ORIGINAL ARTICLE

# SAFETY OF PROPOFOL ANESTHESIA DURING NEUROSURGICAL OPERATIONS

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**Hennadiy P. Pasichnyk[1,4], Jan Bilawicz[2,5], Yaroslav M. Pidhirnyj[3], Romana O. Merza[3]**

[1]STATE INSTITUTION OF SCIENCE «RESEARCH AND PRACTICAL CENTER OF PREVENTIVE AND CLINICAL MEDICINE» STATE ADMINISTRATIVE DEPARTMENT, KYIV, UKRAINE

[2]MEDICAL UNIVERSITY OF WARSAW, WARSAW, POLAND

[3]DANYLO HALYTSKYI NATIONAL MEDICAL UNIVERSITY, LVIV, UKRAINE

[4]SHUPYK NATIONAL HEALTHCARE UNIVERSITY OF UKRAINE, KYIV, UKRAINE

[5]INSTITUTE OF PSYCHIATRY AND NEUROLOGY OF WARSAW, WARSAW, POLAND

## ABSTRACT

**The aim:** The purpose of this study was to assess the safety of propofol use during neurosurgical operations of different durations.

**Materials and methods:** 72 patients were divided into three groups depending on the type of operations; it were group 1 (ventriculostomy), group 2 (hematoma removal), and group 3 (tumor removal), the anesthesia durations in these groups were 65±5 min, 145±7 min and 225±10 min, respectively. Total propofol doses in patients of groups 1, 2, and 3 were 452±22 mg, 710±42 mg, and 966±51 mg, respectively. Before intervention and 1 h post operation, blood gas composition, serum levels of transaminase, triglycerides, creatine phosphokinase, and potassium, rate of urine output, level of mean arterial pressure, and heart rhythm rate were determined.

**Results:** No significant deviations concerning hemodynamic indicators, blood gas composition, changes of creatine kinase activity were found for any group patients during the perioperative period. The rate of urine output in all patients reached above 0.5 ml/kg/h without saluretics use. The deviated transaminase values returned to their normal ones during 24 h post intervention. The triglycerides levels were in normal range proving the absence of propofol doses used on the lipid metabolism.

**Conclusions:** Anesthetic protection of neurosurgical interventions using propofol in doses 2.5-3 mg/kg and 3.60.3 mg/kg/h for induction anesthesia and for anesthesia support, respectively, is safe and does not lead to dangerous undesired consequences. However, the propofol use for prolonged patient sedation and his/her adaptation for prolonged lung ventilation needs further studies.

**KEYWORDS:** propofol, propofol infusion syndrome (PRIS), anesthesia, dose

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## INTRODUCTION

After propofol implementation to clinical practice, it became pretty fast an alternative of other intravenous hypnotics due to its gentle introduction to anesthesia, minimal hemodynamic effect, and fairly quick and predictable anesthesia completion. Due to quick onset of action, distribution phase, and short half-period, propofol is used successfully both for anesthesia induction and support and for continuous patient sedation in intensive therapy clinics [1].

However, in 1991 a case of propofol "withdrawal syndrome" was described after two-week propofol sedation of a one-and-half year girl with severe burns [2]. In 1992, a report was published concerning limb convulsions in two children (2½ and 4 years old) after cessation of continuous high dose propofol infusions, the children having been intubated because the croup as a result of acute respiratory virus infections (ARVIs). Both children made a full recovery [3]. However, in the same time a communication appeared in the "British Medical Journal" about five dead children (aged from four weeks up to 6 years); they all were intubated because of severe ARVIs and were sedated by high propofol doses; all of them had lipidemic blood sera and metabolic acidosis and died from myocardial insufficiency accompanied by bradyarrhythmia. The autopsies of patients having been demonstrated no convincing data, the authors proposed the proposal-carrier emulsion to be a damaging factor in children organisms [4]. Since then, a more meticulous study of propofol pharmacokinetics and pharmacodynamics has begun.

Besides, the propofol infusion syndrome (PRIS) attracted attention due to a publication indicating the propofol to be a single factor of complications development in neurosurgical patients [5].

The PRIS may also develop soon after the introduction of low propofol doses (83 μg/kg/min) during a short period of time. The frequency of PRIS development reaches approximately 1% [6, 7]. It proves the clinicians are to follow closely the PRIS signs appearance at once following the propofol introduction and during all the treatment period regardless of this drug dose.

