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CLINICAL TRIAL REPORT

Combined Ruyi Zhenbao Pills-Baimai Ointment Therapy on Acute Ischemic Stroke: A Multi-Arm, Randomized, Double-Blind, Placebo Controlled Clinical Study

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Background: Ruyi Zhenbao Pills (RZPs) and Baimai Ointment (BMO), prescribed Tibetan formulations, have been confirmed as having a neuroprotective role in animal and cell models of stroke. However, the effects of RZPs and BMO in individuals with acute ischemic stroke (AIS) remain unclear. This is the first multicenter, large-sample, controlled trial to evaluate the therapeutic potential of traditional Tibetan medicine—specifically the RZP and BMO—in the treatment of AIS, thereby extending ethno-pharmacological evidence into modern stroke care.

Methods: A multi-arm, randomized, double-blind, placebo controlled clinical trial was conducted at 21 hospitals in China between December 2020 and September 2022. The inclusion criteria are as follows: individuals diagnosed as AIS, 18 to 75 years of age and within 14 days of AIS onset. Subjects were randomly assigned in a 1:1:1:1 ratio to RZPs+BMO, RZPs, BMO, or placebo. The primary outcome was change of Fugl–Meyer assessment (FMA) score from baseline to day 90.

Results: Four hundred and twenty-three participants were recruited and randomly allocated to the RZPs+BMO group (n=108), RZPs group (n=108), BMO group (n=99), or placebo group (n=108). The change from baseline to D90 in FMA score was 31.22 (SD 16.64) with RZPs+BMO, 29.25 (15.92) with RZPs, 29.88 (15.42) with BMO, and 19.20 (14.38) with placebo (RZPs+BMO group versus placebo group, $P< 0.001$).

Conclusion: Among Chinese patients suffering from AIS, combined RZPs and BMO therapy improved significantly the primary outcome of 90-day motor functions compared with placebo with acceptable safety, indicating that RZPs and BMO might be an effective therapeutic strategy in patients with AIS.

Keywords: Ruyi Zhenbao pills, Baimai ointment, acute ischemic stroke, traditional Tibetan medicine, neuroprotective agents

Introduction

Stroke is positioned as the second most common factor of disability as well as mortality worldwide but has recently ascended as the predominant cause of death in China.[1,2] Given its high mortality and disability, stroke poses the staggering economic and social burden for individuals, families and countries.[3] The two acknowledged approaches of acute ischemic stroke (AIS) to achieve patency are reperfusion and neuroprotection. However, reperfusion therapy including endovascular treatment and intravenous thrombolysis remain limited by a narrow effective window.[1,4] Additionally, the clinical efficacy of various neuroprotective interventions, ranging from established neuroprotective pharmaceuticals (such as edaravone, nerinetide, and vinpocetine) to naturally derived compounds from medicinal herbs (like resveratrol, ginkgolide B, and ginsenoside Rg1), and

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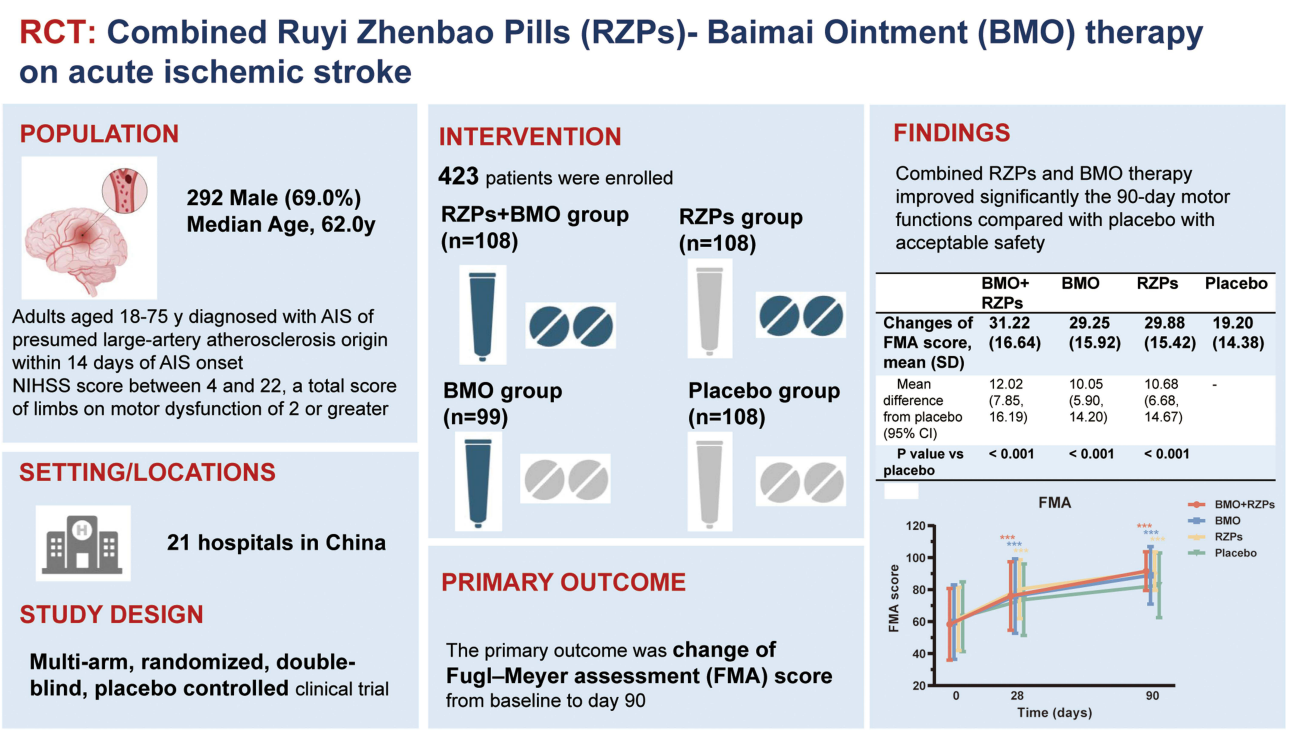
Graphical Abstract



