

A Meta-analysis of the Hospital Stay and Hypoxic Effect of Neuromuscular Blocking Agent Antagonists, Sugammadex and Neostigmine

Nöromusküler Bloke Edici Ajan Antagonistleri olan Sugammadex ve Neostigmin'in Hastanede Kalış ve Hipoksik Etkisi Üzerine bir Meta-analizi

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ABSTRACT

Background: Considering that the postoperative residual curarization rate may vary between 5% and 85% depending on the anesthetic applications, according to current scientific publications, many patients recovering from anesthesia are at serious risk. Our aim in this meta-analysis study is to reveal the comparative effects of sugammadex and neostigmine drugs used for decurarization on hospitalization and hypoxia.

Materials and Methods: The terms “sugammadex”, “neostigmine”, “anesthesia”, “neuromuscular blockade”, “neuromuscular blocking agents” “sugammadex and neostigmine” were searched in the electronic databases of PubMed, DynaMed, Google Scholar. “Clinical research” as search filters, the terms “controlled clinical trial” and “randomized controlled trial” were used, and the data were analyzed by a fixed effect ($I^2 < 25\%$) or random effects ($I^2 > 25\%$) model according to the presence of heterogeneity.

Results: After the database search, a total of 1902 articles were found. After excluding repetitive articles, 1033 articles were reviewed. Whether they were related to the subject or not was determined by reviewing the title and summary sections. The full text of 50 articles that might be relevant is reviewed. As a result, 13 articles were included in the meta-analysis. As a result of the analysis, it was observed that the studies were heterogeneous ($I^2 = 97.9\%$; $I^2 = 90.5\%$). Analysis according to the random-effects model. It was found that the duration of hospital stay and SpO_2 levels after surgery were not different in patients given sugammadex and neostigmine [standardised mean difference (SMD) = -0.0042; 95% confidence interval (CI) (-0.0459-0.0375), $p = 0.8438$; SMD = -0.0017; 95% CI (-0.01076-0.1111); $p = 0.9753$].

Conclusion: The results of this meta-analysis show that sugammadex is no more effective in recovery from neuromuscular blockade than neostigmine in terms of hospital stay and SpO_2 .

Keywords: Sugammadex, neostigmine, neuromuscular blockade, decurarization, meta-analysis

ÖZ

Amaç: Günümüzdeki bilimsel yayınlara göre post operatif rezidüel kürarizasyon oranı anestezi uygulamalara bağlı olarak %5 ile %85 arasında değişebileceği düşünülecek olursa, anesteziyen uyanmakta olan birçok hasta ciddi risk altındadır. Bu meta-analiz çalışmasında amacımız dekürarizasyon için kullanılan sugammadex ve neostigmin ilaçlarının karşılaştırmalı olarak hastane yatışı ve hipoksiye etkisini ortaya koymaktır.

Gereç ve Yöntemler: “Sugammadex”, “neostigmin”, “anestezi”, “nöromusküler blokaj”, “nöromusküler bloke edici ajanlar” “sugammadex ve neostigmin” terimleri PubMed, DynaMed, Google Akademik elektronik veri tabanlarında arandı. Arama filtreleri olarak “klinik araştırma”, “kontrollü klinik araştırma” ve “randomize kontrollü araştırma” ifadeleri kullanıldı. Veriler heterojenite varlığına göre sabit etki ($I^2 < 25\%$) ya da rastgele etki ($I^2 > 25\%$) modeli ile analiz edildi.

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ÖZ

Bulgular: Veritabanı araştırması sonrasında toplam 1902 makaleye ulaşıldı. Tekrarlayan makaleler dışlandıktan sonra 1033 makale incelendi. Konu ile ilişkili olup olmadıkları başlık ve özet bölümlerinin gözden geçirilmesi ile tespit edildi. İlişkili olabilecek 50 makalenin tam metinleri incelendi. Sonuçta 13 makale meta-analize dahil edildi. Yapılan analiz sonucunda araştırmaların heterojen olduğu gözlemlendi ($I^2=\%97,9$; $I^2=\%90,5$). Rastgele etki modeline göre yapılan analiz sugammadex ve neostigmin verilen hastalarda, cerrahiden sonra hastane yatış gün süresi ve SPO_2 düzeylerinin farklı olmadığını saptandı [SMD=-0,0042; %95 güven aralığı (GA) (-0,0459-0,0375), $p=0,8438$; SMD=-0,0017; %95 GA (-0,01076-0,1111); $p=0,9753$].

