Effect of Intraoperative Propofol-Induced Sedation on the Neurotransmitter Levels (Pilot Study)

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Vлияние интраоперационной седации пропофолом на концентрацию нейромедиаторов (пилотное исследование)

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Summary

The aim of the study was to determine the changes in the levels of various neurotransmitters depending on the depth of propofol-induced sedation.

Material and methods. Twenty-four patients were included in a prospective, simple blinded study. All patients underwent elective orthopedic intervention with subarachnoid anesthesia and moderate (group 1, n=12) or deep (group 2, n=12) propofol-induced sedation. Peripheral blood sampling for measurement of neurotransmitter levels was performed before regional blockade (Stage 1), 35–40 min after the start of sedation (Stage 2), and 10–15 min after sedation was terminated and consciousness was recovered (Stage 3).

Results. Deep propofol-induced sedation resulted in a decrease in norepinephrine level at stages 2 and 3. Under moderate sedation, its level decreased at Stage 2 and returned to baseline after restoration of consciousness. The initial concentration of norepinephrine (Stage 1) was higher in Group 2.

Conclusion. Propofol-induced sedation resulted in reduced level of the main stress hormone, which suggests its stabilizing effect on autonomic nervous system.

Keywords: propofol; sedation; neurotransmitter level; norepinephrine

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Currently, the clinical effects of propofol are generally believed to be associated with a direct effect on GABA receptors in the brain, which accounts for their inhibitory effect on the central nervous system (CNS) with the development of drug-induced sleep [1–5]. At the same time, the limbic system structures, particularly the ventrolateral preoptic region of the hypothalamus responsible for natural sleep, are among the main targets for propofol [6,7]. This area consists mostly of GABA neurons, 70% of which are norepinephrine (NE)-inhibitory and 30% are NE-activating [8]. Propofol, having agonist effect on GABA receptors, is perceived to inhibit NE-activating neurons, which activates NE-inhibit-
ing neurons, reduces the NE level and, consequent-
ly, causes drug-induced sleep and anti-stress effect
[9–12]. On the contrary, norepinephrine injection
into hypothalamic area in animals accelerated
recovery time from anesthesia [13].

Another effect of propofol is the midbrain ventral
tegmental area (VTA), which serves as an origin
site for the mesocortical and mesolimbic dopamine
pathways involved in behavioral responses and the
maintenance of wakefulness [14]. For example, in
experiments, the VTA damage or the use of
dopamine receptor antagonists led to prolonged
recovery time after propofol administration [15, 16].

However, the effects of intraoperative sedation
with propofol on the changes in other CNS neuro-
transmitter systems (acetylcholine, serotonin)
remain largely unclear [17]. At the same time, most
of these systems are also responsible for the devel-
opment of various human behavioral responses
that accompany various psychotic conditions, such
as anxiety and depression [18–21]. The origin of
these conditions has not been sufficiently studied
and may be directly related to the changes in brain
neurotransmitter levels [22].

The aim of the study was to examine the changes in the level of various neurotransmitters depending on the depth of propofol-induced
sedation.

Material and Methods

This study was approved by the Local Ethics
Committee of the First Sechenov Moscow State Med-
ical University and registered in ClinicalTrials.gov
#NCT04695509.

A prospective simple blind pilot non-random-
ized clinical trial was performed in 24 patients who
underwent surgery under spinal anesthesia. The labora-
yary specialist responsible for the measure-
ment of neurotransmitter levels was not aware of
group assignment and sedation levels.

Inclusion criteria for the study were patients
aged 18 to 70 years, ASA (American Society of Anes-
thesiologists) class I–II, who underwent orthopedic
interventions on the lower extremities under spinal
anesthesia. The inclusion criteria for the study were
patients with moderate sedation, the target con-
centration of propofol was 1.5 mcg/ml, with deep
sedation — 2.5 mcg/ml.

To ensure patient safety, the routine standard
monitoring was used including assessment of BP,
HR, ECG, SpO2, and capnography (IntelliVue MP40

The Richmond Arousal and Sedation Scale
(RASS) and bispectral index (BIS) (A-2000XP mon-
itor by Medlekprom, Russia) were used to assess the
depth of sedation. The RASS scale values of «-2» to
«-3» (brief eye opening less than 10 seconds or vol-
untary movements without eye contact in response
to voice) and BIS values of 70–90 were considered
as moderate sedation. Deep sedation was diag-
nosed when RASS score was «-4» (eye opening or
voluntary movements in response to physical stim-
ulation) and BIS score was 60–70.

Two intravenous peripheral 18 or 20 G
catheters were inserted before regional anesthe-
sia in the operating room for infusion therapy and
blood sampling. Before spinal anesthesia, an in-
fusion of Sterofundin® (isotonic balanced fluid)
6–8 ml/kg was given.

