Research Article

To explore the influence of remote ischemic postconditioning on oxidative stress and neurological function in patients with ischemic stroke

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Abstract

Objective: The oxidative-antioxidant imbalance following ischemic stroke is a critical mechanism exacerbating neural injury. Remote Ischemic Postconditioning (RIPostC), as a non-invasive intervention, has not yet been fully elucidated in terms of its clinical antioxidant effects and molecular mechanisms. This randomized controlled trial aimed to evaluate the impact of RIPostC combined with conventional therapy on neurological function and the dynamic regulation of serum oxidative stress markers in patients with acute ischemic stroke (AIS). The study explores the influence of RIPostC on oxidative stress and neurological outcomes, providing a theoretical foundation and practical guidance for its clinical application and precision antioxidant therapy.

Methods: A prospective cohort study was conducted, enrolling 78 AIS patients admitted to the Department of Neurology, Affiliated Hospital of Youjiang Medical University for Nationalities, between October 2023 and January 2025. After strict screening based on inclusion and exclusion criteria, eligible participants were randomly allocated to either the control group (n=40) or the experimental group (n=38) using a random number table. The control group received standard treatment per the 2023 Chinese Guidelines for Acute Ischemic Stroke Management, including antiplatelet therapy, circulation optimization, neurotrophic support, lipid regulation, and plaque stabilization. The experimental group underwent additional bilateral upper-limb RIPostC before daily intravenous therapy. The procedure involved inflating pneumatic cuffs on both arms (1–2 cm above the elbow) to 200 mmHg for 5 minutes (ischemia), followed by complete deflation for 5 minutes (reperfusion), constituting one cycle. This intervention was performed twice daily (morning and evening) for seven consecutive days, totaling five cycles per session. Demographic data (gender, age), baseline pathologies (hypertension, diabetes, coronary artery disease, dyslipidemia), and lifestyle factors (smoking, alcohol use) were recorded. Neurological deficits were assessed using the National Institutes of Health Stroke Scale (NIHSS) and Modified Rankin Scale (mRS) on admission and day 7. Fasting venous blood was collected on days 1 and 7 to measure serum glutathione (GSH), superoxide dismutase (SOD), malondialdehyde (MDA), and nitric oxide (NO). Statistical analyses compared outcomes between groups.

Results: 1. Baseline characteristics: No significant differences were observed in gender, alcohol use, hypertension, diabetes, coronary artery disease, dyslipidemia, smoking, or baseline NIHSS/mRS scores (P>0.05), confirming comparability.
2. Neurological function: NIHSS and mRS scores decreased significantly in both groups by day 7 (P<0.05), with greater reductions in the experimental group (P<0.05).
3. Oxidative stress markers:
  ·MDA: No intergroup difference at baseline (P>0.05). Both groups showed significant reductions by day 7 (P<0.001), with lower MDA in the experimental group (P<0.05).
  ·GSH: Comparable at baseline (P>0.05). Increased in both groups by day 7 (P<0.001), with higher GSH in the experimental group (P<0.001).
  ·SOD: No baseline difference (P>0.05). Increased in both groups (control: P<0.05; experimental: P<0.001), with higher SOD in the experimental group (P<0.05).
  ·NO: Comparable at baseline (P>0.05). Increased in both groups (control: P<0.05; experimental: P<0.01), with higher NO in the experimental group (P<0.0001).
4. Safety: Seven adverse events were reported in the experimental group: transient limb pain/numbness (n=5) and minor subcutaneous petechiae (<1 cm, n=2). All resolved spontaneously within 24–72 hours post-treatment, with no systemic complications (e.g., blood pressure fluctuations, arrhythmias, or neurological deterioration).

Conclusion: 1. RIPostC significantly enhances neurological recovery in AIS patients, with greater improvements in NIHSS and mRS scores versus controls at day 7.
2. RIPostC restores oxidative-antioxidant balance, elevating SOD, GSH, and NO while reducing MDA. This suggests neuroprotection via lipid peroxidation inhibition and antioxidant system enhancement.

Keywords: Remote ischemic postconditioning; Acute ischemic stroke; Oxidative stress; Neuroprotection

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Introduction

Acute ischemic stroke (AIS) results from the narrowing or occlusion of cerebral arteries, leading to insufficient blood supply, subsequent cerebral hypoxia-ischemia, and ultimately, neuronal damage and necrosis, impairing brain function [1]. As a prevalent cerebrovascular disorder, AIS is characterized by its high morbidity, disability, and mortality rates [2], coupled with a pronounced tendency for recurrence, posing a significant threat to public health and imposing a heavy burden on patients, families, and socioeconomic development [3]. Clinically, AIS manifests as sudden-onset neurological deficits, such as limb weakness, slurred speech, and facial deviation. Diagnosis relies on clinical presentation, neuroimaging (e.g., cranial CT or MRI), and laboratory tests, with other mimicking conditions excluded before confirmation based on established diagnostic criteria [4]. Post-stroke, patients often suffer from persistent sequelae, including hemiplegia, sensory impairment, and aphasia [3], which severely compromise their quality of life.

Timely restoration of cerebral blood flow is critical for improving outcomes in AIS. Current reperfusion therapies primarily include intravenous thrombolysis and endovascular mechanical thrombectomy, with the former being the first-line option due to its accessibility. However, its strict time window (typically ≤4.5 hours) excludes many patients who miss the optimal treatment opportunity [5]. Recently, remote ischemic postconditioning (RIPostC) has emerged as a novel non-invasive physical intervention. Its "endogenous protective" mechanism involves cyclic transient limb ischemia-reperfusion (e.g., 5-minute occlusion/5-minute release), activating intrinsic anti-injury pathways to enhance remote organ (e.g., brain) tolerance to ischemia [6]. This approach offers a promising therapeutic alternative for AIS.

Growing preclinical and clinical evidence supports RIPostC's neuroprotective effects in AIS, including improved neurological deficits, reduced inflammation, and enhanced functional recovery [7], particularly in patients beyond the thrombolysis time window. Potential mechanisms involve humoral, neural, and immunomodulatory pathways [8], though the exact mechanisms remain incompletely understood.

