

Randomized Control Trial

Ultrasound-Guided Stellate Ganglion Block for the Treatment of Chronic Migraine in Adults: Study Protocol for a Randomized, Open-Label, Blinded Endpoint Trial

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Background: Chronic migraine (CM) is a recurring disorder with a relatively poor prognosis. Microinvasive and nonpharmacological therapies are essential for refractory patients with this condition. To date, only nonrandomized trials have reported the efficacy of the stellate ganglion block (SGB) for CM patients. Whether a combination of SGB and drug therapy is an optimal treatment for CM patients must still be confirmed with randomized controlled studies utilizing standardized oral medications as a control.

Objective: To assess the efficacy and safety of the repeated administration of SGBs over a 4-week period on the basis of standardized oral medications for reducing the severity and number of migraine episodes during the course of a 6-month trial in CM patients for whom prophylactic treatment has failed. The aim of this study was to provide more effective nonpharmacological therapies.

Study Design: A prospective, randomized, open-label, blinded endpoint trial.

Setting: A pain clinic in Beijing, China.

Methods: CM patients from 18 to 65 years of age will be enrolled. Patients unresponsive to migraine prophylaxis will be randomly assigned to receive either SGB with standardized drug therapy (SGB group) or standardized drug therapy alone (drug group) in an effort to determine the efficacy of SGBs for the treatment of CM.

Results: The efficacy and safety of the SGB as a CM treatment will be compared to those of the SGB in combination with drug therapy. Differences in pain relief and functional improvement will be assessed. The primary outcome is the change in mean monthly (defined as a 4-week time span) migraine days during the 6-month follow-up period following the patients' first SGB treatment. Secondly, analgesic medication requirements, quality-of-life assessments, and any SGB complications will also be addressed during the 6-month follow-up period.

Limitations: Neither the investigators nor the patients were blinded to treatment allocation. Additionally, this is a short-term follow-up study.

Conclusions: This study is a randomized controlled trial with a relatively large sample size to demonstrate the potential benefits of combined SGBs and drug therapy for CM patients. In the short term, this combined therapy will likely optimize CM treatment management. Further research will be needed to assess the efficacy of this treatment as a long-term therapeutic option.

Key words: Chronic migraine, stellate ganglion block, monthly migraine days, analgesic effects

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Migraine is essentially a recurrent syndrome accompanied by headache, nausea, vomiting, and increased sensitivity to visual, auditory, and olfactory stimuli as well as skin irritation (1). The specific cause of migraine has yet to be established, and its pathophysiology is also not fully understood. Previous studies have shown that the activation of a mechanism deep in the brain results in the release of pain-producing inflammatory substances around the nerves and blood vessels of the head, inducing a headache (2). Based on the frequency of the headaches, migraine can be differentiated into the categories of episodic migraine (EM) and chronic migraine (CM) (3). As one of the most common neurological disorders, migraine affects approximately 18% of women and 6% of men, while CM affects 2% of the global population (4,5). CM has been shown to be associated with higher levels of migraine-related disability, more severe comorbid medical and psychiatric conditions, and worse socioeconomic status and health-related quality of life than EM (6). Moreover, long-term efforts to cope with CM may also predispose patients to other illnesses. Hence, it is necessary to effectively treat CM.

The first-line treatment for CM is pharmacological, including acute treatments and prophylactic therapies. Although there are many medical options for acute treatment (7), a study conducted by Hirata et al demonstrated that the effectiveness of triptan, over-the-counter (OTC) drugs only, and prescription nonsteroidal anti-inflammatory drugs (NSAIDs)/acetaminophen (ACE) as methods of managing CM ranged from very poor to poor, at 60.9%, 43.1%, and 47.6%, respectively (8). There are various currently available pharmacotherapies for the prevention of CM recurrence (9,10,11). Despite the substantial availability of prophylactic treatment for CM, many patients have poor responses to conventional prophylaxis (12). Moreover, adherence to medications for the prevention of CM is poor, and the rate of CM patients' discontinuation of preventive therapy is also high (13,14). Hepp et al reported that only a minority of patients with CM (40%) had ever taken prophylaxis, and < 25% adhered to oral preventive medications one year after initiating treatment (15). A study from Richard et al found that only 28.9% of CM patients were actively taking migraine prophylaxis, and 79.7% of CM responders reported at least moderate disability (their scores on the Migraine Disability Assessment [MIDAS] were ≥ 11) (16). Thus, for patients with pharmacologically intractable

CM, other well-established and emerging therapeutic options are urgently needed.

