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Antidepressant Effect of Propofol and Its Acute Alterations in Prefrontal-Temporal Cortical Blood Flow in Patients with Depressive Disorder: A Functional Near-Infrared Spectroscopy Study with a Small Sample Size

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Abstract: *Objective*: To investigate the characteristics and significance of near-infrared brain function imaging in patients with depressive disorder after administration of propofol injection. *Methods*: A total of 28 subjects with depressive disorder diagnosed according to DSM-5 criteria were selected from Xi'an Mental Health Center between January 2022 and January 2025. They were randomly divided into an experimental group (propofol group, n=14) and a control group (intralipid group, n=14) using a random number table. The changes in integral value (IV) and centroid value (CV) of the two patient groups before and after treatment were measured using functional near-infrared spectroscopy (fNIRS) technology. *Results*: There was no statistically significant difference in HAMD scores between the two groups of patients at 24 h before treatment ($P > 0.05$). Repeated measures analysis of variance showed that both time factor ($F_{time} = 32.237$, $P_{time} < 0.001$), group factor ($F_{group} = 47.027$, $P_{group} < 0.001$), and their interaction ($F_{interaction} = 31.829$, $P_{interaction} < 0.001$) were statistically significant. The centroid values of the frontal and temporal lobes were consistent at baseline before treatment, with no intra-group changes or inter-group differences at any time point after treatment ($P > 0.05$). The integral values of the frontal and temporal lobes were consistent between the two groups at baseline before treatment, and both showed a time-dependent increase after treatment ($P_{time} < 0.05$). However, the increase in the experimental group was significantly greater than that in the control group ($P_{group} < 0.05$), with a significant interaction effect ($P_{interaction} < 0.05$). *Conclusion*: fNIRS detected specific acute hemodynamic changes in the prefrontal and temporal regions of patients with depressive disorder after propofol intervention. These changes may be related to the mechanism of action of propofol. However, this study did not confirm a direct linear correlation between changes in integral/centroid values and the degree of clinical improvement in depressive symptoms. Propofol intervention combined with deep anesthesia rapidly improved depressive symptoms and was accompanied by enhanced hemodynamic activity in the prefrontal/temporal regions, though its specificity requires further validation.

Keywords: Depressive disorder; Propofol; Functional Near-Infrared Spectroscopy; Cerebral hemodynamics

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1. Introduction

Depressive disorder is a mental illness characterized by a depressed mood and loss of interest or pleasure lasting for at least two weeks, often accompanied by cognitive impairment, sleep/appetite disorders, and other autonomic nervous symptoms [1]. According to foreign scholars, more than 280 million people worldwide currently suffer from depressive disorders, and the global prevalence of depressive disorders is continuously rising. It is estimated that by 2030, depressive disorders will become the disease with the highest global disease burden [2]. Based on existing clinical evidence, propofol can produce a rapid and lasting antidepressant effect by regulating brain electrical activity (such as inducing a high electroencephalogram burst suppression ratio) and enhancing slow-wave sleep, and patients have good tolerance [3]. Therefore, propofol shows promising clinical application prospects in the treatment of depressive disorders. Meanwhile, previous research reports suggest that when patients with depression perform verbal fluency tasks, the increase in oxygenated hemoglobin (oxy-Hb) concentration in the prefrontal cortex is significantly lower than that in healthy controls, and this characteristic is negatively correlated with the severity of depressive symptoms [4]. Existing studies have only confirmed the insufficient activation of the prefrontal cortex in depression itself, while neuroimaging data related to propofol focuses on electroencephalograms and magnetic resonance spectroscopy techniques, and has not been extended to the field of near-infrared imaging. Therefore, this study investigates the characteristics and significance of functional near-infrared spectroscopy (fNIRS) in patients with depressive disorder after administration of propofol injection, aiming to provide a reference for clinical practice.

2. Materials and methods

2.1. General information

From January 2022 to January 2025, 28 subjects with depressive disorders who met the diagnostic criteria in the DSM-5 were selected from Xi'an Mental Health Center. They were divided into an experimental group (propofol group, n=14) and a control group (fat emulsion group, n=14) using a random number method. The study strictly follows the Declaration of Helsinki and has been approved by the Ethics Committee of Xi'an Mental Health Center.

