Remote Ischemic Postconditioning for Ischemic Stroke: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: Remote ischemic postconditioning (RIPostC) appears to protect distant organs from ischemia-reperfusion injury (IRI). However, cerebral protection results have remained inconclusive. In the present study, a meta-analysis was performed to compare stroke patients with and without RIPostC.

Methods: CNKI, WanFang, VIP, CBM, PubMed, and Cochrane Library databases were searched up to July 2016. Data were analyzed using both fixed-effects and random-effects models by Review Manager. For each outcome, risk ratio (*RR*) and mean difference (MD) with 95% confidence interval (*CI*) were calculated.

Results: A total of 13 randomized controlled trials that enrolled a total of 794 study participants who suffered from or are at risk for brain IRI were selected. Compared with controls, RIPostC significantly reduced the recurrence of stroke or transient ischemic attacks (*RR* = 0.37; 95% *CI*: 0.26–0.55; $P < 0.00001$). Moreover, it can reduce the levels of the National Institutes of Health Stroke Scale score (MD: 1.96; 95% *CI*: 2.18–1.75; $P < 0.00001$), modified Rankin Scale score (MD: 0.73; 95% *CI*: 1.20–0.25; $P = 0.00300$), and high-sensitivity C-reactive protein (MD: 4.17; 95% *CI*: 4.71–3.62; $P < 0.00001$) between the two groups. There was no side effect of RIPostC using tourniquet cuff around the limb on ischemic stroke treating based on different intervention duration.

Conclusion: The present meta-analysis suggests that RIPostC might offer cerebral protection for stroke patients suffering from or are at risk of brain IRI.

Key words: Ischemic Stroke; Meta-Analysis; Remote Ischemic Postconditioning

Introduction

Ischemic stroke is a major cause of death and disability worldwide, and the clinical prognosis of acute cerebral ischemia remains poor.[1,2] The brain is more sensitive to ischemia, compared to other organs, and neurons in the ischemic core thereby die within minutes, causing irreversible infarction. At present, it has been considered that the immediate restoration of blood supply in the cerebral and ischemic penumbra and saving dying neurons is the key to the treatment of cerebral infarction. Han's study[3] revealed that in recovering the blood supply of ischemic tissues and saving dying neurons after the reperfusion of

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cerebral blood flow, the body produces a rapid cascade of damage on nerve cells through the combined effect of the complex link, and this eventually leads to neuronal apoptosis or necrosis, and ischemia-reperfusion injury (IRI), which induces further damage. Previous studies have confirmed that energy metabolism disorder, excitatory amino acid toxicity, brain edema, inflammatory cell infiltration, micro-angiogenesis factors, and apoptosis are involved in cerebral IRI.[4-7] Therefore, to reduce the IRI in nerve cell damage effectively and protect nerve cells, there is a need to find a good treatment approach. Since the present exogenous treatment measures for IRI is not ideal, endogenous treatment measures thus become a research focus at present.

Remote ischemic postconditioning (RIPostC) is the application of a transient and brief ischemic stimulus to a distant site from the organ or texture that is afterward exposed to injury ischemia[8] and has been found to reduce IRI in various animal models. The idea of RIPostC initially stemmed from the protection against cardiac IRI by Murry *et al*.[9] The RIPostC organ-protective effects on the animal experiment research mainly concentrated in important organs such as the heart, brain, liver, or spinal cord;[10-13] most researches have confirmed that RIPostC has clear organ-protective effects, and that the protective effect of RIPostC is correlated to stimulus parameters (such as ischemia time and time), which induces the body to achieve a threshold to produce protective information. Few animal studies on the protective effect of RIPostC on other organs, such as the lung, stomach, kidneys, and skin, have been conducted. In humans, RIPostC of the limb has been shown to be effective in protecting against global and focal cerebral ischemia.[14-16] At present, the concept of RIPostC has been extended to different organs and tissues, and clinical trials have mainly focused on cardiac surgery, such as coronary artery bypass grafting and stent implantation. However, the results of several meta-analyses that evaluated the effect of RIPostC on cardiac and renal IRI injury prevention remained inconclusive.[17-20] To date, several clinical trials have been published which analyzed the role of RIPostC in the effect of ischemic stroke.[21] However, published literatures are still limited and drawing conclusions from them remains controversial. Therefore, together with published randomized controlled trials (RCTs), a systematic review to evaluate the effect of RIPostC on brain protection in patients with stroke is needed.

The aim of the present study was to systematically assess the benefits of RIPostC versus no RIPostC in patients undergoing stroke.

Methods

Eligibility criteria

Participants

Participants of any age, gender, or ethnic background, who suffered from stroke, were included in the RCTs.

Interventions and controls

In the RIPostC group, patients received RIPostC therapy, irrespective of the duration, time, and the limb. The control group included placebo, sham operation, or no treatment. When another treatment was combined with RIPostC, the adjunct treatment needed to be the same as the control.

Outcomes measurement

The primary outcome measure included the incidence rate of stroke or transient ischemic attack (TIA) recurrence and the National Institutes of Health Stroke Scale (NIHSS). Stroke and TIA were confirmed by magnetic resonance imaging/magnetic resonance angiography/diffusion-weighted imaging in combination with clinical manifestations. NIHSS was used to evaluate the degree of neurological deficits in patients with stroke, and baseline assessment determined the severity of stroke. The effect of treatment was assessed on a regular basis with reference to the awareness, eye movement, visual field, limb muscle strength and sensation, limb ataxia, language function, and cognitive performance and attention of the patients, as well as other aspects of the test. This was used to objectively reflect the degree of neurological impairment, and the score range applied was 0–42 points. The higher the score was, the more serious the nerve damage. Secondary outcomes included the modified Rankin Scale (mRS), high-sensitivity C-reactive protein (hs-CRP), plasma fibrinogen (FIB), and D dimer (D-D) level changes from the baseline.