The stellate ganglion block (SGB) involves using an anesthetic agent to block sympathetic ganglia in the lower cervical and upper thoracic regions (17). Since the 1940s, the SGB has been used to treat sympathetically mediated painful conditions, including complex regional pain syndrome types I and II, atypical facial pain, postoperative pain, and postherpetic neuralgia (18,19,20). The underlying mechanism for pain relief results from an inhibitory effect on the sympathetic nerves caused by restoring the sympathovagal balance, with a decrease in the blood concentration of norepinephrine and the production of inflammatory mediators, along with an accelerated metabolism of nociceptive substances such as serotonin (21,22). Furthermore, studies have revealed that the SGB can alleviate most of the symptoms of migraine, possibly through the inhibition of sympathetic overactivity or the weakening of the vascular inflammatory response (23). An observational study conducted by Hou et al revealed that 81 migraine patients who underwent SGBs with 6 mL of 0.15% ropivacaine once a week for 4 consecutive weeks experienced significant reductions in the intensity and frequency of migraine attacks within 3 months (24). Yu et al demonstrated that 3 months after the last SGB treatment for elderly patients with migraines, the mean (SD) number of headache days per month significantly decreased, from 23.1(5.5) to 14.0(6.8) days, and 33/52 (64%) patients experienced at least a 50% reduction in acute medication consumption (25). Another report by Yu et al also showed that the SGB was beneficial for CM patients, with effective rates of 90.7%, 82.5%, and 71.1% after one, 2, and 3 months of the last SGB treatment, respectively (26). Similarly, a case report by Moon et al found that SGBs effectively treated CM in and improved the MIDAS scores of 2 patients who responded poorly to oral medications (27). Conversely, 3 previous case reports observed that patients experienced migraines that lasted intermittently for several months after they received SGBs (28-30). Given the above information, the efficacy of the SGB in treating migraine, especially CM, is still disputed, and there is a lack of prospective, randomized controlled studies with larger sample sizes. High-quality research is necessary to verify whether the SGB can effectively optimize CM treatment. We designed this clinical randomized controlled trial (RCT) with a relatively large number of patients to determine the effectiveness of combining the SGB with drug therapy for the treatment of CM.

OBJECTIVES

The primary objective of this trial is to determine whether 4 weeks of weekly standardized drug treatment, whether combined with repeated SGB administration or not, can improve the intensity and frequency of migraine attacks at 6 months (24 weeks). The effects of the intervention on patient safety and quality of life will also be evaluated.

Setting

The experiment is being conducted at Beijing Tiantan Hospital Affiliated to Capital Medical University. All researchers were trained using the same protocol, and all were required to have clinical experience with CM therapies before participating in this study.

Approval of the Study Protocol

The study protocol conforms to the Declaration of Helsinki and has been approved by the Ethics Committee of Beijing Tiantan Hospital (KY2023-263-03-02). The study has also been registered at ClinicalTrials.gov (NCT06322407).

Informed Consent

All enrolled CM patients who have fulfilled the eligibility criteria are being given a verbal explanation of the informed consent form the day before the procedure. Each enrolled patient will have had adequate time to consult with the researchers on any issues or concerns related to the study and to determine whether to participate in this trial. Enrolled patients will sign the written informed consent form and have the right to withdraw from the study at any time throughout its duration.

Study Population

Two hundred and six patients who meet the inclusion criteria will be enrolled in the study. The patients are being randomly assigned to the SGB group (SGB plus standardized drug therapy) or the drug group (standardized drug therapy) at a one-to-one ratio.

