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Effects of Dexmedetomidine on Neuromuscular Blockade: A Pediatric Case Series and Concise Review of Literature

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Abstract

Dexmedetomidine is a potent, highly selective a2-adrenoceptor agonist which has gained great popularity in the anesthesia practice during the last decades. Although its indications and clinical applications have been expanded due to its unique sedative response and safe cardiovascular and respiratory profile, its interaction with non-depolarizing neuromuscular blocking agents has not been extensively studied and results are conflicting. In this article we aimed to present a review of the existing literature investigating the effects of dexmedetomidine on neuromuscular blockade. We also present a case series of 20 pediatric patients undergoing general anesthesia in whom infusion of dexmedetomidine 0.5 mcg/kg ten minutes before the induction of anesthesia was found to significantly reduce the onset time of rocuronium-induced blockade. More studies are needed to further prove this effect.

Keywords: Dexmedetomidine; Neuromuscular blockade; Rocuronium; Onset time; General anesthesia

Introduction

Dexmedetomidine (dex) is a highly selective and potent a_2-adrenoceptor agonist. Dex has sedative, anxiolytic, analgesic, sympatholytic and opioid-sparing properties. It has gained widespread popularity in the Intensive Care Unit (ICU) as well as in the anesthesia setting. Dex induces a sedative response that mimics natural sleep. This "arousable sedation" allows patients to be cooperative and communicative when stimulated. Also, dex offers an option to provide sedation and analgesia with limited cardiac and more importantly respiratory impact. In the last decades, these favorable properties expanded its clinical applications in the anesthetic clinical practice. Dex is also used as an adjuvant to general and regional anesthesia. It has been shown that dex exhibits a dose sparing effect on propofol and inhalation agents' consumption [1]. However, dex effect on non-depolarizing Neuromuscular Blocking Agents (ndNMBAs) action is questionable, since the existing findings are limited and conflicting. Possible mechanisms of its action include inhibition of Acetylcholine (Ach) release from presynaptic membrane in the Central Nervous System (CNS) [2,3], inhibition of epinephrine/norepinephrine release [3], the pharmacokinetics changes induced by dex [2-8], blockade of postjunctional nicotinic Ach receptors [9] and a different CNS site of action [10]. Therefore, we decided to investigate the possible effect of dex on the onset of rocuronium-induced neuromuscular blockade of a pilot sample of pediatric patients undergoing general anesthesia.

Case Description

Background

This case series is part of a prospective comparative, randomized clinical study and serves as a pilot sample. In our tertiary University hospital from May to October 2019, pediatric patients undergoing elective surgery under general anesthesia were enrolled in this sample, after parents' written informed consent was obtained.

Inclusion criteria were: Preschool and school aged children, American Society of Anesthesiologists (ASA) status I-II, general anesthesia, and elective surgery.

Exclusion criteria were: History of hepatic, renal, cardiac, pulmonary or neuromuscular disease, predictable difficult airway, obesity (>95th percentile for age and sex), recent upper or lower respiratory infection, allergy to a_2-agonist and refusal of the parents or child to participate in the study.

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Methods

Sample consisted of 20 pediatric patients, divided into two equally sized groups of 10 patients each (Figure 1). In Dex group (group D) patients received dex IV bolus dose 0.5 mcg/kg 10 min before the induction of anesthesia. In Control group (group C) patients received Normal Saline (N/S) in a similar way. Dex solution was prepared by adding 1 ml of dex (200 mcg/ml) in 49 ml of 0.9% NaCl. Both solutions were prepared by the anesthesia nurse, while the anesthesiologist was blinded to the solution used. No premedication was administered in either group.

At arrival to the operating room, a hand vein was cannulated with a 22/24 G catheter and standard monitoring was applied including Electrocardiogram (ECG), Non-Invasive arterial Blood Pressure (NIBP) and arterial Oxygen Saturation (SpO_2). Depth of anesthesia and neuromuscular blockade were monitored with BIS (No1 Covidien, BIS VIEWTM) and TOF-Watch SX acceleromyography (Organon, Ireland) via surface electrodes applied to the ulnar nerve, respectively. After baseline measurements, infusion of dex or N/S started for 10 min. NIBP, HR, SpO_2, and BIS values were recorded every 3 min until the end of dex infusion. Then, general anesthesia was induced with propofol 3 mg/kg and fentanyl 2 mcg/kg. When BIS value was <60, rocuronium 0.7 mg/kg was administered and neuromuscular blockade was monitored using Train of Four (TOF) pattern (50 mA, 0.2 ms at 2 Hz every 15 sec). Meanwhile, the patient was ventilated with O_2 100%. When TOF value reached 0, the trachea was intubated. T0 (time between the injection of rocuronium and the disappearance of all four twitches) was recorded and defined as the onset time.

