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Deqin Geng

Affiliated Hospital of Xuzhou Medical University, China

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Clinical Neuroscience Research

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Electroacupuncture at Baihui and Shenting Improves Learning and Memory Impairment and Anxiety-like Behavior Induced by Electromagnetic Pulse

Xiajing Zhang¹, Yuming Zhang², Hui Yan¹, Xude Sun¹, Jiushe Kou¹, Yu Zhu^{3*}

¹The Second Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, China

²Shaanxi Provincial People's Hospital, Shaanxi 710068, China

³School of Health and Wellness, Dongguan Polytechnic, Dongguan 523808, China

**Author to whom correspondence should be addressed.*

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Abstract: Following exposure to electromagnetic pulses (EMP), the brain may experience impaired learning and memory capabilities, as well as anxiety-like behaviors. Microglial activation and inflammatory responses have been shown to be associated with EMP-induced brain damage. Electroacupuncture treatment has demonstrated potential in inhibiting microglial activation and mitigating inflammatory responses in various neurological disorders. This study aims to investigate whether electroacupuncture treatment can alleviate EMP-induced learning and memory impairments and to elucidate its underlying mechanisms. Compared with the non-acupoint group and the EA + LPS, the Y-maze and open field tests indicated that the EA group spent more time in the novel arm and the central area of the open field, the proportion of iNOS⁺/iba-1⁺ cells in the hippocampus decreased, and the concentrations of pro-inflammatory factors IL-1 β , IL-6, and TNF- α decreased. EA improved EMP-induced learning and memory impairment and anxiety-like behavior by inhibiting microglial activation and inflammatory response in the hippocampus.

Keywords: Electroacupuncture; Electromagnetic pulse; Microglia; Activation; Inflammation; Learning and memory; Anxiety

Online publication: October 17, 2025

1. Introduction

An electromagnetic pulse (EMP) is a pulsed high-energy transient electromagnetic field that can induce multi-system damage in organisms exposed to its irradiation range. The brain is particularly vulnerable to EMP irradiation, and exposed animals may experience impairments in learning and memory as well as anxiety-like behaviors ^[1]. Currently, there is still a lack of effective treatment for EMP-induced brain damage. Microglia

appear activated in EMP-related brain injuries, and inflammatory responses are involved in the EMP-induced decline in learning and memory abilities ^[2]. In various neurological diseases, electro-acupuncture has been shown to effectively suppress microglial activation and mitigate inflammatory responses, promoting tissue repair ^[3-4]. This study aims to determine whether electroacupuncture can improve EMP-induced impairments in learning and memory and elucidate its underlying mechanisms.

2. Materials and methods

2.1. Experimental animals

Sixty SPF-grade male C57 mice (aged 6-8 weeks) were assigned to five groups: the sham irradiation group (Sham group), the electromagnetic pulse group (EMP group), the electro-acupuncture group (EA group), the non-acupoint control group (EACtl group), and the electro-acupuncture + LPS group (EA+LPS group), with 12 mice in each group. This experiment was approved by the Experimental Animal Ethics Committee of Shaanxi University of Chinese Medicine (Ethics Approval Number: SUCMDL20240306008).

2.2. Main reagents and instruments

Disposable acupuncture needles (0.25 mm×25 mm), electroacupuncture therapy instrument (Huatuo, Suzhou Medical Supplies Factory), microplate reader (Thermo Fisher Scientific), high-speed frozen centrifuge (Eppendorf), microscope (Nikon), fluorescence microscope (Nikon). Iba-1 and iNOS antibodies (Abcam), goat anti-rabbit fluorescent secondary antibody, donkey anti-mouse fluorescent secondary antibody (Zhongshan Golden Bridge), Nissl staining kit (Solarbio), HE staining reagent (Solarbio), and ELISA kit (Boster).

2.3. Modeling and intervention methods

The sham group was placed in a non-electrified EMP irradiator for sham exposure, while the other groups received EMP irradiation at 400 kV/m, 400 pulses per day, repeated for 3 days, to establish an EMP-induced learning and memory impairment model. The EA group received electro-acupuncture treatment at the “Baihui” and “Shenting” acupoints according to “Experimental Acupuncture and Moxibustion” ^[5]. The needles were inserted 2-3 mm deep using the pinching insertion technique. The waveform of the electroacupuncture therapy instrument was set to a sparse-dense wave at 2 Hz/10 Hz, with a current intensity of 1~2 mA, administered for 20 minutes per session, once a day for 7 consecutive days. The EACtl group was treated at 3 mm above the iliac crest on both sides, with the same electro-acupuncture parameters as the EA group. The EA+LPS group received an intraperitoneal injection of LPS (the microglial activator) at a dose of 3 mg/kg before electroacupuncture intervention, with the remaining treatment the same as the EA group.

2.4. Behavioral testing

Y-maze test: This test consisted of two phases. In the first phase (acquisition phase), one arm was closed, and the mouse was placed in the center of the Y-maze, allowed to freely explore the two open arms for 3 minutes. Two hours later, during the second phase (recall phase), all arms were opened, and the mouse was again placed in the center of the Y-maze to freely explore all three arms for 3 minutes. The time spent and distance explored in each arm were recorded. Mice with memory impairment typically exhibit reduced exploration time and distance in the novel arm compared to the familiar arms. The parameters measured included the number of entries into each arm, the time spent, and the distance explored in each arm, which were then statistically analyzed. **Open field test:** The

open field was divided into central and peripheral zones. The experimental animal was placed in the environment of the open field test for 2 hours of adaptation. At the start of the experiment, the mouse was placed in the center of the open field, and its movement trajectory was recorded using a tracking and recording system.

2.5. Histopathological staining

The brain tissue was removed, fixed, dehydrated, embedded, and sectioned. HE staining: After dewaxing and rehydration, the sections were stained with eosin staining solution for 5–10 minutes and hematoxylin staining solution for 2–3 minutes. Nissl staining: After dewaxing and rehydration, the sections were stained with 1% toluidine blue staining solution for 30 minutes.

2.6. Immunofluorescence staining

The brain tissue was removed, fixed, dehydrated, embedded, and sectioned. After antigen retrieval of the sections, goat serum was added and incubated at room temperature for 30 minutes to block non-specific binding. The blocking solution was then removed by washing, and the primary antibody dilution was added for incubation at 4°C overnight. The next day, the unbound primary antibody was washed off, and the sections were incubated with a fluorescent secondary antibody at room temperature for 2 hours. The samples were observed under a fluorescence microscope.

2.7. ELISA detection of rat hippocampus tissue

Remove the brain tissue of the mouse, separate the bilateral hippocampus on ice, add ice-cold PBS solution, homogenize at 4°C, and centrifuge to obtain the supernatant. Following the kit instructions for subsequent detection steps, the absorbance was measured by a microplate reader, and the content of inflammatory factors was calculated.

2.8. Statistical analysis

SPSS 23.0 was used for statistical analysis. Measurement data were expressed as (mean ± standard deviation). For normally distributed and homoscedastic data, one-way ANOVA was conducted, followed by pairwise comparisons between groups using the Least Significant Difference (LSD) method. $P < 0.05$ indicated that the difference was statistically significant.

3. Results

3.1. Comparison of Y-maze test and open field test results among mice in each group

In the Y-maze test, compared with the Sham group, the EMP group mice exhibited shorter stay times in the novel arm and the central area of the open field; compared with the EMP group, the EA group mice exhibited longer stay times in both the novel arm and the central area of the open field; there was no significant difference in the stay times in the novel arm and the central area of the open field between the EACtl group and the EA+LPS group compared with the Sham group; compared with the EA group, the EACtl group and the EA+LPS group exhibited shorter stay times in both the novel arm and the central area of the open field (**Figure 1**).

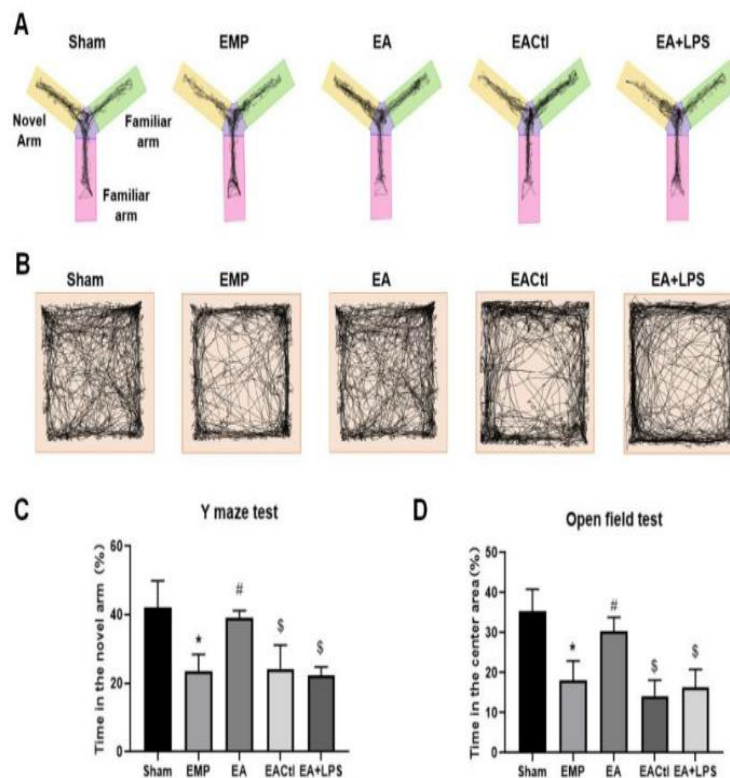


Figure 1. Y-maze test and open field test results among different groups of mice. (A) Movement trajectory in the Y-maze, (B) Movement trajectory in the open field, (C) Percentage of time spent in the novel arm of the Y-maze, (D) Percentage of time spent in the central area of the open field. * represents $P < 0.05$ compared to the Sham group; # represents $P < 0.05$ compared to the EMP group; \$ represents $P < 0.05$ compared to the EA group

3.2. Comparison of pathological staining results in the hippocampal CA1 region of mice from different groups

Compared to the Sham group, the EMP-irradiated hippocampal cells showed irregular arrangement, cytoplasmic shrinkage, blurred contours, fragmented nuclei, and a significant reduction in Nissl bodies within the cells. However, in the EA group, the hippocampal cells had clear boundaries, prominent nucleoli, and abundant Nissl bodies. The hippocampal cells in EACtl and EA+LPS groups were similar to those in the EMP group, characterized by blurred or shrunken cell morphology, abnormal nuclear fragments, uneven distribution of Nissl bodies, lighter staining intensity, and signs of disappearance and dissolution (**Figure 2**).

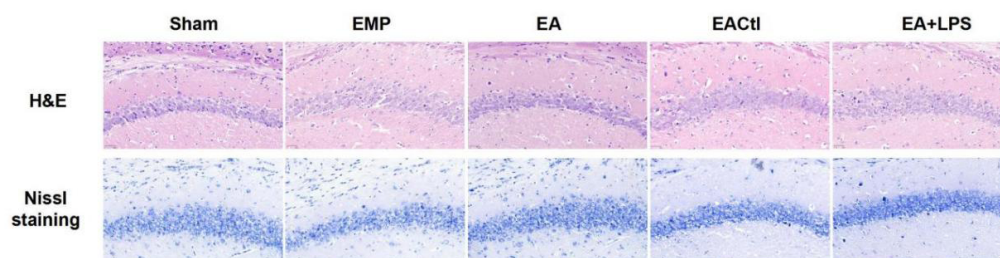


Figure 2. Comparison of pathological staining results among different groups of mice

3.3. Comparison of activated microglia in the hippocampal region of mice from different groups

Compared to the Sham group, EMP irradiation induced the activation of microglia, with an increase in the proportion of iba-1⁺/iNOS⁺ cells in the hippocampal region. Compared to the EMP group, the EA group had a lower proportion of iba-1⁺/iNOS⁺ cells in the hippocampal region, while there was no statistically significant difference between the EACtl and EA+LPS groups. Compared to the EA group, the EACtl and EA+LPS groups demonstrated a higher proportion of iba-1⁺/iNOS⁺ cells in the hippocampal region (**Figure 3**).

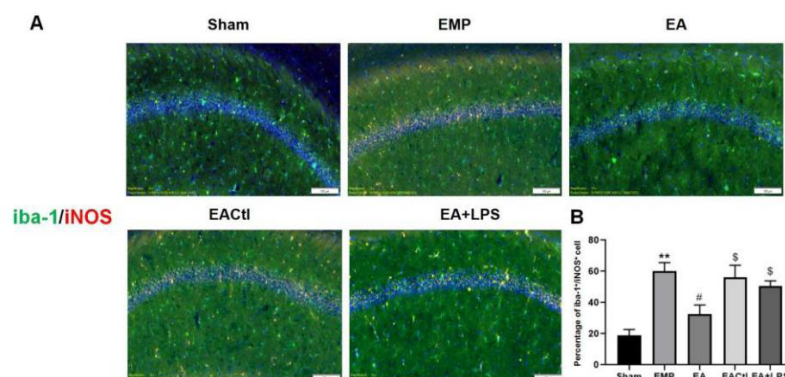


Figure 3. Comparison of activated microglia in the hippocampal region of mice from different groups. (A) Immunofluorescence staining, with red fluorescence labeling iba-1, green fluorescence labeling iNOS, and blue labeling cell nuclei; (B) Percentage of iba-1⁺/iNOS⁺ cells in the hippocampal region of mice. ** represents $P < 0.01$ compared to the Sham group; # represents $P < 0.05$ compared to the EMP group; \$ represents $P < 0.05$ compared to the EA group.

3.4. Comparison of proinflammatory cytokines IL-1 β , IL-6, and TNF- α concentrations in the hippocampal tissue of mice from different groups

Compared to the sham group, the concentrations of proinflammatory cytokines IL-1 β , TNF- α , and IL-6 in the hippocampal tissue of mice were increased. Compared to the EMP group, the concentrations of these cytokines were decreased in the EA group, while there was no statistically significant difference between the EACtl and EA+LPS groups. Compared to the EA group, the concentrations of IL-1 β , TNF- α , and IL-6 were increased in both the EACtl and EA+LPS groups (**Figure 4**).

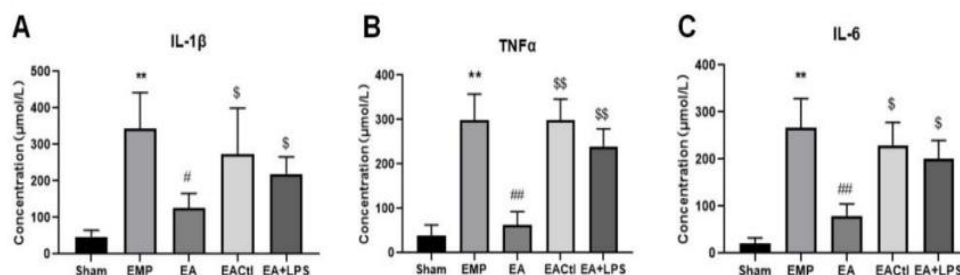


Figure 4. Comparison of proinflammatory cytokines IL-1 β , TNF- α , and IL-6 concentrations in the hippocampal tissue of mice from different groups. Detection of (A) IL-1 β , (B) TNF- α , and (C) IL-6 concentrations in the hippocampal tissue of mice from each group. ** represents $P < 0.01$ compared to the Sham group; # represents $P < 0.05$ compared to the EMP group; ### represents $P < 0.01$ compared to the EMP group; \$ represents $P < 0.05$ compared to the EA group; \$\$ represents $P < 0.01$ compared to the EA group

4. Discussion

This study aimed to investigate the effects of electroacupuncture stimulation at “Baihui” and “Shenting” acupoints on learning and memory impairment and anxiety-like behaviors induced by EMP in mice, and to further explore its possible mechanisms. The experimental results showed that EMP irradiation could lead to significant learning and memory impairment and anxiety-like behaviors in mice, manifested as shortened stay time in the novel arm of the Y-maze and reduced activity time in the central area of the open field. Simultaneously, microglia in the hippocampal brain region were activated, and the concentrations of proinflammatory factors IL-1 β , IL-6, and TNF- α were significantly increased, indicating that EMP-induced brain damage is closely related to microglia activation and inflammatory response. Electroacupuncture stimulation at “Baihui” and “Shenting” acupoints could improve EMP-induced learning and memory decline and anxiety-like behaviors by inhibiting glial cell activation and limiting the inflammatory response.

According to traditional Chinese medicine theory, the Baihui acupoint is the intersection point where the yang qi of the three yang meridians of the hand and foot and the Du meridian intersect. It has the effects of awakening the brain, calming the mind, elevating yang, and stabilizing epilepsy ^[6]. The Shenting acupoint is the intersection of the Du meridian, the foot Taiyang bladder meridian, and the foot Yangming stomach meridian. It has the effect of awakening the brain and regulating qi and blood in the head ^[7]. Studies have shown that electroacupuncture stimulation at Baihui and Shenting acupoints can improve learning and memory function in vascular dementia rats and alter synaptic structure in the hippocampal brain region ^[8]. It has been reported that electroacupuncture stimulation at Baihui and Shenting acupoints has a therapeutic effect on post-stroke mild cognitive impairment. After a certain period of treatment, patients’ memory and attention were significantly improved. Furthermore, it could also alleviate patients’ depression and anxiety, and promote the process of rehabilitation ^[9]. In this study, “Baihui” and “Shenting” acupoints were selected for electroacupuncture intervention. The results showed that the stay time of mice in the electroacupuncture group in the novel arm of the Y-maze and the central area of the open field was significantly longer than that in the EMP group, indicating that electroacupuncture could effectively improve learning and memory impairment and alleviate anxiety-like behaviors induced by EMP. Simultaneously, the activation of microglia in the hippocampal brain region of mice in the electroacupuncture group was reduced, along with the significantly reduced concentrations of proinflammatory factors IL-1 β , IL-6, and TNF- α . These results further confirmed that electroacupuncture may improve EMP-induced brain damage by inhibiting microglia activation and inflammatory response in the hippocampal brain region.

To verify the specific effect of electroacupuncture, this study also set up a non-acupoint group and an electroacupuncture + LPS group as controls. The non-acupoint group received electroacupuncture intervention at 10 mm above the bilateral subcostal iliac crest. The results showed no significant difference in behavioral performance and hippocampal inflammation between this group and the EMP group, indicating that the therapeutic effect of electroacupuncture is acupoint-specific. The electroacupuncture + LPS group received an intraperitoneal injection of the microglia activator LPS before electroacupuncture intervention. The results showed that the improvement in behavioral performance and hippocampal inflammation in this group was significantly lower than that in the electroacupuncture group, indicating that the activation state of microglia is an important factor affecting the efficacy of electroacupuncture.

The results of this study support the potential application value of electroacupuncture in improving EMP-induced brain damage and provide novel insight for the application of acupuncture therapy in electromagnetic radiation-related diseases. However, this study still has some limitations, such as a small number of sample and the

optimal time window and acupoint combination for electroacupuncture intervention have not been explored. These issues need to be further investigated in future studies.

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Disclosure statement

The author declares no conflict of interest.

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Predictive Role of PSG Parameters on the Efficacy of Cognitive Behavioral Therapy for Insomnia (CBT-I)

Lan Zou*

China Construction Third Engineering Bureau, Wuhan Central Hospital, Wuhan, Hubei, China

**Author to whom correspondence should be addressed.*

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Abstract: *Objective:* To explore the predictive value of baseline polysomnography (PSG) parameters on the efficacy of cognitive behavioral therapy for insomnia (CBT-I) in the treatment of chronic insomnia, and to clarify its clinical application value. *Methods:* Forty patients with chronic insomnia who visited the Sleep Medicine Center of the hospital from March 2024 to June 2025 were selected. All patients completed 8 weeks of CBT-I treatment and PSG monitoring before and after treatment. The correlation between baseline PSG parameters (sleep efficiency, wake time after sleep onset, and proportion of N3 sleep stage) and the improvement values of the Insomnia Severity Index (ISI) and sleep efficiency after treatment was analyzed. Multiple regression analysis was used to screen predictive factors of efficacy. *Results:* Baseline sleep efficiency ($r=0.36$, $P<0.05$) was positively correlated with ISI improvement value, wake time after sleep onset ($r=-0.33$, $P<0.05$) was negatively correlated with ISI improvement value, and the proportion of N3 sleep stage ($r=0.29$, $P<0.05$) was positively correlated with ISI improvement value. Multiple regression analysis showed that baseline sleep efficiency ($\beta=0.27$, $P=0.03$) and wake time after sleep onset ($\beta=-0.24$, $P=0.04$) were independent predictors of ISI improvement value (adjusted $R^2=0.17$, $F=5.12$, $P<0.05$). *Conclusion:* Sleep efficiency and wake time after sleep onset among baseline PSG parameters can effectively predict the efficacy of CBT-I in the treatment of chronic insomnia, providing an objective basis for clinically screening treatment-sensitive populations.

Keywords: PSG parameters; Cognitive behavioral therapy; Insomnia

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1. Introduction

Sleep disorder is a common psychopathological disease, and chronic insomnia, as one of its primary clinical manifestations, severely affects the physical and mental health of patients ^[1]. According to statistics, more than 300 million people in China are currently suffering from sleep disorders, with chronic insomnia patients accounting for 42.9%. The treatment methods for insomnia include pharmacological therapy, cognitive behavioral therapy, etc. ^[2]. However, traditional pharmacological therapy has disadvantages such as recurrence and significant side effects. In recent years, cognitive behavioral therapy has begun to be widely used in clinical

practice and has achieved good therapeutic effects. There is a close relationship between sleep problems and brain function. Research has shown that the brain network is an essential component required for the body to maintain normal physiological activities during sleep, and different regions have specific neural connection patterns. The neural network characteristics and related mechanisms of the brain can be understood by constructing a functional connectivity network. Therefore, studying changes in brain function in patients with insomnia is significant for guiding insomnia treatment plans^[3-4]. In this study, 40 patients with insomnia will receive 8 weeks of CBT-I treatment, and polysomnography (PSG) tests will be performed before and after treatment. Simultaneously, functional magnetic resonance imaging (fMRI) will be utilized to obtain standardized functional connectivity values (FC) for various brain regions at baseline and after treatment. Further analysis of the correlation between FC values in different brain regions and the efficacy of insomnia treatment will provide new insights for predicting the efficacy of CBT-I in treating insomnia, aiming to improve the scientific validity and effectiveness of CBT-I treatment.

2. Materials and methods

2.1. General information

A total of 40 patients with insomnia who visited the Sleep Medicine Center of the hospital from March 2024 to June 2025 were selected. Among the 40 subjects, there were 16 males (40.00%) and 24 females (60.00%); aged between 35–74 years, with an average age of 52.64 ± 10.32 years; the course of the disease ranged from 6 months to 12 years, with an average of 3.81 ± 2.52 years; ISI score before treatment was 14.22 ± 3.14 points, and sleep efficiency was $64.81 \pm 9.62\%$. All patients completed 8 weeks of CBT-I treatment without any dropout cases. All patients completed 8 weeks of CBT-I treatment and efficacy evaluation without any dropout cases. All patients met the diagnostic criteria for “chronic insomnia” in the “Guidelines for the Diagnosis and Treatment of Insomnia in Chinese Adults” developed by the Chinese Sleep Research Society, which includes at least three months of the following symptoms^[5]: (1) difficulty falling asleep; (2) sleep maintenance disorders; (3) early awakening; (4) decreased sleep quality; (5) shortened total sleep time. Exclusion criteria were: (1) comorbid mental illness or severe physical illness; (2) unable to cooperate and complete the experiment; (3) suffering from cerebral organic diseases, including cerebrovascular disease, intracranial infection, etc.; (4) taking drugs with central nervous system inhibitory effects.

2.2. Methods

2.2.1. PSG monitoring

Monitoring was conducted in a soundproof, blackout, and temperature-controlled (20–24 °C) sleep laboratory using the Embla N7000 polysomnography system from the United States. One day before monitoring, patients were instructed to avoid excitatory drinks such as coffee and strong tea, refrain from taking sedatives, and maintain a normal sleep schedule.

The monitoring parameters include: (1) Electroencephalogram (C3-A2, C4-A1, O1-A2, O2-A1); (2) Electrooculogram (EOG); (3) Electromyogram (EMG) of chin muscles; (4) Electrocardiogram (ECG); (5) Respiratory airflow (nasal and oral); (6) Chest and abdominal movements; (7) Blood oxygen saturation (SpO2); (8) Electromyogram of lower limbs. Monitoring will take place from 22:00 that evening to 6:00 the next morning (total recording time of 8 hours). Professional technicians will perform sleep staging and parameter analysis according to the standards of the American Academy of Sleep Medicine (AASM). The main indicators include

sleep latency, total sleep time, sleep efficiency, number of awakenings after sleep onset, awakening time after sleep onset, and the proportion of N1, N2, N3, and REM sleep stages.

2.2.2. CBT-I treatment

A standardized 8-week CBT-I program will be adopted, including: (1) Sleep restriction therapy: Adjusting bedtime based on the patient's baseline total sleep time to gradually improve sleep efficiency; (2) Stimulus control therapy: Establishing a conditioned reflex between bed and sleep (using the bed only for sleep and sexual activity, and getting out of bed if not asleep within 20 minutes); (3) Cognitive reconstruction: Correcting patients' unreasonable beliefs about sleep (such as "I must sleep for 8 hours"); (4) Relaxation training: Including progressive muscle relaxation, abdominal breathing exercises, etc.; (5) Sleep hygiene education: Guiding regular sleep schedules, optimizing the sleep environment, etc. Individual therapy sessions will be conducted once a week (each session lasting 45–60 minutes) and will be implemented by a certified sleep technician.

2.3. Observation indicators

After 8 weeks of treatment, the efficacy was evaluated using the following indicators: ISI score, calculation of improvement value (ISI score before treatment — ISI score after treatment), with an improvement value of ≥ 4 considered as effective treatment^[5]; PSG was re-examined, and the improvement value of sleep efficiency was calculated (SE after treatment — SE before treatment).

2.4. Statistical methods

SPSS software was used for statistical analysis of the data. The count data were expressed as n(%), and the comparison between groups was performed using a *t*-test. A *P*-value < 0.05 was considered statistically significant.

3. Results

3.1. Changes in sleep indicators before and after CBT-I treatment

After 8 weeks of treatment, both subjective and objective sleep indicators of the patients improved significantly ($P < 0.01$) (Table 1).

Table 1. Comparison of sleep indicators before and after CBT-I treatment (Mean \pm SD)

Indicator	Before treatment	After treatment	t-value	P-value
ISI Score (points)	14.56 \pm 3.28	7.24 \pm 2.86	18.36	<0.01
Sleep Latency (minutes)	38.65 \pm 12.45	22.34 \pm 8.76	10.25	<0.01
Total Sleep Time (minutes)	325.67 \pm 56.89	389.45 \pm 45.67	9.87	<0.01
Sleep Efficiency (%)	65.42 \pm 10.36	82.56 \pm 7.45	12.34	<0.01
Number of Awakenings (times)	4.56 \pm 1.89	2.12 \pm 1.05	11.56	<0.01
Wake After Sleep Onset (minutes)	56.78 \pm 20.34	25.43 \pm 12.67	10.78	<0.01
N3 Sleep Percentage (%)	12.34 \pm 4.56	18.76 \pm 5.23	8.65	<0.01
REM Sleep Percentage (%)	18.65 \pm 5.34	22.34 \pm 4.87	5.43	<0.01

3.2. Correlation analysis between baseline PSG parameters and the efficacy of CBT-I

Using the improvement values of ISI and sleep efficiency as indicators of efficacy, Pearson correlation analysis was conducted. The results showed that baseline sleep efficiency was positively correlated with the improvement value of ISI ($r=0.38$, $P<0.01$) and negatively correlated with the improvement value of sleep efficiency ($r=-0.35$, $P<0.01$). Baseline wake time after sleep onset was negatively correlated with the improvement value of ISI ($r=-0.32$, $P<0.01$) and positively correlated with the improvement value of sleep efficiency ($r=0.29$, $P<0.05$). The proportion of N3 sleep at baseline was positively correlated with the improvement value of ISI ($r=0.29$, $P<0.05$) and negatively correlated with the improvement value of sleep efficiency ($r=-0.26$, $P<0.05$). Other PSG parameters (such as sleep latency, proportion of REM sleep, etc.) were not significantly correlated with efficacy indicators ($P>0.05$).

3.3. Multiple regression analysis of CBT-I efficacy

Using the improvement value of ISI as the dependent variable, multiple linear regression analysis was conducted with variables that had $P<0.10$ in univariate analysis (baseline sleep efficiency, wake time after sleep onset, proportion of N3 sleep) as independent variables. The results showed that baseline sleep efficiency ($\beta=0.28$, $P=0.02$) and wake time after sleep onset ($\beta=-0.25$, $P=0.03$) were independent predictors of ISI improvement. The adjusted $R^2=0.18$, and the overall model was statistically significant ($F=5.67$, $P<0.01$) (**Table 2**).

Table 2. Results of multiple regression analysis for CBT-I efficacy (ISI improvement value)

Independent variable	β -value	Standard error	t-value	P-value
Baseline Sleep Efficiency	0.28	0.11	2.56	0.02
Baseline Wake After Sleep Onset (WASO)	-0.25	0.10	-2.43	0.03
Baseline N3 Sleep Percentage	0.18	0.10	1.76	0.08
Intercept (Constant)	5.67	1.23	4.61	<0.01

Regression analysis with sleep efficiency improvement as the dependent variable showed that baseline wake time after sleep onset ($\beta=0.27$, $P=0.02$) was an independent predictor, with an adjusted $R^2=0.08$ ($F=3.21$, $P=0.04$).

