Prehospital application of remote ischaemic perconditioning in acute ischaemic stroke patients in Catalonia: the REMOTE-CAT clinical trial

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Summary

Background Acute ischaemic stroke (IS) remains one of the leading causes of morbidity and mortality worldwide. Remote ischaemic perconditioning (RIperC) is a neuroprotective treatment with promising preclinical results, acting through humoral and neural mechanisms. This trial aimed to evaluate the clinical benefits of prehospital-initiated RIperC in acute IS patients.

Methods REMOTE-CAT was a multicentre, randomised, double-blind, sham-controlled trial across four Catalonian stroke centres. Patients over 18 years with stroke symptoms under 8 h, a pre-stroke modified Rankin Scale (mRS) score <3, and motor deficits (RACE motor score ≥1) were randomised 1:1 to active RIperC or sham. RIperC was applied via an automated cuff on the unaffected arm in five 5-min inflation–deflation cycles. Investigators and participants were blinded to treatment. The primary outcome was the proportion of patients with a favourable outcome (mRS <3) at 90 days. The intention-to-treat analysis included all patients receiving at least one inflation–deflation cycle and had a final diagnosis of ischaemic stroke or transient ischaemic attack (ClinicalTrials.gov: NCT03375762).

Findings Between August 2019 and December 2023, 350 patients were screened, with 200 randomised. After 78 exclusions (29 haemorrhagic strokes, 41 stroke mimics, and 8 patients with mRS >3), 122 patients were included in the primary analysis (RIperC group, n = 57; sham group, n = 65). The RIperC group had a higher proportion of mRS <3 at 90 days (64.9%) than the sham group (47.3%), though not statistically significant in the unadjusted analysis (OR 2.03 [95% CI 0.98–4.21], p = 0.057 However, statistical significance was achieved in the post-hoc analysis adjusted for age, baseline status (determined by pre-stroke mRS score), and initial stroke severity (measured by baseline RACE score by paramedics) (OR 2.94 [95% CI 1.21–7.16], p = 0.017). No serious adverse events were observed.

Interpretation Despite the small sample size, our findings suggest that prehospital application of RIPerC is safe and may confer clinical benefit, as indicated in the post hoc adjusted analysis. However, larger, adequately powered trials are required to validate these results, and to determine potential differential effects across underrepresented patient subgroups.

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Research in context

Evidence before this study

Remote ischaemic perconditioning (RIPerC), involving cycles of compression and decompression on a non-paretic limb during ambulance transport, has been investigated as a strategy to induce remote ischaemic tolerance. While two clinical trials have demonstrated its feasibility and safety, no established evidence supports its benefit on neurological outcomes at 90 days despite promising preclinical data. The RESIST trial suggested a potential benefit in patients without large vessel occlusion, particularly those with a lacunar profile.

Added value of this study

Our study further confirms the feasibility and safety of RIPerC in the prehospital setting for patients with suspected ischaemic stroke evolving for less than 8 h and presenting with motor deficits at the time of inclusion. Moreover, in a post hoc analysis adjusted for age, baseline status, and initial stroke severity, a potential benefit of RIPerC was observed.

Implications of all the available evidence

Given the limitations of the sample size, our study highlights the need for clinical trials to confirm the preliminary evidence of RIPerC's benefit.

Introduction

Despite substantial advancements in the implementation of code stroke protocols and the availability of reperfusion therapies, ischaemic stroke (IS) remains a leading cause of morbidity and mortality worldwide, contributing significantly to the global burden of disability and healthcare costs. In this context, neuroprotective strategies that improve outcomes in both patients treated with reperfusion therapies and those who are not treated represent a critical area of research.[1,2] Remote ischaemic perconditioning (RIperC) represents a novel paradigm in neuroprotective treatments, involving brief and controlled cycles of ischemia-reperfusion applied to a limb during cerebral ischemia onset.[3] Preclinical models have highlighted its potential benefits, purportedly mediated through both humoral and neural mechanisms, with effects on oxidative stress, inflammation, haemodynamics, immune responses, autophagy, and apoptosis.[4]

In 2017, the RIPerC among acute IS patients in Catalonia, Spain (REMOTE-CAT) clinical trial[5] was proposed based on initial successful experiences in prehospital application of RIPerC among acute myocardial infarction patients[6,7] and on the demonstration of the feasibility and safety of RIperC in acute IS patients.[8,9] At that time, the RESCUE brain clinical trial, which evaluated the application of RIperC after patient assessment upon arrival at the hospital and following the demonstration of cerebral ischemia on neuroimaging, was started.[10] The hypothesis was that the neuroprotective phenomenon associated with RIperC would improve the outcomes not only for patients receiving reperfusion therapies but also for those who were not.[5] To achieve this, a multicentre project was designed with the intention of recruiting a significant number of patients, total of 572 patients.[5] We present the results of our multicentre, randomized, sham-controlled study conducted to determine whether prehospital RIPerC treatment improves functional outcomes in acute IS patients.

Methods

Study design and participants

REMOTE-CAT was an investigator-initiated, multicentre, randomised, double-blind, sham-controlled study undertaken in four stroke centres in Catalonia (Spain). This clinical trial was conducted in the Catalonia region, with the participation of the Emergency Medical Services (EMS) and four stroke centres (Supplementary Figure S1). Two centres were "mothership centres" performing thrombectomy procedures. One centre operated as a "drip-and-ship" facility and did not perform thrombectomies. The fourth centre performed thrombectomies only during office hours on working days. The details of the study protocol were published previously.[5] We included code stroke patients in the prehospital setting who were older than 18 years, had symptoms of less than 8 h of evolution, had a pre-stroke modified Rankin Scale (mRS) <3, and presented with motor symptoms at the time of inclusion, as determined by a Rapid Arterial Stroke Evaluation (RACE) scale score of one or higher.[11] Exclusion criteria included patients with unknown symptom onset, those in a coma, pregnant patients, participants in other clinical trials, and those with malignancy or significant comorbidity thought to indicate a life expectancy of less than 6 months.

Ethics

The trial was approved was approved by a central ethics committee (Ethics Committee on Clinical Research of

the Hospital Universitari Arnau de Vilanova de Lleida, Spain; code 1744) and by the ethics committee at each participating centre. The clinical trial received approval from the Spanish Medical Agency and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The trial protocol was developed following the CONSORT 2010 guidelines and was registered on ClinicalTrials.gov (NCT03375762).

