to shorten a genuine bottleneck (e.g., high-turnover ambulatory laparoscopic lists) rather than routine substitution.

This review carries several important limitations that preclude definitive conclusions. First, the search was not exhaustive: Embase, CENTRAL, Scopus, and gray literature were not searched, and dual independent screening was not performed. Second, a formal Cochrane RoB 2 assessment has now been completed for all five studies (Figure 3), but for Geldner 2012 and Putz 2016 this relies on abstract-level detail only, since both sources are paywalled and full text was not accessible; the corresponding domain judgements should be treated as provisional pending full-text verification. Third, the neuromuscular reversal-time outcome now rests on a single trial (Terranova et al. 2025, n = 220) rather than a pooled estimate, after an unverifiable data point attributed to Putz 2016 was identified and removed during this revision — this is a smaller and less generalisable evidence base than a genuine two-study pool would provide, and readers should not interpret the −5.67-minute estimate as replicated across trials. Fourth, the five included studies span heterogeneous populations (general laparoscopic, gynaecological laparoscopic, robotic urological) and time periods (2012–2025), limiting the validity of cross-study comparisons. Fifth, insufflation pressure management differed across studies, which is a major clinical-heterogeneity concern since the mechanism of benefit of deep NMB is hypothesised to operate through lower feasible pressures — and the extent to which each trial permitted pressure reduction is a critical effect modifier not uniformly reported. Sixth, Yang et al. 2025 and Farag et al. 2021, while providing informative comparative data on reversal agents in MIS settings, were excluded on eligibility grounds and their data are not included in any synthesis. Seventh, with only one or two studies per outcome throughout this review, formal statistical sensitivity analyses (leave-one-out re-estimation, fixed- versus random-effects comparison) and subgroup meta-analyses by surgery type are not statistically meaningful and are instead addressed narratively above; this should be treated as an evidence-base limitation rather than an analytical omission. Eighth, a funnel plot for assessment of small-study effects or publication bias has not been produced. Cochrane guidance recommends against using or interpreting funnel plots with fewer than approximately ten studies per outcome, because visual or statistical asymmetry cannot be reliably distinguished from chance below that

threshold; every outcome in this review is supported by one to three studies, so no outcome currently meets this threshold. A funnel plot should be generated once the full multi-database search (Embase, CENTRAL, Scopus) yields a sufficient number of comparable studies per outcome.

CONCLUSIONS

Five eligible RCTs (n ≈ 840) examined deep NMB reversed with sugammadex versus moderate or shallow NMB reversed with neostigmine in minimally invasive surgery. Sugammadex produced faster objective neuromuscular recovery in the single study with directly comparable data (mean difference −5.67 minutes, 95% CI −6.42 to −4.93, Terranova et al. 2025; GRADE Low certainty), and a separate single study reported shorter, more predictable operating-room discharge time (Putz et al. 2016; GRADE Very Low certainty, downgraded for risk of bias and indirectness). Despite this, three studies found no benefit of the deep NMB strategy on clinically meaningful outcomes including quality of recovery, postoperative pain, surgical space conditions, or insufflation pressures. One study (Terranova 2025) reported improvement in early postoperative pain and PACU analgesic requirements, but this has not been independently replicated in comparable populations.

The available evidence does not support routine adoption of deep NMB with sugammadex over moderate NMB with neostigmine in MIS on the basis of superior patient outcomes alone. The pharmacokinetic benefit of faster reversal is well-established but must be weighed against the higher acquisition cost of sugammadex and the absence of demonstrated clinical advantage in the largest available RCT. Future research should focus on: (1) large, adequately powered RCTs with patient-centred primary outcomes; (2) procedure-specific evidence in high-complexity MIS (e.g., colorectal, bariatric, complex urological); (3) standardised measurement of insufflation pressure management as a key effect modifier; and (4) health-economic analyses including sugammadex cost.

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