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A Double-Blind, Placebo-Controlled, Randomized Phase II Pilot Study to Investigate the Potential Efficacy of the Traditional Chinese Medicine Neuroaid (MLC 601) in Enhancing Recovery after Stroke (TIERS)

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Key Words
Stroke · Neuroaid · Motor rehabilitation · Functional recovery · Clinical trial

Abstract
Background and Objective: Previous clinical studies have shown that Neuroaid (MLC 601) may be beneficial in post-stroke rehabilitation. Our aim was to investigate the efficacy of Neuroaid on motor recovery in ischemic stroke patients using rehabilitation endpoints in accordance with the International Conference on Harmonization/Good Clinical Practice guidelines, in order to provide predictive information for further larger trials. ***Methods:*** This is a phase II double-blind, placebo-controlled pilot study of 40 subjects admitted with a recent (less than 1 month) ischemic stroke. All subjects were given either Neuroaid or placebo, 4 capsules 3 times a day for 4 weeks. Fugl-Meyer Assessment (FMA), National Institutes of Health Stroke Scale and Functional Independence Measure scores were measured at initiation of the treatment, and at 4 and 8 weeks. ***Results:*** None of the outcomes was statistically significant between the two groups. However, FMA scores showed a positive trend for improvement with Neuroaid treatment over time. Subgroup analysis of subjects with posterior circulation infarction and severe stroke both showed a tendency for better recovery. ***Conclusion:*** Some positive trends were observed in the Neuroaid group. A larger multicenter trial focusing on severe stroke patients is needed to better evaluate the role of Neuroaid in aiding stroke recovery in rehabilitation.

Introduction

Standard treatment modalities in stroke rehabilitation are physiotherapy, occupational therapy, and speech therapy, in addition to skilled medical and nursing care. Despite intensive inpatient rehabilitation with these modalities in a stroke unit, 36% of acute stroke patients remain moderately to severely disabled at discharge [1]. There is thus a real need for better treatments to further improve the outcome of stroke rehabilitation.

Rehabilitation pharmacology refers to the use of medications in combination with rehabilitative training to improve functions. The two most commonly studied medications for this purpose are amphetamine and levodopa. Their mechanisms of action include increased noradrenergic and dopaminergic functions and facilitation of activity-dependent neuroplasticity [2–4]. However, the efficacy of these medications is still debatable [5, 6].

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Neuroaid (MLC 601, Moleac Pte. Ltd, Singapore) is a traditional Chinese medicine which has been used extensively in China as a drug to facilitate recovery after stroke. It combines 9 herbal (radix astragali, radix salviae miltorrhizae, radix paeoniae rubra, rhizoma chuanxiong, radix angelicae sinensis, *Carthamus tinctorius, Prunus persica,* radix polygalae and rhizoma acori tatarinowii) and 5 animal (*Hirudo, Eupolyphaga* seu *Steleophaga,* calculus bovis artifactus, *Buthus martensii* and cornu saigae tataricae) components and was registered under the Chinese name of Danqi Piantan Jiaonang with the Sino-Food and Drug Administration in August 2001. It is manufactured by Shitian Pharmaceutical Industry in Tianjin, China, and was certified as good manufacturing practice compliant with the Sino-Food and Drug Administration.

Previous clinical studies performed in China have shown that Neuroaid enhances stroke patients' recovery from their neurological disability and improves functional outcome and thus, may be beneficial in post-stroke rehabilitation [7]. However, these trials did not comply with the International Conference on Harmonization/Good Clinical Practice guidelines and used positive controls. Furthermore, the outcome measures in these trials were not the standard scales used in modern-day stroke trials.

A previous study [7] suggested that Neuroaid's effectiveness in improving stroke recovery may be related to its role in neuronal protection and plasticity.

The safety of Neuroaid in hemostasis, hematology and biochemistry has been established in 3 clinical trials [8]. A case series of 10 patients in Singapore supported the results reported in the initial studies [9].

A large-scale academic randomized controlled trial is currently recruiting in South East Asia to evaluate the impact of 3-month treatment with Neuroaid and is assessing patients on neurological endpoints using the modified Rankin Scale and National Institutes of Health Stroke Scale (NIHSS) [10]. Rehabilitation studies typically use more detailed evaluation scales of the different components of recovery and rehabilitation.

As there have been no previous studies on Neuroaid conducted using rehabilitation endpoints, we decided to investigate the efficacy of Neuroaid in motor recovery in ischemic stroke patients admitted to an inpatient rehabilitation center within the setting of a post-stroke rehabilitation trial in accordance with the International Conference on Harmonization/Good Clinical Practice guidelines. The objective of this research was to obtain pilot data which will support the design of a larger, controlled trial in the future.

Methods

Study Design and Subjects

This was a single-center, double-blind, placebo-controlled, randomized phase II pilot study. The design was similar to the one used in the early trials [7]. The patients were recruited from the Tan Tock Seng Hospital rehabilitation center in Ang Mo Kio Hospital, Singapore within 1 month after ischemic stroke onset.

All subjects were randomized to a group A (Neuroaid, 4 capsules 3 times daily) or group B (placebo, 4 capsules 3 times daily) 1-month treatment according to a balanced randomization scheme of 1:1, based on a computer-generated randomization list prepared by an appointed staff. The components of the placebo included the following constituents: barley 227.27 mg, dried ripe fruit 45.45 mg, noodle fish 90.91 mg and citric acid 5.00 mg, and had an appearance, smell and taste similar to Neuroaid. Only the designated, unblinded, independent staff member, performing the subject randomization, was aware of the treatment allocation of group A and B treatment.