Preenrollment Evaluation

A preenrollment evaluation is being conducted to determine patients' demographic and preoperative information. Baseline variables, including age, gender, body mass index (BMI), education background, presence or absence of aura, pain laterality (left/right/bilateral), course of disease, previous treatment regimens (medication-based and nonmedication-based), mean numeric rating scale (NRS) score during episodes,

monthly migraine days (MMDs), quality of life, and comorbidities such as hypertension, diabetes mellitus, and sleep disorders are being recorded.

Inclusion Criteria

Patients visiting the pain clinic of Beijing Tiantan Hospital for CM treatment are being consecutively screened for the following criteria:

1. Being between 18 and 65 years of age
2. Having been diagnosed with CM in accordance with the International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria (31)
3. Not having previously received or failed preventive migraine treatment

Exclusion Criteria

Patients are excluded if any of the following criteria apply to them:

1. BMI < 15 kg/m² or > 35 kg/m²
2. Received SGB treatment before
3. History of other neurological diseases
4. History of severe cardiopulmonary, hepatic, or renal disorders
5. History of allergies to any of the drugs intended for use in the trial
6. Long-term use of opioid drugs
7. Coagulation abnormalities prior to SGB (activated partial thromboplastin time greater than 1.5 times the normal value)
8. An infection or mass near the puncture site
9. Changes in neck anatomic structure caused by radiotherapy or surgery
10. Pregnant or lactating
11. History of psychological disorders
12. Refusal to provide informed consent

Withdrawal Criteria

1. Adverse events (AEs, defined as negative or unexpected clinical symptoms across the entire study period) resulting in withdrawal from the study
 2. Showing no response to SGB in the intervention group
 3. Being lost to follow-up
 4. Undergoing other treatments in addition to this study protocol
 5. Voluntary withdrawal
- Any case of withdrawal will result in an immediate consultation managed by the study team, who are involved in decision-making and further monitoring of patients.

Study Interventions

Baseline data and eligibility will be assessed on the day of the visit when the treatment is assigned. All patients will receive only topiramate as the standardized preventive treatment, in accordance with the guidelines for CM treatment. Topiramate will be given at an initial low dose and then gradually increased until optimal effectiveness ensues, intolerable adverse events occur, or the maximum recommended dose is reached. During the 4-week titration period, our goal is to increase the dose to 25 milligrams/week until 50-100 mg/day is achieved, in accordance with the principle of the United States Prescribing Information (USPI) (32) and the European Summary of Product Characteristics (SmPC) (33). Ibuprofen will be given to relieve acute pain fewer than 11 times every month to avoid medication-overuse headache (MOH), and patients' drug usage will be recorded in their headache diaries (34). In addition to a combination of topiramate and ibuprofen, patients in the SGB group will receive an SGB once a week for 4 consecutive weeks. The interval between each separate SGB procedure will be one week (24). Patients with bilateral headaches will receive bilateral SGBs 40 minutes after the first side, and patients with unilateral headaches will receive SGBs on the ipsilateral side (27). The SGB procedures will be performed by the same experienced pain specialists. Patients will be placed in the supine position with slight hyperextension of the neck and will receive SGBs using the B-ultrasound visualization technique (Aurora A5 Ultrasound, Risco Tech Co., Ltd.). A high-frequency ultrasound probe (a 5-12 MHz linear array probe, 3L25H) will be scanned from the clavicle to the mandible to identify relevant landmarks before the procedure. On the short-axis (SAX) view, the prominent anterior tubercle of the C6 vertebra will be located, and the transverse process of the C7 vertebra will be identified by caudal scan. The thyroid, esophagus, prevertebral fascia (PVF), longus colli (LCo) muscle, and Chassaignac's tubercle will be found. After routine sterilization, a sterile 25-gauge 38-mm sterile needle (Becton Dickinson Medical [S] Pte., Ltd.) will be inserted using an in-plane technique just below the PVF on the surface of the LCo muscle. Subsequently, 5 mL of 1% lidocaine (Shanxi Jinxin Shuanghe Pharm Co., Ltd.) will be injected slowly while ensuring the upwards "floating" of the common carotid artery under continuous ultrasound-guided visualization. This process indicates drug diffusion into the surface of the LCo muscle on the medial side of the PVF at the level of the C6 anterior tubercle, confirming that the drug has reached the designated location. Then, the puncture site will be covered with a sterile dressing. The patient

