ORIGINAL ARTICLE

Sugammadex and fast-track anesthesia for pediatric cardiac surgery in a developing country

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ABSTRACT

Objective: There are several physiologic advantages to early tracheal extubation and spontaneous ventilation following surgery for congenital heart disease (CHD). In order for early tracheal extubation to be feasible, effective reversal of neuromuscular blockade is mandatory. Sugammadex reverses neuromuscular blockade with a mechanism that differs from acetylcholinesterase inhibitors. We aimed to study the effect of sugammadex on the fast track extubation.

Methodology: We retrospectively reviewed our experience with the use of sugammadex to reverse neuromuscular blockade following cardiac surgery for CHD in infants and children, during a pediatric cardiac surgical trip of Heart Care International to Tuxtla, Mexico. Demographic data collected included age, weight, type of CHD, and the surgical procedure. Intraoperative data included sugammadex dose, outcome (successful tracheal extubation), and adverse effects, which could be attributed to sugammadex. Sugammadex was administered to 14 patients, who ranged in age from 1 to 16 years of age and in weight from 7.6 to 57.7 kilograms. Statistical analysis was done

Results: All 14 patients underwent successful tracheal extubation in the operating room within 15 min of completion of the surgical procedure. No patient required reintubation of the trachea during the postoperative course. No adverse effects related to sugammadex were noted.

Conclusions: Our preliminary experience demonstrates that sugammadex effectively reverses neuromuscular blockade and allows for early tracheal extubation in pediatric patients following surgery for repair of CHD. Prompt and effective reversal of neuromuscular blockade allows for effective fast-tracking with early tracheal extubation.

Key words: Neuromuscular blockade; Acetylcholinesterase inhibitors; Tracheal extubation; Cardiac surgery; Congenital heart disease; Sugammadex

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INTRODUCTION

There are numerous advantages of early tracheal extubation otherwise known as fast-tracking following surgery for congenital heart disease (CHD).[1-4] Early tracheal extubation not only eliminates the potential morbidity related to an endotracheal tube and mechanical ventilation such as atelectasis, accumulation of secretions, nosocomial infections, and the potential for airway

trauma, it also limits the need for sedation and the antecedent adverse effects including respiratory and hemodynamic depression, tolerance, withdrawal, and delirium. Most importantly, the shift from positive pressure to spontaneous ventilation augments cardiovascular function and improves preload especially in specific clinical scenarios such as the immediate period following surgery and cardiopulmonary bypass (CPB) as well as in single ventricle anatomy.[5-9]

In order for early tracheal extubation to be feasible, several perioperative factors must be ensured including effective control of postoperative bleeding as well as maintenance of hemodynamic and respiratory stability. During the intraoperative care of pediatric patients during surgery for repair of CHD, neuromuscular blocking agents (NMBAs) are administered to ensure immobility and provide muscle relaxation. Such blockade is generally maintained until after sternal closure. At that time, medications that inhibit acetylcholinesterase such as neostigmine are administered to reverse residual neuromuscular blockade and allow for spontaneous ventilation.[10,11] For the reversal of neuromuscular blockade to be feasible, residual neuromuscular function must be present. Furthermore, despite the use of appropriate doses of acetylcholinesterase inhibitors, residual neuromuscular blockade may be present in a significant number of patients during the postoperative period.[10,11] This residual neuromuscular blockade may impact not only respiratory function, but also upper airway patency thereby compromising postoperative ventilation. The effective reversal of neuromuscular blockade may be further compromised by hypothermia which may be present following CPB.[12,13]

Sugammadex (Bridion®, Merck & Co, Whithouse Stations, NJ) is a novel pharmacologic agent, which was approved for clinical use in December 2015 by the United States Food & Drug Administration (FDA). It reverses neuromuscular blockade with a mechanism that differs completely from acetylcholinesterase inhibitors.[14,15] It encapsulates rocuronium or vecuronium and can provide complete recovery even with profound neuromuscular blockade.[16-18] We report our preliminary experience with the use of sugammadex to reverse neuromuscular blockade following CPB and cardiac surgery for repair of CHD in infants and children. Its potential application in this unique clinical scenario is discussed and previous reports of its use in the pediatric population are reviewed.

