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Safety and efficacy of remote ischemic preconditioning in patients with severe carotid artery stenosis before carotid artery stenting: A proof-of-concept, randomized controlled trial

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Keywords
Ischemic Preconditioning; Stroke; Carotid Arteries; Stents; Brain Infarction; Angioplasty

Abstract

Background: Remote ischemic preconditioning (RIPC) has been proposed as a possible potential treatment for ischemic stroke. This study aimed to investigate the frequency of micro-embolic brain infarcts after RIPC in patients with stroke who underwent elective carotid artery stenting (CAS) treatment.

Methods: This study was managed at Shiraz University of Medical Sciences in southwest Iran. Patients undergoing CAS were randomly allocated into RIPC and control groups. Patients in the RIPC group received three intermittent cycles of 5-minute arm ischemia followed by reperfusion using manual blood cuff inflation/deflation less than 30 minutes before CAS treatment. Afterward, stenting surgery was conducted. Magnetic resonance imaging (MRI), including diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC), was acquired within the first 24 hours after CAS.

Results: Seventy-four patients were recruited (79.7% men, age: 72.30 ± 8.57). Both groups of RIPC and control

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had no significant difference in baseline parameters (P > 0.05). Fifteen patients (40.5%) in the RIPC group and 19 (54.1%) patients in the control group developed restricted lesions in DWI MRI. In DWI+ patients, there were no significant differences according to the number of lesions, lesion surface area, largest lesion diameter, cortical infarcts percent, and ipsilateral and bilateral infarcts between the two groups.

Conclusion: Although RIPC is a safe and non-invasive modality before CAS to decrease infarcts, this study did not show the advantage of RIPC in the prevention of infarcts following CAS. It may be because of the small sample size.

Introduction

Stroke is a global health issue worldwide.[1] Meanwhile, large arterial stenosis is considered as an operable cause of ischemic stroke.[2] Carotid artery stenting (CAS) has been increasingly applied as a replacement for the invasive carotid endarterectomy (CEA) in cases with CAS.[3] Nonetheless, transient ischemic attack (TIA), ischemic strokes, intracerebral hemorrhage (ICH), myocardial infarction (MI), and death are the most adverse complications of these interventions.[4] Micro-embolic infarcts have been identified as a crucial issue for CAS, and their deleterious effects on cognition have been well known.[5,6] Thus, despite being a life-saving treatment, CAS can exert disabling side effects. This issue has encouraged researchers to pursue establishing effective alternative preventive strategies for patients with CAS.

Remote ischemic preconditioning (RIPC), mainly administered in patients with cardiovascular disorders,[7] has been recently introduced in the field of neurology as well.[8,9] RIPC is aimed to provide systemic protection against subsequent ischemia in distant organs through repeated episodes of inducing harmless limb ischemia.[10] The exact method and timing for different purposes applied in various studies are diverse. However, the underlying mechanism pivots around inflammatory mediators' complex interaction and responses.[11] The critical role of inflammatory pathways is well-established concerning the stability of plaques and vascular endothelial damage. Accordingly, inflammation biomarkers such as C-reactive protein (CRP) are widely used for evaluation.[12] Although the protective and beneficial effects of RIPC have been demonstrated in some animal and human studies,[8] other studies have reported that clinical outcomes and final infarct size did not differ after RIPC.[9] Nonetheless, data surrounding this matter are scarce, and little is known about the efficacy and safety of RIPC in patients undergoing CAS.

Regarding the large-scale referral of patients with CAS to our center, we designed the current study to determine the outcome of RIPC in a sample population of Iranian patients. In this prospective study, the risk of post-procedural strokes and silent brain infarcts was compared between patients who underwent RICP before CAS and the control group. We hypothesized that RICP might decrease the clinical and magnetic resonance imaging (MRI) presentation of embolic infarcts after CAS. As a perspective, if our hypothesis is true, we may advocate RIPC as a simple, inexpensive, and noninvasive modality before CAS.

Materials and Methods

Patients and design: This prospective interventional study was a proof-of-concept, randomized controlled evaluator-blinded clinical trial. Symptomatic CAS was confirmed by amaurosis fugax, the TIA, and minor or not very severe stroke (in the region supplied by the occluded target vessel), which happened 180 days before the randomization time.

