European Review for Medical and Pharmacological Sciences 2013; 17: 3385-3390

Biochemical markers in total intravenous anesthesia and propofol infusion syndrome: a preliminary study

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Abstract. – OBJECTIVES: To investigate biochemically whether total intravenous anesthesia (TIVA) using propofol creates a risk for Propofol Infusion Syndrome (PRIS).

PATIENTS AND METHODS: Forty patients scheduled for thyroid gland surgery were randomly assigned into Group T or C and premedicated 30 min before operation. Group T received remifentanyl hydrochloride, propofol infusion following anesthesia induction with propofol, vecuronium bromide and intubation. Group C received remifentanyl hydrochloride infusion, 1-1.5 MAC desflurane inhalation following anesthesia induction with thiopental, vecuronium bromide and intubation. Patients were respired 50% O2-air mixture. Blood gas, potassium, lactic acid, CK-MB, myoglobin, troponin I, total carnitine, triglyceride, creatinine concentrations were determined before operation, at intraoperative hour-2, postoperative hour-6.

RESULTS: There were no significant differences between groups in potassium, lactic acid CK-MB, myoglobin, total carnitine or creatinine levels. Triglyceride level at intraoperative hour-2 increased in Group T, decreased at postoperative hour-6. Troponin I was higher in Group C than Group T at intraoperative hour-2 ($p < 0.05$). No asystole, bradycardia, arrhythmia, hypotension or change in urine color was detected.

CONCLUSIONS: The present biochemical findings suggest that TIVA using propofol is safe.

Key Words:
Anesthesia, Intravenous, Propofol, Propofol infusion syndrome, Side effects.

Introduction

Propofol has become a constant component of total intravenous anesthesia (TIVA) and long-lasting sedation with its advantageous effects such as fast and short-term effect together with fast recovery[1]. However, its safety was questioned after a report of death linked to propofol in 1990, in Denmark and following similar reports[2]. The characteristic findings of hyperlipidemia, metabolic acidosis, rhabdomyolysis, myoglobinemia, bradycardia and asystole have been termed as propofol infusion syndrome (PRIS)[3-11]. This fatal syndrome has been first reported in children and then in adults[12].

The reports of PRIS in patients in intensive care units (ICU) lead questioning of the safety of total intravenous anesthesia, which was then reported to be safe in a clinical study[13]. To the best of our knowledge, there is no published study evaluating biochemical parameters in relation with safety of propofol in TIVA. Therefore, the present randomized, prospective study was undertaken to investigate relevant biochemical markers in an attempt to evaluate propofol's safety and risk of PRIS.

Patients and Methods

Forty ASA I-II patients scheduled for thyroid gland surgery ³ 2 h duration were enrolled in the present randomized, controlled and prospective study and randomly assigned in one of the two study groups. The present study was approved by the Local Ethics Committee of Pamukkale University, School of Medicine and written informed consent was obtained from each patient before enrollment. Exclusion criteria were; corticosteroids, catecholamine medication, unbalanced acid/base ratio, history of allergy, abnormal cardiac rhythm, diabetes mellitus and liver diseases.

Blood samples for analysis of biochemical parameters and blood gas level were obtained in the preparation room 30-min before the start of the operation. All patients received atropine sulphate (Atropin ampoul, 0.5 $mg.ml^{-1}$, Biofarma, Istanbul, Turkey) and midazolam (Dormicum, Roche, Istanbul, Turkey) 0.1 $mg.kg^{-1}$ as intramuscular premedication.

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ECG, heart rate, blood pressure, peripheral oxygen saturation (SpO_2), end tidal carbon dioxide ($ETCO_2$) and bispectral index (BIS) were monitored by Datex Ohmeda S/5 ADU anesthesia delivery system in the operation room. Patients were assigned in one of the two study groups by the closed envelope randomization method. The patients in the Group T received intravenous infusion of 1-2.5 $mg.kg^{-1}$ propofol (Propofol 1% Fresenius, Istanbul, Turkey), 0.08 $mg.kg^{-1}$ vecuronium bromide (Norcuron 10 mg flacon, Organon Teknika, Istanbul, Turkey), and 0.05-2 $\mu g.kg.^{-1}dk^{-1}$ remifentanyl hydrochloride (Ultiva 2 mg flacon, Glaxo Smith Kline laçları A , stanbul, Turkey) as analgesic. Anesthesia was maintained by remifentanyl hydrochloride and propofol infusion so that BIS value was 40-60. Group C received 3-7 $mg.kg^{-1}$ thiopental sodium (Pental Sodyum .E. Ulagay laç Sanayi Türk A , stanbul, Turkey), 0.08-0.1 $mg.kg^{-1}$ vecuronium bromide for induction of anesthesia and 0.05-2 $\mu g.kg^{-1}.dk^{-1}$ remifentanyl hydrochloride infusion as intravenous analgesic. Maintenance of anesthesia was achieved by 1-1.5 MAC desflurane (Suprane, Eczacıba ı Baxter, Istanbul, Turkey) and remifentanyl hydrochloride infusion so that BIS value was 40-60.