Sonuç: Bu meta-analizin sonuçları, sugammadexin nöromusküler blokajı tersine çevirmede neostigminde hastanın hastanede yatış süresi ve SPO_2 açısından daha etkili olmadığını göstermektedir.

Anahtar Kelimeler: Sugammadex, neostigmin, nöromusküler blokaj, deküarizasyon, meta-analiz

Introduction

The inability to completely remove the neuromuscular blockade (NMB) formed during anesthesia, known as postoperative residual curarization (PORC), is important for patient morbidity and mortality. Analgesia, on the other hand, is one of the basic procedures applied in anesthesia management to provide amnesia, to get rid of the fear caused by the surgical procedure, and to provide adequate muscle relaxation. Muscle relaxants used in anesthesia applications act on the neuromuscular junction, facilitating intubation and optimizing surgical conditions (1,2,3). Various agents are also used to terminate anesthesia and reverse the effects of muscle relaxants after the surgical procedure. Sugammadex has been added to these recently. There are many recommendations in the literature regarding the use of these agents that reverse the anesthesia process. It has been published that the effects of neostigmine should be examined especially in terms of timing and spontaneous recovery, time to reach the peak, and the American Society of Anesthesiologists physical status classification system (1,4,5).

Scales such as the Glasgow Coma scale and/or Aldrete score are commonly used to evaluate recovery from anesthesia (6,7). Neuromuscular monitoring during and after the operation should be essential for optimal management of neuromuscular blocking drugs. Although there are many different methods, this monitoring can be done with sustained head lift, normal pattern of respiration, sustained hand grip, normal vital capacity and oxygen saturation, eye opening, tongue protrusion and depressor test and/or quadruple train ratio using acceleromyography principle (8,9). However, the evidence confirming the reliability of clinical signs in evaluating the adequacy of reversal from NMB is insufficient and there is no consensus on this issue (7,10).

The most commonly used decurarizing agents for reversal of NMB in anesthesia applications are sugammadex and neostigmine. Although it has been reported in many studies that sugammadex can provide faster and full-term

muscle strength recovery (11,12,13), more definitive results are still needed in this regard.

For this reason, it was planned to conduct a meta-analysis including a large literature search that could reveal the difference between the decurarization effects of sugammadex and neostigmine in terms of hospital stay and SPO_2 levels.

Material and Methods

Clinical and observational studies comparing sugammadex and neostigmine for recovery from NMB caused by aminosteroid NMB agents in patients under general anesthesia were considered. Comparison of sugammadex and neostigmine used for reversal of rocuronium or vecuronium-induced NMB, English and/or Turkish article, adult patients (≥ 18 years old), completeness and compatibility of data, accessibility of full-text version of article and publication in a peer-reviewed journal were used as inclusion criteria for this quantitative meta-analysis. Observational studies, non-clinical studies, pediatric studies, animal experiments, lack of available data, and lack of a full-text version of the article were determined as exclusion criteria.

Articles published in PubMed, DynaMed, Google Scholar electronic databases from January 01, 2015 to April 30, 2022 were searched. Databases were searched using the terms “sugammadex”, “neostigmine”, “anesthesia”, “neuromuscular blocking”, “neuromuscular blocking agents” and “sugammadex and neostigmine”. The terms “clinical trial”, “controlled clinical trial” and “randomized controlled trial” were used as search filters.

Titles and abstracts of articles found in accordance with the rules set for search were independently scanned and irrelevant articles were excluded. The remaining full texts were evaluated whether they met the inclusion criteria. After the data obtained from the studies were written on the designed data collection forms, the findings were independently cross-checked by both authors. Meta-analysis of the data was performed using the PRISMA methodology.

