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Original article

The effect of remifentanil on succinylcholine induced changes in serum potassium and creatine kinase: a prospective randomized double blind study

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Summary. *Background and aim of the work:* Succinylcholine is still included as drugs favored by anesthetists because of its rapid onset and short duration of action. However, it can bring about complications such as hyperkalemia and increased serum creatine phosphokinase (CPK). This study aims at evaluating the effects of remifentanil on succinylcholine-induced postoperative changes in serum potassium and CPK. *Methods:* In this study, 59 patients with short term lower abdominal surgery were randomly divided into two groups. In the first group (control group), 2 ml normal saline was used before injecting anesthetic drugs while in the second group (study group), 1 mcg/kg of remifentanil was injected. The patients were anesthetized with a combination of fentanyl (1 μg/kg) and propofol (2 mg/kg). Besides, succinylcholine (1.5 mg/kg) was used for muscle relaxation and tracheal intubation. Serum potassium (before and 5 min after tracheal intubation), CPK (before anesthetic injection and 24 h after surgery) and hemodynamic parameters (including systolic, diastolic and mean arterial blood pressure and heart rate) were recorded. *Results:* Serum levels of potassium and CPK before and after induction of anesthesia showed no significant difference in both groups. Systolic, diastolic, and mean arterial blood pressure and heart rate in both groups after induction significantly changed. Compared to saline, remifentanil significantly stabilized hemodynamic changes after intubation. *Conclusions:* The results suggest that remifentanil has no prophylactic effect on succinylcholine-induced CPK and potassium levels. However, it improves stability of hemodynamic variables. (www.actabiomedica.it)

Key words: remifentanil, succinylcholine, potassium, creatine phosphokinase

Introduction

Despite the discovery of fast-acting non-depolarizing drugs and the introduction of sugammadex into clinical practice, succinylcholine is still considered as a muscle relaxant commonly used for rapid sequence induction and is unrivaled in terms of high-speed impact, excellent muscle relaxation and creating ideal conditions for tracheal intubation (1).

However, succinylcholine consumption is associated with increased serum creatine phosphokinase (CPK), myoglobin and potassium (2). It is said that muscle damage caused by uncoordinated contractions of adjacent muscle fibers at the time of muscle fasciculation and before paralysis leads to increased CPK (3). Pre-treatment with opioids is considered as methods used for the prevention or suppression of succinylcholine-induced muscle fasciculation. In two studies, pretreatment with alfentanil in pediatric anesthesia reduced the incidence and severity of muscle fasciculation and decreased intra-gastric pressure (4, 5). Remifentanil is among ultra-short-acting-opioids with a short half-life having a more powerful effect than alfentanil (6). In a study conducted to determine

the effect of remifentanil on muscle fasciculation, it was found that pretreatment with remifentanil reduces the duration and severity of succinylcholine-induced fasciculation (7). Yun et al. in a study investigated succinylcholine-induced muscle fasciculation in patients who were pre-treated with remifentanil (8). In their study, electromyography was used to assess the severity of fasciculation. They concluded that pretreatment with remifentanil reduces fasciculation and muscle action potential amplitude. This study however, aims to determine the effect of pretreatment with remifentanil on succinylcholine-induced changes in CPK and serum potassium as an objective factor in patients surgery under general anesthesia with tracheal intubation.

Method

This double-blind clinical trial was approved by the Ethics Committee of Kurdistan University of Medical Sciences, enrolled in Iranian Registry of Clinical Trials (IRCT.ir, ID: 138810141766N3), and written informed consents were obtained from all participants. The study recruited 60 patients with physical status I and II according to the American Society of Anesthesiologists (ASA) referred for selective surgeries in the lower abdomen. The patients were randomly divided into two groups by Random Permeated Blocks. Patients with a history of allergy to the drugs used in the study, pseudocholinesterase deficiency, pulmonary or heart diseases, neuromuscular disorders, taking drugs that interfere with neuromuscular function, hypertension and pregnancy were excluded.

