

## Does Hemoglobine Level Play a Role in Metabolism of Succinylcholine?

### *Hemoglobin Düzeyi Süksinilkolin Metabolizmasında Rol Oynar mı?*

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#### **Abstract**

Butyrylcholinesterase (BChE) deficiency, several drugs or administration of high doses of succinylcholine (SCh) are well known reasons for prolonged succinylcholine clearance. The goal of this study was to investigate the relationship between hemoglobine (Hb) levels and SCh metabolism for the parturients undergoing cesarean sections. One hundred and twenty patients were randomized into three groups (n=40). In Group 1, the Hb levels of the patients were between 9-11 g dL<sup>-1</sup>. In Group 2, the levels were between 11 g dL<sup>-1</sup> and 13 g dL<sup>-1</sup>. Finally in Group 3, the Hb levels of the patients were between 13-15 g dL<sup>-1</sup>. The BChE levels, Hb levels, the time for recovery of neuromuscular function were compared between groups. Group demographics were similar. There was no significant difference between Groups 1 and 2 regarding their drug elimination time (p>0.05). The recovery of neuromuscular functions was significantly faster in Group 3 (p<0.05). The results of our study suggest that anemia may cause prolonged SCh-induced paralysis and apnea for the patients undergoing cesarean section.

**Key words:** Succinylcholine, cesarean, hemoglobine, butyrylcholinesterase.

#### **Özet**

Butiril kolinesteraz (BChE) eksikliği, çeşitli ilaçlar veya süksinilkolinin (SCh) yüksek dozda uygulanması uzamış süksinilkolin klirensinin iyi bilinen nedenlerindedir. Bu çalışmanın amacı sezeryan operasyonu geçiren gebelerde hemoglobin (Hb) düzeyleri ve SCh metabolizması arasındaki ilişkiyi araştırmaktır. Yüz yirmi hasta 3 farklı gruba (n=40) randomize edildi. Grup 1'e Hb düzeyi 9-11 g dL<sup>-1</sup> arasındaki hastalar, Grup 2'ye 11 ile 13 g dL<sup>-1</sup> arasında Hb düzeyi bulunan hastalar, Grup 3'e ise Hb düzeyi 13-15 g dL<sup>-1</sup> arasında olan hastalar dahil edildi. Gruplar arasında BChE, Hb düzeyleri ve nöromüsküler fonksiyon geri dönüş zamanları karşılaştırıldı. Grupların demografik özellikleri benzerdi. Grup 1 ve 2'deki hastalar arasında ilaç eliminasyon zamanı bakımından anlamlı bir fark yoktu (p>0.05). Nöromüsküler fonksiyonların geri dönüşü Grup 3'de anlamlı olarak daha hızlıydı (p<0.05). Çalışmamızın sonuçları aneminin sezeryan operasyonu geçirecek hastalarda uzamış SCh ilişkili paraliziye ve apneye yol açabildiğini göstermektedir.

**Anahtar kelimeler:** Çocuk hasta, üreter taşı, üreterolitiazis, üreteroskopi, devlet hastanesi.

#### **Introduction**

Fast onset and short duration make SCh a useful agent when rapid-sequence induction is planned [1]. Exaggerated potassium release, resulting in life-threatening hyperkalemia and cardiac dysrhythmias or increased intraocular and intracranial pressure or being a potential to trigger malignant hyperthermia limit the use of SCh. However, SCh and rocuronium bromide have been still the most preferred muscle relaxants for emergency cesarean surgeries [2,3]. The optimal dose of SCh is currently recommended 1.0 to 1.5 mg kg<sup>-1</sup> [4]. A dosage of 1 mg kg<sup>-1</sup>

provides a rapid onset, approximately 30 to 60 seconds and a short duration of action about 3 to 5 minutes. There are two types of cholinesterase: Acetylcholinesterase is found in nerve tissue and red blood cells. It is known as red blood cell cholinesterase. On the other hand, BChE is found primarily in the liver. It is also found in the plasma, pancreas, heart and the brain. SCh is hydrolysed by BChE which is synthesised by the liver [5]. Delayed or

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prolonged metabolism of SCh is usually due to interactions with other drugs that inhibit BChE, pregnancy or severe hepatic dysfunction [6]. Abnormal BChE that is related with cholinesterase gene defects, also has been known [7,8] All of these factors result with prolonged apnea. In this study, we investigated whether the Hb levels affect the metabolism of SCh or not. We hypothesized that it is quite possible. By this way, the relationship between anemia and SCh can be clearly revealed and adjustment of the drug dose can be performed.

