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Effect of saline flush on the onset time of sugammadex: A randomized clinical study

Salin yıkamasının sugammadeksin başlangıç zamanı üzerine etkisi: Randomize klinik çalışma

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Abstract

Aim: Several methods have been tried out to shorten the onset time of sugammadex. The objective of this study was to examine the effect of 20 mL saline flush administered immediately after sugammadex on its onset time by using train-of-four (TOF) monitoring.

Methods: This study was initiated after obtaining the approval of the institutional Medical Research Ethics Committee. A total of 60 ASA I-II patients aged between 18-65 years scheduled for elective abdominal surgery in our hospital between August 2017 and January 2018, which would last 1-3 hours under general anesthesia, were enrolled in this study. Patients were randomly divided into two groups as Group S (saline flush group, n=30) and Group C (control group, n=30). Saline flush group received 2 mg/kg sugammadex and 20 ml isotonic saline flush immediately after sugammadex administration, while the control group received 2 mg/kg sugammadex only. TOF monitoring was used to assess neuromuscular block. Electrocardiography, oxygen saturation, noninvasive arterial pressure as well as acceleromyography values measured by TOF monitoring device were recorded and compared between the groups. All patients were continuously monitored intraoperatively and 30 minutes postoperatively.

Results: Both groups were similar in terms of basic clinical characteristics and demographics. There was a statistically significant difference between the groups in terms of the time of TOF to reach 0.9 from 0.2. The mean time of TOF to reach 0.9 from 0.2 was lower in Saline flush group than in control group (85.4 vs 130.5 seconds; *P*=0.001).

Conclusion: Our study demonstrated that 20 mL saline flush administered immediately after sugammadex shortened the onset time of sugammadex.

Keywords: Saline solution, Neuromuscular block, Train-of-four monitoring, Sugammadex

Öz

Amaç: Sugammadeksin etkisinin başlama süresini kısaltmak için çeşitli yöntemler uygulanmıştır. Bu çalışmanın amacı, sugammadeks uygulamasından hemen sonra uygulanan 20 mL serum fizyolojik bolusun, dörtlü uyarı dizisi (TOF) yöntemi ile izlenilerek, etki başlangıç süresini incelemektir.

Yöntemler: Yerel Etik Kurul onamı sonrası Ağustos 2017 ve Ocak 2018 arası genel anestezi altında elektif cerrahi planlanan, ASA I-II statüde, operasyon süresi 1-3 saat sürecek, 18-65 yaş arasında 60 hasta çalışmaya dahil edildi. Hastalar rastgele Grup S (Serum Fizyolojik grubu, n=30) ve Grup C (Kontrol grubu, n=30) olmak üzere iki gruba ayrıldı. Serum Fizyolojik grubuna 2 mg/kg sugammadeks uygulamasından hemen sonra 20 cc izotonik serum fizyolojik bolus olarak uygulandı. Kontrol grubuna ise sadece 2 mg/kg sugammadeks verildi. Nöromüsküler bloğun izlemi için TOF monitörü kullanıldı. Elektrokardiyografi, oksijen satürasyonu, noninvaziv arteriyel basınç ve TOF izleme cihazı ile ölçülen akseleromiyelografi değerleri kaydedildi ve gruplar arasında karşılaştırıldı. Tüm hastalar ameliyat sırasında ve ameliyattan 30 dakika sonra monitorize olarak izlendi.

Bulgular: Her iki grupta temel klinik özellikler ve demografik veriler açısından benzerdi. Gruplar arasında TOF'un 0,2'den 0,9'a ulaşması açısından istatistiksel olarak anlamlı bir fark vardı. TOF'un 0,2'den 0,9'a ulaşma süresi Serum Fizyolojik grubunda kontrol grubuna göre anlamlı olarak düşük tespit edildi (85,4'e ve 130,5 saniye; *P*=0,001).

Sonuç: Çalışmamız göstermiştir ki, sugammadeks uygulamasından hemen sonra uygulanan 20 ml serum fizyolojiğin sugammadeksin etki başlangıç zamanını kısalttığını göstermiştir.

