Summer 2020

Sugammadex Versus Neostigmine In Reducing Postoperative Adverse Effects In The Pediatric Population

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Abstract

Neostigmine and sugammadex are two medications used to reverse the neuromuscular blockade caused by nondepolarizing aminosteroidal neuromuscular blocking agents. Research has shown an association between the use of acetylcholinesterase inhibitors, such as neostigmine, and residual neuromuscular blockade in pediatric patients. Sugammadex has been shown to reduce residual neuromuscular blockade in adults without adverse effects, but minimal research has been performed on the effects of sugammadex in the pediatric population. Therefore, the objective of the present study is to compare sugammadex and neostigmine to determine if using sugammadex instead of neostigmine reduces postoperative adverse effects in the pediatric population. A systematic, computerized search was conducted on PubMed, MEDLINE, EMBASE, and the Cochrane Library, as well as the clinical trials registries: www.controlled-trials.com and clinicaltrials.gov. Studies comparing sugammadex versus neostigmine in the pediatric population receiving nondepolarizing neuromuscular blocking agents were included. The present study shows that sugammadex rapidly and efficiently reverses neuromuscular blockade in the pediatric population with less adverse effects than neostigmine. Furthermore, it has been found to be as safe and effective in the pediatric population as in the adult population.

Sugammadex versus Neostigmine in Reducing Postoperative Adverse Effects in the Pediatric Population

In order to better understand the current anesthesia practices and implications for use of sugammadex versus neostigmine among pediatric patients, it is important to comprehend the function of neuromuscular blocking agents, neuromuscular blockade, and the function of reversal agents. Neuromuscular blocking agents, or paralytics, are routinely administered by anesthesia providers in the operating room. Many pediatric patients receive rocuronium or vecuronium for surgery due to fewer adverse effects. Rocuronium and vecuronium are nondepolarizing neuromuscular blocking agents and act by competitively blocking the binding of acetylcholine at the neuromuscular junction in skeletal muscle. The two agents most often used to reverse nondepolarizing neuromuscular blocking agents are sugammadex and neostigmine.

Sugammadex is a selective relaxant binding agent with a novel approach to reversing nondepolarizing aminosteroidal neuromuscular blocking agents. It noncompetitively binds rocuronium and vecuronium, which separates them from nicotinic receptors at the neuromuscular junction, resulting in the reversal of the neuromuscular blockade. Before sugammadex, acetylcholinesterase inhibitors, such as neostigmine, were the only reversal agents available. These medications work by inhibiting the breakdown of acetylcholine. However, acetylcholinesterase inhibitors are associated with bradycardia, bronchospasm, and other muscarinic side effects. To counter these effects, anticholinergic drugs, such as glycopyrrolate, are administered with acetylcholinesterase inhibitors. However, anticholinergics can produce their own undesirable side effects, such as tachycardia and confusion.

Research has shown an association between the use of acetylcholinesterase inhibitors and residual neuromuscular blockade in pediatric patients. Postoperative residual neuromuscular blockade increases the risk of respiratory complications, such as pulmonary atelectasis, airway obstruction, and decreased oxygen saturation in all populations. Young pediatric patients could be at further risk for respiratory complications due to immature respiratory musculature, diminished functional residual capacity, and reduced surface area for gas exchange.

Several studies have been performed that show the efficacy of sugammadex in reversing neuromuscular blockade in the adult population without adverse effects, but minimal research has been performed on the effects of sugammadex in the pediatric population. Therefore, the purpose of the current study is to provide a comprehensive review of the different implications of the use of sugammadex and neostigmine, and to provide a better understanding of how the use of sugammadex can reduce postoperative adverse effects in the pediatric population.

Methodology

A systematic, computerized search was conducted on PubMed, MEDLINE, EMBASE, and the Cochrane Library, as well as the clinical trials registries: www.controlled-trials.com and clinicaltrials.gov. The search was run on October 27, 2019, November 3, 2019, and November 9, 2019. Date restrictions were placed, limiting the studies to within six years of the date of the search, with no language restrictions applied. The search components “sugammadex”, “neostigmine”, and “pediatric” were used. Studies comparing sugammadex versus neostigmine in the pediatric population receiving nondepolarizing neuromuscular blocking agents were included. The reference lists of the included studies were searched, and relevant studies were included. The studies include male and female pediatric patients less than 18 years of age with a physical status classification of I to IV who had received nondepolarizing neuromuscular

blocking agents and sugammadex or neostigmine. Patients and/or guardians consented to be included in the individual studies.

