Supplemental Digital Content 1

Systematic Review Protocol - Monitoring and Antagonism of Neuromuscular Blockade

# Background

The Anesthesia Patient Safety Foundation requested the American Society of Anesthesiologists via its Committee on Standards and Practice Parameters to consider “residual neuromuscular blocking drug-induced muscle weakness in the postoperative period” for development of a practice guideline.

# Key Questions

In patients receiving neuromuscular blocking agents, what monitoring strategies to guide and confirm recovery (spontaneous or after antagonist drug) will minimize residual neuromuscular blockade and its complications? Questions concerning the economic impact (cost-effectiveness) of quantitative monitoring and reversal agents were posed but considered beyond the scope of the systematic review.

1. What factors affect the performance of quantitative monitoring?
2. What are the comparative performance characteristics (sensitivity, specificity, or accuracy) of quantitative monitoring and peripheral nerve stimulation for identifying residual neuromuscular blockade?
   1. What are the comparative performance characteristics of different quantitative monitors?
3. What are the comparative effects of clinical assessment (e.g., head lift), qualitative assessment (e.g., peripheral nerve stimulator [PNS]), and quantitative monitoring (measuring train-of-four ratios) on residual neuromuscular blockade, pulmonary complications, and other adverse events?
   1. In patients with clinically important residual neuromuscular blockade are outcomes improved with quantitative neuromuscular monitoring compared with peripheral nerve stimulation or no monitoring? Are outcomes modified by the degree of residual neuromuscular blockade?
   2. When using quantitative monitoring, does confirming train-of-four ratio ≥ 0.9 decrease the risk of residual neuromuscular blockade?
4. What are the comparative efficacy and safety of antagonist drugs among patients receiving nondepolarizing neuromuscular blocking drugs?
   1. How does the level of neuromuscular blockade predict the efficacy of neostigmine?
5. What are the antagonism strategies for benzylisoquinolinium neuromuscular blockade?
6. What are the comparative outcomes of selective and treat-all antagonism strategies?

# PICOTS

## Monitoring

### Population(s):

* All surgical patients receiving neuromuscular blocking agents. *Exclusions: critical care*
* Subgroups
* Patient characteristics/co-morbidities
  + Frailty
  + Obesity
  + Diabetes
  + Renal/liver impairment
  + Paretic limb
* Depth or level of blockade
* Complete – post-tetanic count= 0
* Deep – Post-tetanic count ≥ 1; Train-of-four count = 0
* Moderate – Train-of-four count = 1-3
* Shallow – Train-of-four count = 4; Train-of-four fade present, train-of-four ratio = 0.1-0.4
* Minimal – Train-of-four count = 4; Train-of-four fade absent, train-of-four ratio >0.4 but <0.9
* Acceptable recovery – Train-of-four count = 4 without fade; train-of-four ratio ≥0.9 – 1.0
* Age
* ≥ 65
* 18-64
* <18
* Health status
* American Society of Anesthesiologists (ASA) I-II
* ASA III or higher
  + Type of procedure
  + Type of anesthesia
* Volatile
* Total intravenous anesthesia
  + Sex
  + Medications
    - Antibiotics
    - Magnesium infusions
    - Lidocaine infusions
    - Anticonvulsants

### Interventions:

* Quantitative/objective monitoring
* Qualitative/subjective with PNS assessment
* Clinical assessment without PNS

### Comparators:

* No monitoring or assessments

### Outcomes:

* Patient Reported
  + Patient satisfaction (quality of recovery)
  + Nausea
  + Pain/discomfort
* Clinical
  + Residual neuromuscular blockade
  + Train-of-four ratio
  + TOFC (question 2)
  + Post-op reintubation
  + Recurarization (reparalysis)
  + Pulmonary complications
  + Post-operative nausea and vomiting
  + Length of stay (PACU/hospital)
  + Hospital/ICU admission
  + PACU respiratory interventions
  + Time from completion of surgery to extubation

### Timing:

* + - Perioperative period (up to 30 days postop)

### Settings:

* Operating room
* PACU
* ICU
* Medical-surgical floor

## Antagonism

Population(s):

Same as for monitoring

### Interventions:

* Sugammadex
* Neostigmine
* Pyridostigmine

### Comparators:

* No antagonism (spontaneous recovery)

### Outcomes:

* Patient Reported
  + Patient satisfaction (quality of recovery)
  + Nausea
  + Pain/discomfort
* Clinical
  + Time to recovery
  + Inadequate reversal
  + Second antagonist drug (rescue antagonism)
  + Anaphylaxis
  + Bradyarrhythmia
  + Coagulopathy
  + Pregnancy
  + Headache
  + Hypoxia
  + Recurarization (reparalysis)
  + Pulmonary complications
  + Post-operative nausea and vomiting
  + Length of stay (PACU/hospital)
  + Hospital/ICU admission

Timing:

Same as for monitoring

Settings:

Same as for monitoring

## Definitions

Pulmonary complications

Residual neuromuscular block

Adequate antagonism

Qualitative/subjective assessment (with PNS)

Quantitative/objective monitoring

Clinical assessment (without PNS)

## Analytic Framework (Evidence Model)



NMB: neuromuscular blockade; TOFC: train-of-four count; TOFR: train-of-four ratio; PTC: posttetanic count; PONV: post operative nausea and vomiting

## Methods

### Search

The literature search will include publications from 1990 to present.