will be monitored for at least 30 minutes to rule out any SGB-related complications. In the drug group, patients will receive only topiramate and ibuprofen oral therapy until the end of the study. After a 4-week observation period, the doctors will decide whether to continue previous treatment according to each patient's condition or to adjust the therapeutic regimen based on the efficacy of the previous treatment. During each 4-week observation cycle, patients will be required to use electronic diaries to document the frequency and severity of their migraine attacks, use of all migraine treatments, acute medications, caffeine consumption, and, if female, information about their menstrual cycles.

Follow-Up

Patients in both groups are required to observe a follow-up period for 6 months. The following data will be collected: MMDs, proportion of patients who achieved $\geq 50\%$ reduction in MMDs, total effective rate, mean NRS score during headache attacks, patient satisfaction (PS) score, HIT-6 (Headache Impact Test-6) score, MIDAS score, and Pittsburgh Sleep Quality Index (PSQI) score.

Study Outcomes

Primary Outcome

The main outcome is the change from the baseline in mean MMDs across the 6-month follow-up period. The baseline is defined as the number of migraine days in one month (defined as 4 weeks) prior to the first SGB treatment. A migraine day is characterized as one day with symptoms of migraine attack lasting for at least 30 minutes.

Secondary Outcomes

1. Proportion of patients who achieved a $\geq 50\%$ reduction in MMDs at 4, 8, 12, 16, 20, and 24 weeks (35)
2. Total effective rate at 4, 8, 12, 16, 20, and 24 weeks (36)
3. Mean NRS scores during migraine attacks at baseline and weeks 4, 8, 12, 16, 20, and 24
4. PS evaluated by the PS score (0 points indicates unsatisfactory, while 10 points indicate very satisfactory) at weeks 4, 8, 12, 16, 20, and 24 (37,38)
5. HIT-6 score assessed before randomization, at baseline, and at the 4-, 8-, 12-, 16-, 20-, and 24-month follow-up visits (39,40).
6. MIDAS assessed at baseline and at weeks 4, 8, 12, 16, 20, and 24 (41)

7. PSQI scores assessed at baseline and at weeks 4, 8, 12, 16, 20, and 24 (42)
8. Proportion of patients with AEs and serious adverse events (SAEs) at days 0, 1, 2, 3, 4, 8, 12, 16, 20, and 24 weeks

Data Management and Analysis

Sample Size

The main purpose of this study is to compare the prophylactic effect of combined SGB and drug therapy on CM 6 months after a patient's last procedure. Since the effect of the SGB is uncertain in adult patients with CM, the following assumptions are made based on the results obtained from elderly patients with migraines. Based on a review of the available literature and our team's previously published retrospective studies and clinical experience, the mean MMDs of the SGB group were approximately 14.0 days, and the SD was 6.8 days, while the MMDs of the drug group were approximately 23.1 days, with a SD of approximately 5.5 days. Reducing the MMDs by 6 days is clinically significant, based on both statistical calculation and clinical judgement. The number of patients required for each group is 82, as calculated by the Power Analysis and Sample Size software program Version 11 (PASS 11). Allowing for a 20% dropout rate, a total of 206 patients for the study would yield 90% power to detect the significant difference, applying a 2-sided alpha of 0.05.

Statistics

An independent statistician blinded to the entire study will analyze the data with IBM SPSS Statistics software (26.0, IBM). Multiple imputation methods will be used to deal with missing data. All efficacy endpoints of the intention-to-treat population will be analyzed. The normal distribution test will be conducted with the Kolmogorov-Smirnov test. Continuous variables will be expressed as mean \pm SD when normally distributed and compared with Student's t-test, or as median and interquartile range (IQR) when nonnormally distributed and compared with the Mann-Whitney U test. Categorical variables will be presented as numbers with percentages and compared using Pearson's chi-squared or Fisher's exact tests (when the expected values are < 5). The primary outcome will also be compared using Pearson's chi-squared or Fisher's exact tests. For the secondary outcomes, a repeated measures analysis of variance (ANOVA) model will be performed to detect differences over time from the baseline to 6 months,

using the Bonferroni post hoc correction for multiple comparisons. Multivariate analysis will be used to explore the contributing factors of primary and secondary outcomes. After the initial 103 patients are assessed, an interim analysis will be conducted to evaluate trial efficacy and safety. All tests will be 2-tailed, and $P < 0.05$ will be considered statistically significant.