In both groups, muscle relaxation was provided by 0.03 $mg.kg^{-1}$ vecuronium bromide when needed and all patients were respired 50% O_2/air mixture. Remifentanyl infusion was stopped 10 min before the completion of the operation in the study groups. At the time of the last suture placement, propofol and desflurane infusions were stopped. Duration of operation, total propofol and propofol amount/kg/hour were recorded. Extubated patients were discharged from the recovery room when the Aldrete score reached to 9.

For biochemical analysis, arterial blood samples were obtained from all patients before the operation, at intraoperative hour-2, and finally at postoperative hour-6. Arterial blood gas measurements were done by selective electrode technique, serum potassium level by indirect ion selective electrode technique, serum lactic acid level by NADH UV technique, CK-MB, myoglobin and troponin levels by fluorometric enzyme immune assay technique, total carnitine level by kinetic UV technique, triglyceride level by enzyme end point technique and serum creatinine level by alkaline picrate technique (Architect CI 8200, Abbott Lab, Istanbul, Turkey).

Table I. Demographic characteristics in the study groups (mean ± SD)

	Group T (n=20)	Group C (n=20)	*p*
Age (years)	43.60 ± 6.45	45.65 ± 7.53	0.361
Sex (M/F)	4/16	6/14	0.465
Body weight (kg)	65.30 ± 6.43	66.60 ± 5.07	0.482
ASA (II/I)	6/14	6/14	1.000
Operation time (min)	132.35 ± 3.67	134.10 ± 4.12	0.164

Statistical Analysis

Data were evaluated statistically using the SPSS software 15.0 package program (SPSS Inc., Chicago, IL, USA). Frequency distributions, means, standard deviations (SD) and cross tables were utilized for data analysis. Categorical comparisons were performed by Chi-square or Fischer exact test. Parameters were compared between the two study groups by Student's t test and Mann-Whitney U test. For intragroup comparisons at different time points, Repeated Measure of Variance Analysis and Friedman Test were used. In the presence of significant intergroup differences, Bonferroni and Dunnet Test were used. $p < 0.05$ was selected as significant for all statistical analysis.

Results

The study groups were similar in terms of demographic characteristics (Table I). Ten patients suffered from hypertension besides thyroid disease (6 of these were in Group T and 4 in Group C), two patients suffered from COPD: chronic obstructive pulmonary diseases (1 in each of the groups).

Preoperative, intraoperative and postoperative measurements of blood pressure, heart rate, $ETCO_2$, and SpO_2 values were similar both in intra and intergroup comparisons. Intergroup comparisons revealed no significant difference in the first two measurements in BIS values although BIS values were lower in Group C starting from min-15 ($p < 0.05$) (Table II).

Blood gas analyses revealed similar values in blood bicarbonate, base deficiency, and O_2 saturation (SpO_2) both in intragroup and intergroup comparisons ($p > 0.05$). $PaCO_2$ and PaO_2 values were similar in the study groups, and both groups exhibited lower $PaCO_2$ and higher PaO_2 values at intraoperative hour-2 compared to the preoperative values ($p < 0.05$). pH was higher in Group T than Group C at intraoperative hour-2 ($p < 0.001$) (Table III).

Table II. Blood pressure, heart rate, ETCO2, SpO_2 and BIS values in the study groups (mean± SD).