In cardiology, RIPostC has been proven to reduce myocardial infarct size and improve prognosis [9, 10]. In neuroscience, preclinical studies suggest it may confer neuroprotection by modulating oxidative stress, suppressing inflammation, and promoting angiogenesis [11, 12]. In 2006, Zhao et al. [13] first applied ischemic postconditioning to neuroprotection, demonstrating its ability to reduce infarct volume by inhibiting apoptosis and free radical production.

Oxidative stress plays a pivotal role in the pathophysiology of ischemic stroke. Following cerebral ischemia, a surge in reactive oxygen/nitrogen species (ROS/RNS) disrupts the antioxidant defense system, triggering lipid peroxidation, protein denaturation, and DNA damage, directly contributing to neuronal death [14]. Concurrently, damage-associated molecular patterns (DAMPs) released from the ischemic core activate microglia and infiltrating neutrophils, amplifying pro-inflammatory cytokines (e.g., IL-6, TNF-α) and compromising blood-brain barrier integrity, thereby expanding the infarct zone [15]. However, few studies have explored whether RIPostC mitigates oxidative stress to exert neuroprotection. Prior research indicates that inhibiting oxidative stress pathways significantly reduces infarct volume and neurological deficits at 3, 7, and 14 days after middle cerebral artery

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occlusion (MCAO) [16]. Although existing antioxidants (e.g., edaravone) scavenge ROS and alleviate injury, their clinical efficacy is limited by single-target effects, low bioavailability, and side effects. RIPostC, as a multi-target strategy, may synergistically activate endogenous antioxidant pathways and suppress inflammatory signaling, breaking the "oxidative-inflammatory" vicious cycle and offering a novel therapeutic approach.

The mechanisms of RIPostC in ischemic stroke involve multi-pathway modulation:

1. Anti-inflammatory effects: Suppressing pro-inflammatory cytokines (e.g., IL-1β, TNF-α) while promoting anti-inflammatory factors (e.g., IL-10), reducing microglial hyperactivation and peripheral immune cell infiltration [17].

2. Blood-brain barrier preservation: Downregulating matrix metalloproteinase (MMP) activity to mitigate vascular leakage and cerebral edema [18].

3. Antioxidant and anti-apoptotic actions: Inhibiting ROS accumulation and mitochondrial apoptosis pathways to enhance neuronal survival [19, 20].

Both ischemic and reperfusion injuries in AIS trigger acute oxidative stress and inflammation. Oxidative stress is a key pathological factor in ischemia-reperfusion injury, where excessive ROS production drives lipid peroxidation, protein damage, and DNA breaks [21, 22]. RIPostC may reduce malondialdehyde (MDA), a lipid peroxidation byproduct, while elevating antioxidant enzymes like superoxide dismutase (SOD) and glutathione (GSH). Nitric oxide (NO) exhibits dual roles: RIPostC may promote physiological NO release via endothelial nitric oxide synthase (eNOS) while suppressing inducible NOS

(iNOS)-mediated toxicity. A study on RIPostC in MCAO mice demonstrated activation of the Nrf2/HO-1 pathway, increasing total antioxidant capacity (TAC), SOD, and GSH while reducing MDA [20]. Nevertheless, RIPostC's precise mechanisms, clinical potential, and synergistic effects with other therapies require further validation.

Current research predominantly focuses on macroscopic outcomes. Oxidative stress biomarkers hold predictive value, but their sensitivity and specificity warrant multicenter validation to correlate dynamic changes with clinical prognosis. This study innovatively integrates oxidative stress markers (GSH, SOD, NO, MDA) with NIHSS and mRS scores to construct a multidimensional evaluation system, elucidating RIPostC's neuroprotective effects and clinical outcomes.

To our knowledge, this is the first clinical study systematically revealing RIPostC's dynamic regulation of oxidative stress in AIS patients, bridging molecular mechanisms and functional recovery to clarify its "remote conditioning-local protection" mode. RIPostC's simplicity, cost-effectiveness, and safety make it particularly suitable for resource-limited settings, offering significant socioeconomic value. Future directions include optimizing intervention parameters (e.g., ischemia duration, pressure intensity) and developing personalized regimens (e.g., biomarker-guided stratification), positioning RIPostC as a key component in AIS management to reduce disability and improve quality of life. This study will facilitate RIPostC's translation into standardized clinical practice.

1. Materials and Methods

1.1 General Information

A total of 78 patients with acute ischemic stroke (AIS) admitted to the Department of Neurology

from October 2023 to February 2025 were enrolled and randomly assigned to either the control group (n=40) or the treatment group (n=38).

Inclusion Criteria:

1. Age 18–80 years, regardless of sex.

2. Diagnosis of AIS per the 2023 Chinese Guidelines for Acute Ischemic Stroke Management [5], meeting the following criteria:

·Acute onset.

·Focal neurological deficits (e.g., unilateral limb weakness/numbness, aphasia) or, rarely, global neurological impairment.

·Imaging-confirmed ischemic lesion or symptoms persisting >24 hours.

·Non-vascular etiologies excluded.

·No intracranial hemorrhage on CT/MRI.

3. NIHSS score 3–15 and pre-stroke mRS score ≤2.

4. Onset time ≤48 hours.

5. Informed consent obtained, approved by the hospital ethics committee.

Exclusion Criteria:

1. Severe systemic diseases (e.g., NYHA Class III–IV heart failure, Child-Pugh C cirrhosis, CKD Stage 4–5, malignancy).

2. High-risk cardioembolic sources (e.g., moderate-severe mitral stenosis, persistent atrial fibrillation, recent unstable angina).

3. Bleeding diathesis or history of hemorrhagic disorders (e.g., intracranial hemorrhage, cerebrovascular malformations, space-occupying lesions).

4. Cervical spondylosis (active phase) or physical limitations precluding ischemic conditioning.

5. Upper limb vascular compromise (e.g., open wounds, deep vein thrombosis, arterial occlusive disease).

6. Severe cognitive impairment or psychiatric disorders.

7. Large infarcts (>1/3 MCA territory) requiring surgical intervention.

8. Coagulopathy (INR >1.5, aPTT prolongation >10 s, platelets <100×10^9/L).

9. Subclavian artery stenosis ≥50% with steal syndrome or upper limb arterial occlusion.

10. Refractory hypertension (SBP >180 mmHg or DBP >110 mmHg despite treatment).

11. Thrombolysis therapy administered.

1.2 Data Collection

On admission, baseline data were collected, including:

·Demographics (sex, age).

