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ORIGINAL ARTICLE

A Randomized Trial to Assess the Long-term Safety of NeuroAiD among Caucasian Patients with Acute Ischemic Stroke*

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ABSTRACT **Objective:** To assess the long-term (up to 6 months) safety profile of a 3-month regimen of NeuroAiD for acute ischemic stroke. **Methods:** A total of 190 patients with acute ischemic stroke were identified for eligibility in a randomized, double-blind, placebo-controlled clinical trial, of which 150 patients allocated to either receiving NeuroAiD (80 cases) or placebo (70 cases) were analyzed after dropouts due to absence of baseline data, early death, or noncompliance. Both groups received treatment for three months and followed up for another three months after the completion of the treatment. Occurrence of clinical adverse events and laboratory parameters were assessed at 1 month, 3 months (while under treatment) and 6 months (3 months after the completion of treatment). Statistical comparisons between groups were performed using chi-square test or *t*-test whenever appropriate. **Results:** The two groups had comparable baseline characteristics. Mild nausea was more commonly reported in patients taking NeuroAid compared with placebo (P=0.01), of which 9 out of 10 were observed only during the first month of treatment. However, none of the adverse events reported were considered severe or required discontinuation of the study drug. There was no significant change observed in mean arterial blood pressure, haemoglobin, renal and liver laboratory parameters during treatment with NeuroAid and up to 3 months after completion of a 3-month regimen. **Conclusion:** NeuroAiD is safe and does not affect hematologic, hepatic, and renal functions during and long after completion of treatment.

KEYWORDS stroke, NeuroAid, safety

Stroke is a leading cause of death and chronic disability worldwide.[1] Effective proven treatments for stroke, however, have been limited. Due to the complexity of the disease, the search for treatments which specifically act on a single target mechanism to reduce long-term disability has constantly failed, leading to opinions that combination therapies comprising more than one active ingredient may represent a better strategy against stroke.[2,3] NeuroAiD, a Chinese medicine that has been developed to aid post-stroke recovery, is such a therapy with multiple mechanisms and is the subject of a large clinical trial.[4-6]

NeuroAiD composes of nine herbal (including *Radix astragali*, *Radix salvia miltiorrhizae*, *Radix paeoniae rubra*, *Rhizoma chuanxiong*, *Radix angelicae sinensis*, *Carthamus tinctorius*, *Prunus persica*, *Radix polygalae* and *Rhizoma acori tatarinowii*) and five animal components (including *Hirudo*, *Eupolyphaga seu steleophaga*, *Calculus bovisartifactus*, *Buthus martensii* and *Cornu saigae tataricae*).[5] Preliminary studies have shown promising results of NeuroAid's efficacy on the recovery of independence, motor function, vision and cognitive abilities in patients treated after a stroke.[7-9] Furthermore, it has been shown to be safe and does not modify haemostasis, haematology and biochemistry in both normal subjects and stroke patients when given acutely and in the subacute stages.[10,11] However, long-term safety data is scarce. Furthermore, there is no data on its safety among Caucasians.

We, therefore, aimed to assess the safety of NeuroAiD up to 6 months from start of the three-month treatment course for stroke.

METHODS

Study Design

This is a randomized double-blind placebo-controlled clinical trial (IRCT: 138905103663N2).

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Inclusion Criteria

We recruited patients aged between 55 and 90 years old with acute ischemic stroke in the middle, anterior, or posterior cerebral arteries and National Institute of Health Stroke Scale (NIHSS) score of at least 5, who were admitted at Golestan Hospital, Karami Hospital, or Emam Hospital (all in Iran) between February 2010 to June 2010 and confirmed by neuroimaging [either computed tomography (CT) or magnetic resonance imaging (MRI)] within one week of randomization. Only the new lesions were considered to be responsible for the index stroke at the time of eligibility as seen on the baseline imaging (CT or MRI).

Exclusion Criteria

We excluded patients who were admitted to the intensive care unit (as they are more prone to complications), had intracerebral haemorrhage or haemorrhagic conversion, had history of previous stroke or evidence of pre-existing stroke on brain imaging, had significant systemic disease, i.e. chronic obstructive pulmonary disease (COPD), severe asthma, CO_2 narcosis, renal failure, severe congestive heart failure, uraemia, cirrhosis, psychosis, dementia, and brain pathologies other than stroke (e.g. primary brain tumours, metastasis or infectious lesions), and had participated in another clinical trial within 3 months of inclusion.