Anahtar kelimeler: Serum fizyolojik, Neuromuscular block, Dörtlü uyarı dizisi izlemi, Sugammadex

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Introduction

Neuromuscular blocker (NMB) drugs are commonly used for relaxation of skeletal muscle during surgical operations [1]. Reversal of the neuromuscular block depends upon the usage of the agents that inhibit the activity of acetylcholinesterase. Hereby, the relevant receptors are inactivated and neuromuscular blockers are eliminated from the systemic circulation. Lack of complete reversal of the neuromuscular block at the end of the operation may cause postoperative complications such as hypoxemia, respiratory distress and swallowing difficulty, airway problems, and hypercapnia [2]. In order to avoid these complications, depth of the neuromuscular block is assessed using Train-of-four (TOF) nerve stimulation, and a T4/T1 ratio ≥0.9 is recommended for extubation [3]. Anticholinesterases and sugammadex, which have recently become popular, are used for pharmacological antagonism of neuromuscular blockers. Sugammadex is a modified γ-cyclodextrin, binds to neuromuscular blocker agents in steroid form (rocuronium and vecuronium) and forms encapsulation, with which the neuromuscular blocker agent rapidly moves away from neuromuscular junction, providing rapid reversal of the blockage [4].

Various methods and applications have been attempted to shorten onset time of the drugs administered via the intravenous route. Among these are priming principle, timing principle and using high doses [5]. It has been reported in the literature that especially saline flush immediately after intravenous drug administration shortens the onset time [6,7]. Studies in the literature recommend 20 mL saline flush to be administered after adenosine, a drug with a half-life of shorter than 10 seconds and administered via a peripheral vein, to rapidly reach to the heart [6]. Ishigaki et al. [7] have demonstrated that 20 mL saline flush administration immediately after intravenous administration of rocuronium shortens the onset time of the drug. To the best of our knowledge, this is the first study investigating the effect of saline flush administered immediately after sugammadex on the onset time of this drug using TOF monitoring.

Materials and methods

Study population and design

The study was initiated after obtaining the necessary permissions and ethics approval from Bolu Abant Izzet Baysal University Medical Researches Ethics Committee (approval date: March 06, 2017 and decision number: 49). A total of 60 ASA I-II patients aged between 18-65 years scheduled for elective abdominal surgery in our hospital between August 2017 and January 2018, which would last 1-3 hours under general anesthesia, were enrolled in this prospective randomized clinical study. Included patients were informed about the study and written informed consents were obtained. Patients were randomized by using computer-generated random numbers and divided into two groups as Group S (saline flush group, n=30) and Group C (control group, n=30). Patients' basic demographic and clinical features, operation and anesthesia times, perioperative hemodynamic data such as mean arterial pressure and heart rate as well as the reversal times of neuromuscular block measured by TOF monitoring device were recorded and then compared between the groups. Patients aged under 18 and over 65 years, obese patients (those with a body mass index > 30 kg/m2), patients with hypersensitivity to the drugs used in the study or the agents in their composition, those with severe hepatic, renal, cardiovascular diseases and/or neuromuscular diseases, and patients who had emergency surgery, concomitant surgery and those whose time under general anesthesia exceeded 3 hours were excluded from the study.

Perioperative anesthesia management

Patients taken to the operating room were routinely monitored with electrocardiography (ECG), oxygen saturation (SpO2) probes, and noninvasive blood pressure arterial monitorization. An acceleromyography device (TOF Watch SX, Organon, Netherlands) was connected to stimulate the ulnar nerve for assessing neuromuscular block. TOF electrodes were placed on the ulnar edge of the distal forearm; a heat probe was placed in the palm, and a transducer to the inner side of the thumb. A signal stabilization of neuromuscular transmission monitoring was performed. Hand and forearm were wrapped with cotton to prevent peripheral temperature to drop below 32^{o}C. Vascular access was achieved with a 20G cannula placed from the forearm on the operating table.