Eligible patients with the following inclusion criteria were included: age between 18 to 90 years and the presence of internal carotid artery (ICA) stenosis, more than 70% by ultrasound or more than 50% by angiography according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. Patients with the following criteria were excluded: evolving stroke, hemorrhagic transformation of an ischemic stroke within the past 60 days, prior major ipsilateral stroke confounding study endpoints, MI within the past 30 days, chronic atrial fibrillation (AF), bilateral severe stenosis or occlusion of upper limb arteries, allergic reaction or intolerance to medications including aspirin and clopidogrel, and severe dementia.

This is a cross-sectional study performed on patients with symptomatic CAS from January 2016 to January 2018 at Kowsar Hospital, affiliated with Shiraz University of Medical Sciences, Shiraz, Iran.

Written informed consent was taken from all patients. The confidentiality of the patients' data was guaranteed. The study protocol was under the Declaration of Helsinki of bioethics and approved by the Ethics Committee of Shiraz University of Medical Sciences (Approval No.: 93-01-94-8345).

Procedure: The patients were randomly

allocated into the case group (undergoing true RIPC) and the control group (undergoing sham procedure) using block randomization. For all participants in the RIPC group, three consecutive inflations by sphygmomanometer cuff on the right upper arm were performed before CAS. The cuffs were inflated to 200 mmHg for five minutes, followed by a five-minute deflation interval between occasions. Thus, the entire preconditioning phase lasted 30 minutes. The patients in the control group had the same procedure, but the cuff was only inflated to 60 mmHg. Patients, interventionists, and neurologists who evaluated the MRIs were totally blinded to this random allocation.

The details of pre-, intra-, and post-procedural anti-platelet/anti-coagulant regimen, distal embolic protection utilization, stenting, and pre- and post-dilation ballooning were according to our previously published studies.[3,4] All participants were followed for six months after CAS procedures.

According to Rismanchi and Borhani-Haghighi's study[13] and considering α = 0.05 (type 1 error) and 1-β = 0.95 (test power), 37 people were obtained for each group.

$$n = \frac{(Z_{1-\alpha/2}\sqrt{2\bar{p}\,\bar{q}} + Z_{1-\beta}\sqrt{p_1q_1 + p_2q_2})^2}{(\delta)^2}$$

1-β: Test Power=0.95
α: Type 1 error =0.05
Z_(1-β): Critical value=1.645
Z_(1-α⁄2): Critical value=1.96
δ=|p_2-p_1|
$\bar{(p)}$=(P_1+P_2)/2

Imaging: Within the first 24 hours after CAS, a brain MRI was taken using Siemens 1.5 Tesla MRI machine. The studied MRI sequences and procedures were described previously.[13] For evaluating any new ischemic lesion during the trial and differentiating them from old ones, lesions with diffusion restriction [hyperintense in diffusion-weighted imaging (DWI) and hypointense in apparent diffusion coefficient (ADC)] were considered and interpreted.

The primary outcome was the appearance of new micro-embolic brain infarcts (DWI restricted) in patients who underwent CAS. Secondary outcomes were the largest lesion diameter, the number of lesions, accumulated lesion surface area, the average surface area (accumulated lesion surface area/number of lesions), location (cortical vs. subcortical), and laterality (ipsilateral vs. contralateral to the target vessel) of DWI lesions. Two independent neurologists, who were blinded in terms of clinical status and grouping of patients, studied the images, and the differences were later examined and adjusted.

Data analysis was conducted with SPSS software (version 21.0, IBM Corporation, Armonk, NY, USA). Continuous values are presented as mean ± standard deviation (SD) and categorical variables as frequency and percentage. Fisher's exact test, Mann-Whitney test, or Student's t-test were used when mandatory. P-values less than 0.05 were deemed significant.