Since the study is a meta-analysis study, it is not necessary to obtain informed consent from the patients. For this study, the necessary permission (İstanbul Provincial Health Directorate number: E-15086342-903.07.02) was obtained from the institution.

Statistical Analysis

The study was carried out using the meta-analysis technique. Heterogeneity between studies was measured using the I^2 statistic. The Cochran's Q value of 0.1 was used as the threshold to determine whether heterogeneity was present. The I^2 value of 0.05 was considered significant. Egger's regression test was used to assess the risk of publication bias. All p-values were considered 2-tailed and statistical significance 0.05. Calculations were made with R studio (version 4.1.3-2022.02.1 for Windows).

Results

After the database review, a total of 1902 articles were found. After excluding repetitive articles, 1033 articles were reviewed. Whether the articles were related to the subject or not was determined by reviewing the title and abstract sections. The full text of 50 articles that might be relevant is reviewed. As a result, 13 articles were included in this meta-analysis. The selection protocol of the study is given in Figure 1 with the PRISMA flowchart.

When 7 different articles were evaluated, which were compatible with each other, it was found that there was no difference in terms of hospital stay time in patients who were given sugammadex and neostigmine [SMD=-0.0042; 95% confidence interval (CI) (-0.0459-0.0375); $p=0.8438$]. $Q=0.0001$, $I^2=97.9$ $H=6.89$, 95% CI (5.73-8.28) (Figure 2).

Eight articles that were consistent with hospital SpO_2 were evaluated. It was found that there was no difference between the patients given sugammadex and neostigmine in terms of SpO_2 [SMD=-0.0017; 95% CI (-0.01076-0.1111); $p=0.9753$ $Q=0.0001$; $I^2=90.5$ $H=3.25$ 95% CI (2.48-4.26)] (Figure 3).

