# The Invisible Force:
# Optimizing Novel Approaches in Anesthesiology and Infectious Diseases

by

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DISSERTATION

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Thank you to my mom, dad, and my two sisters who have endured my presence for almost three decades and still choose to not only associate with me, but to also wake up at any hour of the night if I needed to call. I can only hope to keep making you proud.

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Thank you for reminding me that the sun still shines above the clouds.

# ABSTRACT

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This work encompasses a theme revolving the OR: specifically, preoperatively, perioperatively, and postoperatively. Chapter 1 describes a novel method whereby biofilm is destroyed using Alternating Magnetic Fields (AMF). Using S. aureus grown on steel washers to simulate prosthetic joints, we were able to intermittently deliver 3s pulses for 15, 30, or 60 minutes to reduce bacterial load. Combined treatment with AMF and ceftriaxone (or linezolid) showed a 5-log decrease in bacterial load after 24 hours, whereas singular treatment with AMF or abx alone showed total regrowth or moderate decrease in bacterial load respectively.

Chapter 2 describes a meta-analysis conducted to assess the safety and efficiency of sugammadex versus neostigmine as neuromuscular blockade (NMB) reversal agents. Neostigmine has been implemented in ORs for many years, but has disadvantages to using neostigmine including autonomic dysfunction like bradycardia and post-operative nausea & vomiting (PONV), and the necessity to administer the drug at the correct time due to its lag time in effect. Sugammadex appears to circumnavigate these problems, but the literature is still not definitive. We performed a meta-analysis that showed sugammadex as having a milder side effect profile compared to neostigmine with reduction in pneumonia (RR = 0.593, 95% CI (0.361, 0.671) and bradycardia (RR = 0. 535, 95% CI (0.424, 0.675), higher PONV risk (RR = 1.21, 95% CI (1.05, 1.39)), and with faster turnaround times.

Chapter 3 describes a survey sent out to ambulatory surgical centers (ASC) on management of patients with obstructive sleep apnea (OSA). The need for a CPAP device in the immediate postoperative period at ambulatory surgical centers remains controversial because these ambulatory patients are healthier and have fewer complications. Only 59.7% of ASCs required their patients to bring their CPAP devices on the day of surgery, and 25.37% reported using a CPAP machine postoperatively within the past 2 years, with the highest CPAP usage at one facility being 20 times in that 2-year period. Studies further in-depth are necessary to assess postoperative complications that require a CPAP device to determine the urgency of ASCs implementing SAMBA's recommendations.

## Chapter Summaries

### Chapter 1: Biofilms and PJI

BACKGROUND: Prosthetic Joint Infections (PJI) are a common complication of implant surgery. Due to biofilm formation, treatment is costly, includes weeks of antibiotic therapy, and even total replacement of the prosthesis. However, a non-invasive thermal method of biofilm destruction has recently been developed: using high-frequency alternating magnetic fields (AMF) to destroy biofilm via induction. OBJECTIVE: Our aim is to investigate the efficacy of intermittent AMF and antibiotics in eradicating biofilm.

METHODS: The experiment used Staphylococcus aureus, a common organism implicated in PJI. Stainless steel rings were used to mimic prosthetic joints. Biofilms of Methicillin Sensitive Staphylococcus aureus (UAMS1-lux) were grown in a shaking incubator for 24 hours, 110rpm at 37°C, using stainless steel rings in Tryptic Soy Broth media. The rings were then resuspended in fresh media and incubated for another 24 hours at 110rpm, 37°C.

RESULTS The results showed a synergistic effect between AMF and antibiotics. At 12 hours, the Abx only and AMF only treatments showed regrowth; however, the combination therapy showed a 2.1 log decrease in biofilm CFU. Similarly, at 24 hours, solo AMF treatment showed total regrowth and Abx only treatment showed modest bactericidal effects (2.1 log reduction). Combination therapy at 24hr showed a 5.35 log reduction and reached the limit of detection at 0.78. CONCLUSION A synergistic effect of AMF and antibiotic treatment was observed for eradication of S. aureus biofilm. This study provides a strong basis for future in vitro and in vivo work using AMF-antibiotic combination therapy. As a non-invasive treatment, AMF could have a significant impact in improving patient quality of life as well as improving healthcare costs associated with PJI.

### Chapter 2: Reversal of Neuromuscular Blockades

BACKGROUND**:** For many years, neostigmine, an acetylcholinesterase inhibitor, was the drug of choice for reversing neuromuscular blockades in the operating room. However, there are disadvantages to using neostigmine including autonomic dysfunction like bradycardia and post-operative nausea & vomiting (PONV), and the

necessity to administer the drug at the correct time due to its lag time in effect. Recent studies have been performed on sugammadex, a new reversal agent, which does not have a "lag time effect." Although it is considered safer, some studies cite harmful effects. Given its rapid rise in usage, a more comprehensive characterization of the clinical and practical aspects of sugammadex compared to the standard of neostigmine is needed.

METHODS**:** In accordance with the PRISMA guidelines, a systematic review of PubMed and Scopus databases was performed in search of publications that compared the efficacy and safety of sugammadex versus neostigmine. All publications that included either endpoints were included irrespective of date of publication, country of origin, language, age range of patients, type of surgical procedure, or ASA grade. Data were analyzed using Microsoft Excel.

RESULTS**:** 57 articles totaling n = 66157 patients met inclusion criteria for this meta-analysis. Compared to neostigmine, sugammadex showed a significant reduction in extubation time (mean difference [MD] = -2.77 min, 95% CI (-3.95, -1.59)), Recovery to TOF >0.9 time (MD =-11.27 min, 95% CI (-12.7, -9.89)), OR discharge time (MD = -3.74 min, 95% CI (-4.77, -2.71)), and PACU discharge time (MD = -8.51 min, 95% CI (-14.9, -2.07)). Sugammadex shows a significant reduction in pneumonia (RR = 0.593, 95% CI (0.361, 0.671)) and bradycardia (RR = 0. 535, 95% CI (0.424, 0.675)), and a significant increase in PONV (RR = 1.21, 95% CI (1.05, 1.39)). No significant difference was found for atelectasis (RR = 0.964, 95% CI (0.853, 1.09)).

CONCLUSION: This study supports that administration of sugammadex as a reversal agent for neuromuscular blockade facilitates faster OR turnover time, extubation time, and PACU discharge time. Sugammadex is associated with lower risk of bradycardia and pneumonia, but higher risk of PONV. In an ongoing study, we are investigating the shorter times of sugammadex in the context of a cost-benefit analysis. These results serve as a strong basis for future work on neuromuscular blockage reversal agents, with large implications in improving the quality of patient care, bolstering the efficiency of the surgery and anesthesiology services, as well as improving healthcare costs of surgery and anesthesia.

## **Chapter 3: Obstructive Sleep Apnea**

BACKGROUND: Obstructive sleep apnea is a common sleep-related breathing disorder that is associated with

significant perioperative complications. In 2012 and 2017, Society of Ambulatory Anesthesia and Society of Anesthesia and Sleep Medicine published consensus statements for the selection of patients with OSA scheduled for ambulatory surgery. Despite these recommendations, the need for a CPAP device in the immediate postoperative period at ambulatory surgical centers remains controversial because these ambulatory patients are healthier and have fewer complications.

OBJECTIVE: This study aims to investigate the compliance rate with this recommendation among busy ASCs.

METHODS: We created a survey to investigate if ASCs require patients to bring their CPAP devices to the facility. The survey measured compliance rates of ASCs to SAMBA's recommended guidelines of having CPAP machines available.

RESULTS: The survey had a response rate of 60.9% encompassing 408,147 cases among 1946 providers. Of the facilities that responded, only 59.7% of them required their patients to bring their CPAP devices on the day of surgery. Out of the 67 facilities that responded, only 25.37% reported using a CPAP machine postoperatively within the past 2 years, with the highest CPAP usage at one facility being 20 times in that 2-year period.

CONCLUSION: This would mean that 40.3% of ASCs that did respond do not have access to a CPAP device on-site and may possibly lack the proper equipment needed to handle these complications. The frequency and fatality rate associated with postoperative respiratory complications requiring a CPAP device are still inconclusive, making the need for CPAP devices during perioperative management controversial. Studies further in-depth are therefore necessary to assess postoperative complications that require the use of a CPAP device to determine the urgency of ASCs implementing SAMBA's recommendations.