### Materials and Methods

After approval by our Local Research Ethics Committee (protocol no: B.10.4.İSM.04.25.00-16-36/3900, date: 09/21/2011), 120 patients with American Society of Anesthesiologists (ASA) physical status 1-2, aged 18 to 40 years were included in this retrospective study. Patients' data were analyzed between November 2008 and October 2010 at Erzurum Nene Hatun Obstetrics and Gynecology Hospital. ASA physical status more than 2 and extremely obese parturients (body mass index >40) were excluded from the study. All patients had a normal airway anatomy, no neuromuscular, renal or hepatic disease and none were taking any drug known to interfere with neuromuscular function. All of the parturients had a history of living in the same city at least two years. The operations were performed by one of four surgeons.

Before the general anesthesia, a peripheral 20 Gauge venous cannula was placed as caution. 10 mL kg<sup>-1</sup> i.v. infusion of 0.9% saline solution was given for fluid maintenance peroperatively. No premedication was applied before the procedure. Noninvasive mean arterial blood pressure was recorded with five minute intervals. Heart rate, arterial oxygen saturation by finger pulse oximetry and respiratory rate were continuously measured. The levels of BChE enzym and Hb, the time for recovery of neuromuscular function, patients' demographics and additional illnesses were recorded.

The ability to ventilate the patients' lungs was tested before induction of anesthesia by applying positive airway pressure via a tightly fitting mask. General anesthesia was induced by propofol 2 mg kg<sup>-1</sup> and succinylcholine 1 mg kg<sup>-1</sup>. The lungs of the patients were mechanically ventilated and ventilation was adjusted to maintain end-expiratory CO<sub>2</sub> between 32–36 mmHg. After the baby was borned, anesthesia was maintained by sevoflurane with end-tidal concentration 1.5% in oxygen–nitrous oxide (FIO<sub>2</sub> = 0.5). Monitoring of neuromuscular function was started using acceleromyography (TOF-Watch SX) by performing intermittently a “train-of-four”. Four equal muscle contractions were accepted as a result of no neuromuscular blockade and recorded

as the time for recovery of neuromuscular function. Adductor pollicis stimulation over the ulnar nerve at the wrist using a standard 2-Hz stimulus every 0.5 s for four bursts was used for monitoring. After obtaining the recovery, atracurium 0.4 mg kg<sup>-1</sup> was applied for the rest of surgery. Atracurium was then reversed with 1.5 mg neostigmine and 0.5 mg atropine after checking again train-of-four monitorization. The total amount of propofol, SCh and atracurium were recorded.

The parturients were assigned into three groups (n=40). In Group 1, the Hb levels of the patients were between 9 and 11 g dL<sup>-1</sup>. In Group 2, the levels were between 11 g and 13 g dL<sup>-1</sup>. Finally in Group 3, the Hb levels of the patients were in the range of 13 g dL<sup>-1</sup> to 15 g dL<sup>-1</sup>.

### Statistical Analysis

Statistical Package for Social Sciences (SPSS) for Windows 10.0 programme was used for statistical analysis. Group size was selected by using proportions sample size estimates ( $\alpha$ : 0.05,  $\beta$ : 0.09). The values were expressed as mean  $\pm$ SD. Pearson correlation coefficient tests were performed for Hb levels and BChE levels. They were analyzed after adjusting for Hb levels and the duration of succinylcholine metabolism. Statistical significance was accepted to be  $P < 0.05$ . One way ANOVA parametric test was used for comparisons between groups for normal distributed parameters, post-hoc test was Tukey Kramer. Kruskal Wallis and Mann-Whitney U statistical tests were used for abnormal distributed parameters, post-hoc test was Dunn. Qualitative data were compared by using Chi<sup>2</sup> test ( $p < 0.05$ ). A  $p < 0.05$  was considered significant.