Statistical analysis was performed using the student's t-test and the Fisher's exact test accordingly. Statistical significance was established at 5% (p<0.05).

Results

Patients' characteristics are presented in Table 1. Most patients were males (70.0% for group D and 55.6% for group C). Mean age was 8.8 years (SD=1.6 years) for group D and 8.9 years (SD=1.7 years) for group C. Almost all patients were ASA I. Mean T0 was 183.1 (SD=38.6) for group D and 229.4 (SD=57.1) for group C and was found to be significantly lower in the group D as compared to group C (Table 1).

Discussion

We searched PubMed, Medline, Embase and Google Scholar regarding the effects of dex on neuromuscular blockade. To our knowledge, our study is the first to investigate the effect of dex on neuromuscular blockade in a pediatric population sample. The existing relevant studies have been carried out in adults, are limited and with contradictory findings (Table 2). In particular T0 was investigated in five studies [2,3,6-8], two of which [6,8] found that dex decreased the onset time of rocuronium and are in accordance with our results. The first one from Yildirim et al. [6], included 75 patients and studied the impact of two different doses of dex (0.5 mcg/kg and 1 mcg/kg) on T0 of rocuronium. They found that both doses of dex shortens T0 [6]. The second one from Aliyeva et al. [8], included 60 patients and they also investigated the effect of dex 0.5 mcg/kg and 1 mcg/kg on T0 of rocuronium. They concluded that only dex 1 mcg/kg reduces T0 [8]. The other three studies [2,3,7], which found no significant difference, examined the impact of similar doses of dex (0.5 mcg/kg or 1 mcg/kg) on neuromuscular blockade induced by various ndNMBAs (rocuronium [2], vecuronium [3] and cisatracurium [7]). Ozcan et al. [3] comments that although dex 1 mcg/kg shortened the T0 of vecuronium by approximately 25 s, it was not statistically significant but could be considerable clinically.

The effect of dex on the duration of ndNMBAs blockade has also been investigated using various parameters: T25 [2,3,5,6,8], T50 [6,8], T75 [6,8], T90 [5], RI [5-8], T4/T1 ratio [4], T1 to recover to 10% of control [7], T1 single twitch depression [4,9,10], and concentration-twitch tension curve [9]. Particularly, all studies except one [8] found that T25, T50, T75, T90 were longer in the dex group. In four studies enhancement of the block measured by T25, T50, T75 and T90, was reported after administration of dex 1 mcg/kg preoperatively with

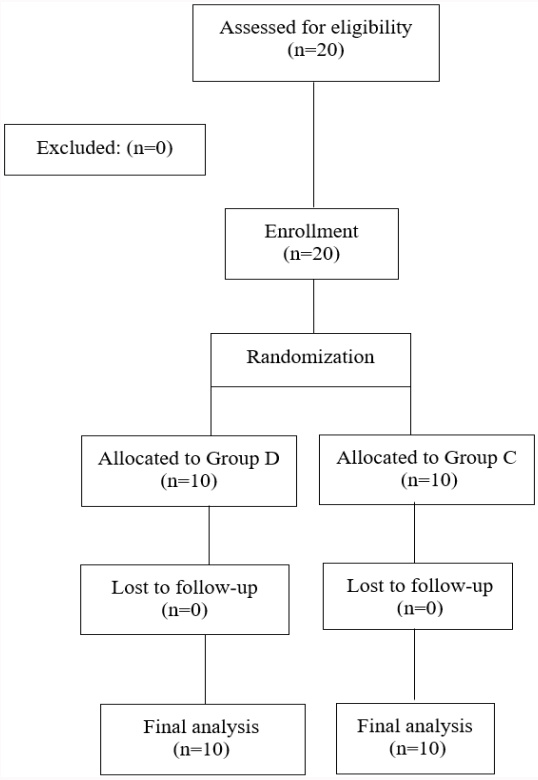

Figure 1: Flow diagram of subjects.

Table 1: Sample characteristics by group.

