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Periprocedural intravenous heparin in patients with acute ischemic stroke treated with endovascular thrombectomy after intravenous thrombolysis

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OBJECTIVE The benefit-to-risk ratio of periprocedural heparin in patients treated with endovascular thrombectomy (EVT) after intravenous thrombolysis (IVT) remains unclear. This study aimed to evaluate the potential effects of periprocedural heparin on clinical outcomes of EVT after IVT.

METHODS The authors retrospectively analyzed patients from multicenter studies treated with EVT after IVT in the anterior circulation. The endpoints were unfavorable outcome (defined as modified Rankin Scale score ≥ 3 at 90 days), 90-day mortality, symptomatic intracranial hemorrhage (SICH), successful recanalization, and early neurological deterioration. Patients were divided into two groups based on whether they were treated with heparin (heparin-treated group) or not (untreated group), and the efficacy and safety outcomes were compared using multivariable logistic regression models and propensity score–matching methods.

RESULTS Among the 322 included patients (mean age 67.4 years, 54.3% male), 32% of patients received periprocedural heparin. In multivariable analyses, the administration of periprocedural heparin was a significant predictor for unfavorable outcome (OR 2.821, 95% CI 1.15–7.326; p = 0.027), SICH (OR 24.925, 95% CI 2.363–780.262; p = 0.025), and early neurological deterioration (OR 5.344, 95% CI 1.299–28.040; p = 0.029). Regarding successful recanalization and death, no significant differences between the groups were found after propensity score matching.

CONCLUSIONS The results showed that periprocedural heparin is associated with an increased risk of unfavorable outcomes and SICH in patients treated with EVT after IVT. Further studies are warranted to evaluate the utility and safety of periprocedural heparin.

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KEYWORDS stroke; thrombectomy; heparin; hemorrhage; prognosis; endovascular neurosurgery; vascular disorders

The superiority of endovascular thrombectomy (EVT) in acute ischemic stroke (AIS) patients with large-vessel occlusion in the anterior circulation has been demonstrated in randomized controlled trials.[1–4] Despite early and complete angiographic reperfusion, approximately 40% of patients treated with EVT could not achieve long-term functional dependence.[5] Thrombotic complications of the thrombectomy procedure and incomplete microvascular reperfusion might be detrimental to neurological recovery.[6,7] Periprocedural heparinization is a conventional practice in preventing thrombosis caused by interventional procedures, addressing factors such as endothelial injuries and catheter-induced stasis. Previous studies have suggested that periprocedural heparinization may de-

ABBREVIATIONS AIS = acute ischemic stroke; ASPECT = Alberta Stroke Program Early CT Score; END = early neurological deterioration; EVT = endovascular thrombectomy; IVT = intravenous thrombolysis; MR CLEAN-MED = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; PTR = puncture to recanalization; SICH = symptomatic intracranial hemorrhage; TOAST = Trial of Org 10172 in Acute Stroke Treatment.

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crease the formation of microthrombi and enhance microvascular reperfusion after EVT, potentially leading to improved clinical outcomes.[8,9] However, the increased risk of hemorrhagic complications offsets the potential beneficial effects of periprocedural heparin on clinical outcomes.[10]

Observational studies have reported that periprocedural heparin is associated with beneficial effects on clinical outcomes, without significantly increasing the risk of hemorrhagic complications.[11,12] However, in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN-MED) it was observed that the risk of symptomatic intracranial hemorrhage (SICH) was significantly higher in patients allocated to the periprocedural heparin group, and there was a nonsignificant association with worse functional outcomes.[13] Previous studies have suggested that intravenous thrombolysis (IVT) could lyse the distal thrombus fragments and change the composition of the thrombus to facilitate thrombectomy, while IVT could also cause distal embolization and potential risk of hemorrhage transformation.[14] Nevertheless, the benefit-to-risk ratio of periprocedural heparin in patients undergoing EVT after IVT remains unclear. Hence, we performed a retrospective multicenter study to evaluate the potential effects of periprocedural heparin on clinical outcomes of EVT after IVT.