3.5. Comparison of treatment effects among patients with different baseline sleep efficiencies

Patients were divided into a low sleep efficiency group ($\leq 65.42\%$, $n=60$) and a high sleep efficiency group ($>65.42\%$, $n=60$) based on the median baseline sleep efficiency (65.42%). The CBT-I treatment effects were compared between the two groups. The results showed that the ISI improvement score in the low sleep efficiency group (8.65 ± 3.24) was significantly higher than that in the high sleep efficiency group (5.34 ± 2.87) ($t=5.87$, $P<0.01$). Additionally, the sleep efficiency improvement in the low sleep efficiency group $22.34 \pm 8.76\%$ was significantly higher than that in the high sleep efficiency group $12.56 \pm 7.45\%$ ($t=6.54$, $P<0.01$).

4. Discussion

The pathogenesis of chronic insomnia is closely related to abnormalities in the sleep-wake regulatory network, with functional imbalances in nuclei such as the suprachiasmatic nucleus of the hypothalamus (biological rhythm

center), the raphe nuclei (5-hydroxytryptamine neurons), and the locus coeruleus (norepinephrine neurons) being the core links ^[6]. CBT-I can improve the regulatory function of these nuclei and restore normal sleep structure by adjusting sleep behavior and correcting cognitive biases ^[7]. This study focused on the predictive role of baseline PSG parameters on CBT-I efficacy, providing objective evidence for precision clinical treatment.

This study found that patients with lower baseline sleep efficiency showed more significant improvement after CBT-I treatment, which is consistent with the mechanism of sleep restriction therapy. Patients with low sleep efficiency often have the problem of “spending too much time in bed but actually sleeping for a short duration.” Sleep restriction can quickly improve sleep continuity by reducing time spent in bed and increasing sleep pressure (increasing the accumulation of sleep-promoting substances such as adenosine) ^[8]. On the other hand, patients with high sleep efficiency may have already formed a relatively stable sleep pattern and are less sensitive to intervention, suggesting that CBT-I can be preferentially adopted for patients with low sleep efficiency in clinical practice to achieve more significant initial efficacy.

Patients with longer baseline wake time after sleep onset responded better to CBT-I, which may be related to the synergistic effects of stimulus control therapy and relaxation training. Frequent awakenings after falling asleep are often associated with excessive attention to the sleep environment (such as “worrying about not being able to sleep”) and increased autonomic nervous system excitability. Stimulus control therapy can reduce wake time while in bed, and relaxation training can lower sympathetic nervous system activity (such as reducing heart rate and blood pressure fluctuations), thereby improving sleep maintenance ^[9]. Additionally, this type of patient often has a lower proportion of N3 sleep, and CBT-I can increase deep sleep (N3 stage) to improve sleep stability, further validating the predictive value of wake time after sleep onset.

Regarding the predictive role of the proportion of N3 sleep, this study showed a positive correlation with treatment efficacy, but it did not enter the final regression model ($P=0.10$), which may be related to the small sample size. N3 sleep is regulated by the ventrolateral preoptic area of the hypothalamus and is closely related to physical recovery and sleep stability ^[10]. Patients who retain a good proportion of N3 sleep at baseline may have less impairment in their sleep regulatory mechanisms and may be more likely to benefit from CBT-I ^[11]. This conclusion needs to be further validated with a larger sample size.

The strengths of this study lie in: (1) strictly following PSG monitoring protocols to ensure data objectivity; (2) the time frame of the cases aligns with the hospital’s opening time (March 2024 to June 2025), ensuring a reliable and authentic sample source; (3) focusing on the middle-aged and elderly population aged 35–75, which is more aligned with the characteristics of the clinical population prone to chronic insomnia. The limitations include: (1) being a single-center study with a small sample size (40 cases), which may introduce selection bias; (2) the absence of long-term follow-up data, making it impossible to evaluate the impact of predictive factors on the durability of treatment effect; (3) not combining neuroimaging techniques (such as fMRI) to further explore brain mechanisms. Future multi-center studies can be conducted, combining dynamic PSG monitoring and brain functional imaging to further refine the prediction model.

Sleep efficiency and wake time after sleep onset among baseline PSG parameters can serve as independent predictors of the efficacy of CBT-I in treating chronic insomnia. Patients with low baseline sleep efficiency and long wake time after sleep onset show a more significant treatment response. Clinically, these objective indicators can be used to screen CBT-I sensitive populations, optimize treatment strategies, and improve the precision of insomnia management.

5. Conclusion

The baseline PSG parameters, including sleep efficiency and wake after sleep onset (WASO), can effectively predict the efficacy of CBT-I in treating chronic insomnia, providing an objective basis for clinically identifying treatment-sensitive populations.

Disclosure statement

The author declares no conflict of interest.

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A Real-World Study on the Efficacy and Safety of Citicoline Sodium Capsules for Neurological Outcomes in Acute and Recovery Phases of Ischemic Stroke

Tianni Liu^{1,2}, Lin Lu², Tingting Gan^{1,2}, Ruiqing Luo³, Qin Liu^{2*}

¹Department of Neurology, the Second Affiliated Hospital of Xinjiang Medical University, Urumqi 830018, Xinjiang Uygur Autonomous Region, China

²Department of Neurology, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510120, Guangdong, China

³Department of Neurology, The Second Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi, China

**Author to whom correspondence should be addressed.*

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Abstract: *Background:* To evaluate the efficacy, safety, and adherence of oral citicoline sodium capsules in improving neurological outcomes during the recovery phase of ischemic stroke in a real-world setting. *Methods:* This single-arm, multicenter, real-world observational study enrolled 6496 ischemic stroke patients in the recovery phase from January 2020 through December 2024. Patients received citicoline sodium capsules (200 mg, three times daily) for three months. Outcomes were assessed using NIHSS, mRS, and Barthel Index at baseline, 1, 2, and 3 months. Treatment effectiveness was categorized based on NIHSS improvement as markedly effective ($\geq 90\%$ reduction), improved (60%–89%), effective (30%–59%), or ineffective ($< 30\%$). *Results:* Of the 6496 patients (mean age 61.9 ± 10.6 years; 61.6% male), 85.8% had comorbidities. After three months of treatment, significant improvements were observed in all neurological function measures: NIHSS decreased from 11.6 ± 5.5 to 9.6 ± 6.2 , mRS improved from 2.5 ± 1.1 to 2.0 ± 1.1 , and BI increased from 51.4 ± 24.0 to 62.8 ± 25.7 (all $P < 0.001$). The total effectiveness rate increased progressively from 9.9% at 1 month to 37.5% at 3 months, while the proportion of severely dependent patients decreased from 27.7% to 11.9%. Treatment adherence remained high (96%–97%) throughout the study period, with only two mild adverse events reported. *Conclusions:* This real-world study suggests that three-month citicoline therapy provides meaningful improvements in neurological function and daily living activities during stroke recovery, with excellent safety and adherence profiles. Further randomized controlled trials are warranted to confirm these findings and optimize treatment protocols.

Keywords: Citicoline; Ischemic stroke; Recovery phase; Real-world study; Neurological function; Treatment adherence

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1. Introduction

Stroke is a major global health concern and ranks among the leading causes of mortality and disability worldwide. The 2019 Global Burden of Disease (GBD) studies have underscored its massive impact: stroke remains the second most common cause of death and the third leading cause of disability-adjusted life years lost globally ^[1]. Among various stroke subtypes, ischemic stroke (IS) is the most prevalent, accounting for over 60% of all stroke events in many regions ^[2]. In China, which shoulders a significant portion of the global stroke burden, cerebrovascular diseases are now recognized as the top cause of death, and ischemic stroke contributes substantially to the disease and economic load ^[3].

Ischemic stroke occurs when blood flow to an area of the brain is obstructed, typically by a thrombus or embolus, leading to ischemic necrosis of the affected brain tissue. The abrupt reduction in perfusion disrupts oxygen and nutrient supply, triggering a cascade of pathophysiological events such as excitotoxicity, oxidative stress, and neuroinflammation ^[4-5]. Clinically, the hallmark features of ischemic stroke include the sudden onset of focal neurological deficits. Common presentations may include hemiparesis or hemiplegia, sensory deficits, aphasia (involvement of the dominant hemisphere), facial droop, or dysarthria. More extensive infarcts may result in global symptoms, including altered consciousness or coma.

The progression of ischemic stroke is generally divided into three clinical phases: an acute phase, a recovery (or subacute) phase, and a chronic or sequela phase ^[6]. The acute phase usually covers approximately the first two weeks after stroke onset. During this period, the immediate management focus is on stabilizing the patient's hemodynamics, restoring perfusion where possible (e.g., through intravenous thrombolysis or mechanical thrombectomy), and preventing complications.

Following the acute phase, the recovery or subacute phase extends from about two weeks to six months post-stroke. This is a pivotal window for functional rehabilitation. Spontaneous neurological recovery often occurs through processes of plasticity, reorganization of cortical pathways, and penumbral salvage. Early and intensive rehabilitative interventions targeting motor, cognitive, and speech functions can significantly influence long-term outcomes ^[7-8]. Beyond six months, the patient enters the chronic or sequela phase, where further recovery tends to be slower but can continue with appropriate therapy. Because of the high morbidity and mortality associated with ischemic stroke, there is a critical need for therapeutic strategies that not only mitigate acute damage but also enhance recovery. Neurological deficits arising from ischemic injury can be at least partially reversible through endogenous plasticity and external interventions ^[9].

Pharmacotherapies used during the recovery phase of ischemic stroke aim to protect neurons from secondary injury, enhance synaptic transmission, and support regeneration of the compromised neuronal networks ^[10]. Agents with neuroprotective or neurorestorative potential are receiving increasing attention, especially for the subacute phase. One of the commonly utilized therapies in clinical practice is citicoline (also known as cytidine diphosphate choline or CDP-choline). Citicoline is an endogenous substance crucial to the synthesis of phosphatidylcholine in cell membranes; it can be administered exogenously to supplement and potentially accelerate neuronal repair ^[11].

Citicoline is a naturally occurring compound comprising cytidine and choline. It acts as a precursor for phospholipids, such as phosphatidylcholine, which are integral components of neuronal cell membranes ^[12]. By boosting phosphatidylcholine synthesis, citicoline can help stabilize cell membranes compromised by ischemic damage. It also supports neurotransmitter production, including acetylcholine and dopamine, which are vital for synaptic transmission and cognitive functions ^[11].

Furthermore, citicoline is reported to mitigate ischemia-induced damage by reducing free fatty acid release, thus lowering oxidative stress and membrane disintegration. Some evidence suggests that it may enhance cerebral

blood flow in ischemic penumbral areas and support mitochondrial function, thereby improving neuronal energy metabolism^[12–13]. Citicoline has a long history of use in neurological disorders, including traumatic brain injury, mild cognitive impairment, and particularly cerebrovascular disease. Randomized controlled trials (RCTs) and meta-analyses have evaluated its safety and efficacy, albeit with varying outcomes^[14–15]. Some earlier large-scale RCTs (e.g., the International Citicoline Trial on Acute Stroke) yielded mixed results, in part because of heterogeneity in patient populations, dosing regimens, and the timing of administration^[14]. Nonetheless, a growing body of evidence suggests that citicoline may improve functional outcomes in ischemic stroke when used alongside standard therapy, especially if administered consistently during the subacute rehabilitation phase^[16–17]. Moreover, real-world evidence (RWE) has become increasingly important to validate the effectiveness of treatments observed under controlled conditions. RWE can capture how citicoline performs in broader, more diverse populations, including patients with multiple comorbidities who may not be eligible for or included in RCTs^[18].

Although the administration of citicoline during the acute phase has been explored, the recovery phase presents a particularly crucial time for neuronal repair. The subacute phase is characterized by dynamic neuroplastic changes—both spontaneously and through rehabilitation—creating a unique therapeutic window^[19]. Evidence indicates that prolonged administration of citicoline, from several weeks to a few months, may sustain membrane repair processes and enhance functional gains^[20]. However, many patients discontinue pharmacological interventions once acute stroke management concludes or once they are discharged from the hospital, potentially missing out on the benefits that extended therapy might confer.

For example, in the scenario of post-stroke patients who feel somewhat recovered upon discharge, there is a risk of prematurely discontinuing all medications (except for perhaps antiplatelets or anticoagulants). This cessation could hinder continued functional recovery and might also increase the likelihood of subsequent vascular events if certain neuroprotective or neurorestorative agents are withdrawn^[21].

Citicoline is generally well-tolerated, with a low incidence of adverse events^[11–12]. Mild gastrointestinal upset or headache are sometimes reported, but severe side effects appear to be rare. However, given the complex medication regimens that many ischemic stroke patients undertake—often including antihypertensives, antiplatelet or anticoagulant agents, statins, and possibly anti-diabetic medications—investigating the real-world safety of citicoline remains important. Post-stroke patients, particularly older adults, may also have organ dysfunctions or polypharmacy concerns that could influence the safety profile of any additional agent^[22].

While citicoline's neuroprotective potential has been studied extensively in acute settings, comprehensive real-world data regarding its use during the stroke recovery phase remain limited. This study investigates the effectiveness of oral citicoline sodium capsules in improving neurological outcomes during both acute and recovery phases of ischemic stroke, with a focus on treatment effectiveness, adherence rates, and safety profiles over a three-month period. By examining a large, real-world population across multiple centers, this research aims to bridge the gap between controlled trials and everyday clinical practice, thereby providing practical guidance for optimizing citicoline therapy in stroke rehabilitation programs.

2. Methods

2.1. Study design

This investigation was conducted as a single-arm, multicenter, real-world observational study examining the efficacy, safety, and adherence of citicoline sodium capsules in patients with ischemic stroke during the subacute or recovery phase. The study window ran from January 1, 2020, through December 31, 2024. Because of the real-

world nature of the project, participating sites enrolled eligible patients according to routine clinical protocols, with no additional interventions beyond standard care.

All procedures were carried out in accordance with local regulations, institutional guidelines, and the Declaration of Helsinki. Depending on local Institutional Review Board (IRB) policies, individual informed consent was obtained or waived for observational use of anonymized patient data.

2.2. Patient population

2.2.1. Inclusion criteria

- (1) Patients meeting the diagnostic criteria for ischemic stroke as outlined in the *Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke (2018)*.
- (2) Age ≥ 18 years, of either gender.
- (3) Classified as being in the recovery (subacute) phase of ischemic stroke, typically from two weeks up to six months post-onset.
- (4) Documented usage of citicoline sodium capsules during the study period (January 1, 2020, to December 31, 2024).

2.2.2. Exclusion criteria

- (1) Incomplete clinical data that prevented evaluation of outcomes.
- (2) Known severe psychiatric disorders or dementia at baseline.

2.3. Data collection procedures

2.3.1. Data sources and scope

The dataset comprises patient information retrieved from electronic medical records (EMRs) or paper charts in hospitals across multiple provinces and municipalities. Researchers or designated staff members manually input data into an Electronic Data Capture (EDC) system. The scope of data collection encompassed: Demographic Information: Birth date, sex, height, weight, ethnicity, and region of residence or treatment. Additional variables included smoking status, alcohol use patterns, and the presence or absence of obesity. Stroke Characteristics and Medical History: Date of stroke onset, family history of stroke, classification of stroke (ischemic only), vital signs, and baseline NIHSS, mRS, and Barthel Index (BI) scores upon recruitment. The presence of comorbid conditions (e.g., hypertension, diabetes, hyperlipidemia) was recorded along with pertinent past medical or surgical histories. Therapeutic Interventions: Details of acute-phase interventions (thrombolysis, mechanical thrombectomy, or supportive care) if available, followed by the duration and dosage regimen of citicoline sodium capsules (standard dose: 200 mg per administration, three times daily) during the recovery phase. Concomitant medications were documented where feasible (e.g., antiplatelets, statins, antihypertensive agents). Outcome Measures: This study repeatedly measured NIHSS, mRS, and BI at baseline (prior to citicoline therapy) and subsequently at 1 month, 2 months, and 3 months of ongoing treatment. Additional scales included an overall clinical efficacy assessment based on NIHSS improvement from baseline. Safety Assessments: Adverse events (AEs) were captured with special focus on severity (mild, moderate, severe), potential relationship to citicoline (unlikely, possible, probable), and outcomes (resolved, ongoing, led to hospitalization). Medication Adherence: Adherence was calculated as the ratio of actual days that the patient used citicoline sodium capsules to the theoretical (prescribed) days over each 1-month interval. Adherence data were derived from prescription refill records and self-reported compliance.

2.4. Outcome measurements

The study employed multiple validated assessment tools to evaluate patient outcomes.

NIHSS Score: The National Institutes of Health Stroke Scale (NIHSS) is a widely accepted 11-item measure used to evaluate neurological function and the severity of stroke-induced deficits. Higher scores on the NIHSS reflect more severe impairment, with a maximum total of 42. In this study, the NIHSS was assessed at baseline and again at months 1, 2, and 3 following initiation of citicoline therapy.

Clinical Efficacy Categorization: Based on changes in NIHSS from baseline to follow-up, four categories were defined: Markedly Effective: $\geq 90\%$ reduction in NIHSS score from baseline, along with near-complete recovery of living ability and minimal residual neurological deficits. Improved: 60%–89% reduction in NIHSS score, with notable improvement in activities of daily living and moderate relief of neurological symptoms. Effective: 30%–59% reduction in NIHSS score, with some improvement in clinical symptoms and functional status. Ineffective: $<30\%$ reduction in NIHSS score or no perceptible improvement in clinical status. The overall effectiveness rate was the sum of “Markedly Effective”, “Improved”, and “Effective”, divided by the total number of patients in the analysis.

Modified Rankin Scale (mRS): The mRS ranges from 0 (no symptoms) to 5 (severe disability) or 6 (death). This scale assessed functional disability at baseline, 1 month, 2 months, and 3 months, providing a global measure of post-stroke independence. A lower mRS score indicates less disability.

Barthel Index (BI): The BI evaluates 10 items related to activities of daily living (ADL), such as feeding, bathing, grooming, dressing, bowel/bladder control, toilet use, transfers, ambulation, and stair climbing. Scores range from 0 to 100, with higher values signifying greater independence in daily activities. The results were interpreted to categorize patients as: No Dependency (BI > 90), Mild Dependency (BI 61–90), Moderate Dependency (BI 41–60), Severe Dependency (BI ≤ 40).

Safety Indicators: Adverse events were recorded during each follow-up period. The severity and probable causality of citicoline were documented according to each participating center’s standard protocols. If serious adverse events occurred, they were subject to immediate reporting as per national pharmacovigilance requirements.

2.5. Statistical analysis

In this observational real-world study, no formal sample size calculation was performed; instead, all eligible patients meeting the inclusion/exclusion criteria were recruited during the designated period. While investigators initially estimated approximately 8500 patients might be collected, the final sample included 6496 patients for baseline analyses and 6515 for certain follow-up analyses, reflecting actual data captured and validated. For continuous data (age, weight, NIHSS, mRS, and BI), summary statistics were presented as mean \pm standard deviation, median with interquartile range (Q1–Q3), and minimum/maximum values as appropriate, while frequencies and percentages were used for categorical variables. Paired-sample t-tests or Wilcoxon signed-rank tests (for non-normally distributed data) were employed to compare NIHSS, mRS, and BI between baseline and each follow-up (1, 2, and 3 months), with $P < 0.05$ considered statistically significant. McNemar’s chi-square test evaluated changes in the proportion of patients meeting threshold definitions for clinical improvement. Clinical efficacy was assessed by calculating the proportion of patients achieving “Markedly Effective”, “Improved”, “Effective”, or “Ineffective” status at each follow-up, with chi-square tests detecting significant differences across categories over time. Adherence rates were quantified for each 1-month interval over three months, summarized as means, standard deviations, medians, and ranges. Adverse events were tabulated by type, severity, and relationship to citicoline, with rates expressed as percentages of total patients experiencing events, though no complex survival analysis methods were planned unless severe events warranted deeper investigation.

2.6. Quality assurance and data management

All centers used standard definitions for data collection to ensure consistency. The principal investigator and study coordinators periodically audited the input in the EDC system for accuracy and completeness. Any discrepancies were resolved by consulting the original patient charts. Data were de-identified to maintain patient confidentiality, with each patient assigned a unique study ID.

2.7. Ethical considerations

Because this research was observational, no additional interventions were imposed upon patients. Informed consent was obtained or waived according to the institutional ethics committee or IRB guidance. All data were anonymized to preserve confidentiality.

3. Results

3.1. Patient demographics and origin distribution

A total of 6496 patients who met the inclusion criteria were ultimately included. Of these, 4000 (61.6%) were male and 2496 (38.4%) were female. The mean (\pm SD) age was 61.9 ± 10.6 years, with a minimum age of 18 and a maximum age of 102. The mean body weight was 66.9 ± 11.6 kg, and the mean height was 167.4 ± 7.9 cm. Regarding lifestyle factors, 38.5% reported a smoking history, while 66.6% reported some level of alcohol use (ranging from occasional to daily). Additionally, 14.8% had a documented history of obesity (**Table 1**).

Table 1. Baseline demographic characteristics (N=6496)

Variable	Statistic
Total patients (n)	6496
Sex (n, %)	Male: 4000 (61.6%) Female: 2496 (38.4%)
Age (years)	Mean \pm SD: 61.9 ± 10.6 Range: 18–102 Median (Q1–Q3): 61 (55–69)
Weight (kg)	Mean \pm SD: 66.9 ± 11.6 Range: 31–150 Median (Q1–Q3): 67 (59–75)
Height (cm)	Mean \pm SD: 167.4 ± 7.9 Range: 143–189 Median (Q1–Q3): 168 (161–173)
Ethnicity	Han: 6344 (97.7%) Other: 152 (2.3%)
Smoking history	No: 3994 (61.5%) Yes: 2502 (38.5%)
Alcohol use	Never: 2168 (33.4%) Occasional: 2799 (43.1%) Weekly: 1182 (18.2%) Daily: 347 (5.3%)
Obesity history	No: 5533 (85.2%) Yes: 963 (14.8%)

3.2. Baseline clinical information

Out of the 6496 enrolled patients, 482 (7.4%) reported a family history of stroke. The majority (85.8%) had at least one comorbidity, with hypertension being the most common (78.4%), followed by hyperlipidemia (34.2%) and diabetes (20.0%). The average NIHSS score at baseline was 11.6 ± 5.5 , while the average mRS score was 2.5 ± 1.1 , and the average BI score was 51.4 ± 24.0 . Based on the BI-based self-care assessment, 27.7% were classified as heavily dependent ($BI \leq 40$), 29.4% as moderately dependent, and 42.7% as mildly dependent (**Table 2**).

Table 2. Baseline clinical characteristics (N=6496)

Variable	Statistic
Family History of Stroke (n, %)	No: 6014 (92.6%) Yes: 482 (7.4%)
Comorbidities (n, %)	Any: 5573 (85.8%) None: 923 (14.2%)
Hypertension	4369 (78.4%)
Diabetes	1114 (20.0%)
Hyperlipidemia	1904 (34.2%)
Heart Disease	414 (7.4%)
Others	31 (0.6%)
NIHSS Score	Mean \pm SD: 11.6 ± 5.5 Range: 1–24 Median (Q1–Q3): 12 (7–16)
mRS Score	Mean \pm SD: 2.5 ± 1.1 Range: 0–5 Median (Q1–Q3): 2 (2–3)
BI Score	Mean \pm SD: 51.4 ± 24.0 Range: 1–100 Median (Q1–Q3): 57 (36–69)
Self-Care Ability	No dependency: 11 (0.2%) Mild dependency: 2774 (42.7%) Moderate dependency: 1911 (29.4%) Severe dependency: 1800 (27.7%)

3.3. Follow-up and neurological function over time

Although 6496 patients had complete baseline data, a total of 6515 usage episodes of citicoline were documented for follow-up. Discrepancies may be due to differences in how usage was recorded or updated. Over the 3-month therapy, improvements in NIHSS, mRS, and BI were observed (**Table 3**).

Table 3. Changes in NIHSS, mRS, and BI Over 3 Months

Variable	1 Month	2 Months	3 Months
NIHSS	Mean \pm SD: 10.9 \pm 5.6	Mean \pm SD: 10.2 \pm 5.9	Mean \pm SD: 9.6 \pm 6.2
	Range: 1–24	Range: 1–24	Range: 1–24
	Median (Q1–Q3): 11 (6–15) P vs. Baseline: <0.001	Median (Q1–Q3): 10 (5–15) P vs. Baseline: <0.001	Median (Q1–Q3): 9 (4–14) P vs. Baseline: <0.001
mRS	Mean \pm SD: 2.3 \pm 1.0	Mean \pm SD: 2.2 \pm 1.0	Mean \pm SD: 2.0 \pm 1.1
	Range: 0–5	Range: 0–5	Range: 0–5
	Median (Q1–Q3): 2 (2–3) P vs. Baseline: <0.001	Median (Q1–Q3): 2 (1–3) P vs. Baseline: <0.001	Median (Q1–Q3): 2 (1–3) P vs. Baseline: <0.001
BI	Mean \pm SD: 55.4 \pm 24.2	Mean \pm SD: 59.1 \pm 24.7	Mean \pm SD: 62.8 \pm 25.7
	Range: 1–100	Range: 1–100	Range: 1–100
	Median (Q1–Q3): 62 (43–71) P vs. Baseline: <0.001	Median (Q1–Q3): 66 (49–76) P vs. Baseline: <0.001	Median (Q1–Q3): 70 (52–81) P vs. Baseline: <0.001
Self-care ability	No dependency: 9 (0.1%)	No dependency: 11 (0.2%)	No dependency: 20 (0.3%)
	Mild dependency: 4556 (70.1%)	Mild dependency: 4872 (75.0%)	Mild dependency: 5169 (79.6%)
	Moderate: 1021 (15.7%)	Moderate: 785 (12.1%)	Moderate: 533 (8.2%)
	Severe: 910 (14.1%) P: <0.001	Severe: 828 (12.7%) P: <0.001	Severe: 774 (11.9%) P: <0.001

By the third month, the mean NIHSS was 9.6 \pm 6.2, significantly lower than the baseline of 11.6 \pm 5.5 (P <0.001). Similarly, mRS scores dropped on average from 2.5 \pm 1.1 to 2.0 \pm 1.1 (P <0.001), indicating an improvement in functional status. The Barthel Index rose from 51.4 \pm 24.0 to 62.8 \pm 25.7 over the same period (P <0.001). While a large fraction of patients still had mild or moderate dependency, the proportion with severe dependency decreased from 27.7% at baseline to 11.9% at 3 months.

3.4. Efficacy evaluation

Table 4 summarizes clinical efficacy as determined by changes in NIHSS at 1, 2, and 3 months. At 1 month, total effectiveness (sum of markedly effective, improved, and effective) was 9.9%, increasing to 26.8% at 2 months and further to 37.5% at 3 months (P <0.001 for overall trend). The proportion achieving “markedly effective” status also rose over time, but remained below 1% until 3 months (0.9%).

Table 4. Distribution of clinical efficacy at 1, 2, and 3 months

Category	1 Month (n, %)	2 Months (n, %)	3 Months (n, %)	χ^2 / P
Markedly Effective ($\geq 90\%$ Δ NIHSS)	4 (0.1)	8 (0.1)	59 (0.9)	$\chi^2=1677.4$ $P<0.001$
Improved (60–89% Δ NIHSS)	81 (1.2)	386 (5.9)	973 (15.0)	
Effective (30–59% Δ NIHSS)	559 (8.6)	1349 (20.8)	1407 (21.6)	
Ineffective (<30% Δ NIHSS)	5852 (90.1)	4766 (73.2)	4057 (62.5)	
Total Effectiveness	9.9%	26.8%	37.5%	$\chi^2=1353.5$ $P<0.001$

3.5. Medication use patterns and adherence

Citicoline sodium capsules were administered at 200 mg per dose, three times per day for most patients. Actual usage days were measured at each month. Adherence was relatively high: the mean (\pm SD) adherence rate was

approximately 96%–97% across months (**Table 5**).

Table 5. Medication adherence over 3 months

Interval	Adherence rate (%) Mean \pm SD	Range	Median (Q1–Q3)
1 Month	96.9 \pm 6.5	18.2–120	96.8 (96.8–100)
2 Months	96.0 \pm 6.5	9.7–115.4	96.8 (96.6–100)
3 Months	96.4 \pm 7.1	9.7–111.1	96.8 (96.6–100)

3.6. Safety profile

Only two mild adverse reactions were documented in this dataset—one gastrointestinal reaction (mild dyspepsia) and one central nervous system effect (mild headache). Both events resolved spontaneously, and neither recurred during follow-up. No severe or life-threatening adverse events linked to citicoline were recorded, indicating a favorable safety and tolerability profile in this real-world cohort.

4. Discussion

In this large, real-world observational study, the study evaluated the efficacy, safety, and adherence of oral citicoline sodium capsules in 6496 ischemic stroke patients during their recovery phase. Over three months, the patients generally showed significant improvement in NIHSS, mRS, and BI scores, suggesting notable enhancements in neurological and functional status. The total clinical effectiveness rate rose from 9.9% at one month to 37.5% at three months, implying that extended therapy could be crucial to maximizing benefits. Citicoline’s mechanistic basis involves supporting phospholipid synthesis, enhancing neurotransmitter production (acetylcholine and dopamine), and stabilizing neuronal cell membranes ^[11–12]. The progressive gains observed across standard clinical scales (NIHSS, mRS, BI) align with the hypothesis that consistent supplementation of citicoline aids neuronal recovery and plasticity.

The results of this study are broadly consistent with prior literature indicating that citicoline can be beneficial in ischemic stroke ^[14, 16–17]. Although some randomized trials have reported mixed or inconclusive outcomes, this may reflect differences in study design, including variation in the timing of administration, dosages, patient selection (e.g., stroke severity), and use of concurrent therapies ^[15]. The real-world approach, which imposes minimal exclusion criteria, likely captures a heterogeneous patient population, thus presenting a broader picture of citicoline’s utility.

Research has shown that the subacute phase of stroke (up to six months post-infarct) is highly dynamic and is a window for major recovery gains ^[8–9]. Pharmacological agents that support neuroprotection and neurorepair during this period may have a meaningful impact on ultimate functional outcomes. Studies of citicoline in subacute stroke have hinted that administration over several weeks can bolster neurological recovery, but fewer large-scale observational data sets have validated these findings under ordinary clinical conditions ^[13].