cell-based therapeutic modalities (such as exosomes and stem cell transplants), requires further validation across multiple dimensions.[5,6] In recent years, gene therapy and nanotechnology have emerged as the two most promising frontiers for acute ischemic stroke, respectively, targeting "molecular modulation" and "precision delivery".[7,8] Nevertheless, their long-term safety remains inadequately characterized, and the high treatment costs continue to represent a critical obstacle to clinical translation—issues that demand further in-depth investigation and optimization.

There is thus an urgent imperative to develop therapeutic strategies with broader applicability and a more favorable safety profile. As a major component of traditional Chinese medicine, Tibetan medicine proposes there are two systems in the human body, white meridian and black meridian.[9,10] White meridian-related diseases are regarded as neurologic dysfunction, including stroke, dementia and dystaxia. Combination of ora and external Tibetan medicine therapy, such as combined Ruyi Zhenbao Pills (RZPs)-Baimai Ointment (BMO) therapy, is traditional therapeutic strategies for white meridian-related diseases in Tibetan medicine.[11] RZPs, a Tibetan medicine compound, is composed of extracts from multiple plants and mineral substances, such as shells, agarwood, licorice. Previous studies showed that RZPs promote neurogenesis and angiogenesis to improve ischemic stroke outcomes in rat model of cerebral ischemia-reperfusion. BMO, a yellow ointment, is composed of extracts from multiple plants and mineral substances, such as turmeric, nutmeg, licorice, musk, camellia, Tibetan fennel.[12] BMO treatment was found in vivo to directly reduce neuroinflammatory responses and neuroprotective effect. Moreover, a clinical trial involving 120 convalescent stroke patients revealed that RZPs significantly enhanced limb motor and sensory functions.[13] Drawing on the outcomes of the animal experiments and clinical trials, we have planned a clinical study to investigate the impact of RZPs and BMO therapy on 90-day motor functions in individuals with AIS attributed to large-artery atherosclerosis.

Methods

Study Design and Patients

From December 2020 to September 2022, an investigator-initiated, multicenter, randomized, double-blind, placebo-controlled parallel-group clinical trial was executed in 21 research centers in China (Supplementary Table 1). To access the efficacy and safety of BMO and RZPs relative to placebo in individuals with AIS, subjects were assigned to receive BMO+RZPs, BMO alone, RZPs alone, or placebo, in a 1:1:1:1 ratio, all in conjunction with guideline-directed standard therapy for AIS. A copy of the study protocol is available in Supplement. Ethics committees of each participating study center gave their approval for this study. All eligible participants or their legal surrogates provided informed consent, consistent with national and local regulations, before the assignment process was initiated. All authors designed and coordinated this trail and an independent safety and data monitoring board supervised the trail, especially the completeness and safety of data, with the assistance of the clinical research organization. The trial was performed in alignment with the Good Clinical Practice principles of the International Conference on Harmonization and the Declaration of Helsinki and adhered to the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines. This trail was registered with https://www.chictr.org.cn (unique identifier: ChiCTR2000036691).

The target population consisted of adults aged 18–75 years who were diagnosed with AIS, which was presumedto be of large-artery atherosclerosis origin within 14 days of AIS onset.[14] They had a National Institutes of Health Stroke Scale (NIHSS) score of 4–22, a total score of limbs on motor dysfunction ≥2 at admission, and a modified Rankin Scale (mRS) score ≤1 prior to the onset of the current stroke. Inclusion and exclusion criteria were described in the Supplementary Table 2.