Written informed consent was obtained from all participants. In the prehospital setting, patients, their legal deputies, or family members were informed about the study by paramedics from basic life support units, who routinely attend to suspected code stroke patients within the study region.[12] Subsequently, all patients or their surrogates provided written informed consent upon hospital arrival. If a patient exhibited severe language impairment or loss of consciousness, and no legal representative or family member was available at the time of admission, immediate consent was deferred. In these cases, where emergency consent was necessary, written informed consent was obtained from the patient or their legal representative during follow-up.

Randomization and masking

The randomization process was performed on a 1:1 ratio using block randomisation (block size 4), stratified by RACE score (1–3, 4–6 and 7–9) into one of the treatment groups. A centralized web server hosted on the EMS cloud was used to allocate randomization. In the prehospital setting, paramedical professionals received the patient's assignment from the EMS coordination centre and applied the RIperC device (active or sham group). Masking was achieved as the RIperC devices were designed identically, and both produced an inflation-like noise, ensuring that paramedical professionals remained unaware of the assigned experimental groups.

Procedures

In the intervention group, an automated cuff (autoRIC™, CellAegis Devices, partner CELL; Toronto; Canada) was placed on the upper non-affected arm and inflated to 200 mmHg for 5 min and then deflated for 5 min. As previously described,[5] the RIperC intervention consisted of five cycles resulting in a total duration of 50 min. For the sham group, a sham cuff that simulated the autoRIC™ device with the same sound and vibration was used. The total number of inflations, as well as any discomfort or complications related to RIPerC were registered. The treatment started in the prehospital setting immediately after randomization and, if necessary, continued in the hospital to complete the five programmed cycles. Blood pressure was recorded upon hospital arrival, at the end of cycles, and 1 h afterwards. The diagnosis was confirmed in the hospital. The target population was patients with IS. We excluded haemorrhagic and mimic stroke patients from the analysis.

All randomized patients underwent standardized clinical assessments, including demographic characteristics, medical history, laboratory values, and stroke severity. Patients were treated according to conventional care procedures following international guidelines[13,14] and received individualized neurorehabilitation as considered appropriate. Time to revascularization therapies, including (MT) thrombectomy and/or intravenous fibrinolysis were recorded.

The National Institutes of Health Stroke Scale (NIHSS) assessment was conducted upon hospital arrival, at 24 h, and at 5 days for patients diagnosed with IS. Clinical evaluations were performed by blinded investigators at each centre, ensuring impartiality regarding group assignment. Similarly, mRS assessment was also conducted at 5 days in each centre. The mRS at 90 days was centrally evaluated through a structured telephone-based interview[15] by two certified assessors blinded to group assignment. In cases where intravenous thrombolysis (IVT) and/or mechanical thrombectomy (MT) were administered, follow-up brain imaging was performed at 24 h using computed tomography (CT) and CT-angiography (CTA), in accordance with guideline recommendations. Patients were classified etiologically according to the definitions from the Trial of ORG 10,172 in Acute Stroke Treatment (TOAST)[16] as large artery atherosclerosis (LAA), small vessel occlusion, cardioembolism, stroke of other determined aetiology, or stroke of undetermined aetiology. The TOAST classification was established after completing the diagnostic workup. If the initial etiological classification was undetermined, the identification of a cardioembolic source during follow-up led to a reclassification of the stroke subtype.

Patients without contraindications who were clinically stable and had provided consent, a brain MRI was preferably performed within the first 7 days following the event, including at least the following sequences: transverse T2-FLAIR, transverse T2*, isotropic diffusion-weighted imaging (DWI) with a b value of 1000 s/mm^2, and transverse 3D time-of-flight MR angiography. The same MRI protocol,[5] previously published, was followed at each stroke centre. An independent review of all MRI scans was conducted by a central imaging core lab (AR).

Clinical data were verified by independent monitors (Clinical research support unit, IRBLleida, Lleida, Spain).

Outcomes

The primary outcome was the proportion of patients with good outcomes, as defined by a mRS score less than 3 at 90 days. The secondary outcome variables included: 1) a shift analysis of the mRS across the full ordinal scale (0 [no symptoms] to 6 [dead]) at 90 days; 2) the proportion of patients with a decrease in the National Institutes of Health Stroke Scale (NIHSS)

score of 4 or more points between baseline and 24–36 h, and 5 ± 1 days; 3) the rate of serious adverse events related to the intervention; 4) the rate of symptomatic intracerebral haemorrhage (SICH) as defined by the Safe Implementation of Thrombolysis in Stroke Monitoring Study protocol[17] at 24–36 h; and 5) acute infarct volume defined as the hyperintense area on the DWI. The infarct volume was calculated by a single, blinded, trained technician using a semi-automated tool included in the OLEA Sphere software (Olea Medical, France).

There was no industry funding or involvement, and no patent application has been filed in relation to this work.

Statistics

The study was designed to have a statistical power of 80% and a two-sided α level of 0.05 to assess the efficacy of RIperC in improving functional outcomes compared to the standard of care. As previously published,[5] we initially estimated a sample size of 572 patients, with an equal allocation (1:1 ratio) to the active or sham groups, to detect a 14% difference in treatment efficacy. This estimation assumed that 40% of patients in the control group would achieve a good outcome, defined as a mRS score less than 3 at 90 days. Additionally, we accounted for a misdiagnosis rate of 29%, comprising 15% for haemorrhagic strokes and 14% for stroke mimics, based on data from the prospective population-based registry of stroke code activations in Catalonia (CICAT) in 2017.[18]

Continuous variables were summarized as means with standard deviations for normally distributed data, and as medians with interquartile ranges (25th–75th percentiles) for non-normally distributed data. The Shapiro–Wilk test was used to assess normality, with a p-value of <0.05 indicating rejection of normality. Categorical variables were summarized using counts and percentages. Statistical comparisons between both groups of intervention were made using Pearson's chi-squared test for categorical variables or Fisher's exact tests when counts were below 5, the t-test for normally distributed continuous variables, and the Mann–Whitney U-test for non-normally distributed continuous variables. Adjusted risk ratios were estimated using log-binomial regression models.

The study aimed to evaluate the effectiveness of RIPerC in patients with IS or transient ischaemic attack (TIA), without expecting a beneficial effect in those with intracerebral haemorrhage (ICH) or stroke mimics. Given that patient enrolment and intervention initiation occurred in the prehospital setting by paramedics, with final diagnoses confirmed upon hospital admission, all randomised patients who received at least one inflation–deflation cycle and were ultimately diagnosed with IS or TIA were included in the intention-to-treat (ITT) analysis. While the original study protocol did not explicitly exclude patients with ICH from the ITT population, this clarification was made in the subsequently published protocol.[5] In addition to the ITT analysis, a complementary safety analysis was conducted, encompassing all randomised patients with an initial suspicion of stroke, including those later diagnosed with ICH or stroke mimics. This broader analysis aimed to assess the safety of RIPerC in the real-world prehospital setting, where the initial stroke code activation is based on clinical suspicion rather than definitive imaging.