Study design

The included published RCTs had no language restrictions.

Exclusion criteria

Studies that met the following criteria were excluded: (1) studies with participants who had any soft tissue or vascular injury and (2) studies that did not report any of the outcomes stated above.

Information sources

Electronic searches

Two English databases (Cochrane Library and PubMed) and four Chinese databases (CNKI, VIP, Wanfang, and CBM) were comprehensively searched up to July 1, 2016. The searched words were divided into three categories: (1) condition (stroke); (2) intervention (remote ischemic preconditioning and RIPostC), remote ischemic preconditioning means intervention before issues of the attack, while RIPostC means intervention after the attack; (3) study type (RCTs). These search terms were adjusted for each database. The search strategy in PubMed is shown in Supplementary Table 1.

Searching for other sources

References of recently reviewed articles and included studies were searched for additional studies.

Data collection

Study selection

The titles and abstracts of articles obtained from the database were independently analyzed by two investigators to ascertain the conformity of inclusion criteria. The full text of the articles was carefully reviewed when the screening of the titles and abstracts was unclear with regard to its admissibility.

Data extraction process

Two reviewers extracted the data after assessing and reaching consensus for eligible studies using a standardized data extraction form. Any conflicts between the two investigators (reviewers) were resolved by discussion with an arbitrator. The same reviewers independently assessed each trial and extracted data on the primary author, date of publication, journal, demographic characteristics of patients (age, gender, and sample size), protocol for RIPostC (location, timing and frequency), course of treatment, and outcomes (incidence of cerebrovascular event, NIHSS, mRS, etc.). Dichotomous data were collected as number (percentage), continuous data were collected as mean ± standard deviation, and the other forms were collected as stated in the articles.

Risk of bias assessment in the individual study

The included studies were evaluated for methodological quality using the Cochrane Collaboration's tool for assessing for risk of bias.[22] Seven domains were evaluated, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Risk of other bias was judged by assessing the baseline balance, data management, funding source, and so on. Judgments were categorized as "low risk of bias," "high risk of bias," or "unclear."

Statistical analysis

Statistical analyses were performed using Review Manager 5.2 (the Cochrane Collaboration, Copenhagen, Denmark). Risk ratios (*RR*s), with 95% confidence intervals (*CI*s), were calculated for dichotomous outcomes. The pooled effects of RIPostC on continuous outcomes were estimated using mean differences (MDs) with 95% *CI*. The meta-analyses were performed using Mantel-Haenszel fixed-effects models when there was no significant statistical heterogeneity in the included studies. A 5% level was taken as significant throughout the study.

Synthesis of results

Statistical heterogeneity was evaluated using the I^2 statistic ($I^2 \geq 50\%$ was considered to indicate heterogeneity). The random-effects model was adopted when I^2 was ≥50% without clinical heterogeneity.

Additional analyses

Subgroup analyses were predefined and performed for primary outcome measures and were used to assess the influence of variables on RIPostC efficacy, as well as to explore the possible causes of heterogeneity. Clinical heterogeneity between trials for the primary outcome was addressed by further subgroup analysis. The following important factors were noted: trials with low risk of bias versus those with high risk of bias; male versus female; treatment duration (≤14 days and >14 days); RIPostC protocol (total duration/day <90 min and ≥90 min); and stroke history (≤14 days and >14 days). Chi-square test was performed, which was set at a $P = 0.05$, in order to identify any subgroup differences. The robustness of the analyses was assessed by performing sensitivity analyses, excluding studies from the overall analysis of high risk of bias, and by considering separate studies of different durations. In addition, studies that did not provide complete data and did not clearly report the dropout data were excluded.

Publication bias assessment

Publication bias was assessed when the group included more than 10 studies through the use of a funnel plot.

Results

Study selection

The searching strategy generated 1436 articles. A total of 1411 articles were removed due to the following: duplicates, articles not related to RIPostC, articles not related to stroke, articles that are not clinical studies, or are other studies. Among these, 16 articles were excluded because these were either nonrandomized studies or evaluated interventions, or had outcomes that were not relevant to this review. The full-text assessment of 25 potentially relevant articles identified 13 eligible trials [Figure 1].[23-35]

Study characteristics

A total of 1251 participants were enrolled in the 13 studies, and all these studies involved TIA or cerebral infarction.[23-35] The number of participants included in the trials ranged from 16[35] to 286.[27] The RIPostC method varied among studies: 12 studies used an inflatable tourniquet around the upper limb,[23-30,32-35] while one study used pressure bandages around the lower limb.[31] All the reported outcomes were measured at the end of treatment, but the timing of measurements varied across trials. The key characteristics of the included studies are summarized in Tables 1 and 2.

Risk of bias assessment

Risk of bias in the included studies was independently assessed by two reviewers according to Cochrane Handbook 5.1. Reviewers' judgments about each risk of bias item presented as percentages across all included studies are presented in Figure 2. Reviewers' judgments about each risk of bias item for each included study are presented in Figure 3.