	Group D (n=10) N (%)	Group C (n=10) N (%)	P
Gender			
Females	3 (30.0)	4 (44.4)	0.650++
Males	7 (70.0)	6 (55.6)	
Age (years)	8.8 (1.6)	8.9 (1.7)	0.842+
BMI (Kg/m²)	17.5 (3.8)	18 (2.9)	0.756+
ASA			
I	10 (100)	9 (90)	>0.999++
II	0 (0)	1 (10)	
T0	183.1 (38.6)	229.4 (57.1)	**0.048**+

Results are presented as mean ± standard deviation (SD); + Student's t-test; ++ Fisher's exact test

BMI: Body Mass Index, ASA: American Society of Anesthesiologists, T0: Time from rocuronium infusion to TOF=0

Table 2: Studies investigating the effect of dexmedetomidine on neuromuscular blockade.

NR	Author/year	Type of study	Protocol / Research question	Sample size / Groups	Results
[2]	Jiaqi Shan et al. 2021	Randomized, multicenter, parallel-group, safety-assessor-blinded, active-controlled	neuromuscular blockade: roc 0.6 mg/kg TOF monitoring Impact of two different doses of dex on T0 and T25	3 groups, 75 patients 10 min before induction of GA received: Group D1 (*n*=25): dex 0.5 mcg/kg Group D2 (*n*=25): dex 1.0 mcg/kg Group C (*n*=25): N/S	T0: NS among the three groups T25: longer in group D2 (62.76 ± 6.33) compared to group D1(42.64 ± 3.92) and group C (42.56 ± 4.04) (p<0.05)
[3]	Ozcan et al. 2011	Prospective, randomized, placebo-controlled	GA, induction: thiopental sodium maintenance: sevoflurane in O_2/N_2O neuromuscular blockade: vec 0.1 mg/kg TOF monitoring Comparison of the effect of dex, fentanyl and remifentanil on T0 and T25	3 groups, 84 patients 10 min before induction of GA received: Group D (*n*=29): dex 1 mcg/kg + 0.5-1 mcg/kg/h during surgery Group F (*n*=30): fentanyl 1.5 mcg/kg + 50 mcg boluses during surgery Group R (*n*=25) remifentanil 1 mcg/kg + 0.05-0.15 mcg/kg/min during surgery	T0: NS among the three groups. T25: longer in group D (68 ± 19) compared to group F (54 ± 13) and group R (57 ± 10) (p<0.05)
[4]	Talke et al. 1999	Prospective clinical study	GA, induction: propofol, alfentanil maintenance: propofol, alfentanil in O_2/N_2O neuromuscular blockade: ~30 min after induction and intubation roc 0.2 mg/kg + 0.2 mg/kg/h TOF monitoring Impact of dex on T1 twitch depression and on T4/T1 ratio	1 group, 10 volunteers 55 ± 10 min after roc infusion and T1 response within the range of 50% ± 3% of pre-roc value received dex: Dex target plasma concentration: 0.6 ng/ml	T1 twitch depression decreased significantly 30min after dex infusion, from 51% ± 2% to 44% ± 9% (p<0.0001) T4/T1: NS during dex infusion roc plasma concentration higher 45 min after dex infusion (p<0.05)
[5]	Memis et al. 2008	Prospective, randomized, placebo-controlled	GA, induction: propofol, alfentanil maintenance: sevoflurane in O_2/N_2O neuromuscular blockade: roc 0.6 mg/kg after intubation + 0.15 mg/kg to maintain T1 within 10% of control TOF monitoring Impact of dex on T25, T90, RI and on total roc dose requirement	2 groups, 40 patients After intubation received: Group D (*n*=20): dex 1 mcg/kg + 0.2 mcg/kg/h during surgery Group C (*n*=20): N/S	T25, T90: longer in group D compared to group C (54 ± 13 *vs.* 35 ± 6.7 and 86 ± 29.2 *vs.* 58 ± 15.3 respectively) (p<0.05) RI: NS among the two groups. Roc dose requirement: significantly lower in group D compared to Group C (p<0.05)
[6]	Yildirim et al. 2019	Prospective, randomized, placebo-controlled, double-blinded	GA, induction: propofol, fentanyl maintenance: sevoflurane in O_2/N_2O neuromuscular blockade: roc 0.6 mg/kg TOF monitoring Impact of two different doses of dex on 90% block time, T0, T25, T50, T75, RI and on total roc dose requirement	3 groups, 75 patients 10 min before induction of GA received: Group D0.5 (*n*=25): dex 0.5mcg/kg Group D1 (*n*=25): dex 1 mcg/kg Group C (*n*=25): N/S	90% block time, T0: shorter in group D0.5 and D1 compared to group C (77.8 ± 19.3 and 83.88 ± 33.9 *vs.* 108.7 ± 35.8 and 81.4 ± 19.2 and 88.64 ± 35.0 *vs.* 113.32 ± 35.9 respectively) (p<0.01) T25, T50, T75, RI: longer in group D1 compared to group C (60.12 ± 12.0, 75.16 ± 15.8, 91.7 ± 21.7 and 30.7 ± 14.7 *vs.* 49.84 ± 16.6, 49.84 ± 16.6, 66.3 ± 19.8 and 16.9 ± 8.9 respectively) (p<0.05) T75, RI: longer in group D0.5 compared to group C (83.5 ±23.9 and 26.7 ± 14.6 vs 66.3 ± 19.8 and 16.9 ± 8.9 respectively) (p<0.01) Roc dose requirement: NS among the three groups (p>0.05)