·Lifestyle factors (smoking, alcohol use).

·Medical history (hypertension, diabetes, coronary artery disease, dyslipidemia).

·Neurological assessments (NIHSS and mRS scores on Day 1 and Day 7).

1.3 Grouping and Treatment Protocols

Control Group:

Received standard therapy per 2023 Chinese Guidelines, including:

·Blood flow restoration.

·Neuroprotection.

·Antiplatelet therapy.

·Intracranial pressure management.

·Lipid-lowering and plaque stabilization.

Experimental Group:

Standard therapy + RIPostC:

·Device: Ischemic conditioning instrument (Model:

ND-IPC-01).

·Procedure: Bilateral upper limb occlusion (1–2 cm above elbow) at 200 mmHg for 5 min, followed by 5 min reperfusion (one cycle).

·Frequency: 5 cycles/session, twice daily (morning/evening) for 7 days.

·Monitoring: Blood pressure, heart rate, respiratory changes, and adverse events (e.g., petechiae, numbness, pain).

1.4 Biomarker Measurement

1.4.1 Serum Sample Collection

·Timing: Fasting venous blood (5 mL) collected on Day 1 and Day 7.

·Processing: Clotted at 4°C for 10–20 min, centrifuged at 3000 rpm (15 cm radius) for 10 min.

·Storage: Serum aliquots (2 mL) stored at –80°C.

1.4.2 Laboratory Assays

·SOD activity: Xanthine oxidase enzymatic reaction.

·MDA concentration: Thiobarbituric acid reactive substances (TBARS) assay.

·NO levels: Microplate colorimetry.

·GSH concentration: Spectrophotometric assay.

·Kits: Purchased from Nanjing Jiancheng Bioengineering Institute.

1.5 Neurological Assessments

·NIHSS: Evaluated neurological deficits (higher scores = worse impairment).

·mRS: Assessed functional recovery (0 = no symptoms; 5 = severe disability).

1.6 Adverse Events

Monitored for:

·Neuro-sensory abnormalities (e.g., limb numbness).

·Dermatological reactions (e.g., erythema/petechiae).

·Hemorrhagic events (e.g., puncture site bleeding).

Documented: Onset time, symptoms, duration, severity, and resolution.

1.7 Statistical Analysis

·Software: SPSS 27.0.

·Normal-distributed data: Mean ± SD; independent/paired t-tests.

·Non-normal data: Median (IQR); Wilcoxon rank-sum test.

·Categorical variables: Chi-square or Fisher's exact test.

·Significance threshold: $P < 0.05$.

2. Results

2.1 Baseline Characteristics

Statistical analysis confirmed no significant differences between groups in:

·Demographics (sex, age, smoking, alcohol use).

·Comorbidities (hypertension, diabetes, CAD, dyslipidemia).

·Baseline NIHSS/mRS scores (all $P > 0.05$).

See Table 2-1 for details.

Table 2-1 Comparison of baseline characteristics between the two groups of patients

Item	Control Group	Experimental Group	t/χ²	P
Number of cases	40	38	—	—
Age (years)	64.7±10.12	66.08±11.67	-0.56	0.578
Male/Female	34/6	30/8	0.48	0.486
Drinking history [n(%)]	19(47.5)	18(47.37)	0.01	0.991
Smoking history [n(%)]	14(35)	18(47.37)	1.23	0.267
Hypertension [n(%)]	36(90)	34(89.47)	<0.01	>0.999
Hyperlipidemia [n(%)]	14(35)	12(31.58)	0.1	0.749
Diabetes [n(%)]	10(25)	10(26.32)	0.02	0.894
CHD [n(%)]	3(7.5)	3(7.89)	<0.01	>0.999
NIHSS score on day 1	4.00(3.00,8.00)	5.00(3.00,7.00)	-0.057	0.955
mRS score on day 1	2.00(1.00,4.00)	3.00(1.00,4.00)	-0.701	0.483

Note: "-" indicates no data. * P < 0.05, ** P < 0.01, the same below.

2.2 Scale Scores and Serological Results

2.2.1 Comparison of NIHSS Scores Between Experimental and Control Groups on Admission Day 1 and Day 7

Prior to analysis, normality testing confirmed that NIHSS scores followed a non-normal distribution, necessitating non-parametric rank-sum tests for statistical comparison.

·Baseline (Day 1): No significant difference in NIHSS scores between groups (P > 0.05), confirming comparability.

·Within-Group Changes (Day 1 vs. Day 7): Control Group: Significant improvement (P < 0.05). Experimental Group: Marked improvement (P <
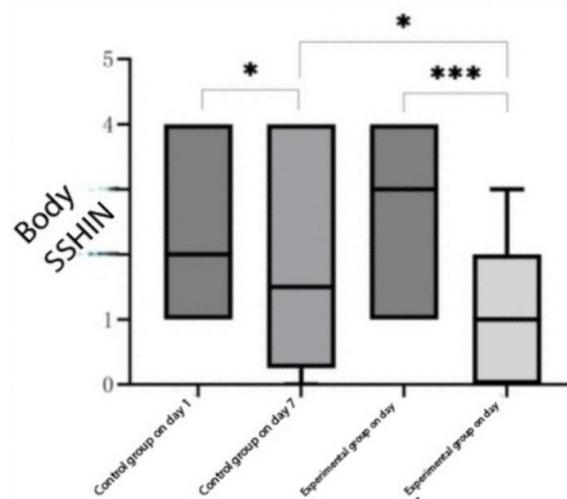
0.001).

·Between-Group Comparison (Day 7): The experimental group exhibited significantly lower NIHSS scores than the control group (P < 0.05).

See Table 2-2 and Figure 1 for details.