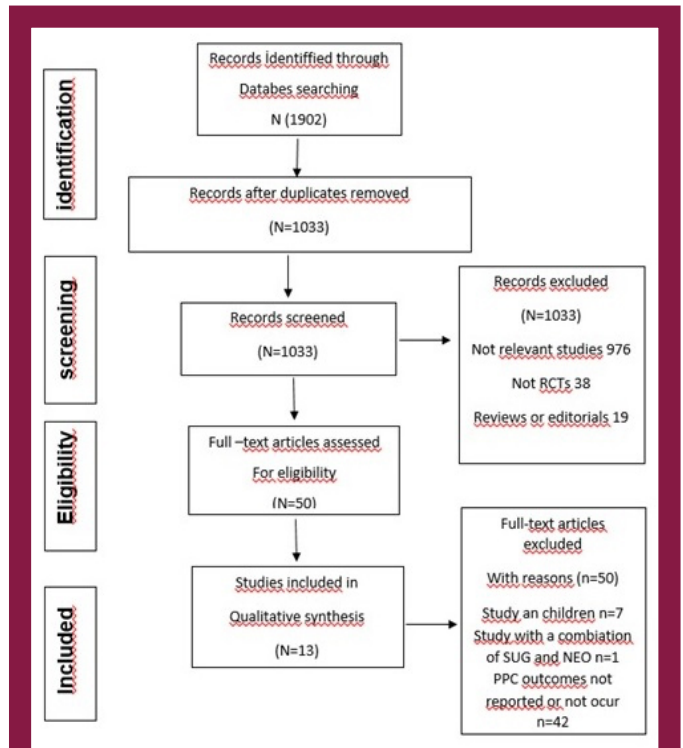


Figure 1. PRISMA flow diagram

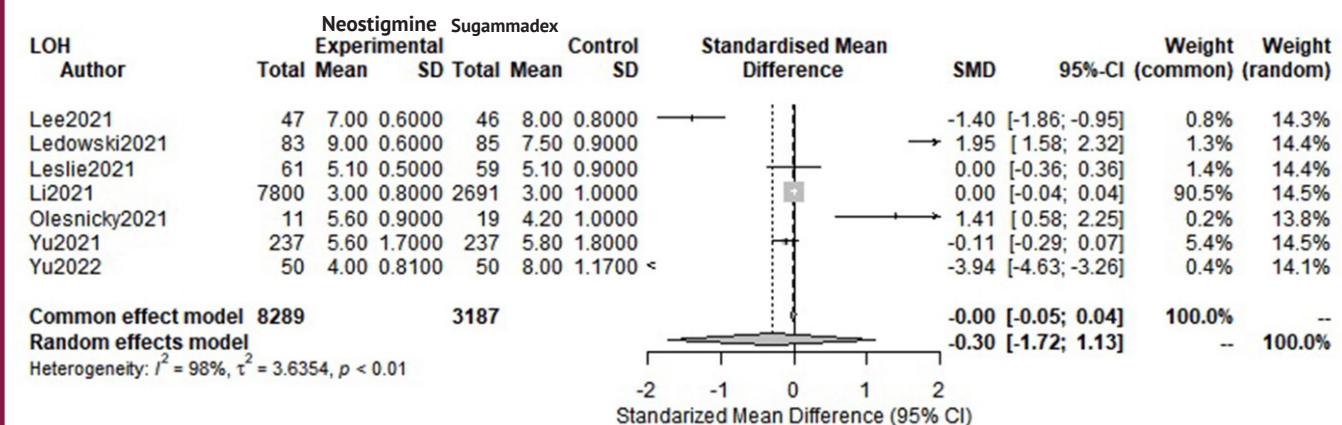


Figure 2. Forest chart related to hospital stay

CI: Confidence interval, SD: Standard deviation, SMD: Standardised mean difference

As a result of the examination for heterogeneity with Funnel plot and Egger's regression test, it was found that the risk of publication bias was low [$p(\text{LOH})=0.78$; $p(\text{SPO}_2)=0.96$] (Figure 4).

Discussion

Despite all the developments in the field of anesthesia, PORC, which still increases the risk of mortality due to the presence of blocked nicotinic receptors in post-operative patients, has not been completely prevented. It has even been reported that 60-70% of nicotinic receptors can remain curarized without causing any clinical symptoms.

The high persistence of residual NMB after surgery may cause respiratory distress and hypoxia due to any residual weakness in the jaw and tongue. It is also associated with adverse patient outcomes such as the inability to clear secretions due to lack of coordinated muscle activity of the pharynx/esophagus and the risk of aspiration. For these reasons, it is very important to detect the persistence of residual NMB. Intraoperative management of NMB is possible using peripheral nerve stimulators and subjective tactile or visual evaluation. Quantitative monitoring is also required to identify patients who have adequate reversal, who recover spontaneously, and who do not require decurarizing agents. Therefore, delayed awakening from

