Effects of dexamethasone on sugammadex reversal times of rocuronium: a systematic review protocol

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Review question/objective: The objective of the review is to identify the effect of dexamethasone on reversal times of rocuronium when utilizing sugammadex as the reversal agent. The incidence of the prolonged time to extubation in patients who have received concurrent dexamethasone and sugammadex therapies as opposed to those who have not received dexamethasone will also be examined. The proposed PICO question is as follows: In patients undergoing reversal of aminosteroidal neuromuscular blockade with rocuronium, does dexamethasone administration affect sugammadex reversal times, as compared to patients who have not received dexamethasone?

Keywords Dexamethasone; reversal time; rocuronium; sugammadex


Background

The use of neuromuscular blockade has existed for decades, since the early 1900s, when curare was first administered as a means of providing “surgical relaxation” for an anesthetized patient. Since then, the use of paralytics in the operating room has become a common practice, as their implementation has proven invaluable. Paralytics have allowed for much safer operating conditions for surgeons performing high-risk surgeries where even the slightest movement by the patient could lead to catastrophic results, or where muscular relaxation is of paramount importance, as in most laparoscopic procedures. Paralytics are also frequently utilized by anesthesia providers during the process of intubation to augment patient relaxation and improve intubating conditions. However, while paralytics are quite useful for the purpose of keeping a patient still during an operation or intubation, their effects lasting beyond the operative period are not only undesirable but can even be harmful. As a result, the need for a reversal agent soon became apparent.

Throughout the years, various reversal agents have been utilized to some effect for the purpose of paralytic agent reversal, they have multiple problems, the most significant of which is residual blockade (the prolonged effects of a paralytic’s actions, despite attempt at paralytic reversal). Residual blockade is of distinct concern as it can lead to potentially life-threatening events such as respiratory distress or even arrest, possibly resulting in reintubation and a prolonged hospital stay. Furthermore, acetylcholinesterase inhibitors carry the additional risk of potentiating acetylcholine’s cholinergic effects, such as severe bradycardia, hypotension, bronchospasm, increased respiratory secretions, nausea and vomiting. This, in turn, drives the need for concurrent administration of anti-muscarinic agents, such as glycopyrrolate, to counter these potentially harmful side effects. With the current reversal regimen exhibiting a plethora of negative side effects, it was clear that a more effective and safe means of reversal was needed. The pharmaceutical company Organon International, a part of Schering-Plough Corporation (now owned by Merck), first discovered sugammadex (sugammadex sodium, generic, Organon International, a part of Schering-Plough Corporation, a part of Merck Incorporated, Kenilworth, NJ, USA). Sugammadex was approved for use in Europe on June 2, 2008 and was recently approved for use in the United States of America, on December 15, 2015. Sugammadex is an innovative drug that was originally discovered as a reversal agent for the paralytic rocuronium.

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However, it has potential to be effective for reversal in other steroidal, non-depolarizing neuromuscular blocking agents (NDNMBAs) as well.\(^6\) It is a modified (gamma)-cyclodextrin that appears to have no effect on acetylcholinesterase, therefore mitigating the need for administration of anticholinergics.\(^2\) This is particularly significant in that previous front-line drugs utilized for the purpose of neuromuscular blockade reversal have had such significant cholinergic side effects as to require secondary and even tertiary drug administration to mitigate these effects.\(^2\) While the use of acetylcholinesterase inhibitors sought to competitively antagonize NMBAs by increasing the amount of available acetylcholine in the synaptic cleft, sugammadex is unique in that it seeks not to affect the function of the synapse but effectively binds the administered paralytic agent such that it is no longer bioavailable. This mechanism of action has been defined as a selective relaxant binding agent (SRBA), thus creating the new pharmaceutical category of SRBAs.\(^1\)

Taking into consideration sugammadex’s primary mechanism of action, that of selective binding of steroidal NDNMBAs, one must consider the effects that other steroidal agents may have in alternatively binding sugammadex, thus altering sugammadex’s intended effects. It is readily recognized that some molecules such as toremifene, fusidic acid and flucloxacillin interact with sugammadex, displacing rocuronium from the sugammadex molecule, as demonstrated by Zwiers et al.\(^7\) Displacement of the intended target drug from the molecule could negatively affect sugammadex’s performance in the role of NDNMBA reversal, thus prolonging paralysis and placing patients at increased risk for adverse respiratory events, such as respiratory failure or arrest. Results generated by Zwiers et al.\(^7\) indicate that any molecule of appropriate size and lipophilicity could cause similar undesirable effects. In particular, this raises the question of the effect that dexamethasone, the most frequently utilized steroid in anesthesia, may have upon sugammadex and its ability to neutralize NDNMBAs.