Table 2- 2 Comparison of NIHSS scores between experimental and control groups

Group	NIHSS Score Day 1 (points)	NIHSS Score Day 7 (points)
Control Group (n=40)	4.00 (3.00, 8.00)	4.00 (1.00, 8.00)
Experimental Group (n=38)	5.00 (3.00, 7.00)	2.00 (1.00, 4.00)
z	-0.057	-2.03
P	0.955	0.042*

Note :*P<0.05, **P<0.0l, ***P<0.00l, ****P<0.000l, the same below.

Figure l NlHSS scores of the two groups of patients

2.2.2 Comparison of mRS Scores between the experimental group and the control group on the first and seventh days after admission

Before conducting the data analysis, the normality test of the mRS Scores of the two groups of patients was first performed. The results indicated that the data were not normally distributed. Therefore, the non-parametric rank sum test was used for statistical analysis of the data. The mRS Scores were performed on the first day of patients'

admission. Through statistical comparative analysis, it was found that there was no significant difference between the two groups (P > 0.05), and they were comparable. There was a significant difference in mRS Scores between the control group on the first day and the seventh day of admission (P < 0.05), and the experimental group also showed extremely significant differences in mRS Scores at these two time points (P < 0.001). When comparing the mRS Scores of the control group and the experimental group on the seventh day of admission, It was found that the difference between the two was also statistically significant (P < 0.05), suggesting that the score of the experimental group was lower than that of the control group. See Table 2-3 and Figure 2

Table 2-3 Comparison of mRS scores between experimental and control groups

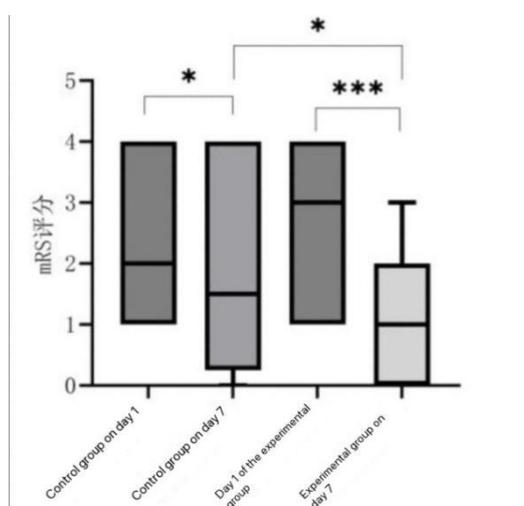| Group	mRS Score Day 1 (points)	mRS Score Day 7 (points)
Control Group (n=40)	2.00（1.00，4.00）	1.50（0.25，4.00）
Experimental Group (n=38)	3.00（1.00，4.00）	1.00（0.00，2.00）
z	-0.701	-2.126
P	0.483	0.031*

Figure 2 mRS scores of the two groups of patients

2.2.3 Comparison of serum index GSH content between the experimental group and the control group on the first and seventh days after admission

Before conducting the data analysis, the normality test of the GSH concentrations of the two groups of patients was first performed. The results indicated that the data were not normally distributed. Therefore, the non-parametric rank sum test was used for statistical analysis of the data. The GSH concentrations of the patients on the first day of admission were compared and analyzed statistically. It was found that there was no significant difference between the two groups (P > 0.05), and they were comparable. The comparison of GSH concentrations on the first and seventh days of admission in the control group showed statistically significant differences (P < 0.001). The comparison of GSH concentrations on the first and seventh days of admission in the experimental group also showed statistically significant differences (P < 0.001). The comparison of GSH concentrations on the seventh day of admission between the control group and the experimental group showed statistically significant differences (P < 0.001). The concentration of GSH in the experimental group increased significantly compared with that in the control group. See Table 2-4 and Figure 3

Table 2- 4 Comparison of serum GSH levels between experimental and control groups

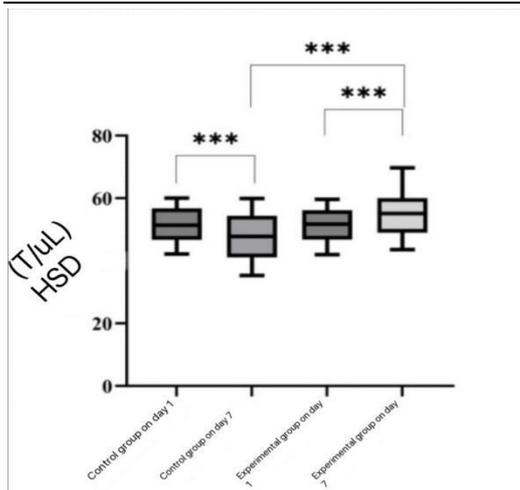| Group	Day 1 GSH(umol/L)	Day 7 GSH(umol/L)
Control Group (n=40)	3.98(3.59，4.55)	4.73(4.34，5.01)
Experimental Group (n=38)	4.05（3.33，4.67）	5.69（5.19，5.97）
z/t	-0.245	-5.059
P	0.8065	0.001**

Figure 3 Comparison of serum GSH levels between experimental and control groups

2.2.4 Comparison of serum MDA content between the experimental group and the control group on the first and seventh days after admission

Before conducting data analysis, the normality test of MDA concentration was first performed on the two groups of patients. The results indicated that the data were not normally distributed. Therefore, the non-parametric rank sum test was used for statistical analysis of the data. The MDA concentration of the patients on the first day of admission was compared and analyzed statistically. It was found that there was no significant difference between the two groups (P > 0.05), and they were comparable. The comparison of MDA concentrations on the first and seventh days of admission in the control group showed statistically significant differences (P < 0.001). The comparison of MDA concentrations on the first and seventh days of admission in the experimental group also showed statistically significant differences (P < 0.001). The comparison of MDA concentrations on the seventh day of admission between the control group and the experimental group showed statistically significant differences (P < 0.05). The MDA concentration in the experimental group decreased significantly compared with that in the control group. See Table 2-5 and Figure 4