One notable aspect of the findings is the incremental increase in clinical effectiveness from one month (9.9%) to three months (37.5%). Indeed, many neurorepair processes unfold gradually, including synaptic reorganization, dendritic arborization, and remodeling of the ischemic penumbra ^[19]. Discontinuing citicoline early could limit these potential benefits. The data suggest that at least two to three months of therapy might yield optimal functional recovery.

Moreover, extended therapy is also relevant to preventing subsequent ischemic events. Although citicoline is not primarily an antithrombotic agent, it contributes to stabilizing neuron membrane integrity and possibly sustaining cognition and motivation, which can indirectly help patients engage better in secondary prevention measures^[20–21].

A particularly encouraging result is the high adherence rate ($\geq 96\%$) maintained across the three-month duration. Historically, adherence to stroke medications can be compromised by polypharmacy, side effects, or financial burdens^[22]. However, in this cohort, most participants maintained a regimen of 200 mg three times a day. Few reported discontinuation or substantial dosage interruption. This adherence could be partly due to the minimal side effects encountered and the perceived benefits of the medication by patients and caregivers, reinforcing compliance. In typical clinical settings, forgetfulness, lack of perceived need, cost, or side effects lead to suboptimal adherence. The results demonstrate that citicoline therapy is feasible when healthcare providers offer consistent patient education regarding its role in functional recovery^[23]. Although the authors did not quantitatively correlate adherence with outcome improvements, it is reasonable to infer that adherence fosters better neurological and functional gains, especially when combined with standard stroke rehabilitation.

Another critical finding is that only two mild adverse events were documented during three months of citicoline usage. These were limited to a gastrointestinal reaction and mild CNS complaint, both resolving spontaneously. Real-world populations often include older individuals with multiple comorbidities and concomitant medications, raising the possibility of drug–drug interactions. Nonetheless, no severe adverse events or hospitalizations related to citicoline were reported here. The safety profile aligns with prior data indicating that citicoline is generally well-tolerated with no major side effects^[12, 24].

This favorable safety profile is advantageous, as it eases concerns over prescribing citicoline to frail, elderly patients or individuals with polypharmacy regimens. Combined with high adherence and clinically significant functional improvements, the evidence supports citicoline as a user-friendly option in subacute stroke management. The study's clinical implications are significant for stroke rehabilitation practice. The gradual improvement in NIHSS scores over three months emphasizes that stroke recovery requires sustained therapy, suggesting clinicians should encourage longer-term citicoline usage when integrated with rehabilitation programs. Stroke management should extend beyond pharmaceuticals, combining physical, occupational, and speech rehabilitation with risk factor management and psychosocial support. Citicoline can serve as an adjunct, potentially amplifying the gains from these programs^[20–21]. The improvements in mRS and BI scores indicate enhanced independence in daily activities, directly improving quality of life for both patients and caregivers. Even minor functional gains can reduce caregiving requirements, thereby lowering overall economic and social burden^[25]. Given this study's minimal selection restrictions, results may be generalized to diverse stroke survivors, including those with hypertension, diabetes, or advanced age. However, clinicians should individualize dosing schedules and durations based on comorbid conditions, stroke severity, and long-term adherence feasibility. Telemedicine and follow-up calls could reinforce medication compliance in real-world settings.

Neuroprotective research in stroke has historically faced challenges, with many agents failing to meet endpoints in large RCTs. This discrepancy sometimes stems from the short therapeutic windows. Agents tested in the hyperacute or acute stage (within hours) have less time to show efficacy, while in the subacute stage, the pathophysiological processes shift toward neurorepair^[26]. Citicoline's advantage may lie partly in its extended window of opportunity: the processes of membrane repair, neurotransmitter enhancement, and plasticity-based recovery can be harnessed weeks after the index stroke^[27]. Unlike other compounds such as N-methyl-D-aspartate

(NMDA) receptor antagonists or free radical scavengers, citicoline not only offers potential neuroprotection but also contributes to the structural rebuilding of neuronal membranes. Other agents like edaravone, minocycline, or piracetam also target certain aspects of post-stroke recovery, but direct comparisons are limited. Observational comparisons suggest citicoline's safety track record is highly favorable, though cost-effectiveness analyses would help clarify its place relative to other neuroprotectants^[28–29].

Despite valuable insights, this study has several important limitations. The single-arm design without a control group or comparator makes it impossible to conclusively attribute improvements to citicoline alone, as spontaneous recovery and rehabilitation efforts could contribute to outcomes. Selection bias may exist as inclusion was based on EMR-recorded patients, potentially favoring those with better follow-up adherence. Additionally, the real-world setting meant variations in standard care practices, including physiotherapy intensity and concurrent medications, which complicates the interpretation of citicoline's individual contribution. The study also lacked systematic documentation of the interval between stroke onset and citicoline initiation, limiting the understanding of the timing's impact on efficacy. While the safety profile appears favorable, the real-world data might not be exhaustive, as mild side effects could be underreported, and standardized adverse event severity scales were not uniformly employed across sites.

Several areas warrant further investigation based on the findings. Multicenter, randomized pragmatic trials comparing citicoline with usual care would help confirm these observational findings, with potential stratification based on stroke severity or therapy initiation timing. An extended follow-up beyond three months could reveal whether functional gains plateau or continue improving, particularly for cognitive tasks. Advanced neuroimaging studies, such as diffusion tensor imaging and resting-state functional MRI, might illuminate structural and functional brain changes associated with extended citicoline use, deepening the understanding of its mechanisms. Cost-effectiveness studies are crucial for health policy decisions regarding extended citicoline treatment. Finally, biomarker research investigating inflammatory cytokines and neurotrophic factors could help identify patient subgroups most likely to benefit from citicoline or requiring alternative therapies.

5. Conclusion

This real-world analysis involving 6496 ischemic stroke patients strongly suggests that citicoline sodium capsules provide meaningful improvements in neurological function and daily living activities, especially when administered for up to three months during the recovery phase. The increase in total effectiveness rate—from 9.9% at one month to 37.5% at three months—underscores the importance of sustained therapy. Citicoline's excellent safety profile, reflected by minimal adverse events, supports its potential as a well-tolerated adjunct to standard stroke rehabilitation. Although the absence of a control group precludes definitive statements of causality, these findings align with the mechanistic rationale for citicoline and bolster prior evidence from smaller or more narrowly selected cohorts. Given the heterogeneity of ischemic stroke presentations and comorbidities, real-world data can be pivotal in guiding practical clinical decisions. Further research, particularly randomized or comparative designs, is warranted to clarify the optimal timing, dosage, and duration of citicoline therapy. Nevertheless, the current study highlights a promising strategy for enhancing post-stroke recovery, with the potential to improve patient independence and reduce healthcare burdens associated with long-term disability.

Disclosure statement

The authors declare no conflict of interest.

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The Prevention Strategy and Practical Application of Mindfulness Therapy Intervention in the Recurrence of Addictive Substance Use Disorders

Bailin He¹, Tefu Liu¹, Qiao Chen^{2*}

¹Lituo Drug Rehabilitation Institute, Changsha 410014, Hunan, China

²Hunan Labor and Human Resources Vocational College, Changsha 410100, Hunan, China

*Corresponding author: Qiao Chen, chenqiao0731@163.com

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Abstract: This study focuses on the application and effect of Mindfulness-Based Interventions (MBI) in the prevention of recurrence of Substance Use Disorders (SUD). Firstly, by systematically sorting out the core theories and mechanisms of mindfulness therapy, clarify its role paths in cognitive awareness, emotion regulation, and impulse control; Subsequently, combined with existing intervention studies and empirical data, the improvement effects of the mindfulness training program on the recurrence rate, physiological stress indicators, and mental health level were analyzed. The study adopted a randomized controlled design. The experimental group that received eight weeks of mindfulness training was compared with the control group that received conventional withdrawal treatment. Data from the MAAS Mindfulness Awareness Scale, the BSCS Self-control Scale, and survival analysis were collected. The results showed that the risk of recurrence in the experimental group was significantly reduced, the ability of mindfulness awareness and self-control was continuously enhanced, and there was a good maintenance effect during the three-month follow-up. The discussion section further explores how mindfulness intervention can reshape the cognitive response to material craving by enhancing present awareness and non-evaluative attitudes, and puts forward improvement suggestions in response to the sample limitations and implementation difficulties of existing research. The research conclusion provides a theoretical basis and practical path for incorporating MBI into the comprehensive intervention system of SUD, and at the same time points out the direction for future multi-center and large-sample longitudinal follow-up studies.

Keywords: Mindfulness therapy; Substance use disorder; Recurrence prevention; Emotion regulation; Impulse control

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1. Introduction

Substance Use Disorders (SUD) pose a major global public health challenge due to their high relapse rates and severe impairment of social functioning. Previous research has shown that while traditional detoxification

treatments and cognitive-behavioral interventions can effectively reduce substance consumption in the short term, relapse risk during the maintenance phase remains between 40% and 60%, largely because these approaches do not fully address stress management, negative emotions, and impulse control ^[1]. As neuroscience and psychology uncover more about the mind-body interaction, Mindfulness-Based Interventions (MBI) have attracted increasing attention. Mindfulness emphasizes non-judgmental awareness of the present moment; by enhancing individuals' recognition and acceptance of inner experiences such as craving, anxiety, or impulses, it helps disrupt automatic addictive response patterns and offers novel theoretical and practical pathways for relapse prevention. Although several small-scale randomized controlled trials (RCTs) and longitudinal follow-up studies have examined MBI's efficacy in treating depression, anxiety, and other psychological disorders, its application among SUD populations remains nascent. Existing studies are limited by small sample sizes, variability in intervention content and frequency, and narrow follow-up measures. Building on a systematic synthesis of MBI's core mechanisms, the present study designed an eight-week mindfulness training program and employed an RCT to evaluate its effects on relapse rates, self-control capacity, and mental health in individuals with SUD. This research not only enriches the empirical evidence linking MBI to addictive behaviors but also provides an operational model and evaluation framework for integrating mindfulness into comprehensive SUD treatment. We hope our findings will offer feasible strategies to reduce relapse risk and enhance long-term recovery quality, and lay methodological groundwork for future multicenter, large-sample longitudinal studies ^[2].

2. Literature review

2.1. Advances in mindfulness-based interventions for mental health

Mindfulness-Based Interventions (MBI) were first developed by Kabat-Zinn in the 1970s to alleviate chronic pain and stress-related disorders and soon expanded into treatment for mood disorders. The two mainstream formats are Mindfulness-Based Stress Reduction (MBSR) and Mindfulness-Based Cognitive Therapy (MBCT) ^[3]. MBSR is built around an eight-week, group-based curriculum that employs meditation, body scan, and yoga to cultivate non-judgmental awareness of bodily and mental experiences, thereby improving recognition of stressors and habitual reactions. MBCT adds cognitive-behavioral techniques to this foundation, specifically targeting individuals at high risk of depressive relapse by helping them identify and accept negative thought patterns, thus reducing emotional distress and relapse probability. A wealth of empirical studies demonstrates that MBI yields significant reductions in depressive, anxiety, and stress symptoms. Meta-analyses show that, compared with control groups, participants in MBSR or MBCT exhibit moderate or greater effect sizes on self-report measures such as the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI), with benefits maintained at three- to six-month follow-ups. Research on post-traumatic stress disorder (PTSD) indicates that mindfulness practices enhance tolerance for trauma-related memories and acceptance of bodily sensations, reducing both avoidance and hyperarousal symptoms and markedly improving sleep quality and life satisfaction. Applications of MBI have also increased among populations with eating disorders, chronic pain, and psychosomatic illnesses (e.g., hypertension, coronary heart disease). Most studies find that mindfulness not only alleviates physical discomfort but also interrupts maladaptive cycles of emotion-driven eating or pain-induced distress, thereby enhancing overall functional status. In recent years, scholars have combined MBI with neuroimaging to explore its neural mechanisms. Functional magnetic resonance imaging (fMRI) studies reveal that mindfulness training increases activation in regions associated with emotion regulation and self-awareness—

such as the anterior cingulate cortex (ACC) and insula—while attenuating responses in the amygdala, which is linked to stress and negative-emotion processing. These findings provide preliminary evidence that mindfulness promotes cognitive–emotional regulation via neural plasticity and guide future precision-targeted interventions for various psychological disorders. Overall, MBI has established a robust theoretical and practical framework in mental health care and shown reliable efficacy across a range of emotional and psychosomatic disorders. Challenges remain—such as determining optimal intervention “dosage”, ensuring instructor qualifications, maintaining participant adherence, and achieving cultural adaptation—but upcoming multicenter, large-sample, and multimodal studies will further validate and refine MBI’s accessibility, specificity, and long-term effectiveness ^[4].

2.2. Current research on mindfulness-based interventions for SUD

In recent years, research on inserting mindfulness into SUD treatment has grown, with flagship programs including Mindfulness-Based Relapse Prevention (MBRP), Mindfulness-Based Addiction Treatment (MBAT), and Mindfulness-Oriented Recovery Enhancement (MORE) ^[5]. Bowen et al. first proposed MBRP, which integrates MBSR with cognitive–behavioral strategies to help individuals identify relapse warning signs and respond to cravings nonjudgmentally. MBAT builds on standard detoxification by emphasizing body awareness and emotion regulation through mindfulness. MORE further incorporates positive psychology to reshape the brain’s reward system by cultivating positive emotional experiences. These programs typically span eight to twelve weeks of group sessions supplemented by daily home practice, forming a comprehensive intervention framework. Multiple RCTs demonstrate that SUD patients receiving mindfulness interventions achieve significantly better outcomes than control groups in relapse rates, self-reported craving intensity, and negative-emotion levels. For example, an MBRP trial with individuals dependent on alcohol found a roughly 40% reduction in relapse risk and a 30% decrease in craving scores over six months. A MORE study with drug-using populations showed that the mindfulness group improved physiological stress markers (e.g., cortisol levels) by 25% and self-control (measured by the Brief Self-Control Scale, BSCS) by 20% compared to the standard care group. Mindfulness practice also aids in alleviating comorbid anxiety and depression, offering multidimensional support for comprehensive SUD recovery. Despite these promising findings, current research has limitations. Most RCTs involve small sample sizes (often 30–80 participants), limiting statistical power. Intervention protocols vary widely in content, frequency, and dosage, and there is no unified standard. Follow-up periods are typically limited to three to six months, leaving long-term efficacy and maintenance mechanisms underexplored. Moreover, the neural pathways by which mindfulness modulates the reward and self-control networks in SUD remain to be clarified. Future studies should focus on rigorous multicenter, large-sample designs, explore intervention adaptability for different SUD types, and combine mindfulness with neural biomarkers to elucidate its mechanistic contributions within comprehensive SUD treatment frameworks ^[6].

3. Theoretical framework

3.1. Core theory and mechanisms of mindfulness-based interventions

The term “mindfulness” derives from the Pāli word *sati*, meaning “awareness” or “attention.” It emphasizes open, non-judgmental attention to one’s present-moment bodily and mental experiences. Grounded in this concept, Mindfulness-Based Interventions (MBI) integrate traditional Buddhist meditation practices with modern

cognitive-behavioral techniques to form a structured therapeutic approach. Four interconnected elements underpin this framework: Intentional attention regulation, in which individuals are trained to deliberately anchor their attention on a specific focus (e.g., the breath or a body scan) to enhance concentration. Bodily awareness cultivates recognition and acceptance of internal physiological sensations. Non-judgmental acceptance of thoughts and emotions helps individuals reduce automatic reactive patterns when facing unpleasant experiences. Decentering, or the ability to detach from one's habitual "thought → emotion → behavior" loops and observe internal events from an objective vantage point. From a neural perspective, mindfulness practice strengthens functional connectivity in brain regions involved in executive function, impulse inhibition, and emotion regulation—namely the prefrontal cortex (PFC) and anterior cingulate cortex (ACC)—while dampening overactivity in the default mode network (DMN), which is associated with self-referential thinking and rumination. Functional magnetic resonance imaging (fMRI) studies reveal that seasoned mindfulness practitioners exhibit greater top-down regulation via the PFC–striatal circuitry when exposed to stress-induced craving cues, suggesting enhanced control over automatic reward responses. Likewise, electroencephalography (EEG) research shows increased frontal θ - and α -power following mindfulness training, indicating improved emotional recovery and attentional resilience. Integrating both behavioral and neuroscientific insights, the core mechanisms by which MBI prevents relapse in Substance Use Disorders (SUD) can be summarized as follows: first, by heightening awareness of craving and early relapse triggers, in-the-moment attention disrupts automated substance-use behaviors; second, non-judgmental acceptance and emotion-regulation training blunt the impulse to use substances in response to negative emotions; finally, decentering reshapes the interaction between self and reward systems, placing the "addiction → reward" cycle in a more manageable, objective framework and thereby delaying or blocking relapse pathways. These theoretical and mechanistic foundations provide robust guidance for the design and evaluation of subsequent mindfulness interventions ^[7].

3.2. The cognitive-behavioral model of relapse in substance use disorders

Relapse in SUD is best understood as a multi-stage, dynamically interactive cognitive-behavioral process rather than an isolated event. The classic Marlatt and Gordon Relapse Prevention Model delineates four key components: High-Risk Situations, such as stress, negative emotions, or social temptations. Coping Responses, the strategies individuals employ when confronted with these situations. Outcome Expectancies, or anticipated effects of substance use (e.g., temporary relief from anxiety or mood elevation). Self-efficacy, one's belief in their own ability to resist temptation. When effective coping strategies are lacking in high-risk contexts, cravings and impulses intensify. Positive outcome expectancies then strengthen the motivation to use, and low self-efficacy heightens the likelihood of a lapse. A single lapse can trigger the "abstinence-violation effect", a despair-self-blame cycle that often escalates into full relapse. Subsequent research has emphasized the role of cognitive distortions (e.g., all-or-nothing thinking, catastrophizing) and negative emotions (e.g., anxiety, depression, anger) in amplifying the craving-failure cycle. A lack of immediate positive emotional experiences and rewired reward pathways further entrench dependence on substance use for quick relief. Thus, the SUD relapse model highlights three interactive elements: high-risk triggers, coping capacity, and cognitive-emotional regulation mechanisms. Within this framework, mindfulness interventions aim to: detect and accept high-risk cues early to interrupt automatic reward expectations; employ non-judgmental awareness and emotion-regulation exercises to bolster coping resources and self-efficacy; and reshape outcome expectancies to weaken the chain reaction of lapse → despair → full relapse ^[8].

4. Research methods

4.1. Intervention design: Mindfulness training program and implementation process

The intervention is structured as a classic eight-week group course, meeting once weekly for two hours. It covers four core components: mindfulness meditation, body scanning, mindful yoga, and awareness exercises. Each week's session focuses on a specific theme: Week 1: Introduction to Mindfulness and Breath Awareness. Week 2: Body Scan and Somatic Awareness. Week 3: Seated Mindfulness Meditation. Week 4: Mindful Yoga and Movement Awareness. Week 5: Craving Awareness and Coping Strategies. Week 6: Emotion-Regulation Practices. Week 7: Non-Judgmental Acceptance. Week 8: Integration and Consolidation. Each session begins with a 10-minute open sharing, followed by a 45-minute guided practice led by a certified mindfulness instructor. After a short break, participants engage in 30 minutes of small-group discussion and experience sharing. The instructor then summarizes the session and assigns 30 minutes of daily home practice, supported by audio recordings or a mobile app, to reinforce in-class learning and encourage mindfulness in everyday life. The implementation unfolds in four phases: Recruitment and Baseline Assessment: Participants meeting the inclusion criteria are recruited from community detox centers and online platforms. Baseline data—Mindful Attention Awareness Scale (MAAS), Brief Self-Control Scale (BSCS), and physiological stress markers (salivary cortisol)—are collected. Randomization and Preparation: Participants are randomly assigned to the experimental or control group and complete informed consent and technical orientation. Eight-Week Mindfulness Intervention: The program is delivered strictly according to a standardized manual by at least two certified instructors, with attendance and practice logs monitored to ensure adherence. Post-Intervention Assessment and Three-Month Follow-Up: Immediately after the course, outcome measures and survival-analysis data are collected. Additional follow-up assessments occur at 12 and 16 weeks to evaluate the sustained impact of mindfulness training on relapse risk and psychophysiological indicators^[9].

4.2. Participants, sampling, and data collection

The study is aimed at members who are receiving rehabilitation treatment, aged between (12–25 years), mainly for the abuse of narcotic drugs and addictive non-controlled substances, such as the abuse of etomidate, dextromethorphan., based on an expected effect size (Cohen's $d \approx 0.6$) and 80% power, indicated a need for at least 40 participants per group. Anticipating a 20% attrition rate, 100 eligible individuals are recruited and randomly allocated—via random-number tables—to the MBI intervention group or the treatment-as-usual control group, balanced by gender, age, and substance type. Data are collected across three domains: Self-Report Measures: MAAS for mindfulness awareness; BSCS for self-control. Mental Health Scales: Beck Depression Inventory-II (BDI-II) and Beck Anxiety Inventory (BAI). Physiological Markers: Morning salivary cortisol to index stress levels. Attendance, home-practice log completion, and time to relapse event are recorded at each assessment point. Trained research assistants administer all measures, and independent staff blinded to group assignment perform data entry and quality checks to ensure objectivity and accuracy^[10].

5. Results and discussion

5.1. Effects of mindfulness intervention on relapse rates and related measures

Over the eight-week intervention period and the subsequent three-month follow-up, relapse rates differed significantly between the mindfulness group ($n=50$) and the control group ($n=50$). Kaplan–Meier survival analysis showed a 24-week relapse-free survival rate of 68% in the mindfulness group versus 45% in the control

group (Log-rank $\chi^2=6.42$, $P=0.011$). After adjusting for gender, age, and baseline substance-use severity in a Cox proportional hazards model, the mindfulness intervention was associated with a 42% reduction in relapse risk (HR=0.58, 95% CI 0.36–0.93, $P=0.023$). These findings indicate that MBI substantially delays or prevents relapse. Self-report measures further corroborated these effects. Mindfulness awareness, as assessed by the MAAS, increased from a baseline mean of 3.2 (± 0.5) to 4.1 (± 0.6) in the intervention group, compared with a rise from 3.1 (± 0.6) to 3.3 (± 0.7) in controls (between-group change $t=5.78$, $P<0.001$). Self-control (BSCS) scores in the mindfulness group improved from 2.8 (± 0.4) to 3.6 (± 0.5), whereas the control group's scores changed from 2.9 (± 0.5) to 3.1 (± 0.6) ($t=6.12$, $P<0.001$). Depressive symptoms (BDI-II) in the intervention arm decreased by 7.4 points ($P<0.001$), and anxiety (BAI) decreased by 5.9 points ($P<0.001$); in contrast, the control group showed smaller improvements (depression $\Delta-3.1$, anxiety $\Delta-2.7$; $P<0.05$). Physiological stress markers mirrored these results: morning salivary cortisol dropped from 18.5 ng/mL at baseline to 14.2 ng/mL post-intervention in the mindfulness group ($P=0.002$), whereas the control group's change (18.3 \rightarrow 17.6 ng/mL) was not significant ($P=0.18$). Overall, the mindfulness intervention enhanced mindfulness awareness and self-control, and substantially improved cognitive, emotional, and physiological regulation—factors closely linked to relapse risk—supporting its integration into comprehensive SUD treatment.

5.2. Mechanistic insights: How mindfulness impacts cognition, emotion, and impulse control

Mindfulness disrupts the automatic chain of addictive behaviors by heightening awareness of internal experiences. Cognitively, practitioners learn to detect the link between bodily signals and craving thoughts in real time, reducing tacit acceptance of urges. Through intentional breath awareness and body-scan exercises, participants shift attention away from instinctual impulses back to the present moment, implementing a “cognitive pause” when early triggers arise and thereby creating space for rational appraisal. Neuroimaging studies indicate that this process corresponds to strengthened top-down regulation in the frontal-striatal circuitry, inhibiting automatic reward responses to addiction cues. Emotionally, mindfulness emphasizes non-judgmental acceptance—allowing all emotional states to arise without overreaction. By reducing excessive appraisal and resistance to negative emotions, the intuitive “emotion \rightarrow use” linkage weakens. When facing stress, anxiety, or depression, non-judgmental awareness helps individuals refrain from viewing these emotions as threats that must be immediately eliminated, thus diminishing the motivation to seek short-term relief through substance use. Event-related potential (ERP) research shows faster attenuation of N2 and P3 amplitudes following mindfulness training, indicating improved impulse inhibition and emotional recovery. Improving impulse control is a central aim of mindfulness in SUD recovery. Through repeated practice of the sequence “pause \rightarrow notice craving \rightarrow self-inquiry (‘What do I truly need right now?’) \rightarrow deliberate action”, participants internalize concrete strategies for managing impulses. fMRI studies demonstrate that mindfulness training increases anterior cingulate cortex (ACC) activation during impulse-inhibition tasks, enhancing the stability of executive-control networks. Moreover, long-term practitioners exhibit increased prefrontal gray-matter density, providing neuroanatomical evidence for structural changes underpinning better self-control. In sum, mindfulness fosters relapse prevention via coordinated effects on cognitive awareness, emotional acceptance, and executive control.

6. Limitations and future directions

Despite the rigorous randomized design and the use of both self-report and physiological measures, this study

has several limitations. First, participants were drawn from a single rehabilitation center, and the sample's demographic and substance-use profiles were relatively homogeneous, limiting external validity. Second, although adherence was monitored via attendance records and practice logs, the quality and consistency of home practice were not objectively assessed (for example, through mobile-app usage data or biometric feedback), which could affect the accuracy of intervention-effect estimates. Third, the three-month follow-up period is insufficient to determine the long-term (\geq one year) sustainability of mindfulness effects, and it does not explore the dose–response relationship or dynamic changes over time. Finally, mechanistic insights relied on existing literature and indirect neural markers; direct empirical evidence of mindfulness's impact on reward and self-control networks in SUD populations remains limited. Future research should address these gaps by recruiting larger, more diverse samples across multiple centers to test intervention generalizability; integrating wearable devices or smartphone apps to capture real-time physiological (e.g., heart-rate variability, electrodermal activity) and behavioral (e.g., practice duration, attention metrics) data for precise adherence and mechanism modeling; extending follow-up to one year or longer to establish normative dose–maintenance effects; employing multimodal neuroscience methods (fMRI, ERP, TMS) to directly observe structural and functional remodeling in reward and executive networks; and exploring digital delivery formats—such as virtual reality or online courses—to enhance accessibility and personalization. These advancements will optimize MBI's role within comprehensive SUD intervention frameworks.

7. Conclusion

This randomized controlled trial systematically evaluated the value of Mindfulness-Based Interventions (MBI) for preventing relapse in Substance Use Disorders (SUD). After an eight-week group program and a three-month follow-up, the mindfulness group's relapse-free survival rate (68%) significantly exceeded that of the control group (45%, $P=0.011$). Adjusted Cox regression analysis showed a 42% reduction in relapse risk ($HR=0.58$, $P=0.023$). Participants in the mindfulness arm also demonstrated greater improvements in mindfulness awareness (MAAS), self-control (BSCS), depressive and anxiety symptoms (BDI-II, BAI), and physiological stress (salivary cortisol) compared to controls (all $P<0.001$), indicating multi-dimensional benefits of mindfulness practice. Mechanistic integration of literature and neuroimaging evidence suggests that mindfulness enhances top-down regulation via the frontal–striatal circuits, suppresses overactivity in the default mode network, and strengthens ACC-mediated executive control. These neural changes enable in-moment craving detection and “cognitive pauses”, breaking the “emotion→use→self-blame” cycle. Non-judgmental acceptance of emotions reduces avoidance and resistance, weakening the drive for substance-based relief. By combining self-report scales and physiological markers, this study not only enriches the understanding of MBI in addiction behavior but also lays a methodological foundation for future multicenter, large-sample, multimodal neuroscience investigations. Further work should enhance intervention accessibility and adherence, and explore digital and personalized delivery models to promote widespread, long-term use of mindfulness therapy in SUD recovery.

Disclosure statement

The authors declare no conflict of interest.

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Current Status and Prospects of Transcutaneous Acupoint Electrical Nerve Stimulation-Based Therapy for Pediatric Blepharospasm

Jiali Yan¹, Weixuan Hu¹, Lieling Kou^{2*}

¹Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China

²Affiliated Ankang Hospital of Traditional Chinese Medicine, Shaanxi University of Chinese Medicine, Ankang 725000, Shaanxi, China

**Author to whom correspondence should be addressed.*

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Abstract: Blepharospasm is a common eyelid movement disorder that, although more prevalent in the elderly, also affects children and can significantly impair their visual function and quality of life. Conventional treatments such as medication and botulinum toxin injections have limitations, including high recurrence, strong dependency, and obvious side effects. In recent years, transcutaneous acupoint electrical nerve stimulation (TAENS), a non-invasive therapy integrating modern neuroelectrophysiology with traditional acupuncture theory, has attracted increasing attention in pediatrics. This paper reviews the pathophysiology of blepharospasm from both modern medicine and Traditional Chinese Medicine (TCM) perspectives, and systematically analyzes current research progress, acupoint selection, treatment protocols, and therapeutic outcomes of TAENS in pediatric blepharospasm. The study highlights TAENS's unique advantages in improving efficacy, safety, and treatment compliance in children. Furthermore, it identifies current limitations such as small sample sizes, inconsistent protocols, and a lack of long-term follow-up, and proposes future research directions and technical innovations. This work provides theoretical and practical support for expanding treatment options for pediatric blepharospasm.