Methods

Study Population

We included patients from two multicenter prospective studies, the Captor trial (ChiCTR1900025256, https://www.chictr.org.cn) and SINOMED SR trial (NCT04973332, clinicaltrials.gov), and a multicenter retrospective registry between January 2019 and January 2020. The inclusion criteria were 1) age ≥ 18 years; 2) AIS due to large-vessel occlusion in the anterior circulation confirmed by CT angiography, MR angiography, or digital subtraction angiography; 3) treatment with EVT after IVT; and 4) prestroke modified Rankin Scale (mRS) score < 2. The exclusion criteria were 1) no available data on periprocedural heparin use and follow-up information, 2) contraindications for IVT, and 3) coagulation factor deficiency or thrombocytopenia.

This study was approved by the local ethics committees and was performed in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments. Informed consent was waived due to the retrospective nature of this study.

Clinical and Imaging Data

Demographic data, medical history, procedure details, images, and laboratory data were retrospectively collected. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) and scores were recorded at baseline and at 24–48 hours after admission. Recovery of neurological function was assessed using the mRS. Radiological images were independently reviewed by two experienced neurologists (K.Y. and M.X.). Early signs of cerebral ischemia were assessed using the Alberta Stroke Program Early CT Score (ASPECTS).

Treatment

IVT was administered to eligible patients according to the American Heart Association/American Stroke Association guidelines within 4.5 hours from the time of symptom onset or when the patient was last known to be well.[27] EVT was performed by experienced neurointerventionists using stent retrievers, aspiration thrombectomy, or a combination of rescue therapies to achieve successful recanalization. The administration of periprocedural heparin was based on center policies and influenced by interventionalists' discretion and patient-related factors. In patients receiving heparinization, the bolus and infusion doses of heparin were determined based on center policies, for example, administering heparin at the bolus dose based on body weight and infusion dose at 1000 IU/hr, or administering heparin at half of the standard dose initially and then infusing the remaining dose 1 hour later. Patients were then divided in two groups based on whether they were treated with periprocedural heparin (heparin-treated group) or not (untreated group).

Clinical Outcome

An unfavorable outcome was defined as a 90-day mRS score of 3–6. Successful recanalization was defined as a modified Thrombolysis in Cerebral Infarction score of 2b or 3. Early neurological deterioration (END) was defined as an increment of at least 4 points at 24 hours after admission. SICH was defined according to the European Cooperative Acute Stroke Study (ECASS III) criteria.[15] Stroke subtypes were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[16]

Statistical Analysis

Continuous variables are presented as mean ± SD or median with interquartile range (IQR) based on the normality test, while categorical variables are presented as count and percentage. Differences in normally distributed variables were compared using the t-test, while nonnormally distributed variables were compared using the Mann-Whitney U-test. Categorical variables were compared using chi-square tests or Fisher's exact tests. Multiple imputations were used to handle missing data with chained equations.

We applied the propensity score–matching algorithm to minimize the potential effect of between-group differences in key variables. The propensity score was generated with variables with a p value < 0.1 in univariable analyses or with variables known to impact clinical outcomes. Patients were then matched in a 1:1 ratio based on the nearest-neighbor algorithm without replacement within the caliper distance of 0.2. We further applied multivariable logistic regression models to compare clinical outcomes between heparin-treated and untreated patients in unmatched and matched cohorts and reported the effect size as odds ratio and 95% CI. Multivariable models were adjusted for the covariates in the propensity score formula. In sensitivity analyses, we systematically investigated the interaction effects of periprocedural heparin on clinical outcomes within distinct subgroups, with a p value for

interaction < 0.05 as indicative of statistical significance. We explored the association of the time from puncture to recanalization (PTR) with unfavorable outcome by different heparin treatments. We also applied the generalized linear mixed model with the research center as a random effect and relevant covariates as fixed effects to reduce the center effects.

All statistical analyses were conducted with R statistical software version 4.2.2 (R Foundation for Statistical Computing), and a two-sided p value < 0.05 was considered to be statistically significant.