Results

Seventy-four patients were recruited (79.7% men, 72.30 ± 8.57 years old); 37 left ICA (LICA) and 37 right ICA (RICA) were stented. The major risk factors of atherosclerosis, including hypertension (HTN), hyperlipidemia, smoking, and diabetes mellitus (DM) were found in 53 (71.6%), 38 (51.4%), 28 (40.0%), and 26 (35.1%) patients, respectively. Moreover, pre-dilation was performed in 17 (23.0%) patients and post-dilation in 65 (87.8%) patients. Pre-procedural and residual stenosis was 78.60 ± 14.45 and 13.75 ± 12.60, respectively.

The baseline parameters of study participants were summarized in table 1. There was no statistically significant difference between the two groups concerning comorbidities, smoking status, clinical status, and baseline laboratory data (P > 0.050).

Closed-cell stents were used in 25 (67.6%) and 27 (75.0%) patients in the RIPC and control groups, respectively. Hybrid-cell stents were used in 12 (32.4%) participants in the RIPC group and 9 (25.0%) participants in the control group (P = 0.480). There was one missing data in the control group.

Of 34 patients (45.9%) who developed diffusion-restricted lesions, 15 (40.5%) patients were in the RIPC group, and 19 (54.1%) patients were in the control group, which was non-significant (P = 0.350).

In all DWI+ patients, on average, each patient had 3.69 ± 3.77 lesions. The largest lesion diameter, average surface area, and accumulated lesion surface area were 11.45 ± 5.56, 30.03 ± 26.45, and 100.08 ± 101.01, respectively. 39.4% of patients had cortical lesions, and 90.9% had subcortical lesions. Meanwhile, 97% of patients represented ipsilateral lesions, and 36.4% did contralateral to the target vessels. Table 2 represents lesion characteristics (factors describing microinfarcts derived from MRI) in RICP and control groups.

Table 1. Comparison of baseline parameters in carotid artery stenting (CAS) groups

Parameters	CAS groups		P
	RIPC (n = 37)	Control (n = 37)	
Age (year)	71.00 ± 8.41	72.78 ± 8.18	0.940**
DWI+ patients	15 (40.5)	19 (51.4)	0.350*
Gender			
Men	31 (83.8)	28 (75.7)	0.380*
Women	6 (16.2)	9 (24.3)	
Comorbidities			
DM	17 (45.9)	9 (24.3)	0.051*
HTN	25 (67.6)	28 (75.7)	0.430*
Hyperlipidemia	23 (62.2)	15 (40.5)	0.060*
EPD use	23 (92.0)	29 (85.3)	> 0.999*
Smoking	13 (35.1)	15 (45.5)	0.370*
Laboratory data			
Creatinine	1.26 ± 0.36	1.23 ± 0.20	0.610***
WBC	7.92 ± 1.93	8.12 ± 2.42	0.120**
Hemoglobin	13.33 ± 1.71	13.11 ± 2.59	0.550**
Platelet	253.62 ± 73.00	246.08 ± 98.50	0.790**
Clinical status			
Asymptomatic	21 (56.8)	13 (35.1)	0.060*
Symptomatic	16 (43.2)	24 (64.9)	
Pre dilation			
Yes	5 (13.5)	12 (32.4)	0.053*
No	32 (86.5)	25 (67.6)	
Post dilation			
Yes	34 (91.9)	31 (83.8)	0.470*
No	3 (8.1)	6 (16.2)	
Stent brand			
Cristallo (hybrid-cell)	12 (32.4)	9 (25.0)	0.480*
Wallstent (closed-cell)	25 (67.6)	27 (75.0)	

Data are presented as mean ± standard deviation (SD) or number and percentage
*Chi-square test; **T-test; ***Mann-Whitney test
CAS: Carotid artery stenting; RIPC: Remote ischemic preconditioning; DWI: Diffusion-weighted imaging; DM: Diabetes mellitus; HTN: Hypertension; EDP: Embolic protection device; WBC: White blood cell

In DWI+ patients, there were no significant differences according to the number of lesions, lesion surface area, largest lesion diameter, cortical infarcts percent, and ipsilateral and bilateral infarcts between RICP and control groups.