Literature Review

Neuromuscular blocking agents are routinely administered during induction by anesthesia providers in the operating room. Not only do they facilitate intubation and mechanical ventilation, but they also improve surgical conditions for the surgeon due to the reduction of muscle tone (Bruintjes et al., 2017; Martini et al., 2014). The reversal of neuromuscular blockade during emergence is an essential aspect of anesthesia and involves neuromuscular monitoring. Incomplete reversal of neuromuscular blockade can result in postoperative pulmonary complications such as aspiration, atelectasis, hypoxemia, and respiratory failure. Therefore, background information about neuromuscular blocking agents and neuromuscular monitoring is necessary in order to fully understand and compare the effects of neostigmine and sugammadex in reversal of neuromuscular blockade.

Depolarizing Neuromuscular Blocking Agent

The only depolarizing neuromuscular blocking agent that is currently used is succinylcholine. It functions by attaching itself to the acetylcholine receptor, resulting in a prolonged depolarization, which inactivates the receptor (Butterworth, Mackey, & Wasnick 2018). Succinylcholine is typically not used in the pediatric population, except in emergency or difficult airway situations. This is because undiagnosed myopathies may be present in children, which could lead to complications if succinylcholine is administered. The most common complications include rhabdomyolysis, hyperkalemia, and profound bradycardia, which can lead to cardiac arrest (Butterworth et al., 2018). Because of this, the U.S. Food and Drug Administration (FDA) issued a black box warning for succinylcholine use in the pediatric

population. If succinylcholine must be administered to a pediatric patient, it is usually administered intramuscularly along with atropine. Atropine, an anticholinergic agent, will prevent the profound bradycardia that can occur with succinylcholine administration in children. Because of the potential for these complications to occur, nondepolarizing neuromuscular blocking agents are preferred in the pediatric population.

Nondepolarizing Neuromuscular Blocking Agents

Nondepolarizing neuromuscular blocking agents work by attaching to acetylcholine receptors at the neuromuscular junction. However, they do not cause a conformational change to the receptor, such as succinylcholine, and do not produce an action potential. Instead, they only block acetylcholine from binding to the receptor.

Nondepolarizing neuromuscular blocking agents can be divided into two different classifications: aminosteroidal and benzylisoquinoline. Aminosteroidal neuromuscular blocking agents, which include rocuronium and vecuronium, are the most commonly used neuromuscular blocking agents. Rocuronium and vecuronium have a steroidal structure with an attached amino group, which is important, as the structure is what allows sugammadex to bind to it. Benzylisoquinoline neuromuscular blocking agents have a different structure which, does not bind to sugammadex, and therefore are not included in the current research. Unlike vecuronium, rocuronium undergoes minimal metabolism and produces no active metabolites. Therefore, the most commonly used neuromuscular agent to induce paralysis in the pediatric population is rocuronium (Tarquinio et al., 2015).

Neuromuscular Monitoring

The level of neuromuscular blockade should be monitored whenever a neuromuscular blocking agent is administered, especially in pediatric patients. Monitoring is essential to

measure the level of neuromuscular blockade and to determine how much agent is required to reverse neuromuscular blockade. The effects of all neuromuscular agents, both depolarizing and nondepolarizing, can be measured. Traditionally, recovery was evaluated by the patient lifting their head for five seconds, squeezing the anesthesia providers' hands, and breathing without difficulty (Yang et al., 2014). Most anesthesia providers now monitor neuromuscular blockade using peripheral nerve stimulators to measure train of four.

Train of four. The concept of train of four monitoring using peripheral nerve stimulators is important as it is used in almost all research involving the administration of paralytics and reversal of neuromuscular blockade. The preferred location for train of four monitoring in pediatric patients is on the ulnar nerve, which contracts the adductor pollicis muscle (Klucka et al., 2019). Stimuli are applied to the ulnar nerve, and the more neuromuscular blocking agent bound to the neuromuscular endplate, the fewer responses to the stimuli. For example, a train of four of zero, or no twitches, indicates that there is > 95% neuromuscular blockade. A train a four of 4 (T4), or four twitches, indicates that there is < 75% neuromuscular blockade (Hunter, 2017). The ratio between the strength of the response of T1 and T4 is known as the train of four ratio.