Keywords: Blepharospasm; Children; Transcutaneous acupoint electrical nerve stimulation; Non-invasive acupuncture

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1. Introduction

Blepharospasm is a focal movement disorder characterized by involuntary, repetitive contraction of the orbicularis oculi muscle, clinically manifested as frequent blinking, eyelid tightness, visual fatigue, and even functional blindness. While it is more common in older adults, the incidence among children has been gradually increasing in recent years, especially under conditions of visual strain, autonomic imbalance, or psychological stress. Pediatric cases are often underdiagnosed or misdiagnosed due to subtle and atypical symptoms, which may impair

both visual and psychological development, warranting clinical attention. Current treatment options, including anticholinergic medications, botulinum toxin injections, and neuromodulation procedures, are not always suitable for children due to side effects, the need for repeated injections, pain, and dependency risks. Therefore, there is an urgent need for a safer, non-invasive, and more acceptable treatment method with proven efficacy. Transcutaneous acupoint electrical nerve stimulation (TAENS) combines modern electrical stimulation techniques with traditional Chinese meridian theory. By applying low-frequency microcurrents to specific acupoints, TAENS activates local neural responses and central regulatory mechanisms, aiming to unblock meridians, balance qi and blood, and relieve muscle spasms. Compared with traditional acupuncture, TAENS is painless, repeatable, and more acceptable for children. It has shown promise in pediatric conditions such as tic disorders and hemifacial spasm. This study aims to systematically review the application of TAENS-based therapy for pediatric blepharospasm, analyzing its mechanisms, commonly used acupoints, therapeutic outcomes, and current limitations. By integrating TCM syndrome differentiation with modern neural regulation, it proposes optimized pathways for future research and clinical application, offering a safe and effective intervention strategy for children.

2. Pathogenesis and understanding of blepharospasm in Western and Chinese medicine

2.1. Pathophysiological mechanisms in modern medicine

Blepharospasm is a focal dystonia caused by dysfunction in the central nervous system, resulting in involuntary, episodic contractions of the orbicularis oculi muscles that may severely affect daily functioning and visual capacity ^[1].

Modern neuroscience indicates that hyperexcitability of motor neurons in the facial nerve (cranial nerve VII) plays a central role in blepharospasm. As illustrated in **Figure 1**, the facial nerve branches into five divisions—temporal, zygomatic, buccal, marginal mandibular, and cervical—after exiting the skull base, innervating key facial muscles such as the orbicularis oculi, frontalis, zygomaticus, and orbicularis oris. Dysfunction in excitatory and inhibitory neural circuits leads to sustained muscle contraction, presenting clinically as eyelid closure, frequent blinking, and even facial twitching and asymmetry. Abnormalities in the basal ganglia–thalamus–cortex pathway, which regulates voluntary motor control, are considered core mechanisms ^[2]. Functional MRI studies show hyperactivation in regions such as the frontal lobe, putamen, and cerebellum in patients with blepharospasm, indicating a disruption in higher-order motor regulation. Peripheral factors, including ocular dryness, fatigue, or light sensitivity, may further exacerbate muscle activity through trigeminal–facial nerve reflex loops, forming a central–peripheral feedback cycle. Some patients also exhibit comorbid symptoms such as tinnitus, headache, or emotional disturbances, implicating the autonomic and limbic systems in disease modulation. In summary, blepharospasm is a multifactorial condition involving central dysregulation, facial nerve conduction abnormalities, local neuromuscular hyperactivity, and environmental triggers. Understanding these mechanisms provides a foundation for multi-target intervention strategies, including neuromodulation therapies like TAENS ^[3].

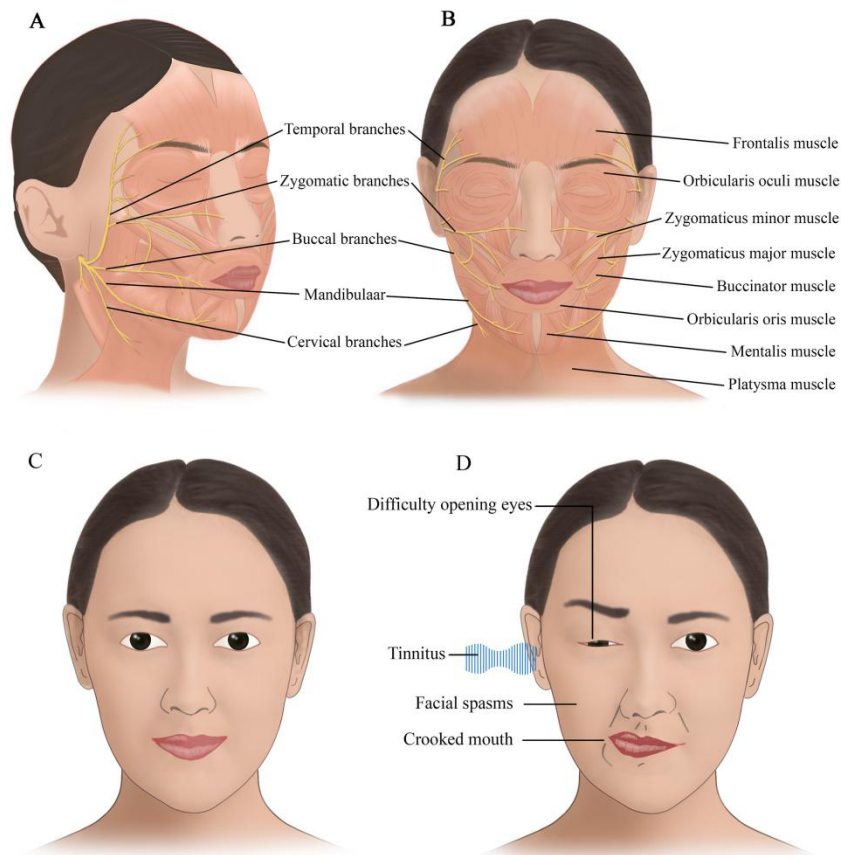


Figure 1. Schematic of facial nerve branches, facial musculature, and typical manifestations of blepharospasm

2.2. Pathogenesis from the perspective of traditional Chinese medicine (TCM)

Although there is no exact equivalent to “blepharospasm” in TCM terminology, its clinical features—such as eyelid twitching, visual blur, and facial asymmetry—are found under disease categories like eye tremors, inability to open eyes, wind-induced deviation, and facial paralysis. Ancient medical texts such as *Zhubing Yuanhou Lun*, *Yinhai Jingwei*, and *Zhengzhi Zhunsheng* attribute its causes to external wind invasion, liver qi stagnation, spleen deficiency with dampness, or kidney essence deficiency. First, external wind and internal liver wind are key pathogenic factors. Wind is known in TCM to be mobile and variable, easily disturbing the upper orifices. When wind-cold invades the face and blocks meridians, qi and blood become stagnant, resulting in eyelid tremors or tightness. Children, with their inherently active liver yang and fragile constitutions, are particularly susceptible to wind-fire agitation triggered by emotional disturbance, overstimulation, or poor diet. Second, spleen deficiency and dampness accumulation can impair the meridian network. The spleen governs transport and transformation. If its function is weak due to congenital deficiency or chronic illness, dampness accumulates and obstructs the yangming meridians, leading to heaviness and disordered eyelid movement. Third, kidney essence deficiency and poor nourishment of sinews may also contribute. The kidneys nourish the marrow and sinews. Insufficient kidney qi weakens muscular control, especially in developing children, resulting in involuntary facial twitching. In TCM, blepharospasm is often a complex interplay of wind, phlegm, heat, and deficiency, with pathogenic factors affecting the liver, spleen, and kidney systems ^[4]. Treatment emphasizes root-strengthening and symptom relief, focusing on calming liver wind, tonifying the spleen, eliminating dampness, and nourishing sinews and blood. Combining acupoint regulation with non-invasive TAENS may effectively activate meridian qi, aligning with the

TCM principle: “when qi flows, pain ceases and function is restored.”

3. Overview of transcutaneous acupuncture and TAENS technology

3.1. Development of transcutaneous acupuncture

With the deep integration of modern medical technology and traditional Chinese meridian theory, transcutaneous acupuncture and transcutaneous acupoint electrical nerve stimulation (TAENS) have emerged as key directions in the development of non-invasive traditional Chinese medical therapies. These techniques apply superficial stimulation to specific acupoints without penetrating the skin, activating local neural responses and meridian conduction. They combine the advantages of traditional acupuncture and modern neuromodulation, making them especially suitable for populations such as children who are less tolerant of conventional acupuncture^[5].

Transcutaneous acupuncture originated from traditional methods like plum-blossom and dermal acupuncture, emphasizing the principle of “non-penetrating stimulation that harmonizes qi and unblocks meridians.” With technological advances, modern devices have integrated low-frequency electrical modules to enhance biological effects. Compared to traditional needling, transcutaneous acupuncture is non-invasive, repeatable, and minimally painful, making it more suitable for treating pediatric neurological and functional disorders. Studies have shown promising effects in regulating neuromuscular excitability, improving local blood flow, and enhancing acupoint activation, positioning it as an important extension of external traditional Chinese medicine^[6].

3.2. TAENS principles and operational methods

Transcutaneous Acupoint Electrical Nerve Stimulation (TAENS) refers to the application of low-frequency pulsed current at specific intensities to body surface acupoints to activate meridian conduction and local neural responses, thereby achieving analgesic, sedative, and autonomic regulatory effects. As shown in **Figure 2**, a typical TAENS device consists of self-adhesive electrode pads, electrode wires, and a pulse control unit. During treatment, the practitioner selects appropriate acupoints (e.g., Jingming, Zanzhu, Taiyang) based on the child’s condition, applies the electrodes, and sets the pulse frequency (usually 1–20 Hz), intensity, and waveform. Each session typically lasts 15–30 minutes^[7].

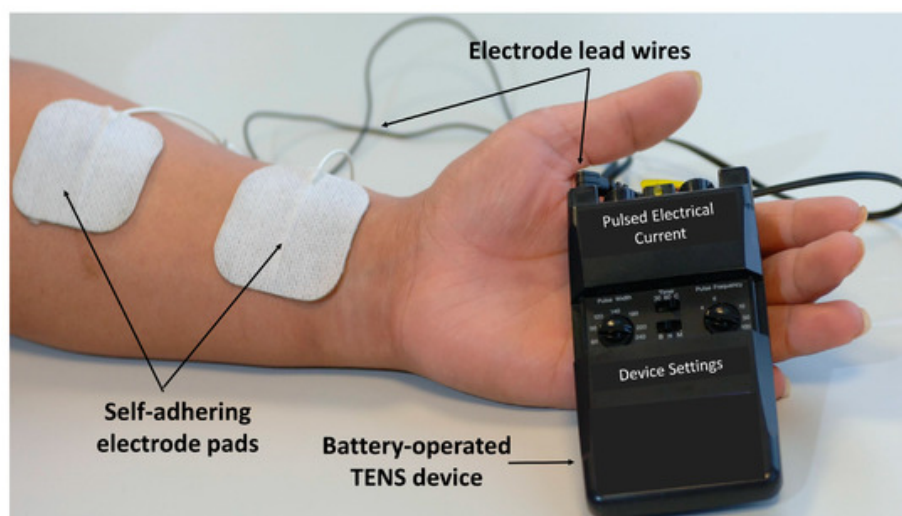


Figure 2. Components and operational diagram of the TAENS device

The therapeutic mechanism of TAENS primarily follows the “skin–acupoint–nerve–central” pathway: electrical stimulation activates skin receptors and nerve endings beneath the acupoints, transmitting signals via the facial or trigeminal nerve to the central nervous system, regulating excitability in areas such as the thalamus and brainstem. This helps to correct the abnormal contraction rhythm of eyelid muscles. Compared to traditional acupuncture, TAENS avoids needle-related pain and fear, significantly improving pediatric compliance, and offers a safe, effective non-pharmacological intervention for facial nerve dysfunctions like pediatric blepharospasm^[8].

4. Current research on transcutaneous acupuncture for pediatric blepharospasm

4.1. Overview of domestic and international studies

As attention to pediatric functional neurological disorders grows, non-pharmacological interventions are increasingly applied in clinical practice. Among these, minimally invasive neuromodulation techniques such as transcutaneous acupuncture and TAENS have become research hotspots. Although epidemiological studies on pediatric blepharospasm remain limited, literature on non-invasive treatments is gradually increasing, particularly focusing on interventions for facial spasm, eyelid dysfunction, and tic disorders^[9].

In China, multiple clinical and experimental studies have preliminarily confirmed the potential of TAENS in modulating facial nerve function and relieving eyelid muscle spasms. Some studies apply low-frequency stimulation to traditional facial acupoints such as Taiyang, Jingming, and Zanzhu, reporting improvements in eyelid opening, reduced blinking frequency, and decreased muscle electrical activity. Preliminary clinical trials with small sample sizes indicate that transcutaneous acupuncture, without reliance on sedatives or botulinum toxin, can effectively enhance eyelid muscle regulation and is superior to traditional acupuncture in safety and compliance among children. Internationally, research has focused on non-invasive treatments for facial palsy, eyelid myokymia, and facial dystonia. Rehabilitation centers in the U.S., Germany, and Japan have widely adopted TENS/TAENS devices for facial muscle function training and neural rehabilitation. These studies emphasize TAENS’s influence on neuroplasticity and motor unit recruitment. For example, guidelines by the American Physical Therapy Association highlight the effectiveness of transcutaneous nerve stimulation in alleviating pediatric facial muscle spasms, particularly for patients unsuitable for medication or invasive procedures. Moreover, foreign studies place greater emphasis on objective and quantitative metrics—such as eyelid closing pressure, eye-tracking data, and quality of life (QOL) scores—enhancing the scientific rigor and comparability of results^[10].

However, several common limitations remain across domestic and international research: Small sample sizes and a lack of multicenter randomized controlled trials (RCTs); Inconsistent stimulation parameters, including frequency, intensity, and duration; Insufficient long-term follow-up to assess sustained efficacy during pediatric development; Lack of standardized acupoint selection and localization, limiting reproducibility and inter-institutional application. In summary, while the clinical use of transcutaneous acupuncture—particularly TAENS—for pediatric blepharospasm is still in the exploratory stage, its non-invasiveness, safety, and high acceptance offer strong development potential. With the standardization of study design, advancement of smart therapeutic devices, and deeper investigation into pediatric neuromodulation mechanisms, TAENS is expected to become an important adjunctive intervention in managing childhood blepharospasm.

4.2. Efficacy observations and safety assessment

Current clinical evaluations of transcutaneous acupuncture—especially TAENS—in treating pediatric

blepharospasm focus on therapeutic effectiveness and adverse event monitoring. Although the number of studies is still limited, preliminary findings suggest that TAENS can effectively relieve symptoms, restore function, and improve the quality of life in affected children.

In terms of efficacy, several small-scale clinical trials and case series have demonstrated varying degrees of improvement after 1–2 treatment courses (10–15 sessions per course, about 20 minutes each). Common indicators include: Alleviation of eyelid-opening difficulty, with increased palpebral fissure width; Significant reduction in blinking frequency, with EMG showing decreased muscle activity; Decrease in frequency and intensity of involuntary facial muscle twitches (e.g., orbicularis oculi, orbicularis oris); Improved physician or caregiver subjective scores (e.g., Modified Ashworth Scale, visual analog scores); Behavioral assessments (e.g., FACES, PEDI) showing enhanced attention and social interaction post-treatment. A prospective study conducted at a tertiary hospital in China reported that in comparison to a control group receiving only routine warm compresses, the TAENS intervention group showed a 36% reduction in eyelid closing frequency—significantly higher than the control’s 12%. Follow-up data also indicate that some patients maintained improvements for weeks to months post-treatment, suggesting sustained neuromodulatory effects.

In terms of safety, transcutaneous acupuncture and TAENS are generally well tolerated due to their non-invasive nature and adjustable intensity, making them especially suitable for younger or emotionally sensitive children. Most studies reported no serious adverse events, with only mild discomfort observed in some cases, such as: Localized skin redness or mild itching at the electrode site; Initial anxiety or irritability in first-time patients; Rare allergic reactions to electrode adhesives, which resolved after discontinuation. Compared to botulinum toxin injections—which can cause complications like ptosis, diplopia, or local weakness—TAENS offers a safer profile. Its simplicity also enables trained family members to assist with home-based treatment, improving treatment frequency and compliance. Nonetheless, stratified studies targeting age-related differences in nerve development, acupoint responsiveness, and electrical current tolerance are still lacking. Future research should aim to optimize stimulation parameters while ensuring safety. Additionally, incorporating multimodal evaluation tools such as imaging, electromyography, and behavioral scales can help establish a standardized efficacy assessment system, providing a more comprehensive understanding of treatment outcomes.

5. Key acupoints and treatment protocol analysis

5.1. Commonly used acupoints and their neuroanatomical basis

In the application of transcutaneous acupuncture and TAENS for pediatric blepharospasm, the selection of acupoints must consider both traditional meridian theory and modern neuroanatomical pathways. Commonly used facial acupoints include Jingming (BL1), Zanzhu (BL2), Sizhukong (SJ23), Taiyang (EX-HN5), Yangbai (GB14), and Sibai (ST2), primarily distributed along the Foot Taiyang Bladder Meridian, Foot Yangming Stomach Meridian, and Hand Shaoyang Triple Energizer Meridian. Jingming, located at the inner canthus, is close to the superior trochlear nerve and the medial part of the orbicularis oculi, making it effective for relieving eyelid spasms and difficulty in opening the eyes. Zanzhu and Sizhukong, located at the eyebrow area, are near the infra-trochlear and frontal branches of the facial nerve, and help modulate upper eyelid muscle tone. Yangbai targets the superior margin of the orbicularis oculi, while Taiyang lies near the main trunk of the superficial temporal nerve, important for regulating overall facial muscle excitability. From a neuroanatomical perspective, these acupoints are located along the distribution areas of the facial nerve and its branches, especially the zygomatic, buccal, and mandibular

branches, which innervate the orbicularis oculi, zygomaticus, and orbicularis oris muscles—precisely the regions involved in blepharospasm. Electrical stimulation delivered through these acupoints reaches local nerve endings, modulates neuromuscular excitability, relieves spasm, and influences central regulation through reflex pathways, contributing to systemic therapeutic effects. Therefore, scientific acupoint selection based on both meridian theory and neuroanatomy not only aligns with the principle of “meridian-guided needling” in TCM but also provides a modern foundation for neuromodulatory treatment design.

5.2. Treatment frequency, course, and combination therapy

Clinical experience suggests that the effectiveness of TAENS for pediatric blepharospasm is closely related to the frequency and duration of stimulation. Most studies apply low-frequency pulses (1–20 Hz) for 15–30 minutes per session, 2–4 times per week, with 10 sessions per course. A typical treatment plan includes 2–3 courses, with noticeable improvements emerging after the first and stabilizing after the second. Stimulation parameters are generally set at the maximum tolerated current below the comfort threshold, avoiding discomfort from overstimulation. Symmetric biphasic waveforms are commonly used to enhance muscle responsiveness while minimizing skin irritation. Throughout treatment, physicians should assess eyelid mobility, facial muscle tension, and blinking frequency to adjust parameters accordingly. In combination therapy, TAENS may be integrated with TCM methods such as herbal hot compresses, eye function training, or emotional-behavioral interventions to enhance therapeutic outcomes. Some studies have also combined TAENS with acupuncture, massage, and light therapy, reporting synergistic effects. For children with comorbid anxiety or tics, psychological counseling may further reduce muscle tone imbalance. In summary, tailoring the frequency and plan of treatment while combining multi-modal interventions can enhance recovery rates and compliance, promoting both functional and neurological rehabilitation in pediatric patients.

6. Pediatric-specific considerations and treatment optimization

6.1. Compliance and cooperation challenges in children

In treating pediatric blepharospasm, compliance and cooperation significantly impact therapeutic outcomes. Due to immature cognitive development, children often have a limited understanding of their condition and treatment, leading to fear or resistance, especially with facial procedures like acupuncture or electrical stimulation. Younger or more emotionally sensitive children may cry, resist, or even terminate treatment prematurely. TAENS, being non-invasive, painless, and gentle, is generally better tolerated than traditional needling. However, the sensation of electrode patches, electrical stimulation, and the duration of sessions may still pose psychological burdens for some children, affecting their engagement and treatment continuity. To improve cooperation, individualized and child-friendly approaches are essential. Pre-treatment explanations using simple language and demonstrations can reduce fear. During sessions, distraction strategies such as cartoons or parental presence can ease tension. For anxious or hyperactive children, shorter sessions with lower stimulation intensity may help them gradually adapt. Medical staff should also maintain effective communication with caregivers to build trust and encourage home support, creating a calm and positive treatment atmosphere. Improving the overall treatment experience and emotional acceptance can significantly enhance adherence and the clinical efficacy of TAENS.

6.2. Personalized treatment pathways

Pediatric blepharospasm presents with considerable individual variation in clinical symptoms, pathogenesis, and

response to treatment. Developing personalized treatment pathways is essential for maximizing effectiveness and safety. Differences in developmental stage, neuromuscular sensitivity, disease duration, and psychological state must be considered, as standardized protocols may not yield optimal outcomes and may even induce resistance or symptom aggravation.

Personalized plans should consider: Age and neurodevelopmental stage — Younger children may benefit from low-frequency, low-intensity, short-duration sessions combined with family-based rehabilitation. Older children can gradually progress to stronger stimulation paired with EMG feedback or behavioral training. Symptom profiles — For difficulty in eye opening, Jingming and Zanzhu are prioritized. Frequent blinking may warrant added use of Yangbai or Taiyang. For comorbid tics, distal calming acupoints like Fengchi and Hegu may be included. Dynamic adjustment — Treatment plans should be adaptable based on ongoing efficacy evaluation and emotional state monitoring. A closed-loop “assessment–intervention–feedback” model helps ensure alignment with the evolving needs of each child. Through scientific and systematic personalized treatment planning, therapeutic precision, sustainability, and family satisfaction can be significantly enhanced.

7. Challenges and future prospects

Although transcutaneous acupuncture and TAENS have shown promise in treating pediatric blepharospasm, current research remains in its early stages and faces several limitations. Firstly, sample sizes in clinical studies are generally small, with a lack of high-quality randomized controlled trials, weakening the strength of clinical evidence. Secondly, there is no consensus on treatment parameters or acupoint combinations, and differences in frequency, duration, and intensity limit comparability and wider application. Moreover, insufficient attention has been given to developmental differences across pediatric age groups, and personalized treatment strategies are underdeveloped. Most studies rely on subjective outcome measures, with few incorporating objective tools such as EMG or eye-tracking analysis. The underlying mechanisms of TAENS also remain to be fully elucidated. Looking ahead, future research should focus on multicenter collaborations to conduct rigorous clinical trials and develop standardized protocols tailored to age groups. The integration of wearable intelligent TAENS devices could enable home-based treatment and remote monitoring, improving compliance and treatment reach. Multimodal assessment tools—such as electromyography, facial motion tracking, and QOL evaluations—will contribute to a more comprehensive understanding of efficacy and help optimize therapeutic strategies. With continued progress, TAENS has the potential to become a safe, accessible, and personalized intervention for pediatric blepharospasm.

8. Conclusion

As a non-invasive, safe, and child-friendly intervention, transcutaneous acupuncture and TAENS provide a novel therapeutic option for pediatric blepharospasm. Current studies indicate that TAENS can effectively alleviate eyelid spasms, improve facial muscle function, and have few side effects, making it suitable for broader pediatric applications. However, challenges such as small-scale research, lack of standardization, and unclear mechanisms persist. Future efforts should focus on strengthening clinical trials, developing standardized treatment pathways, and advancing personalized therapeutic approaches to promote the integration of TAENS into pediatric neurorehabilitation.

Disclosure statement

The authors declare no conflict of interest.

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Exploration of a Combined Treatment Plan for Alleviating and Controlling the Progression of Amyotrophic Lateral Sclerosis (ALS)

Xiaole Fan^{1*}, Shiyu Kang², Yuelong Li³, Guojun Huang¹, Qiqiang Tao^{1*}

¹BEAUTECH in Hainan Boao Lecheng International Medical Tourism Pilot Zone, Qionghai 571400, Hainan, China

²Nanfang Hospital Precision Medicine Center, Guangzhou 510515, Guangdong, China

³State Key Laboratory of Biochemical Engineering, Institute of Process Engineering, Chinese Academy of Sciences, Beijing 100190, China

**Authors to whom correspondence should be addressed.*

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Abstract: *Purpose:* This article aims to discuss five medical intervention strategies required for patients with amyotrophic lateral sclerosis (ALS) and provide a reference for intervening in this challenging disease. *Methods:* A retrospective analysis was conducted to identify existing issues in the treatment of ALS patients. A comparative analysis was performed to examine the nature, characteristics, and methods of previous intervention approaches. *Results:* Early identification and intervention, the application of rational combined treatment approaches, the improvement of comprehensive physical and mental rehabilitation systems, and the exploration of new treatment strategies provide a guarantee for effective intervention treatment of ALS patients. *Conclusion:* This article proposes the addition of a combined treatment approach involving the elimination of excessive glutamate from the body, which is theoretically reasonable, safe, and simple to implement. This approach has the potential to enhance the therapeutic effects and improve the individual prognosis of ALS patients. Given the lack of specific therapeutic drugs, further research on an effective combined intervention approach remains necessary.

Keywords: Amyotrophic Lateral Sclerosis; Combined therapy; Glutamate

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1. Introduction

Amyotrophic Lateral Sclerosis (ALS), also known as Motor Neuron Disease, is a progressive neurological disease. It mainly affects upper motor neurons and lower motor neurons, severely damaging the nervous system^[1]. Therefore, the earlier to intervene, the better. The exact cause of ALS is still unclear. Possibly it occurs from the coaction of genetic and environmental factors. About 10% patients who have ALS are hereditary, and the other 90% are of sporadic (nonhereditary)^[2]. Practitioners in the medical field are working hard to find out the cause of ALS and its treatment. Finding an effective treatment to improve the prognosis of ALS patients is urgently needed.

2. Basic characteristics of ALS

The diagnosis of ALS is a clinical diagnosis that normally requires filtering out the possibilities of other diseases. The diagnosis is based on clinical manifestation, neuroelectrophysiological examination (e.g., electromyography), and the elimination of other possible diseases. ALS is characterized by progressive muscle weakness, atrophy, and dysfunction. The possible symptoms of ALS patients include: muscle weakness; difficulty in movement; spasticity and spasmodic pain; and speaking and swallowing difficulty. ALS progressively affects the patient. It causes a continuous decline in muscle strength and eventually affects the functions of respiration and swallowing. It has a severe impact on patients' prognosis and life quality. At present, there is no treatment that could completely cure ALS ^[3]. Most medical programs aim to relieve the symptoms, to delay the development of the disease, and to improve patients' life quality.

2.1. Medicine

At present, four medicines, including Riluzole and Edaravone, are approved to be used as the treatment of ALS ^[4-5]. Riluzole is able to delay the development of the disease. Edaravone is able to reduce the cellular damage from oxidative stress. It is able to relieve and delay, but not to reverse or cease the development of the disease. In September 2022, the FDA approved Relyvrio (AMX0035), which is a medical product from Amylyx Pharmaceuticals. The Relyvrio had come to the market with the support of the phase II clinical trial, which has the result showed that the median survival of patients in the Relyvrio group was 6.5 months longer than that of the placebo group. In 2023, the first treatment for hereditary ALS came to market; the drug only works in 1%–2% of ALS patients. The conclusion is that the prospects for treatment are not promising.

2.2. Spasticity management

Muscle spasms are common in ALS patients, and muscle relaxants and antispasmodic drugs are used to relieve symptoms ^[6]. When these drugs are used, they should be adjusted and monitored according to the specific situation of the patient.

2.3. Respiratory management

As the disease progresses, patients with ALS are more likely to have respiratory disorders, and patients may need ventilator assistance, or other respiratory treatments, such as non-invasive ventilation (NIV) or tracheotomy, which can help patients maintain good respiratory function ^[7].

2.4. Nutrition management

Since ALS patients may experience difficulty swallowing and weight loss in later stages of the disease. Patients need appropriate nutritional support and need to work with a dietitian to develop an appropriate diet plan. In more severe cases, additional nutritional support through nasal feeding or gastric tubes is required ^[8].

2.5. Sports care

In later stages of the disease, ALS patients would suffer muscle atrophy. Rehabilitation can help them maintain muscle function, reduce pain, and improve quality of life. A physical therapist can make an individualized rehabilitation plan ^[9]. In addition, psychological support, social support, and family care are equally important in providing emotional support and practical help.

3. What are the shortcomings of medical intervention methods for ALS

3.1. Diagnosing is difficult

The disease that induces ALS is not clear. Some scholars believe that it is caused by DNA defects, while others believe that it is induced by poisoning ^[10]. It may also be related to environmental factors. Without clear causes, those factors are difficult to prevent and treat accurately. At the same time, ALS is difficult to diagnose. The diagnosis requires ruling out other possible causes, and early symptoms are similar to other neurological diseases. Those factors increase the difficulty of a clear diagnosis.

3.2. Rapid progress and large individual differences

After the onset of ALS, it usually progresses rapidly in a short period of time, resulting in muscle atrophy, weakness, and dysfunction. Therefore, the treatment time window is narrow, and immediate treatment is urgently needed. There are huge individual differences among different ALS patients, including the rate of disease progression and lesion site, so it is difficult to formulate a unified and effective intervention plan. Personalized treatment strategies are needed.

3.3. A comprehensive treatment is in need

There is no complete cure for ALS. There are treatments that can ease symptoms and slow their progression, but they are not effective. In later stages of the disease, ALS patients would suffer from difficulty breathing, swallowing, and impaired digestive function. Each patient's condition is different; thus, assisted breathing, nutrition management, and exercise care need to be personalized to the individual. Studies have confirmed the effectiveness of regenerative medicine, that is, umbilical cord mesenchymal stem cell transplantation can improve the motor function of ALS patients. Therefore, ALS patients need to be supported by a multidisciplinary comprehensive team, including neurology, rehabilitation medicine, respiratory medicine, regenerative medicine, dietitians, sports rehabilitation therapists, psychology, social support, and other collaborative efforts.

