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

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Влияние 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-

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ing neurons, reduces the NE level and, consequently, 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 target 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 neurotransmitter systems (acetylcholine, serotonin) remain largely unclear [17]. At the same time, most of these systems are also responsible for the development 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 Medical University and registered in ClinicalTrials.gov #NCT04695509.

A prospective simple blind pilot non-randomized clinical trial was performed in 24 patients who underwent surgery under spinal anesthesia. The laboratory specialist responsible for the measurement 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 Anesthesiologists) class I–II, who underwent orthopedic interventions on the lower extremities under spinal anesthesia with intravenous sedation.

Exclusion criteria were patient's refusal to participate in the study and regional block anesthesia, age under 18 and over 70, allergic reactions to propofol, lidocaine, bupivacaine, pregnancy, history of epilepsy, ASA class III or higher, emergency surgery, ineffective spinal anesthesia, psychiatric disorders, anticoagulant or psychotropic therapy.

Patients were recruited at Moscow City Hospital No. 31 (affiliated with the First Sechenov Moscow State Medical University). The plasma levels of neurotransmitters were measured in the clinical laboratory of the B. V. Petrovsky Russian Surgery Research Center.

The patients were assigned to two groups depending 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 anesthesia in the operating room for infusion therapy and blood sampling. Before spinal anesthesia, an infusion 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 cerebrospinal fluid return was used as a criterion for the proper procedure performance. After aspiration test, 10–15 mg of isobaric bupivacaine solution 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 performed with Perfusor Space (B. Braun, Germany) using the target-controlled infusion technique. For patients with moderate sedation, the target concentration of propofol was 1.5 mcg/ml, with deep sedation — 2.5 mcg/ml.

The Richmond Arousal and Sedation Scale (RASS) and bispectral index (BIS) (A-2000XP monitor 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 voluntary movements without eye contact in response to voice) and BIS values of 70–90 were considered as moderate sedation. Deep sedation was diagnosed when RASS score was «-4» (eye opening or voluntary movements in response to physical stimulation) and BIS score was 60–70.

To ensure patient safety, the routine standard monitoring was used including assessment of BP, HR, ECG, SpO_2, and capnography (IntelliVue MP40

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

Parameters	Values in groups		
	1, *n*=12	**2, *n*=12**	***P-value***
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

Table 2. Plasma neurotransmitter levels in the study groups, *Me* [25; 75].

Neurotransmitters	Values in groups at study stages					
	1, *n*=12			2, *n*=12		
	Stage 1	Stage 2	Stage 3	Stage 1	Stage 2	Stage 3
Norepinephrine, pg/ml	130.3 [24.7; 151.0]##	3.3 [0.2; 17.6]*	73.7 [13.4; 142.2]	189.9 [143.3; 223.7] **	18.4 [1.0; 142.8]#	77.4 [8.5; 161.8]
Acetylcholine, pg/ml	36.2 [28.7; 49.4]	49.2 [33.5; 62.6]	35.6 [27.7; 61.1]	53.6 [42.9; 67.7]	51.6 [41.8; 74.3]	47.1 [37.0; 78.9]
GABA, μmol/l	0.02 [0.005; 0.025]	0.04 [0.02; 0.06]	0.035 [0.02; 0.06]	0.015 [0.005; 0.04]	0.04 [0.025; 0.055]	0.003 [0.015; 0.045]
Serotonin, ng/ml	7.5 [3.5; 12.5]	6.2 [5.1; 9.6]	5.0 [4.3; 7.6]	5.0 [4.3; 7.6]	7.7 [5.4; 11.5]	8.3 [6.1; 9.4]
Dopamine, ng/ml	7.3 [0.92; 1478.1]	1.7 [0.66; 98.4]	3.7 [0.4; 10.2]	0.81 [0.17; 4.0]	3.5 [1.5; 11.2]	1.0 [0.27; 3.9]

Note. * — *P*=0.007 vs Stage 1 in group 1; ** — *P*<0.002 vs Stage 3 in Group 2; # — *P*<0.001 vs Stage 1 Group 2; ## — *P*=0.007 vs Stage 1 in Group 2.

monitor, Philips Medizin Systeme Boblingen GmbH, Germany).