Allocation

All included studies were described as randomized allocation. Four studies[27,28,30,35] used a random number table to allocate participants. All other studies claimed to be randomized, but did not describe how the randomization process was undertaken. This potentially created some selection bias. Concealment of allocation before enrollment was mentioned in only one study.[29]

Blinding

Two (15%) studies reported that the participants and investigators were blinded (low risk), while the remaining 11 (85%) studies were not masked to the RIPostC treatment

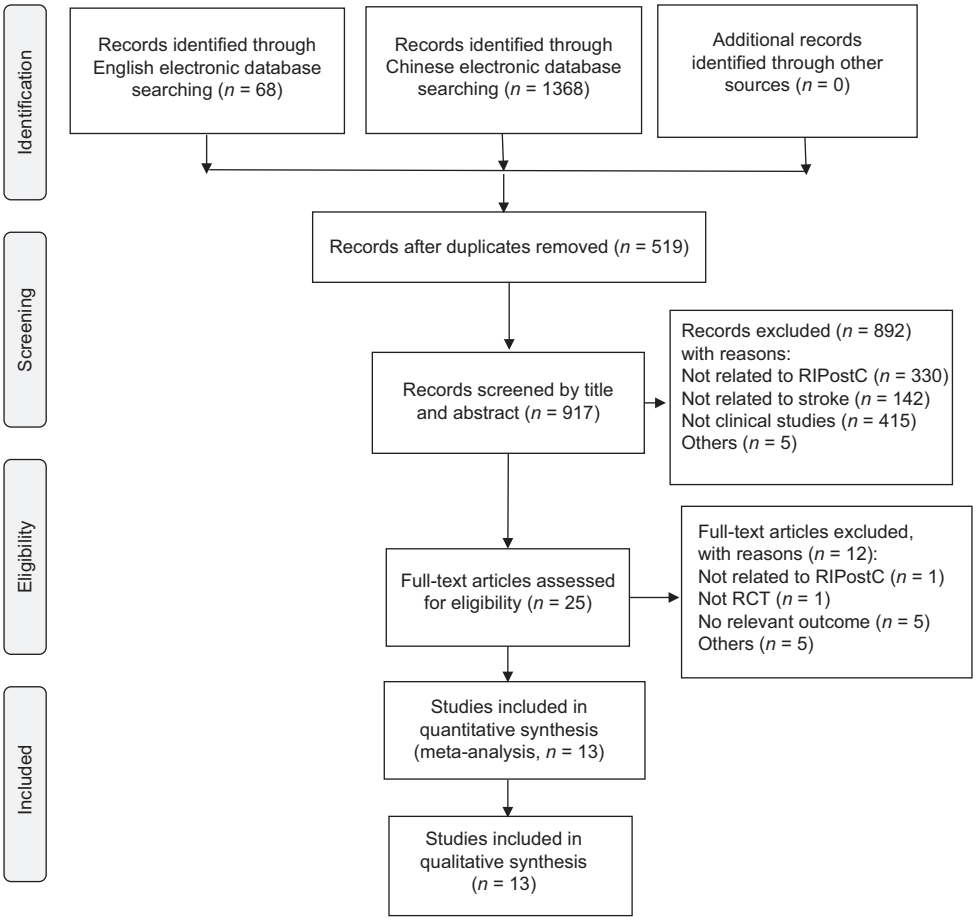

Figure 1: Flowchart of the study screening. RIPostC: Remote ischemic postconditioning; RCT: Randomized controlled trial.

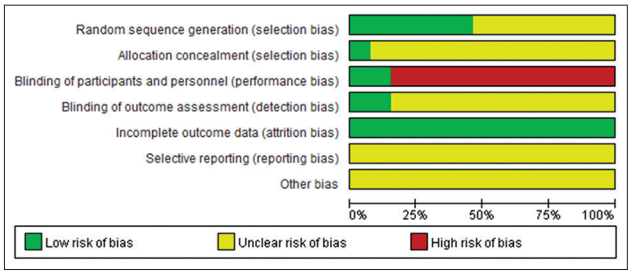

Figure 2: Risk of bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies.

of doctors and patients (high risk). Two (15%) studies were at low risk of detection bias (i.e., they reported that the outcome assessors were blinded), while the remaining 11 (85%) studies did not provide sufficient information for assessment (unclear risk). None of the trials used an appropriate blinding procedure.

Incomplete outcome data

All the included studies were judged to meet the criteria for low risk of incomplete outcome data (data are missing in two groups, and these were both reported and balanced across groups).

Selective reporting

There is no enough information to judge whether it is high risk or low risk for all the included studies.

Other bias

None of the trails reported the data management, statistical plan, or implementation process. All the included studies were judged by the investigators to meet the criteria for unclear.

Outcomes measurements

Incidence of stroke event

Data regarding stroke event incidence were available in seven trials (615 participants: 357 participantsin the RIPostC group and 258 participantsin the control group) and were included in the meta-analysis. The incidence of stroke event was nominally lower in the RIPostC group than that in the control group ($RR = 0.37$; 95% CI: 0.26–0.55; $P < 0.00001$; Figure 4). There was low statistical heterogeneity among the included trials (heterogeneity, $\chi^2 = 3.53$; $I^2 = 0\%$; $P = 0.62$).

The National Institutes of Health Stroke Scale score

Nine studies reported the NIHSS score. The meta-analysis revealed that RIPostC could significantly reduce the NIHSS score, when compared with the control group, through the random-effects model (MD: −2.60; 95% CI: −4.18–−1.02; $P < 0.001$). The heterogeneity among the included trials was significant (heterogeneity, $\chi^2 = 280.64$; $I^2 = 97\%$; $P < 0.00001$; Figure 5).

