

Blood Biomarkers Alterations with Administration of Propofol for Anaesthesia Maintenance during Long term Oral and Maxillofacial Surgeries

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Abstract

Objective: This prospective study performed to evaluate blood biomarkers alterations with administration of propofol for maintenance of anaesthesia during long oral and maxillofacial surgeries in order to estimate the risk of Propofol Infusion Syndrome (PRIS). This rare syndrome often would be happened in long duration or high dose infusion which is characterized by the combination of metabolic acidosis, acute bradycardia and/or asystole, and rhabdomyolysis and can be fatal.

Methods: Patients undergoing maxillofacial surgeries (>3h) were the subjects of this quasi experimental prospective clinical trial study. Induction of anaesthesia was performed with midazolam 0.025 mg/kg, fentanyl 2 µg/kg, thiopental sodium 5 mg/kg, and atracurium 0.5 mg/kg. Infusion of propofol was initiated (100 µg/kg/min) for maintenance of anaesthesia. Serum potassium level, creatine kinase, lactate and blood PH, were evaluated at baseline, and at 2, 4, 6 hours following the initiation of propofol infusion. Generalized estimating equation was used to evaluate the longitudinal changes for each of the evaluated biomarkers. The relation between the biomarkers and the following factors were appraised by using covariance linear (enter mode) regression analysis: age, gender, weight, administered dose of dexamethasone and epinephrine, duration of surgery, and a history of trauma prior to surgery.

Results: A total of 55 participants, 31 women and 24 men, were studied. The mean duration of surgery was 4.8(1) hours. Despite the rise in the level of potassium and creatine kinase and the reduction of blood PH, no case of hyperkalemia or severe metabolic acidosis was observed. Serum lactate level gradually increased to higher than normal in few patients; though did not necessitate any intervention. All alterations were statistically significant. Potassium and creatine kinase level at baseline had relation to pre-surgical trauma.

Conclusion: Maintenance of anaesthesia with 100 µg/kg/min propofol along with administration of low-dose epinephrine and dexamethasone did not cause clinically important alterations in blood biomarkers during long-duration maxillofacial surgeries and might not cause PRIS.

Key words: Hyperkalemia, Metabolic acidosis, Propofol, Propofol Infusion Syndrome.

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Introduction:

Propofol is an intravenous sedative-hypnotic agent, broadly used for induction and

maintenance of general anaesthesia and inpatient sedation, as well as continuous sedation at intensive care units (ICU). The superiority of this medicine over other anesthetic agents is

mainly due to its quick onset of action and rapid recovery of consciousness. Moreover, its minimal effect on blood pressure leading to reduced intra-operative bleeding makes it particularly advantageous for out- and in-patient oral and maxillofacial surgeries (1-4).

Despite all the advantages, serious adverse effects such as refractory bradycardia, cardiac asystole, metabolic acidosis, and rhabdomyolysis have been reported with higher doses (>4mg/kg/h) or long-term (>48h) infusion of this agent (1, 4-6). A few cases have also demonstrated the occurrence of these symptoms with short term or low-dose infusions of propofol (7-11). These rarely seen but fatal symptoms, having been called the Propofol Infusion Syndrome (PRIS) since 1998 (5) and has resulted in debates regarding the safety of propofol in different medical settings.

Although propofol has been proved as a safe and efficacious sedative agent for outpatient oral surgeries (1, 12-13), the probability of an increased risk of PRIS, still remains obscure, when propofol is used for maintenance of anaesthesia in long-duration oral and maxillofacial surgeries. Besides, the concomitant use of catecholamines and corticosteroids has been suggested as a risk factor for incidence of PRIS (4).

Administration of these medicines is common in oral and maxillofacial surgeries for elimination of bleeding and inflammation, so raises concern about the safety of this anesthetic agent in maxillofacial surgeries.

Metabolic derangements revealed by monitoring certain biochemical markers such as electrolytes, serum creatine kinase, serum lactate, and blood PH, that can serve as an early manifestations of PRIS (4,6). This prospective study aimed to evaluate the propofol-induced alterations in these biochemical parameters during long oral and maxillofacial surgeries (>3h) and to determine the relationship between these changes and different durations of surgeries.