Randomization and Masking

After the successful completion of the pre-screening process, participants were randomly assigned (1:1:1:1) in BMO +RZPs, BMO, RZP, or placebo groups using a central computer-based randomization system (Figure 1). The

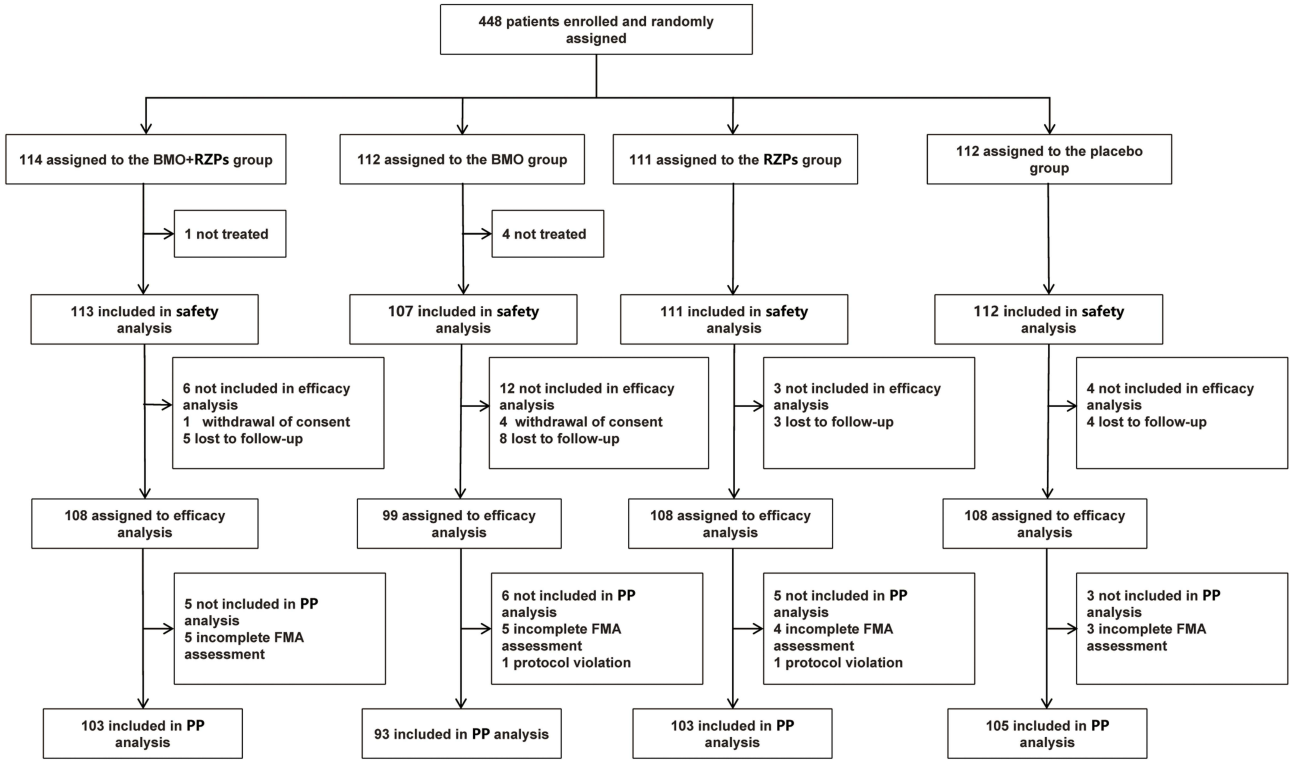


Figure 1 Trial profile.
Abbreviations: BMO, Baimai Ointment; FMA, Fugl–Meyer assessment; ITT, intention-to-treat; PP, per-protocol; RZPs, Ruyi Zhenbao Pills.

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randomization sequence was constructed using SAS V9.4 (SAS Institute Inc) using simple randomization by an independent statistician completely uninvolved the current trial. Each randomizing number was double-blindingly bound to package number of study drugs. The placebos have identical characteristics to BMO and RZPs, respectively, such as forms, package, label, and odor. Investigators obtained the randomizing number and corresponding study drugs via the central random allocation management system. In this trial, all patients, sites investigators, physicians, nurses and assessors were blinded to the grouping assignment of participants.

Procedures

Gansu Cheezheng Tibetan Medicine Co., Ltd. and Tibet Cheezheng Tibetan Medicine Co., Ltd. provided the trial drugs (Ruyi Zhenbao Pills and Baimai Ointment) and the matching placebos. One fingertip unit is an amount of medicine dispensed from the ointment tube from the crease of the distal interphalangeal joint to the index finger with a length of about 3cm (approximately 1g and 2% body surface area of an adult). In the BMO+RZPs group, patients received oral RZPs 2.5 g (0.5 g/pill, 5 pills) twice daily for 8 weeks and topical BMO application in affected limbs (upper limb 5–8 fingertip units or lower limb 8–12 fingertip units) twice daily for 8 weeks. The ingredients and other information about BMO and RZPs were described in the Supplementary Table 3. The BMO group received topical BMO application in affected limbs and matching RZPs placebo. The RZP group received oral RZPs and matching BMO placebo. The placebo group received both RZPs and BMO placebos, all trial medications were dosed twice daily for 8 weeks.