Table 2-5 Comparison of serum MDA levels between experimental and control groups

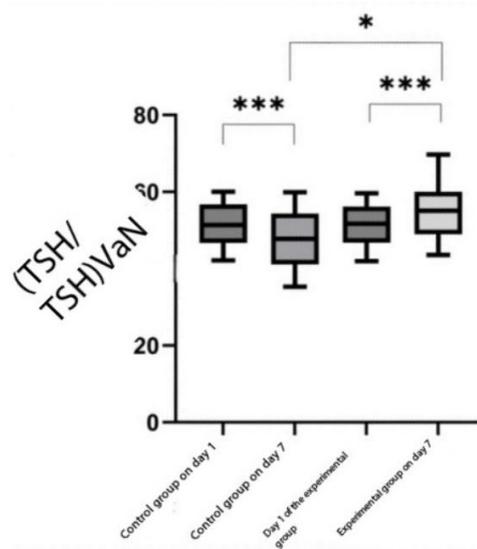| Group	Day1 MDA(nmol/mL)	Day7 MDA(nmol/mL)
Control Group (n=40)	5.67(2.46，6.43)	4.40（3.40，4.91）
Experimental Group (n=38)	5.87（4.97，6.86）	3.92（3.48，4.71）
z	-1.7	-2.164
P	0.089	0.030*

Figure 4 Comparison of serum MDA levels between experimental and control groups

2.2.5 Comparison of serum index NO content between the experimental group and the control group on the first and seventh days after admission

Before conducting the data analysis, the normality test of NO concentration was first performed on the two groups of patients. The results indicated that the data were not normally distributed. Therefore, the non-parametric rank sum test was used for statistical analysis of the data. The NO concentration of the patients on the first day of admission was compared and analyzed statistically. It was found that there was no significant difference between the two groups (P > 0.05), and they were comparable. The comparison of NO concentrations on the first and seventh days of admission in the control group showed statistically

significant differences (P < 0.05). The comparison of NO concentrations on the first and seventh days of admission in the experimental group also showed statistically significant differences (P < 0.01). Compared with the NO concentration on the seventh day of admission in the experimental group, the comparison was statistically significant (P < 0.0001). The NO concentration in the experimental group increased. While the control group showed a decrease. See Table 2-6 and Figure 5

Table 2- 6 Comparison of serum NO levels between experimental and control groups

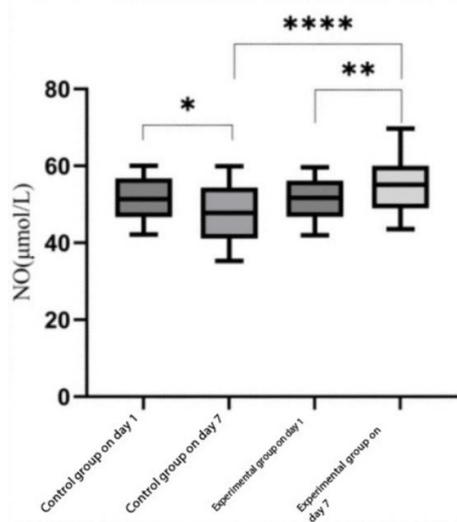| Group	Day 1 NO(μmol/L)	Day 7 NO(μmol/L)
Control Group (n=40)	51.336（46.71，56.78）	47.78（41.07，54.36）
Experimental Group (n=38)	51.70（46.74，56.17）	55.08（48.99，60.00）
z	0.25	-4.57
P	0.8026	0.000**

Figure 5 Comparison of serum NO levels between experimental and control groups

2.2.6 Comparison of serum index SOD content between the experimental group and the control group on the first and seventh days after admission

Before conducting the data analysis, the normality test of

SOD content was first performed on the two groups of patients. The results indicated that the data were not normally distributed. Therefore, the non-parametric rank sum test was used for statistical analysis of the data. Regarding the SOD content of the patients on the first day of admission, through statistical comparative analysis, it was found that there was no significant difference between the two groups (P > 0.05), and they were comparable. There was a significant difference in SOD content between the first day and the seventh day of admission in the control group (P < 0.05), and the comparison of SOD content in the experimental group at these two time points also showed an extremely significant difference (P < 0.001). When comparing the SOD concentration on the seventh day of admission between the control group and the experimental group, It was found that the difference between the two was also statistically significant (P < 0.05), and the SOD concentration in the experimental group was significantly higher than that in the control group. See Table 2-7 and Figure 6

Table 2- 7 Comparison of serum SOD levels between experimental and control groups

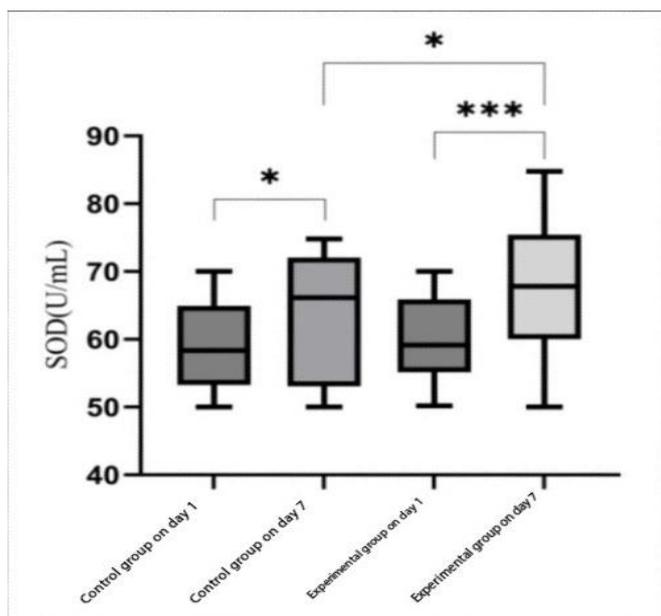| Group	Day 1 SOD(U/mL)	Day 7 SOD(U/mL)
Control Group (n=40)	58.36（53.28，64.94）	66.14（53.06，72.05）
Experimental Group (n=38)	59.13（55.17，65.90）	67.82（60.02，75.44）
z	-0.66	-1.98
P	0.5094	0.048*

Figure 6 Comparison of serum SOD levels between experimental and control groups

2.3 Safety Evaluation

During the intervention process of remote ischemic postconditioning treatment, a total of 7 adverse reaction events related to compression operation were observed in the experimental group. Among them, 5 patients complained of transient pain and mild numbness in the limbs under cuff compression, and 2 patients had subcutaneous petechiae with a diameter of less than 1cm at the site of continuous compression. All the above symptoms presented self-limiting characteristics and no special medical intervention was carried out. During the operation, no significant fluctuations related to treatment occurred in vital signs such as blood pressure, pulse, and respiration of all patients in the experimental group. See Table 2-8