Results

Study Population

A total of 322 AIS patients (mean age 67.4 years, 54.3% male) treated with EVT after IVT were included from 19 centers in this study after excluding 1108 patients (Supplementary Fig. 1). Of these patients, 103 (32.0%) received periprocedural heparin during EVT, and the median dose was 3000 IU (range 2000–5000 IU). Patients who received periprocedural heparin had higher proportions of atrial fibrillation, hyperlipidemia, and recombinant tissue plasminogen activator thrombolytics; lower proportions of male sex, atherosclerosis, and cardioembolism stroke etiology; and lower systolic blood pressures and ASPECTS values (all p < 0.05) (Supplementary Table 1). After propensity score matching, 59 patients who received periprocedural heparin were matched to 59 patients who did not receive periprocedural heparin. The differences in the two treatment groups were reduced with an absolute mean difference ≤ 0.20 for variables that were included in the propensity score formula (Supplementary Fig. 2), except stroke etiology and thrombolytics (Table 1).

Clinical Outcomes

In univariable analyses, age, hypertension, diabetes mellitus, atrial fibrillation, hyperlipidemia, PTR time, fasting blood glucose, international normalized ratio, baseline NIHSS score, and ASPECTS were significantly associated with a 90-day unfavorable outcome (all p < 0.05) (Supplementary Table 2). After propensity score matching, the rates of unfavorable outcome were 44.1% and 62.7% in the heparin-treated and untreated groups, respectively (Fig. 1). The rates of SICH (16.9% vs 3.4%) and END (23.7% vs 10.2%) were also higher in the heparin-treated group than in the untreated group. The predicted probabilities of unfavorable outcome and their association with PTR time by different heparin treatments are presented in Fig. 2. The heparin-treated group had a higher predicted probability of unfavorable outcome given the same PTR time as the untreated group. The crude rates of clinical outcomes are shown in Supplementary Table 3. Periprocedural heparin was associated with an increased risk of SICH (OR 5.816, 95% CI 1.989–18.543; p = 0.002) and END (OR 3.629, 95% CI 1.572–8.577; p = 0.003) after EVT. In multivariable analyses, the administration of periprocedural heparin remains a significant predictor for unfavorable outcome (OR 2.821, 95% CI 1.15–7.326; p = 0.027), SICH (OR 24.925, 95% CI 2.363–780.262; p = 0.025), and END (OR 5.344, 95% CI 1.299–28.040; p = 0.029) (Table 2). Regarding outcomes of intracranial hemorrhage, successful recanalization, and death, no significant differences were found between the two groups before and after propensity score matching.

In subgroup analyses, there were no significant interaction effects on the probability of unfavorable outcome in different subgroups except sex (male: OR 6.000, 95% CI 2.035–19.485; female: OR 0.782, 95% CI 0.270–2.232; *P* for interaction = 0.009) (Supplementary Fig. 3). Furthermore, the associations between periprocedural heparin and unfavorable outcome (OR 2.821, 95% CI 1.126–7.071; p = 0.027), SICH (OR 24.925, 95% CI 1.498–414.686; p = 0.025), and END (OR 5.344, 95% CI 1.184–24.127; p = 0.029) were still significant in a generalized linear mixed model with center as the random effect (Supplementary Table 3).

Discussion

In the present study, we found that administration of periprocedural heparin in AIS patients treated with EVT after IVT was associated with worse functional outcome at 90 days and an increased risk of SICH, without significant differences in recanalization status and mortality after propensity score matching. Our findings suggested that periprocedural heparin might not provide a beneficial effect for patients treated with EVT after IVT.

Periprocedural heparinization is often used by interventionists in endovascular procedures to prevent thrombotic complications.[17] The Multi Mechanical Embolus Removal in Cerebral Ischemia (Multi MERCI) and Thrombectomy Revascularization of Large Vessel Occlusions in Acute Ischemic Stroke (TREVO 2) trials analyzed the effects of periprocedural heparin on clinical outcomes after EVT and observed that periprocedural heparin was independently associated with favorable functional outcomes and unrelated to hemorrhagic complications and mortality.[12,18] The potential benefits of heparin may be due to its inhibitive effects on platelet aggregation and thrombus formation, which could restore the incomplete reperfusion and dissolve neutrophil extracellular traps in the microvascular circulation.[7,19] However, these studies were limited by the small sample size and the heterogeneity of treatment strategies.