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria

(1) Age between 20 and 45 years old.

(2) Meets the diagnostic criteria for depressive disorders in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), diagnosed by a psychiatrist [5].

(3) Total score on the Hamilton Depression Scale (HAMD-17) is ≥ 17.

(4) Has not received propofol or other anesthetic treatments in the past 3 months.

(5) Volunteers to participate in this study, signs the informed consent form, and is able to cooperate with the completion of treatment and various assessments.

2.2.2. Exclusion criteria

(1)Subjects comorbid with schizophrenia, obsessive-compulsive disorder, post-traumatic stress disorder, tic disorder, etc.

(2) Pregnant and perinatal women.
(3) Abnormal electrocardiogram.
(4) Allergic to propofol or fat emulsion components.
(5) Safety indicators such as liver and kidney function, electrolytes, and blood glucose exceed normal levels by more than 3 times.
(6) Subjects with unstable hypertension, poor blood glucose control, and those concomitant with major physical diseases.
(7) Body mass index > 28 kg/m2.
(8) Subjects with ASA classification grade IV or above.
(9) HAMD suicide assessment item 11 score greater than 2.

2.3. Methods

2.3.1. Experimental group

The anesthesiologist slowly administers propofol 2–3 mg/kg intravenously for induction (Manufacturer: Xi'an Libang Pharmaceutical Co., Ltd.; National Medical Approval Number: H19990282; Specification: 20 mL), and repeats small doses (50–100 mg) based on the electroencephalogram to maintain a deep state of anesthesia for at least 15 minutes. Wait for the subject to fully recover. During the anesthesia process, continuously monitor the electrocardiogram, non-invasive blood pressure, pulse oxygen saturation, and other vital signs. The entire process is managed by an anesthesiologist with clinical experience of ≥ 3 years, equipped with emergency equipment and medications. Subjects recover in a dedicated anesthesia recovery room and are observed for at least 1 hour. They can only leave the treatment room after fully waking up and their vital signs are stable. During the recovery period, psychiatrists assess suicide risk to ensure the safety of discharge.

2.3.2. Control group

Subjects undergo the same pre-treatment preparation and receive an equal amount of fat emulsion (Manufacturer: Sichuan Kelun Pharmaceutical Co., Ltd.; National Medical Approval Number: H20183271; Specification: 1000 mL). Wait for the subject to fully recover. Monitoring measures and recovery management are the same as those in the experimental group.

Both groups of patients received systematic treatment guided by DSM-5 [5] after the study concluded.

2.4. Observation indicators

The Hamilton Depression Rating Scale (HAMD) score was used as the primary clinical observation indicator, with secondary indicators including the Integral Value (IV) and Centroid Value (CV). HAMD assessments were conducted by uniformly trained evaluators at 24 hours before treatment, as well as at 2 hours, 6 hours, and 24 hours after full recovery from treatment. Secondary indicators were assessed using the NirSmart_6000 portable functional near-infrared spectroscopy (fNIRS) device (manufactured by Danyang Healcrest Medical Equipment Co., Ltd.) at the same time points—24 hours before treatment, and 2 hours, 6 hours, and 24 hours after full recovery—to calculate the Integral Value (IV) and Centroid Value (CV), which reflect temporal changes in the fNIRS signal.

The Integral Value (IV) refers to the area under the curve of oxy-Hb concentration changes during the task period or a specific time window, reflecting the overall intensity or total activation of brain region activity during that period [4, 6]. The fNIRS device was used to record oxy-Hb concentration changes in regions such as the frontal

and temporal lobes while subjects performed cognitive tasks (e.g., verbal fluency tests). The modified Beer-Lambert law was applied to convert light intensity signals into oxy-Hb concentration changes. The calculation formula is as follows:

$$IV = \int_{t_1}^{t_2} \Delta HbO(t)\, dt$$

Centroid value: Refers to the time point at which the change in oxy-Hb concentration reaches its peak, reflecting the temporal characteristics of activation [6]. Using the amplitude of HbO change in each channel as the weight, the spatial coordinate mean of the activated channels is calculated. The calculation formula is as follows, where x_i and y_i represent the channel position coordinates.