The higher the train of four ratio, the more neuromuscular blockade reversal has occurred. Until recently, a train of four ratio of 0.7 was considered to be a sign of sufficient neuromuscular recovery (Tajaate et al., 2018). This was based on the fact that tidal volume and vital capacity, two important respiratory parameters, begin to recover at a train of four ratio of 0.7 (Fuchs-Buder et al., 2016). However, new research shows that a train of four ratio of ≥ 0.9 is now considered to be a sign of sufficient neuromuscular recovery (Plummer-Roberts et al., 2016). Even though a train of four ratio of 0.9 is now considered to be the standard cutoff for sufficient

neuromuscular recovery, it is important to note that residual neuromuscular blockade may persist in some patients at that level.

Residual Neuromuscular Blockade

Residual postoperative neuromuscular blockade occurs when the patient experiences residual muscular weakness related to the incomplete reversal of neuromuscular blocking agents. Residual blockade can occur whether or not the patient has been given a reversal agent. Research by Brull et al. (2018) shows that residual neuromuscular blockade occurs in 20-60% of patients receiving a nondepolarizing neuromuscular agent, such as rocuronium. According to Yang et al. (2014), residual neuromuscular block occurs in 2-64% of patients regardless of the type of neuromuscular blocking agent. Fortier et al. (2015), investigated the incidence of residual block in patients that had received rocuronium or vecuronium and had been given a reversal agent. The study showed that the incidence of residual block, even after having received a reversal agent, was 56%. Another study by Brueckmann et al. (2015), found that 43% of patients arriving in the post anesthesia care unit had residual blockade with a train of four ratio < 0.9 and 11% of patients were found to have a train of four ratio < 0.7. A survey conducted in the United States and Europe amongst anesthesia providers showed that 77% of those surveyed felt that residual neuromuscular blockade was a major public health issue (Naguib et al., 2010).

Residual neuromuscular blockade after administration of nondepolarizing neuromuscular blockers has been found to cause postoperative pulmonary complications in all populations. Residual paralysis postoperatively leads to impaired function of the upper airway with increased pharyngeal dysfunction and swallowing difficulties, leading to increased risk for aspiration (Tajaate et al., 2018). Residual paralysis can lead to respiratory insufficiency due to decreased muscle strength, as well as increasing the risk for upper airway obstruction during inhalation and

increasing the risk for silent aspiration (Fuchs-Buder et al., 2016; Hristovska et al., 2017). Patients in the post anesthesia care unit with respiratory complications were found to have higher incidences of residual neuromuscular blockade than patients without complications (Fuchs-Buder et al., 2016). Other complications resulting from residual neuromuscular blockade include hypoxemia, hypercarbia, and atelectasis (Wiatrowski et al., 2018). Failure to ensure the reversal of neuromuscular blockade and to monitor for residual paralysis can lead to respiratory failure, prolonged intubation, and admission to the intensive care unit (ICU) (Murphy, 2018). Some pediatric patients are at even greater risk due to their immature respiratory musculature, diminished functional residual capacity, and reduced surface area for gas exchange. Other factors that put young pediatric patients at greater risk for postoperative respiratory failure include collapsible airways, loss of protective reflexes, and poor lung compliance (Trachsel et al., 2016).

Sugammadex

Sugammadex, which was developed by Merck Pharmaceuticals under the trade name Bridion, was approved for use in adults in the United States by the Food and Drug Administration (FDA) on December 2015, after eight years of clinical trials (Murphy, 2016). Sugammadex has been approved for use in adults and children aged 2-17 years in Europe since 2008 and in Japan since 2010. In the United States, the FDA has not approved sugammadex for use in children due to concerns regarding hypersensitivity and allergic reactions (Young et al., 2016). A great deal of research has been performed in the United States comparing neostigmine and sugammadex in adults; however, the same research on the pediatric population of the United States is scarce.

Sugammadex is a selective relaxant binding agent with a unique approach to reversing nondepolarizing aminosteroidal neuromuscular blocking agents. Its structure consists of a

modified gamma cyclodextrin ring designed to encircle aminosteroidal neuromuscular blocking agents, such as rocuronium or vecuronium (Nag et al., 2013). Sugammadex is able to bind to rocuronium and vecuronium at a ratio of 1:1 (Cada et al., 2016). The mechanism of action of sugammadex is unique in that it is a direct method of removing nondepolarizing neuromuscular blocking agents, as opposed to neostigmine, which uses an indirect method.