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# Chapter 1: Before the Operating Room

## Introduction: Biofilms and Prosthetic Joint Infections

Annually, knee replacement surgeries are one of the most common procedures worldwide. Over one million procedures are performed in the United States alone each year, and it is projected to increase by more than 600% to ~3.5 million by the year 2030 due to a rapidly growing aging population and overall health trends[1]. Metal implants such as prosthetic joints are widely employed for these procedures, and about 2% of these implants become infected every year[1]. Currently, this complication poses a challenge for both patient and provider. Treatment of prosthetic joint infections (PJI) mainly relies on multiple revision surgeries. Initial surgery is performed to remove the infected implant and a temporary spacer is placed[2]. Antibiotics are then administered for several weeks to clear the residual infection. Once the patient is confirmed to be free of infection, a final surgery is performed to implant a new prosthesis[3].

Surgical treatment of PJIs is both invasive to the patient and expensive to treat. The projected cost of treating PJI is $1.6 billion in 2020 in the United States alone, posing a significant economic burden to the health care system[4]. Furthermore, the failure of treatment may occur in over 20% of patients; surprisingly, literature and guidance on treatment in this setting are scarce[5-7].

A significant obstacle to treatment success of PJIs and other metal implant infections (MII) is due to the formation of biofilms on the implant surface. A biofilm is a thin aggregate (tens to hundreds of micrometers) of bacteria and extracellular polymeric substances (EPS)[8]. EPS forms a robust matrix that physically blocks many active compounds in medicines at a molecular level as well as at a larger scale by providing a barrier to the surrounding environment, rendering these organisms up to 1000-fold more resistant to antibiotics while providing protection from the immune system[9]. This physical defense, combined with many other mechanisms of bacterial drug resistance such as efflux pumps or

altered proteins, pose a significant challenge to biofilm destruction and is a major contributor to multidrug resistance[10].

As nonsurgical methods would be a major advance to eradicating biofilm, many methods have been proposed to counter these resistance mechanisms. Physical approaches such as electrical currents[11-13], ultrasound[14], heat[15, 16], and shock waves[17] are either hard to apply, impractical, or have limitations for use on metal implants. A potentially safer and more effective method of biofilm removal off metal implants is by employing alternating magnetic fields (AMF). AMF can be delivered from outside the body and does not suffer from penetration depth limitations or complex wave distortions through tissue boundaries. When metal implants are exposed to AMF, electrical currents are induced on the surface, resulting in the generation of heat[18].

Previous studies have shown the feasibility and effectiveness of biofilm elimination by AMF[19]. After only a few minutes of AMF treatment, there was significant reduction of biofilm on stainless steel washers. However, this method requires sustained temperatures of 50 to 80°C for several minutes to be effective and would be impractical in a clinical setting. Furthermore, incomplete eradication of biofilm would lead to complete regrowth shortly thereafter. A strategy to combat this obstacle would be to consider combination therapy of both AMF and antibiotic; AMF and ciprofloxacin in combination were observed to be more effective than AMF or ciprofloxacin alone in reducing biofilm and prevented its recurrence for up to 24 hours post-treatment[20, 21]. Additionally, intermittent AMF (iAMF) could address the safety concerns on sustained elevated temperatures. Short duration exposures could be delivered repeatedly with sufficient cool-down time in between exposures, allowing for thermal doses that are therapeutic on the implant surface without a harmful rise in tissue temperature[22]. Here, we investigate if similar synergistic effects are still achieved by iAMF and antibiotic treatment of *S. aureus* biofilms on stainless steel washers.

## Experimental Procedures/Methods

Biofilm of S. aureus (UAMS1, provided by M. Smeltzer) was grown on stainless steel rings (316 L, 3/4″ OD, 0.035″ wall thickness, 0.2″ height, cut from McMaster Carr, P/N 89785K857, USA). An isolated colony was inoculated into 3ml of Tryptic Soy Broth (TSB, Becton-Dickinson by Thermo-Fisher Scientific) and incubated at 37 °C for 18 h at 220 RPM. A working solution was made by adding culture to sterile phosphate-buffered saline (PBS). The bacterial concentration was adjusted with TSB using a UV spectrophotometer (Genesys 20, Thermal Scientific) at 600 nm until the optical density (OD) read between 0.07 and 0.08, indicating a concentration of ~ $10^8$ CFU $mL^{-1}$. The working solution was then diluted to obtain a bacterial concentration of $5 \times 10^5$ CFU $mL^{-1}$. Biofilm was prepared on each metal ring by placing the ring in 5 mL of the bacterial solution in a 50 mL conical tube. The submerged ring was then incubated at 37 °C for 48 h at 110 RPM in a shaking incubator (Innova42, New Brunswick Scientific). Media was replenished midway at 24 h by exchanging the solution with 5 mL of fresh PBS.

We constructed a system whereby AMF exposures was delivered to multiple 50ml conical tubes held in solenoid coils, each containing stainless steel rings (Figure 1). A plastic holder was included in each tube in order to keep the rings in place during treatment. The coils were arranged as a parallel resonant circuit using a capacitor selected to tune the resonant frequency to approximately 500 kHz. To measure temperature of the ring and the media, fiber optic temperature sensors were used to ensure accurate measurements as they are not affected by electromagnetic interference. All other settings followed those of Wang *et al.*[18] and can be found in Appendix A.

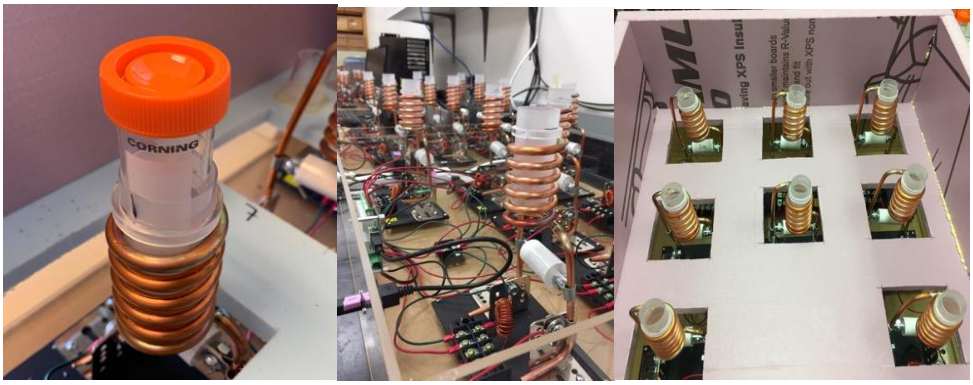


**Figure 1.** The coil system in the lab for the AMF treatment of biofilms. A stainless-steel washer with bacterial biofilm is placed in media in a Falcon tube (left). The tube is placed in a coil and treated with iAMF.

Treatment was defined as a series of AMF doses each separated by a fixed time. Each iAMF dose is composed of multiple AMF exposures. During each exposure, AMF is on for a few seconds and the rings are heated. The exposures are separated by fixed time intervals to allow rings to cool to the initial temperature between exposures.

After each intermittent dose, the rings were rinsed in 10 mL fresh antibiotic-containing media to remove planktonic bacteria. Then the rings were transferred again to 10 mL of fresh antibiotic-containing media and incubated at 37 °C. Untreated rings, Antibiotics only, AMF only, and a combination of AMF + Abx were tested. Biofilms in the latter 2 categories underwent 3s pulses of AMF exposure every 5 minutes for 15, 30, or 60 minutes at a target temperature of 65°C every 12 hours for 24 hours. Ceftriaxone (2.0µg/ml) was used for the Abx conditions. Before and after each iAMF dose, and at the treatment endpoint, the rings were harvested and rinsed in 5 mL PBS and then transferred to 4 mL PBS.

To determine colony-forming units (CFU), the rings were sonicated in an ultrasonic water bath for 5 min and bacterial density on the ring surface was quantified by plating on blood agar plates (TSA w/sheep blood, Thermo Fisher Scientific) using a standard serial dilution drip method. Three biological replicates were obtained for each experimental condition, and three technical replicates were utilized per experiment.

## Results

For the experiment with Ceftriaxone, at 12 hours, the Abx only and AMF only treatments showed regrowth; however, the combination therapy showed a 2.4 log decrease in biofilm CFU (Figure 2). Similarly, at 24 hours, solo AMF treatment showed total regrowth and Abx only treatment showed modest bactericidal effects (2.1 log reduction). Combination therapy at 24hr showed a 5.35 log reduction and reached the limit of detection at 0.78.

For Linezolid, the abx only condition showed little to no bactericidal effect at 1$^{st}$ dose, and showed no significant changes from baseline at 24 hours. The AMF condition shows more than a 3-log decrease on first dose but demonstrates complete regrowth at 24 hours. The combination therapy shows a 2-log decrease after the first dose and continued to decrease for a total of a 5-log decrease at 24 hours.