After obtaining a history and description of the study, patients were divided into two groups. Prior to drug injection, a blood sample was taken to measure serum potassium and CPK levels. After connecting the standard monitors, 1 μg/kg fentanyl was injected into all patients at time zero. The pretreatment-drug was injected in the form of remifentanil 1 μg/kg (study group) or saline (control group) within 30 seconds. The drugs were prepared in similar syringes with equal volume of 2 ml by a technician colleague then covered with a reverse adhesive. Induction of anesthesia in the two groups was performed using propofol 2 mg/kg and muscle relaxation using succinylcholine 1.5 mg/kg. Tracheal intubation was performed in all patients by the same person. Maintenance of anesthesia was done with lsoflurane 0.8-1.2% and O2/N2O ratio of 50:50. A second blood sample was taken 5 min after anesthesia induction in order to measure potassium and the third sample taken 24 hours after surgery to measure serum CPK. The normal range of potassium in serum was considered as 3.5-4.5 mmol/l and patients with serum potassium before anesthesia outside the range were excluded. Systolic (SBP), diastolic (DBP), mean arterial blood pressure (MAP) and patients' heart rate (HR) were measured prior and after the induction of anesthesia and after tracheal intubation. Patient and all those involved in data collection were unaware of the grouping. Using statistical software SPSS 16, statistical t-test, chi-square and Mann-Whitney test were used for data analyses.

Results

Out of the 64 patients enrolled in the study, 60 were randomly selected but only 59 patients completed the study. Four patients were not randomized due to the withdrawal of consent in 3 cases and cancelation of surgery in 1 case. After randomization, one patient in the study group was removed due to high potassium levels in the first serum sample. Patients in both groups were comparable in terms of demographic characteristics and duration of surgery (Table 1). Serum potassium difference in prototype and the sample after tracheal intubation was 0.02 mmol/l on the average and the two groups were not significantly different in this respect. Serum CPK level increased with no significant difference 24 h after surgery in both groups (Table 1). Hemodynamic parameters after induction of anesthesia in both groups significantly decreased compared to baseline values. This reduction was more severe in the study group than in the control group. However, hemodynamic parameters increased after intubation (Table 2). This increase was significant in the control group compared to the study group ($P = 0.002$).

Discussion

The results of the study showed that CPK increased 24 h after surgery in both groups. The mean

Table 1. Demographic characteristics and biochemical value for patients of both groups

	Remifentanil N=29	Saline N= 30	P value
Age years	33.3 ± 11.7	29.9 ± 11.5	0.2
Sex (M/F)	19/10	20/10	0.5
Wight (Kg)	68.1 ± 11	71.3 ± 14.9	0.3
CPK			
Before induction	68 ± 33	75 ± 25	0.3
24 h after surgery	91 ± 36	97 ± 28	0.5
Potassium			
Before induction	3.9 ± 0.2	3.9 ± 0.2	0.9
5 min after tracheal intubation	3.9 ± 0.1	3.9 ± 0.1	0.8

Table 2. Hemodynamic values in different times in patients of both groups

	Remifentanil N=29	Saline N= 30	P value
Systolic blood pressure			
Before induction	131 ± 15	139 ± 21	0.2
After induction	110 ± 22	117 ± 19	0.1
1 min after intubation	123 ± 25	146 ± 22	0.01
Diastolic blood pressure			
Before induction	83 ± 15	80 ± 16	0.9
After induction	63 ± 15	70 ± 15	0.1
1 min after intubation	75 ± 19	97 ± 16	0.001
Mean arterial pressure			
Before induction	101 ± 15	96 ± 17	0.2
After induction	78 ± 17	85 ± 17	0.1
1 min after intubation	92 ± 21	115 ± 17	0.001
Heart Rate			
Before induction	89 ± 15	82 ± 17	0.08
After induction	78 ± 12	80 ± 14	0.7
1 min after intubation	83 ± 16	95 ± 16	0.001

CPK increase in study and control groups was 22±3 and 22±2 IU/L respectively, and the differences were statistically non-significant between the groups.