[7]	Liu et al. 2016	Prospective, randomized, placebo-controlled	GA, induction: propofol, fentanyl, midazolam maintenance: propofol, remifentanil neuromuscular blockade: Cisatracurium 0.15 mg/kg TOF monitoring Impact of dex on: T0, TOF no reaction, T1 to recover to 10% of control, RI and total cisatracurium dose requirement in the elderly (E) and the young/middle-aged (Y) population	4 groups, 80 patients 10 min before induction of GA received: Group DE (*n*=20): dex 0.5 mcg/kg + 0.4 mcg/kg/h during surgery Group CE (*n*=20): N/S Group DY (*n*=20): dex 0.5mcg/kg + 0.4 mcg/kg/h during surgery Group CY (*n*=20): N/S	T0: NS among the four groups TOF no reaction: longer DE and DY compared with CE and CY (43.8 ± 8.5 *vs.* 37.4 ± 6.3 and 39.3 ± 7.6 *vs.* 34.7 ± 5.5 respectively) (p<0.05) T1 to recover to 10% of control: longer in group DE and DY compared to CE and CY (61.1 ± 8.9 *vs.* 49.9 ± 5.8 and 53.6 ± 9.3 *vs.* 44.8 ± 6.4 respectively) (p<0.01) RI: NS among the four groups Cisatracurium dose requirement: lower in group DE and DY than in group CE and CY (p<0.05)
[8]	Aliyeva et al. 2009	Prospective, randomized, placebo-controlled	GA, induction: propofol, fentanyl maintenance: desflurane in O_2/N_2O neuromuscular blockade: roc 0.6mg/kg TOF monitoring Impact of two different doses of dex on T0, T25, T50, T75, RI and on total roc dose requirement	3 groups, 60 patients 10 min before induction of GA received: Group A (*n*=20): dex 1 mcg/kg + 0.5 mcg/kg/h during surgery Group B (*n*=20): dex 0.5 mcg/kg + 0.25 mcg/kg/h during surgery Group C (*n*=20): N/S	T0: shorter in group A (1.13 ± 0.23) compared to group B (1.24 ± 0.22) and group C (1.50 ± 0.36) (p < 0.05) T25, T50, T75, RI: NS among the three groups Roc dose requirement: NS among the three groups (p=*2.71*)
[9]	Narimatsu et al. 2007	Experimental *in vitro* study (rats)	Rats were killed with an overdose of isoflurane 1. Impact of dex, clonidine and yohimbine on roc concentration-indirectly elicited single twitch tension curve (supramaximal stimulation of the phrenic nerve) 2. Further impact of dex and clonidine on twitch depression (65% of control) by roc	1. Group D (*n*=6 each): pretreated with dex 0.05 or 50 μM) Group C (*n*=6 each): pretreated with clonidine 0.05 or 50μM) Group Y (*n*=6): pretreated with yohimbine 50μM Group DY (*n*=6): pretreated with dex + yohimbine (50μM each) Group CY (*n*=6): pretreated with clonidine + yohimbine (50 μM each) Group C (*n*=9): no pretreatment 2. Group D (*n*=9): dex Group C (*n*=6): clonidine Both concentrations (μM) were increased in a stepwise manner Group C (*n*=6): control	1. Dose-dependent leftward shift of the roc concentration-twitch tension curve (pretreatment with 50 μM of dex, clonidine and yohimbine alone or in combination) (p<0.01) 2. Dose-dependent further decrease on roc twitch suppression (>30 μM of dex or clonidine) (p<0.01)
[10]	Weinger et al. 1995	Experimental *in vivo* study (rats)	GA, induction: halothane maintenance: halothane in O_2 neuromuscular blockade: ~30 min after induction and intubation vec 0.05 mg/kg + 0.0015-0.003 mg/kg/min TOF monitoring Impact of three varying doses of dex on T1 twitch depression.	3 groups, 27 rats after at least 15min of stable 50% T1 depression received: Group D1 (*n*=11): dex 10 mcg/kg Group D2 (*n*=5): dex 30 mcg/kg Group D (*n*=6): dex 100 mcg/kg Group C (*n*=5): N/S	T1 depression: NS among the three groups