The modified Rankin Scale score

Merely two of the included studies reported the mRS score. The meta-analysis revealed that postconditioning could

Table 1: Summarized study design of included randomized trials

Study	RIPostC protocol				Control	Course of treatment (days)	Outcomes reported	Side effect
	Cycles × I/R	Cuff pressure (mmHg)	Limb	Total duration (min)				
Ma *et al*.[35]	5 × 5 min × 5 min	200	Upper arm	90	Blank	1800	Incidence of cerebrovascular accidents; mRS score and severity of stenotic cerebral vessel; serum cAMP; HIF-1; VEGF	NR
Meng *et al*.[34]	5 × 5 min × 5 min	200	Upper arm	90	Placebo	300	Incidence of recurrent stroke; the time to which mRS recovers to 0–1; the time point of RIPostC intolerance	NR
Ru Juan *et al*.[33]	5 × 5 min × 5 min	180–200	Upper arm	45	Blank	180	Incidence of recurrent stroke; cerebral metabolism and cerebral blood flow	NR
Wang *et al*.[25]	3 × 5 min × 5 min	200	Upper arm	25	Placebo	14	NIHSS score; BDNF	NR
Yang *et al*.[32]	5 × 5 min × 5 min	180	Upper arm	90	NR	180	Incidence of recurrent stroke	NR
Peng *et al*.[31]	3 × 5 min × 10 min	Pressure bandages	Thigh	35	Blank	14	NIHSS; BI scores and the FMA	NR
Feng *et al*.[30]	5 × 2 min × 4 min	NR	Upper arm	52	Blank	180	NIHSS score; infraction volume; incidence of recurrent stroke; blood pressure	NR
Meng *et al*.[29]	5 × 5 min × 5 min	200	Upper arm	90	Placebo	180	Safety monitoring results: blood pressure and heart rate; local skin and muscle. Clinical outcome evaluation: Inflammation; coagulation and fibrinolysis; stroke and TIA recurrence; NIHSS score	Three cases with transient sporadic petechiae
Zhang *et al*.[27]	3 × 5 min × 5 min	200	Upper arm	60	Blank	3	NIHSS score; hs-CRP; FIB, D-D	NR
Jiang *et al*.[28]	5 × 5 min × 5 min	200	Upper arm	90	Placebo	180	Infraction volume; NIHSS score; blood pressure; hs-CRP ; Cystatin c	NR
Chen[26]	5 × 5 min × 5 min	200–220	Upper arm	90	Placebo	14	NIHSS score; hs-CRP	NR
Meng *et al*.[24]	3 × 5 min × 5 min	200	Upper arm	60	Blank	3	NIHSS score; serum glucose	NR
Chen *et al*.[23]	5 × 5 min × 5 min	200	Upper arm	90	Placebo	180	Infraction volume; NIHSS score; blood pressure; incidence of cerebrovascular accidents	Two cases with limb mild pain, the symptoms disappeared completely after 30 min rest

1 mmHg = 0.133 kPa. I/R: Ischemic/reperfusion; mRS score: Modified Rankin Scale; Serum cAMP: Serum cyclic adenosine monophosphate; HIF-1: Hypoxic inducible factor-1; VEGF: Vascular endothelial growth factor; NIHSS: National Institute of Health Stroke Scale; BDNF: Brain-derived neurotrophic factor; BI: Barthel Index; FMA: Fugl-Meyer assessment; TIA: Transient cerebral ischemic attacks; hs-CRP: High-sensitivity C-reactive protein; FIB: Fibrinogen; D-D: D-Dimer; NR: Not report; RIPostC: Remote ischemic postconditioning.

significantly reduce the mRS score, when compared with the control group (MD = −0.73; 95% *CI*: −1.19–−0.27; *P* = 0.002; heterogeneity, $\chi^2 = 1.33$; $I^2 = 25\%$; *P* = 0.25; Figure 6).

High-sensitivity C-reactive protein

Three studies reported hs-CRP. The meta-analysis revealed that postconditioning could significantly reduce hs-CRP, when compared with the control group (MD: −3.64; 95% *CI*: −4.71–−3.10; *P* < 0.00001; heterogeneity, $\chi^2 = 25.88$; $I^2 = 0\%$; *P* = 0.88; Figure 7).

Fibrinogen and D-Dimer levels

Merely one study[27] reported FIB and D-D levels as the outcome to evaluate the effect of RIPostC on stroke patients. The reported data revealed that RIPostC can reduce the levels of FIB (MD: −1.27; 95% *CI*: −1.49–−1.05; *P* < 0.00001) and D-D (MD: −0.32; 95% *CI*: −0.38–−0.26; *P* < 0.00001).

Additional analysis

Subgroup analysis

The subgroup analysis based on treatment duration (≤14 days and >14 days), RIPostC protocol (total duration/day <90 min and ≥90 min), and stroke history (≤14 days and >14 days) could not address the heterogeneity of the meta-analysis for the NIHSS score. The results are presented in Table 3.

Sensitivity analysis

To assess for the robustness of the present findings, a sensitivity analysis was performed. A random-effects model was used when statistical heterogeneity was high, which did not alter the results (data not shown). The sensitivity analysis, which deleted each trial one at a time, revealed that no single study significantly altered the summary MD for the NIHSS score. Merely two studies had low risk of bias relating to allocation concealment and the blinding of participants. At the end of the treatment, the NIHSS score was lower in patients who received placebo than those who received blank.