Informed consents were obtained from all participants as approved by the ethics committee of the Joundishapour Medical University which is responsible for the three hospitals involved in this study.

Interventions

Eligible patients were randomly allocated to either receiving NeuroAiD or placebo as an add-on treatment within the first week after the stroke at a dose of 4 capsules 3 times a day for 3 months. Patients who required tube feeding were given the study treatment by opening the capsules and administering the diluted powder contents through the tube.

NeuroAiD and matching placebo was supplied by the Golestan Hospital pharmacy as funded by the university. NeuroAiD was manufactured by Moleac (Singapore) where each batch of the product underwent in-process and finished product quality control for both safety and efficacy using standardized assays.

One-to-one treatment allocation was performed according to a computer-generated randomization list prepared at the start of the study, kept individually sealed by an appointed study staff, and opened upon identification of an eligible patient. All patients received standard treatment for stroke, including anti-thrombotic therapy, statin, blood pressure control, anti-diabetic medications, and other treatments deemed medically necessary.

Observation Items

Baseline information including age, gender, race, history of hypertension, diabetes mellitus, or hyperlipidemia, NIHSS, cerebral artery involved, Trial of Organon 10172 in Acute Stroke Treatment (TOAST) classification, and laboratory tests results for haemoglobin, blood urea nitrogen (BUN), creatinine, sodium, potassium, alanine transferase (ALT), and aspartate aminotransferase (AST) were collected. NIHSS and modified Rankin Scale (mRS) were performed at 3 months (at completion of treatment). Patients were monitored for 6 months and data on blood pressure, haemoglobin, BUN, creatinine, sodium, potassium, as well as occurrence of adverse events, were collected at 1, 3, and 6 months (3 months after completion of treatment).

The following normal ranges were used to assess whether blood parameter values were abnormal: mean arterial blood pressure (MABP) 60–110 mm Hg, haemoglobin 12–7 g/dL, BUN 8–25 mg/dL, creatinine 0.6–1.5 mg/dL, sodium 135–145 mEq/L, potassium 3.5–5.5 mEg/L, ALT 7–56 U/L, and AST 5–40 U/L.

Statistical Analysis

Summary data were reported as numbers and proportions for categorical variables and as mean ± standard deviations for continuous variables. Whenever appropriate, comparisons between groups were performed using chi-square test (or Fisher's exact test in cases of cells having less than the expected number of observations) for categorical variables, and *t*-test (or ANOVA for repeated measures) for continuous variable to compute for statistical significance. A *P* value less than 0.05 was considered significant difference.