NR: Number of Reference; N/S: Normal Saline; NS: Not Statistically Significant; GA: General Anesthesia, dex: Dexmedetomidine; roc: Rocuronium; vec: Vecuronium; TOF: Train of Four; T0: Onset Time, T25: Time for TOF to return to 25%; T50: Time for TOF to return to 50%, T75: Time for TOF to return to 75%; T90: Time for TOF to return to 90%; RI: Recovery Index-time of a block to recover from 25% to 75%; 90% block time: t to achieve 90% block compared to baseline, TOF no reaction: t the T1 remains 0

or without intraoperatively infusion [2,3,5,6]. Dex 0.5 mcg/kg also prolonged T75 and T1 to recover to 10% of control in two studies [6,7]. Talke et al. [4] also showed a decrease in T1 twitch depression with 0.6 ng/ml target plasma concentration of dex. Narimatsu et al. [9] reported that high dose of dex, beyond clinical range, caused a leftward shift of the rocuronium concentration-twitch tension curve and further twitch suppression, in contrast to Weinger et al. [10] who found no significant difference on T1 twitch suppression. RI was measured in four studies [5-8] and only in one [6] RI was prolonged after dex 0.5 mcg/kg and 1 mcg/kg administration. The sympatholytic action of dex was considered responsible for the prolongation of ndNMBAs blockade in most studies. Dex reduces the blood supply of liver and kidney and since rocuronium metabolism mainly depends on liver and kidney blood flow, the altered pharmacokinetics may explain the increase in the duration of action in a dose-dependent way [2-8]. Another possible mechanism is the prevention of Ach release from the presynaptic membrane of the CNS. Clonidine, an older a_2-agonist, can inhibit the release of Ach, enhancing the block of ndNMBAs. Since dex is more potent and 27 times more selective for a_2-receptors than clonidine, it may in a similar way prolong the neuromuscular blockade of ndNMBAs [2,3]. Ozcan et al. [3] pointed out that epinephrine and norepinephrine have been reported to antagonize the neuromuscular block by increasing Ach release from prejunctional sites in skeletal muscles in experimental studies. A_2-agonists inhibit norepinephrine release and therefore may potentiate neuromuscular blockade. Narimatsu et al. [9] investigated *in vitro* the effects of clinical and experimental doses of dex, clonidine and yohimbine (a_2-antagonist) on rat diaphragms under rocuronium-induced blockade. Only high experimental concentrations of Micromolar range (μM) of dex and clonidine, much greater than their therapeutic concentrations, enhanced the neuromuscular blockade. Since this action was not antagonized by yohimbine, they indicated that the enhancing effect on neuromuscular blockade was a result of competitive or non-competitive blockade of postjunctional nicotinic Ach receptors at the neuromuscular junction, independent of the α_2-adrenergic agonist mechanism of dex. Weinger et al. [10] investigated the impact of dex (10, 30 and 100 mcg/kg) on a vecuronium-induced T1 twitch depression in anaesthetized rats. T1 was not significantly affected by dex, therefore suggesting that its action at the neuromuscular junction may be attributed to secondary mechanisms such as cardiovascular depression or a result from a different CNS site of action.

Conclusion

In this concise review both enhancement and no significant alteration have been reported for the effect of dex on neuromuscular blockade. Clinical heterogeneity could justify these different results since different doses and times of dexmedetomidine administration, different types of studies and patient population have been identified. Duration of the blockade was more frequently investigated than onset time of ndNMBAs and pharmacokinetic mechanism was considered the most possible reason for the enhancement of the block.

Preliminary data from our study, albeit with a relatively small sample size, demonstrate that dex shortens the onset time of rocuronium in pediatric patients.

Further larger studies are needed to confirm this effect, to investigate whether this effect has implications on dosing of ndNMBAs and to explain the possible mechanism of action of dex on the neuromuscular blockade to this particular population.

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