Sugammadex does not bind to plasma protein or red blood cells and does not require administration of anticholinergics, as it has no effect on acetylcholine, acetylcholinesterase, or acetylcholine receptors (Sugammadex, 2019). Sugammadex and the sugammadex-rocuronium complex are not metabolized by the body and are excreted unchanged by the kidneys (Nag et al., 2013). The recommended dosage of sugammadex for adults depends upon the level of neuromuscular blockade. If two or more twitches are present (≥ T2), the dose is 2 mg/kg. If there is deep neuromuscular blockade, with no twitches, but a post-tetanic count of 1-2, then the reversal dose is 4 mg/kg. If there is deep neuromuscular blockade, with no twitches, and a post-tetanic count of zero, then the reversal dose is 16 mg/kg (Merck Sharp & Dohme Corp., 2018). 16mg/kg is considered the maximum dose of sugammadex and is typically given in a ‘cannot intubate, cannot ventilate’ situation (Hunter, 2017).

Neostigmine and Glycopyrrolate

Neostigmine functions by binding to acetylcholinesterase, which allow acetylcholine to build up at the neuromuscular junction. This allows acetylcholine to compete with nondepolarizing neuromuscular blockers at acetylcholine receptors. Although acetylcholinesterase inhibitors seem to be ideal for reversing nondepolarizing neuromuscular blockade, there are some issues associated with them. The indirect method in which they reverse neuromuscular blockade means that reversal can be unpredictable and recurarization is possible

(Hristovska et al., 2017). Recurarization occurs when the reversal medication wears off and there is still sufficient neuromuscular blocking agent available in the body to cause residual neuromuscular blockade. Another problem with acetylcholinesterase inhibitors is the autonomic parasympathetic responses that occur after administration. Neostigmine is associated with bradycardia, bronchospasm, dysrhythmias, miosis, and other muscarinic side effects (Neostigmine, 2019). These agents have also been implicated in causing postoperative nausea and vomiting (Koyuncu, 2015; Paech, 2018).

Anticholinergic agents, such as glycopyrrolate, are administered with acetylcholinesterase inhibitors to blunt the autonomic parasympathetic responses that occur. Glycopyrrolate is generally administered with neostigmine as they have a similar onset and duration of action. However, glycopyrrolate can cause its own side effects such as tachycardia and confusion.

Limitations of neostigmine. Although neostigmine has been used to reverse neuromuscular blockade for more than 50 years, it does have its disadvantages. In order for neostigmine to adequately reverse neuromuscular blockade, it is currently recommended there be at least 2 twitches (≥ T2) present using train of four monitoring. Research conducted by Tajaate et al. (2018), shows that neostigmine was not effective in maintaining reversal of neuromuscular blockade in individuals with less than 2 twitches using train of four monitoring. If neostigmine is given with fewer than two twitches (≤ T2), there is an increased chance of recurarization occurring during the postoperative period. Recurarization is the return of neuromuscular blockade after some period of recovery. Thus, administration of neostigmine for reversal of deep neuromuscular blockade is not recommended.

Furthermore, due to the pharmacokinetics of neostigmine, reversal to a train of four ratio of > 0.9 can take more than 10 minutes. Although the onset for neostigmine is 1 minute, it does not reach its peak effect until about 9 minutes. This constraint of neostigmine may be explained as a ceiling effect. Because neostigmine works indirectly at acetylcholine receptors, there is a point where acetylcholinesterase inhibition reaches 100%. However, even with complete acetylcholinesterase inhibition, acetylcholine levels have not reached a point where they can overcome the competitive inhibition of nondepolarizing neuromuscular blockers, such as rocuronium (Tajaate et al., 2018). Thus, giving more neostigmine would not have any further effect at reversing neuromuscular blockade. This plateau is termed the ceiling effect and is why there is a total maximum dose of 0.7 mg/kg or 5mg, whichever is less, during reversal (Hristovska et al., 2017). Several studies involving administration of neostigmine for reversal of neuromuscular blockade revealed it took more than 15 minutes for a train of four ratio > 0.9 after administration of neostigmine (Hristovska et al., 2017; Ozgun et al., 2014).