The primary efficacy analysis assessed the difference in the proportion of patients with good outcomes, defined as an mRS score of 2 or less at 90 days, using a binomial regression model. The published protocol[5] initially proposed adjusting for variables exhibiting baseline differences between the two groups as covariates. However, given the absence of such differences, as outlined in the results section, the primary outcome was initially analysed without adjustment. A post-hoc analysis was subsequently conducted, adjusting for age, baseline stroke severity as assessed by the RACE score (determined by paramedics during initial prehospital evaluation), and pre-stroke functional status as measured by the mRS, to explore the potential impact of confounders. Regression results were reported as odds ratios (ORs) with 95% confidence intervals (CIs), derived from model coefficient estimates. A per-protocol (PP) analysis was conducted as a secondary sensitivity analysis, including only patients with confirmed ischaemic stroke and a pre-stroke mRS score of less than 3 who completed all five treatment cycles.

Secondary outcomes included the shift in the mRS at 90 days, estimated by differences in the proportion of patients across each mRS category using an ordinal logistic regression model. The model estimated the overall treatment effect as an OR with a 95% CI). Additionally, we evaluated differences in the proportion of patients with worsening in the NIHSS score by more than 4 points at 24 h and 5 days compared to baseline between the two treatment groups. These outcomes were analysed using Pearson's chi-squared test or Fisher's exact test when the expected cell frequency was less than 5. Finally, differences in the volume of ischaemic lesions observed on DWI were expressed by analysing the differences in median and interquartile range (25th–75th percentiles) between the two groups using the Mann–Whitney U test.

An adjusted ordinal logistic regression model was employed to assess the heterogeneity of the effect of RIPerC vs sham on the primary outcome across prespecified subgroups. Post-hoc subgroup analyses were performed using logistic regression models fitted for each variable, incorporating both main effects (treatment group: sham/RIPerC), the sublevels of each variable, and their interaction term. Estimated marginal means were subsequently used to compute the odds ratios and their 95% confidence intervals for each sublevel. All statistical tests were 2-sided, and $p < 0.05$ was

considered statistically significant. SPSS version 27 (IBM Corporation), and R version 4.1.0 (R Development Core Team; http://www.r-project.org) were used for the statistical analyses.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Patients

Between August 19, 2019, and December 15, 2023, 350 patients were screened, and 200 patients were randomized (Fig. 1). Three factors led to the premature discontinuation of the trial after 34% of the planned sample size had been enrolled. Mainly, the onset of the COVID-19 pandemic, the insufficient funding, and the publication of studies with futile results, such as the RESCUE BRAIN[10] and the RESIST studies,[19] contributed to this premature conclusion.

Of the 200 randomized patients, 122 (61.0%) were included in the primary analysis after excluding 29 (14.5%) with haemorrhagic stroke, 41 (20.5%) stroke mimics, and 8 (4%) IS patients with pre-stroke mRS ≥ 3. Consequently, 57 (28.5%) patients were assigned to receive RIperC prior to hospitalization (active group), and 65 (32.5%) were assigned to the sham group (Fig. 1). Data from the 200 randomised

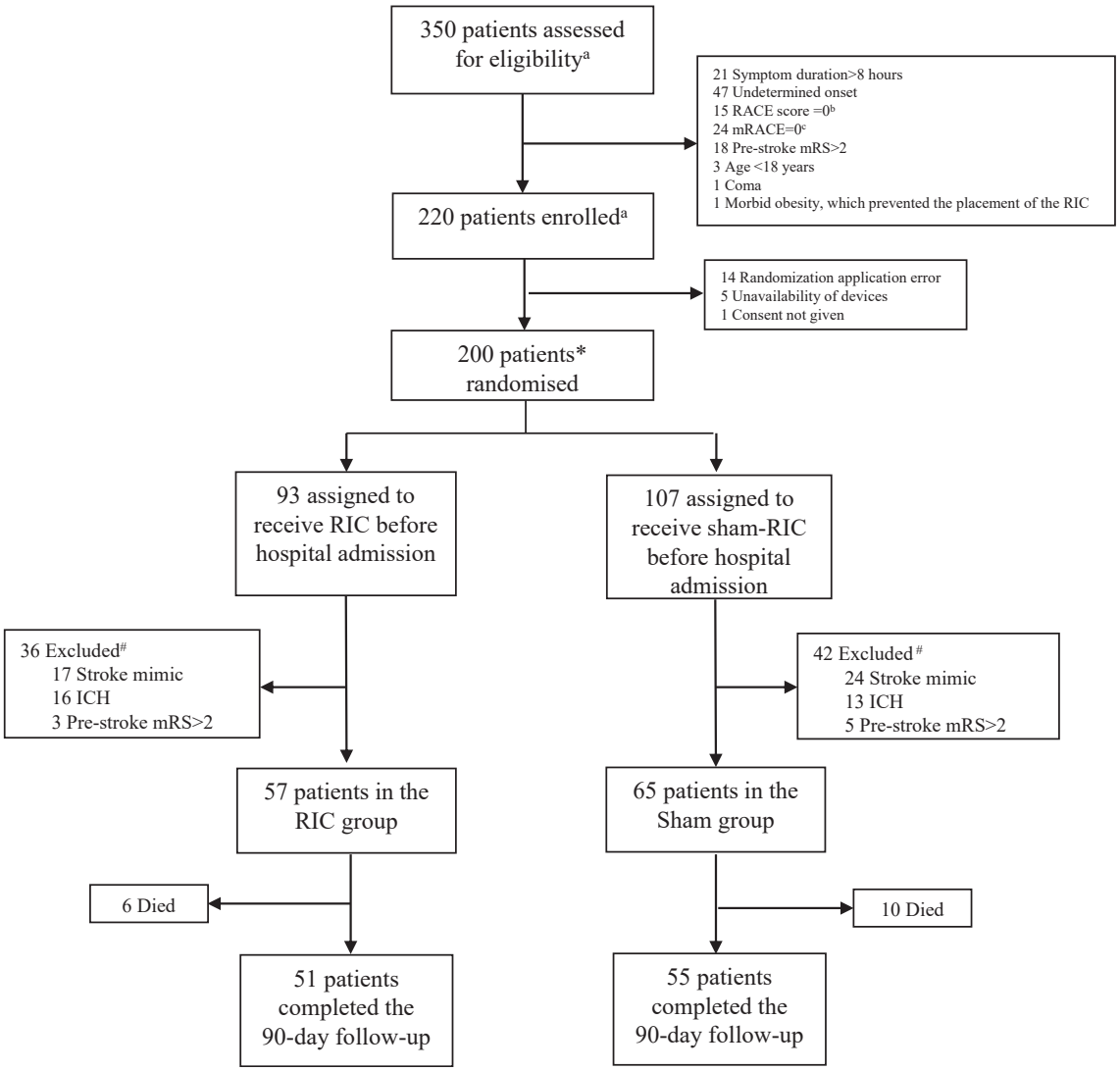

Fig. 1: **Flow of patients in the trial**. RACE, The Rapid Arterial Occlusion Evaluation Scale; mRACE, Motor item of the Rapid Arterial Occlusion Evaluation Scale; mRS, modified Rankin Scale; RIC, remote ischaemic conditioning.