Aseptic lumbar puncture using a 27 G Pencil
Point needle was performed under local anesthesia
with lidocaine at the L2–L4 level. The cere-
brosplai fluid return was used as a criterion for
the proper procedure performance. After aspiration
test, 10–15 mg of isobaric bupivacaine solu-
tion was injected.

The touch sensitivity (pinprick) test was used
to evaluate the sensory block, the motor block was
evaluated using the Bromage scale.

Intravenous infusion of propofol was per-
formed with Perfusor Space (B. Braun, Germany)
using the target-controlled infusion technique. For
patients with moderate sedation, the target con-
centration of propofol was 1.5 mcg/ml, with deep
sedation — 2.5 mcg/ml.

Patients were recruited at Moscow City Hospi-
tal No. 31 (affiliated with the First Sechenov
Moscow State Medical University). The plasma lev-
els of neurotransmitters were measured in the clin-
ical laboratory of the B. V. Petrovsky Russian Sur-
gergy Research Center.

The patients were assigned to two groups de-
pending on the depth of sedation: moderate
(Group 1, n=12) and deep (Group 2, n=12). As
shown in Table 1, the groups were comparable in
age, sex, and body measurements.

Two intravenous peripheral 18 or 20 G
catheters were inserted before regional anesthe-
sia in the operating room for infusion therapy and
blood sampling. Before spinal anesthesia, an in-
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nosed when RASS score was «-4» (eye opening or
voluntary movements in response to physical stim-
ulation) and BIS score was 60–70.

To ensure patient safety, the routine standard
monitoring was used including assessment of BP,
HR, ECG, SpO2, and capnography (IntelliVue MP40

Table 1. Demographic parameters and body measurements in the study groups, Me[25, 75].

| Parameters          | Values in groups | P-value |
|---------------------|------------------|---------|
|                     | 1, n=12          | 2, n=12 |         |
| Male, n (%)         | 6 (50)           | 3 (25)  | 0.4     |
| Female, n (%)       | 6 (50)           | 9 (75)  |         |
| Age, years          | 51.5 [41.0; 60.5]| 55.5 [33.0; 50.0]| 0.91 |
| Height, cm          | 169.0 [164.5; 182.5]| 172.0 [167.5; 175.0]| 0.73 |
| Weight, kg          | 83.5 [63.0; 100.0]| 72.5 [62.5; 81.5]| 0.31 |
For pairwise comparisons, the differences were considered significant at $P<0.05$. However, the changes in dopamine levels at all stages were highly variable. Most likely, the study of larger samples of patients will lead to a clearer understanding of patterns of dopamine concentration changes and their possible causes.

At the same time, in both groups a decrease in plasma NE concentration was noted when the sedative effect developed (stage 2). The decrease in NE level was not affected by the drug dose or the depth of sedation (no differences between the groups at stages 2 and 3).

Upon awakening, patients’ plasma NE levels rose and did not differ from baseline values in group 1 ($P=0.62$). In the group with deep sedation, when the dose of propofol was accordingly higher, the NE level on awakening was significantly lower than the baseline values ($P<0.002$).

Interestingly, differences between the groups in the baseline NE levels were found ($P=0.007$). The differences were not related to body measurements, age, or sex.

**Discussion**

Our data demonstrate the stabilizing effect of propofol on the autonomous nervous system regardless of the depth of medical sedation. Norepinephrine is a stress hormone produced mainly in the postganglionic fibers of the sympathetic nervous system and, to a lesser degree, in the adrenal medulla [23-26].

The lack of changes in the levels of other brain-derived neurotransmitters (ACh, etc.) may indicate that they cannot be studied in the blood plasma due to their low concentrations. However, this conclusion requires additional studies due to the fact that these mediators are almost not metabolized in the brain and can enter the circulation with delay. In general surgical practice, it is impossible to perform a study with microdialysis fluid sampling from human brain structures during sedation [27].

The findings indicating the lack of changes in plasma dopamine concentration during sedation in the groups contradict several animal studies, which,
on the contrary, describe its reduced level during propofol infusion [28]. At the same time, the authors note that after discontinuation of propofol infusion and awakening, dopamine level returned to the baseline values [29].

Surprisingly, the baseline plasma NE levels differed between the groups, which could be related to the predominance of women in the second group and probable more intense stress response [30]. Although the groups did not differ significantly in gender, this requires further and thorough research to identify possible gender differences in the development of preoperative stress.

Different patterns of change of NE level on recovery from sedation among the groups are most likely related to the residual effect of propofol and a longer recovery of autonomic response to perioperative stress in the group with deep sedation.

This is a pilot study that cannot fully explain the patterns of neurotransmitter level changes following the use of anesthetics, which warrants randomized clinical trials.

**Conclusion**

Sedation with propofol reduces the blood level of norepinephrine, which indicates its stabilizing effect on the autonomic nervous system.

This stabilizing effect is independent of the drug dose and the depth of sedation.

The recovery rate of blood norepinephrine concentration depends on the dose of propofol.

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