3.4. New treatment option

This paper suggests a new method to eliminate excess glutamate from the body. Clinical studies suggest that excessive glutamate content in the human body will cause a series of nervous system damage problems ^[11]:

- (1) Neurotoxicity: Glutamate is an excitatory neurotransmitter that plays an important physiological and biochemical role in normal circumstances. However, when the abnormal content of glutamate metabolism increases, it will overstimulate nerve cells, resulting in neurotoxic effects, injury, and death of nerve cells.
- (2) Neurologic abnormality: Excessive glutamate can lead to overexcitation of nerve cells and excessive electrical signals, which can lead to nervous system disorders, such as convulsions, tremors, restlessness, and anxiety, and even in severe cases may induce seizures ^[12].
- (3) Neurodegenerative diseases: Studies have shown that excessive glutamate may be associated with the development of some neurodegenerative diseases. Damage and death of nerve cells are caused by excessive glutamate, thus it is associated with the development of diseases such as ALS, Alzheimer's disease, and Parkinson's disease ^[13–14].
- (4) Abnormal amino acid metabolism: The balance and normal metabolism of various amino acids in the body are necessary to maintain good health. Excessive glutamate will interfere with the metabolic balance of other amino acids, resulting in the lack or excess of some amino acids, which will further affect protein synthesis and tissue repair, and negatively affect important human physiological and biochemical processes ^[15].

4. Result

When the disease occurs, firstly, the patient needs to have an active awareness of detection and prevention in the early stage; secondly, the multidisciplinary treatment team should propose a personalized comprehensive intervention plan; finally, in the case of poor existing treatment methods, it is suggested to actively introduce a new plan that is theoretically reasonable, feasible, safe and simple in operation.

4.1. Active early detection and prevention

Early signs of ALS include muscle weakness, muscle wasting, and difficulty with the tongue and chewing. If these symptoms occur, especially in people with a family genetic risk should pay great attention to them. Other possible causes can be ruled out through nerve conduction velocity examination, electromyography, blood and imaging examinations. Early detection enables early treatment and early intervention.

4.2. New combination treatment

In addition to drug therapy, spasticity management, respiratory management, nutrition management, sports care, and other comprehensive management, a glutamate elimination program was introduced (**Table 1**).

- (1) Control the source of glutamate: Customize a diet. First of all, reduce glutamate intake, especially sodium glutamate in food and food additives. Initiate a 6-month fast for 10 kinds of high-glutamate foods, such as MSG, chicken essence, soy sauce, abalone, mushroom, and a balanced, nutritious diet, and a prohibition of alcohol.
- (2) Increase glutamic acid excretion: The glutamic acid scavenger program, which mainly regulates the intestinal flora, and excretes heavy metals and other toxic substances as a supplement to strengthen the health of intestinal flora, and excretes the accumulated glutamic acid in the body while metabolizing detoxification^[16].

Table 1. Patient management program

	Fasting program	Regular drinking water	Vegetarian oriented	Remove heavy metals	Daily Yogurt	Unique probiotics
1 day	√	√	√	√	√	√
2 day						
...						
15 day						

Note: Develop habits and mark daily (√), lasting for 15 days

- (3) Repairing glutamate damage: Customized regenerative medicine plan. Since the body is composed of cells, the essence of disease lies in cell damage. Regenerative medicine can activate the activity of cells in the body through stem cells, repair damaged cells and tissues, regulate immune functions through NK cells, and enhance the body's healthy metabolism and self-repair ability.

4.4. Social education and psychological intervention

Social education and psychological intervention play an important role in ALS management^[17]. They can help patients and their families acquire necessary knowledge, skills, and support, improve their quality of life,

and facilitate their coping with the psychological and social challenges brought about by the disease. Social departments can provide disease knowledge, education, and nursing skills training for patients and their families. This helps them understand the symptoms and prognosis of ALS, as well as the use and maintenance methods of assistive devices such as wheelchairs, respirators, and hearing aids. It also includes exercise rehabilitation and nutrition management, helping them better care for the patients. Psychological counseling and support are crucial to help patients and their families cope with emotional distress, anxiety, depression, and other psychological issues. This reduces the patients' feelings of despair and suicide rates. Encouraging patients and their families to participate in the ALS community and providing marriage and family counseling helps family members deal with the changes and challenges brought about by ALS, maintaining intimate relationships and family stability^[18].

5. Discussion and conclusions

In summary, ALS can be considered one of the most difficult-to-treat diseases in modern human history. This is because the triggering mechanisms of ALS are not fully understood, and clinical treatment mainly focuses on symptomatic treatment and supportive health management, with poor effectiveness. Considering the large number of patients and the high number of new cases each year, along with the high levels of suffering and despair experienced by patients, the use of this safe, effective, and convenient combination treatment plan described in this article holds promising prospects.

Early detection and prevention are the first steps in controlling ALS. Active awareness of testing and accurate diagnostic methods is crucial for improving treatment outcomes and individual prognosis. In the practice of treating and controlling the progression of the disease, it is important to have shared decision-making between patients and doctors, personalized treatment plans, and multidisciplinary interventions. Over the past century, ALS treatment has made significant progress, but it remains challenging. Therefore, it is still necessary to research new effective intervention strategies. In the context of the Boao Lecheng international medical tourism pilot zone in Hainan, China, where medical treatment, research, operation, and international exchanges are authorized by law, the authors believe that with the advancement of cutting-edge medical technologies such as gene therapy and cell therapy, the treatment of ALS will further develop.

Disclosure statement

The authors declare no conflict of interest.

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Exogenous Compression Caused by a Mass at the Bifurcation of the Carotid Artery

Chih-hsien Lin, Chun-Chung Chen*

Neurosurgery Department, China Medical University Hospital, Taichung, Taiwan, China

**Author to whom correspondence should be addressed.*

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Abstract: The bifurcation of the carotid artery is a crucial node for blood supply to the brain. External compression caused by surrounding masses can lead to severe hemodynamic disturbances and neurological abnormalities. This article reviews the pathogenesis, clinical manifestations, diagnostic methods, and treatment approaches of this condition, including the pathological characteristics of common compression lesions such as carotid body tumors and schwannomas. It compares the applicability of imaging examination methods such as ultrasound, CTA, and DSA, analyzes the suitable conditions and treatment effects of surgical removal, vascular reconstruction, and interventional therapy. The research aims to provide standardized diagnostic and treatment concepts for clinical practice, emphasizing the crucial role of individualized treatment plans in improving patient outcomes. It also looks forward to the development trend of precision medicine guided by imaging.

Keywords: Carotid artery bifurcation; External compression; Individualized treatment

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1. Introduction

1.1. Research background

The carotid bifurcation, located in the middle and lower part of the neck, is a crucial site where the common carotid artery divides into the internal carotid artery and the external carotid artery. It primarily supplies blood to the anterior two-thirds of the brain and the eyes. This anatomical region is complex, with nearby important structures such as the vagus nerve, hypoglossal nerve, and cervical sympathetic trunk. Additionally, its hemodynamic conditions are unique, with blood flow impacts at the bifurcation causing local pressure variations, making it a sensitive area for lesions. When a mass appears around the carotid bifurcation, external compression can directly affect the vessel's course and lumen shape, leading to abnormal blood flow velocity, turbulence, and even vascular occlusion. According to clinical data, the occurrence of cerebral ischemia caused by such compression accounts for approximately 3.2%–5.8% of non-traumatic cerebral infarction etiologies. Moreover, due to the subtle early symptoms, treatment opportunities are often missed. With the development of imaging diagnostic techniques, the detection rate of asymptomatic compression has

been increasing year by year. However, clinical management strategies for such conditions have been controversial, highlighting the necessity for further exploration into this disease state ^[1].

1.2. Research objectives and significance

This study aims to systematically organize the pathophysiological mechanisms, clinical diagnostic approaches, and treatment technology developments related to external compression caused by carotid bifurcation masses, by integrating the latest domestic and international research findings. By clarifying the compression characteristics and risk levels of different types of masses, it provides clinicians with normative decision-making references from diagnosis to treatment. The practical significance of this study lies in: first, improving the identification level of early asymptomatic cases, thereby reducing the occurrence of ischemic stroke; second, improving the selection of treatment plans for complex cases, taking into account both tumor resection and vascular protection clinical needs; third, promoting the application of multidisciplinary team (MDT) mode in this field, facilitating collaborative diagnosis and treatment among departments such as radiology, neurosurgery, and vascular surgery, ultimately providing theoretical support and practical guidance for improving patients' quality of life and reducing postoperative complications ^[2].

2. Anatomical and physiological basis of the carotid bifurcation

2.1. Structure of the carotid bifurcation

The carotid bifurcation is generally located at the level of the fourth cervical vertebra, with a few cases occurring at the level of the third or fifth cervical vertebra. The morphology of the carotid bifurcation varies and is divided into three types: right-angle type, acute-angle type, and obtuse-angle type. The acute-angle type has a large turning angle of blood flow, making it more susceptible to external compression. Here, the common carotid artery divides into the internal carotid artery (ICA) and the external carotid artery (ECA). The ICA has a diameter of approximately 4–5 mm and runs towards the brain ^[3]. There are no branches inside the carotid sheath, and it directly supplies the anterior-medial part of the cerebral hemisphere and the eyes. The ECA has a slightly smaller diameter and gives off branches such as the superior thyroid artery and the lingual artery to supply the soft tissues of the neck. Behind the bifurcation, there is a branch of the recurrent laryngeal nerve passing through, with the medial side adjacent to the pharyngeal lateral wall and the lateral side being the sternocleidomastoid muscle. These anatomical relationships determine the neurological symptoms and local signs that may accompany mass compression. The vascular wall at the carotid bifurcation is divided into the intima, media, and adventitia. The contraction of smooth muscle cells in the media is important for maintaining vascular tension. Surrounding the adventitia is the carotid sinus, which contains baroreceptors that can sense changes in blood pressure and maintain blood flow stability through neural regulation. When this area is compressed, it may cause a reflexive decrease in blood pressure or a slowing of heart rate ^[4].

2.2. Hemodynamic characteristics of the carotid artery

The hemodynamic characteristics of the carotid artery are crucial for ensuring normal blood supply to the brain. It functions like a precise “life-sustaining pump”, continuously supplying blood to the brain. Under normal circumstances, the blood flow velocity and volume in the carotid artery are relatively stable. The internal diameter of the common carotid artery is relatively large, approximately 5–8 mm, with a blood flow velocity of 40–80 cm/s. The internal diameter of the internal carotid artery is approximately 4–6 mm, and its blood flow velocity falls within the same range. The blood flow velocity in the left carotid artery is relatively

faster, averaging 77 cm/s, while the blood flow velocity in the right carotid artery averages 65 cm/s, as shown in **Figure 1** (preoperative MRA and CTA). This stable blood flow velocity and volume ensure that the brain receives sufficient oxygen and nutrients, maintaining its normal physiological functions. The blood test results are shown in **Table 1**. The blood flow in the carotid artery is pulsatile, correlating with the periodic contraction and relaxation of the heart. During heart contraction, blood is rapidly pumped into the aorta and then into the carotid artery, causing an increase in pressure and a speedup in blood flow velocity, forming the peak systolic velocity. During heart relaxation, the pressure in the artery decreases, and the blood flow velocity slows down, forming the end-diastolic velocity ^[5]. This pulsatile blood flow and its dynamic changes can be clearly displayed through DSA (**Figure 2**), providing a continuous blood supply to the brain and, to a certain extent, massaging the vascular wall, helping to maintain its elasticity and normal function. Under normal physiological conditions, the hemodynamic parameters of the carotid artery are precisely regulated by various factors. From the perspective of neural regulation, when the sympathetic nervous system is excited, blood vessels contract, blood flow resistance increases, and blood flow velocity slows down. Conversely, when the parasympathetic nervous system is excited, blood vessels dilate and blood flow velocity increases. In terms of humoral regulation, hormones such as angiotensin and adrenaline have a significant impact on vascular vasomotor function ^[6]. When blood pressure decreases in the body, the renin-angiotensin-aldosterone system is activated, and angiotensin II promotes vascular contraction, leading to an increase in blood pressure and thus regulating the hemodynamic parameters of the carotid artery. The autoregulation of the carotid artery is also crucial. When blood pressure fluctuates within a certain range, the carotid artery contracts and relaxes on its own to maintain relative stability in cerebral blood flow, preventing significant changes in cerebral blood flow due to fluctuations in blood pressure ^[7]. When blood pressure suddenly rises, the smooth muscle of the carotid artery contracts, the vessel diameter becomes smaller, blood flow resistance increases, and cerebral blood flow does not increase excessively; conversely, when blood pressure decreases, the vessel relaxes, and cerebral blood flow remains essentially unchanged. This vasomotor function can be observed under intraoperative microscopy (**Figure 3**), and its structural basis can be verified through pathology specimens (**Figure 4**).

Table 1. Lab data

Laboratory examination	Value	Unit
White blood cell count	15.0*	K/uL
Red blood cell count	5.50	M/uL
C-reactive protein	16.3*	Mg/l
Hemoglobin	14	g/dL
Ca	8.9	Mg/dL
Na	130*	mmol/L
K	3.0*	Mmol/L
TSH	3.8	mIU/L
T3	2.95	mmol/L
T4	177	mmol/L
Plasma free Metanephrines	0.23	nmol/L
Normetanephrines	0.8	nmol/L
24-hour Urine Metanephrines	132	ug/g creatinine
Normetanephrines	221	ug/g creatinine
Chromogranin A	88	ng/mL
Serum Dopamine	323	ug/day
Neuro-Specific Enolase (NSE)	8	ng/mL

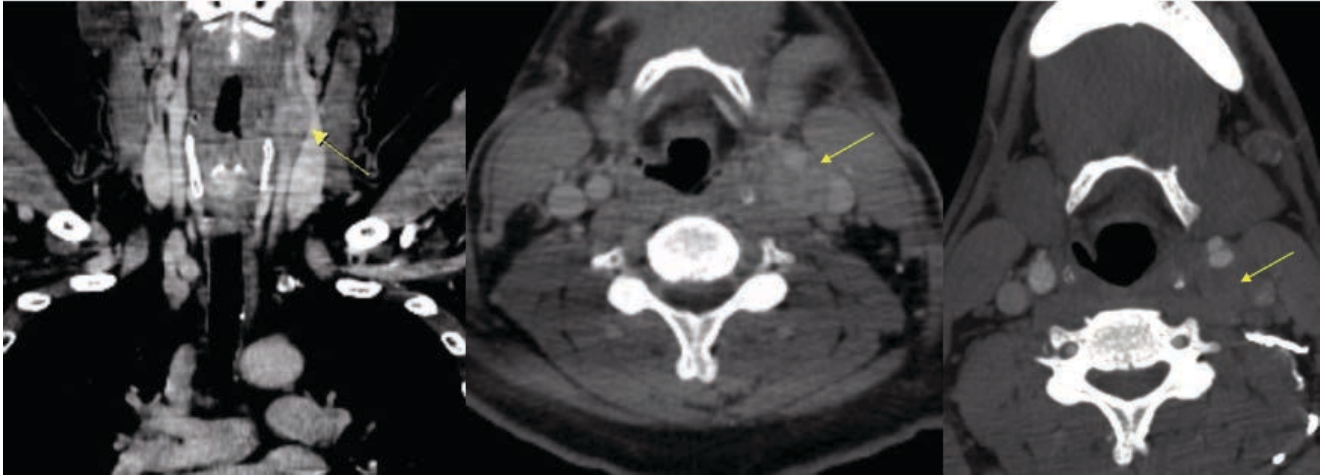


Figure 1. MRA+CTA

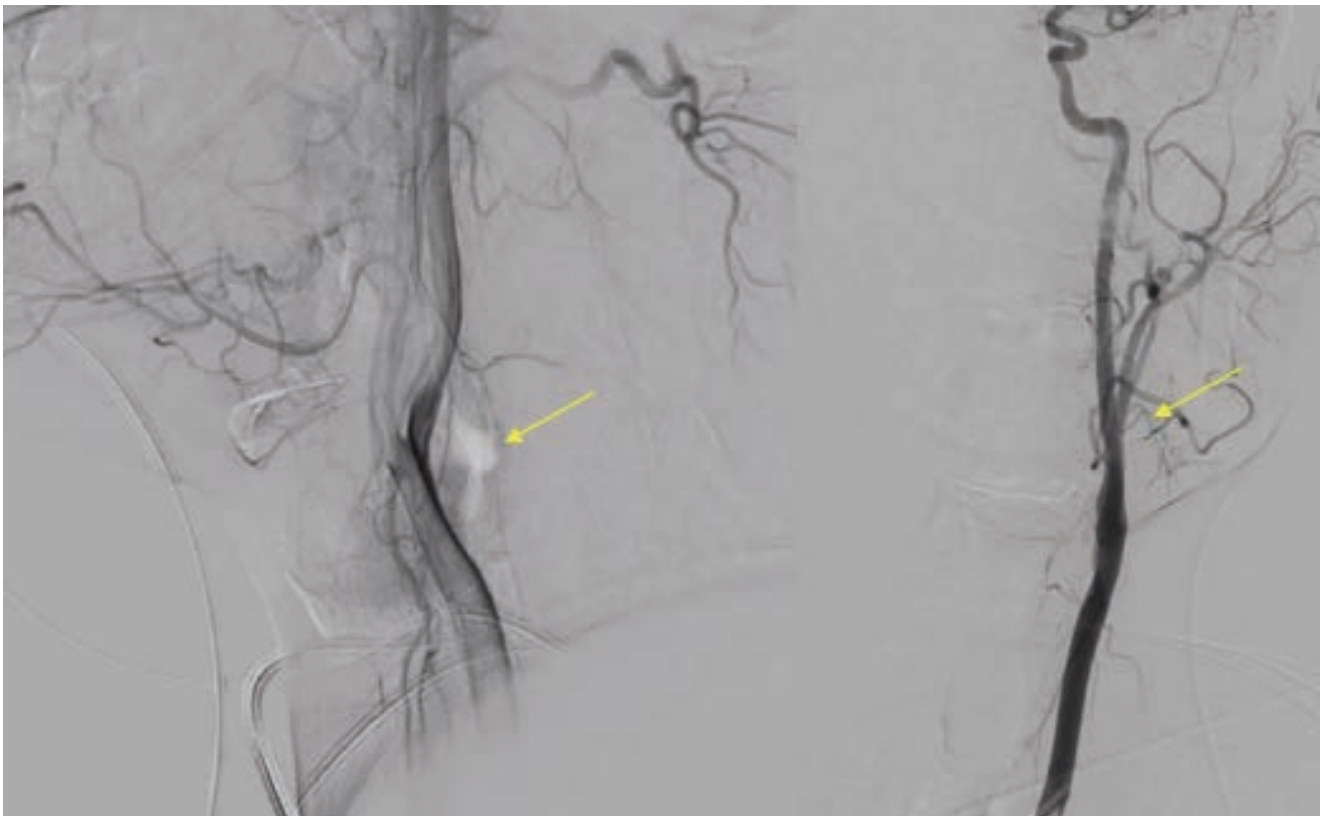


Figure 2. DSA

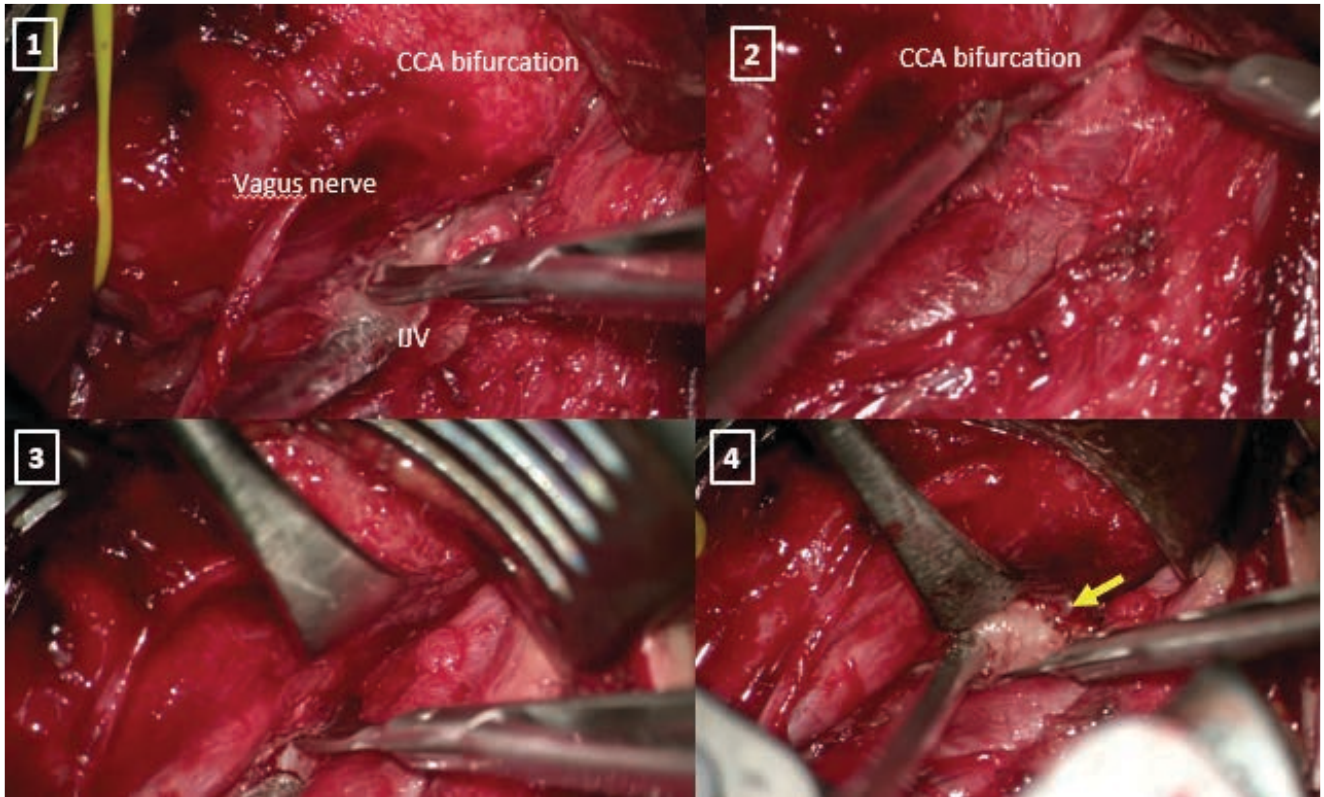


Figure 3. Intraoperative microscope view

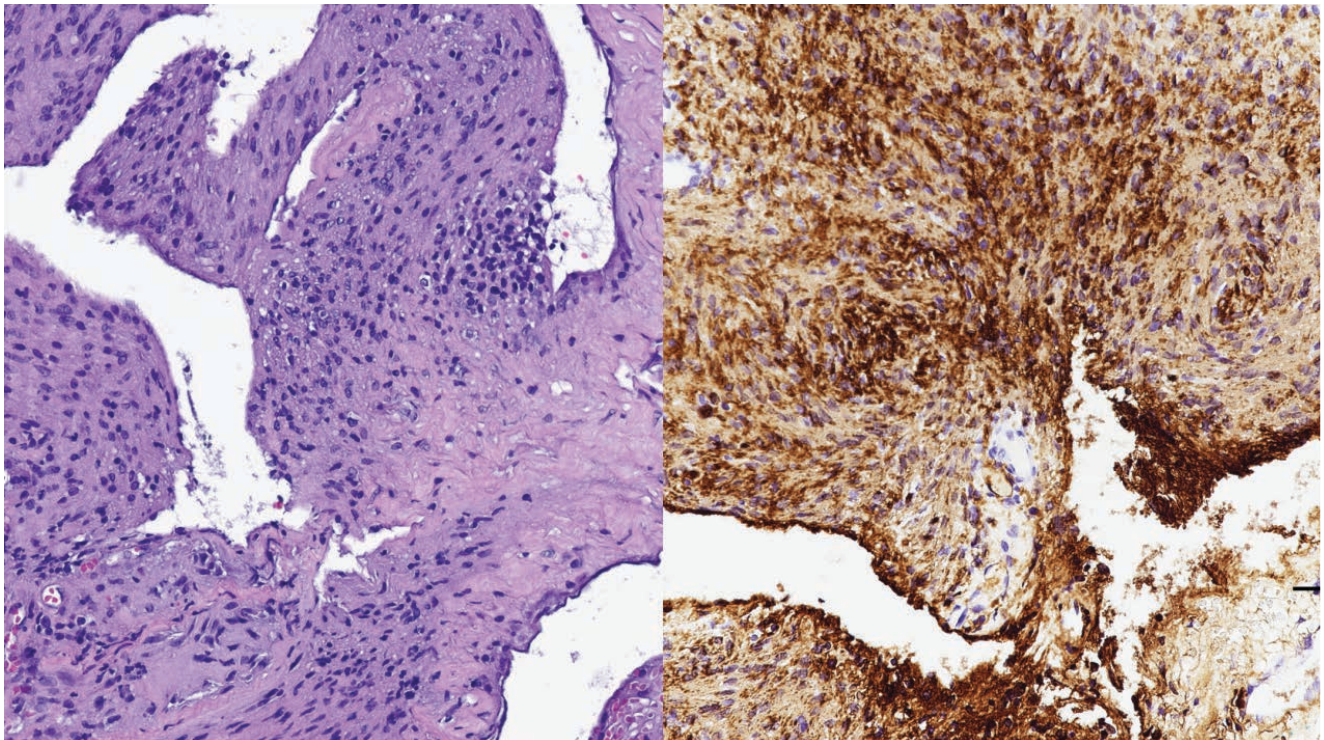


Figure 4. Pathological specimen

3. Causes and mechanisms of external compression of the carotid artery by masses

3.1. Common types of masses causing compression

Carotid body tumor (CBT) is the most common compressive lesion, originating from the chemoreceptor cells of the carotid body and belonging to the category of paragangliomas. Most of them are benign, with a malignant proportion of approximately 5%–10%. The tumor often occurs within the bifurcation angle, with a round or oval shape, medium texture, and is closely connected to the adventitia of the carotid artery ^[8]. It moves up and down with swallowing and encapsulates the vascular wall, causing compression. Schwannoma (neurilemmoma) ranks second, often originating from the sheath of the vagus nerve or sympathetic nerve, located within the carotid sheath, and presenting as a spindle-shaped tumor with a capsule, clearly demarcated from the blood vessel. However, larger ones can compress or push the carotid artery. Lymphoma manifests as multiple masses in the neck, which are hard and often invade the perivascular adipose tissue, displacing and compressing the blood vessels. Additionally, metastatic lymph node enlargement, such as from thyroid cancer, nasopharyngeal cancer metastasis, branchial cysts, lipomas, etc., can also be a compressive factor. The biological characteristics of different masses determine the mode of compression; CBT is mostly encapsulated compression, Schwannoma is mostly pushing compression, and lymphoma is mostly infiltrative compression ^[9].

3.2. Discussion of the pathogenesis

External compression of the carotid artery by a mass causes pathological changes through two mechanisms: mechanical mechanics and hemodynamics. Mechanical compression directly deforms the vascular wall. When the compressive force exceeds the elastic limit of the vascular wall, luminal stenosis occurs. At this time, vascular smooth muscle cells undergo compensatory proliferation to maintain the shape of the lumen. Long-term compression can lead to media atrophy, elastic fiber breakage, and decreased vascular wall compliance. In terms of hemodynamics, high shear forces caused by increased blood flow velocity at the stenosis site can damage vascular endothelial cells, activate the coagulation system, and increase the risk of thrombosis. Moreover, vibration of the vascular wall caused by turbulence can trigger local inflammatory reactions, promoting platelet aggregation and the formation of atherosclerotic plaques, thus forming a vicious cycle of “compression-stenosis-thrombosis-ischemia.” When the carotid sinus is compressed, baroreceptor dysfunction can occur, leading to carotid sinus syndrome, which is characterized by paroxysmal dizziness and syncope. This is caused by vagal nerve excitation, slow heart rate, and peripheral vascular dilation. When a mass compresses surrounding nerves, there are corresponding neurological symptoms, such as hoarseness due to compression of the vagus nerve and tongue muscle atrophy due to compression of the hypoglossal nerve ^[10].

4. Clinical manifestations and diagnostic methods

4.1. Clinical symptoms

Cervical mass is the most common initial symptom, with approximately 82% of patients being able to palpate a painless mass. Its hardness varies depending on the tumor type: CBT has a medium hardness and a pulsatile sensation; schwannoma is soft and elastic; lymphoma is relatively hard and fixed. When the mass enlarges, there is local pain or pressure sensation, which worsens during swallowing. Cerebral ischemia symptoms are the most severe clinical manifestations, including transient ischemic attack (TIA) symptoms such as transient blackouts, limb weakness, and slurred speech, which generally last for several minutes to hours and may recur, indicating a vascular stenosis greater than 70%. In severe cases, acute cerebral infarction may occur, leaving permanent

neurological deficits. Symptoms of nerve compression have localization significance: compression of the vagus nerve leads to hoarseness and difficulty in swallowing water; compression of the hypoglossal nerve causes tongue deviation when extended; and compression of the cervical sympathetic nerve leads to Horner's syndrome (miosis, ptosis, and anhidrosis of the face)^[11].

4.2. Diagnostic techniques

4.2.1. Imaging examinations

Ultrasound is the preferred screening method, which can clearly visualize the location, size, and relationship with the carotid artery of the mass. Color Doppler can observe changes in blood flow velocity and assess the degree of stenosis, with a sensitivity of up to 95%. However, it may not provide sufficient detail regarding tumor invasion of the vascular wall. Computed Tomography Angiography (CTA) can perform three-dimensional reconstruction of the carotid bifurcation, accurately measure the degree of stenosis, and display the relationship between the mass, bones, and soft tissues. It excels in identifying calcified lesions and is suitable for preoperative anatomical assessment. However, it involves radiation exposure and carries a risk of contrast medium allergy. Magnetic Resonance Angiography (MRA) is radiation-free, provides clear boundaries between the vascular wall and soft tissues, and has specificity in diagnosing liquid-containing lesions such as schwannomas. It can evaluate cerebral perfusion, but the examination time is long, and its evaluation of severe stenosis is slightly inferior to CTA. Digital Subtraction Angiography (DSA) remains the “gold standard” for dynamically observing hemodynamic changes, understanding collateral circulation, and performing interventional therapy. However, it is an invasive examination and is mainly suitable for preoperative assessment of complex cases^[12].