Randomization, Allocation, and Blinding

Randomization will be performed on the day of enrollment. Eligible patients are being randomly allocated to either the SGB group (SGB plus standardized drug therapy) or drug group (standardized drug therapy). The allocation sequence will be performed by a random number table, which has been created through the block randomization method by a computer-generated list using the RAND function in Microsoft Excel (Microsoft Corporation). The arrangement block layering method was applied to ensure a balanced distribution of patients based on the selected major features. Four strata were generated according to gender (male, female), age (18-34 years, 35-49 years, 50-65 years), NRS scores (mild: score of 1-3, moderate: score of 4-6, and severe: score \geq 7) during attacks, and course of disease (3-12 months, 13-36 months, \geq 37 months). Each enrollment session was applied as a block in the permuted block randomization procedure, and each block had a different length. The allocation sequences will be prepared and kept in sealed, opaque, consecutively numbered envelopes by an independent statistician. After the patients enter the consultation room, a physician will open the package and subsequently make preparations according to the allocation schedule. This study is an open trial in which neither the patients nor the research clinicians are blinded to treatment allocation so that the physicians can care for the patients safely. Moreover, patients are also made aware of the treatment allocation to ensure their well-being and safety. However, to maintain objectivity, the endpoint assessors, data statisticians, and follow-up members are blinded to treatment allocation. Before study commencement, all researchers received standardized training on treatment strategies, assessment, and quality control. All interventions will be carried out in agreement with clinical practice guidelines.

Safe Assessment

During the follow-up period, the details of any AEs or adverse device effects reported by the patients will

be documented in the CRF. The record will include the reason, time of initiation, duration, severity, relationship with the intervention, therapeutic principles, and prognosis. The incidence of AEs will be reported by the patients and recorded by the researchers in charge of follow-up. SGB-related adverse events and complications such as hoarseness, dysphagia, dizziness, sore throat, upper limb numbness, headache, cough, dyspnea, hematoma, epidural and intrathecal anaesthesia, and more will be recorded by experienced pain physicians during SGB procedures and posttreatment follow-ups.

All AEs during the study period will be observed and recorded in the CRF in detail during the 6-month follow-up period. Once an AE occurs, it will be immediately reported to the institutional review board (IRB) and treated by the research team. SAEs leading to hospitalization or death will be reported to the ethics committee, competent authorities, and trial sponsors

within 24 hours. The trial will be monitored regularly and terminated instantly by the IRB if necessary. All AEs that occur during this study will be treated free of charge until the patients recover.

RESULTS

Patient Flow

The schedule of enrollment, interventions, and assessments during participation is shown in Table 1.

Enrollment

The first patient was enrolled in June of 2024. The study is intended to end around December of 2025. The flow chart of patient enrollment is presented in Fig. 1.