Neostigmine is associated with several muscarinic side effects, which is why it is administered with an anticholinergic such as glycopyrrolate. Even with administration of an anticholinergic, some muscarinic effects can occur. The most common side effects of neostigmine administration are bradycardia, bronchoconstriction, miosis, laxation, and nausea and vomiting. Bradycardia, bronchoconstriction, and nausea/vomiting are even more of a concern in the pediatric population as any of them can lead to hypoxemia and respiratory complications.

Comparison of Neostigmine and Sugammadex

As previously mentioned, neostigmine requires that at least 2 twitches (≥ T2) be present using train of four monitoring before administration. When neostigmine is given with fewer than

two twitches (≤ T2), there is increased incidence of recurarization. Sugammadex does not require any twitches to be present using train of four monitoring, and it can even be used when there is a deep neuromuscular block with no post-tetanic twitches. Furthermore, there is less incidence of residual neuromuscular blockade with administration of sugammadex than with neostigmine. A study by Brueckmann et al. (2015) on adults showed that 0% of the patients reversed with sugammadex had any residual neuromuscular blockade, while 43% of the patients reversed with neostigmine had residual blockade.

Sugammadex has also been found to have less adverse effects than neostigmine. Bradycardia, which was found to be the most common side effect associated with neostigmine administration, was present in 14% of patients. However, only 2% of patients receiving sugammadex experienced any bradycardia (Koyuncu et al., 2015). Information provided by Merck Pharmaceuticals, the manufacturer of sugammadex, suggests that bradycardia is possible, however, studies have shown that the incidence of bradycardia is lower in groups receiving sugammadex versus neostigmine (Gaver et al., 2017; Hristovska et al., 2017; Hunter, 2017). Issues concerning administration of sugammadex and QT prolongation were found to be not clinically relevant (Honing et al., 2019).

Postoperative pulmonary complications are more common in patients receiving neostigmine versus sugammadex. A study by Ledowski et al. (2014) showed that reversal with sugammadex, or no reversal, had less postoperative pulmonary complications than administering neostigmine for reversal. This implies that sugammadex reduces the risk of postoperative pulmonary outcomes by more efficiently reversing residual neuromuscular blockade and presenting fewer adverse effects. It also implies that reversal with neostigmine was found to not be beneficial and actually had a harmful association with postoperative complications.

Postoperative nausea and vomiting are among the most common postoperative complications after anesthesia. Research shows that there is a decreased incidence in postoperative nausea and vomiting with administration of sugammadex versus neostigmine (Gonheim et al., 2018; Koyuncu et al., 2015). The study by Koyuncu et al. (2015), demonstrated that administration of sugammadex lowered the incidence of nausea and vomiting postoperatively, while administration of neostigmine increased the incidence of nausea and vomiting postoperatively. It is suggested that this could be due to the faster recovery from neuromuscular blockade using sugammadex, but it may also be due to the muscarinic effects of neostigmine administration.

Sugammadex and the Pediatric Population

There have been many studies that show the efficacy and safety of sugammadex in reversing neuromuscular blockade in the adult population without adverse effects. However, the pharmacokinetic and pharmacodynamic profiles of medications differ between adult patients and pediatric patients. For example, the extracellular space is greater in children than adults and this, at times, requires higher doses of medications. Furthermore, in neonates, the neuromuscular junction is not fully developed and the affinity of receptors to rocuronium is reduced. Thus, larger doses of rocuronium are required, which can cause difficulties during emergence (Turk et al., 2019). Anesthesia-related complications during the perioperative period have been found to be a significant cause of childhood morbidity (Mir-Ghassemi et al., 2015). Therefore, the use of sugammadex is investigated to determine if it is safe in the pediatric population.

Although there is little research in the United States regarding administration of sugammadex in the pediatric population, there are several studies from around the world that show it is safe in the reversal of neuromuscular blockade with minimal side effects. A systematic

review by Honing et al. (2019) researched the safety of sugammadex in different age groups. The review determined that sugammadex is equally as safe and effective in pediatric patients as in adult patient after studying adverse effects between all groups. Adverse effects associated with sugammadex use in adults, including anaphylaxis, hypersensitivity, QT prolongation, and anticoagulation, were investigated and were found not to be clinically significant.