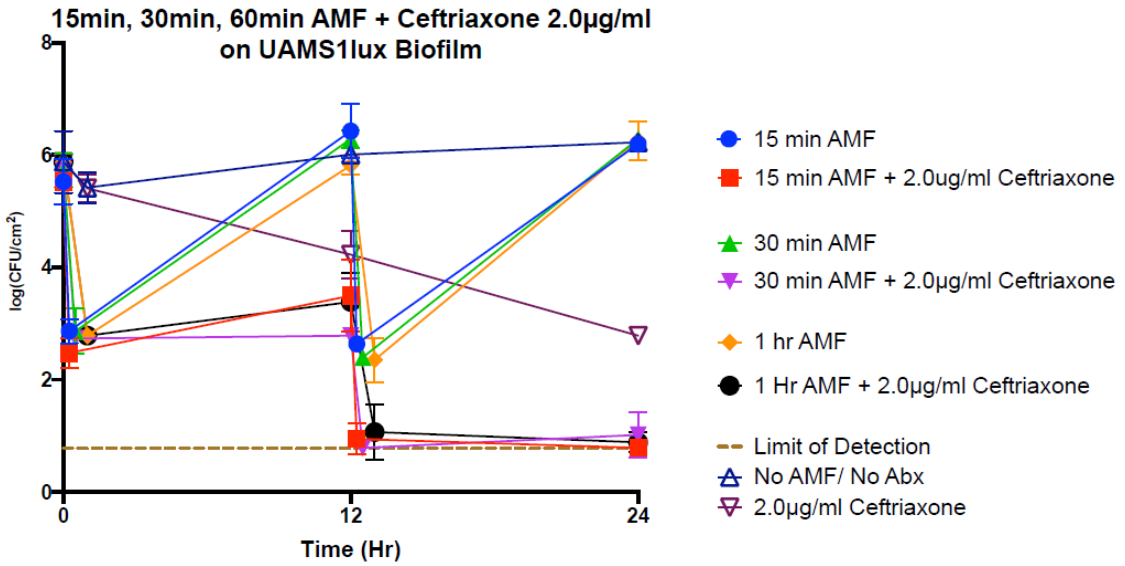


**Figure 2. Combination treatment with AMF and ceftriaxone shows synergy in biofilm reduction.** Experiments were assayed independently three times with two replicates for each condition. Error bars represent standard deviation from the mean.

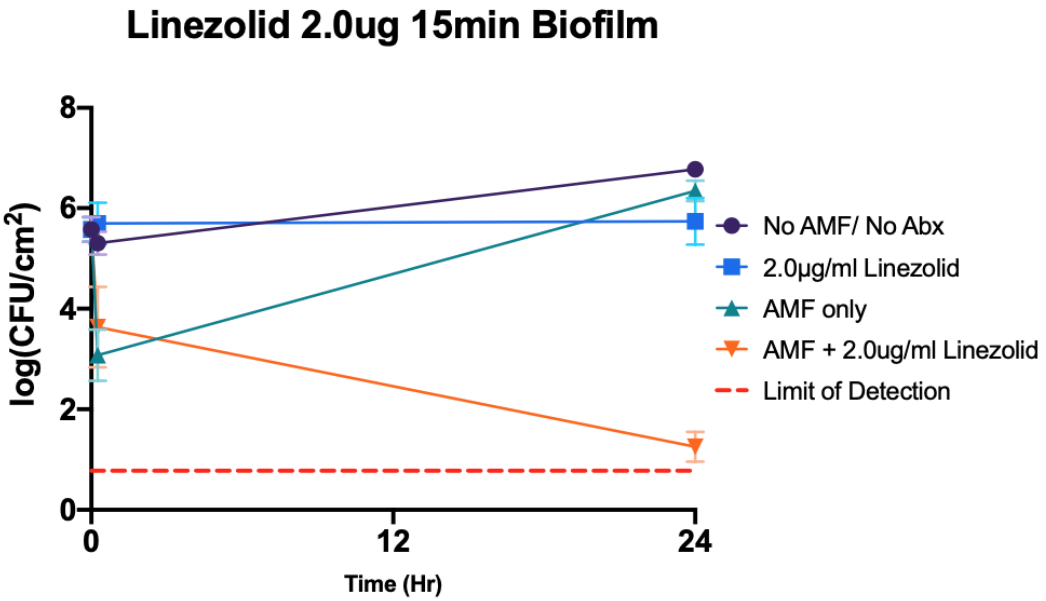


**Figure 3. Combination treatment with AMF and linezolid shows synergy in biofilm reduction.** Experiments were assayed independently three times with two replicates for each condition. Error bars represent standard deviation from the mean.

## Conclusions and Future Considerations

Heat has been known for many years as a means to kill bacteria, however, there are major hurdles in implementing these antibacterial effects in the human body. There are many studies that demonstrate the strong therapeutic effect of heat generated via AMF and antibiotics on the eradication of biofilm [15, 20]. Pijls et al. reported that there was an enhanced effect with AMF and antibiotics in *S. aureus* biofilms on titanium alloy than with either treatment alone. One concern of clinical adoption of AMF stems from its narrow therapeutic index—specifically, the ability to reduce ability to reduce biofilm through thermal effects while minimizing neighboring tissue damage. Here, we developed a method, intermittent AMF, that could deliver AMF to infected metal implants that could aid in moving towards these goals of maintaining efficacy while limiting any toxicity. The premise of iAMF is that brief exposures to the surface of an implant with sufficient cool-down time in between exposures will result in a therapeutic dose capable of eradicating biofilm while protecting surrounding tissues from damage.

We demonstrate that even iAMF exposures of a few seconds can reduce biofilm burden by 1–2 log in vitro. However, in the absence of more frequent dosing, there is regrowth back to baseline within 12 h. While more frequent dosing with iAMF could be used, an alternative approach would be to use iAMF to enhance the activity of antibiotics. In combination, iAMF and antibiotics resulted in a dramatic decrease in biofilm burden over either treatment alone.

There are certain limitations to this study. As this study was only performed in vitro, it is not clear how iAMF and antibiotics will translate in vivo. These studies are currently ongoing. Finally, it remains unclear whether the non-heat-related component of iAMF, specifically current deposition itself, has any role in disrupting biofilm.

There remain several unknowns regarding the ultimate deployment of iAMF in the clinical

setting. This includes the optimal number of doses of iAMF that would lead to a durable treatment response as well as the optimal target temperature that would maintain efficacy while minimizing any potential safety concerns. Future and ongoing studies include exploring iAMF for safety and efficacy in a large animal model of implant infection. The translation to real-life medical implants could be challenging: first, the positioning of the implant may vary for different patients, even between treatments for the same patient, which can lead to inconsistent treatments. Second, because of the complexity of the implant, it can be difficult to achieve uniform heating for predictable biofilm elimination, which requires a more sophisticated coil design customized for a particular implant. In addition, other possible mechanisms of this interaction remain to be explored. This includes determining whether heat activates or results in stress response in pathogens in a way that makes them more responsive to specific antibiotics. Finally, current studies are focused on determining the response of iAMF and specific antibiotics in various strains of the same genus and species in order to determine the range of CFU reduction that will likely be achieved under various parameters. The hope is in the not-too-distant future, a non-invasive approach such as iAMF could be used with antibiotics to treat PJI without removal of the infected implant.

# Chapter 2: Inside the Operating Room

## Introduction to Neuromuscular Blockades and Its Reversal Agents

Neuromuscular blockades (NMB) are widely used in anesthesiology to facilitate the intubation process, optimize surgical conditions, and assist with mechanical ventilation when the patient has poor lung compliance[23]. Succinylcholine has been the largely undisputed NMB agent of choice for many years until recently. First discovered in 1906 by Hunt & Taveau in animals and then later with its clinical introduction in 1951, succinylcholine has been used by many anesthesiologists throughout a long period of time[24]. This depolarizing muscle relaxant binds directly to the postsynaptic ACh receptors of the motor endplate, causing continuous stimulation of these receptors and effective paralysis[25]. It is not without its downsides, however. Major side effects of succinylcholine include hyperkalemia, malignant hyperthermia, fasciculations, and bradycardia.

To circumnavigate these concerning side effects, anesthesiologists have implemented other NMBs such as pancuronium in the past. In 1994, rocuronium was developed as a better, less tachycardiac and histamine releasing alternative to pancuronium. Its major side effect includes hepatotoxicity. Compared to succinylcholine, it has a longer half-life (30-90min vs. 10-15min)[25].

Given NMBs vital role in the OR, a suitable NMB reversal agent must be utilized. For many years, neostigmine, an acetylcholinesterase inhibitor, was the drug of choice for reversing the effects of neuromuscular blockades in the OR. However, there are disadvantages to using neostigmine including autonomic dysfunction like bradycardia and post-operative nausea & vomiting (PONV)[26]. To counteract these adverse effects, glycopyrrolate is administered with neostigmine[24]. Furthermore, neostigmine has a significant potential to delay turnover times in the OR as it takes anywhere from 13 minutes to 45 minutes see its reversal effects[26].