Characteristics	All	RIPerC	Sham	p-value
n (%)	122	57 (46.7)	65 (53.3)	
Age, mean (SD) years	71.9 (14.2)	71.3 (14.2)	72.5 (14.3)	0.640
Age, median (IQR)	74.0 (63.8.0–82.0)	73.0 (63.0–82.0)	75.0 (65.0–82.0)	0.651
Sex female, n (%)	46 (37.7)	21 (36.8)	25 (38.5)	0.854
Comorbidities				
Hypertension, n (%)	82 (67.2)	35 (61.4)	47 (72.3)	0.201
Hypercholesterolemia, n (%)	65 (53.0)	32 (56.1)	33 (50.8)	0.553
Current smoking, n (%)	23 (18.9)	14 (24.6)	9 (13.8)	0.131
Diabetes, n (%)	46 (37.7)	22 (38.6)	24 (36.9)	0.849
Coronary artery disease, n (%)	16 (13.1)	8 (14.0)	8 (12.3)	0.778
Peripheral artery disease, n (%)	6 (4.9)	1 (1.8)	5 (7.7)	0.213
Atrial fibrillation, n (%)	23 (18.9)	8 (14.0)	15 (23.1)	0.203
Prior acute ischaemic stroke, n (%)	23 (18.9)	11 (19.3)	12 (18.5)	0.906
Prior transient ischaemic attack, n (%)	6 (4.9)	1 (1.8)	5 (7.7)	0.213
Prior recent transient ischaemic attack (24 h and 7 days before), n (%)	3 (2.5)	0 (0)	3 (4.6)	0.398
Clinical characteristics				
RACE[a] scale, n (%)				
1–3	44 (36.1)	20 (35.1)	24 (36.9)	0.975
4–6	46 (37.7)	22 (38.6)	24 (36.9)	
7–9	32 (26.2)	15 (26.3)	17 (26.2)	
Prehospital mRS[b], median (IQR)	0 (0–1.0)	1.0 (0–1.0)	0 (0–1.0)	0.410
Prehospital mRS[b], n (%)				
0	63 (51.6)	26 (45.6)	37 (56.9)	0.243
1	34 (27.9)	20 (35.1)	14 (21.5)	
2	25 (20.5)	11 (19.3)	14 (21.5)	
Admission NIHSS[c], median (IQR)	9.0 (4.0–18.0)	8.0 (4.0–19.0)	9.0 (4.0–16.0)	0.672
Systolic BP at admission, mean (SD), mmHg	153.8 (30.1)	155.4 (33.3)	152.4 (27.1)	0.589
Diastolic BP at admission, mean (SD) mmHg at admission	83.9 (17.0)	84.7 (18.6)	83.3 (15.5)	0.658
Glucose level at admission, mean (SD), mg/dL	142.7 (48.1)	143.5 (45.7)	142.0 (50.5)	0.864
Aetiology				
Large artery atherosclerosis, n (%)	21 (17.2)	13 (22.8)	8 (12.3)	0.179
Cardioembolism, n (%)	42 (34.4)	14 (24.6)	28 (43.1)	
Undetermined, n (%)	35 (28.7)	16 (28.1)	19 (29.2)	
Unhabitual, n (%)	7 (5.7)	4 (7.0)	3 (4.6)	
Small vessel, n (%)	17 (13.4)	10 (17.5)	7 (10.8)	
Neuroimaging				
ASPECTS[d], median (IQR)	10.0 (9.3–10)	10.0 (10.0–10.0)	10.0 (9.0–10.0)	0.550
Large vessel occlusion, n (%)[g]	60 (49.2)	27 (47.4)	33 (50.8)	0.708
M1 or T occlusion	43 (71.7)	23 (85.2)	20 (60.6)	0.102
M2 occlusion	14 (23.7)	3 (11.5)	11 (33.3)	
Other occlusion	3 (5.1)	1 (3.8)	2 (6.1)	
Acute phase treatments				
No acute phase treatment, n (%)	36 (30.0)	18 (34.0)	18 (28.1)	0.718
Isolated intravenous fibrinolytic treatment, n (%)	30 (25.6)	12 (22.6)	18 (28.1)	
Mechanical thrombectomy with or without IVT[h], n (%)	51 (43.6)	23 (43.4)	28 (43.8)	
Transport models for mechanical thrombectomy, n (%)				
mother ship[e]	23 (45.1)	12 (52.2)	11 (39.3)	0.357
drip and ship[f]	28 (54.9)	11 (47.8)	17 (60.7)	
Time from onset of symptoms to needle, median (IQR) hours	1.9 (1.4–2.5)	1.7 (1.4–2.4)	1.9 (1.3–2.5)	0.675
Time from door to needle, median (IQR) minutes	25.0 (19.0–32.0)	22.0 (18.5–29.5)	25.5 (19.5–34.0)	0.211
Time form onset of symptoms to femoral puncture, median (IQR) hours	4.4 (3.2–5.9)	4.2 (3.3–5.6)	4.5 (2.9–6.0)	0.850
Time from door to femoral puncture, median (IQR) hours	1.0 (0.9–1.9)	1.1 (0.9–1.8)	1.0 (0.7–1.5)	0.608

RIPperC, remote ischaemic perconditioning; SD, standard deviation; IQR, interquartile range. [a]The Rapid Arterial Occlusion Evaluation (RACE) Scale (with scores ranging from 0 [no findings] to 9 [severe neurological impairment]. [b]The modified Rankin Scale (mRS) score, with scores ranging from 0 (no symptoms) to 6 (death). [c]Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating worse neurologic deficits. [d]Alberta Stroke Program Early Computed Tomography Scores (ASPECTS) range from 0 to 10, with lower values indicating larger infarction. ASPECTS values were adjudicated by the core laboratory. [e]Mother ship: direct transport to a thrombectomy-capable centre. Time to admission was determined by transport time to the allocated thrombectomy-capable centre. [f]Drip and ship: transport to the closest local stroke centre with no thrombectomy capabilities. After initial evaluation in local stroke centres, subsequent transfer to a thrombectomy-capable centre was organized. [g]The M1 segment was defined as the horizontal segment of the middle cerebral artery, terminating at the genu adjacent to the limen insulae. The carotid T occlusion was defined by the intracranial carotid bifurcation occlusion with involvement of A1 and M1 segments. The M2 segment was defined as the segment of the middle cerebral artery distal to the genu adjacent to the limen insulae. [h]IVT, Isolated intravenous fibrinolytic treatment.