The MR CLEAN-MED study assessed the safety profile of periprocedural unfractionated heparin in patients treated with EVT and allocated patients to receive different doses of unfractionated heparin. The results suggested that routine periprocedural unfractionated heparin would increase the risk of SICH without benefiting functional recovery.[13] The retrospective analysis of the Acute Ischaemic Stroke Cooperation Group of Endovascular Treatment (ANGEL) registry study revealed that heparinization was significantly associated with an increased risk of SICH and a lower chance of functional dependence after EVT.[8] Thus, the therapeutic effect of heparin may be neutralized by the concern for hemorrhagic risks. Since there is no standard protocol for periprocedural heparin at present, heparin is empirically administered at the discretion of interventionists. The safety concern may impede periprocedural heparin from routine use in EVT.

TABLE 1. Baseline characteristics of propensity score–matched groups

	Untreated Group (n = 59)	Heparin-Treated Group (n = 59)	p Value
Mean age, y	70.0 (9.9)	69.1 (10.5)	0.639
Male sex, n (%)	33 (55.9)	28 (47.5)	0.461
Median SBP, mm Hg	142.0 [127.5, 159.5]	149.0 [138.0, 160.0]	0.181
Median DBP, mm Hg	85.0 [76.5, 90.0]	80 [74, 90.0]	0.466
Vascular risk factors, n (%)			
Hypertension	46 (78.0)	42 (71.2)	0.526
Diabetes mellitus	7 (11.9)	9 (15.3)	0.788
Atrial fibrillation	27 (45.8)	30 (50.8)	0.713
Hyperlipidemia	11 (18.6)	15 (25.4)	0.505
Smoking	11 (18.6)	15 (25.4)	0.505
Median baseline NIHSS score	15.0 [12.0, 19.5]	15.0 [12.0, 18.0]	0.746
Median baseline ASPECTS	8.0 [7.0, 10.0]	9.0 [7.0, 9.5]	0.608
TOAST class, n (%)			<0.001
Atherosclerosis	26 (44.1)	15 (25.4)	
Cardioembolism	30 (50.8)	21 (35.6)	
Other etiology	3 (5.1)	23 (39.0)	
Median OTP time, mins	275.0 [194.0, 365.0]	295.0 [229.0, 370.0]	0.299
Median PTR time, mins	70.0 [50.0, 115.0]	67.0 [50.0, 120.0]	0.761
Thrombolytics, n (%)			0.005
rt-PA	48 (81.4)	48 (81.4)	
Tenecteplase	7 (11.9)	0 (0.0)	
Other	2 (3.4)	1 (1.7)	
Unknown	2 (3.4)	10 (16.9)	
Anesthesia, n (%)			0.353
General anesthesia	14 (23.7)	9 (15.3)	
Conscious sedation	45 (76.3)	50 (84.7)	
Clot location, n (%)			0.177
MCA, M1	27 (45.8)	30 (50.8)	
MCA, M2	10 (16.9)	6 (10.2)	
ICA	14 (23.7)	8 (13.6)	
Other	8 (13.6)	15 (25.4)	
Rescue therapy, n (%)	17 (28.8)	23 (39.0)	0.331
Laboratory results			
Mean FBG, mmol/L	7.4 (2.1)	7.6 (2.9)	0.681
Median creatinine, μmol/L	66.8 [54.5, 74.4]	68.4 [55.0, 77.0]	0.576
Mean INR	1.06 (0.16)	1.07 (0.10)	0.477
Median APTT, sec	34.80 [30.25, 37.95]	28.70 [25.70, 34.80]	0.011

APTT = activated partial thromboplastin time; DBP = diastolic blood pressure; FBG = fasting blood glucose; ICA = internal carotid artery; INR = international normalized ratio; MCA = middle cerebral artery; OTP = onset to puncture; rt-PA = recombinant tissue plasminogen activator; SBP = systolic blood pressure.
Means are presented as mean (SD) and medians as median (IQR).