One concern of the FDA regarding administration of sugammadex to children involves issues with anaphylaxis. Several studies have shown that there is no clinically significant relationship between administration of sugammadex and anaphylaxis or hypersensitivity reactions. Sari et al. (2013) conducted a study to determine if there were any side effects associated with administration of sugammadex in children. The study included infants, children, and adolescents receiving rocuronium for neuromuscular blockade during surgery. The results show that there was no hypersensitivity, bradycardia, or bronchospasm related to the administration of sugammadex. Another study conducted by Tadakoro et al. (2018) searched for an association between the administration of sugammadex in children and anaphylaxis. The study found that 0.056% of patients had a 'probable' anaphylactic reaction associated with administration of sugammadex. Therefore, no significant association was found between the administration of sugammadex and anaphylaxis in pediatric patients (Tadakoro et al., 2018).

As previously mentioned, bradycardia in one study was reported to occur in about 2% of the adult population. Bradycardia in children is associated with sudden death and is considered an early warning sign. However, studies show that the incidence of bradycardia in children is low, and it is more common in children receiving neostigmine than sugammadex (Gaver et al., 2017; Honing et al., 2019; Liu et al, 2017). A study by Simonini et al. (2019) noted that the one

complication that could be related to sugammadex was increased bradycardia as the dose of sugammadex increased.

Sugammadex has been shown to quickly and efficaciously reverse rocuronium induced neuromuscular blockade in the pediatric population. Reversal occurs when sugammadex binds rocuronium to form a sugammadex-rocuronium complex, thus removing it from the neuromuscular endplate. Several studies show that pediatric patients were able to reach a train of four ratio > 0.9 significantly faster than and more predictably than using neostigmine (Alonso et al., 2014; Ammar et al., 2017; Gaver et al., 2017; Ghoneim et al., 2018; Liu et al., 2017; Ozgun et al., 2014; Plaud et al., 2009; Young et al., 2016). Furthermore, other recovery parameters, such as muscle strength, head elevation, and return of consciousness appeared faster in the group receiving sugammadex (Ozgun et al., 2014).

Plaud et al. (2009) compared reversal of neuromuscular blockade by rocuronium in infants, children, adolescents, and adults. In the study, he administered a placebo or 2mg/kg of sugammadex to patients with two twitches (T2) using train of four monitoring. The results showed that the group given the placebo took 21.0, 19.0, 23.4, and 28.5 minutes, respectively, to reach a train of four ratio of 0.9. However, the group receiving sugammadex took 0.6, 1.2, 1.1, and 1.2 minutes, respectively, to reach a train of four ratio of 0.9 (Plaud et al., 2009). This is significantly faster than the group receiving the placebo. No recurarization was observed and, although some adverse events were observed, they were not found to be linked to sugammadex administration.

Although there is little research involving sugammadex and neonates, the studies that have been performed show that sugammadex is just as safe, fast, and predictable in that population (Alonso et al., 2014; Turk et al., 2019). Alonso et al. (2014) conducted a study on the

effect of sugammadex on neonates to determine its efficacy and safety. The results show that, although the neonatal patients showed profound neuromuscular block after administration of rocuronium, a dose of 4 mg/kg of sugammadex was sufficient to reach a train of four ratio > 0.9 within minutes (Alonso et al., 2014). Furthermore, there were no observed adverse events, recurarization, or change in vital signs. Turk et al. (2019) conducted a retrospective study on the effects of sugammadex on neonates who were administered rocuronium. The mean age of the patients studied was 10.3 days, the mean weight of the patients was 3.0 kg, and the mean dose of sugammadex administered was 3.6 mg/kg. The results show that the time it took to reach a train of four ratio > 0.9 was 88 seconds (Turk et al., 2019). There were no signs of recurarization, and no adverse effects were noted.

Dosing of sugammadex in the pediatric population is unclear as only recommendations are available. In countries where sugammadex is approved in children, the recommended dose for children aged 2-17 years is 2 mg/kg. No recommendations are currently available for children aged less than 2 years. This is due to a lack of data related to the administration of sugammadex in infants and neonates. Matsui et al. (2019) studied the effects of sugammadex in reversing rocuronium induced neuromuscular block in infants and children. The study consisted of administering different doses of sugammadex to determine the appropriate dosage in infants and children. Sugammadex was administered when the post-tetanic count reached 1-2, with one group receiving 1 mg/kg, the second group receiving 2 mg/kg, and the third group receiving 4 mg/kg. The results showed that 1 mg/kg of sugammadex was not sufficient to reach a train of four ratio > 0.9 (Matsui et al., 2019). No difference was seen in the time necessary to reach a train of four ratio > 0.9 between the groups receiving 2 mg/kg and 4 mg/kg. This is significant, as it had been previously thought that a dose of 4 mg/kg was required to reverse deep

neuromuscular blockade. The authors noted that the faster recovery in infants and children versus adults could be related to the larger relative cardiac output present in infants and children (Matsui et al., 2019).