Table 1: **Baseline demographic, clinical, and treatment characteristics of the patients.**

Variables	All	RIperC group	Sham group	p-value
n (%)	122	57 (46.7)	65 (53.3)	
RIperC application				
Onset to RIperC application, median (IQR), min	1.1 (0.7–2.0)	1.1 (0.7–1.8)	1.2 (0.6–2.2)	0.949
RIperC application completed, n of total (%)	103 (84.4)	44 (77.2)	59 (92.2)	0.021
Number of completed cycles, mean (SD)	4.5 (1.4)	4.3 (1.6)	4.7 (1.1)	0.077
Related complications				
Related complications, n (%)	5 (4.1)	5 (8.8)	0	0.020
Severe pain, n (%)	1 (0.8)	1 (1.8)	0	0.467
Mild pain, n (%)	3 (2.5)	3 (5.3)	0	0.099
Transient erythema, n (%)	3 (2.5)	3 (5.3)	0	0.099
Persistent complications, n (%)	0	0	0	
Blood pressure dynamics				
Systolic BP at the time of randomization, mean (SD), mmHg	154.8 (30.1)	155.4 (33.3)	152.4 (27.1)	0.589
Diastolic BP at the time of randomization, mean (SD) mmHg	83.9 (17.0)	84.7 (18.6)	83.3 (15.5)	0.658
Systolic BP when RIperC finished, mean (SD), mmHg	151.2 (24.8)	152.2 (24.4)	150.4 (25.3)	0.712
Diastolic BP when RIperC finished, mean (SD) mmHg	82.5 (15.2)	82.7 (13.8)	82.3 (16.5)	0.901
Systolic BP 1 h after RIperC was completed, mean (SD), mmHg	144.7 (23.9)	148.1 (22.7)	141.5 (24.7)	0.149
Diastolic BP 1 h after RIperC was completed, mean (SD) mmHg	81.4 (14.3)	83.4 (13.8)	79.5 (14.7)	0.150
Intravenous antihypertensive treatment required, n (%)	17 (13.9)	9 (15.8)	8 (12.3)	0.561

RIperC, remote ischaemic perconditioning; SD, standard deviation; IQR, interquartile range; mRS, modified Rankin Scale; BP, blood pressure.

Table 2: **Variables related to the application of remote ischaemic conditioning.**

patients, 93 (46.5%) assigned to active group and 107 (53.5%) assigned to sham, were also analysed, primarily to assess the safety of RIperC in all patients with an initial suspicion of stroke in the prehospital setting. The results are presented in Supplementary Table S3.

Among the 122 patients with ischaemic stroke ischemic and pre-stroke mRS <3, the median time from symptom onset to RIperC application was 1.1 h (IQR, 0.7–2.0), while the median NIHSS score at admission was 9.0 (IQR, 4.0–18.0). Thirty-two (26.2%) patients had a RACE scale value between 7 and 9. Cardioembolism, present in 42 (34.4%) patients, was the most frequent etiological TOAST subtype. Baseline demographic and clinical characteristics were similar between the groups. Sixty of the 122 patients (49.2%) had a large vessel occlusion (LVO). Thirty (25.6%) were treated with IVT alone, while 51 (43.6%) received MT. In 28 of the 51 (54.9%) MT-treated patients, the drip-and-ship model was used. LVO and reperfusion therapy rates were similar between the groups (Table 1).

Safety outcomes

The mean prehospital systolic blood pressure (BP) was 153.8 mmHg (SD: 30.1), and the mean diastolic blood pressure was 83.9 mmHg (SD: 17.0) (Table 2). There were no significant group differences in systolic or diastolic BP levels at the time of randomization, at the end of RIperC application, or 1 h after the completion of RIperC cycles between the two groups (Table 2). In contrast, significant differences were observed in the proportion of patients who completed the five cycles of RIperC, with 44 out of 57 (77.2%) in the RiPerC group compared to 59 out of 65 (92.2%) in the sham group (p = 0.021).

In the active group, complications, predominantly mild (only one patient reported severe pain), were observed in 9% of patients, while no complications were noted in the sham group (Table 2). No significant difference in 90-day mortality was observed between the groups: 6 out of 57 (10.5%) in the RIPerC group vs 10 out of 65 (15.4%) in the sham group. No patient experienced symptomatic intracerebral haemorrhage (SICH). However, the rate of parenchymal hematoma type 1 (PH1) or type 2 (PH2) was similar between the groups, with 2 out of 57 in the RIPerC group vs 3 out of 65 in the sham group.

In the global study of the 200 randomised patients, a lower proportion of patients completed all cycles in the RIperC group compared with the Sham group (71.0% vs 87.5%, p = 0.004). Patients in the RIperC group also had a higher incidence of complications related to RIC application (8.6% vs 1.9%, p = 0.047) compared with those in the ICH (3.4%) and IS (3.8%) groups (Supplementary Table S2).

Primary outcome

The proportion of patients with a 90-day mRS <3 was higher in the RIperC group, with 37 out of 57 (64.9%) compared to 31 out of 65 (47.3%) in the sham group. Although this indicates a trend, the difference did not reach statistical significance in the unadjusted analysis (OR 2.03 [95% CI 0.98–4.21], p = 0.057) (Table 3 and Fig. 2). However, statistical significance was achieved in the post-hoc analysis adjusted for age, baseline status (determined by pre-stroke mRS score), and initial stroke severity (measured by baseline RACE score) (OR 2.94 [95% CI 1.17–6.70], p = 0.017) (Table 3 and Fig. 2).