At 29 days (plus or minus 3 days) after commencing treatment, all patients had a follow-up visit, A trained investigator conducted a structured face-to-face interview. The follow-up visit included clinical assessments, neurological functional deficits, such as NIHSS score, Fugl–Meyer assessment (FMA),[15] mRS assessment, Barthel index (BI), Tibetan medicine stroke symptom grading quantitative score (TM-SSGQS) and Tibetan medicine subdivision disease element diagnosis of stroke (TM-SDEDS), and safety assessment. TM-SSGQS and TM-SDEDS used in this study were developed on the basis of classical Tibetan medical texts, including the Four Tantras (*rGyud-bzhi*), and in accordance with the clinical trial protocol; their reliability and discriminant validity have been preliminarily verified, as detailed in the supplementary methodological appendix. At 56 days (plus or minus 3 days) after commencing treatment, all patients also had the follow-up visit, including clinical assessments, neurological functional deficits (mRS assessment, TM-SSGQS and TM-SDEDS) and safety assessment. At 90 days (plus or minus 7 days) of the current stroke onset, all patients had another follow-up visit, including neurological functional deficits (NIHSS score, FMA, mRS assessment, BI, TM-SSGQS and TM-SDEDS) and standard imaging examination (CT or MRI). The complete study schedule was described in the Supplementary Table 4.

Outcomes

The primary efficacy outcome was the changes of FMA score from baseline to D90. The secondary efficacy outcomes included changes of FMA score from baseline to D29, the percentage of subjects with changes of NIHSS score from baseline to D29≥4, the percentage of subjects with mRS score ≤2 on D90, the percentage of subjects with BI score ≥95 on D90, the changes of TM-SSGQS from baseline to D90, the changes of TM-SDEDS (wind, fire, and water) from baseline to D90 and occurrence of stroke/cerebrovascular events from baseline to D90. The safety endpoints were the following: laboratory test values, adverse, serious adverse events and death.

Statistical Analysis

Groups were assigned to receive BMO+RZPs, BMO, RZP, or placebo. The efficacy and safety were compared in this trail (BMO+RZPs vs placebo, BMO vs placebo, RZPs vs placebo, BMO+RZPs vs BMO, and BMO+RZPs vs RZPs). Consequently, α was determined to be 0.025/5 based on Bonferroni correction. The projected change from baseline in the FMA score on Day 90 was 35 points for the BMO+RZPs group, and 26 points for the placebo group (standard deviation, SD, 17). With α set at 0.005 and power at 0.80, 96 subjects were required for each group. Accounting for a dropout rate of 20%, the total sample size was calculated to be 480 patients (120 patients per group).

The data analysis was executed using SAS software (version 9.4). Continuous data were expressed as mean (SD) or median (IQR) and compared using analysis of variance (ANOVA) or Kruskal–Wallis *H*-test. Categorical variables were

presented as counts (percentages) and compared using the Chi-square test and Fisher's exact test. The efficacy outcomes were assessed across the four groups. For continuous data, means with 95% confidence intervals were calculated for each group, and mean differences (95% confidence intervals) between groups were assessed. For categorical variables, logistic regression analysis was used to calculate the odds ratios (ORs) and their 95% confidence intervals (CIs). In terms of the primary efficacy outcome, a superiority test will be conducted to make comparisons among BMO and RZPs versus placebo, the combination group versus BMO and RZPs, and the combination group versus placebo. To account for multiplicity in the primary efficacy indicators, the Bonferroni method will be employed for adjustment, with an α value set at 0.005 for one-sided tests (equivalent to 0.01 for two-sided tests). Additionally, the assessment of the primary efficacy endpoint was completed through covariance analysis, with adjustments made for center and baseline scores. All other statistical tests except the primary efficacy indicator, two-sided tests ($P<0.05$) were executed.

Results

Baseline Characteristics

Between December 9, 2020, and September 18, 2022, 448 participants were randomly assigned (114 [25.4%] to BMO +RZPs, 111 [24.8%] to BMO, 111 [24.8%] to RZP, and 112 [25%] to placebo). Five participants received no treatment, and therefore the safety analysis encompassed 443 patients. Twenty-five (5.6%) of 448 patients did not meet criteria for efficacy analysis, 423 patients (108 to BMO+RZPs, 99 to BMO, 108 to RZP, and 108 to placebo) were eventually added in the efficacy analysis. The per-protocol analysis encompassed 404 patients (Figure 1).

As shown in Table 1, baseline demographics and clinical characteristics (such as age, sex, BMI, transient ischemic attack, previous stroke, diabetes mellitus, mRS score prior to onset, FMA score and NIHSS score) were similar across the four groups in the efficacy analysis set (n=423). Nevertheless, subjects in the BMO group have higher incidence of hypertension (88 [81.5%] in BMO+RZPs, 84 [84.85%] in BMO, 80 [74.1%] in RZP, and 71 [65.7%] in placebo, P =0.006).