RESULTS

Patients Inclusion and Baseline Characteristics

Ninety-five patients were identified for each

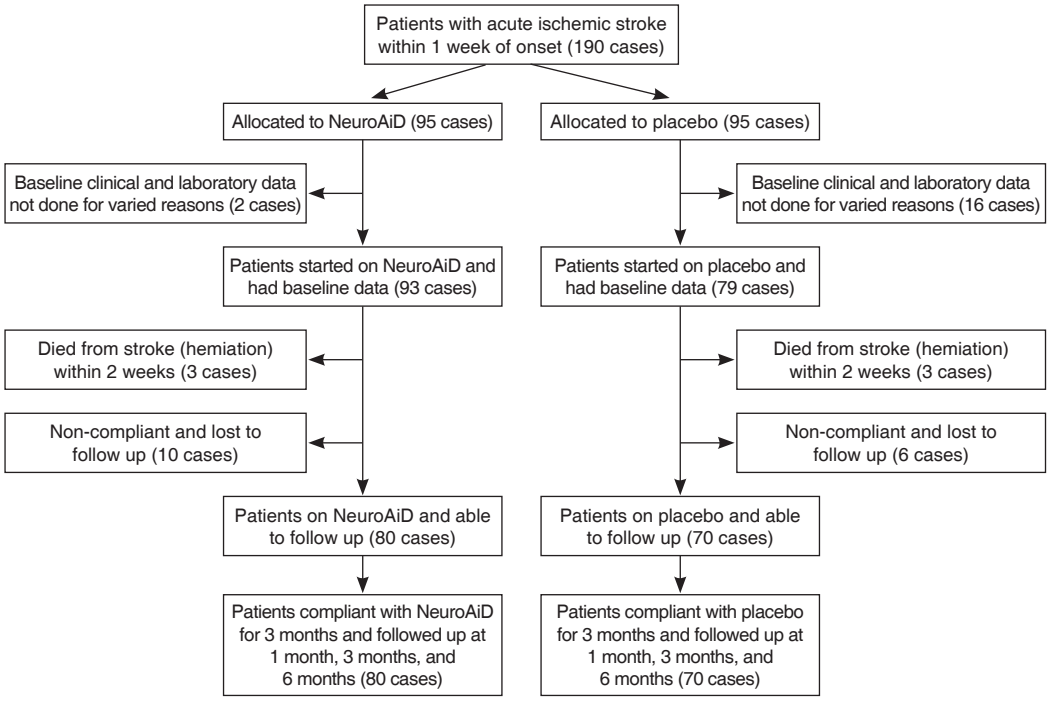

Figure 2. Study Flowchart

treatment arm, but 18 patients (2 in the NeuroAiD group and 16 in the placebo group) were unable to comply with baseline requirements for clinical and laboratory data for varied reasons, including unavailability of information from referring hospital, patient refusal, and missed procedures by non-study staff. Ninety-three patients had baseline data and were started on NeuroAiD and 79 patients on placebo. Three patients in each group died within 2 weeks of stroke onset. These deaths were deemed to be due to the underlying severe stroke and resulting cerebral herniation. Among the remaining patients, 16 had poor follow-up compliance and data were available for analysis in 150 patients (80 patients on NeuroAiD and 70 patients on placebo). Among these 150 patients, all were compliant to the allocated treatment, none died, and all were able to follow up for the 1, 3 and 6-months assessments (Figure 1). All patients were Caucasians. Baseline characteristics were similar between the two groups (Table 1).

Table 1. Baseline Characteristics of Cohort

Item	NeuroAid group (80 cases)	Placebo group (70 cases)	*P*-value
Age ($\bar{x} \pm s$, year)	76.7 ± 8.7	75.9 ± 7.8	ns
Female gender (Case, %)	38 (48)	30 (43)	ns
Risk factor (Case, %)			
Hypertension	53 (66)	51 (73)	ns
Diabetes mellitus	39 (49)	29 (41)	ns
Hyperlipidemia	40 (50)	30 (43)	ns
NIHSS ($\bar{x} \pm s$, score)	16.3 ± 3.5	16.6 ± 3.8	ns
Cerebral artery affected (Case, %)			
Middle cerebral artery	40 (50)	33 (47)	ns
Anterior cerebral artery	20 (25)	15 (22)	
Posterior cerebral artery	20 (25)	22 (31)	
TOAST classification (Case, %)			
Large vessel disease	61 (76)	52 (74)	ns
Cardioembolism	9 (11)	12 (17)	
Small vessel disease	10 (12)	6 (9)	

Note: ns, not statistically significant difference

Table 2. Comparison of Blood Parameters Monitored at Baseline, 1 Month, 3 Months and 6 Months ($\bar{x} \pm s$)