### Criteria for Inclusion/Exclusion of Studies

1. Publication Types
   * Published journal articles, reports
   * Language restrictions: English language only
   * Limited to humans
   * Grey literature
2. Study Designs
   * Include
     + Randomized clinical trials
     + Non-randomized clinical trials
     + Quasi-randomized designs (e.g., before-after studies, interrupted time series)
     + Cohort studies
     + Case-control studies
     + Other observational studies (e.g., diagnostic accuracy)
   * Exclude
     + Case reports and case series
     + Surveys, questionnaires
     + Letters
     + Editorials
     + Systematic reviews and meta-analyses (for reference checking)

### Search Strategies

Comprehensive bibliographic database searches will be conducted by a medical librarian using PubMed, EMBASE, and SCOPUS in June 2021 and updated in June 2022. In addition, the Cochrane Central Register of Controlled Trials will be queried; task force members provided potentially relevant studies; references from systematic reviews and meta-analyses will be hand-searched; and trial registries will be searched.

### Data Abstraction and Management

Title/abstract and full-text screening together with data extraction will be performed on the DistillerSR platform.1 All screening will be conducted in duplicate, with disagreements resolved by consensus or a third reviewer as needed.

Anticipated data extraction includes study characteristics (e.g., design, dates, setting, centers, country, funding, registration, subgroups, surgery, and anesthetic), study arms (e.g., intervention, participant characteristics, intervention, and outcomes reported), and outcome detail according to type (e.g., patient-reported or clinical; continuous, dichotomous [includes relative effects], rating scales [Likert, visual analog, numeric]). As required, figures will be digitized. A single reviewer will extract study data followed by verification.2

### Risk of Bias of Individual Studies

Risk of bias assessment for randomized trials will be conducted using the Cochrane risk of bias tool.3 The tool includes appraisals of potential bias in the randomization process, deviations from intended interventions, missing data, outcome measurement, and selection of reported results. An algorithm is used to obtain a rating (low, some concerns, high) for each domain. The overall risk of bias is based on the individual domain assessments reflecting the most severe judgment (for example, if one domain is judged high risk, then the overall risk of bias is considered high risk).

Risk of bias assessment of non-randomized studies of interventions (e.g., observational studies of interventions including cohort, case-control, and quasi-randomized designs) will utilize the ROBINS-I tool (Risk Of Bias In Non-randomised Studies of Interventions).4 The tool conceptually compares the study to a hypothetical pragmatic target randomized trial; systematic differences between non-randomized and hypothetical randomized trials define potential bias. The appraisal includes potential bias due to confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and outcome reporting. The overall risk of bias is determined based on the 7 domain assessments and includes low, moderate, serious, and critical risk of bias as well as no information on which to base a judgement about risk of bias.

Risk of bias for diagnostic accuracy studies will be appraised with the QUADAS 2 tool (Quality Assessment of Diagnostic Accuracy Studies).5 The tool focuses on evaluating risk of bias and applicability corresponding to internal and external validity. Four risk of bias are included: patient selection (random, avoid case-control design); index test (interpreted without knowledge or reference standard results; prespecified thresholds); reference standard (likely correct classification of target conditions, interpreted without knowledge of index test results); patient flow (appropriate interval between index and reference tests; same reference standard for all patients; intention to diagnosis analysis). Applicability domains are included: patient selection (match between included patients and target population); index test (consistency of index test with review question); reference standard (target condition defined by index test matches review question). Risk of bias is judged as low, high, or unclear. Applicability is rated similarly. Observational results (including single arms of randomized controlled trials) to examine train-of-four confirmation prior to extubation will be appraised using the CLARITY tool.13

Risk of bias will be assessed independently by two reviewers with discrepancies resolved by discussion, or a third reviewer as needed.

### Evidence Synthesis

As appropriate based on clinical and methodological heterogeneity, study results will be pooled in either pairwise or network meta-analyses. Random effects models will be used as the goal of pooling is to estimate unconditional effects.6 Statistical heterogeneity will be evaluated using *I*2, and for values exceeding 25%, meta-regression considered if feasible.7 Small study effects and the potential for publication bias will be evaluated using funnel plots, regression-based tests, and adjustment methods.8 Relative effects will be pooled as risk ratios9 and continuous measures as mean differences or standardized mean differences. Analyses will be conducted using R and any applicable packages.8,10,11 Prespecified subgroups well be analyzed as feasible.