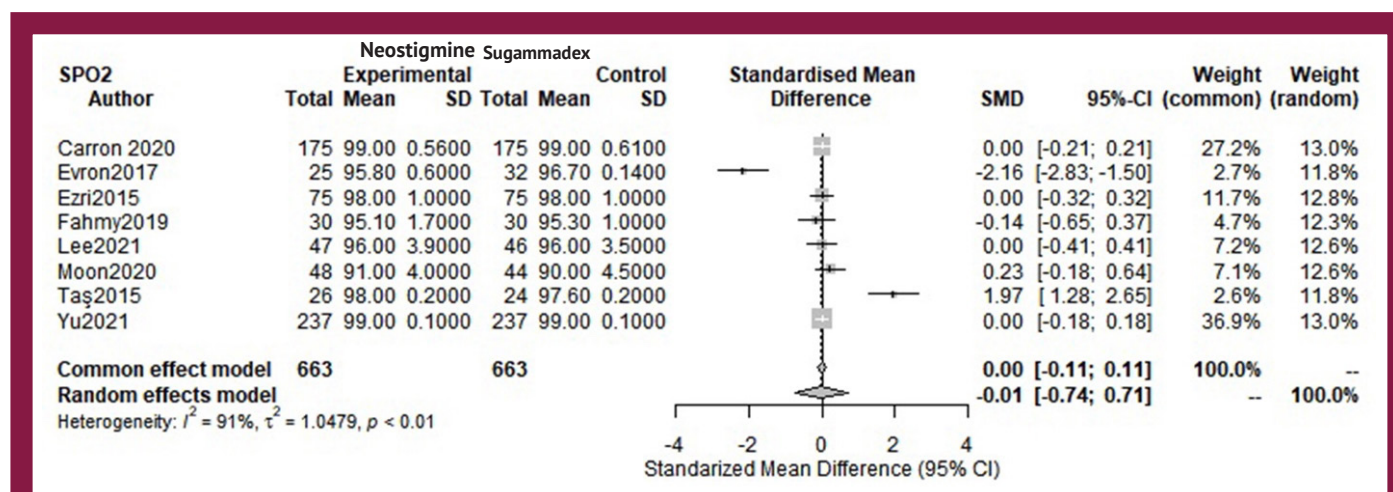


Figure 3. Forest chart for SPO_2

CI: Confidence interval, SD: Standard deviation, SMD: Standardised mean difference

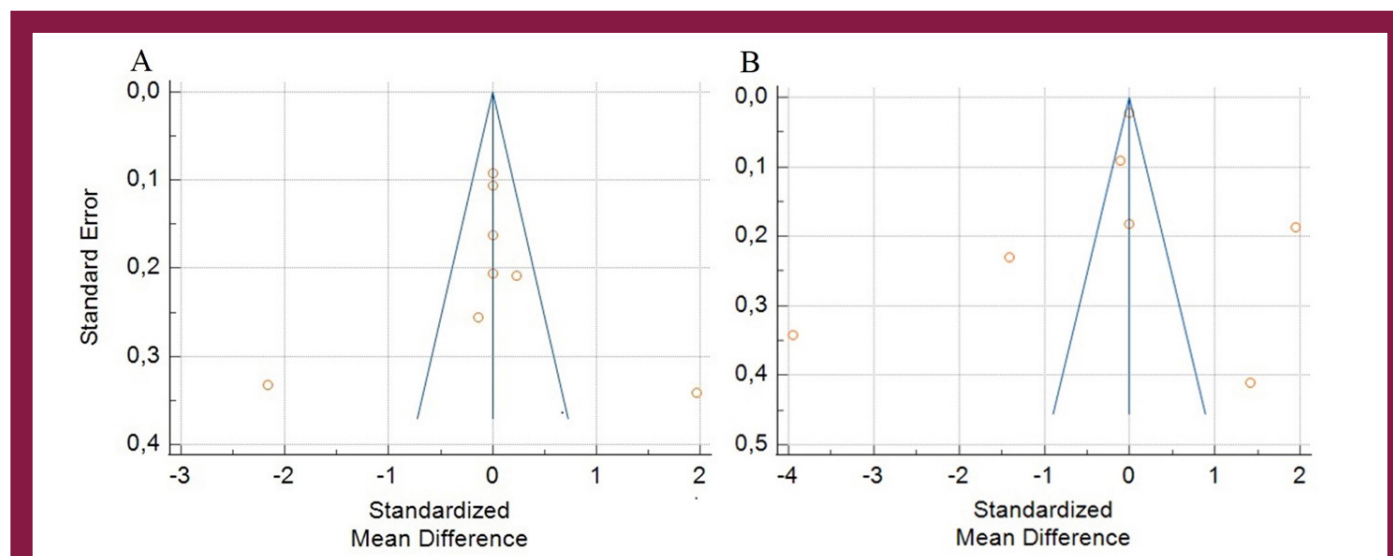


Figure 4. Funnel plots. The distribution of A) SPO_2 and B) LOH values associated with publication bias and heterogeneity is seen

anesthesia is still one of the biggest difficulties faced by the anesthesiologist (14,15,16,17). The most common cause of delayed awakening after anesthesia is anesthetic agents and drugs used in the perioperative period (18,19,20). However, some metabolic and chronic diseases (such as hypoglycemia/hyperglycemia, electrolyte imbalance, hypoxia, hypercapnia, central anticholinergic syndrome, chronic hypertension, liver disease, renal diseases, hypoalbuminemia, uremia and severe hypothyroidism), gender, obesity, cachexia, hypothermia, age and structural disorders of the central nervous system and psychological diseases may all cause delayed awakening after general anesthesia (17,18,21,22,23,24,25).