Blood parameters	Baseline			1 month			3 months			6 months		
	NeuroAid (80 cases)	Placebo (70 cases)	*P*	NeuroAid (80 cases)	Placebo (70 cases)	*P*	NeuroAid (80 cases)	Placebo (70 cases)	*P*	NeuroAid (80 cases)	Placebo (70 cases)	*P*
MABP (mm Hg)				103.5 ± 18.0	103.5 ± 17.2	0.99	106.9 ± 16.8	106.5 ± 15.5	0.87	105.7 ± 18.7	106.6 ± 14.9	0.76
Change from 1 month							3.4 ± 9.6	3.0 ± 8.5	0.77	2.2 ± 19.6	3.1 ± 21.0	0.78
Out of range (Case)				37	35	0.74	46	42	0.84	40	40	0.55
Haemoglobin (g/dL)	11.8 ± 1.0	11.8 ± 1.1	0.96	11.6 ± 0.9	11.1 ± 0.7	<0.001	11.8 ± 0.9	11.6 ± 0.9	0.27	11.9 ± 1.0	11.8 ± 0.9	0.63
Change from BL				–0.2 ± 0.9	–0.7 ± 1.2	<0.005	–0.0 ± 0.8	–0.2 ± 0.8	0.21	0.1 ± 0.8	–0.0 ± 0.6	0.57
Out of range (Case)	47	42	0.92	40	58	<0.05	39	42	0.35	35	36	0.50
BUN (mg/dL)	9.8 ± 2.1	11.0 ± 2.1	<0.001	9.7 ± 2.0	9.8 ± 1.8	0.73	9.4 ± 1.7	10.1 ± 1.7	<0.05	9.7 ± 2.0	9.9 ± 1.8	0.57
Change from BL				–0.1 ± 2.2	–1.1 ± 2.6	<0.01	–0.4 ± 2.0	–0.9 ± 2.6	0.14	–0.1 ± 2.1	–1.1 ± 2.6	<0.05
Out of range (Case)	7	2	0.14	6	4	0.67	6	3	0.42	7	3	0.29
Creatinine (mg/dL)	0.99 ± 0.24	1.00 ± 0.23	0.75	0.91 ± 0.18	0.96 ± 0.21	0.19	0.94 ± 0.20	0.98 ± 0.21	0.31	0.96 ± 0.20	0.94 ± 0.17	0.47
Change from BL				–0.07 ± 0.27	–0.04 ± 0.30	0.52	–0.04 ± 0.30	–0.02 ± 0.31	0.65	–0.02 ± 0.25	–0.06 ± 0.27	0.42
Out of range (Case)	1	0	0.74	0	0	0.95	0	0	0.95	0	0	0.95
Sodium (mEq/L)	140.5 ± 3.5	140.4 ± 3.4	0.81	140.2 ± 3.7	140.2 ± 3.9	0.99	140.2 ± 3.5	140.4 ± 3.8	0.73	140.4 ± 3.6	140.4 ± 3.5	0.89
Change from BL				–0.3 ± 5.3	–0.8 ± 5.3	0.88	–0.3 ± 5.2	0.0 ± 5.2	0.69	–0.1 ± 5.1	–0.0 ± 3.7	0.94
Out of range (Case)	16	13	0.84	17	16	0.83	16	15	0.85	16	14	1.00
Potassium (mEq/L)	4.4 ± 0.5	4.4 ± 0.5	0.73	4.4 ± 0.4	4.4 ± 0.5	0.42	4.4 ± 0.4	4.4 ± 0.5	0.92	4.4 ± 0.4	4.4 ± 0.5	0.76
Change from BL				0.1 ± 0.5	–0.0 ± 0.6	0.31	0.0 ± 0.6	0.0 ± 0.6	0.87	0.0 ± 0.4	0.0 ± 0.3	0.90
Out of range (Case)	3	2	0.77	0	0	0.95	0	0	0.95	0	1	0.62
ALT (U/L)	23.6 ± 5.5	24.9 ± 5.6	0.16	24.0 ± 5.7	24.2 ± 5.6	0.81	23.0 ± 5.1	25.4 ± 5.7	<0.01	22.5 ± 5.2	24.0 ± 5.0	0.08
Change from BL				0.4 ± 6.5	–0.6 ± 6.1	0.31	–0.5 ± 7.7	0.5 ± 8.0	0.41	–1.1 ± 7.2	–0.9 ± 6.8	0.86
Out of range (Case)	0	0	0.95	0	0	0.95	0	0	0.95	0	0	0.95
AST (U/L)	26.1 ± 6.4	26.4 ± 6.5	0.78	25.3 ± 6.1	25.4 ± 5.9	0.89	25.5 ± 6.0	25.9 ± 5.6	0.67	24.7 ± 5.6	26.5 ± 5.3	0.05
Change from BL				–0.8 ± 6.1	–1.0 ± 5.5	0.86	–0.6 ± 8.1	–0.5 ± 9.3	0.94	–1.4 ± 8.0	0.1 ± 7.4	0.24
Out of range (Case)	3	3	0.87	0	0	0.95	0	0	0.95	0	0	0.95

Notes: MABP, mean arterial blood pressure; BUN, blood urea nitrogen; ALT, alanine transferase; AST, aspartate aminotransferase; BL, baseline

Outcomes

At 3 months (upon completion of treatment), the mean NIHSS for the NeuroAiD group improved to 8.3±2.5 while that for the placebo group improved to 8.2±2.7 (*P*=0.77). The mRS distribution at 3 months was likewise similar between the two groups.