Table 2- 8 Comparison of safety between the experimental group and the control group

Item	Control Group	Experimental Group	P
Number of cases	40	38	—
Limb numbness [n(%)]	0 (0.0)	5 (13.16)	0.025
Pain sensation [n(%)]	0 (0.0)	5 (13.16)	0.025
Subcutaneous petechiae [n(%)]	0 (0.0)	2 (5.26)	0.230
Death [n(%)]	0 (0.0)	0 (0.0)	—

3. Discussion

This randomized controlled trial investigated the therapeutic efficacy of remote ischemic postconditioning (RIPostC) in patients with ischemic stroke. The results demonstrated that RIPostC significantly reduced NIHSS and mRS scores in the experimental group, indicating its effectiveness in improving neurological function and clinical outcomes. Furthermore, biochemical analyses revealed decreased serum MDA levels and increased SOD, GSH, and NO levels in the experimental group, suggesting that RIPostC may exert neuroprotective effects by mitigating oxidative stress. These findings provide new evidence supporting the potential clinical benefits of RIPostC.

3.1 Current Research Status of RIPostC in Acute Ischemic Stroke Treatment

Acute ischemic stroke (AIS) accounts for approximately 87% of all stroke cases and represents a major cerebrovascular emergency caused by sudden occlusion or severe stenosis of cerebral arteries [23]. The core pathological process involves energy metabolism failure in the affected brain region, ultimately leading to irreversible neuronal death and glial cell necrosis. The primary treatment goal for AIS is timely vascular recanalization to salvage potentially reversible ischemic penumbra tissue, with current strategies including thrombolysis and endovascular thrombectomy [5,23].

In recent years, RIPostC has garnered significant attention in AIS treatment. Liang et al. [24] demonstrated that RIPostC promotes neurological recovery and reduces brain injury in animal models, with 21-day RIPostC treatment showing greater infarct volume reduction compared to 2-day treatment in middle cerebral artery occlusion (MCAO) rats. This suggests that prolonged RIPostC duration may enhance therapeutic efficacy.

As a non-invasive physical intervention, RIPostC exerts neuroprotective effects through multiple mechanisms, including enhanced cerebral ischemic tolerance, reduced ischemia-reperfusion injury, inhibition of neuronal apoptosis, and promotion of angiogenesis and collateral circulation formation [25,26]. Clinical studies have confirmed that RIPostC not only slows neurological deficit progression but also reduces stroke recurrence risk, leading to its incorporation into standardized treatment protocols for ischemic cerebrovascular diseases.

Emerging evidence indicates that RIPostC alleviates cerebral ischemia-reperfusion injury by modulating oxidative stress responses [27]. Additional studies suggest that RIPostC may downregulate the mitogen-activated protein kinase (MAPK) signaling pathway, reducing neutrophil activation and pro-inflammatory cytokine production while increasing anti-inflammatory factors [28]. Experimental studies have demonstrated RIPostC's ability to activate anti-apoptotic gene networks and inhibit neuronal apoptotic cascades [29]. Clinical trials have further confirmed the safety and efficacy of RIPostC in promoting neurological recovery in AIS patients [30].

These collective findings highlight RIPostC's multifaceted neuroprotective mechanisms and its potential as a valuable adjunct therapy in AIS management. Our study contributes to this growing body of evidence by demonstrating RIPostC's beneficial effects on both clinical outcomes and oxidative stress markers in human subjects. Further research is warranted to optimize treatment protocols and explore potential synergistic effects with existing therapies.

3.2 Analysis of the mechanism by which remote ischemic postconditioning mediates neuroprotective effects in ischemic stroke through regulating oxidative stress pathways

The essence of oxidative stress is the imbalance of the generation and clearance homeostasis of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS). The core mechanism lies in the dynamic imbalance between the pro-oxidation mechanism and the endogenous antioxidant defense system. Ultimately, it led to the collapse of the REDOX signal network [14]. In the pathological process of acute ischemic stroke, the oxidative stress response, as the core injury mechanism, runs through the entire disease. After the occurrence of cerebral ischemia, the oxidative stress response will be activated, generating excessive ROS, and then causing damage to nerve cells [31]. Therefore, a major treatment after the occurrence of cerebral ischemia is antioxidant therapy, which enhances the antioxidant defense capacity by reducing the generation of ROS, eliminating the generated ROS, and increasing antioxidant substances [32]. Studies have found that RIPostC exerts neuroprotective effects through multiple pathways, among which regulating the oxidative stress pathway is one of the key mechanisms. Chen et al. [33] found through research that RIPostC can effectively down-regulate the expression of key signaling molecules in neutrophils, including Myeloid Differentiation Primary Response 88. MyD88, Tumor Necrosis Factor Receptor-Associated Factor 6 (Tumor necrosis factor receptor-associated Factor 6) TRAF6 and p38 Mitogen-Activated Protein Kinase

(P38-MAPK). This discovery reveals the potential mechanism of RIPostC at the molecular level. Further studies have shown that RIPostC can significantly reduce the number of neutrophils in the brain and peripheral blood of rats by inhibiting the MyD88/TRAF6/p38-MAPK signaling pathway. This effect is not limited to a reduction in quantity. RIPostC can also lower the activation status of these cells, thereby reducing their destructive role in the inflammatory response. In addition, RIPostC can also inhibit the release of ROS. Reactive oxygen species are the key mediators in oxidative stress responses, and their excessive production can lead to damage to cells and tissues. This discovery provides new ideas and possible drug targets for new treatment methods of stroke. By deeply understanding the mechanism of action of RIPostC, it is expected to develop more effective therapeutic strategies to reduce the damage of oxidative stress to the brain and improve the prognosis and quality of life of patients. Therefore, this study delves deeply into the mechanism of RIPostC in neuroprotection of ischemic stroke, with a focus on analyzing how it achieves neuroprotective effects by regulating the oxidative stress pathway.