Table 1 Demographic and Baseline Clinical Characteristics

Characteristics	BMO+RZPs (n=108)	BMO (n=99)	RZPs (n=108)	Placebo (n=108)	*P*
Age, median (IQR), y	62 (55–69)	63 (55–69)	60 (55–68)	61 (53.5–68)	0.716
Sex, n (%)					0.753
Female	33 (30.55)	27 (27.27)	37 (34.26)	34 (31.48)	
Male	75 (69.44)	72 (72.73)	71 (65.74)	74 (68.52)	
BMI (IQR), (kg/m^2)	24.79 (21.97–27.34)	24.80 (23.05–26.23)	24.78 (22.67–27.71)	24.22 (22.24–26.32)	0.710
Previous stroke or transient ischaemic attack, n (%)	5 (4.6)	8 (8.1)	4 (3.7)	3 (2.8)	0.356
Coronary heart disease, n (%)	44 (40.7)	35 (35.4)	35 (32.4)	40 (47.0)	0.823
Hypertension, n (%)	88 (81.5)	84 (84.85)	80 (74.1)	71 (65.7)	0.006
Diabetes mellitus, n (%)	32 (29.6)	41 (41.4)	46 (42.6)	50 (46.3)	0.068
Dyslipidemia, n (%)	34 (31.5)	35 (35.4)	41 (38.0)	43 (39.8)	0.610
mRS score prior to onset, n (%)					0.259
0	98 (90.7)	86 (86.9)	93 (86.1)	101 (93.5)	
1	10 (9.3)	13 (13.1)	15 (13.9)	7 (6.5)	
FMA score, median (IQR)	63.00 (46.00–75.00)	65.00 (47.00–80.00)	64.50 (50.50–77.00)	66.50 (50.50–81.00)	0.376
NIHSS score, median (IQR)	6.00 (4.00–8.00)	5.00 (4.00–7.00)	5.00 (4.00–7.00)	5.00 (4.00–7.00)	0.504
BI score ≥ 95, n (%)	0 (0.00)	1 (1.01)	1 (0.93)	2 (1.85)	0.751

Notes: Data are n (%) or median (IQR). BI, Barthel index; BMI, body mass index; BMO, Baimai Ointment; FMA, Fugl–Meyer assessment; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale, RZPs, Ruyi Zhenbao Pills.

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Efficacy Outcomes

Results of the primary, and secondary efficacy outcomes were presented in Table 2 and Supplementary Table 5. At baseline, the FMA score was similar across the four groups. After 56 days treatment, BMO+RZPs, BMO and RZP dramatically increased the changes of FMA score from baseline to D90 when compared with placebo (primary endpoint, Table 2). Figure 2 shows the FMA score changes (total, lower-extremity and upper-extremity) during the 90 days of follow-up. Nevertheless, there were no difference of changes of FMA score from baseline to D90 across the BMO+RZPs group, BMO group and RZP group (Table 2). Significant BMO and RZP-associated increase in the changes of FMA score from baseline to D29 (key secondary endpoint) were coincident, with BMO and/or RZPs-treated subjects having greater increase from baseline versus those received placebo (Table 2).

In addition, BMO+RZPs, BMO and RZP groups had better outcomes, which the proportions of subjects (mRS score ≤ 2and BI score ≥ 95) on D90 were higher compared with placebo group. BMO and RZPs in combination significantly improved the changes of TM-SSGQS from baseline to D90 compared with placebo group, whereas BMO or RZPs alone did not impact these. Similarly, patients with BMO and RZPs in combination had greater the changes of TM-SDEDS on D90 (water) than patients with placebo, while BMO or RZPs alone did not impact these. BMO and/or RZPs treatment did not influence the other predetermined secondary outcomes, including the changes of NIHSS score from baseline to D29 ≥

Table 2 Primary and Secondary Efficacy Outcomes (Efficacy Analysis)

