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Research article

Recovery from rocuronium with sugammadex in children premedicated with dexamethasone for prevention of postoperative nausea and vomiting

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ABSTRACT

Sugammadex is a cyclodextrin specifically designed to reverse the action of rocuronium through encapsulation. Theoretically, it is possible that sugammadex can encapsulate cortisone. The primary outcome of the present study is to investigate any possible alteration in the efficacy of sugammadex as a reversal of rocuronium due to dexamethasone injection in children undergoing strabismus surgery. The secondary outcome is to assess any possible side effects of sugammadex in these groups of patients.

Methods: Patients were randomly divided by a closed envelope method into 2 groups 40 patients each. All children were subjected to standard controlled general anesthesia with ETT. Intravenous (IV) dexamethasone 0.5 mg·kg^{-1} after induction of GA was given in group I (dex group), while IV metoclopramide 0.25 mg·kg^{-1} was given for group II (met group) as prophylactic antiemetics.

Measurements: Duration after sugammadex injection to reach 90% TOF ratio was measured by TOF watch SX acceleromyography. Clinical duration of extubation after sugammadex injection was measured. Any signs of residual curarization, respiratory insufficiency or muscle weakness were recorded in the PACU for two hours postoperatively.

Results: Time to reach 90% TOF was statistically significantly higher in the dex group (60.11 ± 1.98 s) than the met group (23.11 ± 2.36 s) with a P value of 0.001. Clinical time of extubation after sugammadex was higher in the dex group (72.8 ± 2.23 s) than the met group (37.61 ± 2.45 s) with a P value of 0.0001.

Conclusions: The present study demonstrated that the interaction between sugammadex and dexamethasone may have a clinical effect on the duration of reversal of rocuronium.

1. Introduction

Sugammadex is the first introduction of a new class of drugs called selective relaxing binding agents that encapsulate aminosteroid non depolarizing muscle relaxants terminating their effects [1]. Sugammadex is a cyclodextrin specifically designed to encapsulate rocuronium. cyclodextrin is not deep enough to accommodate the large structure of the aminosteroid agents, so it is modified by the addition of eight side-chains to extend the cavity, allowing the hydrophobic steroidal rings of the aminosteroid agents to be accommodated [2]. Evidence advocates that sugammadex-rocuronium complexes remain stable over time and are pH- and temperature-independent. Therefore, drug interactions with other molecules seem to be rare. However, a potential change in efficacy could not be excluded for certain drugs, Theoretically, it is possible that sugammadex can encapsulate cortisone, atropine and verapamil [3]. Pediatric strabismus surgery is associated with frequent early and late postoperative nausea and vomiting (PONV). Prophylactic dexamethasone in doses of 0.15–0.5 mg·kg^{-1} has been found to be an effective antiemetic drug for children undergoing tonsillectomy and strabismus surgery [4]. The primary outcome of the present study is to investigate any possible alteration in the efficacy of sugammadex as a reversal of rocuronium due to dexamethasone injection in children undergoing strabismus surgery. The secondary outcome is to assess the safety of sugammadex in these groups of patients through close monitoring of the patients in the operating room and the Post Anesthesia Care Unit (PACU) as well for 2 h.

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2. Patients and methods

This randomized controlled study was carried out in Alexandria Main University Hospitals on 80 ASA I and II patients aged 1–6 years scheduled for strabismus surgery under general anesthesia after taking a written informed consent from their parents and approval of the local ethical committee. All procedures were performed by the same surgeon. Patients were randomly divided by a closed envelope method into 2 groups; 40 patients each. Patients were excluded from this study if they had known difficult airway, had any neuromuscular, cardiac, hepatic, renal or metabolic disorder. Patients were also excluded if they are on chronic steroidal or non-steroidal therapy. Complete history has been taken from the parents including emphasis on patient fasting as recommended by the 'American Society of Anesthesiologists' and all patients were subjected to thorough clinical examination. Children were sedated with intramuscular midazolam 0.1 $mg{\cdot}kg^{-1}$ 30 min before the procedure and an intravenous access was obtained. Anesthesia was induced after preoxygenation for two minutes with 100% oxygen. Induction was done with fentanyl 1 $\mu g{\cdot}kg^{-1}$, propofol 3 $mg{\cdot}kg^{-1}$ and rocuronium 0.6 $mg{\cdot}kg^{-1}$. Patients were intubated after loss of 3 twitches of TOF (train of four) via a peripheral nerve stimulator TOF watch SX acceleromyography. Anesthesia was maintained with sevoflurane 3%. Intravenous (IV) dexamethasone 0.5 $mg{\cdot}kg^{-1}$ after induction of GA was given in group I (dex group), while IV metoclopramide 0.25 $mg{\cdot}kg^{-1}$ was given for group II (met group) as prophylactic antiemetics. Standard anesthesia monitoring (non-invasive arterial blood pressure, electrocardiogram, pulse oximeter and end tidal capnography) were attached for all patients using multichannel monitor (Draeger Medical Systems, Inc. Telford, USA). All patients received lactated ringer solution according to the 4/2/1 rule.