	Preop	1st min	15th min	30. min	60. min	90. min	120. min	Postop	p^*
MAP (mmHg)	86.3 ± 12.2	82,3 ± 10.7	82.8 ± 12.6	83.3 ± 12.3	83.2 ± 9.6	85.6 ± 9.7	82.5 ± 9.8	85.3 ± 11.5	>0.05
Group T	84.3 ± 11.2	82.9 ± 9.3	83 ± 10.7	81.7 ± 8.3	83 ± 10.3	83.7 ± 9.4	83.9 ± 10.4	82 ± 7.6	>0.05
Group C	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	
p^{**}									
HR (beat/min)	75.8 ± 5.5	76.8 ± 5.9	75.3 ± 5.5	75 ± 6	75.2 ± 5	75.5 ± 5.5	75.2 ± 6.5	77.2 ± 5	>0.05
Group T	76.5 ± 5.8	77.2 ± 6.5	76.7 ± 4,9	76.5 ± 5.3	76.8 ± 5.2	76.5 ± 5.9	76.4 ± 5.5	78.1 ± 5.6	>0.05
Group C	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	
p^{**}									
$ETCO_2$ (%)	35 ± 0.1	35.6 ± 0.7	35.6 ± 0.7	35.7 ± 0.6	35.6 ± 0.7	35.5 ± 0.7	35.6 ± 0.8	35.2 ± 0.4	>0.05
Group T	35.1 ± 0.3	35.5 ± 0.7	35.4 ± 0.5	35.5 ± 0.5	35.7 ± 0.6	35.4 ± 0.5	35.5 ± 0.5	35.1 ± 0.5	>0.05
Group C	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	
p^{**}									
SpO_2 (%)	98 ± 0.3	98.5 ± 0.5	98.4 ± 0.7	98.4 ± 0.5	98.3 ± 0.5	98.2 ± 0.5	98.4 ± 0.5	98.5 ± 0.5	>0.05
Group T	98.1 ± 0.5	98.4 ± 06	98.6 ± 0.5	98.6 ± 0.5	98.5 ± 0.5	98.4 ± 0.5	98.5 ± 0.5	98.3 ± 0.4	>0.05
Group C	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	
p^{**}									
BIS	97.4 ± 0.6	32 ± 2	50.2 ± 3.5	50.5 ± 2.4	50.4 ± 3.7	50.6 ± 3.5	51 ± 3.5	94.8 ± 1.5	<0.001
Group T	97.3 ± 0.7	>0.05	43.8 ± 1.8	42.6 ± 2.1	44.7 ± 2.8	44.6 ± 1.5	45.4 ± 2.5	95.8 ± 1.4	<0.001
Group C	>0.05	31.5 ± 1.3	<0.001	<0.001	<0.001	<0.001	<0.001	<0.05	
p^{**}									

p^*: intragroup comparisons; p^{**}: intergroup comparisons

Potassium, lactic acid, CK-MB, myoglobin, total carnitine, and serum creatinine values were all similar in intra and intergroup comparisons (Table III). Troponin values were higher in Group C at the intraoperative and postoperative measurements; triglyceride values were higher in Group T at intraoperative hour-2 but decreased to normal levels at postoperative hour-6 ($p < 0.05$) (Table III). No asystole, bradycardia, arrhythmia, hypotension or change in urine color was detected in any of the patients.

Discussion

Propofol infusion syndrome (PRIS) occurs as a result of long-standing and high dose of propofol infusion, which is characterized by heart failure, kidney failure, hyperkalemia, hyperlipidemia, rhabdomiolisis, and metabolic acidosis that is basically an iatrogenic clinical entity. Dosage and duration are major risk factors, but there are also reports related to low dose[3-11,14-20]. The number of case reports in both children and adults is increasing[14-17], but evidence-based data is still lacking on its frequency[15].

The fact that there are reports of PRIS in TIVA besides long-term sedation has led questioning of the safety of propofol. The literature is mainly based on case reports and statistical comparisons of biochemical data have not been published before[3-11,14-16,20]. To the best of our knowledge, this is the first prospective study comparing total intravenous anesthesia with propofol and inhalation anesthesia in adult patients.

Mechanically ventilated patients with diagnoses of head trauma, severe infections, congenital abnormalities have a major place in the literature on PRIS cases[3-11,14-16,20]. It is well-known that mechanical ventilation has undesired effects such as decrease in heart volume, liquid retention, decrease in urine discharge, decrease in liver perfusion, difficulty in cerebral venous circulation, increase in intracranial pressure, volumetric pulmonary trauma, pulmonary damage due to the high oxygen concentration and nosocomial pneumonia.[21] Each of these side effects may trigger PRIS. In the present patient population, hypertension and COPDs were not among the diseases additional to thyroid disease, which could be the primary and triggering factor for PRIS.

Table III. Blood gas analyses and biochemical parameters in the study groups (mean ± SD).