Discussion

Summary of evidences

In the present study, the included RCTs were reviewed to evaluate the effect of RIPostC, which is a noninvasive and nonpharmacological method for stroke. With statistical significance, RIPostC decreased the risk of cerebrovascular

Table 2: Demographic characteristics of patients for included trials

Study	Age (years)		Male/female		Sample size (control versus study)	Population
	Control	Study	Control	Study		
Ma *et al*.[35]	52.90 ± 7.70	52.80 ± 12.70	5/3	3/5	8 versus 8	Intracranial arterial stenosis
Meng *et al*.[34]	60.00 ± 9.40	61.10 ± 10.10	19/11	21/17	30 versus 38	Transient ischemic attack or cerebral infarction within 30 days
Ru Juan *et al*.[33]	54.0 ± 12.00	50.00 ± 13.00	41/19	49/36	60 versus 85	Transient ischemic attack or cerebral infarction
Wang *et al*.[25]	NR	NR	4/5	5/4	9 versus 9	Acute cerebral infarction within 48 h
Yang *et al*.[32]	NR	NR	NR	NR	14 versus 32	Transient ischemic attack or cerebral infraction
Peng *et al*.[31]	NR	NR	NR	NR	20 versus 20	Acute cerebral infarction within 72 h
Feng *et al*.[30]	NR	NR	NR	NR	38 versus 44	Transient ischemic attack or cerebral infarction
Meng *et al*.[29]	84.20 ± 1.60	83.50 ± 2.30	17/11	18/12	28 versus 30	Transient ischemic attack or cerebral infarction within 7 days
Zhang *et al*.[27]	54.89 ± 8.39	55.8 ± 8.63	69/67	84/66	136 versus 150	Acute cerebral infarction within 72 h
Jiang *et al*.[28]	65.31 ± 7.36	64.82 ± 8.55	25/16	22/19	41 versus 41	Acute cerebral infarction within 48 h
Chen[26]	61.78 ± 8.63	61.55 ± 8.53	22/14	23/13	36 versus 36	Acute cerebral infarction within 3–24 h
Meng *et al*.[24]	NR	NR	NR	NR	69 versus 69	Acute cerebral infarction within 6–72 h
Chen *et al*.[23]	52.17 ± 8.62	53.96 ± 10.34	69/51	43/37	80 versus 120	Transient ischemic attack or cerebral infarction

Data are presented as mean ± SD or *n*. NR: Not report; SD: Standard deviation.

Table 3: Subgroup analysis of NIHSS score based on treatment duration, RIPostC protocol, and stroke history

Subgroup	Number of study, *n*	Number of patients, *n*	Estimated effect (MD, 95% *CI*)	I^2 (%)	Analysis model	*Z*	*P*
Treatment duration (days)							
≤14	5	626	2.38 (−4.52, −0.24)	98	Random	2.18	0.030
>14	4	350	2.88 (−5.11, −0.65)	92	Random	2.54	0.010
RIPostC protocol (total duration, min)							
<90	5	508	2.26 (−4.45, −0.07)	98	Random	2.02	0.040
≥90	4	468	3.01 (−5.09, −0.94)	92	Random	2.85	0.004
Stroke history (days)							
≥14	7	756	2.25 (−3.91, −0.59)	97	Random	2.66	0.008
>14	2	220	3.77 (−7.41, −0.13)	91	Random	2.03	0.040

NIHSS: National Institute of Health stroke scale; RIPostC: Remote ischemic postconditioning; MD: Mean difference; *CI*: Confidence interval.

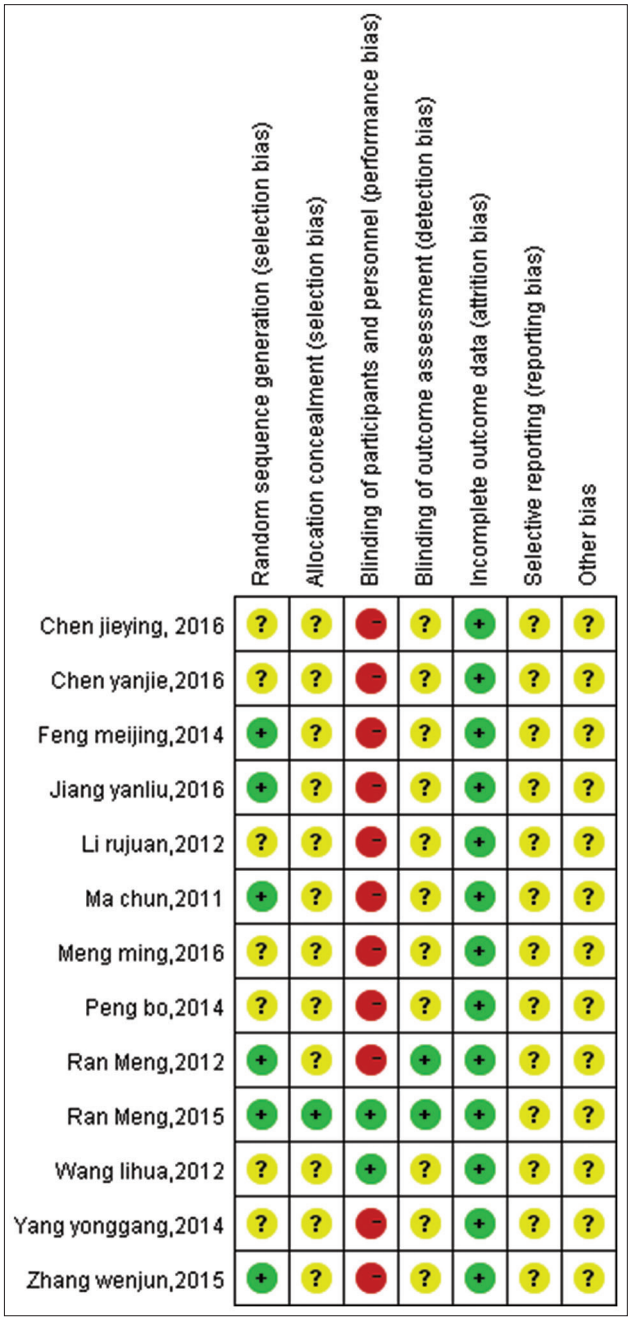

Figure 3: Risk of bias assessment summary: Review authors' judgments about each risk of bias item for each included study. Green: Low risk of bias; Yellow: Unclear risk of bias; Red: High risk of bias.