After anesthetic induction of the patients was provided with 2 mg/kg propofol (Propofol Lipuro 1% ampoule, B. Braun, Germany) and 1 mcg/kg Fentanyl (Fentanyl ampul 0.05 mg/mL, Janssen, Belgium), TOF device was calibrated. Rocuronium bromide (Myocron vial 50 mg/mL, Vem Ilac, Turkey) was administered at a dose of 0.6 mg/kg, TOF device was set to automatically read every 16 seconds and measurements began. For train-of-four (TOF) monitoring, four supramaximal stimuli of 2 Hz were given in 0.5 seconds, and ratio of the fourth response to the first was recorded. Block degree was determined according to the number of responses. Patients were intubated when TOF was 0. Maintenance of anesthesia was performed using 50% O2+N_2O and 4-6% desflurane. At the end of the operation, 10 mg/kg paracetamol (Perfalgan 10 mg/mL vial, Bristol-Myers Squibb, USA) was used for postoperative analgesia. In order to maintain TOF ≤0.2, additional rocuronium was intravenously administered as needed. Group S (saline flush group) received 2 mg/kg sugammadex (Bridion vial 200 mg/2mL, Organon, Oss, Netherlands) intravenously for 3-5 seconds, after which 20 ml of isotonic saline was flushed. Group C (control group) received 2 mg/kg sugammadex intravenously for 3-5 seconds. Inhalation anesthesia was not ended until measurements were completed to prevent patients from feeling pain during TOF measurements. TOF measurement and inhalation anesthesia were terminated when a TOF ratio of 0.9 or higher was observed. Time of TOF ratio to reach 0.9 from 0.2 was recorded. Patients were extubated and transported to the postoperative recovery room. Those with an Aldrete score ≥9 were taken to the ward. In addition, heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and SpO_2 were recorded just before anesthetic induction, at the 5th, 10th, 30th and 60th post-induction minutes and 10th and 30th postoperative minutes.

Sample size calculation

Primary endpoint of our study was time of TOF ratio to reach 0.9 after saline flush. Sample size estimation was based on the method described by Filho et al. [8]. In order to detect a 25% change time of TOF ratio to reach 0.9 (120 (40) sec control values in the study by Filho et.), with an α error of 0.05 and a power of 95%, we found that the sample size should be at least 30 patients per group. Estimating an approximate 10% dropout rate, we included 33 patients in each group. The sample size estimation was performed using G Power 3 Calculator.

Statistical analysis

Data were analyzed using SPSS (Statistical Package for Social Sciences for Windows 11.5) package software. Normality of continuous variables was analyzed with Kolmogorov Smirnov test. Descriptive statistics were expressed as mean (standard deviation) for continuous variables, and as number (percentage) for categorical variables. Continuous variables were compared between the groups with "Independent Sample t test" and "Mann-Whitney U test" where appropriate. Chi-square test was used in comparison of the categorical variables. Split Plot Anova Test was used in comparison of changes of heart rate and mean arterial pressure over time between the two groups. A *P*-value <0.05 was considered statistically significant.

Results

The study initially included 66 patients who underwent isolated abdominal surgery from August 2017 to January 2018 in our hospital. Six patients rejected to participate in the study, who were excluded (Figure 1). The two groups were similar in terms of demographics and basic clinical characteristics (Table 1). No significant difference was found between the groups in terms of intraoperative and postoperative heart rate values (Figure 2) or intraoperative and postoperative mean arterial pressure (MAP) values (Figure 3).

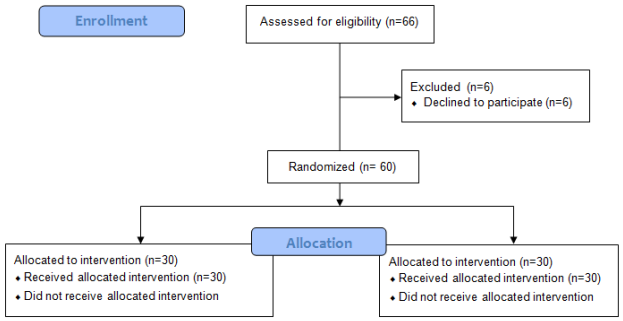


Figure 1: Flow-diagram

There was a statistically significant difference between the groups in terms of the time of TOF to reach 0.9 from 0.2. The mean time of TOF to reach 0.9 from 0.2 was significantly lower in Saline flush group than in control group (Table 2).