### Results

All patients were included in the statistical analysis. One hundred and twenty patients underwent cesarean section in our study. There were 40 patients in each group with similar baseline characteristics. The demographic values of the groups were shown in Table 1 ( $p > 0.05$ ). Patients were of respective mean ages 28 years (Group 1), 26 years (Group 2) and 30 years (Group 3). The range was between 18 to 37 years. Body mass index was 27 kg/m<sup>2</sup> in each group. Patients were of American Society of Anesthesiologists mostly Class II in Group 1 (59%), Class I (69%) in Group 2 and again Class II (54%) in Group 3. The mean duration of surgical procedure did not differ between groups (Table 2). Both of the groups were comparable with regard to the total amount of propofol, atracurium and SCh as shown in Table 2. Time to reappearance of train-of-four after SCh administration was significantly shorter in Group 3 than in the other groups (7.291  $\pm$  4.8 minutes) ( $p < 0.05$ ). Group 1 and 2 had a similar mean duration of paralysis after SCh (9.202  $\pm$  1.9 min versus 9.356  $\pm$  3.8 min) as shown in Figure 1.

**Table 1:** Demographic data (values expressed as mean  $\pm$  SD)

	Group 1	Group 2	Group 3
Age	28.66 $\pm$	26.73 $\pm$	30.13 $\pm$
(years)	6.62	5.37	2.07
Weight	78.45 $\pm$	73.48 $\pm$	76.59 $\pm$
(kg)	7.45	10.56	9.07

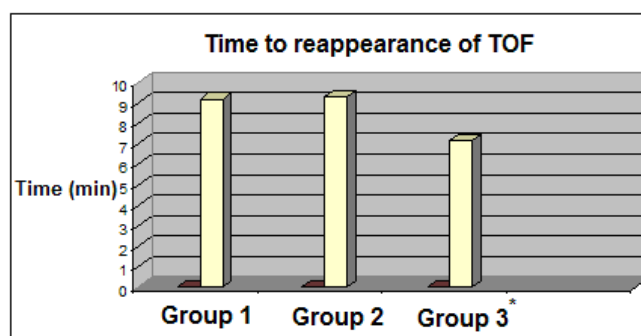
Group 1: The patients with Hb levels 9 to 11 g dL<sup>-1</sup> (n=40), Group 2: The patients with Hb levels 11 to 13 g dL<sup>-1</sup> (n=40), Group 3: The patients with Hb levels 13 to 15 g dL<sup>-1</sup> (n=40). p>0.05

**Table 2:** Duration of surgery and the amount of drugs used (values expressed as mean  $\pm$  SD)

	Group 1	Group 2	Group 3
Duration of surgery (minute)	33.8 $\pm$ 0.5	36.4 $\pm$ 5.8	32.3 $\pm$ 2.6
Propofol (mg)	162.5 $\pm$ 54.2	156.6 $\pm$ 46.5	160.3 $\pm$ 28.1
Succinylcholine (mg)	78.7 $\pm$ 15.4	73.8 $\pm$ 16.0	76.5 $\pm$ 20.6
Atracurium (mg)	31.38 $\pm$ 4.2	29.5 $\pm$ 8.6	30.6 $\pm$ 0.4

Group 1: The patients with Hb levels 9 to 11 g dL<sup>-1</sup> (n=40), Group 2: The patients with Hb levels 11 to 13 g dL<sup>-1</sup> (n=40), Group 3: The patients with Hb levels 13 to 15 g dL<sup>-1</sup> (n=40). p>0.05

The correlations between the levels of Hb and BChE parameters were evaluated with Pearson correlation test. There was a positive correlation between these parameters in Group 3. The two-tailed p value was 0.0389 and considered significant. However there was no significant difference in Group 1 and 2. The two-tailed p value was 0.1819 for Group 1 and 0.2036 for Group 2.

**Figure 1.** Time to reappearance of TOF after SCh administration (values expressed as mean  $\pm$  SD).

Group 1: The patients with Hb levels 9 to 11 g dL<sup>-1</sup> (n=40), Group 2: The patients with Hb levels 11 to 13 g dL<sup>-1</sup> (n=40), Group 3: The patients with Hb levels 13 to 15 g dL<sup>-1</sup> (n=40). \*p<0.05.

The mean Hb levels had a stronger correlation with the mean duration values to reappearance of train-

of-four after SCh administration in Group 3 (p=0.0297) but the difference between these correlations was not statistically significant in Group 1 or 2 (p>0.05).

Four patients had hypotension (mean arterial pressure under 50 mmHg) at preintubation after propofol induction. Three of these four patients were treated with ephedrine 10 mg due to hypotension. One of them was treated with colloid infusion. A heart rate under 40 beat/min was accepted as bradycardia. None of the patients had bradycardia requiring treatment. No patient exhibited clinical signs of muscle weakness after extubation.