Methods:

This quasi-experimental clinical trial was in accordance with Helsinki Declaration and was approved by the ethical committee of Shahid Beheshti University of Medical Sciences. The study was performed on patients undergoing long-duration oral and maxillofacial surgeries in our teaching hospital, Tehran, Iran in 2011. Patients within 18-60 years of age who were a class I or II according to the American Society of Anaesthesiologists (ASA) physical status classification were enrolled in this study. The exclusion criteria were: history of drug abuse, allergies to egg and soya bean, history of respiratory and/or renal disease, surgical procedures lasting for less than 3 hours, severe hypotension during surgery, and malignant hyperthermia. Furthermore, patients who received blood transfusion or any medicine, other than those included in the treatment plan were also excluded. Written informed consent was obtained from each participant following explanation of the study process and aims.

At surgery, patients were pre-medicated with midazolam 0.025 mg/kg, fentanyl 2 µg/kg, thiopental sodium 5 mg/kg, and atracurium 0.5 mg/kg and were intubated at the bispectral index (BIS) of 40-60. Subsequently, infusion of propofol was initiated (100 µg/kg/min) in order to maintain the BIS reading at 40-60. Along with propofol infusion, all patients received IV bolus of dexamethasone (8 mg, repeated at 4 hour intervals by intravenous administration), as well as local Anaesthesia (lidocaine 2%, epinephrine 1/100000 in 10 cc, administered subcutaneous). Remifentanyl with dose of 0.05 µg/kg/min was used as analgesic agent.

Heart rate, blood pressure, oxygen saturation (SPO₂), end-tidal CO₂ (ETCO₂), and temperature were monitored from prior to induction of anaesthesia until the patient was transferred to recovery room. Evaluation of serum electrolyte level (including potassium level and blood PH),

serum creatine kinase, and serum lactate was performed for all participants at baseline, and then at 2, 4, and 6 hours post-propofol infusion. The relation between the evaluated biomarkers and the following factors was also appraised: age, gender, body weight, administered dose of dexamethasone and epinephrine, duration of surgery, and a history of trauma prior to surgery. At the end of surgery, all patients were reversed by neostigmine 0.07 mg/kg and atropine 0.01 mg/kg. All statistical analyses were performed using statistical package for the social sciences (SPSS) software, version 16. Quantitative data were presented by mean (standard deviation) while qualitative data were reported by frequencies and percentages. Generalized estimating equation with exchangeable correlation structure was used to evaluate the longitudinal changes for each of the studied biomarkers. To assess the effect of different factors on the measured biomarkers, covariance linear (enter mode) regression analysis was performed. The level of significance was defined as p-value less than 0.05.

Results:

A total of 67 patients were enrolled for oral and maxillofacial surgeries under general anaesthesia with duration of more than 3 hours, were enrolled in this study. Twelve patients required blood transfusion or infusion of tri-nitroglycerin (TNG) during the surgery, hence were excluded from the experiment. The remaining 55 participants with an average age of 31.1 years old (SD=12.5, range 18-60 years old) consisted of 31 women (56.4%) and 24 men (43.6%) were followed until the end of this trial. The average body weight of the patients was 54.4 kg (SD=8.5, range 43-70 kg). The average duration of surgery was 4.8 hours (SD=1, range 3-6.5 hours). Table 1 demonstrates the frequencies and percentages of different types of surgeries performed on the participants. The average amount of dexamethasone and epinephrine received by the patients during surgery was 10.5 mg/kg (SD=3.7, range 8-16 mg/kg) and 57.3 µg/kg (SD=21.6, range 0-90µg/kg), respectively.

Table 1- The frequencies and percentages of different types of surgeries performed on participants.

Type of surgery	Number of patients	Percentage
Orthognathic surgery	14	25.5
Recent trauma	7	12.7
Previous trauma	4	7.3
Aesthetic	12	21.8
Condylectomy	3	5.5
Bone grafting	4	7.3
Pathologies	11	20

In table 2 the average values for serum potassium, blood pH, serum creatine kinase, and serum lactate, measured at baseline and at 2, 4, and 6 hours during the surgery, is demonstrated. It should be noted that duration of surgery was less than 4 hours in 2 patients and less than 6 hours in 38 patients. The level of potassium was increased (Diagram 1) and blood pH reduced (Diagram 2) after initiation of propofol infusion.

Time had a significant effect on potassium level and blood pH, with a 0.034 mEq/L increment per hour and 0.012 decline per hour, respectively ($p<0.001$). Nevertheless, no case of hyperkalemia (potassium level > 5mEq/L) or severe metabolic acidosis (pH<7.3) was observed. Serum creatine kinase was also significantly increased after the initiation of propofol infusion, demonstrating an increase of

17.445 IU per hour Diagram3).

Table 2- The average values for serum potassium, blood PH, serum creatine kinase, and serum lactate, measured at baseline and at 2, 4, and 6 hours during the surgery.