	BMO+RZPs (n=108)	BMO (n=99)	RZPs (n=108)	Placebo (n=108)
Primary outcomes				
Changes of FMA score from baseline to D90, mean (SD)	31.22 (16.64)	29.25 (15.92)	29.88 (15.42)	19.20 (14.38)
Mean difference from placebo (95% CI)	12.02 (7.85, 16.19)	10.05 (5.90, 14.20)	10.68 (6.68, 14.67)	–
P value vs placebo	< 0.001	< 0.001	< 0.001	–
Mean difference from RZPs (95% CI)	1.34 (−2.96, 5.64)	−0.63 (−4.92, 3.67)	–	–
P value vs RZPs	0.700	0.564	–	–
Mean difference from BMO (95% CI)	1.97 (−2.50, 6.44)	1.00 (Ref.)	–	–
P value vs BMO	0.434	–	–	–
Secondary outcomes				
Changes of FMA score from baseline to D28, mean (SD)	17.74 (12.01)	16.20 (10.64)	18.55 (12.32)	10.64 (9.98)
Mean difference from placebo (95% CI)	7.10 (4.14, 10.06)	5.56 (2.74, 8.39)	7.91 (4.90, 10.92)	–
P value vs placebo	< 0.001	< 0.001	< 0.001	–
Changes of NIHSS score from baseline to D28≥4, n (%)	29 (26.85)	26 (26.26)	27 (25.00)	21 (19.44)
OR from placebo (95% CI)	1.52 (0.80, 2.88)	1.48 (0.77, 2.84)	1.38 (0.72, 2.63)	–
P value vs placebo	0.198	0.243	0.327	–
mRS score ≤2 on D90, n (%)	99 (96.12)	85 (90.43)	97 (93.27)	73 (69.52)
OR from placebo (95% CI)	10.85 (3.68, 32.03)	4.14 (1.86, 9.24)	6.07 (2.54, 14.53)	–
P value vs placebo	< 0.001	< 0.001	< 0.001	–
BI score ≥ 95 on D90, n (%)	66 (64.08)	60 (63.83)	76 (73.08)	48 (45.71)
OR from placebo (95% CI)	2.12 (1.21, 3.70)	2.10 (1.19, 3.70)	3.22 (1.81, 5.75)	–
P value vs placebo	0.008	0.011	<0.001	–
Changes of Tibetan medicine stroke symptom grading quantitative score from baseline to D90, mean (SD)	5.67 (3.17)	5.56 (3.33)	5.20 (2.70)	4.78 (3.39)
Mean difference from placebo (95% CI)	0.89 (−0.01, 1.79)	0.78 (−0.16, 1.72)	0.42 (−0.41, 1.26)	–
P value vs placebo	0.026	0.058	0.126	–
Changes of Tibetan medicine subdivision disease element diagnosis of stroke (fire) from baseline to D90, mean (SD)	2.14 (2.73)	2.36 (2.99)	1.98 (3.16)	1.68 (2.45)
Mean difference from placebo (95% CI)	0.46 (−0.25, 1.17)	0.69 (−0.08, 1.46)	0.30 (−0.47, 1.08)	–
P value vs placebo	0.216	0.103	0.998	–
Changes of Tibetan medicine subdivision disease element diagnosis of stroke (water) from baseline to D90, mean (SD)	2.78 (3.44)	1.99 (2.71)	2.49 (2.96)	2.02 (2.78)
Mean difference from placebo (95% CI)	0.76 (−0.10, 1.61)	−0.03 (−0.80, 0.74)	0.47 (−0.31, 1.25)	–
P value vs placebo	0.043	0.872	0.182	–
Changes of Tibetan medicine subdivision disease element diagnosis of stroke (wind) from baseline to D90, mean (SD)	1.78 (2.52)	1.67 (2.18)	1.69 (2.12)	1.92 (2.81)
Mean difference from placebo (95% CI)	−0.15 (−0.88, 0.58)	−0.25 (−0.95, 0.45)	−0.23 (−0.91, 0.45)	–
P value vs placebo	0.741	0.857	0.989	–
Stroke/cerebrovascular events from baseline to D90, n (%)	1 (0.93)	1 (1.01)	1 (0.93)	1 (0.93)
OR from placebo (95% CI)	1.00 (0.06, 16.20)	1.09 (0.07, 17.69)	1.00 (0.06, 16.20)	–
P value vs placebo	1.000	0.951	1.000	–

Abbreviations: BI, Barthel index; BMO, Baimai Ointment; CI, confidence interval; D28 indicates day 28; D90, indicates day 90; FMA, Fugl–Meyer assessment; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio, RZPs, Ruyi Zhenbao Pills, SD, standard deviation.