### Grading the Strength of Evidence

The strength (certainty) of evidence for important outcomes will be appraised using GRADE (Grading of Recommendations Assessment, Development and Evaluation)12 and American College of Cardiology Foundation/American Heart Association frameworks.14 In GRADE, randomized controlled trials start as high strength of evidence and nonrandomized studies start as low. The strength may be downgraded based on summary study-level risk of bias, inconsistency, indirectness, imprecision, and publication bias. Strength may be upgraded if the effect is large, a dose-response is present, or if unaccounted residual confounding would likely have increased the effect.

# Protocol Revisions

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| --- | --- | --- |
| **Date** | **Section** | **Modification** |
| 7/19/2021 | Section II. Monitoring PICOTS | Population revised to surgical patients |
| 8/10/2021 | Section II. KQ3a | Removed “(informed by direct or indirect evidence)” |
| 8/10/2021 | Section III. Monitoring PICOTS | Subgroups removed type of anesthesia, volatile and TIVA |
| 2/15/2022 | Section I. | Revised systematic review question from “In patients receiving neuromuscular blocking agents, what are optimal strategies for assessing the degree of neuromuscular blockade and the subsequent use of reversal agents?” to  “In patients receiving neuromuscular blocking agents, what monitoring strategies to guide and confirm recovery (spontaneous or after reversal agent) will minimize residual neuromuscular blockade (RNMB) and its complications?” |
| 2/15/2022 | Section II. Monitoring KQ3a | Removed “health” before outcomes |
|  | Section II. Monitoring KQ3b | Removed “health” before outcomes, changed rNMB to RNMB, and removed “(residual neuromuscular blockade)” |
|  | Section II. Monitoring KQ3c | Changed from " What is the threshold for predicting the benefit of reversal agents?’ to “Difference in use of 0.9 or 1.0 for AMG?” |
|  | Section II. Antagonism KQ4 | Removed “on recovery time and complications?” |
|  | Section II. Antagonism KQ4a | New question added “How does the level of NMB predict the efficacy of neostigmine?” |
|  | Section II. Antagonism KQ4b | New question added “Subgroups with antagonist drug” |
|  | Section III. PICOTS | Monitoring outcomes added “TOFC2(question 2)” |
|  | Section III. PICOTS | Antagonism interventions removed edrophonium |
|  | Section III. PICOTS | Antagonism outcomes clinical added “Time to recovery” |
| 8/10/2022 | Section III. Monitoring PICOTS | Subgroups added type of anesthesia, volatile and TIVA.  Changed qualitative monitoring to qualitative assessment |
| 8/26/2022 | All | Replaced reversal with antagonism |

# References

1. Evidence Partners: DistillerSR. Ottawa, Canada, 2020

2. PCORI: Methodology Standards (11: Standards for Systematic Reviews) https://www.pcori.org/research-results/about-our-research/research-methodology/pcori-methodology-standards#Systematic%20Reviews, 2021

3. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernan MA, Hopewell S, Hrobjartsson A, Junqueira DR, Juni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT: RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366:l4898

4. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hrobjartsson A, Kirkham J, Juni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schunemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JP: ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016; 355:i4919

5. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM, Group Q-: QUADAS-2: A revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011; 155:529-36

6. Hedges LV, Vevea JL: Fixed-and random-effects models in meta-analysis. Psychol Method 1998; 3:486-504

7. Thompson SG, Higgins JP: How should meta-regression analyses be undertaken and interpreted? Stat Med 2002; 21:1559-73

8. Schwarzer G, Carpenter JR, Rücker G: Meta-analysis with R. New York, Springer, 2015

9. Xiao M, Chu H, Cole SR, Chen Y, MacLehose RF, Richardson DB, Greenland S: Controversy and debate : Questionable utility of the relative risk in clinical research: Paper 4: Odds ratios are far from “portable” — A call to use realistic models for effect variation in meta-analysis. J Clin Epidemiol 2022; 142:294-304

10. Team RC: R: A Language and Environment for Statistical Computing. 2020, http://www.r-project.org/index.html

11. B'Eliveau A, Boyne DJ, Slater J, Brenner D, Arora P: BUGSnet: An R package to facilitate the conduct and reporting of Bayesian network meta-analyses. BMC Med Res Methodol 2019; 19:196

12. Schunemann H, Brozek J, Guyatt G, Oxman A: GRADE Handbook, 2019, https://gdt.gradepro.org/app/handbook/handbook.html

13. Busse J, Guyatt G: Tool to assess risk of bias in cohort studies, https://www.Evidencepartners.Com/resources/methodological-resources/

14. Valentine JC, Pigott TD, Rothstein HR: How many studies do you need? A primer on statistical power for meta-analysis. J Educat Behav Stat 2010; 35:215-47