The levels of neurotransmitters were measured at the following stages of the study: stage 1 — before regional block, stage 2 — 35–40 minutes after the start of sedation, stage 3 — 10–15 minutes after the end of sedation and restoration of consciousness (RASS «0», BIS 90-100).

Blood samples were centrifuged in 367525 BD (Becton Dickinson) Vacutainer 10 ml tubes with K2 ethylenediaminetetraacetate (EDTA) at 4000 rpm for 8 min, and the separated plasma was aliquoted into 363706 BD (Becton Dickinson) Microtainer 0.5 ml tubes with K2-EDTA and frozen at -20°C until analysis. Subsequently, dopamine, serotonin, gamma-aminobutyric acid (GABA), acetylcholine (ACh), and norepinephrine (NE) levels were measured by enzyme-linked immunosorbent assay (ELISA).

Statistical analysis of the data was performed using MS Excel and Statistica 12. Quantitative variables were presented as medians (*Me*) and 25–75% percentiles [25; 75]. The Shapiro–Wilk's test was used to check the normality of data distribution.

Analysis of categorical variables was performed using Fisher's exact test. Mann–Whitney *U*-test was used to compare quantitative variables between groups. A nonparametric Friedman test was used for comparisons between three stages of the study. Nonparametric Wilcoxon's test for dependent samples with Bonferroni correction was used for multiple pairwise comparison of neurotransmitter concentrations at different stages of the study in each group. For pairwise comparisons, the differences were considered significant at $P<0.017$; for intergroup comparisons, at $P<0.05$.

Results

Data analysis showed that the changes in plasma serotonin, ACh, dopamine, and GABA levels depending on propofol dose and associated anesthetic suppression of consciousness were not significant (Table 2).

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.