The effect of RIperC remained neutral in both the unadjusted and adjusted analyses, including adjustment

Characteristics	All	RIperC	Sham	p-value	OR (95% CI)	p-value	Adj. OR (95% CI)[e]	p-value
Primary outcomes								
mRS[a] score at 90 days < 3								
Target IS patients, n = 122	68 of 122 (55.7)	37 of 57 (64.9)	31 of 65 (47.7)	0.056	2.03 (0.98–4.21)	0.057	2.94 (1.21–7.16)	0.017
All randomized patients, n = 200	101 of 200 (50.5)	45 of 93 (48.4)	56 of 107 (52.3)	0.577	0.85 (0.49–1.49)	0.578	1.24 (0.62–2.5)[f]	0.546
IS with completed cycles (PP analysis), n = 103)	56 (54.4)	28 (63.6)	28 (47.5)	0.103	1.94 (0.87–4.31)	0.105	2.35 (0.89–6.2)	0.086
Secondary outcomes of the target IS patients, n = 122								
mRS[a] score at 90 days, median (IQR)	2.0 (1.0–4.0)	2.0 (1.0–3.0)	3.0 (1.0–4.0)	0.086				
mRS[a] score at 90 days								
0	14 (11.5)	8 (14.0)	6 (9.2)		0.57 (0.3–1.08)	0.084	0.57 (0.3–1.09)	0.088
1	24 (19.7)	13 (22.8)	11 (16.9)					
2	30 (24.6)	16 (28.1)	14 (21.5)					
3	19 (15.6)	7 (12.3)	12 (18.5)					
4	12 (9.8)	4 (7.0)	8 (12.3)					
5	7 (5.7)	3 (5.3)	4 (6.2)					
6	16 (13.1)	6 (10.5)	10 (15.4)					
The difference in NIHSS[b] score between 24 h and baseline ≥4	7 (5,7)	2 (3.5)	5 (7.7)	0.447	2.29 (0.43–12.30)	0.333	2.38 (0.43–13.13)	0.319
The difference in NIHSS[b] score between day 5 and baseline ≥4	10 (8.2)	2 (3.5)	8 (12.3)	0.102	3.86 (0.79–18.99)	0.097	4.06 (0.81–20.33)	0.088
Acute infarct volume (n = 101), median (IQR) cm^3	4.00 (0.53–29.6)	2.76 (0.28–25.82)	6.14 (0.88–26.85)	0.184				
90-day stroke recurrence, n (%)	6 (4.9)	1 (1.8)	5 (7.7)	0.213	4.67 (0.53–41.19)	0.166		
Safety outcomes								
Serious adverse events related to the intervention, n (%)	0	0	0					
Symptomatic intracerebral haemorrhage[c] at 24–36 h	0	0	0					
Non symptomatic intracranial haemorrhage PH1 or PH2[d]	4 (3.3)	2 (3.5)	3 (4.6)	0.390				

RIPperC, remote ischaemic perconditioning; OR, Odds ratio; CI, confidence interval; IS, ischaemic stroke; IQR, interquartile range; PP, per-protocol. [a]The modified Rankin Scale (mRS) score, with scores ranging from 0 (no symptoms) to 6 (death). [b]Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating worse neurologic deficits. [c]Symptomatic intracerebral haemorrhage defined by the Safe Implementation of Thrombolysis in Stroke Monitoring Study protocol as parenchymal haemorrhage type 2 or remote parenchymal haemorrhage associated with an increase of 4 or more points in the NIHSS score at the 24-h follow-up. [d]Parenchymal haemorrhage type 1 (PH1) was defined as hematoma in ≤30% of the infarcted area with some slight space-occupying effect; Parenchymal haemorrhage type 2 (PH-2) was defined as dense hematoma >30% of the infarcted area with substantial space-occupying effect. [e]Analysis adjusted for age, baseline stroke severity according to RACE score, and pre-stroke functional status as measured by the mRS. [f]Analysis adjusted for age, baseline stroke severity according to the RACE score, pre-stroke functional status as measured by the mRS and final diagnosis (ischaemic stroke, haemorrhagic stroke or stroke mimic).

Table 3: **Primary, secondary and safety outcomes.**

for the final diagnosis), when considering all randomized patients (OR 0.85 [95% CI 0.49–1.49], p = 0.854 and OR 1.24 [95% CI 0.62–2.50], p = 0.546, respectively). Conversely, a trend that did not reach statistical significance was observed in the per-protocol analysis of the 103 patients who completed all treatment cycles (sensitivity analysis), both in the unadjusted and adjusted analyses (OR 1.94 [95% CI 0.87–4.31], p = 0.105; OR 2.35 [95% CI 0.89–6.20], p = 0.086, respectively).

Secondary outcomes

The analysis in the entire range of the 90-day mRS did not show significant differences between groups (p = 0.619). A higher proportion of patients exhibited neurological worsening at 24 h in the sham group (7.7%, 5 out of 65) compared to the RIperC group (3.5%, 2 out of 57), OR 2.29 [95% CI 0.43–12.30], p = 0.333. By day 5, the proportion in the sham group increased to 12.3% (8 out of 65), while it remained constant at 3.5% (2 out of 57) in the active group. However, these differences were not statistically significant, OR 3.86 [95% CI 0.79–18.99], p = 0.097). Among the 101 patients (82.8%) who underwent MRI according to the predefined protocol, the infarct volume measured on DWI was smaller in the RIperC group (2.76 cc, IQR 0.03–25.82) compared to the sham group (6.14 cc, IQR 0.88–26.85). However, the difference was not statistically significant (p = 0.184).

Subgroup analyses

Subgroup analyses based on age, sex, baseline mRS, administered reperfusion therapy, EVT model, time to RIperC, aetiology, and adherence to RIperC treatment revealed no significant heterogeneity in the effect of RIperC on the primary outcome. However, in the subgroup of patients with milder stroke severity at