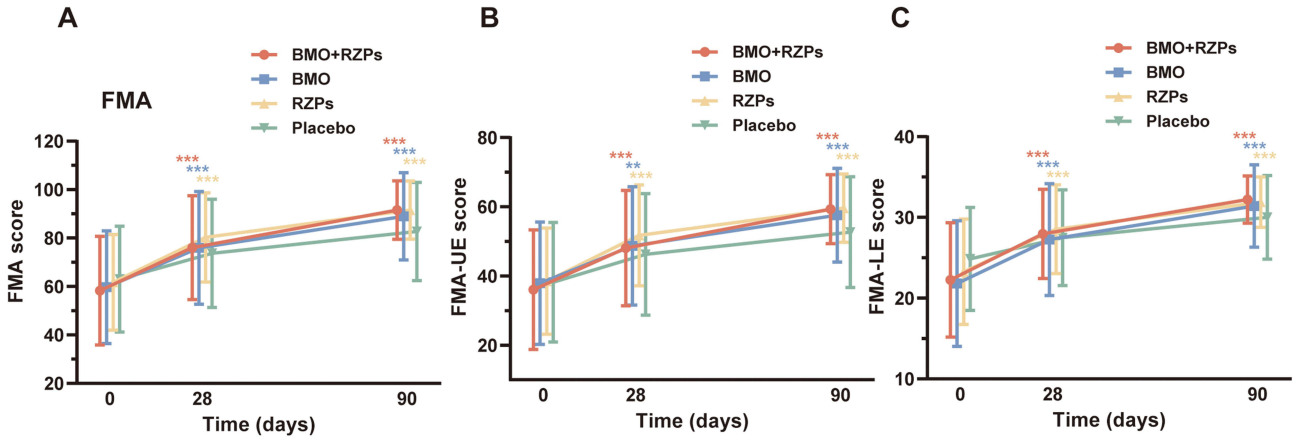

Figure 2 Graphical Representation of the FMA Changes of the Four Groups. (**A**) FMA, (**B**) FMA-UE and (**C**) FMA-LE. **p<0.01, ***p<0.001.
Abbreviations: BMO, Baimai Ointment; FMA, Fugl–Meyer assessment; FMA-LE, Fugl-Meyer Assessment of Lower-extremity; FMA-UE, Fugl Meyer Assessment of Upper-extremity; RZPs, Ruyi Zhenbao Pills.

4, the changes of TM-SSGQS from baseline to D90, the changes of TM-SDEDS (wind and fire) from baseline to D90 and occurrence of stroke/cerebrovascular events from baseline to D90. We also demonstrated the results for primary and secondary efficacy outcomes based on the per-protocol analysis (Supplementary Table 5).

Safety Outcome

The four groups had similar incidences of adverse events (Supplementary Table 6). As shown in Table 3, serious adverse events during 90 days of follow-up were uncommon. Death occurred in BMO group (n=1), cerebral haemorrhage occurred in placebo group (n=1), and cerebral infarction occurred in both the BMO+RZPs group (n=1) and placebo group (n=1), which indicating four treatment groups had similar incidences of serious adverse event.

Discussion

This study is the first multicenter, randomized, double-blind, placebo-controlled trial conducted in patients with AIS to systematically evaluate the efficacy and safety of oral RZPs combined with topical BMO, thereby filling a gap in the evidence base for Tibetan medicine formulations in this field. This trial presumed large-artery atherosclerosis origin revealed that RZPs and BMO therapy improved the primary outcome of 90-day motor functions, as well as secondary outcomes of 29-day motor functions and 90-day functional recovery. Participants who received a combination of RZPs and BMO therapy within 14 days after symptom onset had similar outcomes of 90-day motor functions as those who received RZPs or BMO alone. Notably, our findings indicated no significant difference in adverse events among treatment groups.

From the perspective of Tibetan medicine, AIS falls within the category of "white-meridian disease" with its pathogenesis attributed to the derangement of rlung (vital wind) and the obstruction of meridians by blood stasis. Taken orally, RZPs invigorate rlung, quicken the blood, and open the mind; applied topically, BMO warms and unblocks

Table 3 Serious Adverse Events Recorded During 90 Days of Follow-Up

Characteristics	BMO+RZPs (n=113)	BMO (n=107)	RZPs (n=110)	Placebo (n=112)
N (%) of serious adverse events	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)
Deaths	0 (0)	1 (0.93)	0 (0)	0 (0)
Cerebral haemorrhage	0 (0)	0 (0)	0 (0)	1(0.9)
Cerebral infarction	1(0.9)	0 (0)	1(0.9)	0 (0)

Abbreviations: BMO, Baimai Ointment; RZPs, Ruyi Zhenbao Pills.

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the white meridians, disperses stasis, and reduces swelling. Together, the internal and external administration addresses both root and branch, yielding a combined therapeutic approach. As the traditional Tibetan medicine, the specific active ingredients and mechanism of RZPs and BMO remain unclear, whereas several studies have verified that RZPs and BMO played a neuroprotective role in neurological disorders.[16,17] In the preclinical model of cerebral ischemia-reperfusion, RZPs improved neurological function via facilitating neurogenesis, angiogenesis and neurotrophic factor expression. RZPs also effectively reversed cerebral edema, neuroinflammation and apoptosis by multifunctional cytoprotective pathways.[18] Furthermore, other findings confirmed RZPs pretreatment inhibited inflammatory cell infiltration, vacuolation of neuronal cells and fibrosis to exert anti-migraine effect in nitroglycerin-induced migraine rat model.[19] Topical application of BMO ameliorated the motor deficit via modulating astrocytes activation and neurotrophic factors expression in rat model of cerebral palsy, which was induced by lipopolysaccharide with hypoxia-ischemia.[20] BMO treatment increased pain sensitivity thresholds for mechanical and thermal stimuli through regulating T cell receptor signaling pathways and core regulatory elements of tumor necrosis factor in a complete Freund's adjuvant-induced animal model of chronic inflammatory pain.[21] BMO alleviated pain hypersensitivity, peripheral nerves damage via PI3K/AKT as well as MAPKs signaling pathways in diabetic peripheral neuropathy.[22]

A previous randomized placebo-controlled clinical trial demonstrated 4-week RZPs treatment improved limb motor and sensory functions in patients with convalescent stroke (the disease course ranging from 15 days to 6 months).[13] A case report exhibited a combination of BMO with massage therapy improves the active motor ability in subjects with high tone of upper limb flexor after stroke,[23] suggesting the potential therapeutic effect of BMO on stroke-related limb motor dysfunction. Different with the previous trails, we focus on the effect of patient with AIS (within 14 days of stroke onset). Given considering the combination of oral and topical Tibetan medicine regarded as the classical theory in Tibetan medical system, we performed the current randomized, double-blind, placebo controlled clinical trial. Consistent with other studies,[24] our findings showed RZPs and BMO therapy improved the 90-day motor functions and outcomes in patients with AIS of presumed large-artery atherosclerosis origin.