METHODOLOGY

This retrospective review and data presentation were approved by Heart Care International (HCI, Greenwich, CT) and the Institutional Review Board of Nationwide Children's Hospital (Columbus, Ohio). The patients reported were cared for during a pediatric cardiac surgical trip of Heart Care International to Tuxtla, Mexico. The operating room, intraoperative anesthetic, and HCI records of patients undergoing cardiac surgery for CHD during the HCI September 2015 trip to Tuxtla, Mexico were retrospectively reviewed. Demographic data collected included age, weight, type of CHD, and the surgical procedure. Intraoperative data included sugammadex dose, outcome (successful tracheal extubation), and adverse effects, which could be attributed to sugammadex.

RESULTS

The study cohort included 15 patients; however, one patient had a prolonged surgical procedure on cardiopulmonary bypass (CPB) and did not meet criteria for immediate tracheal extubation. The remaining study cohort included 14 patients. Their demographic data are listed in Table 1. The surgical procedures are outlined in Table 2. Thirteen of the procedures were performed via sternotomy using CPB while the PDA was ligated via thoracotomy without the need for CPB.

Table 1: Demographic data of the study cohort

Variable	Data
Number	14
Age	17 months to 16 years (5.4 ± 4.5 years)*
Weight (kg)	7.6 to 57.7 (17.1 ± 12.9)*
Gender (M:F)	5:9

*Data given Range (Mean ± Standard Devition)

Table 2: Type of cardiac surgical procedures

Procedure	Number
Closure of atrial septal defect (ASD)	5
Tetralogy of Fallot repair	3
Closure of a ventricular septal defect (VSD)	2
Closure of an ASD and VSD	2
Repair of atrioventricular canal defect	1
Ligation of a patent ductus arteriosus	1

Anesthetic care was tailored to promote fast track anesthesia and rapid tracheal extubation in the operating room at the conclusion of the surgical

procedure. This included intravenous induction (ketamine or propofol) or inhalation induction with sevoflurane. Neuromuscular blockade was provided by intermittent doses of rocuronium. Maintenance anesthesia included fentanyl (10-15 μg/kg) and sevoflurane. Following anesthetic induction and endotracheal intubation, arterial and central venous access was obtained.

Following sternal closure, as the subcutaneous tissues were opposed, sugammadex (2-4 mg/kg) was administered and spontaneous ventilation allowed. Within 60-120 seconds following the administration of sugammadex, all patients resumed spontaneous ventilation. Morphine was titrated based on respiratory rate to provide postoperative analgesia and dexmedetomidine administered to prevent emergence delirium. All 14 patients underwent successful tracheal extubation in the operating room within 15 min of completion of the surgical procedure. No patient required reintubation of the trachea during the postoperative course. No adverse effects related to the administration of sugammadex were noted.

DISCUSSION

Sugammadex is a novel pharmacologic agent that represents the first non-competitive antagonist for the reversal of neuromuscular blockade. Given its unique chemical structure, it forms a one-to-one complex with rocuronium, encapsulating the drug in the plasma and thereby reducing its effective concentration at the neuromuscular junction.[17-19] This pharmacology results in the rapid termination of neuromuscular blockade even when administered immediately following rocuronium. Dosing recommendations are based on the degree of residual neuromuscular blockade with doses of 2 mg/kg recommended for patients with 1-2 twitches of the train-of-four (TOF) and 4 mg/kg recommended for patients with only post-tetanic twitches. Doses of 16 mg/kg are recommended for the rapid termination of neuromuscular blockade immediately following large doses of rocuronium which have been administered for endotracheal intubation.[20]

The potential utility of sugammadex in reversing neuromuscular blockade was demonstrated in a prospective trial of 110 adult patients, who were randomized to receive either rocuronium or succinylcholine for endotracheal intubation.[21] Anesthesia was induced and maintained with propofol and an opioid followed by rocuronium (1.2 mg/kg) or succinylcholine (1 mg/kg). Sugammadex (16 mg/kg) was administered 3 min after rocuronium administration. Neuromuscular function was monitored by acceleromyography. Mean times to recovery of (T1) to 10% and 90% of baseline were significantly faster in the rocuronium-sugammadex group than the succinylcholine group. The time from sugammadex administration to recovery of T1 to 10%, recovery of T1 to 90%, and recovery of the TOF ratio to 0.9 was 1.2, 2.9, and 2.2 min. Recurrence of neuromuscular blockade was not noted and there were no serious adverse events. The evidence from these clinical trials is supported by preliminary anecdotal experiences in clinical care demonstrating effective reversal of neuromuscular blockade following failed rapid sequence intubation with rocuronium.[22]