It is believed that after injection of succinylcholine, muscle fibers damage due to depolarization occurs before they suffer paralysis. The result of this muscle injury reflects as clinical fasciculation and postoperative myalgia. Irreversible changes in delicate muscle spindles or non-coordinated contractions of muscle fibers lead to cracking of connective tissues, electrolyte imbalance, prostaglandins release and CPK raise (9). The entry of calcium into the muscle may cause muscle damage and increase CPK too (10). Tissue trauma during surgery leads to a significant increase in CPK which peaks within 24 h and is normalized after 5 days. In fact, normal tissue damage is the leading cause of increase in myoglobin, CPK and LDH (10). An increased succinylcholine-induced CPK level

is also similar to CPK increase after tissue trauma that occurs 24 hours after injection (11). Therefore, differentiating the factor that increases CPK is not possible. To reduce the bias of increased CPK resulting from surgical trauma, samples of this study were selected from short-term lower abdominal surgeries (herniorrhaphy). Accordingly, we believed that; surgery trauma had minimal impact on the results of the study.

Traditionally, serum CPK measurements remain the best marker to determine and monitor injury or skeletal muscle illness (12). Although CPK is the most common marker of skeletal muscle damage, it is not ideal for various reasons such as lack of specificity and an inability to distinguish damage between fast or slow muscle fibers. Also, in liver diseases, and multi-organ failure with low glutathione concentration, CPK level is disproportionately low (13). In our study, immediately before the induction of anesthesia, 1 mcg/kg fentanyl was injected intravenously in all patients. Subsequently, the drugs used in the study (saline or remifentanil) were injected and anesthesia was induced with propofol. Comparing the effects of two common drugs used for induction of anesthesia, sodium thiopental and propofol, on succinylcholine-induced myalgia, most studies report that propofol is a better drug. McClymont reported an incidence of myalgia with propofol and thiopental as 19 and 63%, respectively (14). However, some researchers believe that there is no relation between myalgia and increased CPK (15). For the maintenance of anesthesia, we used isoflurane. Although sevoflurane and isoflurane have less effect on succinylcholine-induced increase in biochemical markers compared with halothane and enflurane, this increase also occurs after anesthesia with isoflurane and sevoflurane (16).

Traditionally, it is believed that succinylcholine injection leads to an increase in serum potassium content. Most studies reported an average change in potassium after administration of succinylcholine as "Very Modest" and reported a peak in 1 to 6 minutes interval after the succinylcholine injection (17). In this study, increased mean serum concentration of potassium in the blood sample taken 5 minutes after tracheal intubation from patients in both groups was 0.02 mmol/l. This increase was not statistically significant in both groups. It should be noted that a history of myopathy and high potassium levels in the initial sample (>4.5 mmol / lit) was among the exclusion criteria in this study. Therefore, it is possible that patients with preoperative unexpected high levels of potassium are more likely to experience increase in potassium level. Very slight increase in serum levels of potassium serum in the present study may be related to Fentanyl-propofol combinations used for induction. This little and no significant increase in potassium cannot be attributed to pretreatment with remifentanil.

Based on the results of this study, baseline values of all hemodynamic parameters (SBP, DBP, MAP, and HR) measured in our study were comparable in both groups and showed no significant difference. These parameters decreased following induction of anesthesia in patients of both groups. This reduction in hemodynamic parameters was more in the study group than in the control group; however, the difference was not statistically significant between the two groups. After tracheal intubation, hemodynamic parameters increased again. This increase in the control group was significantly higher than the study group (Table 1). Blood pressure and heart rate are among the most common parameters used during anesthesia to assess cardiovascular status. One of the main challenges for anesthetists is to avoid drastic changes in BP and HR during induction of anesthesia and tracheal intubation. To put off these stimuli and prevent hypersecretion of catecholamines, various drugs are used. Potent opioids such as fentanyl, alfentanil, sufentanil and remifentanil are among drugs used for this purpose (18). Better control of hemodynamic responses after tracheal intubation with remifentanil in this study is consistent with results of other studies (19, 20).

Conclusion

We concluded that in healthy subjects succinylcholine-induced potassium changes following induction of anesthesia with fentanyl - propofol combination is minimal and pre-treatment with remifentanil has no effect on it. Our results showed that remifentanil has no effect on succinylcholine-induced CPK changes. However, remifentanil limits cardiovascular responses following tracheal intubation.

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