Sugammadex is a newer reversal agent that has gained more popularity recently. In a 2017 study by O'Reilly-Shah et al., out of nearly 12,000 respondents across 183 countries, nearly 62%

reported that sugammadex is relevant to their practice[27]. A large portion (69.4%) of respondents also reported that they limited their use of sugammadex due to concerns about adverse events, cost or cost benefit concerns, limited supply, or other reasons.

Sugammadex is a γ-cyclodextrin agent developed for the specific reversal of rocuronium and— to a lesser extent due to steric hindrance— vecuronium or pancuronium, and functions by means of encapsulation (chelation)[28, 29]. Theoretically, this NMBA reversal agent does not interfere with the acetylcholinesterase receptor, thereby not producing the muscarinic side effects associated with neostigmine[29]. Although it is considered safer, some studies still cite harmful effects. Given its rapid rise in usage, a more comprehensive characterization of the clinical and practical aspects of sugammadex compared to the standard of neostigmine is needed.

## Methods

In accordance with the PRISMA guidelines, a systematic review of PubMed and Google Scholar databases was performed in search of publications that compared the efficacy and safety of sugammadex versus neostigmine. Search terms and MeSH keywords used included “sugammadex and neostigmine,” “complications,” “OR discharge times,” “TOF > 0.9,” “PACU,” “Extubation,” “Atelectasis,” “Bradycardia,” “Pneumonia,” and “PONV.”

Primary outcome measured was any postoperative complications. Secondary outcomes measured were recovery times and PACU turnover times.

All publications that contained either endpoints were included irrespective of date of publication, country of origin, language, age range of patients, type of surgical procedure, or ASA grade. Additional unpublished works and theses were searched using Google Scholar. In January 2022, a top-up search was performed. Our search returned 248 RCTs and articles (Figure 4). Of those searched, 83 were duplicates, 1 was removed from the database, 22 were inaccessible, 21 had abstracts unrelated to the topic, 61 had insufficient sufficient data or significant bias, and 4 full-text screens were not related to the topic. After the exclusion process, 56 studies have been included in this meta-analysis.

Two review authors independently screened and examined all potentially eligible primary trials and decided on their inclusion in the review. Furthermore, we independently extracted data from each trial and evaluated data on methods and outcomes. Resulting data was analyzed using Microsoft Excel according to the method prescribed by Neyeloff et al[30].

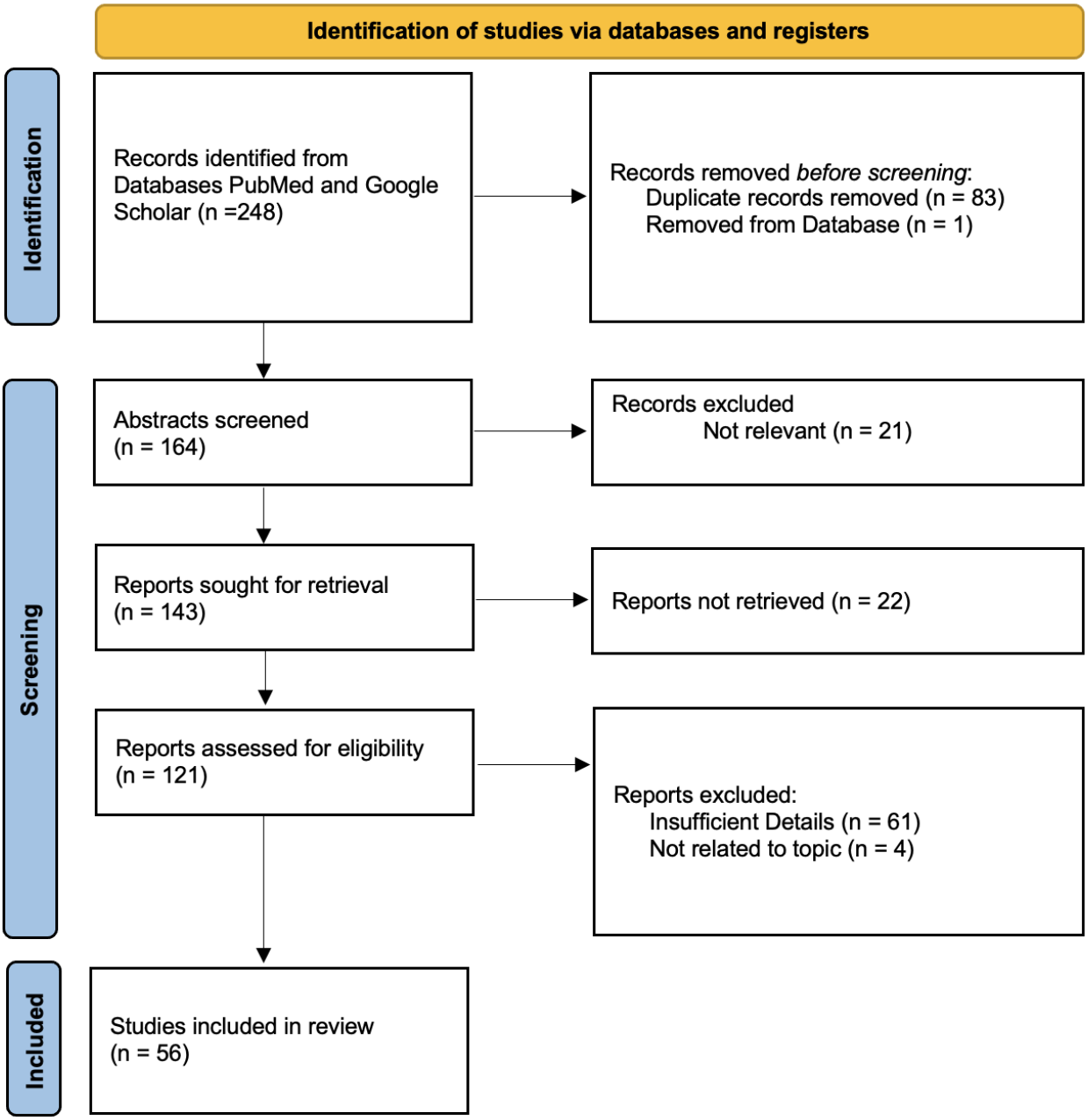


**Figure 4: PRISMA flow diagram.** The diagram shows the study selection process and provides reasons for exclusion of the records screened. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

## Results

57 articles totaling n = 66157 patients met inclusion criteria for this meta-analysis. Sugammadex shows a significant reduction in pneumonia (RR = 0.60, 95% CI (0.36, 0.68)) and bradycardia (RR = 0. 54, 95% CI (0.42, 0.67)), and a significant increase in PONV (RR = 1.21, 95% CI (1.05, 1.39)) (Figures 6-8). No significant difference was found for atelectasis (RR = 0.964, 95% CI (0.853, 1.09)) (Figure 5).

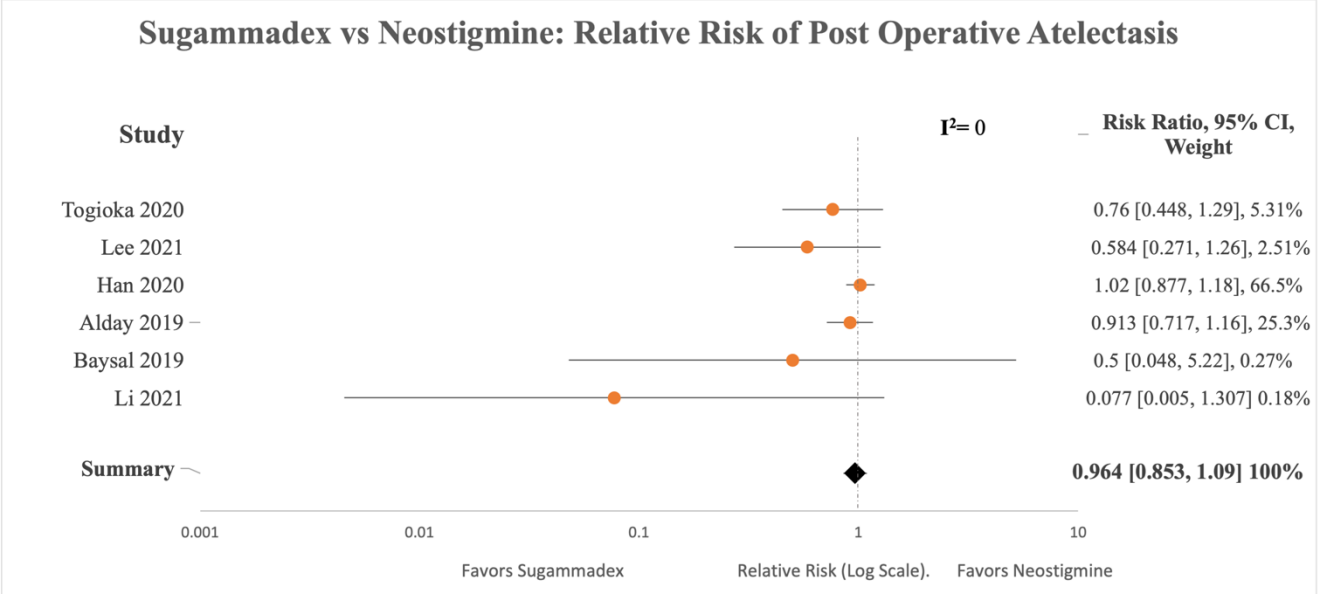


**Figure 5:** The Relative Risk of Postoperative Atelectasis between Sugammadex and Neostigmine. CI = confidence interval