**Table I.** Indicators in patients before and after propofol-using anesthesia

| INDICATOR | NORM | Group 1 | | Group 2 | | Group 3 | |
|---|---|---|---|---|---|---|---|
| | | 2st stage | 2nd stage | 1st stage | 2nd stage | 1st stage | 2nd stage |
| MAP, mm Hg | >65 | 70±6 | 77±8 | 67±7 | 68±5 | 66±6 | 70±10 |
| Heart rate per minute | 70-80 | 78±4 | 80±4 | 72±5 | 82±4 | 78±6 | 78±2 |
| pH | 7.35-7.45 | 7.37±0.12 | 7.27±0.13 | 7.43±0.12 | 7.40±0.18 | 7.37±0.10 | 7.29±0.12 |
| $pO_2$, mm Hg | 83-108 | 89±10 | 90±10 | 87±8 | 89±10 | 89±10 | 92±4 |
| $pCO_2$, mm Hg | 36-44 | 42±6 | 40±6 | 48±6 | 40±6 | 48±6 | 42±2 |
| AST, U/l | <35 | 32±6 | 34±6 | 32±5 | 35±4 | 34±4 | 40±6 |
| ALT, U/l | <45 | 42±6 | 44±6 | 34±2 | 38±8 | 32±6 | 48±2 |
| $K^+$, mM/l | 4.5-5.4 | 4.5±0.6 | 4.0±0.6 | 4.9±0.2 | 4.6±0.9 | 4.4±0.4 | 4.5±0.6 |
| Rate of urine output, ml/min | >0.5 | 0.6±0.5 | 0.8±0.3 | 0.6±0.5 | 0.9±0.7 | 0.5±0.1 | 0.6±0.5 |
| Creatine phosphokinase (MM-isomer), U/l | 24-170 | 98±12 | 99±11 | 98±6 | 108±12 | 128±23 | 139±9 |
| Triglycerides, mM/l | 0-1.7 | 0.6±0.2 | 0.6±0.1 | 0.4±0.3 | 0.5±0.1 | 0.8±0.1 | 0.7±0.2 |

## THE AIM

The aim of this investigation was the evaluation of propofol use safety during neurosurgical interventions of different durations.

## MATERIALS AND METHODS

We have investigated 72 patients having undergone neurosurgical interventions – ventriculostomies, removal of intracranial hematomas, and intracerebral tumors. According to the ASA, the anesthesia risks were assessed as a risk of II-III degrees.

The study was conducted according to the principles of the Council of Europe Convention on Human Rights and Biomedicine, World Medical Association Declaration of Helsinki on the ethical principles for medical research involving human subjects, and current Ukrainian regulations. The local ethics committee approved the study protocol. All the patients signed an informed consent.

All the patients were divided into three groups according to the anesthesia duration, these indicators having been 65±5 min, 145±7 min and 225±10 min for patients of groups 1, 2, and 3, respectively. The patients of the group 1 underwent endoscopic ventriculostomy; decompressive craniotomy accompanied by subdural hematoma removal and intracranial tumor removal were realized for patients of groups 2 and 3, respectively. In all cases, propofol (2.5-3 mg/kg) was taken for induction anesthesia. After fentanyl (100 μg) and myorelaxants introduction, tracheal intubation was made followed by the establishment of mechanical lung ventilation. The respiratory support was carried out using an anesthesia and respiratory station «Drager Prim- us Anesthesia Machine + Sevofluran» and an oxygen-air mixture containing FiO2 (40 %). To support the state of anesthesia, propofol was taken at a dose 3.6±0.3 mg/kg/h. The total propofol doses were 452±22 mg, 710±42 mg, and 966±51 mg for patients of groups 1, 2, and 3, respectively. In all cases, diazepine tranquilizers (diazepam) were used for premedication 40 min before the start of intervention. The rate of infusion therapy (balanced crystalloids) during surgery was 2-3 ml/kg/h.

Blood gases as well as the levels of transaminases, triglycerides, creatine phosphatase (its MM-isomer), and potassium ions levels were determined in all cases before surgery (1st stage) and in 1 h following the surgery completion (2nd stage); rate of urine output, level of mean arterial pressure (MAP), and heart rate were also checked.

Our data are presented as an arithmetic mean ± standard deviation (M ± δ). Examination of the correspondence of the indicator distribution to normal ones was carried out according to the Kolmogorov-Smirnov consistency criterion, comparison of indicators in progressive dynamics was realized using the Wilcoxon criterion [8].

## RESULTS

According to the data available [9,10], the PRIS includes in most cases the following clinical symptoms: incomprehensive metabolic acidosis, lactic acidosis, progressing and refractory bradycardia, refractory heart insufficiency and/ or cardiovascular collapse, hepatomegaly, hyperglyceridemia, signs of muscle damage (increased levels of creatine phosphokinase, myoglobulinemia and/or myoglobinuria), acute kidney failure, fever. We decided to investigate some signs able to testify the development of different symptoms demonstrating the negative propofol effect in neurosurgical patients. Our results are presented in the Table I.