References

1. *Sahinovic M.M., Struys M.M.R.F., Absalom A.R.* Clinical Pharmacokinetics and Pharmacodynamics of Propofol. *Clin. Pharmacokinet.* 2018; 12 (57): 1539–1558. DOI: 10.1007/s40262-018-0672-3. PMID: 30019172
2. *Sorokina E.Y.* Propofol in modern multicomponent general anesthesia. *Meditsina neotlognykh sostoyaniy.* 2014; 3 (58): 69–75. [in Russ.].
3. *Karnaukh E.V., Suleymanov R.L.* Propofol is a promising induction non-inhalation anesthetic in modern anesthesiology. *European Student Scientific Journal.* 2014; 3: 15. [In Russ.].
4. *Nishizawa T., Suzuki H.* Propofol for gastrointestinal endoscopy. *United European Gastroenterol J.* 2018; 6 (6): 801–805. DOI: 10.1177/2050640618767594. PMID: 30023057
5. *Tang P., Eckenhoff R.* Recent progress on the molecular pharmacology of propofol. *F1000Res.* 2018; 7: 123. DOI: 10.12688/f1000research. 12502.1. PMID: 29445451
6. *Tao L., Fan W., Yongxing S., Baoguo W.* Detection of electrophysiological activity of amygdala during anesthesia using stereo-EEG: A preliminary research in anesthetized epileptic patients. *Biomed. Res. Int.* 2020; 2020: 1–9. DOI: 10.1155/2020/6932035. PMID: 33102588
7. *Jie Y., Zhuxin L., Yu Z., Yi Z., Yuan W., Song C., Bao F., Hao Y., Lin Z., Wenjing Z., Tian Y.* GABAergic ventrolateral pre-optic nucleus neurons are involved in the mediation of the anesthetic hypnosis induced by propofol. *Mol. Med. Rep.* 2017; 16 (3): 3179–3186. DOI: 10.3892/ mmr.2017.7035. PMID: 28765955
8. *Liu Y.* Histaminergic H1 and H2 receptors mediate the effects of propofol on the noradrenalin-inhibited neurons in rat ventrolateral preoptic nucleus. *Neurochem Res.* 2017; 42 (5): 1387–1393. DOI: 10.1007/ s11064-017-2187-y. PMID: 28185047
9. *Liu Y.-W., Zuo W., Ye J.-H.* Propofol stimulates noradrenalin-inhibited neurons in the ventrolateral preoptic nucleus by reducing GABAergic inhibition. *Anesth & Analg.* 2013; 2 (117): 358–363. DOI: 10.1213/ANE.0b013e318297366e. PMID: 23780420
10. *Jung S.M., Cho C.K.* The effects of deep and light propofol anesthesia on stress response in patients undergoing open lung surgery: a randomized controlled trial. *Korean J Anesthesiol.* 2015; 3 (68): 224. DOI: 10.4097/kjae.2015.68.3.224. PMID: 26045924
11. *Miner J.R., Moore J.C., Plummer D., Gray R.O., Patel S., Ho J.D.* Randomized clinical trial of the effect of supplemental opioids in procedural sedation with propofol on serum catecholamines. *Acad. Emerg. Med.* 2013; 20 (4): 330–337. DOI: 10.1111/acem.12110. PMID: 23701339
12. *Mickey B.J., White A.T., Arp A.M., Leonardi K., Torres M.M., Larson A.L., Odell D.H., Whittingham S.A., Beck M.M., Jessop J.E., Sakata D.J., Bushnell L.A., Pierson M.D., Solzbacher D., Kemdrick E.J., Weeks 3rd H.R., Light A.R., Light K.C., Tadler S.C.* Propofol for treatment-resistant depression: A pilot study. *Intern. J. Neuropsychopharmacol.* 2018; 21 (12): 1079–1089. DOI: 10.1093/ijnp/pyy085. PMID: 30260415
13. *Bao F., Tian Y., Jie Y., Xingrui G., Mazhong Z.* Noradrenergic transmission in the central medial thalamic nucleus modulates the electroencephalographic activity and emergence from propofol anesthesia in rats. *J. Neurochem.* 2017; 130 (6): 862–873. DOI: 10.1111/jnc.13939. PMID: 28092095
14. *Hui C., Dan X., Yu Z., Yan Y., JunXiao L., ChengXi L., Wei S., Tian Y., Jin L.* Neurons in the Locus Coeruleus Modulate the Hedonic Effects of Sub-Anesthetic Dose of Propofol. *Front. Neurosci.* 2021; 15: 1–9. DOI: 10.3389/fnins.2021.636901. PMID: 33767609
15. *Li K., Zhou Y., Fu B.* Dopaminergic D1 receptors in nucleus basalis modulate recovery from propofol anesthesia in rats. *Iran. J. Basic Med. Sci.* 2019.23 (3): 298–302. DOI: 10.22038/IJBMS.2019.37716.8962. PMID: 32440315
16. *Pain L., Gobaille S., Schleef C., Aunis D., Oberling P.* In vivo dopamine measurements in the nucleus accumbens after nonanesthetic and