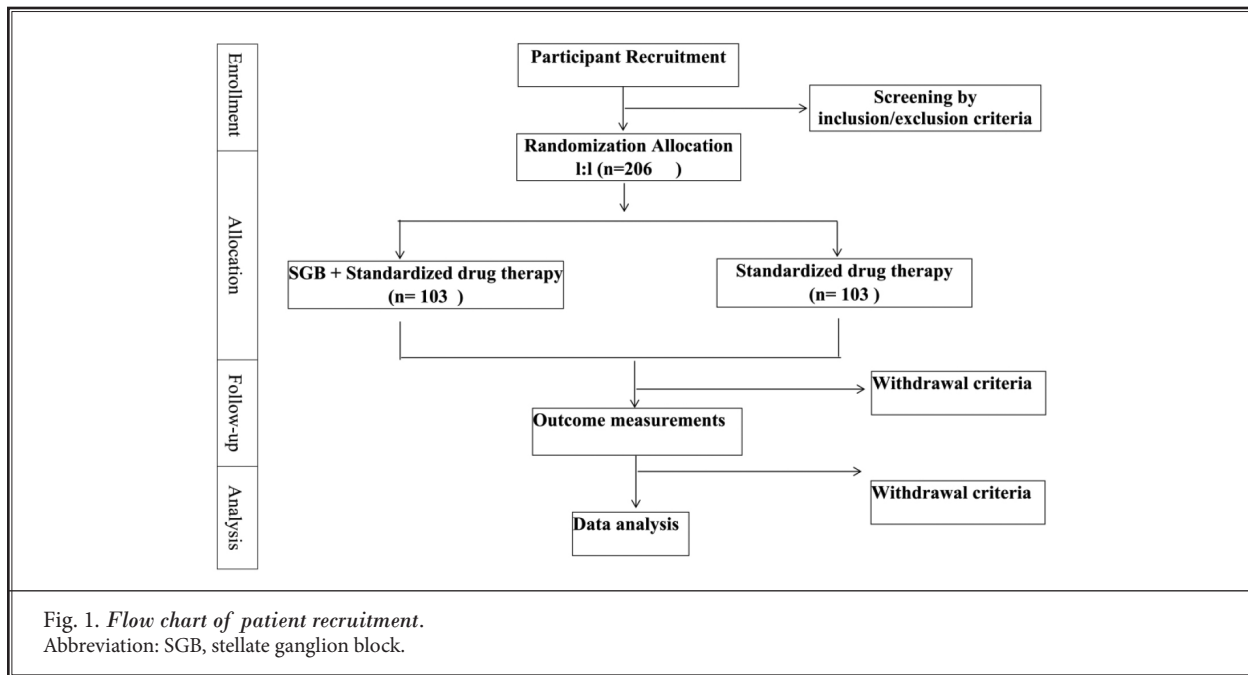
Baseline Data

Before randomization, the baseline variables, including demographic characteristics, preoperative

Table 1. *The schedule of enrollment and assessment.*

	Enrollment	Allocation	Post-Procedure									Close-Out
	0d	0d	+1 w	+2 w	+3w	+4w	+8w	+12w	+16w	+20w	+24w	
Enrollment												
Eligibility screening	×											
Informed consent	×											
Allocation		×										
Intervention												
SGB		×										
Medication management		×										
Assessment												
Baseline data	×											
Change from baseline in mean MMDs						×	×	×	×	×	×	
Proportion of patients achieved ≥ 50% reduction in MMDs						×	×	×	×	×	×	
Total effective rate						×	×	×	×	×	×	
NRS score during headache attack						×	×	×	×	×	×	
PS score						×	×	×	×	×	×	
HIT-6 score	×					×	×	×	×	×	×	
MIDAS score	×					×	×	×	×	×	×	
PSQI score	×					×	×	×	×	×	×	
Adverse events		×	×	×	×	×	×	×	×	×	×	

Abbreviations: d, day; w, week; SGB, stellate ganglion block; MMDs, monthly migraine days; NRS, numeric rating scale; PS score, patient satisfaction score; HIT-6, headache impact test version 6; MIDAS, migraine disability assessment; PSQI, Pittsburgh Sleep Quality Index.



data, and quality of life were recorded. The baseline data are being presented as shown in Table 2.

Data Analysis

The course of this study is proposed to run from June 2024 to December 2025 and will include 206 patients (103 patients in each group).

Efficacy

The MMDs, total effective rate, mean NRS score during headache attack, and quality of life (assessed by the HIT-6, MIDAS, and PSQI) on the day of operation and every 4 weeks after the operation will be shown for each patient in the 2 groups. Significant differences between these groups will be assessed. In addition, the response rates of both groups will be calculated and compared. The results will be presented as shown in Table 3.