Biomarkers		Baseline N=55	At 2 h N=55	At 4 h N=53	At 6 h N=17
Potassium	Average	3.93 (SD=0.29)	3.96 (SD=0.25)	4.06 (SD=0.3)	4.09 (SD=0.27)
	Range	3.4-4.8 7.38	3.4-4.5 7.37	3.5-4.8 7.34	3.5-4.5 7.32
PH	Average	7.38 (SD=0.06)	7.37 (SD=0.09)	7.34 (SD=0.09)	7.32 (SD=0.07)
	Range	7.3-7.54	7.3-7.55	7.3-7.5	7.3-7.44
Creatine kinase (IU/L)	Average	76.5 (SD=32.5)	114.2 (SD=39)	144.4 (SD=61.3)	191.2 (SD=57.6)
	Range	13-170	33.5-196	35-360	109-340
Lactate	Average	8.69 (SD=3.82)	12.12 (SD=5.76)	14.82 (SD=6.53)	18.32 (SD=7.07)
	Range	4.3-20	4.2-26	4.8-29.2	6.5-34

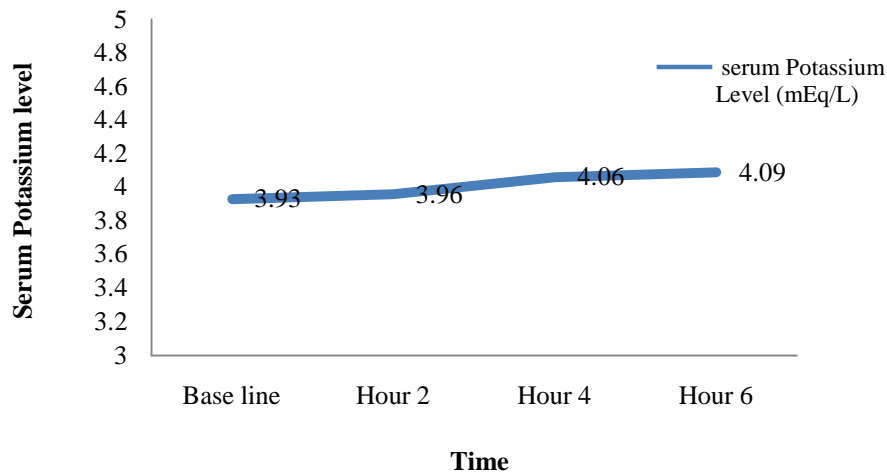


Diagram 1- Mean level of serum potassium (mEq/L) at different times of measurement