Adverse events were not observed in any of the patients and the perioperative period was completed uneventfully.

Table 1: Demographics and basic clinical features of the groups

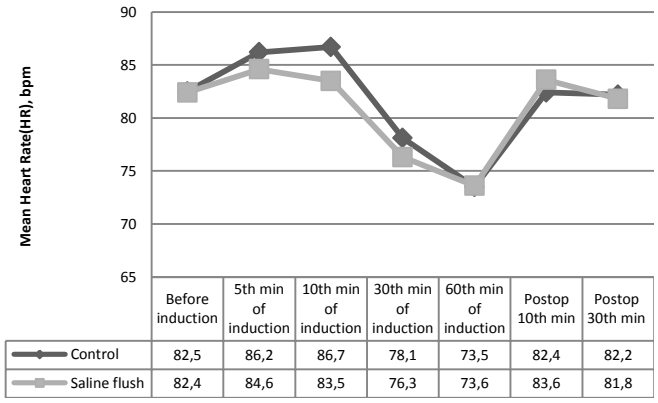
Variables	Control group (n=30)	Saline flush group (n=30)	*P*-value
Age (year)	42.5(13.6)	40.3(13.6)	0.536*
Gender - Female	18 (60.0%)	14 (46.7%)	0.084†
Mean Aldrete score	9.7(0.4)	9.5(0.5)	0.118**
Body Mass Index (kg/m^2)	25.7(3.0)	25.8(3.2)	0.955**
ASA ½	10/20	11/19	0.791†
Operation Time (min)	100.4(53.8)	106.7(33.1)	0.629*
Anesthesia Time (min)	109.6(54.6)	117.8(35.3)	0.493*

Data were presented as mean (standard deviation) or number (percentage), Statistical tests for the analysis were as follows: *Mann-Whitney U Test, **Independent Sample T Test, †Chi-Square Test

Table 2: Comparison of mean times of TOF to reach 0.9 from 0.2 between the groups

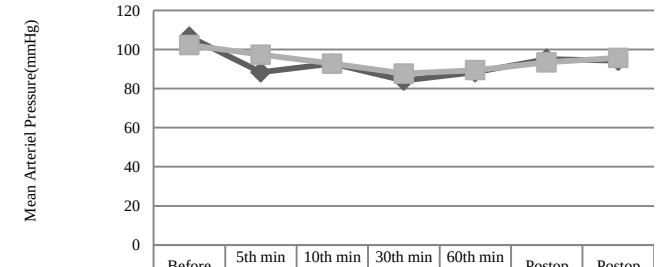
Variable	Control Group (n=30)	Saline Flush Group (n=30)	*P*-value
The mean time of TOF 0.2-0.9 (second)	130.5(61.9)	85.4(33.1)	0.001*

Data were presented as mean (standard deviation), Statistical test for the analysis was as follow: *Mann-Whitney U Test



	Before induction	5th min of induction	10th min of induction	30th min of induction	60th min of induction	Postop 10th min	Postop 30th min
Control	82,5	86,2	86,7	78,1	73,5	82,4	82,2
Saline flush	82,4	84,6	83,5	76,3	73,6	83,6	81,8

Figure 2: Comparison of heart rates between the groups



	Before induction	5th min of induction	10th min of induction	30th min of induction	60th min of induction	Postop 10th min	Postop 30th min
Control	106,5	88,3	92,7	84,1	88,3	95,1	94,2
Saline flush	102,2	97,3	92,7	87,7	89,4	93,4	95,7

Figure 3: Comparison of mean arterial pressures between the groups

Discussion

This study showed that 20 mL saline flush administered immediately after sugammadex (2 mg/kg) accelerated its time of onset, shortened the time of TOF to reach 0.9 from 0.2, and contributed to rapid reversal of neuromuscular block.