According to results of our investigations, we had no statistically significant deviations in hemodynamics data in all three patient groups during all the period of anesthesia and postoperative period. We did not observe any cardiac arrhythmias having being seen on the cardio monitor and detected in ECG data having being written on paper media with an interval of 15 min. All the further ECG results were analyzed together with specialists in functional diagnostics and cardiology.

The indicators of blood gases in our patients had no significant deviations both before interventions and during postoperative period.

The rate of urine output in all propofol-anesthetized patients was above 0.5 ml/kg/h without saluretics use.

We have not found any changes of the creatine phosphokinase (its MM-isomer) activity. In patients of the group 3, the transaminase deviations from the upper normal limit returned to their normal activity in 24 h after surgeries.

The triglyceride levels in our patients did not overstep the bounds of normal physiological ranges; we evaluate these data as the absence of propofol effect in these doses on the lipid metabolism.

## DISCUSSION

While carrying out our investigation we have found out the propofol use in doses taken for neurosurgical interventions of varying complexity and duration is rather safe. We have not seen any significant changes concerning different organs activity and any PRIS signs.

The propofol infusion syndrome is interpreted as mitochondrial lipid metabolism damage being a consequence of continuous use of this drug. It is accompanied by the development of hypertriglyceridemia, metabolic acidosis, arrhythmias leading to refractory bradycardia, hyperlipidemia, rhabdomyolysis, and myoglobinemia [11].

The PRIS is thought to develop as a result of fatty acids utilization damage in mitochondria leading to some chang- es in the chain of tissue respiration. The role of mitochon- drial defects in this process is not proved; however, there are some suspicions concerning individual peculiarities of some persons prone to PRIS development. There are also hypotheses taking into consideration some metabo- lite-mediated damages and neuro-muscular defects [12]. In some literary sources describing the PRIS pathophysiology there are opinions propofol to increase the activity of malonyl-coenzyme A leading to the inhibition of carnitine palmitoyl transferase 1. As a result, long-chain fatty acids become unable to enter the mitochondria [13]. Beta-spiral oxidation and respiratory chain disengage, so neither middle-chained nor short-chain free fatty acids cannot be utilized; this circumstance leads to myocytolysis process. The energy supply is lower than the need for it; the energy deficiency leads to necrosis in cardiomyocytes and peripheral muscles. Besides, free fatty acid accumulation becomes a cause of arrhythmias development.

At the same time, some researchers underline the propofol to possess negative inotropic effect due to the decrease of sympathetic tone and antagonism to beta-blockers and calcium channels. It leads to increased body need for catecholamine supporting the hemodynamics stability. Because of the increase of “catecholamine wave” it is necessary to speed up the pace of propofol infusion aiming to assure the sufficient sedation [14]. In such a way, “the enchanted circle” closes.

To avoid the PRIS development, it is necessary to adhere strictly to the algorithm including additional examination of patients for whom propofol should be used for anesthesia during interventions of different duration as well as for medical sedation in intensive care units; it is also necessary to determine the levels of triglycerides, lactate dehydrogenase, creatine phosphokinase, transaminases etc. For the same purpose, propofol dosing and duration of application should be optimized. To reduce the lipid load and to prevent any possible bacterial contamination, it would be better to apply 2% propofol-EDTA solution and its combination with other hypnotics, pain killer drugs, benzodiazepines [15].

In the Discussion the authors demonstrate their results achieved for their scientific purposes; they consider the originality of these results and of their methodological approaches as well as some limitations of data obtained.

## CONCLUSIONS

Regardless the anesthesia duration, the propofol use for anesthesia of neurosurgical interventions in doses of 2.5-3.0 mg and 3.60.3 mg/kg/h for induction anesthesia and for the support of anesthesia is a safe approach; it does not lead to undesired effects in the perioperative period.

The safety problem of propofol use for patient prolonged sedation and his/her adaptation for long mechanical lung ventilation needs further studies.

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**ORCID and contributionship:**
*Hennadiy P. Pasichnyk:0000-0002-4481-5696* [A,B,D,F]
*Jan Biławicz: 0000-0003-4129-9275* [A,B,E]
*Yaroslav M. Pidhirnyj: 0000-0002-6926-9257* [B-E]
*Romana O. Merza:0000-0002-4746-9004* [B,C]

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## CORRESPONDING AUTHOR
**Hennadiy P. Pasichnyk**
State Institution of Science «Research and Practical Center of Preventive and Clinical Medicine» State Administrative Department 5 Verhnia St., 01014 Kyiv, Ukraine
tel: +380631357688
e-mail: docpasichnyk@gmail.com

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