Neuromuscular monitoring was carried out according to the international consensus guidelines using TOF watch SX acceleromyography at adductor pollicis muscle [5]. The surface skin electrodes were placed over the ulnar nerve at the wrist of the contralateral arm to the non-invasive blood pressure cuff. The peripheral nerve stimulator was switched to TOF mode (0.2 ms duration, 2 Hz frequency) every 15 s. The number of thumb twitches elicited indicates the degree of receptor occupancy and the level of neuromuscular block. The desired level of block is usually one twitch. Intraoperative rocuronium were given on the basis of TOF. At the end of surgery, sugammadex in a dose of 2 $mg{\cdot}kg^{-1}$ for the reversal of blockade induced by rocuronium was given for patients of both groups. Extubation after assessment of TOF response (TOF > 0.9) was done in the left lateral head down position. Standard pediatric extubation criteria were used to determine the suitability of immediate extubation and patients were transferred to the post anesthesia care unit (PACU). Postoperative analgesia consisted of paracetamol 15 $mg{\cdot}kg^{-1}$ every 6 h.

2.1. Measurements

- Duration after sugammadex injection measured by TOF watch SX acceleromyography to reach 90% TOF ratio
- Clinical duration of extubation after sugammadex injection
- Any signs of residual curarization, respiratory insufficiency or muscle weakness were recorded in the PACU for two hours postoperatively.

2.2. Sample size calculation

A minimum of 40 patients for each group was required to achieve a power of the study of 90% in order to detect a difference of 20% between the null hypotheses of both groups. It was calculated by using Med Calc statistical software assuming an area under ROC to be 0.80, an alpha of 0.05 and the power of the study to be 90.0%.

2.3. Statistical analysis

Data was analyzed by using SPSS® software (Statistical package for social science for personal computers) using (t and chi-square X^2 testes), data was expressed as mean ± SD and $P \leqslant 0.05$ was considered significant.

3. Results

A total of 98 patients were screened for eligibility for the study; 92 patients met inclusion criteria and were approached to participate in the study, and 12 parents refused to engage their children in the study (Fig. 1). There were no statistically significant differences between the two studied groups as regards demographic data (age, gender and weight) (Table 1). There were no statistically significant differences between the two studied groups regarding the duration of surgery (Table 2).

Regarding the recovery time of patients from the muscle relaxant effects of rocuronium by sugammadex, the time to reach 90% TOF was statistically significantly higher in the dex group (60.11 ± 1.98 s) than the met group (23.11 ± 2.36 s) with a P value of 0.001. Clinical time of extubation after giving sugammadex was higher in the dex group (72.8 ± 2.23 s) than the met group (37.61 ± 2.45 s) with a P value of 0.0001 (Fig. 2, Table 3). Potential haemodynamic side effects such as bradycardia, tachycardia, hypotension or hypertension were not observed in both groups. No complications related to muscle relaxation were recorded during the two hours' postoperative duration in the PACU.

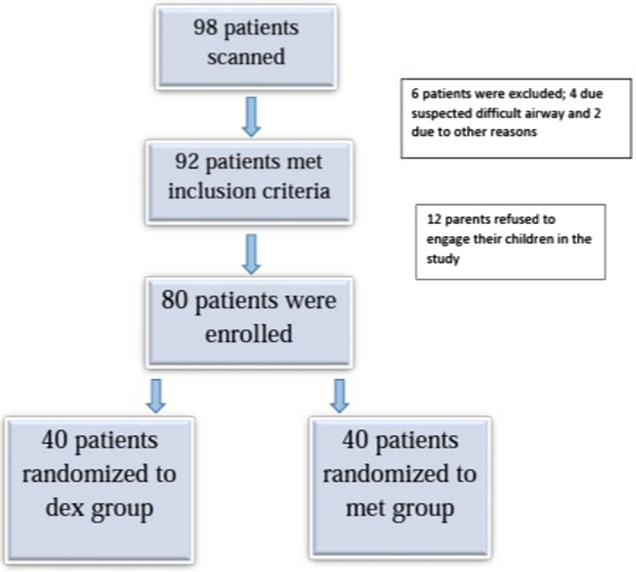

Figure 1. Flow diagram.

Table 1
Demographic data of the two studied groups.

	Dex		Met		P
Age (years)					
Range	1.08–5.08		1.75–6.08		0.0682
Mean ± S.D.	2.85 ± 1.14		3.40 ± 1.21		
Gender					
Male	19	47.5%	22	55.0%	0.365
Female	21	52.5%	18	45.0%	
Weight (kg)					
Range	10.0–19.0		11.0–22.0		0.0741
Mean ± S.D.	14.0 ± 2.31		15.0 ± 2.52		

P is significant if ⩽0.05.

Table 2
Duration of surgery in both groups.

Duration of surgery (min)	Dex	Met
Range	25.0–35.0	24.0–30.0
Mean ± S.D.	28.18 ± 2.2	27.50 ± 1.77
P	0.0688	

P is significant if ⩽0.05.