According to current scientific publications, there is limited data on the rate of PORC. It has been reported that this rate can vary between 5% and 85% depending on various anesthetic applications, and the negative effects of PORC can be seen in approximately half of the patients even with neostigmine (26). On the other hand, it has been suggested that sugammadex is more suitable for preventing the formation of residual curarization and postoperative respiratory complications. It has also been suggested that sugammadex is more suitable than neostigmine for restoring diaphragmatic function. However, there are also studies reporting that there is no difference in general between the two decurarization agents (27,28,29,30). According to the results of this meta-analysis, the fact that there was no significant difference between sugammadex and neostigmine in terms of hospital stay time, which is a measure of patient mobilization, is a results against the above information about sugammadex. However, it should be kept in mind that the study carried out is only about the length of hospital stay and SPO_2 levels, and therefore more and more comprehensive studies are needed for general judgment.

Inadequate neuromuscular monitoring and insufficient decurarization can be listed among the reasons that increase the risk of PORC. Sugammadex, a new molecule in decurarization, is a cyclodextrin group drug that selectively binds to aminosteroid rocuronium and vecuronium (NMB agents), thus providing rapid excretion and decurarization. Sugammadex has created a new option for reversing NMB and preventing residual paralysis. It shows its effect by encapsulating the free molecule very tightly at a ratio of 1:1 and forming complexes to form a stable complex. It also acts on neuromuscular blocking agents with similar aminosteroid structures such as vecuronium. Compared with neostigmine used to reverse NMB, sugammadex has been reported to be faster in reversing rocuronium-induced blockade, and patients can potentially be discharged faster after general anesthesia (31,32,33,34,35,36).

Neostigmine, a cholinesterase inhibitor, is traditionally used for decurarization. Neostigmine indirectly inactivates the enzyme by covalently binding to the acetyl cholinesterase enzyme located at the neuromuscular junction. Thus, acetylcholine cannot be broken down and competes with NMB agents for postsynaptic receptors. Neostigmine has a ceiling effect and may not generate adequate rebound at a deep NMB. In contrast to sugammadex, side effects such as bradycardia, autonomic disorders, nausea and vomiting have been reported. In addition, cholinesterase inhibitor agents used in decurarization may have serious side effects, especially since they stimulate the muscarinic system as well as nicotinic receptors. All these negative effects also increase the postoperative pulmonary complications that affect the respiratory system after anesthesia. It was found that the SPO_2 values measured during extubation of sugammadex, which is known to reverse rocuronium (or vecuronium)-induced NMB more rapidly, were not different from neostigmine in recovery from medium and deep NMB (37,38,39,40). In this meta-analysis study, which we conducted in the light of the above information, the hypoxic effects of sugammadex and neostigmine, which can be defined by SPO_2 levels, which can vary due to their autonomic effects, were compared. No difference was found in this meta-analysis in terms of hypoxic effects of both agents. Although they have different mechanisms of action on NMB, these findings show that similar SPO_2 values will be achieved with the use of sugammadex and neostigmine. Contrary to all these data, in a cohort from the USA (41), it was reported that the use of sugammadex was associated with a lower incidence of major pulmonary complications, although the exact mechanism is not known. All these studies show that there is a need for more comprehensive studies comparing the use of sugammadex and neostigmine in decurarization.

Conclusion

The results of this meta-analysis show that sugammadex is no more effective in recovery from NMB than neostigmine in terms of hospital stay and SPO_2 .

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Ethics

Ethics Committee Approval: The study is a meta-analysis study, it is not necessary.

Informed Consent: Since the study is a meta-analysis study, it is not necessary to obtain informed consent from the patients. For this study, the necessary permission (Istanbul Provincial Health Directorate number: E-15086342-903.07.02) was obtained from the institution.

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Authorship Contributions

Surgical and Medical Practices: H.Y., Concept: H.Y., F.Ö., Design: H.Y., F.Ö., Data Collection or Processing: H.Y., F.Ö., Analysis or Interpretation: F.Ö., Literature Search: H.Y., Writing: H.Y., F.Ö.

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