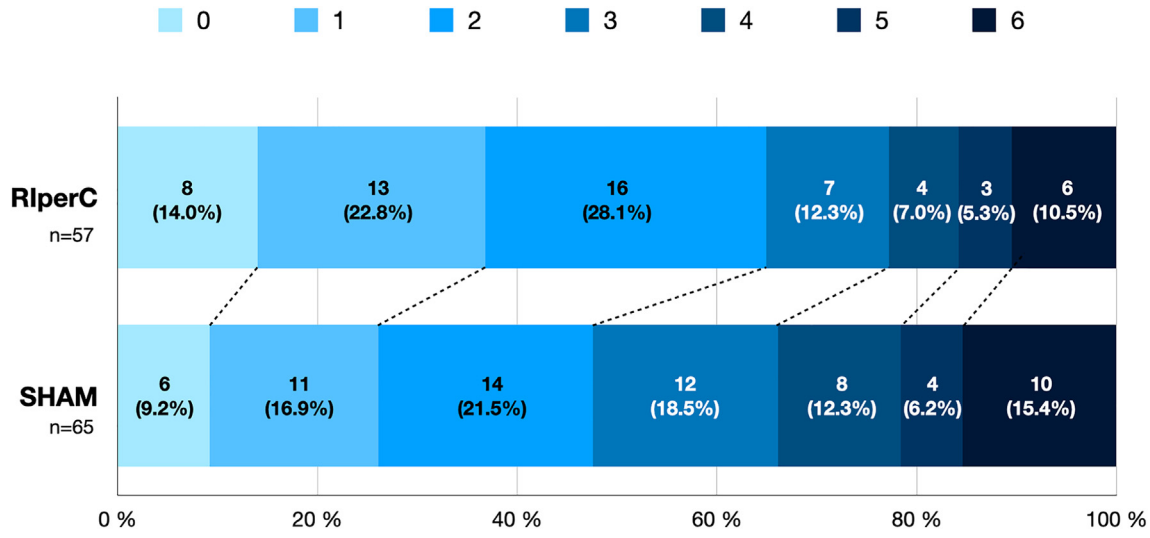

***Fig. 2:* Distribution of modified Rankin Scale score between remote ischaemic conditioning and sham groups**. Differences in modified Rankin Scale (mRS) scores between groups at 90 days are presented. Each stratum is shown as a percentage, with the raw distribution of scores displayed. The mRS scores range from 0 to 6 (0 = no symptoms; 1 = symptoms without clinically significant disability; 2 = slight disability; 3 = moderate disability; 4 = moderately severe disability; 5 = severe disability; and 6 = death.

admission (NIHSS 0–5), RIperC treatment significantly improved the 90-day prognosis (Fig. 3).

Discussion

In this clinical trial, we observed a higher proportion of patients in the RIPerC group achieving the primary endpoint of an mRS <3 at 90 days. However, it is important to note that this result reached statistical significance only after a post-hoc adjustment, which accounted for potential confounders such as age, pre-stroke functional status (mRS), and baseline stroke severity (RACE score, as assessed by paramedics in the prehospital setting). As in previous studies, we have demonstrated that the application of RIperC is both feasible and safe in the prehospital setting for patients with IS, where the code stroke has been activated.[8,19,20]

Over the last decade, interest in RIperC has increased as a safe, cost-effective strategy for universal neuroprotection.[3,21,22] Our study was conceived within this context in 2017, though it was not initiated until 2019.[5,21] Previous neutral results from RIPerC trials, such as RESIST[19] and RESCUE-BRAIN,[10] predicted similarly neutral outcomes in our primary endpoint. However, subgroup analysis revealed that RIPerC was beneficial in patients with minor stroke. To date, only studies on postconditioning with remote ischaemic conditioning applied shortly after stroke onset[23,24] or local ischemic postconditioning following successful reperfusion[25] have shown clearly positive results.

We observe a better significant outcome in patients with minor stroke at admission in RIPerC group. But these findings should be interpreted with caution, as study was not specifically designed to evaluate subgroups. Furthermore, in the subgroup analysis based on stroke severity as determined by the NIHSS, this assessment was performed upon hospital arrival, whereas RIPerC was initiated earlier in the prehospital setting. Conversely, no differences were observed when patients were stratified by baseline stroke severity as assessed by paramedics using the RACE score. Minor stroke patients comprised less than 40% of the sample, while those without LVO accounted for one out of two patients. Previous studies, including the one by Hougaard et al.[8] and the RESIST trial,[19,20] did not report these findings. In both studies, as in ours, RIperC was initiated during patient transport in the ambulance. However, in Hougaard's study,[8] RIPerC was applied manually, whereas both RESIST[19,20] and our study utilized an automated device that administered five 5-min cycles. The RESIST study, which had a design very similar to that of REMOTE-CAT, recruited 737 acute IS patients who underwent RIPerC in the prehospital setting. It did not observe significant differences in the functional outcomes of patients at the 90-day follow-up.[19] Besides the sample size difference, RESIST patients had a lower baseline NIHSS score (mean 4.5 vs 9 in REMOTE-CAT). Furthermore, the prevalence of vascular risk factors was lower in RESIST[19,20] compared to REMOTE-CAT. Unlike RESIST, which reported a benefit of RIPerC in patients with acute IS due to small vessel disease, REMOTE-CAT did not find significant differences in outcomes based on stroke aetiology. However, as with small vessel disease, a benefit was seen in patients without LVO. Another relevant trial, RESCUE BRAIN,[10]