The crude proportion of unfavorable outcomes and hemorrhagic complications in patients treated with EVT after IVT was similar to that in a recent meta-analysis of 6 randomized controlled trials.[20] This highest level of evidence revealed that EVT after IVT had a small but insignificant advantage in functional outcomes (50.7% vs 49.0%) and successful recanalization (88.4% vs 84.3%). Although IVT could facilitate thrombectomy by lysing residual thrombus fragments and altering thrombus properties,[21] IVT was also involved in the development of distal embolization and SICH.[22,23] Wischmann et al. observed that periprocedural unfractionated heparin was significantly associated with an increased risk of unfavorable functional outcome, particularly in patients treated with EVT after IVT.[24] It is postulated that periprocedural heparin may interact synergistically with thrombolytic drugs to

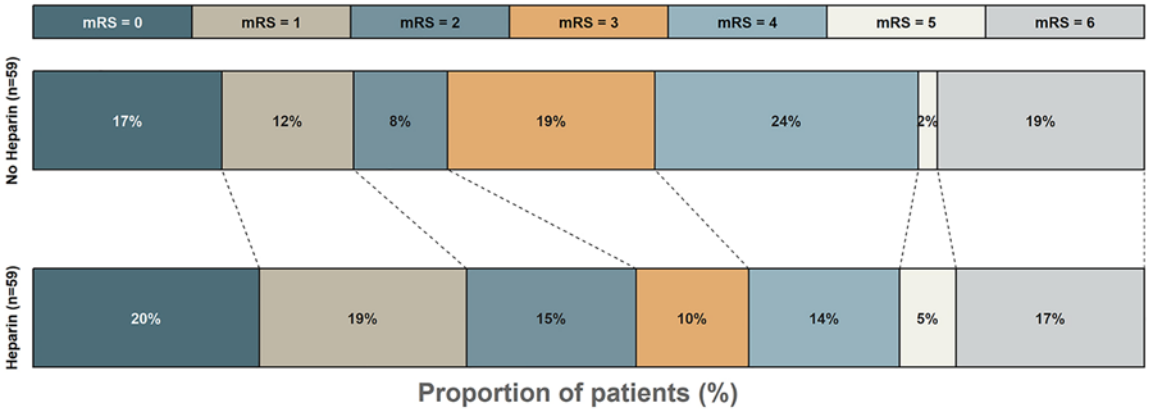

FIG. 1. Distribution of mRS scores at 90 days after propensity score matching. Figure is available in color online only.

increase the risk of hemorrhagic complications in patients with endothelial injury and prolonged operation time.[25] Meanwhile, the softening effects of heparin on thrombus may generate clot fragments and aggravate distal embolization related to IVT.[8] Thus, periprocedural heparin appeared to provide no benefit in AIS patients treated with EVT after IVT.

In line with previous studies, our study found that the rate of successful recanalization was not significantly different in heparin-treated and untreated groups. The post hoc analysis of the MR CLEAN-MED study indicated that the reperfusion status did not influence the harmful effect of periprocedural heparin after EVT.[10] Yang et al. found that newer-generation devices and thrombectomy techniques may overshadow the potential benefit of heparin on artery recanalization.[8] Zhu et al. retrospectively analyzed the efficacy of heparin during EVT in patients with tandem lesions and found that heparin was not associated with better angiographic outcomes.[26] They suggested that periprocedural heparin should be administered depending on relevant factors of comorbidities, infarct volume, and baseline medications, and antiplatelet therapy should always be the first choice, rather than heparin.

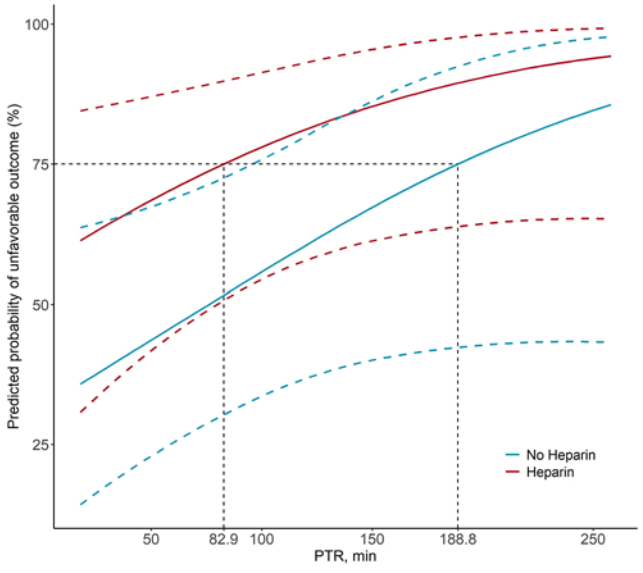

FIG. 2. Predicted probability of unfavorable outcome and association with PTR time. The graph illustrates the increase in the rate of unfavorable outcome as PTR progresses by different groups. *Solid lines* represent the predicted probabilities, and *dashed lines* indicate the corresponding 95% CIs. Figure is available in color online only.