To date, sugammadex has not received FDA approval for use in children and there are limited data regarding its use in the pediatric population. However, its use has already been reported in a "cannot intubate-cannot ventilate" scenario immediately following the administration of vecuronium to a 10-month-old infant when endotracheal intubation failed and bag-valve-mask ventilation was problematic.[23] Its anecdotal use has also been reported for effective reversal of neuromuscular blockade in difficult clinical scenarios such as children with neuromuscular diseases including myasthenia gravis, Duchenne muscular dystrophy, other myopathic conditions, and renal failure.[24-27] Additional anecdotal experience suggests its use in scenarios where reversal of neuromuscular blockade with acetylcholinesterase inhibitors may be relatively contraindicated including myotonic dystrophy and Angelman syndrome.[28,29]

In our cohort of patients, we noted effective reversal of neuromuscular blockade in 14 pediatric patients following surgery for CHD. Recovery of neuromuscular function was adequate, allowing for effective ventilation and eventual tracheal extubation in the operating room immediately following the surgical procedure. In many cases, reversal was attempted with significant blockade present as a dose of rocuronium (0.3-0.5 mg/kg) had been administered to provide neuromuscular blockade to facilitate sternal closure. Reversal was effective despite mild hypothermia (35-36 °C) as a result of cooling during CPB. With the return of spontaneous ventilation, there was an improvement in hemodynamic variables especially in patients with thickened ventricles and diastolic

dysfunction.

Despite its routine use in the operating room, the primary clinical concern with neostigmine is the potential for residual neuromuscular blockade which has been shown to increase the incidence of critical postoperative respiratory events in adults.[30-32] Although the incidence is lower in children, residual neuromuscular blockade was noted in 28.1% of pediatric patients with severe residual blockade (TOF ratio ≤ 0.7) being present in 6.5%.[33] In two pediatric trials comparing neostigmine with sugammadex, reversal of neuromuscular blockade was faster and more complete with sugammadex.[33,34] Neostigmine may also impact postoperative respiratory function as it impairs upper airway dilator muscle activity, an effect not seen with sugammadex.[35]

Reversal of either vecuronium or rocuronium has been reported. Dosing is based on the TOF response with 2 mg/kg used when there are ≥ 2 twitches of the TOF and 4 mg/kg if there are 1-2 post-tetanic twitches. The maximum dose of 16 mg/kg is recommended for reversal immediately following an intubating dose of rocuronium (1.2 mg/kg). While costs vary significantly from region to region, our current acquisition costs (March 2016) when using sugammadex are relatively equivalent to the combination of neostigmine and glycopyrrolate.

The reported adverse effects with sugammadex have generally been minor and self-limited including nausea, vomiting, pain, hypotension, and headache. Severe adverse effects during pre-clinical trial included bradycardia, anaphylaxis and anaphylactoid reactions. The latter occurring within 5 min of its administration. Cases of marked bradycardia, some of which have resulted in cardiac arrest, have been observed within minutes after administration. Administration of an anticholinergic agent such as atropine or an inotropic agent such as epinephrine is recommended if clinically significant bradycardia is observed. While no clinically significant bleeding complications were noted, mild prolongation of the prothrombin time (PT) and partial thromboplastin time (PTT), lasting for 60 min, were noted in patients receiving large doses of sugammadex (16 mg/kg).[37] Should reinstitution of neuromuscular blockade be required following reversal with sugammadex, a non-steroidal neuromuscular blocking agent (cis-atracurium) should be used.[38]

CONCLUSION

In summary, our preliminary data regarding the use of sugammadex to reverse neuromuscular blockade in a cohort of pediatric patients undergoing surgery for CHD shows that prompt and effective reversal of neuromuscular blockade allows for effective fast-tracking with early tracheal extubation, which may be particularly beneficial when there are concerns regarding the hemodynamic effects of positive pressure ventilation. Reversal with sugammadex offers the advantage of a decreased incidence of residual neuromuscular blockade and may be advantageous in clinical situations where reversal of neuromuscular blockade is problematic including patients with intense residual blockade, in the presence of hypothermia, and in those with myopathic conditions which increases the sensitivity to NMBAs. As noted above, it may also be indicated when the use of neostigmine is contraindicated.

Conflict of interest: Nil declared by the authors

Author contribution: All authors took part in study design and conduction, review and finalization of the manuscript; JDT: First draft preparation; JDT, DM, JC, RM: Provided clinical acre to patients, conduction of the study work, study design and conduction, review and finalization of manuscript; JU: Study design and conduction, review and finalization of manuscript

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