Some pharmacological and non-pharmacological methods are used to decrease the time of onset of drugs, namely, increasing drug dose, elevation of the extremity where the drug is administrated and saline flush after administration of drugs from the peripheral vein. Administration of rocuronium at a dose of 0.9-1.2 mg/kg instead of its normal dose 0.6 mg/kg is stated as an appropriate alternative to succinylcholine for neuromuscular block during rapid induction [9,10]. IV drug administration from a peripheral vein is typically followed by a fluid bolus application in many clinic applications. Although saline flush application has been performed via a peripheral vein and its effects have been shown in some studies, we could not find a study about saline flush after sugammadex. Kulkarni et al. [11] have used the saline flush method and extremity elevation together after rocuronium administration, and found that it shortened time of onset of rocuronium. A study conducted in dogs during cardiac arrest concluded that bolus injection of 20 mL saline after dye administration resulted in enhanced dye circulation time and a higher peak levels [12]. American Heart Association (AHA) declared that administration of a resuscitation drug from a peripheral vein during cardiopulmonary resuscitation should be followed by 20 mL fluid bolus to accelerate flow of the drug into the central circulation [6]. In their study with 48 patients, Ishigaki et al. [7]

administered neuromuscular blockade with 0.6 mg/kg rocuronium in patients in the control and saline groups, and found that the onset time of the drug was 90 seconds in the control group and 60 seconds in the saline bolus group. Nitahara et al. [13] investigated the effect of 20 mL saline bolus injection following 0.1 mg/kg vecuronium administered from a peripheral vein with elevation of extremity and found onset time of neuromuscular block as 128.3 seconds in the control and 104.6 seconds in the saline flush group. Iwasaki et al. [14] compared administration of vecuronium from a pulmonary artery catheter to the right atrium, and administration from dorsal vein of the hand, and found the onset time as 82 seconds in dorsal vein administration and 11 seconds in administration to the right atrium. Similarly, in our study we found that onset time of drug effect was 50 seconds shorter in saline flush group than the control group.

Sugammadex is the first relaxant binding agent used in reversal of the block provided by neuromuscular blockers. Decurarization with sugammadex has been a new approach for a rapid and safe reversal of neuromuscular block provided by rocuronium or vecuronium [15,16]. Time required for TOF to reach 0.9 in reversal of deep neuromuscular block under sevoflurane anesthesia was found to be 18 folds shorter with sugammadex compared to neostigmine [17].

In a randomized controlled study by Blobner et al. [18] on 198 patients, 2 mg/kg sugammadex or 50 μg/kg neostigmine were administrated when TOF was 0.2 in patients with neuromuscular block provided by rocuronium. Times of TOF ratio to reach 0.9 were measured as 1.4 minutes in the sugammadex group and 17.6 minutes in neostigmine group. Shields et al. [19] investigated the efficacy of different doses of sugammadex in reversal of the neuromuscular block provided by rocuronium. In the study conducted in 30 patients, neuromuscular block was initially provided with 0.6 mg/kg rocuronium, and the time of TOF to reach 0.9 (the time of reversal of neuromuscular block) was found as 150 seconds with 2 mg/kg dose of sugammadex. In our study, we find the mean time of TOF to reach 0.9 from 0.2 was 130.5 (61.9) seconds in the control group, while this duration dropped to 85.4 (33.1) seconds in the group who received saline flush. We think this might be due to saline flush causing sugammadex to rapidly enter the systemic circulation and accelerating its effect. Saline flush of 20 mL administered immediately after sugammadex (2 mg/kg) caused sugammadex to rapidly enter the systemic circulation, shortened its time of onset and the time of TOF to reach 0.9 from 0.2, and contributed to rapid reversal of neuromuscular blockade.

Limitations

The main limitations of the present study were the relatively small sample size, the single-centered design, limited data, and the lack of a long follow-up during the postoperative period. However, further, larger scale studies are needed to confirm this effect and achieve stronger evidence.

Conclusion

We suggest that saline flush administration would be helpful in the cases where a rapid reversal of neuromuscular block is desired.

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