event in patients undergoing ischemic stroke, when compared with controls. In the present meta-analysis, a total of 13 trials were included, which enrolled 794 patients. To our knowledge, this is the first meta-analysis that focused on the effect of RIPostC on ischemic stroke. These results revealed that RIPostC was better, compared with placebo or no add-on treatment, in the incidence of stroke events and NIHSS scores. In the secondary outcome measurement, including the mRS scores and plasma levels of hs-CRP, patients in the RIPostC group were better than the controls. In terms of safety, there was a report of three patients in the process of RIPostC treatment[29] and patients with locally scattered ecchymosis. However, these symptoms disappeared after stopping RIPostC. Another study[23] revealed that two patients with limb compression training appeared to have mild pain, and these symptoms completely disappeared after a 30-min rest. All studies reported no death, regardless of whether it was from the RIPostC group or control group.

The protective effect of RIPostC on patients with IRI is more complex, but remains unclear, and this might be related to the patient's body in terms of anti-oxidation, anti-infection, the regulation of protein expression, and so on. In recent years, a study reported[36] that hs-CRP was potentially related to the occurrence and development of atherosclerosis and was considered to be one of the factors of cerebral infarction. The FIB level reflects the decline of the body's fibrinolytic activity and is regarded as one of the risk factors of cerebral infarction.[37] D-D can be used as a sensitive indicator for the early diagnosis of cerebral infarction.[38] This study revealed that RIPostC reduced hs-CRP levels. A study also reported that RIPostC can reduce the levels of FIB and D-D.[27] Therefore, it can be speculated that RIPostC has a certain role in promoting the recovery of neurological function in patients with ischemic stroke.

At present, there are few studies on the intensity of RIPostC implementation. Loukogeorgakis *et al*.[39] carried out a study (5-min ischemia/5-min reperfusion, two cycles) on the protection of the skeletal muscle of the upper limb and obtained the conclusion that it has an obvious protective effect. In addition, Li *et al*.[40] also reported that the intensity of the skeletal muscle after 5-min ischemia/1-min reperfusion can have a significant protective effect on the myocardium. However, there are few studies on RIPostC of different intensities, and there is no report on whether this mode intensity is the best and the other treatment intensity is different. In addition, there are also no reports on the effects of the time window of the limb ischemia and intensity of treatment on the degree of ischemia. Hence, it is necessary to conduct a study to find a better solution for the treatment of RIPostC. The results reported by Loukogeorgakis *et al*.[39] indicated that there may be a minimum threshold value for the protective effect of RIPostC. At the right time, 5 min of treatment intensity can have a significant role in myocardial protection, when the implementation of strength is ≤3 min, losing significant protective effect on the heart. However, in a 5-min basis, an increase in processing intensity does not increase the protective effect.[41]

The optimal conditioning protocol (cycles × I/R) for RIPostC to elicit organ protection in humans remains unknown. One laboratory study conducted by Xin *et al*.[42] revealed that 3–4, and not 1–2 cycles of 5-min/5-min RIPostC, could provide additive cardioprotection to local postconditioning, and similar results were obtained in four cycles of 3-min/3-min or 1-min/1-min. Prasad *et al*.[41] did not find any protective effect for three cycles of 3-min RIPostC on the cardiac enzyme levels of cardiac troponin T or MB isoenzyme of creatine kinase (CK-MB), percutaneous coronary intervention (PCI)-related myonecrosis rate, or myocardial infarction (MI) occurrence. Two cycles of

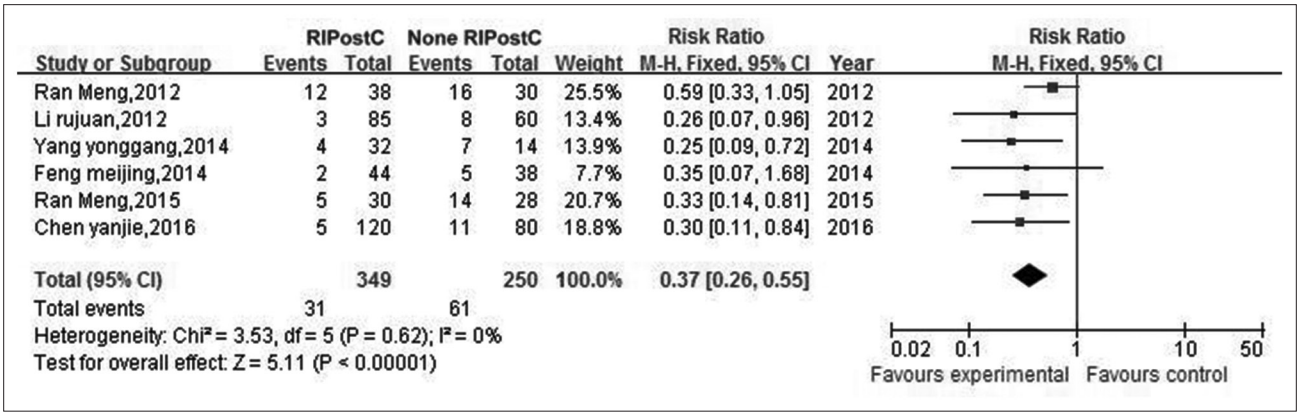

Figure 4: Forest plot for incidence of cerebrovascular event. RIPostC: Remote ischemic postconditioning; *CI*: Confidence interval.