Based on brain MRI findings, 22 (55.0%) patients in the RIPC group did not show lesions following stenting, while 15 (44.1%) patients showed brain lesions in MRI. In the control group, these were 18 (45.0%) patients versus 19 (55.9%) patients in the MRI- and MRI+ groups, respectively. The difference was not significant (P = 0.350). In addition, there were no significant differences between MRI+ and MRI- groups after doing CAS regarding mean age, gender, comorbidities, smoking, pre-dilation, laboratory data, clinical status, and lesion characteristics.

Discussion

In this study, we picked out the results from the composite endpoint according to previous studies that found changes relevant to the specific organ system. Although most studies have concentrated on how RIPC affects clinical stroke,[14] we studied the incidence and size of infarction following CAS.

Our results are consistent with some other studies investigating RIPC in patients who underwent CEA, abdominal aneurysm repair, or peripheral revascularization. They reported no difference between case and control groups regarding biomarkers or outcomes.[15]

In this line, some studies showed no significant effect on final infarct size and risk of tissue infarction after RIPC in stroke patients.[9] However, other studies have documented reduced white matter lesions and tissue risk of infarction following RIPC.[16] It may be due to differences in the design and method of the studies. Particularly, the method of induction of ischemia/reperfusion cycles was different.

Table 2. Comparison of factors describing microinfarcts based on magnetic resonance imaging (MRI) in two groups

Parameters	MRI positives group		P
	RIPC (n = 15)	Control (n = 19)	
Lesion surface area (mm^2) (mean ± SD)	101.24 ± 111.52	99.12 ± 94.66	
Maximum	387.72	398.89	0.580**
Minimum	11.50	11.61	
Average surface area (mm^2) (mean ± SD)	30.07 ± 19.85	30.00 ± 31.50	
Maximum	90.63	150.00	0.420**
Minimum	11.50	8.73	
Number of lesions (mean ± SD)	3.40 ± 3.62	3.94 ± 3.99	
Maximum	12.00	18.00	0.280**
Minimum	1.00	1.00	
Largest lesion diameter (mm) (mean ± SD)	10.93 ± 5.02	11.89 ± 6.08	
Maximum	23.00	29.00	0.620**
Minimum	5.50	5.00	
Contralateral infarct (%)	40.00	33.30	0.690*
Ipsilateral infarct (%)	100	94.40	> 0.999*
Cortical infarct (%)	46.70	33.30	0.430*
Subcortical infarct (%)	80.00	100	0.080*
Bilateral infarct (%)	40.00	55.60	0.370*

*Chi-square test; **Mann-Whitney test

MRI: Magnetic resonance imaging; RIPC: Remote ischemic preconditioning; SD: Standard deviation

The duration of the pre-procedural interval for preempted RICP differed from several days to several months.[8,17,18] As an instance, Zhao et al. documented that RICP could diminish both incidence and the average surface area in patients who underwent CAS.

Their RIPC method was done with synchronous bilateral upper arm ischemia using an electric auto-control device with cuffs. It consisted of five rounds of five-minute ischemia and five-minute reperfusion, which were repeated two times a day for two weeks before CAS, that obviously differed from our method.[8]

We did not observe serious local or systemic adverse effects following the RIPC procedure, except in one participant in the RIPC group who experienced cuff extrusion-related petechiae on the arm. This complication has similarly occurred in some previous studies.[8,13] Besides, since most patients tolerated the RIPC method, it seems to be a low-cost, safe, and accessible strategy to apply to those undergoing CAS. However, mainly due to the small sample size, we could not detect a better outcome after RIPC.

The most substantial drawback of the current study was the small sample size. Moreover, using manual cuff pressure may cause an operator error. Hence, using digital cuff pressure may be better. For further follow-up in the next six months, it is better to do another DWI MRI.

Conclusion

Although RIPC was a safe and non-invasive modality before CAS to decrease infarcts, this study did not show the advantage of RIPC in the prevention of infarcts following CAS. However, further large-scale trials may be worthwhile to determine the efficacy of RIPC in the prevention of symptomatic or asymptomatic embolic stroke after CAS. Furthermore, the optimal treatment protocol for RIPC needs further investigation.

Conflict of Interests

The authors declare no conflict of interest in this study.

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