$$CV_x = \frac{\sum_{i=1}^{N} \Delta HbO_i \cdot x_i}{\sum_{i=1}^{N} \Delta HbO_i}, \quad CV_y = \frac{\sum_{i=1}^{N} \Delta HbO_i \cdot y_i}{\sum_{i=1}^{N} \Delta HbO_i}$$

2.5. Statistical methods

The research data were analyzed using SPSS 24.0. Measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$), with HAMD analyzed using repeated measures ANOVA. Paired t-tests were used for comparisons within groups before and after treatment, while independent sample t-tests were used for comparisons between groups at the same time point. Pearson correlation analysis was used to assess the correlation between changes in oxy-Hb and changes in total HAMD scores in the experimental group. Count data were expressed as frequency (percentage), and comparisons between groups were made using the χ^2 test or Fisher's exact test. All tests were two-sided, and a P-value < 0.05 was considered statistically significant.

3. Results

3.1. Comparison of baseline data between the two groups

There was no statistical difference in baseline data between the two groups ($P > 0.05$), as shown in **Table 1**.

Table 1. Comparison of baseline data between the two groups

Baseline characteristics	Test group (n=14)	Control group (n=14)	Statistical value	*P*-value
Mean age ($\bar{x} \pm s$, years)	28.69 ± 6.81	28.42 ± 6.17	0.110	0.913
Gender (n)			0.190	0.663
Male	4 (28.57%)	3 (21.43%)		
Female	10 (71.43%)	11 (78.57%)	0.243	0.622
Family history (n)	3 (21.43%)	2 (14.29%)	0.319	0.750
Mean BMI (kg/m²)	21.45 ± 2.35	21.56 ± 2.47	0.121	0.905

3.2. Comparison of HAMD between two groups of patients

There was no statistically significant difference in HAMD scores between the two groups of patients 24 hours before treatment ($P > 0.05$). Repeated measures ANOVA showed that there were statistically significant differences in time factors (F_{time}=32.237, $P_{time} < 0.001$), group factors (F_{group}=47.027, $P_{group} < 0.001$), and the interaction between the two ($F_{interaction}$=31.829, $P_{interaction} < 0.001$), as shown in **Table 2**.

Table 2. Comparison of HAMD at different treatment time points between two groups of patients ($\bar{x} \pm s$, points)

Group	n	24h before treatment	2h after full awakening	6h after full awakening	24h after full awakening
Test group	14	36.89 ± 5.17	25.31 ± 5.29	25.56 ± 5.33	25.12 ± 5.31
Control group	14	36.71 ± 5.33	30.78 ± 5.38	30.81 ± 5.35	31.84 ± 5.39
$F_{time/interaction/group}$			F_{time}=32.237，$F_{interaction}$ =47.027，F_{group} =31.829		
$P_{time/interaction/group}$			P_{time} ＜ 0.001，$P_{interaction}$ ＜ 0.001，P_{group} ＜ 0.001		

Note: Through Mauchly's test of sphericity (Mauchly's W=0.913, P > 0.05), the hypothesis of sphericity was adopted for the test of within-group effects.

3.3. Comparison of near-infrared spectroscopy brain functional imaging systems between two groups of patients

The centroid values of the frontal and temporal lobes showed no significant differences at baseline before treatment. After treatment, no within-group changes or between-group differences were observed at any time point (P > 0.05). The integral values of the frontal and temporal lobes were consistent between the two groups at baseline before treatment. After treatment, both groups exhibited a time-dependent increase (P_{time} < 0.05), but the increase was significantly greater in the experimental group compared to the control group (P_{group} < 0.05), with a significant interaction effect ($P_{interaction}$ < 0.05). See **Tables 3**, **4**, **5**, and **6**.

Table 3. Comparison of frontal lobe region integral values between the two patient groups at different treatment time points ($\bar{x} \pm s$).