Dexamethasone is a commonly utilized drug, as it has many applications: the treatment of edema, use in multimodal analgesia and prophylactic treatment of postoperative nausea and vomiting.\(^5,9\) As dexamethasone is so widely utilized, its potential impact on sugammadex reversal is also quite broad. Dexamethasone is very similar in size and shape to rocuronium, having the same cyclopentanoperhydrophenanthrene structure and very similar dimensions, per Buonanno et al.\(^9\), indicating that it is likely to interact with sugammadex.\(^8\) The impact of preferential binding of dexamethasone by sugammadex could result in several negative outcomes such as prolonged reversal times leading to extended time in the recovery room, or even re-intubation due to persistent neuromuscular blockade. Several research studies have been conducted to analyze the effects of dexamethasone on sugammadex. One such study, published by Buonanno et al.,\(^9\) indicates that dexamethasone has no effect on sugammadex reversal times. Another study, performed in the pediatric population by Gulec et al.,\(^10\), also demonstrates that dexamethasone appears to have no effect on the efficacy of sugammadex to reverse the paralytic effects of rocuronium, nor does it impact time to extubation. However, other studies contradict these findings, such as the study by Zwiers et al.,\(^7\) indicating that there is the potential for dexamethasone to interact with sugammadex, allowing for the possibility of an inhibitory affect on sugammadex’s reversal of rocuronium. Yet another study by Rezonja et al.,\(^8\) performed in an in-vitro setting on human muscle cells, indicates that dexamethasone inhibits sugammadex’s ability to effectively reverse rocuronium. Furthermore, multiple case studies have also indicated that sugammadex, administered per recommended dosages, has proven inadequate in reversing rocuronium when delivered in the presence of dexamethasone.\(^11,12\)

The potential for inhibition of sugammadex in its intended role as a paralytic reversal agent would have significant clinical impact in a number of areas: it could prolong the reversal time, resulting prolonged anesthesia delivery time, prolonged time in the operating room, prolonged recovery time and the potential for re-intubation. Each of these events would have cascading effects in requiring additional anesthesia monitoring, additional post-anesthesia care unit staff time and additional staff utilization in the intensive care unit (ICU), should a patient need to be re-intubated and admitted to the ICU for ventilatory support. Any one of these effects results in increasing personnel utilization and overall hospital costs.

As the aforementioned studies have yielded conflicting results, and the potential impact of sugammadex inhibition is so far-reaching, an analysis of the information is indicated. As a comprehensive
search of PubMed, Embase and Web of Science has revealed that no analysis yet exists, nor has a systematic review been done, we propose a systematic review to analyze the existing data addressing the issue of concurrent administration of dexamethasone and sugammadex, and any possible aberrant effects that may be noted in sugammadex’s expected performance, namely, time to reversal of rocuronium. We will also consider the secondary outcome of time to extubation between subjects who have received dexamethasone concurrently with sugammadex for paralytic reversal, and those who have not received dexamethasone.

Inclusion criteria

Types of participants
The current review will consider studies that include patients who have received sugammadex in the presence of dexamethasone for reversal of aminosteroidal neuromuscular blockade. Patients who have received sugammadex for paralytic reversal without also receiving dexamethasone will serve as the comparator. Patient inclusion criteria will consist of patients from three to 71 years, and patients of an American Society of Anesthesiologists physical status III or less. Exclusion criteria will be patients with renal failure and a known diagnosis of neuromuscular disorder or are taking drugs already known to interact with sugammadex.

Types of interventions
The review will consider studies that evaluate the concurrent administration of sugammadex and dexamethasone and its effects on reversal times of rocuronium, as evidenced by a train-of-four (TOF) ratio >0.9, as compared to reversal times of rocuronium by sugammadex without the concurrent administration of dexamethasone, by the same standard of measure.

Outcomes
The current review will consider studies that include the following outcome measure: time to reversal of rocuronium after administration of sugammadex as evidenced by TOF ratio >0.9. A secondary outcome to be considered: prolonged time to extubation.

Types of studies
The review will consider both experimental and epidemiological study designs including randomized controlled trials, non-randomized controlled trials, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies for inclusion.

Search strategy
The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of Embase and MEDLINE will be undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Third, the reference list of all identified reports and articles will be searched for additional studies. Studies published in any language will be considered for inclusion in this review. Studies published after the year 2008 (the year sugammadex was made commercially available) will be considered for inclusion in this review.

The databases to be searched include: Embase, PubMed and Web of Science
The search for unpublished studies will include: MedNar, ProQuest Dissertations and Theses.
Initial keywords to be used will be: dexamethasone, sugammadex, rocuronium and reversal time.