Interestingly, our findings showed monotherapy or combination therapy of RZPs and BMO were able to facilitate the outcomes in patients with AIS of presumed large-artery atherosclerosis origin. The results were possibly due to the sample size were limited, and most of the patients in the current study were mild ischemic stroke. Hence, future large-scale randomized, controlled trial studies are imperative to clarify the potency between monotherapy or combination therapy of RZPs and BMO. Our current trail evaluated the efficacy and safety of combined RZPs-BMO therapy, and further provided credible evidence for traditional Tibetan medicine.

Moreover, due to simple randomization in the current study, the baseline hypertension in the four groups were not full balanced. Although patients in the RZPs+BMO group, BMO group and RZPs group have higher prevalence of hypertension than the placebo group, three treatment group had better 90-day functional outcomes compared to the placebo group. The data indicated there has been a benefit with BMO and RZPs therapy in AIS patients.

Finally, the trail was the first multi-center randomized controlled research to access the therapeutic function of RZPs and BMO in AIS, and our study provides a solid and reliable evidence-based medical evidence for Tibetan medicine for AIS treatment. As two traditional Tibetan medicines, RZPs and BMO, have flexible administration modes (oral and topical), which provide a variety of effective treatment options for AIS patients with different symptoms. For example, patients presenting with dysphagia may receive BMO for topical use to improve AIS-related symptoms. Considering a dilemma in traditional neuroprotective drugs of AIS, traditional Tibetan medicine can provide a promising treatment strategy for AIS.

Our current study has some limitations. First, RZPs and BMO are Tibetan medicine compounds of multiple mineral and plant products, whereas the specific active ingredients and mechanism of RZPs and BMO remain to be explored. Second, we only focus on the AIS of presumed large-artery atherosclerosis origin in the present study, it is worth expanding other stroke types, such as cardiogenic embolism and small artery occlusion. Third, patients with performed endovascular therapy were excluded from our trail. Future research is required to evaluate neuroprotective effect of RZPs and BMO in AIS patients receiving endovascular therapy. Finally, this study was conducted in the Chinese population, it should be conservative to generalize our research findings to other populations.

Conclusions

In summary, this trial demonstrates that RZPs and BMO—used either alone or in combination—produce clinically meaningful motor-function improvements within 90 days in patients with AIS attributable to large-artery atherosclerosis while maintaining a favorable safety profile. This allows individuals with AIS-related motor impairment to make personalized choices between oral and topical administration according to their needs. The findings not only open a new therapeutic avenue for AIS but also, for the first time, rigorously validate the integration of Tibetan medical principles with contemporary stroke management through robust clinical evidence.

Trial Registration

ChiCTR, ChiCTR2000036691. Registered 29 August 2020, URL: https://www.chictr.org.cn.

Abbreviations

RZPs, Ruyi Zhenbao Pills; BMO, Baimai Ointment; AIS, Acute ischemic stroke; FMA, Fugl–Meyer assessment; FMA-LE, Fugl-Meyer Assessment of Lower-extremity; FMA-UE, Fugl Meyer Assessment of Upper-extremity; TM-SSGQS, Tibetan medicine stroke symptom grading quantitative score; TM-SDEDS, Tibetan medicine subdivision disease element diagnosis of stroke; CONSORT, Consolidated Standards of Reporting Trials; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; BI, Barthel index; CI, Confidence interval; BMI, Body mass index; ITT, Intention-to-treat; PP, Per-protocol; IQR, Interquartile range; SD, Standard deviation.

Data Sharing Statement

The datasets used and/or analyzed in this trail are accessible from the corresponding author, Juexian Song, provided the request is reasonable.

Ethics Approval and Consent to Participate

Ethics committees of each participating study centers approved the research and all eligible centers or their legal surrogates had given informed consents according to national and local regulations before the assigning procedure was started.

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We appreciate the participation of all individuals in this study. This paper has been uploaded to [Researchgat] as a preprint: [https://www.researchgate.net/publication/383539288_Combined_Ruyi_Zhenbao_Pills-Baimai_Ointment_Therapy_on_Acute_Ischemic_Stroke_A_Multi-Arm_Randomized_Double-Blind_Placebo_Controlled_Clinical_Study].

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Disclosure

All authors declare that the research was executed without any commercial or financial ties which might be seen as a potential conflict of interest.

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