Group	n	Before treatment	2h after full recovery	6h after full recovery	24h after full recovery
Study group	14	51.74 ± 10.71	61.09 ± 12.37	70.59 ± 15.68	77.69 ± 17.38
Control group	14	51.88 ± 10.62	52.39 ± 11.32	53.01 ± 14.19	54.62 ± 15.34
$F_{time/interaction/group}$			F_{time}=15.266, $F_{interaction}$= 3.454, F_{group} = 14.845		
$P_{time/interaction/group}$			P_{time}<0.001, $P_{interaction}$= 0.036, P_{group}< 0.001		

Note: Mauchly's test of sphericity indicated that the assumption of sphericity was met (W = 0.925, P > 0.05). Therefore, the within-subjects effects were tested under the assumption of sphericity.

Table 4. Comparison of frontal lobe region centroid values between the two groups at different treatment time points ($\bar{x} \pm s$).

Group	n	24h before treatment	2h after full recovery	6h after full recovery	24h after full recovery
Study group	14	56.26 ± 13.17	56.11 ± 13.22	56.09 ± 13.54	56.14 ± 13.87
Control group	14	56.30 ± 13.33	56.14 ± 13.45	56.84 ± 13.36	57.79 ± 12.89
$F_{time/interaction/group}$			F_{time}= 0.890, $F_{interaction}$= 0.796, F_{group} = 1.600		
$P_{time/interaction/group}$			P_{time}= 0.450, $P_{interaction}$= 0.500, P_{group} = 0.217		

Note: Mauchly's test of sphericity indicated that the assumption of sphericity was met (W = 0.965, P >0 .05). Therefore, the within-subjects effects were tested under the assumption of sphericity.

Table 5. Comparison of temporal lobe region integral values between the two groups at different treatment time points ($\bar{x} \pm s$).

Group	n	24h before treatment	2h after full recovery	6h after full recovery	24h after full recovery
Study group	14	66.26 ± 9.42	75.63 ± 9.94	94.42 ± 14.67	116.36 ± 19.15
Control group	14	66.31 ± 9.46	68.32 ± 9.58	69.83 ± 9.94	71.89 ± 10.77
$F_{time/interaction/group}$			F_{time}= 30.603, $F_{interaction}$ = 18.856, F_{group} = 58.109		
$P_{time/interaction/group}$			P_{time}< 0.001, $P_{interaction}$< 0.001, P_{group} < 0.001		

Note: Mauchly's test of sphericity indicated that the assumption of sphericity was met (W = 0.943, P >0 .05). Therefore, the within-subjects effects were tested under the assumption of sphericity.

Table 6. Comparison of temporal lobe region centroid values between the two groups at different treatment time points ($\bar{x} \pm s$).

Group	n	24h before treatment	2h after full recovery	6h after full recovery	24h after full recovery
Study group	14	60.37 ± 10.89	60.52 ± 10.92	60.49 ± 11.11	60.69 ± 11.42
Control group	14	60.71 ± 10.91	60.96 ± 11.08	61.09 ± 11.84	61.23 ± 12.32
$F_{time/interaction/group}$			F_{time}= 1.142, $F_{interaction}$ = 1.417, F_{group} = 1.358		
$P_{time/interaction/group}$			P_{time}= 0.338, $P_{interaction}$= 0.244, P_{group} = 0.254		

Note: Mauchly's test of sphericity indicated that the assumption of sphericity was met (W = 0.885, P >0 .05). Therefore, the within-subjects effects were tested under the assumption of sphericity.

3.4. Correlation analysis between near-infrared spectroscopy brain functional imaging system and HAMD in experimental group patients

Pearson correlation analysis suggested that there was no significant correlation between the integral value of the frontal lobe region and the total score change of the Hamilton Depression Scale in the experimental group (r =-0.345, P = 0.227); there was no significant correlation between the centroid value of the frontal lobe region and the total score change of the Hamilton Depression Scale in the experimental group (r =0.318, P = 0.268); there was no significant correlation between the integral value of the temporal lobe region and the total score change of the Hamilton Depression Scale in the experimental group (r =-0.209, P = 0.474); there was no significant correlation between the centroid value of the temporal lobe region and the total score change of the Hamilton Depression Scale in the experimental group (r =-0.068, P = 0.817).