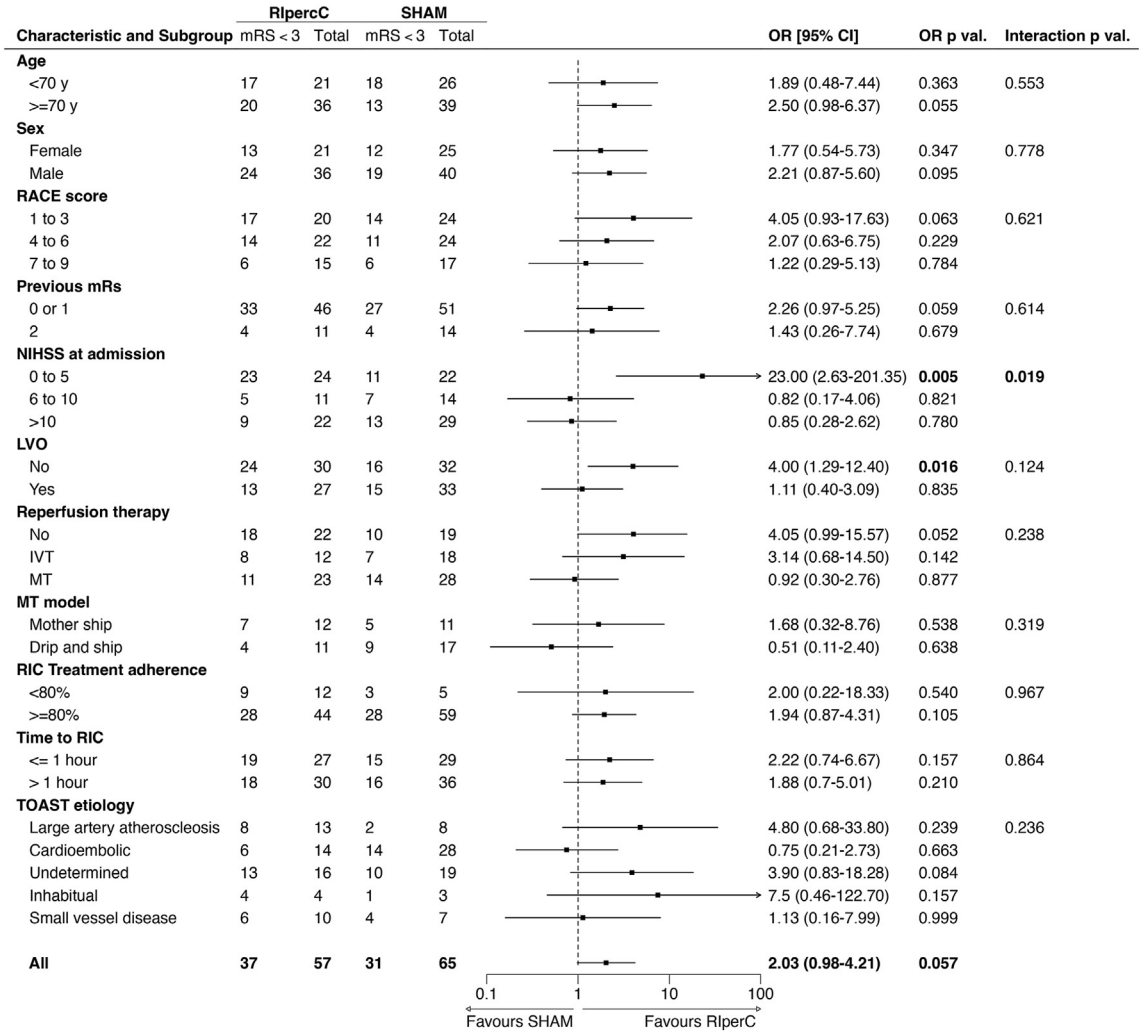

***Fig. 3:* Subgroup analyses**. RACE, The Rapid Arterial Occlusion Evaluation Scale; NIHSS, National Institutes of Health Stroke Scale; LVO, Large vessel occlusion; MT, Mechanical Thrombectomy; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

differed in that RIPerC was applied in-hospital, with a median time from symptom onset to RIPerC application of 3.7 h, and excluded patients with NIHSS <5 and those with stroke outside the carotid territory. A potential explanation for some of the differences in results across studies is the variation in the time window for patient inclusion from symptom onset. In the RESCUE-BRAIN trial,[10] this window was limited to less than 4 h, while in RESIST[19] it was 6 h, and in our study, it was extended to 8 h. In our case, the chosen time window was based on the criteria used in the REVASCAT study.[26] Given that our study included patients who were potential candidates for thrombectomy, this temporal limit was selected as it aligned with the recommended timeframe for stroke code activation, as outlined by the Catalonia Stroke Plan at the time the study was designed.

Nevertheless, our results should be interpreted cautiously given the small sample size. It is difficult to explain the precise pathophysiological mechanism behind the observed benefit of RIperC in these subgroups, especially considering the unclear mechanisms of action of remote ischaemic conditioning.[4,22] However, one possible explanation may involve the attenuation of post-reperfusion injury, as animal models have demonstrated that RIPerC exerts positive effects before, during, and after intracranial occlusion.[4] The lack of benefit in patients with LVO may be partly due to the effects of anaesthetics and sedatives on ischaemic tolerance mechanisms induced by RIperC.[27] It is important to note that patients receiving reperfusion therapy in our study were managed with excellent process indicators, such as door-to-needle times of less than 30 min and door-to-puncture times of 1 h. In this

context, it is possible that RIperC does not provide additional benefit in patients who receive early reperfusion therapy. Paradoxically, no benefit was observed in patients managed via the "drip and ship" approach, where MT was delayed. We value the use of a prehospital scale, such as the RACE scale,[11] for patient selection. This allowed us to stratify patients based on initial stroke severity and to avoid including stroke mimics. At randomization, patients without motor deficits were excluded.

We acknowledge that our results are subject to scrutiny. Besides the primary limitation of our small sample size, which represented only 34% of the estimated necessary sample size, there are other factors to consider. As previously described, the main reasons for not reaching the anticipated sample size included a lack of funding to involve more centres and the impact of the COVID-19 pandemic, which temporarily halted recruitment. Additionally, the long duration of the trial may have introduced differences in the application of reperfusion therapies between patients recruited early and late in the study. Another important limitation of our study is that, in the RIperC group, 13 of 57 patients (23%) did not complete the full five-cycle protocol, primarily due to technical issues related to the battery life of the AutoRIC device, with only one patient experiencing significant limb pain. The optimal protocol for the application of RIperC remains uncertain. In the RESCUE Brain study, cycles were applied to the lower limbs,[10] whereas in both the RESIST study[19] and our own, they were applied to the non-paretic upper limb. In contrast, the RICAMIS study[24] applied cycles to both arms twice daily for 10–14 days and demonstrated a positive effect of remote ischaemic conditioning on the functional prognosis of patients who did not receive reperfusion therapy. A subgroup of patients in the RESIST study[19] also underwent remote ischaemic conditioning for seven days. Future studies should consider the application of repeated remote ischaemic postconditioning following RIPerC. Theoretically, this approach could enhance the potential benefits of RIPerC in mitigating reperfusion injury or exerting neuroprotective effects, while also promoting neurorepair.[28] Finally, one important limitation of this study is the possibility that paramedics identified treatment allocation despite the use of a sham device designed to closely resemble the active device in appearance, weight, and inflation noise. Although this approach aimed to minimise perceptual differences between groups, unblinding cannot be ruled out. Future studies could incorporate an assessment of blinding efficacy by systematically asking paramedics to identify the treatment allocation, allowing for a more precise evaluation of potential bias.

In conclusion, despite the limitations of a small sample size our findings suggest that prehospital application of RIPerC is safe and may confer clinical benefit, as indicated in the post-hoc adjusted analysis. However, larger, adequately powered trials are required to confirm these results and to explore potential differential effects across underrepresented patient subgroups. Meta-analyses incorporating published studies,[10,19] along with the data from our trial, will be essential to better define the clinical utility of RIPerC.

Contributors

Drs Purroy and Mauri had full access to all data in the study and take responsibility for the integrity of the data and the accuracy.

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All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

The corresponding author will consider requests for access to the data reported in this article.

Editor note

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Declaration of interests

We declare no competing interests.

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In preparing this manuscript, we utilized the artificial intelligence tool ChatGPT, developed by OpenAI, solely for enhancing the English language expression. This assistance was confined to linguistic and grammatical aspects, with no impact on the scientific content, data interpretation, or study conclusions.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103208.

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