Adverse Events

Adverse events reported include nausea, vomiting, epistaxis, gastrointestinal bleeding, abdominal pain and headache. There was a statistically higher occurrence of nausea in the NeuroAid group as compared with placebo (*P*=0.01, Figure 2), but none was severe enough to lead to the discontinuation of NeuroAiD. In the NeuroAiD group, 10 cases of nausea were reported exclusively during the first 3 months of participation in the study, of which 9 occurred only within the first month of treatment. The rest of the other adverse events reported were not statistically different between the two groups.

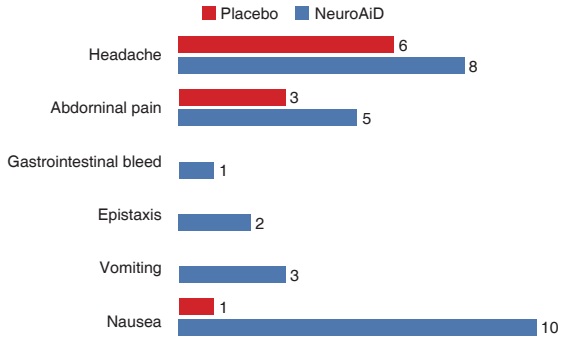

Figure 2. Adverse Events Reported during the Study Period (Case)

For the NeuroAid group, there was no statistical difference in MABP, haemoglobin, renal, and hepatic parameters at the different specified timepoints up to 6 months compared with baseline. There was, likewise, no difference between NeuroAiD and placebo at all assessment timepoints for MABP, creatinine, sodium, potassium, ALT and AST. However, a statistically significant drop was observed in haemoglobin at 1 month in the placebo group as compared with baseline assessment (*P*<0.0001) and also as compared with the NeuroAid group (*P*<0.001, Table 2). Compared with the baseline values, there was also a statistically significant drop in BUN in the placebo group at 1 month (*P*<0.001), 3 months (*P*<0.005), and 6 months (*P*=0.001). This was mainly due to the fact that the baseline BUN in the placebo group was higher than in the NeuroAid group (*P*<0.001). There was no difference when the proportions of patients with abnormal results were compared.

DISCUSSION

Proven and approved treatments for acute ischemic stroke are few. Previous clinical and animal studies on the use of NeuroAid for neuroprotection and neurorestoration in stroke have shown encouraging results in.[4,5,7-9] However, practitioners who are unfamiliar with the use of Chinese medicine may have concerns about its safety.

Our results confirm the safety of using NeuroAid in patients with acute ischemic stroke as previously reported.[10,11] Our study, nevertheless, contributes further to the existing data on the safety profile of NeuroAiD. Previous safety data were mainly on Asian patients. Ours is assessing the safety of NeuroAiD among Caucasians. Furthermore, we have shown that no delayed side effects occur on blood pressure, hematological, hepatic, and renal parameters not just during treatment but even long after completion of a 3-month regimen of NeuroAiD.

While nausea was more commonly reported by patients in the NeuroAiD group, this was mild and occurred mostly during the first month of treatment. Subsequently, nausea was reported uncommonly and no more than in the placebo group. None of the reported adverse events was serious.

Most safety studies on treatments for stroke are collected during the time that patients are taking the product. Even while therapies may be shown to be safe during the treatment course, it would certainly be of interest for practitioners to assess whether a treatment, particularly one derived from Chinese medicine, may still exhibit remote side effects even after completion and discontinuation of treatment. We had the opportunity to assess this in NeuroAiD. Most safety data from studies on NeuroAiD were during patients were still within the 3-month regimen. This is among the first systematically collected data that extends up to another 3 months after completion of treatment. How long after completion of treatment should a patient be followed up for safety remains ambiguous and, indeed, longer term follow-up of such patients need to be considered.

There are several limitations in our study. The

number of patients included and the number of adverse events were relatively small which made demonstrating significant differences more difficult. Furthermore, we had some patients who were non-compliant and lost to follow up. However, all patients who came back for their 1 month visit were all followed up to 6 months.

We did not find a significant difference in NIHSS and mRS at 3 months between the NeuroAiD and placebo groups with the size of our present study. This is currently being investigated in an on-going large multicentre trial.[6] Nonetheless, we have shown that the use of NeuroAiD is safe during and long after completion of treatment.

Conflict of Interests

None of the authors has any competing interest to declare.

Author Contributions

All authors (RBS, AH, AHM) contributed equally to this study, including conception and design, acquisition of data, analysis and interpretation of data. In addition, RBS drafted the manuscript. All authors have read, given final approval, and take public responsibility for the content of the version to be published.

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