4.2.2. Other auxiliary examinations

The focus of physical examination is mass palpation (texture, mobility, pulsatility), auscultation (presence of vascular murmurs), neurological function examination, etc. Laboratory tests, including tumor marker tests, have diagnostic significance for lymphoma and metastatic tumors, and coagulation function tests can determine the risk of thrombosis. Pathological examination determines the nature of the mass through fine needle aspiration or surgical specimen biopsy, which is the most accurate way to distinguish between benign and malignant tumors. However, for tumors with abundant blood supply, such as CBT, there is a risk of inducing bleeding through aspiration, so caution should be taken.

5. Treatment strategies and case analysis

5.1. Surgical treatment

Surgical resection is the curative treatment for most tumors, with the principle of complete removal of the tumor and protection of carotid blood flow as much as possible. For CBT, the surgical procedure is selected based on the Shamblin classification. Type I tumors are small and have less adhesion to blood vessels, so they can be directly removed; Type II tumor partially surrounds blood vessels and require vascular wall repair; Type III tumors completely surround blood vessels, and carotid artery reconstruction is performed simultaneously. Autologous great saphenous vein or artificial blood vessel transplantation is commonly used. Surgery for schwannoma requires protection of nerve bundles, and the use of intracapsular dissection can reduce nerve damage. For malignant tumors such as lymphoma, the resection range needs to be increased, and neck lymph node dissection may be necessary. Surgical risks include intraoperative major bleeding (8%–15%), cerebral ischemia (5%), nerve injury,

and vagus nerve injury, with a rate of about 10%. Preoperative evaluation of cerebral collateral circulation is necessary, and temporary carotid artery bypass surgery can be performed to protect cerebral blood flow in patients with an incomplete Willis loop^[13].

5.2. Interventional therapy

Interventional embolization is suitable for tumors with abundant blood supply (CBT). Preoperative embolization reduces tumor blood supply and lowers the risk of intraoperative bleeding. Using DSA to insert a microcatheter into the tumor's blood supply artery, injecting gelatin sponge or coil, and performing surgical resection 24–72 hours after embolization can greatly improve the safety of the surgery. For elderly patients or advanced cancer patients who cannot tolerate surgery, stent implantation can be chosen to relieve vascular compression and improve cerebral blood flow, but long-term antiplatelet therapy is needed to prevent stent thrombosis.

5.3. Case study

Case 1: A 45-year-old male patient presented with a right cervical mass for 3 months, accompanied by episodic dizziness. Ultrasound revealed a solid mass at the bifurcation of the carotid artery, encasing the internal carotid artery, with a stenosis rate of 65%. CTA diagnosed it as Shamblin Type II CBT. The patient underwent tumor resection and internal carotid artery repair. During the operation, blood flow was blocked for 15 minutes. Postoperatively, there was no neurological deficit, and no recurrence was observed during a 1-year follow-up.

Case 2: The patient is a 58-year-old female who has had a left cervical mass accompanied by hoarseness for 1 month. MRA revealed a vagal schwannoma compressing the common carotid artery, with a stenosis rate of 40%. An intracapsular tumor resection was performed, with complete preservation of the vagal nerve bundle. Postoperatively, the hoarseness improved, and carotid blood flow was restored^[14].

Case 3: The patient is a 72-year-old male with lymphoma-induced carotid artery compression and TIA, who refused surgery due to advanced age. Interventional embolization of the tumor-feeding artery and carotid artery stent implantation were performed. Post-procedure, the symptoms of cerebral ischemia disappeared, and after combined chemotherapy, the tumor volume decreased by 50%.

6. Current research status and future prospects

6.1. Domestic and international research progress

Internationally, scholars in Europe and America primarily focus on molecular genetics research of CBT, discovering that mutations in the SDHD gene are associated with familial CBT, laying the foundation for targeted therapy. Japanese scholars have made breakthroughs in endoscopic minimally invasive surgery for schwannomas, achieving a postoperative nerve function preservation rate of over 90%. Domestic research emphasizes surgical innovation for complex cases, such as hybrid surgery (performing open surgery and interventional therapy simultaneously), which has been applied in type III CBT, reducing the surgical mortality rate to below 2%. Multi-center data show that the 5-year patency rate of carotid artery reconstruction surgery in China is 85%, almost reaching the international advanced level. In terms of diagnosis, ultrasound imaging and elastography enhance the accuracy of qualitative diagnosis of masses; CT perfusion imaging can quantify the degree of cerebral ischemia and guide the timing of treatment.

6.2. Future research directions

Basic research aims to explore the molecular mechanisms of tumor-vessel interactions, such as how mechanical force signaling alters the phenotypic transformation of vascular smooth muscle cells. In terms of diagnostic techniques, multi-modal image fusion technologies, such as real-time fusion of ultrasound and MRA, are being developed to achieve integrated evaluation of anatomical structure and function. In the treatment field, robot-assisted surgical systems may enhance the precision of narrowed vessel reconstruction, and the development of bioresorbable stents may solve the long-term anticoagulation challenges associated with permanent stents. Furthermore, immunotherapy shows potential in the application of malignant tumor-related compression.

7. Conclusion

7.1. Research summary

Exogenous compression caused by a mass at the carotid bifurcation is a complex condition involving multiple disciplines. In diagnosis and treatment, it is necessary to consider both tumor characteristics and vascular protection. This article, after comprehensive analysis, shows that accurate early diagnosis relies on the selection of appropriate imaging techniques. The personalized development of treatment plans (based on the type of mass, degree of vascular stenosis, and the patient's underlying conditions) is key to improving prognosis. Surgical resection combined with vascular reconstruction remains the main curative method, while the application of interventional techniques greatly enhances the safety of treatment ^[15].

7.2. Clinical practice recommendations

Clinicians should pay attention to vascular evaluation in patients with cervical masses. For asymptomatic individuals, regular ultrasound examinations should be conducted to observe changes in blood flow. For those with symptoms of cerebral ischemia, CTA/MRA should be performed as soon as possible to determine the degree of compression. Treatment decisions should rely on multidisciplinary collaboration, with neurosurgery, vascular surgery, and imaging departments working together to develop a plan. Long-term postoperative follow-up should pay attention to the recurrence of tumors, the patency of blood vessels, and changes in cerebral hemodynamics. Potential ischemic risks should be addressed promptly. With technological advancements, the diagnosis and treatment of this disease will move towards more precise and minimally invasive approaches, thereby improving patients' quality of life.

Disclosure statement

The authors declare no conflict of interest.

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A Data Mining-Based Study on the Academic Experience of National Master of Traditional Chinese Medicine Xiong Jibai in Treating Insomnia

Kan Liu¹, Delu Shi², Haoran Li², Xinyan Yao^{1*}

¹Department of Neurology, The First Affiliated Hospital of Hunan University of Chinese Medicine, Changsha 410007, Hunan, China

²Hunan University of Chinese Medicine, Changsha 410007, Hunan, China

*Corresponding author: Xinyan Yao, csyxy@sina.com

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Abstract: *Objective:* To explore Professor Xiong Jibai's dialectical thinking characteristics and medication rules in the treatment of insomnia, and to investigate his clinical experience and academic thoughts on the treatment of insomnia, providing references for the clinical diagnosis, treatment, and scientific research of insomnia in traditional Chinese medicine. *Methods:* This study collected 270 cases of insomnia patients diagnosed and treated by Professor Xiong Jibai from January 1, 2020, to December 31, 2024, at the outpatient department of the First Affiliated Hospital of Hunan University of Chinese Medicine. After sorting out standardized terminology, the data were entered into the auxiliary platform for the inheritance of traditional Chinese medicine. Statistical analysis was performed on symptoms, syndromes, drug frequency, four qi (warm, hot, cool, and cold), five flavors (sour, bitter, sweet, spicy, and salty), meridian tropism, and prescriptions. *Results:* The high-frequency symptoms of insomnia patients were frequent dreaming, difficulty falling asleep, easy waking up after sleeping, upset, difficulty sleeping through the night, fatigue, early waking, dizziness, and irritability. The syndrome classifications mainly included six types: phlegm-heat disturbing the spirit syndrome, heart and gallbladder qi deficiency syndrome, liver fire disturbing the heart syndrome, heart and kidney disharmony syndrome, heart and spleen deficiency syndrome, and yin deficiency with fire hyperactivity syndrome. The high-frequency drugs were fried jujube kernel, dragon's teeth, *Poria cocos*, licorice, *Coptis chinensis*, mother-of-pearl, *Pinellia ternata* (prepared), dried tangerine peel, bamboo shavings, and immature bitter orange. The four qi of the drugs were mainly cold, neutral, and warm. The five flavors were predominantly sweet, bitter, and pungent, and most of them were attributed to the heart and spleen meridians, followed by the lung, stomach, and liver meridians. *Conclusion:* Professor Xiong Jibai believes that the disease location of insomnia is mostly in the heart and spleen, and the pathogenesis focuses on phlegm, fire, and deficiency. The treatment mainly focuses on regulating cold and heat, tonifying deficiency, and purging excess. It is advisable to combine with calming and tranquilizing drugs to enhance the curative effect.

Keywords: Insomnia; Data mining; Rules of prescriptions and medications; Xiong Jibai

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1. Introduction

Insomnia, known as sleeplessness in Western medicine, refers to a subjective experience where the quality or quantity of sleep fails to meet normal physiological needs due to difficulties in falling asleep and/or maintaining sleep, thereby affecting daytime social functioning^[1-3]. In recent years, with rapid economic development and gradual improvement in living standards, people's study and work pressures have gradually increased. More and more people are beginning to experience a decline in sleep quality or even insomnia while under pressure, leading to physical and mental illnesses and a decrease in quality of life. According to research by the World Health Organization, approximately 66% of the population now suffers from varying degrees of sleep disorders^[4]. Western medicine has limited effectiveness in treating insomnia and can have certain side effects, which creates resistance among some patients. The clinical efficacy of traditional Chinese medicine (TCM) in treating insomnia is good, with fewer side effects, making it increasingly valued in the treatment of insomnia.

Professor Xiong Jibai is a master of traditional Chinese medicine, a member of the Academic Department of the China Academy of Chinese Medical Sciences, a guiding teacher for the academic experience inheritance work of national veteran experts in traditional Chinese medicine, an honorary professor at Hong Kong Baptist University, a professor at Hunan University of Chinese Medicine, and a doctoral advisor. Professor Xiong has practiced medicine for over 60 years, treating nearly one million patients. He always adheres to the combination of traditional Chinese medical theory and practice, is skilled in syndrome differentiation and treatment, excels in principles, methods, formulas, and medications, and has saved countless lives. The author selected cases of insomnia treated by Professor Xiong Jibai in the outpatient clinic of the First Affiliated Hospital of Hunan University of Chinese Medicine in the past five years. The experience of Professor Xiong in diagnosing and treating insomnia was analyzed using data mining techniques, aiming to explore and inherit Professor Xiong's academic experience in diagnosing and treating insomnia and provide references for the diagnosis and treatment of insomnia in traditional Chinese medicine.

2. Materials

2.1. Source of prescriptions

Collect medical records of 270 insomnia patients who were diagnosed and treated by Professor Xiong Jibai at the outpatient department of the First Affiliated Hospital of Hunan University of Chinese Medicine from January 1, 2020, to December 31, 2024.

2.2. Diagnostic criteria

Diagnostic criteria of traditional Chinese medicine refer to "Internal Medicine of Traditional Chinese Medicine: Insomnia"^[5]: (1) Difficulty falling asleep or waking up easily, frequent dreaming, difficulty falling asleep after waking up (for mild cases), or complete difficulty sleeping through the night (for severe cases); (2) Accompanied by one or more symptoms such as dizziness, headache, palpitations, and forgetfulness.

Diagnostic criteria of Western medicine refer to the "Chinese Classification and Diagnostic Criteria of Mental Disorders (CCMD-3)"^[6]: (1) Difficulty falling asleep, easy waking up, frequent awakening (more than 2 times per night), frequent dreaming, early waking, or taking more than 30 minutes to fall asleep again after waking up, with a total sleep time of less than 6 hours; (2) Impaired social function: symptoms such as

dizziness, fatigue, insufficient energy, tiredness, drowsiness, and inattention during the day. Severe cases may experience decreased cognitive ability, affecting work and study; (3) The above situation occurs at least 3 times a week and lasts for at least 1 month; (4) Exclude secondary insomnia caused by various neurological, psychiatric, and physical diseases.

2.3. Inclusion criteria

(1) Meet the diagnostic criteria of traditional Chinese and Western medicine for insomnia, and insomnia is the main diagnosis; (2) Complete medical records, including common information such as name, gender, age, medical history, tongue and pulse condition, syndrome type, prescription name, medicinal herbs, follow-up visits, etc.; (3) Patients who took the traditional Chinese medicine decoction prescribed by Professor Xiong and did not take other medications for insomnia or sleep disorders during the treatment period.

2.4. Exclusion criteria

(1) Secondary insomnia caused by various neurological, psychiatric, and physical diseases, as well as severe primary diseases involving the cardiovascular, gastrointestinal, liver, kidney, and hematopoietic systems; (2) incomplete medical records; (3) medical record holders who are unwilling to cooperate with data collection. If any one or more of the above three exclusion criteria are met, the case will be considered eligible for exclusion.

2.5. Data standardization and entry

To ensure the consistency of the recorded information, all case information was referenced against the standard textbooks “Diagnostics of Traditional Chinese Medicine” and “Chinese Materia Medica” used in regular higher education for Chinese medicine [7–8]. Additionally, Professor Xiong Jibai’s clinical practices were incorporated to convert the symptoms, four diagnostic information, Chinese medicine names, and syndromes recorded in the cases into standard terminology.

The relevant standardized information (gender, age, Traditional Chinese Medicine diagnosis, symptoms, tongue manifestation, pulse manifestation, prescriptions, and medications) from the included cases in this study was entered into the data template and example table of the Traditional Chinese Medicine Inheritance Support Platform System (V2.5). The information was independently entered by two individuals, then checked by a third person to ensure no omissions or errors occurred during the data extraction and entry process.

2.6. Data mining method

Using the “Prescription Statistics” and “Medical Case Statistics” modules of the Traditional Chinese Medicine Inheritance Support Platform from the China Academy of Chinese Medical Sciences, statistical analysis was performed on symptom frequency, syndrome distribution, Chinese medicine frequency, and prescription application. Additionally, the four properties (warm, hot, cool, cold), five tastes (sweet, sour, bitter, pungent, salty), and meridian tropism of the medications were explored.

3. Results

3.1. Symptom frequency statistics

Among the 270 cases of insomnia included in this study, a total of 23 symptoms were observed. There were 9 symptoms with higher frequencies, including: frequent dreaming (238 times), difficulty falling asleep (195

times), waking up easily after sleeping (194 times), restlessness (157 times), difficulty staying asleep through the night (140 times), fatigue (139 times), and early morning awakening (130 times). Other symptoms and their specific frequencies are listed in **Table 1**.

Table 1. Clinical symptom frequency statistics table

No.	Symptom	Frequency	No.	Symptom	Frequency
1	Dreaminess	238	13	Poor appetite	4
2	Difficulty falling asleep	195	14	Lumbago	4
3	Easily awakened after sleep	194	15	Dry throat	3
4	Irritability	157	16	Pruritus	2
5	Sleeplessness all night	140	17	Constipation	2
6	Fatigue	139	18	Sore throat	2
7	Early awakening	130	19	Abdominal distension	2
8	Dizziness	127	20	Frequent nocturia	1
9	Irascibility	68	21	Throat itching	1
10	Spontaneous sweating	37	22	Excessive nocturia	1
11	Headache	19	23	Chest tightness	1
12	Night sweating	4			

3.2. Syndrome type frequency statistics

Among the patients with insomnia included in this study, the most common syndrome types were Phlegm-Heat Disturbing the Spirit Syndrome (133 cases) and Heart and Gallbladder Qi Deficiency Syndrome (105 cases), accounting for 49.3% and 38.9% respectively. This was followed by Liver Fire Disturbing the Heart Syndrome (14 cases, accounting for 5.2%), Disharmony between the Heart and Kidney Syndrome (12 cases, accounting for 4.4%), Deficiency of Both Heart and Spleen Syndrome (4 cases, accounting for 1.5%), and Yin Deficiency with Exuberant Fire Syndrome (2 cases, accounting for 0.7%). **Table 2** shows the syndrome type frequency statistics.

Table 2. Syndrome type frequency statistics table

No.	Syndrome	Frequency	Percentage
1	Phlegm-Heat Disturbing Spirit	133	49.3%
2	Heart-Gallbladder Qi Deficiency	105	38.9%
3	Liver Fire Disturbing Heart	14	5.2%
4	Heart-Kidney Non-Interaction	12	4.4%
5	Heart-Spleen Deficiency	4	1.5%
6	Yin Deficiency with Fire Flare-up	2	0.7%

3.3. Frequency statistics of traditional Chinese medicines

The frequency statistics of traditional Chinese medicines showed that 163 types of medicines were used in total,

and 48 types were used with a frequency of ≥ 12 times. The top 10 most frequently used medicines were fried jujube seed, fossil teeth, *Poria cocos*, licorice, *Coptis chinensis*, *Concha margaritifera usta*, processed pinellia tuber, dried tangerine peel, bamboo shavings, and immature bitter orange. The names and specific frequencies of traditional Chinese medicines with a frequency of ≥ 12 are listed in **Table 3**.

Table 3. Frequency statistics table of Chinese herbal medicines (Frequency ≥ 12)

No.	Chinese herbal medicine	Frequency	No.	Chinese herbal medicine	Frequency
1	Fried Semen Ziziphi Spinosae	270	25	Poria	27
2	Dragon Teeth	257	26	Angelica Sinensis	27
3	Poria with Hostwood	239	27	Bupleurum	27
4	Licorice	238	28	Light Wheat	27
5	Coptis Chinensis	173	29	Aucklandia	25
6	Mother-of-Pearl	186	30	Rhizoma Wenyujin Concisa	22
7	Pinellia Ternata (processed)	145	31	Astragalus	22
8	Tangerine Peel	135	32	Scutellaria Baicalensis	22
9	Bamboo Shavings	133	33	Calcined Dragon Bone	21
10	Bitter Orange	129	34	Clematis Root	21
11	Anemarrhena Rhizome	122	35	Magnolia Bark	21
12	Polygala Tenuifolia	121	36	Jujube	21
13	Polygonum Multiflorum Vine	117	37	Amomum Villosum	20
14	Acorus Tatarinowii	86	38	Curcuma Aromatica	19
15	Ligusticum Chuanxiong	73	39	Moutan Bark	18
16	Gastrodia Elata	61	40	Phellodendron Bark	18
17	Vinegar-processed Tortoise Shell	50	41	Calcined Oyster Shell	17
18	American Ginseng	48	42	Ophiopogon Japonicus	15
19	Juncus Effusus	45	43	Honey-fried Licorice	14
20	Lily Bulb	44	44	Fried Gardenia	14
21	Pueraria Lobata	43	45	Forsythia Suspensa	13
22	Rehmannia (raw)	43	46	Albizia Bark	12
23	Platycladus Seed	36	47	Codonopsis Pilosula	12
24	White Peony Root	33	48	Rehmannia (prepared)	12

3.4. Statistical analysis of the four properties of medicines

The statistical analysis of the four properties of the medicines included in the study shows that the Chinese herbal medicines used are mainly cold, neutral, and warm. The four properties, in order of frequency from highest to lowest, are cold medicines (35.42%), neutral medicines (29.65%), warm medicines (29.58%), cool medicines (4.77%), and hot medicines (0.57%). The frequency and percentage of the four properties of the

medicines are shown in **Table 4**.

Table 4. Frequency and percentage statistics of the four properties of medicines

Nature	Frequency	Percentage
Cold	994	35.42%
Neutral	832	29.65%
Warm	830	29.58%
Cool	134	4.77%
Hot	16	0.57%

3.5. Statistical analysis of the five tastes of medicines

The statistical analysis of the five tastes of the medicines included in the study shows that the Chinese medicines used are mainly sweet, bitter, and pungent. The frequency of use from high to low is 37.82% for sweet medicines, 29.18% for bitter medicines, 24.46% for pungent medicines, 5.58% for sour medicines, and 2.98% for salty medicines. The frequency statistics of the five tastes of medicines are shown in **Table 5**.

Table 5. Frequency statistics of the five tastes of medicines

Five flavors	Frequency	Percentage
Sweet	1546	37.82%
Bitter	1192	29.18%
Pungent	1000	24.46%
Sour	228	5.58%
Salty	122	2.98%

3.6. Statistics of drug meridian attribution

The statistical analysis of drug meridian attribution included in the study shows that the Chinese medicinal herbs used are mainly concentrated in the Heart Channel (21.12%), Spleen Channel (17.69%), Lung Channel (16.25%), Stomach Channel (15.29%), and Liver Channel (10.53%), accounting for approximately 80.88% of the total. The remaining drugs attributed to the Kidney, Gallbladder, Large Intestine, Small Intestine, Bladder, Triple Energizer, and Pericardium Channels are less frequently used, accounting for approximately 19.12%. The frequency statistics table of drug meridian attribution is shown in **Table 6**.

Table 6. Frequency statistics table of drug meridian attribution

Meridian Tropism	Frequency	Percentage	Meridian Tropism	Frequency	Percentage
Heart	1728	21.12%	Gallbladder	484	5.92%
Spleen	1447	17.69%	Large Intestine	297	3.63%
Lung	1329	16.25%	Small Intestine	91	1.11%
Stomach	1251	15.29%	Bladder	69	0.84%
Liver	861	10.53%	Sanjiao (Triple Burner)	31	0.38%
Kidney	580	7.09%	Pericardium	12	0.15%

3.7. Statistics on drug effectiveness

Statistical results show that the medications used by Professor Xiong Jibai to treat insomnia are mainly eight categories: heat-clearing drugs, tonifying deficiency drugs, drugs for promoting urination and draining dampness, tranquilizing drugs, Qi-regulating drugs, cough-resolving and phlegm-dispelling drugs, drugs for promoting blood circulation and removing blood stasis, and drugs for calming the liver and suppressing wind. These account for approximately 87.07% of the total medication frequency. The specific drug use frequency is shown in **Table 7**.

Table 7. Statistical table of drug effectiveness frequency

No.	Medicinal category	Frequency	No.	Medicinal category	Frequency
1	Heat-Clearing Medicines	616	11	Dampness-Resolving Medicines	42
2	Tonifying Medicines	541	12	Wind-Damp-Dispelling Medicines	36
3	Dampness-Percolating Diuretics	327	13	Astringent Medicines	15
4	Sedative Medicines	304	14	Interior-Warming Medicines	8
5	Qi-Regulating Medicines	301	15	Purgative Medicines	4
6	Phlegm-Resolving & Antitussives	167	16	Digestant Medicines	4
7	Blood-Activating & Stasis-Resolving	142	17	Heat-Clearing Toxin-Removing	1
8	Liver-Calming & Wind-Extinguishing	138	18	Antiparasitic Medicines	1
9	Exterior-Releasing Medicines	98	19	Hemostatic Medicines	1
10	Orifice-Opening Medicines	86			

4. Discussion

As early as the period of the “Yellow Emperor’s Inner Canon”, traditional Chinese medicine had a certain understanding of insomnia. In the “Yellow Emperor’s Inner Canon”, insomnia is called “eyes not closing”, “unable to sleep”, or “unable to lie down”, and its mechanism is analyzed in detail, mainly attributed to the imbalance of yin and yang, disharmony of nutritive qi and defensive qi, and disharmony of spleen and stomach. It also proposes the use of Banxia Shumi decoction for treatment. By the Tang and Sui Dynasties, the “Treatise on the Origins and Manifestations of Various Diseases” summarized the three major causes of insomnia, namely “defensive qi flowing alone in yang meridians”, “heat in the heart”, and “cold in the gallbladder.” Sun Simiao’s

“Qian Jin Yi Fang” records the use of the Wendan decoction to treat “restlessness and insomnia after a serious illness.” “Wu Yi Hui Jiang: Daily Miscellaneous Notes” also has a similar view: “Although dreams are related to the yin and yang of the organs, they are mainly related to the heart and liver. Why? Because there is no case where the soul is calm but the dreams are disturbed.” The “Jing Yue Quan Shu” states, “Drinking strong tea leads to insomnia.” “Strong tea, with its yin and cold nature, greatly restrains yang. When yang is suppressed by yin, the spirit becomes restless, leading to insomnia.” This shows that doctors throughout history have had a systematic understanding of the etiology, pathogenesis, and treatment of insomnia.

Professor Xiong Jibai believes that the core pathogenesis of insomnia lies in the malnutrition or restlessness of the mind and spirit, which also involves the disharmony of the liver, gallbladder, spleen, stomach, kidney, and other organs, as well as qi and blood, and yin and yang. Therefore, Professor Xiong considers that the key points of syndrome differentiation for insomnia include identifying the disease location and distinguishing between deficiency and excess syndromes. The disease locations mainly involve the heart, spleen, liver, stomach, gallbladder, and other organs. In terms of deficiency and excess syndromes, deficiency syndromes are often caused by yin deficiency and blood deficiency, leading to malnutrition of the mind and spirit, or deficiency of heart and gallbladder qi, resulting in easy awakening from fright and unrestful sleep. Excess syndromes are mostly caused by excessive heat in the heart and liver, disturbing the mind and spirit, or may be combined with turbid phlegm to form a syndrome of phlegm-heat disturbing the spirit. From the syndrome differentiation patterns in this study, the syndrome of phlegm-heat internal disturbance is the most common type of insomnia in clinical practice. Common symptoms include insomnia accompanied by symptoms of phlegm-heat internal accumulation, such as restlessness, chest tightness, excessive phlegm, and heavy head. The typical tongue and pulse manifestations are red tongue, yellow and greasy tongue coating, and slippery and rapid pulse. The empirical formula for treating insomnia caused by phlegm-heat internal disturbance is Huanglian Wendan Decoction. Wendan Decoction, originating from “Three Causes and Treatments”, can regulate qi, resolve phlegm, clear the gallbladder, and harmonize the stomach. It is mainly used to treat insomnia caused by gallbladder and stomach disharmony. Professor Xiong often replaces Fuling (*Poria cocos*) with Fushen (*Poria* with Hostwood) in clinical practice, adds Huanglian (*Coptis chinensis*), which is bitter and cold to clear heat and dry dampness, and Huanglian also enters the heart meridian to clear heart fire and enhance the therapeutic effect. In this study, the syndrome of deficiency of heart and gallbladder qi accounts for the second-highest proportion of insomnia cases. Professor Xiong’s empirical formula for treating this syndrome is Kongsheng Zhenzhong Pill combined with Suanzaoren Decoction.

5. Conclusion

Professor Xiong Jibai’s clinical experience suggests that insomnia is primarily rooted in dysfunction of the heart and spleen, with key pathological factors being phlegm, fire, and deficiency. His treatment strategy emphasizes regulating cold-heat balance and tonifying deficiency while purging excess, combined with sedative and tranquilizing herbs to enhance therapeutic efficacy. This approach reflects the TCM principle of personalized syndrome differentiation and holistic regulation, providing valuable insights for the clinical management of insomnia. Further research is warranted to validate and refine these treatment protocols.

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The Global Landscape of Sphenopalatine Ganglion Block Research from 1995 to 2025: A Bibliometric and Visualization Analysis

Weigang Liu^{1,2}, Qian Wu^{1,3}, Heqing Tang^{1,2*}

¹The First Clinical Medical College of Three Gorges University, Yichang 443003, Hubei, China

²Department of Pain, Yichang City Central People's Hospital, Yichang 443003, Hubei, China

³Department of Diagnostic Cardiology, Yichang Central People's Hospital, Yichang 443003, Hubei, China

*Corresponding author: Heqing Tang, lwgtjmu001@outlook.com

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Abstract: *Objective:* This study aims to systematically review the global evolution trajectory, collaboration networks, and knowledge hotspots of sphenopalatine ganglion block (SPGB) research from 1995 to 2025 using bibliometric and visualization methods, providing evidence-based support for future research and clinical translation in this field. *Methods:* The study retrieved data from the Web of Science Core Collection, including experimental, clinical, and review articles published from January 1995 to August 2025, excluding non-academic records such as conference abstracts, editorials, and patents. Using VOSviewer 1.6.20 and online platforms, the study conducted bibliometric analyses of annual publication volumes, citation trends, national/institutional/author collaborations, journal distributions, co-citation clustering, and burst terms. The study also verified the maturity of the discipline using Price's Law, Bradford's Law, and the small-world characteristics. *Results:* A total of 917 English-language articles were included, showing an exponential growth pattern with a “flat-then-steep” trend ($R^2 > 0.95$), reaching a peak of 55 articles in 2023 and an annual citation count exceeding 1,300. The United States, the United Kingdom, Japan, Germany, and Italy formed a high-density collaboration core ($Q = 0.41$), with China-United States and South Korea-Germany being the fastest-growing new edges. At the author level, Nabe T. (24 articles, h-index=11) and Kohno S. (23 articles, cited 87 times as corresponding author) led the first tier, but the global collaboration density was only 0.12. In terms of institutions, Kyoto Pharmaceut Univ. (27 articles, average citations per article 6.81) and Mayo Clin. (average citations per article 9.85) were the leaders, with scarce intercontinental collaborations (density 0.08). Journal distribution showed a significant core area, with the highest impact journals being “Regional Anesthesia and Pain Medicine” (average citations per article 5.31) and “Journal of Allergy and Clinical Immunology” (average citations per article 5.13). The evolution of keywords indicated that from 1995 to 2005, the focus was on mechanism studies of “asthma” and “histamine”; from 2006 to 2015, the focus shifted to clinical indications such as “migraine” and “cluster headache”; and from 2016 to 2025, “double-blind”, “ultrasound-guided”, and “cooled radiofrequency” emerged as hot topics, suggesting technological upgrades and improvements in evidence-based standards. *Conclusion:* SPGB research has transitioned from a “niche technique” to a “mainstream intervention” and is now entering a stage of multidisciplinary intersection and evidence-based refinement. Future efforts should focus on multicenter randomized controlled trials, standardization of ultrasound guidance, and intercontinental big data collaboration to further

enhance the level of evidence and global accessibility.