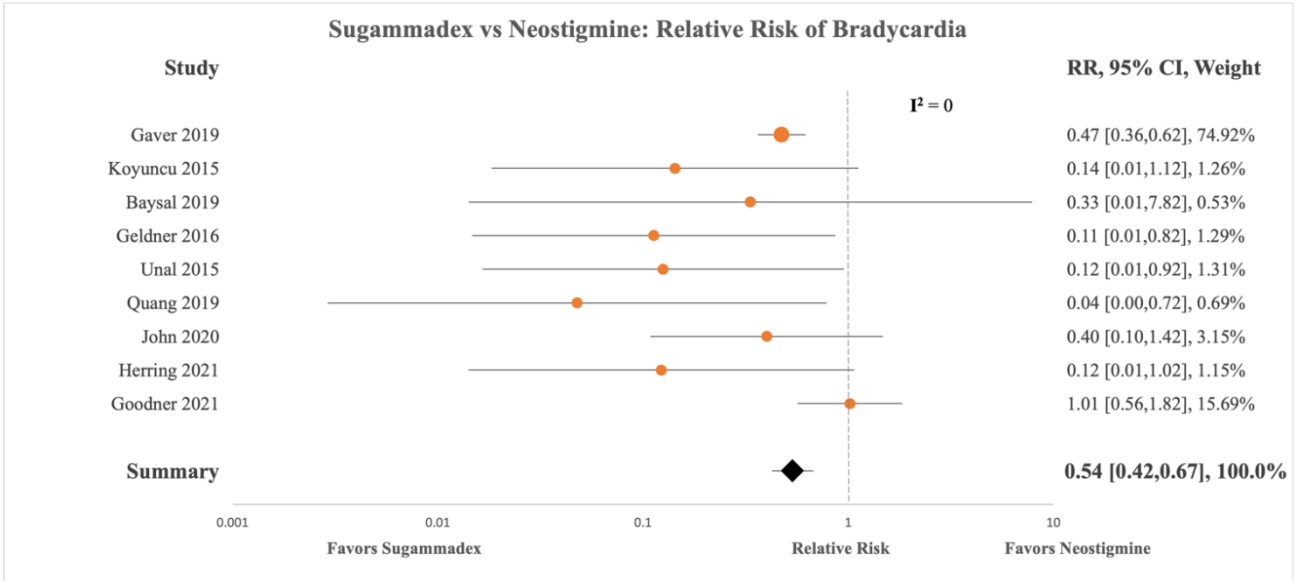


**Figure 6:** Forest plot of relative risk of bradycardia when sugammadex vs neostigmine is administered. RR = Relative Risk; CI = Confidence Interval.

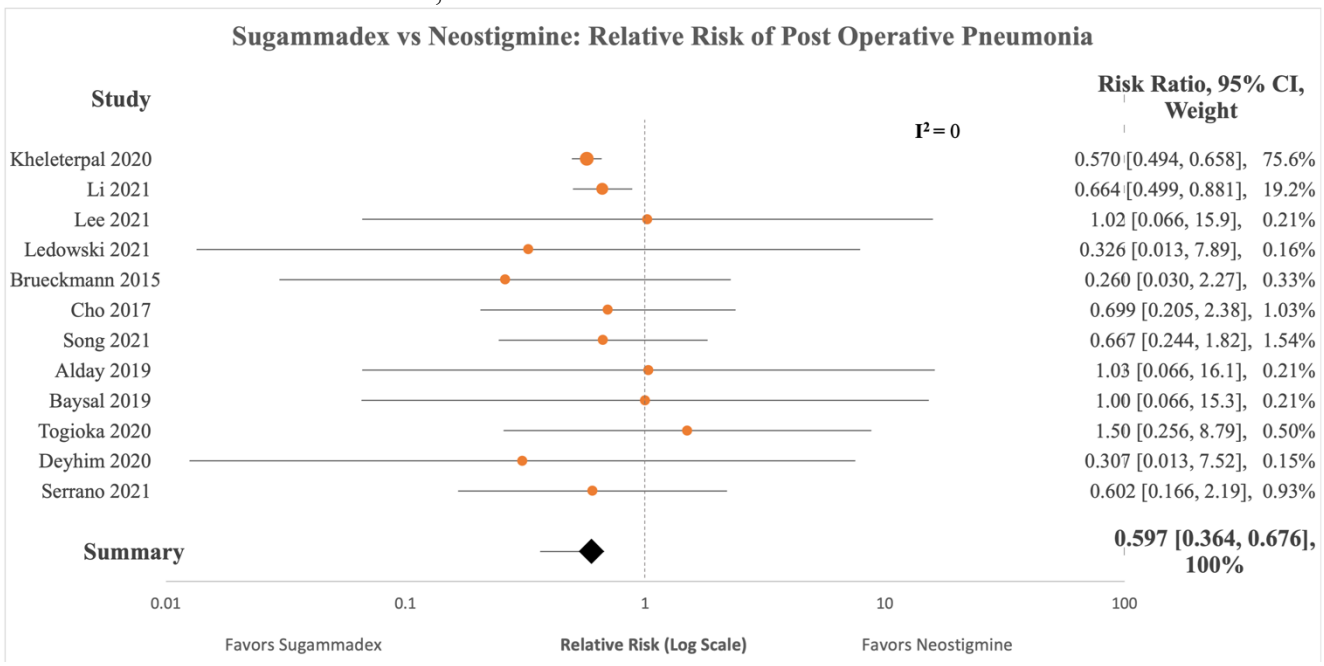


**Figure 7:** Forest plot of relative risk of postoperative pneumonia when sugammadex vs neostigmine is administered. RR = Relative Risk; CI = Confidence Interval.

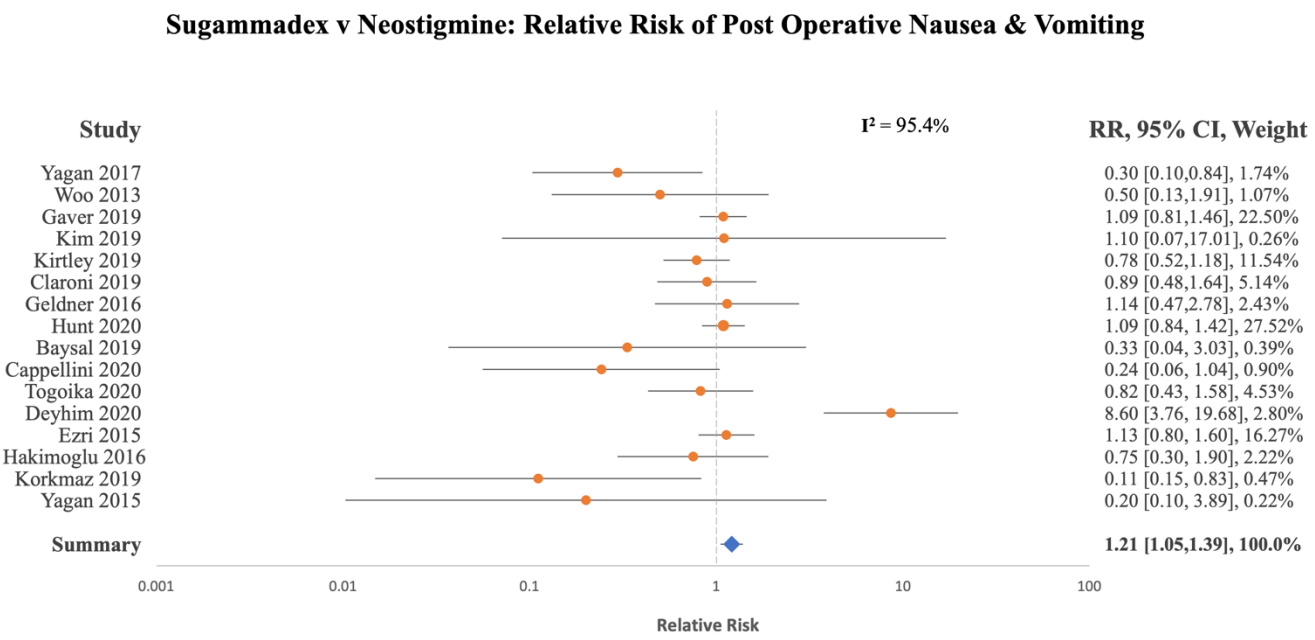


**Figure 8:** Forest plot of relative risk of postoperative nausea and vomiting (PONV) when sugammadex vs neostigmine is administered. RR = Relative Risk; CI = Confidence Interval.