3.3 Research Status of Serum GSH, MDA, SOD, NO and RIPostC in ischemic Stroke

The brain is the organ most vulnerable to oxidative stress. During cerebral ischemia-reperfusion, the production of a large amount of ROS and RNS exceeds the capacity of the body's antioxidant system, leading to lipid peroxidation, protein oxidation, mitochondrial damage, etc., and further causing neuronal damage and neurological deficits [34]. Biomarkers such as GSH, MDA, SOD and NO in serum play an important role in evaluating oxidative stress status and neurological function impairment. As an emerging

therapeutic strategy, the impact of RIPostC on these biomarkers has become a research hotspot. This study confirmed that remote ischemic postconditioning can significantly improve neurological deficits after acute ischemic stroke, and the mechanism may be closely related to regulating the balance of the oxidation-antioxidant system. GSH is a core endogenous antioxidant molecule that maintains REDOX homeostasis within cells. It directly neutralizes free radicals through its sulfhydryl group, thereby antagonizing ROS-mediated oxidative damage. MDA, as a stable end product generated by the free radical chain oxidation reaction of polyunsaturated fatty acids, its level can be used as a key biomarker for quantitatively evaluating the lipid peroxidation rate and oxidative stress intensity of biological membrane systems (such as cell membranes and mitochondrial membranes), and indirectly reflect the pathological process of tissue damage related to oxidative stress. SOD, as an important component of the antioxidant enzyme system, can catalyze the disproportionation reaction of superoxide anion radicals, generating hydrogen peroxide and oxygen, thereby alleviating the oxidative stress response. NO, as an important signaling molecule, has extensive physiological functions in the nervous system. In patients with ischemic stroke, excessive production of NO can lead to neurotoxic effects. The experimental results of this study show that after RIPostC intervention, the level of MDA in serum decreased significantly, while the contents of SOD, GSH and NO increased significantly. This suggests that RIPostC exerts neuroprotective effects by inhibiting lipid peroxidation reactions, enhancing endogenous antioxidant capacity and improving vascular endothelial function. MDA, as the terminal product of the lipid peroxidation chain reaction, its concentration change dynamically

characterizes the severity of tissue oxidative damage. In this study, RIPostC significantly reduced the level of MDA, indicating that it effectively inhibited free radical mediated membrane lipid peroxidation, which was consistent with the findings of Chen et al. [33] in the focal cerebral ischemia model. In addition, SOD and GSH, as key antioxidant enzymes, when their activities increase, can eliminate superoxide anions and hydrogen peroxide, maintaining intracellular REDOX homeostasis. This study observed significant upregulation of SOD and GSH, suggesting that RIPostC may enhance the antioxidant defense system through pathways such as activating the Nrf2/ARE signaling pathway, thereby reducing neuronal oxidative damage. NO plays a dual role in ischemic brain injury: at low concentrations, it exerts a protective effect by dilating blood vessels and inhibiting platelet aggregation, while at high concentrations, it reacts with superoxide anions to form more toxic peroxnitrite. In this study, the level of NO increased after RIPostC intervention, which might be related to the upregulation of eNOS activity. It promotes the recovery of cerebral blood flow and inhibits inflammatory responses, which is consistent with the claim proposed by Peng et al. [35] that RIPostC upregulates endothelial nitric oxide synthase through the PI3K/Akt pathway to protect the brain from global cerebral ischemia/reperfusion injury. This study verified that RIPostC has the effects of reducing oxidative stress responses, protecting nerve cells from damage, and promoting the recovery of neurological function. This discovery provides new ideas and strategies for the treatment of ischemic stroke. However, this research is limited to the analysis of serum biomarkers. In the future, it is necessary to combine histopathology and molecular biology techniques to further verify the mechanism.

3.4 Neuroprotective mechanism of RIPostC: Scavenging oxygen free radicals and alleviating oxidative stress

RIPostC is a very promising therapeutic intervention measure. It has been experimentally found that it can reduce ischemia/reperfusion injury of the heart, kidneys, brain and skeletal muscles. In terms of neuroprotection, the mechanism of RIPostC is closely related to the scavenging of oxygen free radicals and the alleviation of oxidative stress [36]. Studies have pointed out that excessive production of reactive oxygen species by mitochondria is the main factor leading to oxidative stress. This excessive ROS can cause damage to the lipid and protein components of neuronal membranes [34]. RIPostC is regarded as an effective therapeutic strategy, which alleviates focal cerebral ischemia/reperfusion (I/R) injury in rats by inhibiting oxidative stress responses. The underlying mechanism may be related to RIPostC reducing the generation of ROS in brain tissue and promoting the clearance of ROS [37]. SOD is an antioxidant enzyme that plays a key role in living organisms and is also an effective free radical scavenger. SOD plays a protective role by reducing the biological activity of oxygen free radicals and alleviating the damage of oxygen free radicals to the structure and function of biological membranes [38]. GSH is also an important antioxidant substance within cells, capable of directly reacting with free radicals to eliminate them. Additionally, it serves as a substrate for glutathione peroxidase, participating in the reduction of hydrogen peroxide to water, thereby alleviating oxidative reactions. RIPostC can enhance the activity of SOD, which not only significantly reduces the generation of oxygen free radicals in brain tissue, but also further accelerates their clearance rate, thereby exerting a significant brain protective effect [37]. MDA is one of the end products of lipid peroxidation

reaction, and its content in the body can precisely reflect the degree of oxidative stress. When the body suffers from ischemia/reperfusion injury, the oxygen free radicals in the body increase sharply, resulting in a significant intensification of lipid peroxidation reactions, and the content of MDA also increases significantly accordingly. This elevated MDA not only further promotes lipid peroxidation reactions, but also causes direct damage to cell membranes, mitochondrial membranes and other important biological membranes, disrupting the integrity and fluidity of the membranes, thereby seriously affecting the normal physiological functions and metabolic activities of cells [39]. Elevated MDA level and decreased activities of SOD and GSH can suggest that the body is in an oxidative stress state. Under physiological conditions, NO has functions such as dilating blood vessels and regulating blood flow. However, under oxidative stress, excessive NO can react with ROS to generate more toxic active nitrogen, exacerbating brain tissue damage. Studies have found that RIPostC activates eNOS through the PI3K/Akt pathway, increases NO production, and improves cerebral blood perfusion. After RIPostC intervention, the level of NO in the ischemic area increased by 2 times, while the production of peroxynitrite was reduced and vascular endothelial injury was alleviated [35]. The results of this study suggest that the levels of SOD, GSH and NO in the experimental group were higher than those in the control group, while the level of MDA was lower than that in the control group. This is consistent with the previous research results. The levels of MDA in the experimental group all decreased compared with those before treatment, and the decrease in the experimental group was greater than that in the control group. After the treatment, the MDA levels of the two groups of patients decreased, indicating that both