Safety

The occurrence of all AEs will be identified by follow-up with the researchers. The details of AEs, such as reason, severity, duration, treatment, prognosis, etc., will be recorded and reported. The results will be presented as shown in Table 4.

DISCUSSION

The trial is an RCT with a relatively large sample size, meant to examine the analgesic effects of the SGB

as an adjuvant therapy option for CM patients and possibly provide guidance for CM management. As a PROBE study, this project has a lower cost, greater similarity to standardized clinical practice, and better application in routine medical care than previous studies with the same goals (43). To our knowledge, only a few past studies designed to confirm the effect of combined SGB and drug therapy on CM have been performed, and they were prospective controlled trials with small sample sizes. This study will provide novel advances in the efficacy and feasibility of the SGB as a treatment for CM.

Limitations

The current protocol also has some limitations. First, an open-label design instead of a blinded, placebo-controlled design will be used in this trial. Investigators and patients will not be masked to treatment allocation. As a result, the effect of the SGB may be overestimated. Secondly, the study period in this trial is limited to 6 months. Consequently, the long-term effectiveness of the SGB on CM cannot be assessed. Additionally, this study is a single-center trial. Therefore, it is essential to conduct multi-center studies with larger sample sizes to achieve more robust evidence.

CONCLUSION

This randomized controlled study aims to demon-

Table 2. Demographic characteristics and preoperative data.

		SGB Group	Drug Group	P value
Age (Years)	18-34			
	35-49			
	50-65			
Gender	Male			
	Female			
BMI (kg/m ²)	Mean ± SD			
Education background	Middle school			
	High school			
	University			
With aura				
Pain laterality	Left			
	Right			
Course of disease (months)	3-12			
	13-36			
	≥ 37			
Comorbidity	Hypertension			
	Diabetes mellitus			
	Sleep disorder			
NRS score during headache attack	1-3 score			
	4-6 score			
	≥ 7 score			
Mean MMDs	Mean ± SD			
Previous treatment regimens	Medication-based			
	Non-medication-based			
HIT-6 score	Mean ± SD			
MIDAS score	Mean ± SD			
PSQI score	Mean ± SD			

Abbreviations: SGB, stellate ganglion block; BMI: body mass index; NRS: numeric rating scale; MMDs: monthly migraine days; HIT-6, headache impact test version 6; MIDAS, migraine disability assessment; PSQI, Pittsburgh Sleep Quality Index.

strate that the combined application of SGBs and drug therapy is superior to drug-only treatment for the management of CM. It is highly probable that this combination treatment will further enhance and optimize CM management. However, further research is needed to evaluate the long-term efficacy of this treatment.

Table 3. The assessment of effectiveness between the 2 groups.

	Time Point	SGB Group	Drug Group	P value
MMDs	4 weeks			
Total effective rate (%)				
NRS score during headache attack				
HIT-6 score				
MIDAS score				
PSQI score				
MMDs	8 weeks			
Total effective rate (%)				
NRS score during headache attack				
HIT-6 score				
MIDAS score				
PSQI score				
MMDs	12 weeks			
Total effective rate (%)				
NRS score during headache attack				
HIT-6 score				
MIDAS score				
PSQI score				
MMDs	16 weeks			
Total effective rate (%)				
NRS score during headache attack				
HIT-6 score				
MIDAS score				
PSQI score				
MMDs	20 weeks			
Total effective rate (%)				
NRS score during headache attack				
HIT-6 score				
MIDAS score				
PSQI score				

Abbreviations: SGB, stellate ganglion block; NRS: numeric rating scale; MMDs: monthly migraine days; HIT-6, headache impact test version 6; MIDAS, migraine disability assessment; PSQI, Pittsburgh Sleep Quality Index.

Table 4. Complications following intervention.

	SGB Group n = 103	Drug Group n = 103	P-value
No complication			
Hoarseness			
Dysphagia			
Dizziness			
Sore throat			
Upper limb numbness			
Headache			
Cough			
Dyspnoea			
Haematoma			
Epidural and intrathecal anaesthesia			

Abbreviations: Data described number (%); SGB, stellate ganglion block

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