anesthetic doses of propofol in rats. *Anesth. Analg.* 2002; 95 (4): 915–919. DOI: 10.1097/00000539-200210000-00022. PMID: 12351267
17. *Wang Y., Yu T., Yuan C., Yuan J., Luo Z., Pan Y., Zhang Y.* Effects of propofol on the dopamine, metabolites and GABAA receptors in media prefrontal cortex in freely moving rats. *Am. J. Transl. Res.* 2016; 8 (5): 2301–2308. PMID: 27347337
18. *Mineur Y.S., Cahuzac E.L., Mose T.N., Bentham M.P., Plantenga M.E., Thompdon D.C., Picciotto M.R.* Interaction between noradrenergic and cholinergic signaling in amygdala regulates anxiety- and depression-related behaviors in mice. *Neuropsychopharmacol.* 2018; 43 (10): 2118–2125. DOI: 10.1038/s41386-018-0024-x. PMID: 29472646
19. *Aggarwal S., Mortensen O.V.* Overview of Monoamine Transporters. *Curr. Protoc. Pharmacol.* 2017; 1 (79): 12.16.1–12.16.17. DOI: 10.1002/ cpph.32. PMID: 29261228
20. *Uzbekov M.G., Maksimova N.M.* Monoamine-hormonal reletions in the pathogenesis of anxiety depression. *Zhurnal nevrologii i psikhiatrii im. S.S. Korsakova. Spetsvypuski.* 2015; 115 (1–2): 52-55 [In Russ.]. DOI: 10.17116/jnevro2015 1151252-55
21. *Gainutdinov M.Kh., Khakimova D.M., Kalinnikova T.B., Shagidullin R.R.* On the role of the cholinergic system in the stress response of the body and depression. *Ul'yanovskij mediko-biologicheskij zhurnal.* 2019; 1: 93–102. [In Russ.]. DOI 10.34014/2227-1848-2019-1-93-102
22. *Zhang Y., Yu T., Liu Y., Qian K., Yu B-W.* Muscarinic M1 receptors regulate propofol modulation of GABAergic transmission in rat ventrolateral preoptic neurons. *J. Mol. Neurosci.* 2015; 55 (4): 830–835. DOI: 10.1007/s12031-014-04. PMID: 25294312
23. *Morozov V.N., Khadartsev A.A.* On the modern interpretation of stress mechanisms. *Vestnik novyh meditsinskikh tekhnologij.* 2010; 17 (1): 15–17. [In Russ.].
24. *Khadartsev A.A., Morozov V.N., Karaseva Yu.V., Khadartseva K.A., Fudin N.A.* Pathophysiology of stress as a balance of stress and anti-stress mechanisms. *Vestnik nevrologii, psikhiatrii i nejrokhirurgii.* 2012; 2: 16–21. [In Russ.].
25. *Gibbons C.H.* Basics of autonomic nervous system function. *Handb. Clin. Neurol.* 2019; 160: 407–418. DOI: 10.1016/B978-0-444-64032-1.00027-8. PMID: 31277865
26. *Elżbieta W.T., Krzysztof O., Zoran S., Szymon B., Hanna M.* Choosing the optimal method of anaesthesia in anterior resection of the rectum procedures-assessment of the stress reaction based on selected hormonal parameters. *Endokrynol Pol.* 2018; 69 (4). DOI: 10.5603/EP.a2018.0038. PMID: 29952408
27. *Moreno-Castilla P., Perez-Ortega R., Violante-Soria V., Balderas I., Bermudez-Ratoni F.* Hippocampal release of dopamine and norepinephrine encodes novel contextual information. *Hippocampus.* 2017; 27 (5): 547–557. DOI: 10.1002/hipo.22711. PMID: 28176408
28. *Qi C., Shurong L., Yuping H., Xiaohong W., Juan D., Xiaolin W., Bingyin S., Jun L.* Toxicological effects of propofol abuse on the dopaminergic neurons in ventral tegmental area and corpus striatum and its potential mechanisms. *J. Toxicol. Sci.* 2020; 45 (7): 391–399. DOI: 10.2131/jts.45.391. PMID: 32612007
29. *Yi Z., Huan G., Zikun D., Tian Y., Jie Z., Xiaoli L., Chengxi L.* Dopamine D1 Receptor in the nucleus accumbens modulates the emergence from propofol anesthesia in rat. *Neurochem. Res.* 2021; 46 (6): 1435–1446. DOI: 10.1007/s11064-021-03284-3. PMID: 33683630
30. *Liu Y., Zhao J., Guo W.* Emotional roles of mono-aminergic neurotransmitters in major depressive disorder and anxiety disorders. *Front Psychol.* 2018; 9: 2201. DOI: 10.3389/fpsyg.2018.02201. PMID: 30524332

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