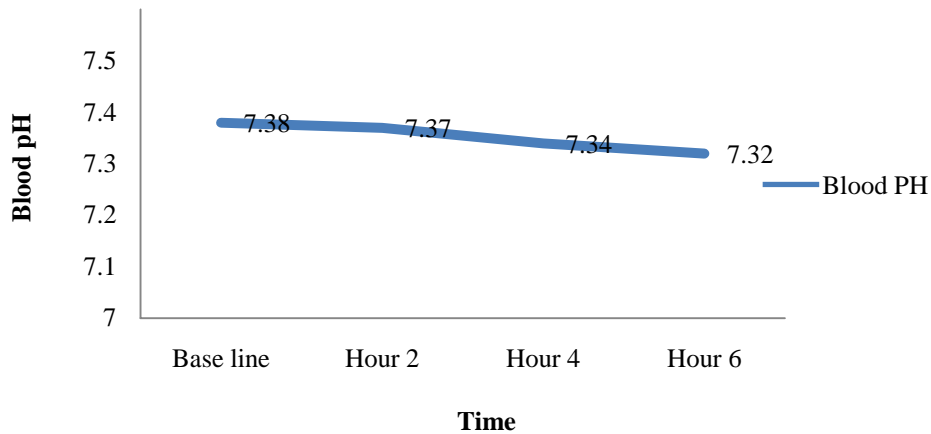


Diagram 2- Mean blood PH at different times of measurement

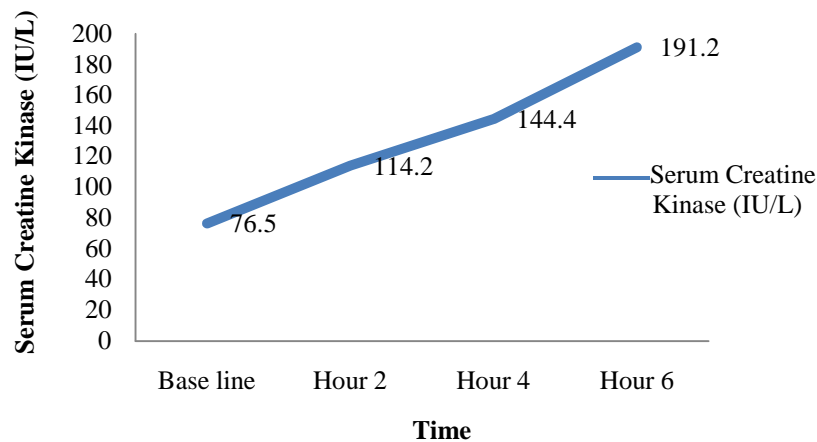


Diagram 3- Mean level of serum creatine kinase at different times of measurement

Creatine kinase level was not increased to higher than the normal level (<240 IU/L) in any of the patients. On the other hand, the level of serum lactate gradually increased from the baseline level and reached to the levels higher than 19.8 mg/dL in some patients (normal range in venous blood sample: 4.5-19.8 mg/dL); (Figure 4). This increase was statistically significant (1.555 mg/dL increase per hour, $p < 0.001$); however, it was not presented any clinically important manifestation in any of the patients and did not necessitate further intervention. Given these results, PRIS occurred in none of the participants who received propofol infusion with dose of 100 $\mu\text{g}/\text{kg}/\text{min}$ for more than three hours.

According to the covariance regression analysis,

serum potassium level at baseline was only relevant to trauma and was increased in traumatic patients ($p = 0.04$). Moreover, potassium level was directly related to the duration of surgery within 2 hours post-infusion ($p = 0.042$) and at 4 hours post-infusion ($p < 0.001$).

Creatine kinase level at baseline was also related to trauma ($p = 0.029$). In addition, creatine kinase level at 4 hours post-infusion was found to have a positive relation with the duration of surgery ($p = 0.008$), while it was reduced by the increase of dexamethasone dose ($p = 0.035$).

Blood pH and serum lactate level had no significant relation with the factors considered for regression analysis.

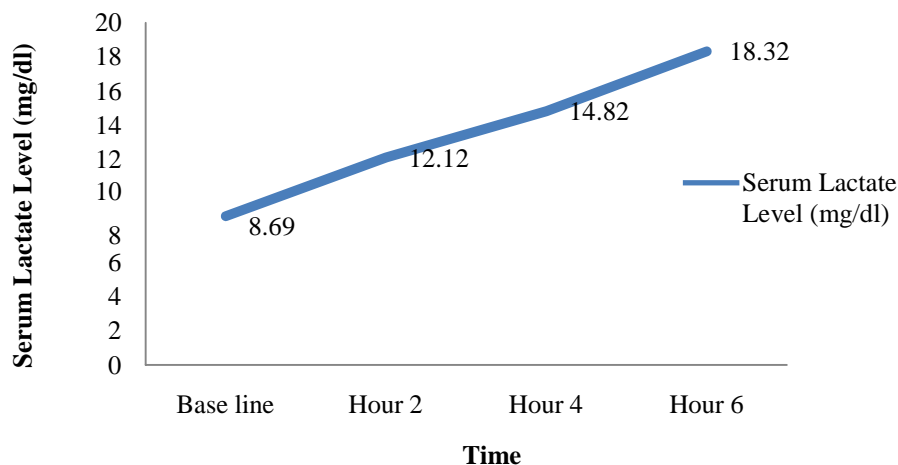


Diagram 4- Mean level of serum lactate at different times of measurement

Discussion:

Our current knowledge about the etiology, risk factors, and diagnostic symptoms of PRIS is limited to the findings reported in case reports and retrospective studies, probably due to its rare incidence (14). Propofol infusions longer than 48 h or with doses greater than 4 mg/kg/h are considered the major risk factors for PRIS (1,4-6)

This rare syndrome would be happened in long duration and/or high dose propofol infusions which are characterized by the combination of metabolic acidosis, acute bradycardia and/or asystole with cardiac and renal failure and rhabdomyolysis which is often fatal (2, 4-6).

This prospective study aimed to assess biomarker changes associated with propofol administration for maintenance of anaesthesia during long term oral and maxillofacial surgeries. Alterations in biomarker levels, although statistically significant, were not clinically important in any of the patients. None of our patients, in whom general anaesthesia was maintained with propofol for more than 3 hours, were affected with PRIS.