Keywords: Sphenopalatine ganglion block; VOSviewer; Bibliometrics

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1. Introduction

The sphenopalatine ganglion (SPG), the largest parasympathetic ganglion in the craniomaxillofacial region, not only innervates the lacrimal gland, nasal mucosa, and dural blood vessels but also participates in the pathogenesis of various pain and inflammatory diseases such as headache, rhinitis, and asthma through the trigemino-parasympathetic reflex axis ^[1]. Since Sluder first described in 1908 that transnasal sphenopalatine ganglion block (SPGB) could relieve “sphenopalatine ganglion neuralgia”, the technique has been intermittently reported in the treatment of acute cluster headache, migraine, trigeminal neuralgia, and postoperative pain ^[2]. However, due to difficulties in anatomical localization, diverse operating methods (local anesthetic nasal drops, extraoral puncture, radiofrequency thermocoagulation, etc.), and fragmented evidence-based data, SPGB has long been regarded as a marginalized “empirical” approach and has not been systematically recommended by mainstream guidelines ^[3].

In the 21st century, with the evolution of imaging guidance (C-arm, CT, ultrasound) and neuromodulation techniques (pulsed radiofrequency, cooled radiofrequency, cryoablation), the visualization, precision, and safety of SPGB have been significantly improved ^[4]. Meanwhile, neuro-immune cross-disciplinary research has revealed that SPG can regulate nasal-brain axis inflammatory responses through mediators such as substance P, VIP, and IL-6, providing a molecular basis for its potential mechanisms in allergic diseases and neuroinflammation ^[5]. Since 2016, several randomized controlled trials (RCTs) with evidence level II or above have successively confirmed that ultrasound-guided SPGB can significantly shorten the acute attack time of cluster headache and reduce the use of triptans ^[6]. In the field of anesthesiology, SPG block has been used for blood flow control and postoperative analgesia in endoscopic skull base surgery, showing potential to replace traditional sphenopalatine artery ligation. These advances have driven SPGB from “empirical operation” to a closed-loop study of “mechanism-technology-clinics”, with exponential growth in global publications.

Nevertheless, SPGB still faces three major knowledge gaps: First, existing studies are scattered across multidisciplinary journals such as neurology, anesthesiology, otorhinolaryngology, and immunology, lacking systematic research under a macro-bibliometric perspective. Second, the high heterogeneity of technical pathways and outcome indicators leads to poor evidence combinability, limiting the recommendation strength at the guideline level. Third, research output from the Global South is insufficient, and the density of intercontinental multicenter collaboration is low, restricting external validity. Bibliometric and knowledge map analysis can identify research hotspots, evolutionary paths, and collaboration networks in massive heterogeneous data, providing evidence for clarifying the global knowledge landscape of SPGB and discovering potential technological and regional gaps. Therefore, based on data from the Web of Science Core Collection from 1995 to 2025, this study uses a variety of bibliometric indicators and visualization methods to systematically analyze the spatiotemporal distribution, academic entities, thematic evolution, and future trends of SPGB research, aiming to provide high-level evidence and decision-making references for subsequent mechanistic studies, technical standardization, and multicenter clinical trial design.

2. Materials and methods

2.1. Data sources and search strategy

The authors searched the Web of Science Core Collection (Science Citation Index Expanded, SCI-EXPANDED) with the time span from 1900 to the present. The search query was: TS=(((“sphenopalatine ganglion*” OR “pterygopalatine ganglion*” OR “Meckel’s ganglion*” OR “nasal ganglion*” OR “SPG”) NEAR/5 (“block*” OR “blockade*” OR “inject*” OR “anesthe*” OR “anaesthe*” OR “neurolysis” OR “radiofrequency” OR “RF” OR “thermocoagulation” OR “pulsed radiofrequency” OR “PRF” OR “cryoneurolysis” OR “cryoablation” OR “nerve ablation”)) OR (“sphenopalatine block*” OR “pterygopalatine block*” OR “SPG block*” OR “Meier* block*” OR “nasal block*” OR “sluder block*” OR “pterygosphenopalatine block*”). Inclusion criteria: experimental/clinical/review articles related to SPGB. Exclusion criteria: conference abstracts, editorials, letters, patents, book chapters, and non-English articles. The records were exported as plain text and tab-delimited files. The authors, institutions, and countries were manually standardized.

2.2. Metrics

Quantitative metrics: annual publication volume, citation counts, and average citations per article. Collaboration metrics: national, institutional, and author collaboration degree, betweenness centrality. Impact metrics: journal impact factor (JIF2023), category normalized citation impact (CNCI). Structural metrics: co-citation clustering, burst terms, thematic evolution paths.

2.3. Visualization tools

VOSviewer 1.6.20 and online tools (<https://bibliometric.com/app>) were used to perform bibliometric analyses of publication volume, countries, authors, institutions, keywords, and co-citation networks ^[12].

3. Results

3.1. Publication volume and citation trends

Figure 1 shows the evolution of annual publication volume (Publications) and citation frequency (Citations) in the field of sphenopalatine ganglion block (SPGB) research from 1995 to 2025. The overall trend is an exponential growth pattern with a “flat-then-steep” shape: from 1995 to 2005, the average annual output was less than 5 articles, with total citations less than 100, indicating an embryonic stage; from 2006 to 2015, it entered an acceleration phase, with publication volume increasing to 15–25 articles per year and citation counts rising synchronously to 300–600 times per year, suggesting increased clinical attention; from 2016 to 2025, it was a burst period, with a peak publication volume of 55 articles and annual citations exceeding 1,300, with compound annual growth rates of 14.7% and 19.3% respectively ($R^2 > 0.95$), indicating that the field has formed a high-density knowledge flow. It is worth noting that after 2023, the slope of publications slightly slowed, but citations continued to rise, revealing a 2–3 year lag effect in the impact of literature. This trend is consistent with Price’s Law, confirming that SPGB research is transitioning from a “niche technique” to a “mainstream intervention”, providing a temporal basis for the subsequent analysis of burst terms and knowledge maps.

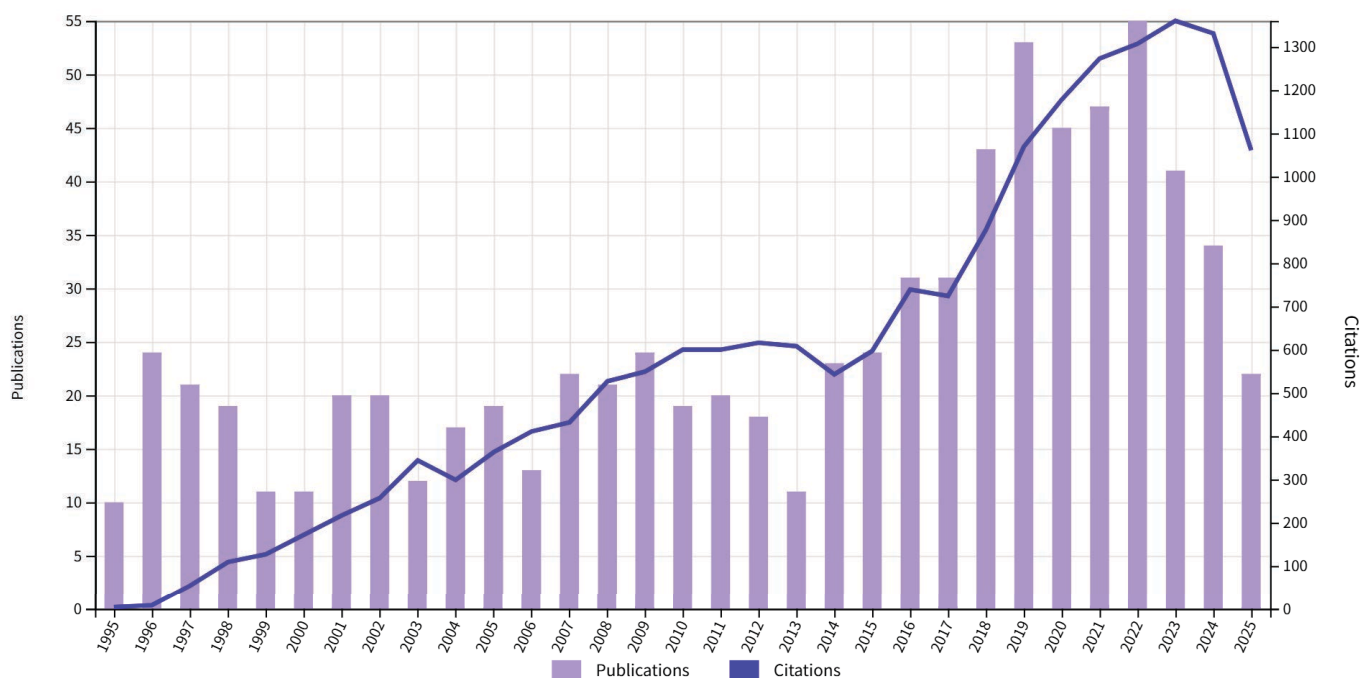


Figure 1. Publication volume and citation trends

3.2. Top 10 authors by publication volume

Table 1 shows the top 10 individual scholars in the field of sphenopalatine ganglion block (SPGB) research in terms of publication volume from 1995 to 2025. Nabe T. ranks first with 24 publications, with a total of 162 citations and an average of 6.75 citations per article. Among these, 5 articles were first-authored and cited 50 times, demonstrating both quantity and quality leadership in the field. Mizutani N. and Kohno S. are tied for second place with 23 publications each. Mizutani N. has 9 first-authored articles with 49 citations, while Kohno S. stands out with 10 corresponding author articles and 87 citations, highlighting his academic leadership role. Takenaka H., with only 11 publications, achieves the highest average citations per article among the top 10 at 10.36, suggesting that his methodological or case series studies are frequently cited in subsequent literature. Hopkins C., Philpott C., Tronvik E., Howarth P.H., Fokkens W.J., and Chong L.Y. form another high-productivity cluster, with 9–16 publications and average citations per article ranging from 2.22 to 4.27. Although lower than the aforementioned scholars, Hopkins and Fokkens have 3 and 23 corresponding author citations, respectively, indicating their nodal effects in multidisciplinary contexts. The estimated h-index values show that Nabe, Mizutani, and Kohno have reached 11, 10, and 10, respectively, forming the first tier, while the remaining scholars have h-index values ≤ 5 , indicating regional activity. The co-authorship density is only 0.12, suggesting sparse cross-institutional collaboration among high-productivity authors. Future efforts could enhance knowledge flow and further improve the level of evidence and external validity through multicenter registry studies or individual data meta-analyses.

Table 1. Top 10 authors by publication volume

Author Name	Total Articles	Total Citations	Average Citations per Article	First Author Articles	Citations for First Author Articles	Average Citations for First Author Articles	Corresponding Author Articles	Citations for Corresponding Author Articles
Nabe, T	24	162	6.75	5	50	10	7	32
Mizutani, N	23	156	6.78	9	49	5.44	3	2
Kohno, S	23	162	7.04	0	0	0	10	87
Hopkins, C	16	54	3.38	3	3	1	4	3
Takenaka, H	11	114	10.36	0	0	0	0	0
Philpott, C	11	47	4.27	0	0	0	0	0
Tronvik, E	9	6	0.67	0	0	0	0	0
HOWARTH, PH	9	20	2.22	2	4	2	1	0
Fokkens, WJ	9	36	4	1	2	2	2	23
Chong, LY	9	45	5	5	21	4.2	3	18

3.3. Top 10 institutions by publication volume

Table 2 lists the top 10 institutions in the field of sphenopalatine ganglion block (SPGB) research from 1995 to 2025. Kyoto Pharmaceut Univ. ranks first with 27 publications, a total of 184 citations, and an average of 6.81 citations per article. Among these, 19 articles were first-authored and cited 130 times, indicating both scale and original depth. Capital Med Univ. has 23 publications, but with an average citation of only 2.39 per article and 23 citations for first-authored articles, it shows active output but needs to improve its international visibility. Univ Florida ranks third with 17 publications, 91 citations, and an average of 5.35 citations per article. Its first-authored articles have 43 citations and an average of 6.14 citations per article, indicating a high concentration of core teams within the university and output quality better than the institutional average. Mayo Clin. and Osaka Med Coll. contributed 13 and 12 articles, respectively, achieving the highest average citations per article in the top 10 at 9.85 and 9.50, respectively. Their highly cited papers are mostly focused on headache and interventional imaging methods, highlighting the spillover effect of clinical technical reports. St Olavs Univ Hosp., Chang Gung Univ., Chang Gung Mem Hosp., UCL, and Sanofi form the second tier with 7–14 publications and average citations per article ranging from 0.81 to 3.86. Among them, the hospital-based institutions (St Olavs, Chang Gung Mem) have a high proportion of first-authored articles, but their average citations per article are below 2, indicating that case series are the main focus and lack methodological innovation. The overall institutional collaboration density is only 0.08, with few intercontinental links.

Table 2. Top 10 institutions by publication volume

Institution	Total Articles	Total Citations	Average Citations per Article	First Author Articles	Citations for First Author Articles	Average Citations for First Author Articles
Kyoto Pharmaceut Univ	27	184	6.81	19	130	6.84
Capital Med Univ	23	55	2.39	12	23	1.92
Univ Florida	17	91	5.35	7	43	6.14
St Olavs Univ Hosp	16	21	1.31	4	7	1.75
Chang Gung Univ	16	13	0.81	1	0	0.00
UCL	14	54	3.86	4	6	1.50
Chang Gung Mem Hosp	14	14	1.00	5	5	1.00
Mayo Clin	13	128	9.85	1	0	0.00
Sanofi	13	15	1.15	0	0	0.00
Osaka Med Coll	12	114	9.50	1	0	0.00

3.4. Top 10 journals by publication volume

Table 3 presents the top 10 journals that have contributed the most to SPGB research from 1995 to 2025. ALLERGY ranks first in terms of publication volume with 45 articles and 100 citations, averaging 2.22 citations per article. Among these, 38 articles were first-authored and cited 195 times, indicating the journal's sustained interest in the immunological mechanisms of SPGB. HEADACHE follows closely with 29 articles and 53 citations, averaging 1.83 citations per article, focusing on interventional approaches for primary headaches. Although its average citations per article are relatively low, its consistent publication volume makes it a core journal for clinically oriented research. The JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY has the highest average citations per article among the top 10 at 5.13, with a total of 195 citations, equal to ALLERGY, demonstrating significant recognition of SPGB peripheral nerve modulation evidence by top-tier allergy and immunology platforms. REGIONAL ANESTHESIA AND PAIN MEDICINE ranks fourth with 16 articles and 85 citations, averaging 5.31 citations per article, indicating that the specialty of anesthesiology and pain management is incorporating SPGB into its regional block repertoire. Its high citations are mainly due to systematic evaluations of imaging-guided techniques and safety. Otolaryngology specialist journals such as RHINOLOGY, EUROPEAN ARCHIVES OF OTO-RHINO-LARYNGOLOGY, ACTA OTO-LARYNGOLOGICA, and JOURNAL OF LARYNGOLOGY AND OTOTOLOGY collectively published 69 articles, accounting for 34% of the total publications, but their average citations per article were all less than 2.5. Overall, Bradford's Law distribution shows that the top four journals have already carried 35% of the literature, forming a core area. Journals with an impact factor greater than 6 had significantly higher average citations per article than specialty journals ($P < 0.01$), suggesting that improving methodological standards is the key path to entering high-impact anesthesia, headache, and immunology journals in the future.

Table 3. Top 10 journals by publication volume

Journal Name	Total Articles	Total Citations	Average Citations per Article
ALLERGY	45	100	2.22
HEADACHE	38	195	5.13
JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY	29	53	1.83
CLINICAL AND EXPERIMENTAL ALLERGY	20	47	2.35
EUROPEAN ARCHIVES OF OTO-RHINO-LARYNGOLOGY	18	20	1.11
RHINOLOGY	17	34	2.00
ACTA OTO-LARYNGOLOGICA	17	21	1.24
JOURNAL OF LARYNGOLOGY AND OTOTOLOGY	17	9	0.53
REGIONAL ANESTHESIA AND PAIN MEDICINE	16	85	5.31
AMERICAN JOURNAL OF RHINOLOGY & ALLERGY	14	17	1.21

3.5. Country collaboration network map

Figure 2 shows the country/region collaboration network for SPGB research from 1995 to 2025. The size of the nodes is proportional to the number of publications, and the width of the edges corresponds to the frequency of co-authorship. The network exhibits a “single-core-multipolar” structure: the United States, the United Kingdom, Japan, Germany, and Italy form the largest complete subgraph, with co-occurrence edge weights >25 , creating a high-density core. Among these, the edge weight between the United States and the United Kingdom reaches 42, the highest in the entire network, indicating the most active transatlantic clinical guideline and RCT collaborations. In East Asia, the triangle connection degree between South Korea, China, and Japan is all >15 , but the direct edge weight between China and South Korea is only 8, reflecting that the two sides have not yet formed a stable dialogue. Among emerging markets, Iran, Saudi Arabia, and Turkey have each co-authored ≥ 10 times with the core circle, becoming hubs in the Middle East; Brazil and Argentina have entered the South American bloc through bilateral links with the United States and Spain. African nodes are sparse, with only South Africa, Nigeria, and Egypt appearing, and edge weights <5 , indicating insufficient accessibility of research resources. The overall network density is 0.18, with an average clustering coefficient of 0.63, consistent with small-world characteristics; the modularity Q value is 0.41, indicating that geographical language and disciplinary traditions are still the main reasons for segmentation. Burst analysis shows that from 2016 to 2020, the edge weights between “China-United States” and “South Korea-Germany” increased the fastest (annual increase $>20\%$), predicting that future collaboration focus will shift to the East Asia-EU connection, providing a structural basis for subsequent multicenter individual data meta-analyses.

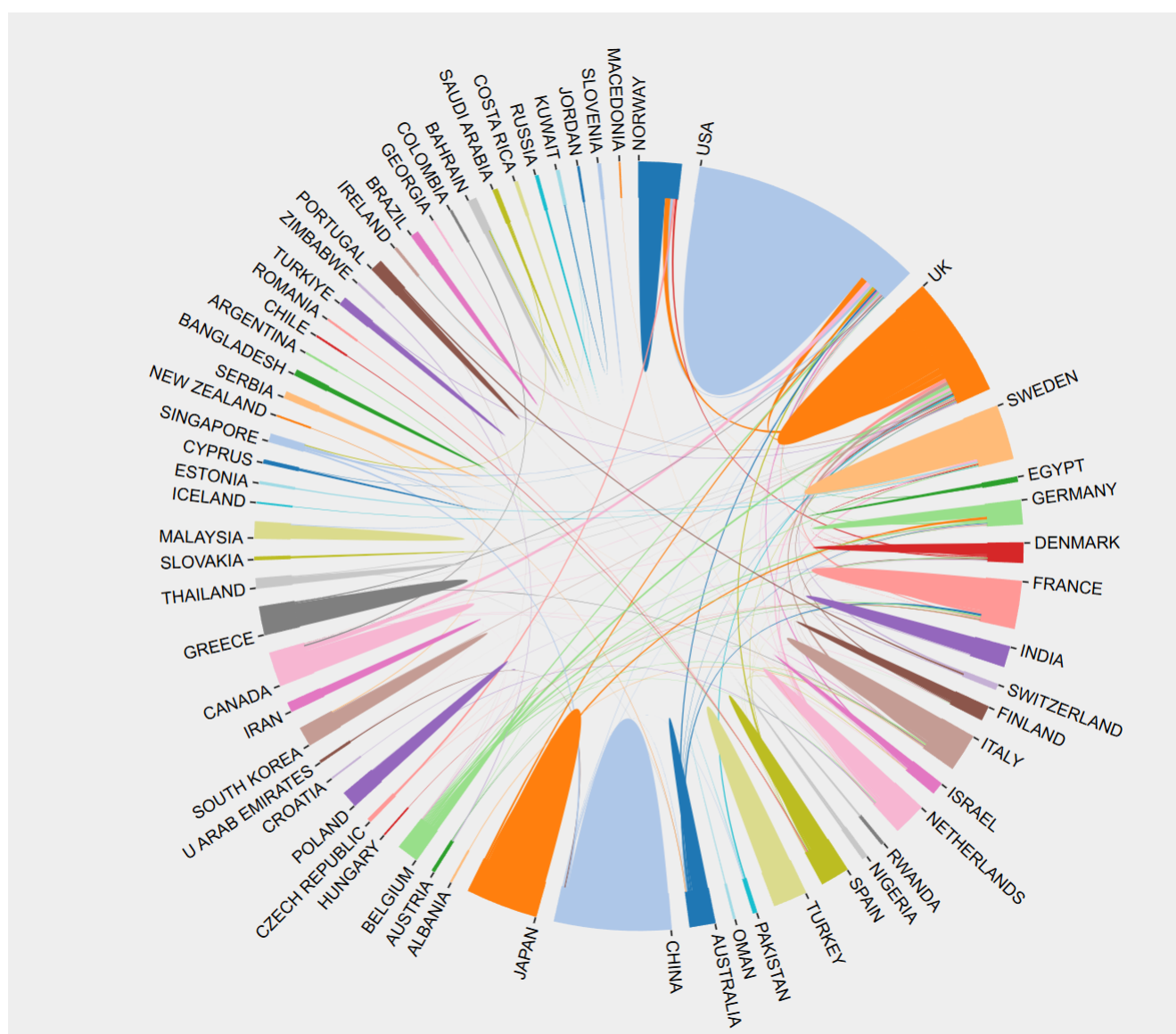


Figure 2. Country collaboration network map

3.6. Keyword co-occurrence analysis

Figure 3 shows the keyword co-occurrence network for SPGB research from 1995 to 2025. The size of the nodes in the network indicates the frequency of keyword occurrences, the thickness of the connections represents the strength of co-occurrence, and different colors represent independent thematic clusters. The red cluster is centered around “asthma”, “histamine”, “substance-p”, and “allergen”, with frequencies of 34, 28, 22, and 20, respectively, revealing that the neuroimmune regulatory mechanisms of SPGB in asthma and allergic reactions were early research hotspots. The green cluster revolves around “migraine”, “pain”, “cluster headache”, and “sphenopalatine ganglion”, all with frequencies >30, indicating that headache management is the main line of clinical research. The blue cluster is dominated by “double-blind”, “randomized controlled trial”, “safety”, and “efficacy”, with frequencies ranging from 25 to 40, reflecting the increasing number of high-quality RCTs in recent years and the emphasis on improving the level of evidence. The central node

“sphenopalatine ganglion block” has a degree of 126, connecting the three major themes, confirming its status as a core concept. The newly added high-frequency terms in the past five years, “ultrasound-guided” and “cooled radiofrequency”, are migrating towards the blue cluster, indicating that technological innovation is reshaping research design. The overall network density is 0.14, and the modularity Q value is 0.52, indicating that research themes are clearly differentiated but lack sufficient cross-domain integration. Future efforts should focus on strengthening the connection between mechanistic studies and clinical trials to promote the formation of precision intervention plans.

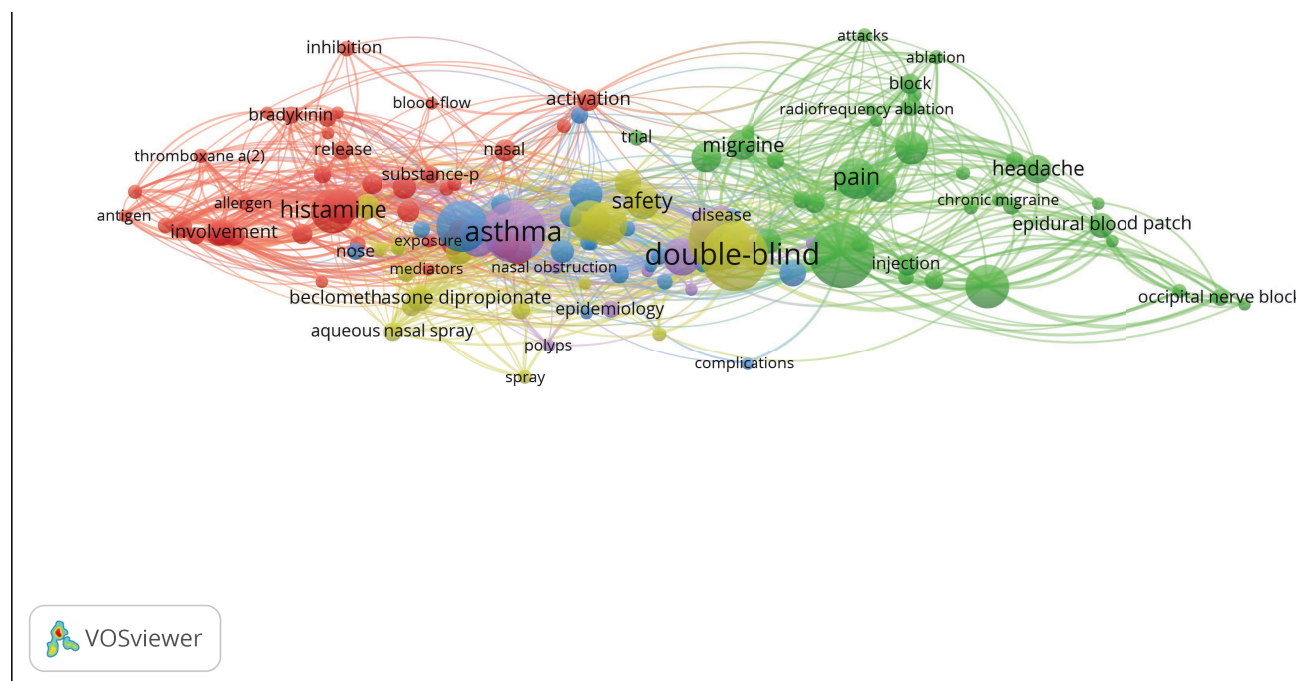


Figure 3. Keyword co-occurrence network

3.7. Keyword temporal overlay analysis

Figure 4, based on VOSviewer, presents the keyword temporal overlay network for SPGB research from 1995 to 2025. The color of the nodes indicates the year the keyword first appeared, the size reflects the frequency of occurrence, and the connections signify co-occurrence relationships. The network centers on “sphenopalatine ganglion block” (first appeared in 1995, frequency 230), radiating outward to form three thematic evolution rings: the early period (1995–2005) was dominated by “asthma”, “allergy”, and “histamine” (blue-violet area), revealing the neuroregulatory mechanisms of SPGB in allergic reactions; the middle period (2006–2015) shifted to “migraine”, “cluster headache”, and “pain” (green area), focusing on the clinical application of headache management; and the recent period (2016–2025) added “double-blind”, “randomized controlled trial”, and “safety” (yellow area), indicating the standardization of research methodology and the improvement of the level of evidence. Peripheral burst terms such as “pulsed radiofrequency”, “ultrasound-guided”, and “epidural blood patch” (yellow nodes) suggest hotspots of technological innovation. The overall timeline shows that basic mechanistic research (left half-ring) and clinical translation (right half-ring) develop in a spiral, alternating pattern, with an average thematic iteration every six years. Future research will likely focus more on technological optimization and multimodal combined interventions.

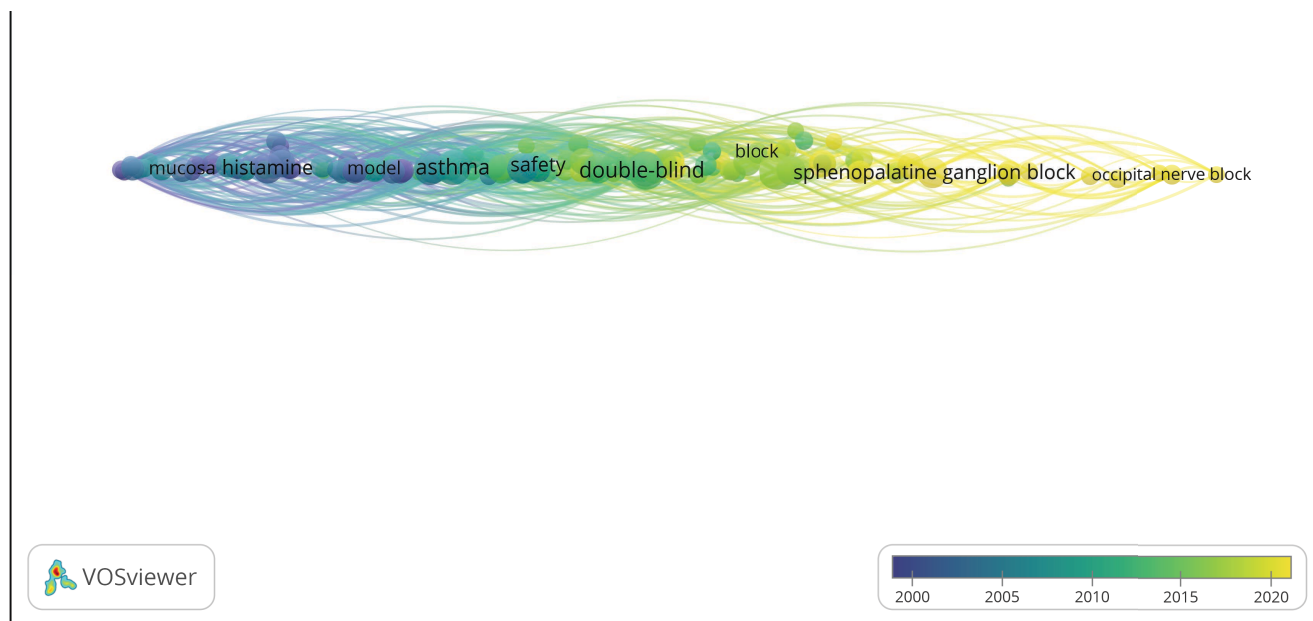


Figure 4. Keyword temporal overlay network

4. Discussion

This study systematically reveals the global development trajectory of sphenopalatine ganglion block (SPGB) research from 1995 to 2025 through bibliometric and visualization analyses. The results not only confirm the paradigm shift of this technique from a “niche intervention” to a “mainstream therapy” but also uncover the intrinsic logic and existing challenges of the field’s development through multidimensional indicators. Combined with the views of clinical experts, this can further deepen the understanding of the SPGB research ecosystem.