		Preoperative	Intraoperative h-2.	Postoperative h-6.	*p**
pH	Group T	7.37 ± 0.02	7.38 ± 0.03	7.37 ± 0.02	>0.05
	Group C	7.37 ± 0.01	7.43 ± 0.02	7.37 ± 0.01	<0.05
	*p***	>0.05	<0.001	>0.05	
$PaCO_2$	Group T	38.7 ± 1.59	32.3 ± 1.63	38.6 ± 1.64	<0.05
	Group C	38.55 ± 1.67	32.55 ± 1.39	39.05 ± 1.64	<0.05
	*p***	>0.05	>0.05	>0.05	
Pa O_2	Group T	114.45 ± 13.95	213.2 ± 18.13	>0.05	<0.05
	Group C	114.55 ± 12.42	208.5 ± 10.72	116.8 ± 10.16	<0.05
	*p***	>0.05	114.05 ± 10.52	>0.05	
HCO_3	Group T	23.45 ± 2.04	23.25 ± 1.65	23.35 ± 1.5	>0.05
	Group C	23.2 ± 1.15	23.35 ± 1.53	23.05 ± 1.1	>0.05
	*p***	>0.05	>0.05	>0.05	
BE	Group T	1.36 ± 0.71	1.5 ± 0.63	1.49 ± 0.71	>0.05
	Group C	1 ± 0.65	1.23 ± 0.64	1.18 ± 0.6	>0.05
	*p***	>0.05	>0.05	>0.05	
$\%sO_2$	Group T	98.15 ± 0.44	98.9 ± 0.45	98.5 ± 0.51	>0.05
	Group C	98.2 ± 0.41	99 ± 0.01	98.65 ± 0.49	>0.05
	*p***	>0.05	>0.05	>0.05	
K	Group T	3.82 ± 0.17	3.93 ± 0.18	3.91 ± 0.15	>0.05
	Group C	3.82 ± 0.24	3.93 ± 0.27	3.9 ± 0.23	>0.05
	*p***	>0.05	>0.05	>0.05	
Lactic acid	Group T	1.1 ± 0.45	1.15 ± 0.45	1.12 ± 0.46	>0.05
	Group C	1.02 ± 0.5	0.98 ± 0.44	1.03 ± 0.46	>0.05
	*p***	>0.05	>0.05	>0.05	
CK-MB	Group T	11.2 ± 4.46	12 ± 5.09	11.2 ± 4.36	>0.05
	Group C	10.65 ± 4.34	11.75 ± 4.77	11.7 ± 5.78	>0.05
	*p***	>0.05	>0.05	>0.05	
Myoglobin	Group T	34.3 ± 5.56	36.15 ± 9.86	34.6 ± 7.13	>0.05
	Group C	33.9 ± 11.82	36.3 ± 11.82	31.65 ± 9.52	>0.05
	*p***	>0.05	>0.05	>0.05	
Total carnitine	Group T	31.95 ± 5.77	32.35 ± 5.69	32.6±5.78	>0.05
	Group C	32.45 ± 8.44	33.35 ± 7.33	33.5±8.06	>0.05
	*p***	>0.05	>0.05	>0.05	
Troponin I	Group T	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	>0.05
	Group C	0.02 ± 0.01	0.04 ± 0.02	0.03 ± 0.01	<0.05
	*p***	>0.05	<0.01	<0.05	
Creatinine	Group T	0.86 ± 0.08	0.89 ± 0.1	0.9 ± 0.12	>0.05
	Group C	0.83 ± 0.12	0.89 ± 0.11	0.86 ± 0.1	>0.05
	*p***	>0.05	>0.05	>0.05	
Triglyceride	Group T	90.7 ± 7.55	133.8 ± 8.79	93.43 ± 6.27	<0.001
	Group C	91.15 ± 6.53	93 ± 6.89	92.1 ± 6.95	>0.05
	*p***	>0.05	<0.001	>0.05	

*p**: intragroup comparisons; *p***: intergroup comparisons

It has been reported that catecholamine and corticosteroid usage may also be triggering factors for PRIS[6,10-12]. Catecholamines increase cardiac output, thereby, lead to a linear decrease in blood propofol concentration and increase the need for propofol. Increasing the dosage of propofol further increases catecholamine demand and damage heart and peripheral muscle cells[12,14]. Corticosteroids on the other hand, lead to muscle and protein destruction, eventually creating the conditions required for PRIS[12,15]. Therefore, these known triggering factors for PRIS; catecholamines and corticosteroids were not applied in the present study.