There were no difficult intubations or deaths. All patients were intubated successfully on first attempt. There were no clinically meaningful differences between treatment groups in physical findings or laboratory parameters.

## Discussion

The usage of SCh is often limited as the side effects of SCh include malignant hyperthermia, acute rhabdomyolysis with hyperkalemia, postoperative myalgia, transient ocular hypertension, constipation and changes in cardiac rhythm including ventricular dysrhythmias, bradycardia and cardiac arrest [9,10]. Bradycardia is especially an important fact for the pediatric patients. As succinylcholine is often used to facilitate neonatal and pediatric rapid sequence intubation in the emergency department, Bethany Fleming et al. [11] recommended to use atropine before SCh administration. Patients consider avoidance of postoperative myalgia mostly important and sometimes they may even will to pay money for a muscle relaxant that is not associated with this side effect [12]. However, SCh and rocuronium are still the most preferred neuromuscular block agents for rapid sequence intubation [13]. Rocuronium is recently the best alternative to succinylcholine for rapid sequence induction [14]. Additionally, rocuronium takes more place instead of SCh for the emergency surgeries because there are several case reports about SCh related asystole [15,16]. Rocuronium has the shortest onset time as a nondepolarizing neuromuscular blocking agent but after all, this time is longer than SCh.

We administered nondepolarizing neuromuscular blocking agent to parturients after a depolarizing agent during cesarean surgery. Then we reversed atracurium at the end of the surgical procedure. Both the operations were emergency cesarean sections and the duration of starvation was not usually enough for the patients. Consequently, an emergency endotracheal crash intubation had to be carried out. Train of four monitoring provided appreciable benefit to patients, thus we did not come upon a complication about prolonged apnea.

General anesthesia is the fastest way for anesthetising patients but is associated with increased maternal morbidity and mortality. Kinsella SM et al. [17] described the 'rapid sequence spinal' to minimise anesthetic time for cesarean section. It is an expedient method when we have really enough time. Therefore, the patients including the study were informed about spinal anesthesia during the preoperative visit and the patients who refused regional anesthesia were included to the study protocol, so general anesthesia was performed. The molecule SCh is rapidly hydrolyzed by serine pseudocholinesterase (BChE).

Pseudocholinesterase, or plasma cholinesterase, is an enzyme made by the liver and present in the bloodstream [18]. The clinical duration of action is 3 to 5 minutes and normal neuromuscular function returns within 15 minutes [19].

BChE deficiency is an inherited or acquired condition in which the metabolism of SCh, mivacurium or ester local anesthetics is potentially impaired [20]. HELLP syndrome is a life-threatening obstetric complication and also associated with decreased BChE activity due to impaired liver function [21]. Deficiency or reduced activity of this enzyme results in significant prolongation of mivacurium or SCh induced neuromuscular blockade. BChE activity may be affected by different disease states or by drug administrations. Physiologic reductions may occur with extremes of age and during pregnancy [22].

On the other side, some authors also concluded that women at childbirth and at third trimester show a significant increase in BChE levels compared to nonpregnant patients [23]. Genetic variants of BChE

result in differences in clinical response to SCh. Duration of neuromuscular blockade can be further increased by nongenetic factors. These factors include head and neck related malignancies, high oestrogen levels in parturients at term and medication like metoclopramide or depakine [5]. Hemoglobine levels do not take place in the usual knowledge. This study has evaluated the hypothesis that Hb levels can play a role on BChE activity. Hereby we observed the patients in three different groups. There was no statistically change for the duration of neuromuscular blocking in Hb levels from 9 to 13 g dL<sup>-1</sup> but when the levels increase, a statistically shorter duration time for SCh occurred. The parturients who had Hb levels more than 13 g dL<sup>-1</sup> had high pseudocholinesterase levels and as a result, the reappearance time for train-of-four was shorter in this group. This clinical trial showed us that high Hb levels may affect the duration of SCh metabolism.

In the present study, the mean duration of action was 8.6 minutes. The values were more than 5 minutes. This difference may be related with high altitude. Erzurum city exists in approximately 1900 meters altitude. The patients in this study were living in the same city at least 2 years.

### Conclusion

Although acute and chronic exposure to high altitude induces various physiological changes, including modifications of hormonal release [24], there is no evidence about the effect of high altitude on BChE activity in the literature. We think that further studies can be performed about this subject. The results of our study suggest that anemia may cause prolonged SCh-induced paralysis and apnea for the patients undergoing cesarean section.

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