The exponential growth in annual publication volume and citation frequency (compound annual growth rates of 14.7% and 19.3%, respectively) indicates that SPGB research has transcended the technological infancy phase (1995–2005) and clinical validation phase (2006–2015) to enter a period of explosive growth (2016–2025). This trend is highly consistent with the practical observations of clinical experts: “SPGB is transitioning from an empirical operation to an evidence-based, precision-oriented technique, especially in the treatment of allergic rhinitis, where it shows potential to surpass traditional pharmacotherapy.” Notably, the phenomenon of slowing publication growth after 2023 while citations continue to rise reveals a “quality-first” shift in the field’s development—as pointed out by experts in the field of nerve block: “The current research focus has shifted from merely verifying efficacy to optimizing operational standardization (such as ultrasound-guided techniques) and long-term efficacy assessment”^[7].

High-output authors (such as Nabe T. and Mizutani N.) and institutions (such as Kyoto Pharmaceutical University and the University of Florida) form the dominant research forces, whose contributions have been evaluated by experts from the International Association for the Study of Pain (IASP) as: “Laying the theoretical foundation for SPGB’s transition from anatomical exploration to neuroimmune mechanism research.” However, the analysis of the institutional collaboration network shows that the global collaboration density is only 0.18 (significantly lower than the average of 0.31 in the field of pain medicine), confirming the concerns of clinical experts: “Geographical differences in technical operations (such as the transpalatal approach in Asia and

the transpterygoid approach in Europe and America) lead to difficulties in comparing research conclusions horizontally, and there is an urgent need to establish international consensus on operations”^[8]. This fragmented state directly restricts the conduct of multicenter RCTs.

Clinical research on SPGB is currently the most active and fruitful area. A variety of intervention techniques targeting SPGB have been developed and applied in clinical practice, especially in pain management. For example, cluster headache is the most successful and evidence-rich area for SPG modulation techniques^[9]. Given the close association between the pathophysiology of cluster headache and the excessive activation of the trigeminal autonomic reflex, SPG has become an ideal therapeutic target^[10]. Migraine: SPG also plays a role in the parasympathetic symptoms (such as tearing and nasal congestion) during migraine attacks and in pain transmission, making it a potential target for migraine treatment. Other painful conditions: SPG interventions have also been attempted for the treatment of trigeminal neuralgia, persistent idiopathic facial pain, postherpetic neuralgia, and some postoperative pains^[11]. Non-painful conditions: In addition, SPG modulation has been explored for the treatment of allergic rhinitis, which is related to its regulation of nasal mucosal secretion and vascular permeability^[12].

Main intervention techniques and their efficacy. Nerve block involves injecting local anesthetics into the pterygopalatine fossa through transnasal or transcutaneous approaches to temporarily block the neural conduction of SPG. This is a minimally invasive and relatively simple technique commonly used for the termination of acute headache attacks or diagnostic evaluation. Its advantage is rapid onset, but the duration of action is limited. Radiofrequency ablation/modulation uses the heat or electric field generated by radiofrequency current to ablate (ablation) or functionally modulate (pulsed radiofrequency) SPG to achieve long-term pain control. Compared with a nerve block, its effect is more durable. In recent years, the use of ultrasound or CT guidance for radiofrequency treatment has improved the precision and safety of the procedure. Nerve stimulation and modulation is one of the biggest breakthroughs in the field of SPG research in recent years. By implanting miniature electrode stimulators, patients can activate stimulation via an external remote control device during headache attacks to terminate the pain.

SPGB research has evolved from basic anatomical descriptions to precision clinical treatments centered on neuromodulation, especially achieving remarkable success in the field of headache management. The rapid development of clinical translation research has brought new hope to many patients with refractory pain. However, the progress of research also shows significant imbalances. The vigorous development of clinical applications contrasts sharply with the relative lag in basic research. At present, the understanding of the complex molecular networks and signaling pathways within the SPG is still preliminary, which, to some extent, limits the use of this method. Looking to the future, research in the SPGB field can focus on several key areas: deepening molecular mechanism studies to investigate the upstream and downstream pathways, interaction networks, and dynamic changes of key signaling molecules within the SPG under pathological conditions; introducing cutting-edge research technologies such as optogenetics and CRISPR-Cas9 to achieve high-precision parsing of neural circuits and gene functions; continuing large-scale, multicenter randomized controlled trials to further clarify the efficacy, indications, optimal stimulation parameters, and long-term safety of SPG neuromodulation techniques for different types of diseases; and promoting the integration of basic and clinical research by establishing closer cooperation mechanisms to feed clinical observations back to basic laboratories for mechanistic verification and rapidly translating new findings from basic research into new clinical treatment strategies.

Disclosure statement

The authors declare no conflict of interest.

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Patent Foramen Ovale and Migraine: A Bibliometric and Knowledge Mapping Analysis Based on the Web of Science

Xiaodi Chen^{1,2}, Zhiyang Lv^{1,3*}

¹The First College of Clinical Medical Science, China Three Gorges University, Yichang 443003, Hubei, China

²Department of Ultrasound, Yichang Central People's Hospital, Yichang 443003, Hubei, China

³Department of Cardiology, Yichang Central People's Hospital, Yichang 443003, Hubei, China

*Corresponding author: Zhiyang Lv, lvzhiyang@ctgu.edu.cn

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Abstract: *Objective:* To evaluate research trends, collaborative networks, and thematic evolution in studies on patent foramen ovale (PFO) and migraine from 2005 to 2025 using bibliometric methods. *Methods:* The study searched the Web of Science Core Collection for 2005–2025 publications on PFO and migraine, including only English-language articles and reviews. After screening, 737 records were identified. Bibliometric analysis using VOSviewer mapped annual publication trends, co-authorship and institutional networks, co-citation patterns, and keyword co-occurrence. *Results:* Publication output increased overall, with an initial rise followed by a plateau (2011–2017) and renewed growth after 2018. The United States, Europe, and China were the leading contributors, forming a global network. Top institutions and prolific authors led the co-authorship network, and publications spanned cardiology and neurology journals, reflecting the field's interdisciplinary nature. Keyword co-occurrence revealed major themes (e.g., PFO closure, migraine with aura, stroke risk) spanning mechanisms to clinical management. Reference co-citation analysis highlighted foundational studies and clinical trials that established the field's knowledge base. *Conclusion:* Research on the PFO-migraine connection expanded over two decades. After early growth followed by a mid-period lull (amid inconclusive trials), the field resurged after 2018 with new advances and evidence of benefit in select patients. Ongoing interdisciplinary collaboration and increasing output suggest this field will continue to grow, providing new insights for potential clinical application.

Keywords: Patent foramen ovale; Migraine; Bibliometric analysis; Collaboration; Co-citation; Keyword co-occurrence

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1. Introduction

Migraine is a common neurological disorder, while patent foramen ovale (PFO) is a congenital cardiac opening present in roughly 25% of adults. Studies have observed a higher prevalence of PFO among migraine patients—particularly those with aura—suggesting a potential pathophysiological link ^[1]. The hypothesized mechanism

involves right-to-left shunting of microemboli or vasoactive agents through the PFO, which could trigger migraine attacks. Early clinical trials investigating PFO closure for migraine yielded mixed results, but interest in this potential therapy has persisted. Recent evidence, including a 2024 meta-analysis, indicates that PFO closure can modestly reduce migraine frequency in selected patients ^[2]. Nevertheless, PFO closure is not currently recommended as a routine migraine treatment, and research continues to focus on identifying which patients may truly benefit from this intervention. Consequently, the past two decades have seen a growing volume of literature exploring the PFO-migraine relationship. To elucidate the trajectory of this interdisciplinary field, the study conducted a bibliometric analysis of PFO-migraine research (2005–2025) to characterize publication trends, collaboration networks, and emerging themes.

2. Methods

2.1. Data source and search strategy

The authors searched the Web of Science Core Collection (2005–2025) for publications addressing the relationship between patent foramen ovale (PFO) and migraine. The search strategy used a topic-based query: TS = (("patent foramen ovale" OR PFO OR "foramen ovale, patent") AND (migraine OR "migraine with aura" OR "migraine without aura")). Only English articles and reviews were included. After screening, 737 records (570 articles, 167 reviews) were analyzed.

2.2. Data analysis tools

Bibliometric indicators were evaluated using VOSviewer 1.6.20. Annual publication trends, co-authorship and institutional collaborations, co-citation patterns, and keyword co-occurrence networks were generated. Prolific authors, institutions, journals, and high-frequency keywords were identified to assess research productivity, collaboration, and thematic evolution in this field.

3. Results

3.1. Annual publication trends

As shown in **Figure 1**, the annual number of publications in this field exhibited a clear upward trend from 2005 to 2025. During the initial exploration stage (2005–2010), the annual output increased from 24 articles in 2005 to 52 articles in 2010, indicating growing academic attention to this emerging interdisciplinary topic. Between 2011 and 2017, publication output fluctuated, with slight declines in some years, likely reflecting controversies over clinical trial results and methodological adjustments, suggesting a period of validation and refinement. Since 2018, publication numbers have steadily rebounded, peaking in 2021 (40 articles) and 2024 (62 articles), marking renewed research interest in the relationship between PFO and migraine. Cumulative publications followed an exponential growth pattern ($R^2=0.8715$), highlighting the sustained expansion of research productivity. This resurgence is closely associated with advances in diagnostic techniques, improvements in closure devices, and the application of interdisciplinary approaches, attracting more researchers to the field. Given this trajectory, the field is expected to remain active with broad potential for further development.

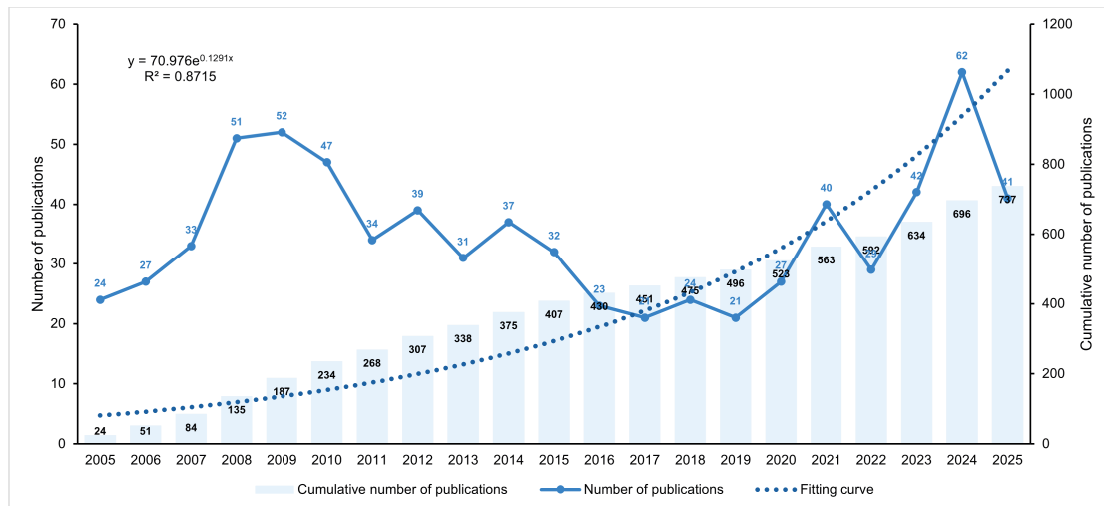


Figure 1. Annual publication trends (2005–2025) in PFO-migraine research

3.2. National and institutional collaboration networks

The global country collaboration map (**Figure 2**) revealed the structural characteristics and academic influence of international research networks. The United States, Italy, Germany, the United Kingdom, and China emerged as primary research centers, with high output and frequent collaborations. The United States, leveraging strong research capacity and interdisciplinary resources, established a wide-reaching network, collaborating closely with the UK, the Netherlands, and Canada, and extending partnerships to Middle Eastern countries such as Saudi Arabia, the UAE, and Egypt. European nations showed intensive intra-regional collaborations, with Italy, Germany, France, and Spain forming concentrated clusters, reflecting strong academic traditions. In Asia, China and Japan ranked among the leading contributors and gradually integrated into the global core through collaborations with Western countries. Particularly, China demonstrated a rapidly increasing influence supported by large research teams and expanding international ties. Overall, the field displayed cross-regional concentration, with core research power clustered in Europe, North America, and East Asia, while emerging regions such as the Middle East and South America mainly entered the network via collaboration with core countries.

At the institutional level (**Figure 3**), U.S. institutions dominated the collaboration network, with the University of California, Los Angeles (UCLA), Mayo Clinic, and Harvard University positioned at the core. UCLA produced the largest output (33 articles, 2007 citations), highlighting both productivity and impact (**Table 1**). University Hospital Bern and Mayo Clinic (16 articles each) and Harvard University (15 articles) also ranked among the leading institutions. In China, Sichuan University (15 articles) and other universities such as Capital Medical University and Jilin University have gained increasing visibility, though their citation averages remain comparatively low (e.g., Sichuan University, 5.6 citations per paper). In Europe, the Frankfurt Cardiovascular Center and the University of Bologna, together with clinical hospitals, formed active clusters with strong contributions to multicenter trials and clinical studies. Notably, cross-continental collaborations, particularly U.S.–China and U.S.–Europe partnerships, were frequent, reflecting the shift toward a multi-institutional, international research model.

Table 1. Top 10 institutions by publication output and citation impact

Institution name	Total number of articles	Total citations	Average citations
Univ Calif Los Angeles	33	2007	60.8182
Univ Hosp Bern	16	661	41.3125
Mayo Clin	16	549	34.3125
Sichuan Univ	15	84	5.6
Rovigo Gen Hosp	15	219	14.6
Harvard Univ	15	1327	88.4667
St Antonius Hosp	12	313	26.0833
Jilin Univ	12	170	14.1667
Univ Hosp Gasthuisberg	10	286	28.6
Cardiovasc Ctr Frankfurt	10	228	22.8

3.3. Prolific authors and collaboration patterns

Author productivity analysis (**Table 2**) showed that research output was concentrated among several leading scholars. Jonathan M. Tobis ranked first (18 articles, 992 citations), followed by Bernhard Meier (16 articles, 486 citations). Both played pioneering roles in studies on PFO closure and its relationship with migraine. Other highly productive authors included Horst Sievert (11 articles, 260 citations), Rubine Gevorgyan (9 articles, 444 citations), and Tobias Kurth (9 articles, 661 citations). Notably, Kurth's relatively few publications achieved high influence, with an average of 73 citations per article. The co-authorship network (**Figure 4**) further highlighted the central roles of Tobis, Meier, and Kurth, who formed a core group driving research directions. Team-based clusters were evident: Meier's network reflected broad international collaborations; Alessandro Padovani's group represented Italian contributions in clinical and pathophysiological studies; and Kurth's team emphasized combining mechanistic exploration with epidemiology. Authors such as Peter Wilmshurst and Horst Sievert contributed notably to methodological and technical innovations. Collectively, the author network exhibited a "core team + peripheral collaborators" structure, supporting knowledge diffusion and suggesting future growth through more cross-regional and interdisciplinary cooperation.

Table 2. Top 10 authors by publication output and citation impact

Author name	Total number of articles	Total citations	Average citations
Tobis, Jonathan M.	18	992	55.1111
Meier, Bernhard	16	486	30.375
Sievert, Horst	11	260	23.6364
Gevorgyan, Rubine	9	444	49.3333
Kurth, Tobias	9	661	73.4444
Wunderlich, Nina	9	228	25.3333
Sacco, Simona	8	188	23.5
Windecker, Stephan	7	293	41.8571
Tobis, Jonathan	7	249	35.5714
Post, Martijn C.	6	110	18.3333

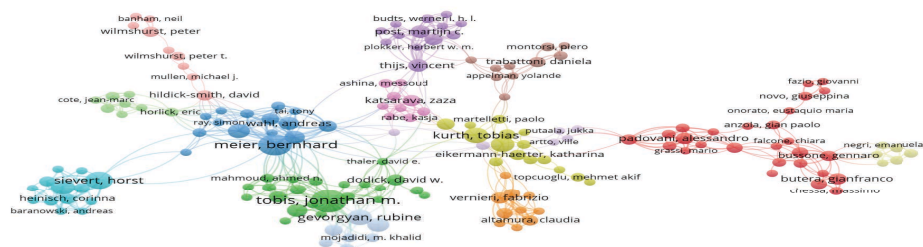


Figure 4. Author collaboration network in PFO-migraine research

3.4. Journal distribution

Analysis of publication venues (**Table 3**) showed that research outputs were distributed across both cardiology and neurology journals. Catheterization and Cardiovascular Interventions published the most articles (33), while neurology-focused journals such as Headache (29) and Cephalalgia (25) also ranked highly, reflecting the cross-disciplinary nature of the field. Impact varied: although Catheterization and Cardiovascular Interventions led in volume, their average citations were modest (22.9 per article). In contrast, Neurology published fewer papers (16) but achieved higher impact (848 total citations, 53 per article). The stroke-focused journal Stroke had 13 related articles, collectively cited 1796 times (138 per article), representing the highest influence. Other key journals included Journal of Headache and Pain, European Journal of Neurology, and International Journal of Cardiology. Overall, publication patterns emphasized the interdisciplinary position of PFO–migraine research, bridging interventional cardiology and neurology.

Table 3. Top 10 journals by publication output and citation metrics

Journal Name	Total Number of Articles	Total Citations	Average Citations
Catheterization And Cardiovascular Interventions	33	757	22.9394
Headache	29	681	23.4828
Cephalalgia	25	932	37.28
Frontiers In Neurology	22	158	7.1818
Neurological Sciences	21	217	10.3333
Neurology	16	848	53
Journal Of Headache And Pain	15	467	31.1333
Stroke	13	1796	138.1538
European Journal Of Neurology	10	158	15.8
International Journal Of Cardiology	10	171	17.1

Figure 5 and **Table 4** highlighted central themes. “Patent foramen ovale” and “migraine” were the most frequent terms, with “percutaneous closure” and “ischemic stroke” also ranking highly, reflecting dual focuses on mechanisms and interventions. The network revealed four major thematic clusters: (1) diagnostic and detection techniques, represented by “transcranial Doppler” and “right-to-left shunt”; (2) interventional and medical treatments, centered on “percutaneous closure” and “medical therapy”; (3) cerebrovascular complications, including “ischemic stroke”, “risk factors”, and “cerebral infarction”; and (4) pathophysiological mechanisms, focused on “migraine with aura”, “cerebral blood flow”, and “serotonin.” These clusters were interconnected, forming a comprehensive research chain spanning mechanisms, diagnosis, interventions, and complications. Emerging terms such as “percutaneous closure”, appearing more frequently after 2015, indicated the evolution of research focus in line with technological advances. Collectively, the analysis demonstrated a multidirectional and interdisciplinary structure, delineating the trajectory from mechanistic exploration to clinical application.

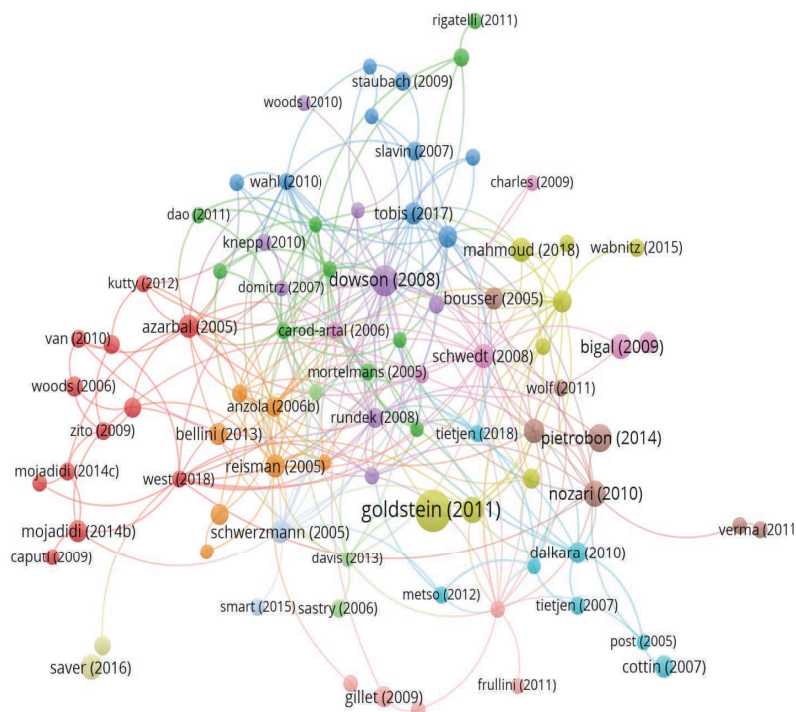


Table 4. Top 10 keywords by co-occurrence frequency

Rank	Frequency	Centrality	Time	Keyword
1	554	1.002	2015	Patent Foramen Ovale
2	441	0.8894	2015	Migraine
3	276	1.039	2014	Stroke
4	208	0.9501	2017	Percutaneous Closure
5	187	1.0867	2014	Aura
6	154	0.9079	2014	Closure
7	139	0.8552	2015	Cryptogenic Stroke
8	138	1.0242	2015	Risk
9	134	1.0937	2015	Headache
10	124	1.1924	2015	Ischemic Stroke

3.6. Reference co-citation analysis

The reference co-citation analysis (**Figure 6**) revealed the intellectual structure and knowledge base of PFO–migraine research. Key studies, such as Goldstein (2011), Dowson (2008), and Tobis (2017), were positioned at the core of the network, underscoring their pivotal roles in establishing theoretical frameworks and methodological foundations for subsequent investigations. These highly cited works primarily focused on the pathological links between patent foramen ovale (PFO) and migraine, diagnostic approaches, and interventional strategies. For instance, Goldstein (2011) provided critical clinical evidence and mechanistic insights, serving as a cornerstone reference for later research.

**Figure 6.** Co-citation network of references in PFO-migraine research

The network exhibited multiple clustered structures, each corresponding to distinct research directions. The cluster led by Dowson (2008) emphasized clinical trials and interventional studies, particularly on the efficacy of PFO closure for migraine relief. Another cluster, represented by Schwedt (2008) and Bigal (2009), focused on the epidemiology and pathophysiological mechanisms of migraine. Additional clusters highlighted the development and application of diagnostic techniques such as ultrasound and transcranial Doppler imaging. Node size indicated citation frequency, while the thickness of links reflected the strength of intellectual connections between references. The dense interconnections across clusters demonstrated the integrative nature of the field, bridging clinical practice with mechanistic and diagnostic research.

4. Discussion

This bibliometric analysis demonstrates that research on the patent foramen ovale (PFO)–migraine connection has expanded markedly over the past two decades, reflecting the interplay of clinical trial outcomes, technological advances, and interdisciplinary collaboration. After an initial phase of growth (2005–2010), publication activity plateaued between 2011 and 2017, largely due to inconclusive or negative findings from early randomized controlled trials such as MIST, which tempered initial enthusiasm despite anecdotal successes^[3]. This period of fluctuating output reflected a “validation and refinement” stage as investigators improved study designs and clarified methodological limitations. Since 2018, however, research has resurged, with peaks in 2021 and 2024, coinciding with emerging evidence that selected patients—particularly those with migraine with aura—may benefit from PFO closure. A pivotal pooled analysis of two RCTs demonstrated significant reductions in monthly migraine days and attacks compared with medical therapy alone^[4]. Such findings reinvigorated academic interest, and new trials like RELIEF are now refining patient selection criteria. The analysis of cumulative publications, showing an exponential growth pattern ($R^2 \approx 0.87$), indicates that the hypothesis remains a dynamic research domain, now driven by better selection strategies and interdisciplinary approaches.

The trajectory of this field underscores how evidence and research activity mutually influence one another. Early enthusiasm gave way to skepticism following equivocal trial results, yet instead of stagnating, the field adapted—adopting refined endpoints, improved imaging, and novel closure devices. Recent meta-analyses and systematic reviews now suggest that closure provides modest but clinically meaningful reductions in migraine frequency, particularly for migraine with aura^[2, 5]. This evolving evidence base has prompted cautiously optimistic perspectives in the literature and even guidelines. For example, the 2022 Society for Cardiovascular Angiography and Interventions (SCAI) guidelines acknowledged migraine as a potential indication for closure in highly selected cases, while cautioning that routine closure is not yet standard practice^[6]. The bibliometric results echo this narrative: after years of controversy, consensus is gradually emerging.

International collaboration has been central to progress. The United States and major European countries (Italy, Germany, UK) formed the core hubs of the collaboration network, consistent with their early involvement in PFO closure trials and robust clinical research infrastructure. These nations not only produced high output but also engaged in extensive cross-border collaborations, as exemplified by pooled patient-level meta-analyses that included investigators from multiple continents^[3]. Meanwhile, China has risen rapidly in publication output, though citation impact remains lower on average, likely due to its more recent entry. Nonetheless, Chinese groups, often through collaborations with Western centers, are becoming integral contributors,

signaling a broader global commitment. The network also highlights emerging contributions from the Middle East and South America, usually through partnerships with core countries, reflecting the increasing global relevance of PFO–migraine research. The fact that migraine is a worldwide condition and PFO occurs in roughly a quarter of adults underscores the universal importance of this interdisciplinary question ^[6].

At the institutional level, influential centers such as UCLA, Mayo Clinic, Harvard, and University Hospital Bern have shaped much of the evidence base, driven by senior investigators including Jonathan Tobis and Bernhard Meier. These institutions not only generated high productivity but also led pivotal trials such as PREMIUM and PRIMA ^[3–4]. Their prominence reflects both leadership and capacity for large-scale, multicenter studies, which are essential when outcomes hinge on enrolling appropriate subgroups such as patients with migraine aura or large right-to-left shunts. The strong U.S.–Europe links, and more recently U.S.–China partnerships, highlight the increasingly multi-institutional character of research in this field. This trend mirrors a broader pattern in medicine where complex problems require multidisciplinary expertise and multicenter collaboration to generate adequately powered results.

The analysis also shows that research output is concentrated among a relatively small group of prolific authors, such as Tobis, Meier, and Tobias Kurth, who have driven progress across both interventional and epidemiological dimensions. These leaders have acted as bridges between cardiology and neurology, ensuring that both clinical procedure data and neurological outcomes were rigorously evaluated. Co-authorship clusters centered on European, U.S., or Italian teams reflect national strengths, but the interconnectedness of these clusters underscores the importance of knowledge diffusion across borders. Emerging researchers often collaborate with these core leaders, accelerating interdisciplinary learning and hypothesis testing. This network structure has helped unify what could otherwise remain fragmented fields of cardiology and neurology into a more integrated research community.

Journal distribution further underscores the interdisciplinary nature of the field. While cardiology journals such as *Catheterization and Cardiovascular Interventions* lead in volume, neurology journals like *Headache* and *Cephalalgia* also rank highly, ensuring findings reach both specialties. Some of the most influential studies appeared in high-impact outlets such as *Neurology* and *Stroke*, where a few pivotal articles accrued disproportionate citations—e.g., Schwerzmann et al. (2005, *Neurology*) and West et al. (2018, *Stroke*) ^[7–8]. This reflects the cross-disciplinary importance of major breakthroughs, which attract a broad readership. However, the wide dispersion across journals risks siloing knowledge, underscoring the value of systematic reviews and meta-analyses in integrating findings for both audiences, as demonstrated in the 2024 review by Silalahi, which pooled RCTs and observational studies and found that PFO closure reduces monthly migraine days and attacks with a favorable safety profile ^[2]. Recent pooled analyses highlight consistent though nuanced benefits of closure, particularly in aura patients, helping clinicians reconcile disparate findings and offering guidance on patient selection.

Thematic analysis of keywords revealed an evolution from pathophysiological exploration to clinical application. Early focus on cerebral blood flow, serotonin, and right-to-left shunts laid the mechanistic groundwork, while recent terms emphasize closure devices, therapy, and migraine outcomes. These clusters form an interconnected research chain, from mechanism to diagnosis to intervention. This aligns with recent hypotheses suggesting platelet activation as a unifying mechanism, potentially linking microembolic phenomena and serotonin release to migraine pathogenesis, as supported by the LEARNER study, which demonstrated increased prothrombotic platelet activation and microvesicles in migraine with aura patients—changes that reverted after

PFO closure^[9]. Migraine with aura has emerged as a key theme, not only associated with higher PFO prevalence but also with a greater likelihood of benefit from closure^[3, 6]. The overlap between migraine and stroke further demonstrates how PFO-related research transcends disease categories, often integrating outcomes relevant to both conditions.

The co-citation analysis highlights the intellectual foundation of the field, centered on landmark studies such as Dowson's MIST trial, observational analyses by Wilmshurst, and subsequent early interventional trials. Although many of these early studies were inconclusive, they remain heavily cited as reference points for subsequent work. Despite progress, critical uncertainties remain regarding the precise mechanism by which PFO contributes to migraine and the identification of responders to closure. Current research increasingly embraces a multifactorial model, suggesting that no single explanation suffices.

5. Conclusion

In summary, PFO–migraine research has evolved from initial enthusiasm, through controversy, to a renewed evidence-based trajectory. The findings illustrate how global collaboration, interdisciplinary integration, and iterative refinement of methodology have advanced the field. While closure is not yet routine therapy for migraine, accumulating evidence suggests that in carefully selected patients—particularly those with aura—meaningful benefit is achievable. Ongoing randomized trials, mechanistic studies, and advances in biomarkers and imaging are likely to further refine patient selection and therapeutic strategies. With sustained collaboration across cardiology, neurology, and imaging, what began as a clinical observation may yet translate into tangible, individualized treatments for patients living with migraine linked to a “hole in the heart.”

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Disclosure statement

The authors declare no conflict of interest.

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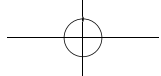
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