As previously mentioned, sugammadex can be administered for reversal of deep neuromuscular blockade. Therefore, it can be given even when there are no twitches and a post-tetanic count of zero. Studies have shown that sugammadex is able to reverse deep neuromuscular blockade in the pediatric population with no adverse effects (Ammar et al., 2017; Franz et al., 2018). Ammar et al. (2017) compared neostigmine and sugammadex in reversing rocuronium induced neuromuscular blockade in children. In the study, one group of children received 0.35 mg/kg neostigmine along with 0.02 mg/kg of atropine, while the other group received 4 mg/kg of sugammadex. The group receiving neostigmine/atropine had to wait until two twitches (T2) were present with train of four monitoring before reversal. The group receiving sugammadex received the dose once they had a post-tetanic count of 1-2, meaning that they had zero twitches with train of four monitoring. The results showed that reversal time with the sugammadex group was significantly faster than with the neostigmine/atropine group (Ammar et al., 2017). The neostigmine/atropine group reached a train of four ratio > 0.9 at 12.6 minutes versus the sugammadex group which reached a train of four ratio of > 0.9, from a deeper block, at 2.5 minutes. Notably, some individuals in the neostigmine/atropine group required an additional dose due to recurarization. Ammar et al. (2017) went on to mention that pediatric patients with cardiovascular or respiratory issues should receive sugammadex instead of neostigmine/atropine because they may not tolerate the adverse effects associated with it.

Franz et al. (2018) conducted a study to compare the effects of sugammadex and neostigmine for reversal of rocuronium or vecuronium induced neuromuscular block in pediatric

patients under 2 years of age. The study found that sugammadex is able to be given sooner than neostigmine because it can be given if the patient has a deep neuromuscular block, while neostigmine requires the presence of at least two twitches (T2) using train of four monitoring.

Sugammadex has also been found to be associated with less incidence and lower severity of emergence agitation. Kim et al. (2018) conducted a study of children aged 1 to 13 years who received sugammadex after receiving rocuronium for strabismus surgery. The data shows that the group that received sugammadex had lower incidences of emergence agitation and lower severity of emergence agitation than the group receiving pyridostigmine (Kim et al., 2018).

Limitations of Sugammadex

Although the development of sugammadex is a breakthrough for the reversal of neuromuscular blockade, it does have some limitations. As previously mentioned, sugammadex encapsulates aminosteroidal nondepolarizing neuromuscular blocking agents. Therefore, it will not work on depolarizing neuromuscular blockers or benzylisoquinoline nondepolarizing neuromuscular blocking agents. It has also been found that sugammadex will also encapsulate other steroidal compounds, such as estrogen compounds, flucloxacillin, and some antifungal medications (Ledowski et al., 2014). Administration of an aminosteroidal nondepolarizing neuromuscular blocking agent after administration of sugammadex will not produce a neuromuscular block, as sugammadex will continue to function for hours after administration (Sugammadex, 2019). A waiting time of 24 hours is recommended before re-administration of rocuronium or vecuronium. Benzylisoquinoline nondepolarizing neuromuscular blocking agents may be used instead for neuromuscular blockade. Sugammadex is an expensive medication and may not be available for use in all hospital settings. Therefore, alternative neuromuscular blockade reversal agents must be available. Sugammadex is not recommended for individuals

with severe renal impairment or on dialysis as the sugammadex-rocuronium complex is excreted unchanged via the kidneys.