Assessment of methodological quality
Quantitative papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix I). Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Data extraction
Quantitative data will be extracted from papers included in the review using the standardized data extraction tool from JBI-MAStARI (Appendix II). The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives. Authors of primary studies will be contacted for missing data.
Data synthesis
Quantitative papers will, where possible, be pooled in statistical meta-analysis using JBI System for the Unified Management of the Assessment and Review of Information (JBI SUMARI). All results will be subject to double data entry. Effect sizes expressed as odds ratio (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard Chi-square and also explored using subgroup analyses based on the different quantitative study designs included in this review. Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

Acknowledgements
We would like to acknowledge the time and expertise that Alysha Sapp, Dr Monica Jenschke and Dr Dru Riddle contributed to this work.

References
Appendix I: MASTARI appraisal instruments

### JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
<th>Not Applicable</th>
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<td>1. Was the assignment to treatment groups truly random?</td>
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<td>2. Were participants blinded to treatment allocation?</td>
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<td>3. Was allocation to treatment groups concealed from the allocator?</td>
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<td>4. Were the outcomes of people who withdrew described and included in the analysis?</td>
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<td>5. Were those assessing outcomes blind to the treatment allocation?</td>
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<td>6. Were the control and treatment groups comparable at entry?</td>
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<td>7. Were groups treated identically other than for the named interventions</td>
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<td>8. Were outcomes measured in the same way for all groups?</td>
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<td>9. Were outcomes measured in a reliable way?</td>
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<td>10. Was appropriate statistical analysis used?</td>
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**Overall appraisal:**
- Include [ ]
- Exclude [ ]
- Seek further info. [ ]

**Comments (including reason for exclusion):**

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## JBI Critical Appraisal Checklist for Descriptive / Case Series

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<tbody>
<tr>
<td>1. Was study based on a random or pseudo-random sample?</td>
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<td>2. Were the criteria for inclusion in the sample clearly defined?</td>
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<td>3. Were confounding factors identified and strategies to deal with them stated?</td>
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<td>4. Were outcomes assessed using objective criteria?</td>
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<td>5. If comparisons are being made, was there sufficient descriptions of the groups?</td>
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<td>6. Was follow up carried out over a sufficient time period?</td>
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<td>7. Were the outcomes of people who withdrew described and included in the analysis?</td>
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<td>8. Were outcomes measured in a reliable way?</td>
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<td>9. Was appropriate statistical analysis used?</td>
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**Overall appraisal:**
- Include ☐
- Exclude ☐
- Seek further info ☐

**Comments (including reason for exclusion)**

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JBI Critical Appraisal Checklist for Comparable Cohort/Case Control

Reviewer ___________________________ Date ___________________________

Author ___________________________ Year ______ Record Number ______

1. Is sample representative of patients in the population as a whole? [ ] Yes [ ] No [ ] Unclear [ ] Not Applicable

2. Are the patients at a similar point in the course of their condition/illness? [ ] Yes [ ] No [ ] Unclear [ ] Not Applicable

3. Has bias been minimised in relation to selection of cases and controls? [ ] Yes [ ] No [ ] Unclear [ ] Not Applicable

4. Are confounding factors identified and strategies to deal with them stated? [ ] Yes [ ] No [ ] Unclear [ ] Not Applicable

5. Are outcomes assessed using objective criteria? [ ] Yes [ ] No [ ] Unclear [ ] Not Applicable

6. Was follow up carried out over a sufficient time period? [ ] Yes [ ] No [ ] Unclear [ ] Not Applicable

7. Were the outcomes of people who withdrew described and included in the analysis? [ ] Yes [ ] No [ ] Unclear [ ] Not Applicable

8. Were outcomes measured in a reliable way? [ ] Yes [ ] No [ ] Unclear [ ] Not Applicable

9. Was appropriate statistical analysis used? [ ] Yes [ ] No [ ] Unclear [ ] Not Applicable

Overall appraisal: Include [ ] Exclude [ ] Seek further info. [ ]

Comments (Including reason for exclusion)

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Appendix II: MASTARI data extraction instrument

**JBI Data Extraction Form for Experimental / Observational Studies**

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<td>Author</td>
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<td>Journal</td>
<td>Record Number</td>
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**Study Method**

- RCT
- Quasi-RCT
- Longitudinal
- Retrospective
- Observational
- Other

**Participants**

- Setting
- Population

**Sample size**

- Group A
- Group B

**Interventions**

- Intervention A
- Intervention B

**Authors Conclusions:**

**Reviewers Conclusions:**
### Study results

#### Dichotomous data

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#### Continuous data

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