the remote ischemic postconditioning technique and conventional treatment can alleviate the oxidative stress state of the body, reduce the level of lipid peroxidation, and reduce the damage of free radicals to cells, thereby protecting nerve cells to a certain extent and alleviating the neurological dysfunction caused by stroke. The decrease in MDA in the experimental group was greater than that in the control group ($P < 0.05$), highlighting the significant advantage of remote ischemic postconditioning technology in reducing lipid peroxidation, which may be related to its more effective scavenging of free radicals and enhancement of antioxidant defense mechanisms through specific signaling pathways. The levels of SOD and GSH in both groups of patients increased after treatment, indicating that both treatment methods can enhance the body's antioxidant capacity, promote the improvement of the activity of the antioxidant enzyme system, help the body better cope with oxidative stress injury, maintain the intracellular REDOX balance, and are of great significance for the protection of the structure and function of nerve cells. The increase of SOD/GSH in the experimental group was more significant ($P < 0.05$, $P < 0.0001$), further proving that the remote ischemic postconditioning technique has unique advantages in activating the antioxidant enzyme system of the body. It may increase the synthesis or activity of antioxidant enzymes to a greater extent by activating specific antioxidant signaling pathways, thereby scavenging free radicals more effectively. Reduce brain tissue damage and promote the recovery of neurological function. The level of NO in the experimental group increased, while that in the control group decreased. The difference between the two groups was significant ($P < 0.0001$). NO plays a key role in regulating vascular tension and promoting vasodilation,

and its level changes directly reflect the alterations in vascular endothelial function. Remote ischemic postconditioning techniques may promote the generation and release of NO by improving endothelial cell function and increasing the expression or activity of NO synthase. The increase of NO level in the experimental group is helpful to promote vasodilation, increase cerebral blood perfusion, improve the supply of oxygen and nutrients to brain tissue, alleviate cerebral ischemia-reperfusion injury, and has positive significance for the recovery of neurological function after stroke. The decrease in NO level in the control group may further affect the vasodilation function, which is not conducive to the recovery and maintenance of cerebral blood flow. Based on this, this study believes that RIPostC has a dual mechanism of antioxidation and vascular protection in acute cerebral ischemia, providing a theoretical basis for clinical promotion.

3.5 The clinical translational value of RIPostC

Traditional neuroprotection strategies (such as thrombolysis and endovascular thrombectomy) are limited by narrow time Windows, strong equipment dependence and high costs. However, RIPostC only requires a brief ischemia-reperfusion cycle of the limb through the cuff, which is simple to operate and has extremely low costs. In this clinical trial, the improvement rate of neurological function in the RIPostC group was significantly different from that in the control group (P<0.05), and it was highly safe, with only 7 patients experiencing adverse reactions. This indicates that RIPostC can serve as an important supplement to existing treatment methods, especially in areas with scarce medical resources. Animal experiments have shown that even if RIPostC intervention is initiated 6 hours after ischemia, the infarct volume can still be reduced by approximately 40%. This discovery challenges the traditional rigid notion that "time is the brain", suggesting that RIPostC may partially compensate for the defect of delayed vascular recanalization by activating endogenous repair mechanisms. If its efficacy in patients beyond the time window can be verified through multi-center clinical trials in the future, it will greatly expand the treatment population of AIS.

4. Deficiencies and Prospects

1. The sample size is relatively small and there is a lack of clinical multicenter data.

2. Ischemic strokes caused by different reasons, the size of the infarction focus and the infarction location were not grouped, making it impossible to comprehensively and systematically evaluate the therapeutic effect of RIPostC on ischemic stroke.

3. Limited by the research design period, the 90-day longitudinal follow-up of serum biomarker profiles, the degree of neurological deficits in NIHSS, and multimodal neuroimaging parameters was not conducted, resulting in the inability to dynamically evaluate the medium - and long-term regulatory effects of distant ischemic adaptation therapy (RIPostC) on post-stroke neural plasticity.

At present, remote ischemic postconditioning treatment for ischemic stroke in China is still in a continuous development stage. There is still a lack of a large number of clinical experimental studies for verification. In the future, it is still necessary to expand the sample size in clinical studies and conduct follow-up at different stages for patients after treatment. The specific effects of RIPostC on different cell types (neurons, astrocytes, microglia) in the brain were analyzed using single-cell sequencing

technology; Establish an animal model of "limb - brain" remote signal transmission to clarify new communication mechanisms such as exosome and mitochondrial transfer. Develop intelligent RIPostC equipment to achieve individualized adjustment of pressure and cycle times; To explore the role of RIPostC in the secondary prevention of stroke, especially its long-term protective effect on patients with cerebral small vessel disease. Combined with artificial intelligence technology, a therapeutic effect prediction model based on oxidative stress/inflammation biomarkers is constructed.

5. Conclusion

This study reveals that RIPostC has a significant effect in reducing NIHSS score and mRS Score in patients with acute ischemic stroke, indicating that it can improve the neurological dysfunction of patients with acute ischemic stroke and contribute to the recovery of neurological function.

Remote ischemic postadaptation can effectively alleviate oxidative stress in patients with acute ischemic stroke and promote the recovery of neurological function. This study found that RIPostC can significantly reduce the MDA content in the serum of patients with acute ischemic stroke and increase the contents of SOD, GSH and NO in the serum. It is suggested that the potential brain protection mechanism of RIPostC may be related to the reduction of oxidative stress responses. Remote ischemic post-adaptation technology is expected to become a simple, safe and effective neuroprotective measure.

The vast majority of the enrolled patients could tolerate it and there were no serious adverse reactions, suggesting that RIPostC is a safe and effective treatment method.

Conflict of Interest

None.

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