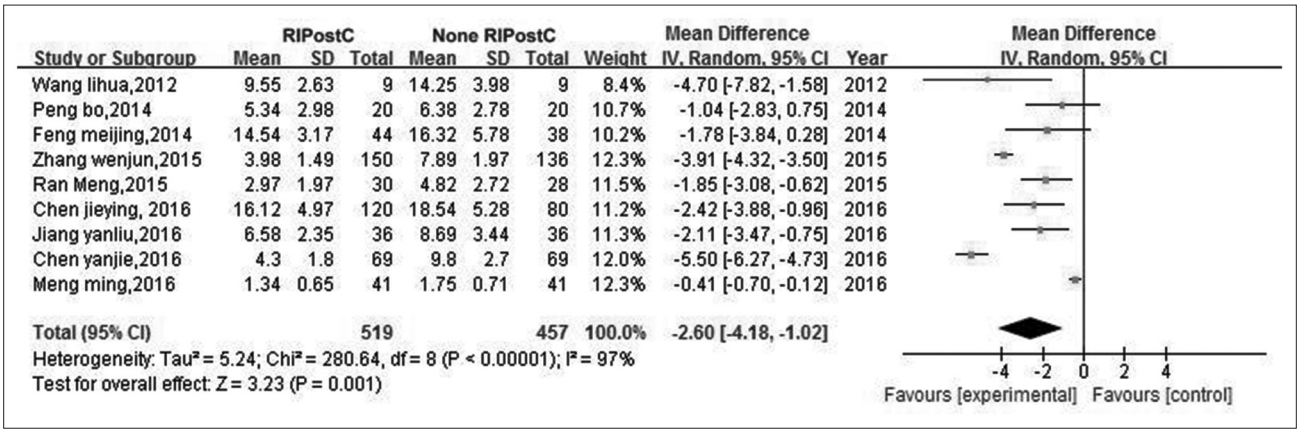

Figure 5: Forest plot for National Institutes of Health Stroke Scale score. RIPostC: Remote ischemic postconditioning; *CI*: Confidence interval.

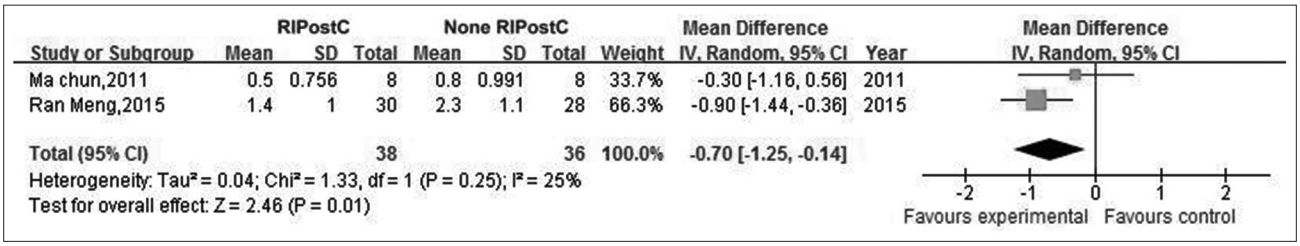

Figure 6: Forest plot for modified Rankin Scale score. RIPostC: Remote ischemic postconditioning; *CI*: Confidence interval.

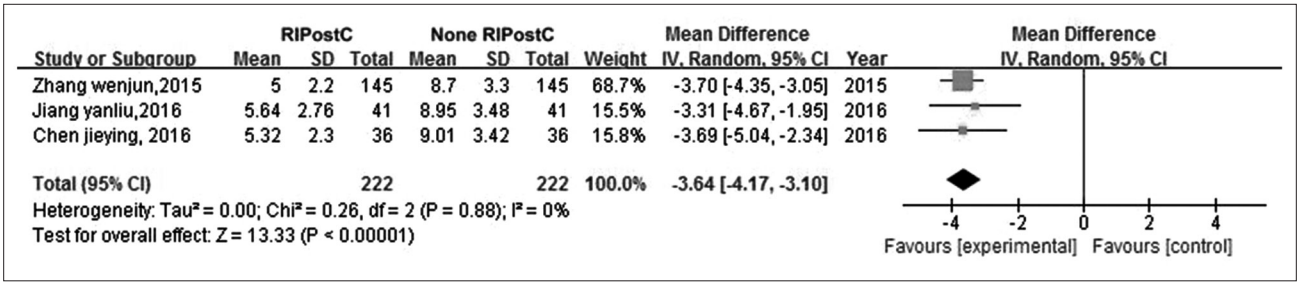

Figure 7: Forest plot for high-sensitivity C-reactive protein. RIPostC: Remote ischemic postconditioning; *CI*: Confidence interval.

5-min RIPostC were also proven to reduce cardiac enzyme levels and the PCI-related myonecrosis rate in the study conducted by Ghaemian *et al.*[43] Moreover, one cycle of 5-min RIPostC remained to be cardioprotective in Zografos *et al.*'s study.[44] In summary, the present evidence suggests that 5-min ischemic stimulus for conditioning protocol in RIPostC is essential. In this review, eight of 13 of the included studies used five cycles of 5-min/5-min, three studies used three cycles of 5-min/5-min, one study used three cycles of 5-min/10-min, and one study used five

cycles of 2-min/4-min for conditioning. This might influence the results of RIPostC on patients with stroke. Due to the quantity of included studies, a subgroup analysis could not be conducted. Future studies should verify whether the increase in conditioning cycle of RIPostC might result in enhanced organ protection in these clinical settings. Therefore, it is possible that some studies used a form of conditioning, which is not sufficient to achieve the maximal protective effect.

This review revealed that the adjunct use of RIPostC resulted in a larger reduction in NIHSS scores. This result suggests that the estimated effect of RIPostC as a cointervention to conventional treatment is relevant and potentially important to stroke patients in real-world practice.