4. Discussion

Near-infrared brain functional imaging utilizes the relative transparency of biological tissues in the near-infrared spectrum (650–900 nm). By emitting near-infrared light through the scalp and skull, it detects changes in the optical properties of hemoglobin in the cerebral cortex. Based on existing clinical evidence, abnormal activation of the prefrontal cortex in patients is closely related to emotional regulation disorders, and thus is commonly used in the clinical evaluation of mental illnesses [6]. Propofol is a short-acting intravenous anesthetic that enhances inhibitory neurotransmission by activating gamma-aminobutyric acid type A receptors (GABA_A) while inhibiting N-methyl-D-aspartate (NMDA) receptors and reducing glutamatergic excitatory transmission [7]. Recent studies have indi-

cated that propofol can directly bind to and inhibit the dopamine transporter (DAT), blocking dopamine reuptake while increasing striatal dopamine concentrations and activating D1-type medium spiny neurons (MSNs), thereby improving core symptoms of depression [8]. Furthermore, clinical research has found that patients with depression have inadequate GABAergic inhibition and excessive glutamatergic excitation, and propofol's bidirectional regulation may restore this balance [9]. Therefore, propofol has promising applications in the treatment of depressive disorders. Currently, propofol is commonly used in clinical settings to assist electroconvulsive therapy, exerting a neuroprotective effect on patients with depression.

In this study, it is observed that compared to the fat emulsion group, patients in the propofol group had significantly lower HAMD scores after fully waking up from treatment. It is hypothesized that the mechanism is related to propofol's ability to modulate the dopamine system and reverse the core symptoms of depressive disorders (anhedonia). Additionally, propofol can promote GABA/glutamate balance, indirectly exerting an antidepressant effect. The results of this study also suggest that the integral values of the frontal and temporal regions in the experimental group were higher than those in the control group ($P < 0.05$). fNIRS can reflect brain activity, especially in the frontal and temporal regions, so near-infrared brain functional imaging signals can be used as predictors of clinical efficacy for patients with depression [4].

The results of this study are similar to those of previous studies, which reported that after antidepressant treatment, patients showed enhanced activation of the prefrontal cortex, and the degree of activation was positively correlated with symptom relief[10]. Propofol may affect neural activity in relevant brain regions (manifested as increased fNIRS integral values) by modulating GABAergic and/or dopaminergic systems, thereby improving depressive symptoms. Whether it involves deeper levels of neural plasticity changes (such as functional connectivity reorganization) or cytoprotective mechanisms (such as autophagy) remains to be explored in future research. However, this study did not find a significant correlation between IV and CV and HAMD. This contradiction may be due to the small sample size of the study, which limits the statistical power to detect correlations. At the same time, the selected IV and CV indicators may not capture the neural activity features most relevant to clinical improvement. Additionally, a mismatch in the main clinical evaluation time points may also be an important factor affecting the results. Furthermore, this study used fat emulsion as a control, which can match the physical characteristics of the drug solvent but cannot exclude the influence of the deep anesthesia process itself on the neurological state. The rapid decrease in HAMD scores and changes in fNIRS signals observed in the experimental group may partly stem from nonspecific physiological stress responses triggered by the loss of consciousness-awakening cycle.

Future studies need to adopt active placebos (such as short-acting benzodiazepines) to balance the intensity of intervention. Although there was no direct correlation between fNIRS indicators and HAMD improvement in this study, propofol may exert antidepressant effects through multi-level mechanisms, including rapid relief of neuronal excitability imbalance by GABA enhancement/glutamate inhibition; neuronal oscillation reorganization: enhancement of slow-wave sleep promotes synaptic homeostatic regulation [3]; and dopaminergic system activation may induce synaptic remodeling [8]. The frontal activation captured by fNIRS may only reflect acute mechanisms, while HAMD improvement involves the cumulative effects of mechanisms, which may be the reason for the mismatch in their time courses.

5. Conclusion

In summary, propofol intervention combined with the process of deep anesthesia can rapidly improve depressive

symptoms, accompanied by enhanced hemodynamic activity in the prefrontal/temporal lobes. However, its specific effects require further validation.

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Disclosure statement

The authors declare no conflict of interest.

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