4. Discussion

The present study demonstrated that dexamethasone given intravenously after induction of general anesthesia in a dose of 0.5 mg·kg^{-1} in children aged 1–6 years delayed the reversal effect of sugammadex to rocuronium. Children in the present study received a single dose of dexamethasone after induction of general anesthesia in strabismus surgery for prophylaxis against postoperative nausea and vomiting. It is well known that sugammadex (Bridion; MSD), is a modified cyclodextrin that exerts its action as a neuromuscular block reversal agent through encapsulation of the steroidal neuromuscular blocking agent molecules thereby preventing their action at the neuromuscular junction [6]. After injection of sugammadex, it immediately encapsulates the free intravascular rocuronium which results in a concentration gradient shifting rocuronium from the peripheral compartment, so a higher sugammadex dose leads to a more rapid and effective reversal of sugammadex [7]. Due to the structural similarity between aminosteroid muscle relaxants and dexamethasone, concerns have been raised about possible corticosteroid influences in the reversal of neuromuscular block by sugammadex [8]. Cyclodextrins have long been used as complexes with lipophilic drugs especially steroids like dexamethasone to increase their water solubility [9]. So, theoretically, corticosteroids might interfere with the neuromuscular blocking reversal action of sugammadex. The early report by Zhang [10] documented that sugammadex affinity to rocuronium is very much higher than that to corticosteroids, however different doses of the drugs have not been well identified as well as the duration of exposure. Additionally, Zwiers et al. [11] in their study on different models of drug interactions with sugammadex, concluded that only 3 drugs can displace sugammadex from its site of action with rocuronium which are toremifene, fusidic acid, and flucloxacilline. Karalapillai et al. [12] mentioned in their review about the uses of sugammadex in the intensive care that theoretically it can bind drugs other than the aminosteroid neuromuscular blockers like cortisone and atropine although the affinity of sugammadex to such drugs is low relative to rocuronium and vecuronium. However, the routine use of dexamethasone in our institution for prophylaxis against postoperative nausea and vomiting in strabismus surgery in pediatrics has raised our attention that children with strabismus recover from anesthesia after a longer duration from those who undergo other pediatric procedures. Concomitantly, Rozenja et al. [13] in a recent report on in vitro experiments of human muscle cells and embryonic fat spinal cord found that dexamethasone in a high clinical concentration has prolonged the reversal effect of sugammadex to rocuronium in a dose dependent manner. They documented that dexamethasone in a high dose can diminish the efficiency of sugammadex and even higher doses of sugammadex can't lead to complete reversal of rocuronium due to the low displacement potential of dexamethasone. On the contrary, Gulec et al. [14] found that IV dexamethasone, given after induction of anesthesia, at a dose of

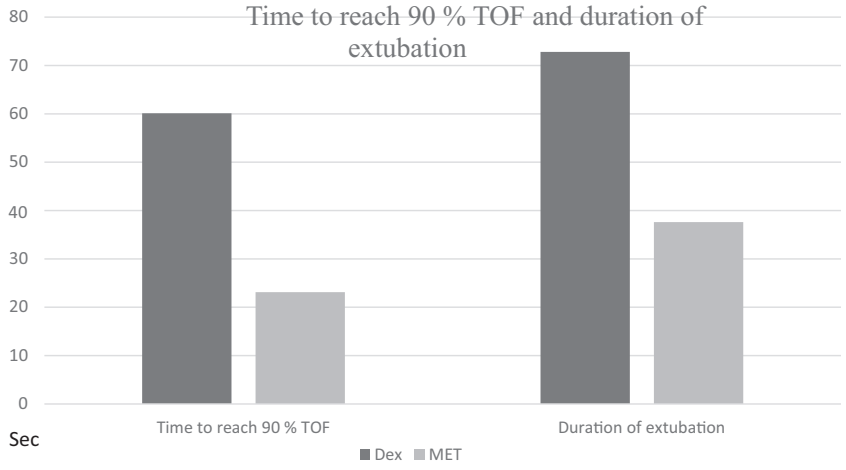

Figure 2. Time to reach 90% TOF and duration of extubation.

Table 3
Duration to reach 90% Train of four and clinical duration.

	Time to reach 90% TOF (s)		Clinical duration (s)	
	Dex	Met	Dex	Met
Range	55.0–62.0	18.0–29.0	66.0–76.0	32.0–43.0
Mean ± SD	60.11 ± 1.98	23.11 ± 2.36	72.8 ± 2.23	37.61 ± 2.45
P	0.001*		0.0001*	

P is significant if ⩽0.05.

0.5 mg·kg^{-1}, did not substantively affect the reversal time of sugammadex in pediatric patients undergoing adenoidectomy and/or tonsillectomy.

Finally, we can conclude from the present study that the interaction between sugammadex and dexamethasone may prolong the duration of reversal of rocuronium after general anesthesia in children aged 1–6 years. Yet, there are some limitations in the present study; a single dose of dexamethasone and a single dose of sugammadex were used and the plasma level at the time of sugammadex injection was not measured. The effect of chronic steroid therapy on sugammadex reversal of rocuronium still can't be judged from the present study.

Conflict of interest

None declared by the authors.

Funds

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