Compared to neostigmine, sugammadex showed a significant reduction in extubation time (mean difference [MD] = -2.77 min, 95% CI (-3.95, -1.59)), Recovery to TOF >0.9 time (MD =-17.6 min, 95% CI (-22.2, -13.1)), OR discharge time (MD = -3.74 min, 95% CI (-4.77, -2.71)), and PACU discharge time (MD = -8.51 min, 95% CI (-14.9, -2.07)) (figures 9-12).

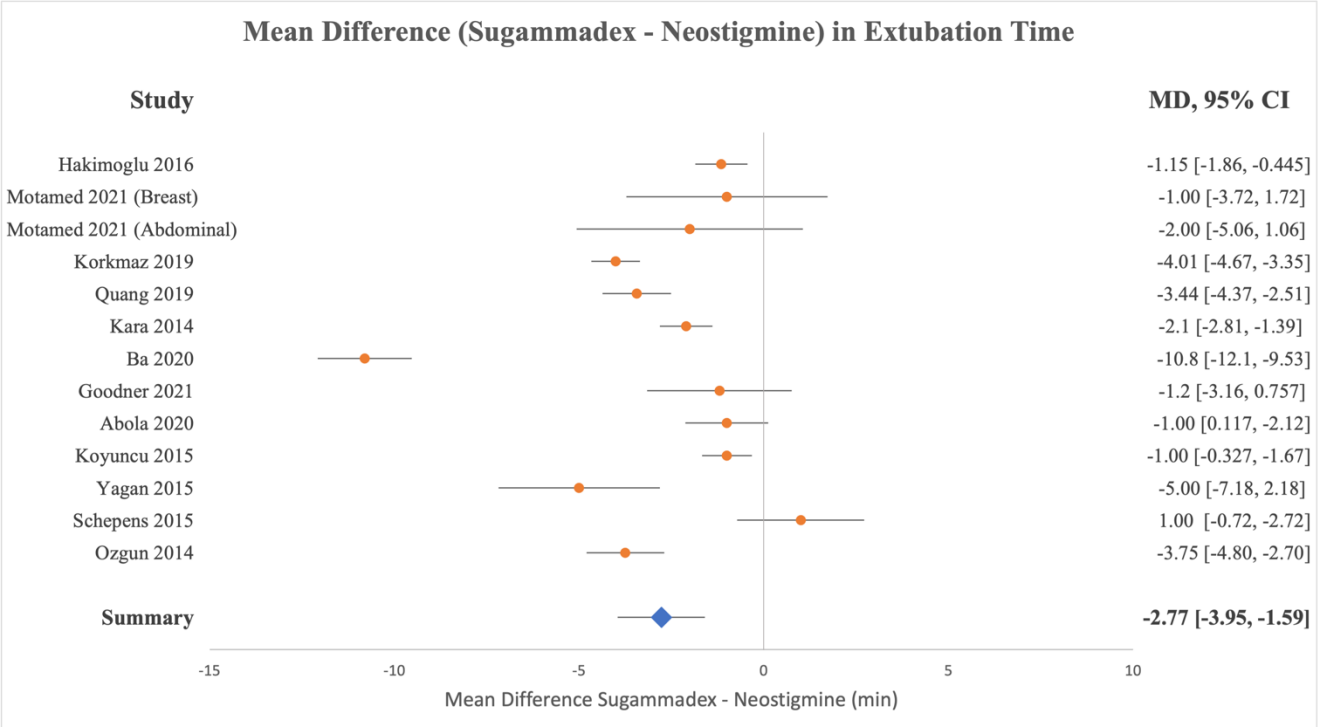


**Figure 9:** Forest plot of the mean difference of extubation time in minutes when comparing sugammadex against neostigmine. MD = Mean Difference; CI = Confidence Interval.

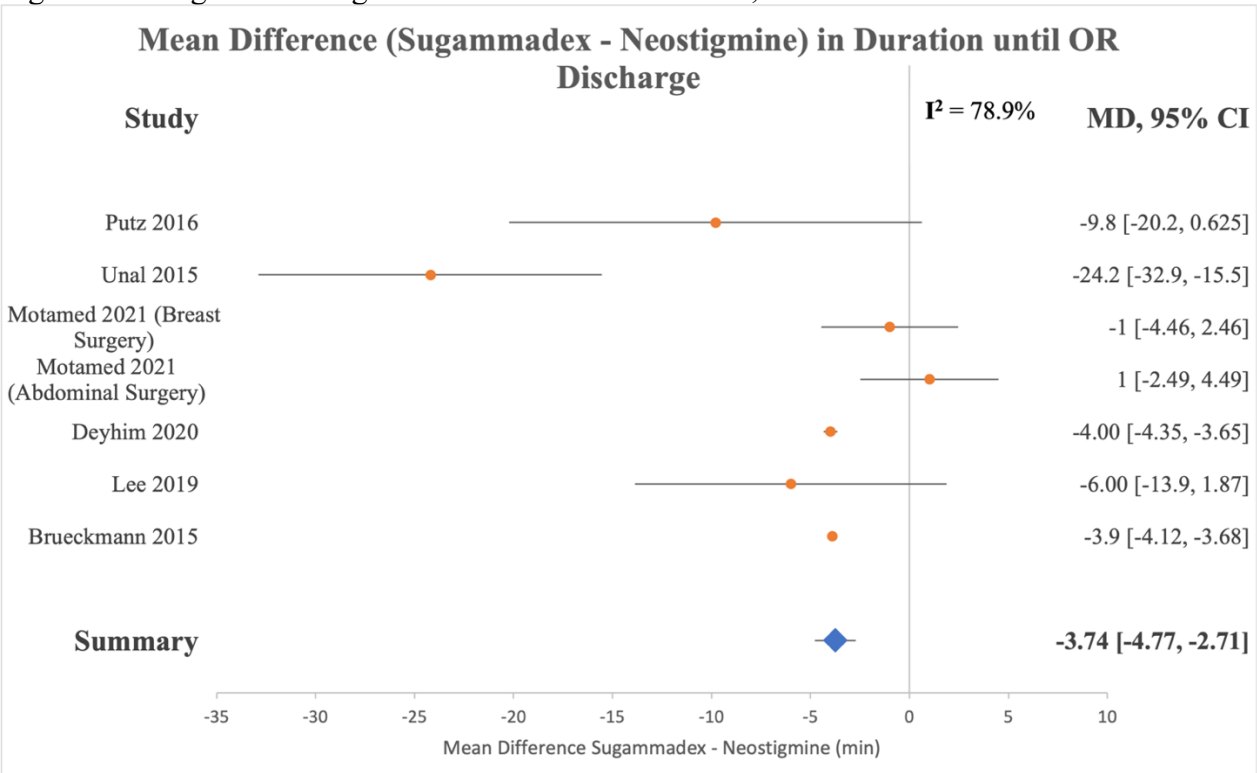


**Figure 10:** Forest plot of the mean difference in discharge time from the OR in minutes when comparing sugammadex against neostigmine. MD = Mean Difference; CI = Confidence Interval; $I^2$ =

heterogeneity between the studies.