Sugammadex has been associated with hypersensitivity reactions and anaphylactic shock. Tadakoro et al. (2018) suggest that the gamma cyclodextrin structure of sugammadex may be responsible for the reactions. These structures are found in foods, dyes, and fat soluble vitamins and supplements. Another possibility is that the cyclodextrin structure may somehow alter the body's immune response. Takazawa et al. (2016) suspect the sugammadex-rocuronium complex may be to blame. The most frequent symptoms associated with sugammadex related anaphylaxis are hypotension, tachycardia, and skin rash (Iwasaki et al., 2017). Bradycardia and a prolonged QT interval have occurred with some individuals soon after administration of sugammadex (Sugammadex, 2019). If bradycardia is observed and is symptomatic, it should be treated immediately with anticholinergics. Rahe-Meyer et al. (2014) suggest that prolongation of the activated prothrombin time, prothrombin time, and international normalized ratio (INR) can occur after administration with sugammadex.

Discussion

Sugammadex and neostigmine/glycopyrrolate are the most common agents used for reversal of neuromuscular blockade induced by aminosteroidal nondepolarizing neuromuscular blocking agents in adults. However, sugammadex has not been approved by the FDA for use in the pediatric population in the United States. The other option for reversal in children would be administration of neostigmine and glycopyrrolate, although this combination can cause a myriad of adverse effects. Neostigmine is associated with more postoperative pulmonary complications than sugammadex, and one study suggested that it is directly associated with prolonged post anesthesia care unit stay. Furthermore, neostigmine and glycopyrrolate cannot be used to reverse

deep neuromuscular blockade. Several studies have shown that sugammadex reversed neuromuscular blockade significantly faster than neostigmine with less side effects, and it can also be used to reverse deep neuromuscular blockade. Sugammadex is associated with decreased anesthesia time, decreased recovery time, and decreased length of hospital stay, as well as less postoperative complications, such as nausea, emergence agitation, and recurarization. It has been suggested that pediatric patients with cardiovascular or respiratory issues should receive sugammadex instead of neostigmine/atropine because they may not tolerate the adverse effects associated with administration. Furthermore, sugammadex is so unique in its function it has been suggested that it should be included in enhanced recovery after surgery (ERAS) protocols (Young et al., 2016)**.** Sugammadex use in pediatric populations has been shown to be as equally safe and effective as in adult populations with minimal adverse effects.

Off-label use of medications is common in pediatrics. It can be considered acceptable if the benefits outweigh the risks, especially in a life-threatening situation. Fortunately, European guidelines exist for sugammadex use in children and they can be utilized, if such a situation were to arise. One such situation would be a 'cannot intubate, cannot ventilate' situation. If sugammadex were to become a standard of care in the United States for pediatric patients, the patient could receive a larger dose of rocuronium in an emergent situation instead of having to administer succinylcholine, as the resulting deep neuromuscular block could easily be reversed without adverse effects.

There are a few limitations in the research that require discussion. There is not much research that has been done on the subject in the United States, as it is difficult to obtain permission to perform research on children. Furthermore, the use of sugammadex in children has not been approved by the FDA. The FDA's concern is more than likely due to the rare

hypersensitivity and anaphylactic reactions that have occurred, along with episodes of bradycardia that have been reported in adults. Merck Sharp & Dohme Corp. (2018) did conduct several juvenile animal studies during preclinical trials. One of the studies compared bone deposition of sugammadex between juvenile and adult rats. Sugammadex deposition in juvenile rats was found to be 13% while deposition in adults was only 3% following a single IV dose of 30mg/kg. Another study dosed 7 day old rats daily with increasing doses of sugammadex for 28 days. The study showed that ulna and femur bone lengths were found to be 3% shorter in groups receiving 120 and 500 mg/kg daily (Merck Sharp & Dohme Corp., 2018). Tooth and enamel malformation, as well as discoloration, was also observed.

Most of the studies that have been published are European studies, and most of those have relatively small sample sizes. Several of the studies are retrospective observational studies. Furthermore, the studies are limited by the accuracy of data collection and the level of blinding and randomization. Lastly, some of the studies have an unclear risk of bias.

Conclusion

Sugammadex, a selective relaxant binding agent, employs a novel method of inactivating nondepolarizing neuromuscular blocking agents, which rapidly and efficiently reverses neuromuscular blockade in the pediatric population. Administration of sugammadex is safe at all ages, works significantly faster than neostigmine in reversing neuromuscular blockade, and has fewer adverse effects than neostigmine. Furthermore, it has the ability to reverse from a deep neuromuscular blockade, which neostigmine cannot do. It has been found to be equally as safe and effective in the pediatric population as in the adult population. Nonetheless, more research should be performed on the subject, particularly long-term studies, to gather more data to ensure its effectiveness and safety in the pediatric population.

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