To our knowledge, this is the first study to analyze the safety and efficacy outcomes of periprocedural heparin in patients treated with EVT after IVT. However, our study had several limitations. First, this was a retrospective study with a limited sample size, which might generate uncontrolled confounders and a lack of applicability. Second, the decision to use heparinization was based on center policies and influenced by the discretion of the interventionalists. Because heparin administration was not a standardized yes versus no decision, concerns of bias that affect the results could be raised. Although we tried to reduce center-related confounding by adjusting for the center effects, residual confounding may still exist; for example, centers using heparin more frequently may have better-equipped facilities. Third, we were unable to provide detailed information about the type of heparin and the flushing method during EVT. Fourth, we could not investigate the dose-dependent relationship between heparin and the risk of hemorrhagic complications. Fifth, merging the three datasets might generate potential biases because of the different inclusion and exclusion criteria. However, the inclusion and exclusion criteria of our study were included in the three datasets by limiting the time window and the occlusion site and excluding patients illegible for IVT as well as those with missing heparinization information. Finally, another limitation of our study was that neurointerventionalists checked activated partial thromboplastin time for coagulation function testing, which was comparable to activated clotting time. We could not detect the time-dependent changes of activated partial thromboplastin time and activated clotting time at different time points during hospitalization, which might provide additional information on the appropriate use of heparin.

TABLE 2. Clinical outcomes of propensity score–matched groups

	Untreated Group (n = 59)	Heparin-Treated Group (n = 59)	Unadjusted Model (heparin vs no heparin)		Adjusted Model (heparin vs no heparin)*	
			OR (95% CI)	p Value	OR (95% CI)	p Value
Unfavorable outcome: mRS score 3–6	26 (44.1)	37 (62.7)	2.135 (1.029–4.507)	0.044	2.821 (1.15–7.326)	0.027
SICH	2 (3.4)	10 (16.9)	5.816 (1.446–39.036)	0.027	24.925 (2.363–780.262)	0.025
ICH	14 (23.7)	20 (33.9)	1.648 (0.74–3.748)	0.224	2.046 (0.822–5.324)	0.130
Successful recanalization: mTICI score 2b or 3	53 (89.8)	51 (86.4)	0.722 (0.224–2.218)	0.570	0.705 (0.166–2.824)	0.620
END	6 (10.2)	14 (23.7)	2.748 (1.013–8.305)	0.056	5.344 (1.299–28.040)	0.029
Death	5 (8.5)	5 (8.5)	1.000 (0.264–3.786)	>0.999	0.924 (0.185–4.604)	0.921

ICH = intracranial hemorrhage; mTICI = modified Thrombolysis in Cerebral Infarction.
Values are given as number of patients (%) unless otherwise indicated.
* Variables in the model: age, sex, hypertension, diabetes mellitus, atrial fibrillation, hyperlipidemia, smoking, baseline NIHSS score, baseline ASPECTS, PTR time, fasting blood glucose, and international normalized ratio.

Conclusions

Our study found that periprocedural heparin was associated with an increased risk of unfavorable outcomes and SICH in patients treated with EVT after IVT. Further randomized controlled trials are warranted to evaluate the utility and safety of periprocedural heparin in EVT after IVT.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Wang, Yuan, Xie. Acquisition of data: Wang, Yuan, Huang, Zhong, Xie, Ye, Han, Lv, Zhao. Analysis and interpretation of data: Wang, Yuan, Zhong, Xie, Ye. Drafting the article: Wang, Yuan, Xie, Zhao. Critically revising the article: Liu, Wang, Huang, Zhong, Zhao. Reviewed submitted version of manuscript: Wang, Huang, Han. Approved the final version of the manuscript on behalf of all authors: Liu. Statistical analysis: Wang, Yuan. Administrative/technical/material support: Liu, Wang, Zhong, Zhao. Study supervision: Liu, Wang.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplementary Figures and Tables. https://thejns.org/doi/suppl/10.3171/2024.1.JNS232584.

Data Availability

The data that support the findings of this study are available from the corresponding author on reasonable request.

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