So it seems close observation of the patient is the key to prevention of mortality associated with PRIS. Frequent monitoring of certain chemical biomarkers; even if not definite, has been recommended for early diagnosis of PRIS (15). Metabolic acidosis and an increase in blood lactate level are suggested as significant diagnostic indicators (14-15). These laboratory findings have mainly been reported in association with long durations of propofol infusion (15). Burow, *et al.* (2004) reported a patient in whom metabolic acidosis developed following high-dose propofol-induced anaesthesia (16). In the absence of other causative factors for metabolic acidosis, propofol was suggested as the potential cause.

In the current study, blood PH decreased during the surgery but remained within the normal

range. Therefore, metabolic acidosis did not occur in any of the patients. The decline in PH was presumed to be due to the traumatic nature of the surgeries. It has been suggested that trauma and subsequent reduction in tissue perfusion can lead to metabolic acidosis (17). In addition, in the present study the level of serum lactate gradually increased by time and went beyond the normal value. On the contrary, in a retrospective study which appraised arterial blood lactate in patients under propofol-based general Anaesthesia, lactic acidosis was not seen in any of the patients after 8 hours (18).

Fudickar, *et al.* (2008) reported a case in which PRIS occurred while patient's serum lactate was within the normal range (19). These findings might suggest lactic acidosis to be an unspecific marker for diagnosis of PRIS. Several factors can contribute to lactic acidosis; namely, tissue hypoxia, hyperventilation, inflammation, and surgical trauma (19, 20). In only a few patients in the present study serum lactate were increased almost twofold, requiring no further intervention.

Creatine kinase is another biomarker which has shown an increase in patients affected with PRIS (14, 15). In the current study, the level of serum creatine kinase was increased but did not pass the normal limits. A relation was found between the level of creatine kinase and trauma before surgery. Creatine kinase is an indicator of muscle necrosis and increases with trauma and surgery (14, 21). In addition, this study found a negative relation between the level of creatine kinase and administration of dexamethasone. The anti-inflammatory effects of dexamethasone might have reduced rhabdomyolysis, and so the subsequent release of creatine kinase in blood.

Moreover, in this study we evaluated the level of serum potassium which demonstrated a mild increase during the surgery. Again, hyperkalemia was not detected in any of the participants. The increase in serum potassium level was also found to be related to trauma

before surgery. Mali, *et al.* (2009) observed hyperkalemia as an isolated sign of PRIS when short-term infusions of 3 mg/kg/h propofol were administered for anaesthesia (10). However, development of hyperkalemia can also be due to a sundry of reasons including administration of certain drugs, malignant hyperthermia, blood transfusion, and severe acidosis (10, 22).

Epinephrine is commonly administered during oral and maxillofacial surgeries to provide hemostasis (13). This vasopressor agent has been introduced as one of the risk factors for occurrence of PRIS during propofol-induced anaesthesia/sedation (4). Several reports of PRIS are in cases with concomitant use of propofol and epinephrine (23, 24). A retrospective cohort study reported 3 occurrences of PRIS among 30 patients, in intensive care units, who received propofol for sedative purposes (dosage, up to 134 µg/kg/min; for 86-135 hours) with catecholamine simultaneously (25). Corticosteroids such as dexamethasone have also been associated with an increased risk of PRIS (4). In the current study, relatively low doses of epinephrine and dexamethasone were administered during surgery (average dose of 57.3 µg/kg and 10.5 mg/kg, respectively).

To our knowledge, this is the first prospective study evaluating the biomarker changes associated with PRIS during oral and maxillofacial surgeries. The obtained results demonstrated that maintenance of anaesthesia with 100 µg/kg/min propofol along with administration of low-dose epinephrine and dexamethasone is an acceptable protocol for long-duration oral and maxillofacial surgeries. While alterations in chemical biomarkers did not

appear to be a direct effect of propofol, precise monitoring of the patient is strongly recommended even when maintenance doses of propofol are to be used.

It is not disputable that more precise results could have been accomplished if a controlled randomized design comparing propofol with another anaesthetic agent could be implemented in this study. However, according to the guidelines of our department, administration of other types of anesthetic agents for long term maintenance would not be ethically approved and also conducting classic randomized controlled trials are not possible in many surgical interventional studies (26).

Conclusion:

Maintenance of anaesthesia with 100 µg/kg/min propofol along with administration of low-dose epinephrine and dexamethasone did not cause clinically important alterations in blood biomarkers during long-duration maxillofacial surgeries and might not lead to Propofol Infusion Syndrome.

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Conflict of Interest: “None Declared”

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