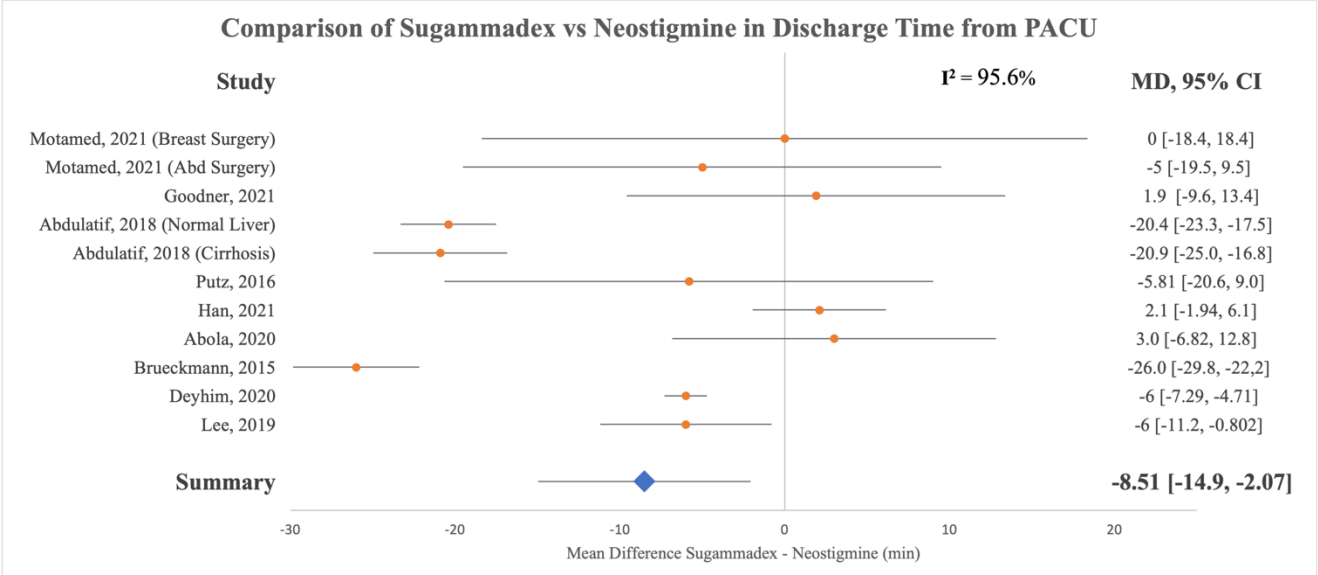


**Figure 11:** Forest plot of the mean difference in discharge time from the PACU in minutes when comparing sugammadex against neostigmine. MD = Mean Difference; CI = Confidence Interval; $I^2$ = heterogeneity between studies.

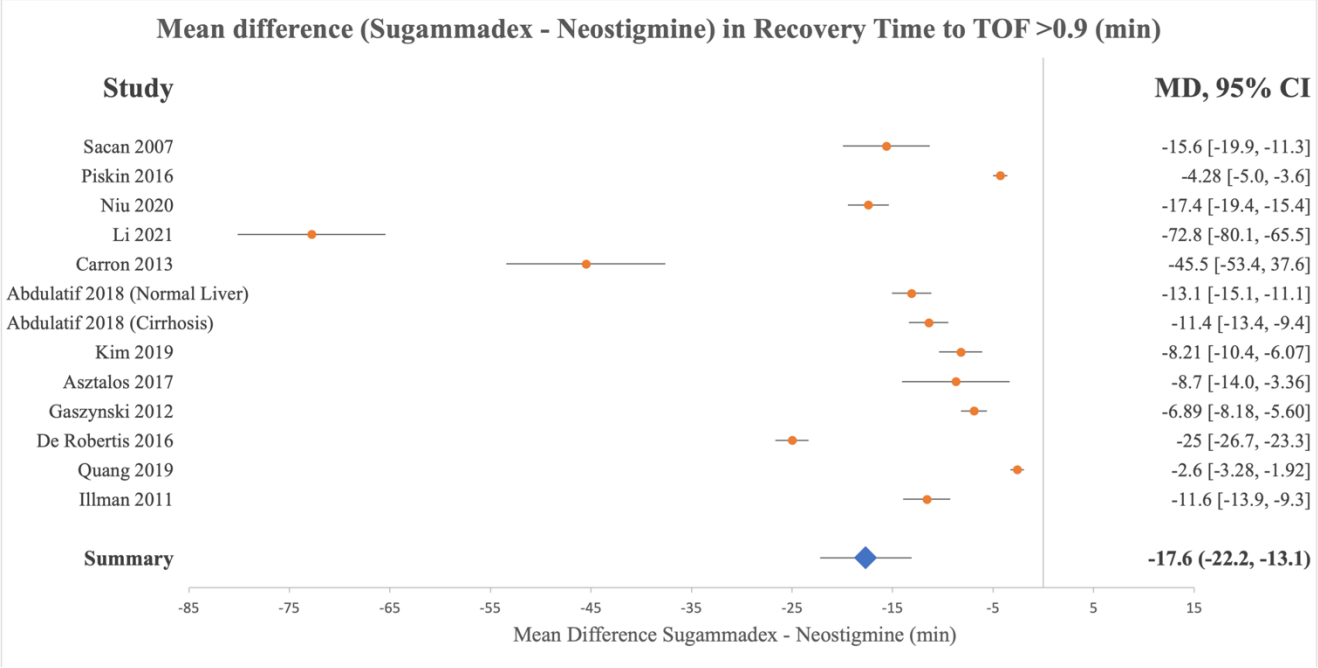


**Figure 12:** Forest plot of the mean difference in time required for the patient to recover to TOF > 0.9 in minutes when comparing sugammadex against neostigmine. MD = Mean Difference; CI = Confidence Interval.

## Discussion & Conclusion

Our results show that administration of sugammadex as a reversal for NMB facilitates faster OR turnover time, extubation time, and PACU discharge time. Sugammadex is associated with lower risk of bradycardia and pneumonia, but higher risk of PONV. In other words, sugammadex has a milder side effect profile compared to neostigmine. Compared with elimination of the more cumbersome need to time administration as in neostigmine's case, sugammadex has potential to be the NMB reversal agent of choice for clinicians.

The main limitation of this study is that 22 reports were not able to be retrieved and could sway the results of the analysis. Additionally, the $I^2$ value for PONV was 95.4%, which denotes that there is a great deal of heterogeneity between the studies. However, a large $I^2$ statistic does not completely rule out the validity of the result; the size of the individual study's confidence interval must be taken into account[31, 32]. In our analysis, the heavily weighted larger studies have a much smaller CI and would thus have medians that fall closer to the true value. Although we submit that our findings are reasonable, more studies in the future investigating the effects of NMB reversal agents on PONV is warranted.

Overall, sugammadex has a safer profile than neostigmine for neuromuscular blockade. Despite the clinical benefit of sugammadex, its higher cost often influences the choice of NMB reversal method. A study done by Jiang et al.[33] analyzed nearly 10,000 surgical procedures and reported that sugammadex reduced postoperative pulmonary complications events by 12% (58 cases) among the modeled procedures when compared to neostigmine, leading to a budget impact of –$3,079,703 (–$309 per modeled procedure, or a 10.9% reduction in total costs).

In an ongoing study, we are investigating the shorter times of sugammadex in the context of a cost-benefit analysis. These results serve as a strong basis for future work on neuromuscular blockade

reversal agents, with large implications in improving the quality of patient care, bolstering the efficiency of the surgery and anesthesiology services, as well as improving healthcare costs of surgery and anesthesia.

# Chapter 3: After the Operating Room

## Introduction: Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) plays a significant role in the planning of perioperative management of patients. OSA is characterized by recurrent episodes of partial (hypopnea) or complete (apnea) interruption in breathing during sleep, and symptoms include loud snoring, nocturnal awakening, and daytime sleepiness[34, 35]. Physically, patients with OSA commonly have a wider neck circumference and a smaller pharyngeal space, leading to airway obstruction that can pose a significant challenge in perioperative management. Its etiology is multifactorial, and management is predicated on the severity of obstruction.

OSA has been linked to causing certain cardiovascular diseases such as hypertension, coronary artery disease, and atrial fibrillation. Classically, OSA is treated with weight loss management and a Continuous Positive Airway Pressure (CPAP) machine, which provides a constant positive pressure through the pharyngeal space, stimulating muscle activity in the pharynx, allowing for more airflow[36]. The risks associated with perioperative management of patients with OSA include ineffective mask ventilation and intubation, postoperative airway obstruction, and other complications resulting from comorbid conditions[37]. Asphyxiation and aspiration are the major risks in the perioperative management of patients with OSA, as many medications used by anesthesiologists depress muscle activity and suppress arousal responses, resulting in the airway being inaccessible during operations[38].

In 2012 and 2017, SAMBA (Society of Ambulatory Anesthesia) and SASM (Society of Anesthesia and Sleep Medicine) published consensus statements for the selection of patients with OSA scheduled for ambulatory surgery[39, 40]. Despite these guidelines, the need for a CPAP device in the immediate postoperative period remains controversial. At many ASCs, CPAP devices are not currently being used because the patients at these facilities are healthier and usually have only mild-to-moderate

OSA. Also, patients may forget to bring the CPAP device or it is not feasible for them to bring it for the same-day surgery. Many anesthesiologists have observed that the CPAP machines are not being used at the ASCs as recommended. Reasons for the noncompliance with the recommendations include the quick emergence and recovery of the patients for the faster day surgery cases, and these patients are only in the PACU for an average of 1 hour postoperatively at ASCs.

This study aims to investigate the compliance rate with this recommendation among busy ambulatory surgery centers (ASC) who mainly have healthy patients with mild-to-moderate OSA or those with OSA and well-managed comorbidities, as the need for CPAP machines in the postoperative period at these ASCs remains unclear. To this end, we decided to conduct a survey of medical directors of ASCs throughout the United States (US).