Propofol and remifentanyl combination is frequently used in total intravenous anesthesia applications because their metabolism is not dependent on any specific organ[21-24]. A large-scale study comprising 6161 patients reported that this combination is effective and safe in total intravenous anesthesia[13]. However, there were no biochemical analysis in that study which is based solely on clinical observation and hemodynamic parameters. The present work presents biochemical data as well as hemodynamic parameters. According to our findings, there were no cases of hypotension, bradycardia, asystole, or change in

urine color in either T or C groups that may create a suspect of PRIS during the clinical follow-ups. Furthermore, systolic, diastolic, mean blood pressure, heart rate, $ETCO_2$, BIS were all stabile during the hemodynamic follow-up.

Various biochemical parameters and ECG findings have been investigated as markers in PRIS in numerous studies[8-11,17]. ST peaks in ECG similar to those in Brugada syndrome, lactic acid, arterial blood gas analysis, serum potassium, creatinine, triglyceride, total carnitine, CK-MB, troponin I and myoglobin are widely accepted ones among these markers[7-12,14-16]. However, a consensus is still lacking not only on clinical findings as early signs but also biochemical parameters as early markers. Bradycardia and hypotension are frequent side effects of propofol that are mostly related to application speed and high dose, and they cannot be regarded as early signs of PRIS[25-27]. Furthermore, it has been stated that the ST peaks in ECG similar to Brugada syndrome cannot be accepted as early signs of PRIS but rather as signs of sudden death[28]. Greenish color of urine is another frequent finding, but it has been reported that it is due to propofol infusion and thus not specific for PRIS[14]. In this report, all hemodynamic parameters were stabile and no change was observed in ECG. These findings are in line with those of Schmidt et al[13]. Moreover, these findings of no increase in CK-MB, myoglobin, troponin I levels in Group T provide further support for the remark of no myocardial damage.

Blood gas and lactic acid analysis in PRIS cases have indicated development of metabolic acidosis. Lactic acidosis particularly in short-term propofol infusion-related PRIS cases has been suggested as an early sign[8,9,17,29]. In spite of the fact that lactic acidosis is the most frequent finding of PRIS, the case report by Fudickar et al[11] where there was no lactic acidosis, drove the attention on other possible underlying and triggering factors[8,9,19].

Burow et al[8] suggested that metabolic acidosis can be explained by propofol with no other cause in a case report of increase in lactic acid production by cardiac depression, spoiling of lactic acid metabolism by liver damage, inhibition of mitochondrial respiration, creation of metabolic acidosis through sepsis development by emulsion. It has been also stated that in patients with mitochondrial function failure, high fat content in propofol emulsions leads to toxicity and muscle biopsy may help diagnosing mitochondrial diseases[19]. Therefore, avoiding propofol usage in these patients prevents development of PRIS. It has been suggested that fast infusion of chlorine containing liquids result in hyperchloremic metabolic acidosis together with accompanying hypoxia, anemia, shock, diabetes mellitus, decreased blood flow in liver and eventually may trigger development of PRIS[29].

In the present study, demand per hour and preoperative fasting duration were considered for liquid management of patients and basal liquid demand was provided by balanced electrolyte solution. Overdose and too fast liquid application was avoided. Arterial blood gas analysis did not reveal metabolic acidosis. However, $PaCO_2$ values showed insignificant decreases in both groups in the intraoperative period, which is likely to be explained by mechanical ventilation. None of the patients exhibited any sign of mitochondrial disease.

Recently, propofol has been used safely even in patients with renal deficiency, but kidney damage and resultant hyperkalemia, increase in serum creatinine level have been reported in PRIS cases[4,7,12,30]. In the present study, there was no sign of potassium, creatinine increase and change in urine color or decrease in urine discharge in Group T. Thus, there was no finding that indicates kidney damage in Group T.

Increase in triglyceride concentration is widely accepted as a marker of PRIS[14-16]. It has been reported that triglyceride concentration increases at intraoperative hour-2 due to propofol and decreases to normal levels at postoperative hour-8[31]. In this work, increased triglyceride concentration was detected at intraoperative hour-2 and it decreased to normal level at postoperative hour-6. These increases and following decreases in triglyceride levels are in line with the previous reports and may be explained by the fat content of propofol emulsion.

Conclusions

Within the limits of the present findings of the evaluated biochemical parameters, it can be concluded that TIVA using propofol is safe and it does not create a risk for PRIS. Larger scale studies with longer operation times are warranted to better clarify this issue.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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