Limitations

Although the meta-analysis provided information on the role of RIPostC in ischemic stroke patients, several limitations should be considered. First, most of the methodological quality of the included studies is not high. The present study revealed that remote postconditioning reduced the incidence of stroke or TIA. Second, in the parameters for conditioning, the procedure of postconditioning was not unified in the included studies. Finally, in the present review, RCTs of various interventions were included to gain a broad perspective on evidences regarding the use of RIPostC for ischemic stroke, and this caused heterogeneity in the meta-analysis. In addition, clinical and methodological heterogeneity could not be well addressed by subgroup or sensitivity analysis. Therefore, most results presented in this review were the average effects of RIPostC on stroke estimated by a random-effects model.

Conclusion

In summary, this study reveals that RIPostC decreases the risk of cerebrovascular event in patients undergoing ischemic stroke, when compared with controls. However, the included studies are of low methodological quality and had a limited scope, and the results have some inevitable biases. Future research should clarify the mechanism, in order to explore the full play of its cerebral protective effect. At the same time, it is necessary to have a high-quality, large scale, multi-center RCT for RIPostC.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

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Conflicts of interest

There are no conflicts of interest.

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远端缺血后适应治疗缺血性中风随机对照试验的系统综述和荟萃分析

摘要

背景： 远程缺血后处理(RIPostC)可保护远处器官免受缺血再灌注损伤。然而，这一方法在关于脑保护的方面还没有定论。所以，我们对使用RIPostC和不使用RIPostC对缺血性中风患者的治疗疗效进行荟萃分析。

方法： 计算机检索PubMed、The Cochrane library、CNKI、维普和万方等中英文数据库，检索时限均为各数据库建库至2016年7月，纳入所有以RIPostC为干预措施的随机对照试验，对纳入研究进行方法质量的评价并提取数据，采用Cochrane 协作网提供的RevMan 软件进行数据分析。

结果： 经过筛选，我们共纳入13个研究，794例患者。Meta分析结果显示：与对照组相比，RIPostC能有效减少脑卒中和短暂性脑缺血发作(TIA)复发率(危险比[*RR*]= 0.37; 95% 可信区间[*CI*]:0.26 – 0.55; *P* <0.00001)，降低美国国立卫生研究院卒中量表(NIHSS评分,均差[MD]:1.96; 95% *CI*: 2.18 – 1.75; *P* <0.00001)、改良RANKIN量表(mRs评分,MD: 0.73; 95% *CI*: 1.20–0.25; *P*=0.00300)和超敏C反应蛋白(hs-CRP, MD: 4.17; 95% *CI*: 4.71 – 3.62; *P*<0.00001)。此外，RIPostC在肢体周围使用止血带袖对不同干预时间治疗缺血性中风无副作用。

结论： 此研究分析表明，RIPostC可能对脑缺血再灌注损伤的患者或处于脑缺血再灌注损伤危险的患者提供脑保护作用。

Supplementary Table 1: Search strategy in PubMed

Categories	Search terms
Condition	1. Stroke (MeSH terms)
	2. Strokes
	3. Apoplexy
	4. CVA
	5. CVAs
	6. Cerebrovascular accident
	7. Cerebrovascular accidents
	8. Cerebrovascular apoplexy
	9. Apoplexy, cerebrovascular
	10. Cerebrovascular stroke
	11. Cerebrovascular strokes
	12. Stroke, cerebrovascular
	13. Strokes, cerebrovascular
	14. Vascular accident, brain
	15. Brain vascular accident
	16. Brain vascular accidents
	17. Vascular accidents, brain
	18. Cerebral stroke
	19. Cerebral strokes
	20. Stroke, cerebral
	21. Stroke, acute
	22. Acute stroke
	23. Acute strokes
	24. Strokes, acute
	25. Cerebrovascular accident, acute
	26. Acute cerebrovascular accident
	27. Acute cerebrovascular accidents
	28. Cerebrovascular accidents, acute
	29. Brain infarction
	30. Cerebral infarction
	31. #1-#30/OR
Intervention	32. RIPostC
	33. Remote ischemic preconditioning
	34. Ischemic preconditioning
	35. Ischemic preconditioning limb
	36. Remote preconditioning
	37. Remote ischemic postconditioning
	38. Ischemic postconditioning
	39. Remote postconditioning
	40. #32-#39/OR
Study type	41. Randomized controlled trial (publication type)
	42. Controlled clinical trial (publication type)
	43. Randomized (title/abstract)
	44. Placebo (title/abstract)
	45. Clinical trials as topic (MeSH: No extended)
	46. Randomly (title/abstract)
	47. Trial (title)
	48. Animals (MeSH terms)
	49. #41-#47/OR NOT (#48 NOT #49)
	50. #31 AND #40 AND #49

Comprehensive Chinese search strategy: #1: 中风 OR 脑梗死 OR 脑缺血 OR 脑血管病; #2: 远端缺血预处理 OR 远程缺血预处理 OR 远端缺血预适应 OR 远程缺血预适应 OR 肢体缺血预适应 OR 肢体缺血预处理 OR 远端缺血后适应 OR远程缺血后处理 OR 远端缺血后适应 OR 远程缺血后适应 OR 肢体缺血后适应 OR 肢体缺血后处理; #3: #1 AND #2. (#1: stroke OR cerebral infarction OR cerebral ischemia OR cerebrovascular disease; #2: Remote ischemic preconditioning OR Ischemic preconditioning limb OR Remote ischemic postconditioning OR Ischemic postconditioning limb; #3: #1 AND #2.) CVA: Cardiovascular accident; RIPostC: Remote ischemic postconditioning.