## Methods

We created a survey to investigate if the ASCs that accept OSA patients require the patients to bring their CPAP devices to the facility (Table 1). Additionally, we inquired if those ASCs used CPAP devices in the immediate postoperative period within the past 2 years. The survey was validated by five practitioners of busy ASCs to confirm whether any of the questions were difficult to understand or to answer via email, and a reminder email was sent if no response was received within a month. The results of the survey were analyzed using spreadsheets and presented as percentages.

| Questions asked in the survey to the ASC's |
| --- |
| Number of surgical procedures per year. |
| Number of anesthesiologists/anesthesia providers. |
| Do you have patients with OSA in your facility? If yes, please proceed with the next question. |
| Do you ask your patients to bring their CPAP machine to the ASC? If not, why? |
| How often have you had to use a CPAP machine in your facility in the past 2 years? |

**Table 1: Survey to Investigate if the ASCs That Accept OSA Patients Require Patients to Bring Their CPAP Devices to the Facility**. Additionally, we inquired if those ASCs used CPAP devices in the immediate postoperative period within the past 2 years.

## Results

The survey had a response rate of 60.9% (67 of 110 ASC medical directors that submitted the survey), encompassing 408,147 cases among 1946 providers. Of the facilities that responded, only 59.7% of them required their patients to bring their CPAP devices on the day of surgery. Out of the 67 facilities that responded, only 25.37% (17/67) reported using a CPAP machine postoperatively within the past 2 years, with the highest CPAP usage being 20 times at one facility during that 2-year period.


**Figure 13. ASC's compliance with SAMBA recommendations for perioperative management of patients with OSA.**

## Conclusions and Future Considerations

Obstructive Sleep Apnea is a respiratory condition that increases the risk of CV disease, notably atrial fibrillation, hypertension, and coronary artery disease. Perioperatively, it also increases the risk for ineffective mask ventilation and intubation, postoperative airway obstruction, asphyxiation, and aspiration. In 2012 and 2017, SAMBA (Society of Ambulatory Anesthesia) and SASM (Society of Anesthesia and Sleep Medicine) published consensus statements for the selection of patients with OSA scheduled for ambulatory surgery[35, 40]. The recommendations include:

1. Patients with a known diagnosis of OSA and optimized comorbid medical conditions can be considered for ambulatory surgery if they are able to use the CPAP device in the postoperative period.

2. Patients with presumed diagnosis of OSA, based on screening tools such as the STOP-Bang questionnaire and optimized comorbid conditions can be considered for ambulatory surgery if postoperative pain can be managed predominantly with non-opioid analgesic techniques. It is not necessary to postpone surgery in this patient population.

3. OSA patients with non-optimized comorbid conditions may not be ideal candidates for ambulatory surgery.

4. Patients receiving preoperative CPAP should be instructed to bring their CPAP device to the ambulatory care facility unless one is available at the facility.

5. Continued use of PAP therapy at previously prescribed settings is recommended during periods of sleep, both preoperatively and postoperatively. Adjustments may need to be made to the settings to account for perioperative changes such as facial swelling, fluid shifts, recent pharmacotherapy, and pulmonary function.

The survey we conducted showed that 59.7% of the ASC facilities (40) that responded adhered to SAMBA's recommendations, having access to CPAP devices on-site to treat immediate postoperative complications in patients with OSA (Table 1). This would mean that 40.3% of ASCs (27/40) that did respond do not have access to a CPAP device on-site and, as a result, may possibly lack the proper equipment needed to handle these complications. However, approximately 75% of the ASCs that followed SAMBA's recommendations by having CPAP available did not actually use the CPAP device postoperatively within the last two years. The highest reported CPAP usage rate was only 20 times in that 2-year period at one facility. The frequency and fatality rate associated with postoperative respiratory complications requiring a CPAP device at ASCs with healthier OSA patients are still inconclusive, making the need for CPAP devices during perioperative management at these facilities controversial. Therefore, more in-depth studies are necessary to assess postoperative complications that require the use of a CPAP device in order to determine the urgency of ASCs implementing SAMBA's recommendations. A proposal for correction of this problem of not using the CPAP devices at the ASCs as recommended could include the following:

a. Bring a permanent hospital CPAP and get approval by Biomed,

b. Train nurses how to use the CPAP device,

c. Assign PACU nurses one to one with OSA patients,

d. Keep OSA patients in PACU longer.

Other considerations for future OSA studies for postoperative treatment will also need to include the new hypoglossal nerve stimulator devices (Inspire) as treatment considerations for OSA in the perioperative period.

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# Appendix

## Appendix A – In Vitro AMF System from Wang et al.

A custom-designed system composed of multiple solenoid coils was constructed to deliver programmed AMF exposures to stainless-steel rings with existing biofilm held in 50 mL conical tubes. The parameters of AMF exposure were assigned using custom-developed software operating on a personal computer. A function generator (33250A, Agilent Technologies) was used to produce an RF signal. The signal was input into a 1000 W RF amplifier (1140LA, Electronics & Innovation), and the amplified signal was directed to the appropriate coil using a USB-controlled relay system. Each coil was constructed using 0.25-in. diameter copper tubing formed into a 6-turn solenoid with 1 cm pitch between turns (Fig. 1a). The coil diameter was chosen to accommodate a 50 mL conical tube holding the infected ring and media. A plastic holder was included in each conical tube to hold the ring in place, so the orientation was maintained across all coils. The coils were driven electrically as a parallel resonant circuit using a capacitor selected to tune the resonant frequency to approximately 500 kHz. The working frequencies of the coils ranged from 507 to 522 kHz. A matching inductor was also included in series with the resonant circuit to transform the impedance of each coil to 50 ohms for efficient power transfer. The complete system included four insulated boxes each containing eight coils, enabling the treatment of up to 32 samples with iAMF in a single experiment. The coils worked at 8 Vpp with a 50% duty cycle (100 ms per 200 ms) for the experiments described in this paper. A circulating fan with an integrated heater (Miller Manufacturing, MN, USA) was also incorporated into each box to keep the samples at 37 °C during extended-length experiments.

The strength of the AMF in the coil was characterized using a commercial 2D magnetic field probe (AMF Lifesystems, Inc., MI, USA). A Rogowski current probe (TRCP3000 current probes, Tektronix Inc., OR, USA) was used to measure the electrical current through the coils during operation.

To characterize AMF heating, uninfected metal rings were exposed for varying durations to reach desired maximum temperatures. The temperature of each ring exposed to AMF was measured using a fiber-optic temperature sensor (PRB-G40-2M-STM-MRI, Osensa Innovations, Burnaby, BC, Canada) attached to the center of the inner surface of the ring with high-temperature epoxy (Epotek 353ND, Epoxy Technologies, CA, USA. Tests were performed to confirm that the epoxy was unaffected by the AMF and did not produce false heating. Ring temperatures were recorded at a rate of 2 Hz using a laptop computer. The temperature change during iAMF of media was also measured by placing the thermal sensor located in the center of the ring immersed in media. The use of fiberoptic temperature sensors enabled accurate temperature characterization during AMF exposures since they are immune to electromagnetic interference.

Finite element simulations were performed using the commercial simulation software COMSOL Multiphysics (Comsol v5.5, Los Angeles, CA, USA) to model the interaction between AMF and a metal implant and to study the uniformity and magnitude of AMF-induced heating. A quasistatic approximation of Maxwell's equation and Penne's bioheat transfer model was used for electromagnetic and thermal simulations. The thermal dose is calculated as cumulative equivalent minutes (CEM43) which gives the time–temperature relation in equivalent minutes as

$$\mathrm{CEM43} = \int_{t_0}^{t_{final}} R^{43-T(t)}\,dt$$

where, R is the temperature dependence of the rate of cell death (R = 0.5 for T > 43, R = 0.25 for 43 ≥ T ≥ 39), dt is the time interval, to and tfinal are initial and final heating periods respectively in minutes. The thermal toxicity due to implant heating is determined based on the tissue damage radius CEM 240 min (irreversible damage) from the implant surface.

## Vitae

Jonathan Vachon (April 29, 1994 – Present) is a fourth-year medical student at UT Southwestern Medical School in Dallas, TX. He graduated from Washington University in St. Louis with a B.A. in Molecular Biology & Biochemistry, with minors in Psychological & Brain Sciences and Jazz Studies. In addition to his medical studies and aspirations in the field of Anesthesiology, Jonathan has worn many hats throughout his professional and personal life, including being a high school chemistry teacher; an award-winning musician, conductor, and arranger; and a professional E-Sports competitor. Jonathan has a fiery passion for education and global health, and he hopes to continue his work in local, national, and international communities for years to come.