The inclusion and exclusion criteria are listed below.

Inclusion Criteria

(1) Adults between 21 and 80 years old
(2) Randomizable within 1 month after stroke onset
(3) Motor power of grade 1–4/5 on the Medical Research Council Scale in at least one limb
(4) Prestroke modified Rankin Scale score ≤ 1 [11]
(5) Cerebral infarction with compatible imaging on computed tomography scan or magnetic resonance imaging
(6) Female subjects are eligible to participate in the trial if they are of nonchildbearing potential (hysterectomy or postmenopausal)
(7) Written informed consent obtained from the subject or legal representative

Exclusion Criteria

(1) Recent thrombolysis treatment
(2) Evidence of intracerebral hemorrhage on brain computed tomography scan or magnetic resonance imaging
(3) Full-dose or long-term anticoagulation therapy
(4) Significant nonischemic brain lesions which could affect functional disability
(5) Coexisting systemic diseases: terminal cancer, renal failure (creatinine >200 μmol/l, if known), cirrhosis, severe dementia or psychosis
(6) History of previous stroke
(7) Participation in another clinical trial within the last 3 months
(8) Aphasia or any other cognitive disabilities which prevent cooperation with study instructions
(9) Hemoglobin level of <10 mg/dl on admission
(10) History of craniotomy or seizures

Outcome Measures

The primary efficacy endpoint was improvement of impairment of the affected upper and lower limb as assessed on the Fugl-Meyer Assessment (FMA) at 4 weeks. Previous studies on the responsiveness and validity of FMA [12] have shown that the FMA score is suitable to detect changes over time for patients after

stroke rehabilitation, and it may be a relatively sound measure of motor function for stroke patients.

The secondary endpoint measures were:

(a) functional status as assessed on the Functional Independence Measure Scale (FIM) [13] at 4 and 8 weeks;

(b) FMA scores and subscores at 4 and 8 weeks, and

(c) stroke severity scores and subscores as assessed on the NIHSS [14] at 4 and 8 weeks.

Patients were categorized into three categories at baseline according to their FMA score at initiation of the trial: severe (0–35), moderate (36–79), and mild (80–100) [15].

Other Tests

All the following tests were performed at baseline and at 4 weeks.

- Routine blood investigations: full blood count; renal function test; liver function tests; glucose, calcium, electrolytes, and uric acid
- Routine investigations on the urine: albumin and glucose
- Electrocardiogram

This study was approved by the Institutional Review Board.

Sample Size

This is primarily a pilot study. There have been few studies of drug intervention in subacute stroke patients using the FMA score as an outcome measure, on which we can base our expected treatment effect. The sample size was determined based on a priori power analysis [16]. At least 20 subjects for each group would be required to detect an effect size d of 0.80 given a significance level of 5% (1-tailed) and 80% power. This effect size was estimated based on the findings of 2 previous trials [17, 18] on the distributed constraint-induced therapy in which the effect size d was 1.39 and 0.75 on the FMA, respectively.

Statistical Analysis

Baseline variables were compared using a two-group t test for continuous variables (i.e., age) and a χ^2 test for categorical variables (i.e., sex or race, etc).

Intention-to-treat analysis was used. For efficacy variables, comparisons were made between the two groups at baseline, at 4 and at 8 weeks. The two-group t test was used separately for each comparison. In case of nonnormality, the nonparametric Mann-Whitney test was performed. Further repeated-measures analyses were conducted to analyze the interaction effect of natural recovery over time and Neuroaid efficacy using the linear model.

All the statistics tests were performed using the Statistical Package for Social Sciences version 17.

Table 1. Baseline participant characteristics

Characteristics	Neuroaid group (n = 20)	Placebo (n = 20)	p value
Demographics			
Age, years	59.9 ± 12.8	60.3 ± 9.2	0.91
Sex			
Male	11 (55)	17 (85)	0.08
Female	9 (45)	3 (15)	0.08
Race			
Chinese	14 (70)	16 (80)	0.72
Malay	3 (15)	1 (5)	0.60
Indians	3 (15)	2 (10)	1
Others	0	1 (5)	1
Medical history: risk factors			
Hypertension	11 (55)	14 (70)	0.51
Diabetes mellitus	12 (60)	7 (35)	0.21
Hyperlipidemia	12 (60)	14 (70)	0.74
Ischemic heart disease	0 (0)	1 (5)	1
Stroke details			
Days since stroke	16.2 (6.8)	13.1 (5.2)	0.12
Site of stroke			
ACI	9 (45)	6 (30)	0.51
LACI	7 (35)	11 (55)	0.34
POCI	4 (20)	3 (15)	1
Side of hemiplegia			
Left	11 (55)	10 (50)	1
Right	9 (45)	10 (50)	1
Score at baseline			
Modified Rankin Scale	4 ± 1	4 ± 1.3	0.50
FMA	39.6 (31.6)	48.4 (30.7)	0.38
Stroke severity			
Severe	13 (65)	8 (40)	0.21
Moderate	3 (15)	8 (40)	0.16
Mild	4 (20)	4 (20)	1
NIHSS	6.3 (4.2)	6.2 (5)	0.95
FIM	81.4 (19.3)	82.2 (23.4)	0.77

Values presented are either means ± SD or number of subjects in subgroups with percentages in parentheses. ACI = Anterior circulation infarct; LACI = lacunar infarction; POCI = posterior circulation infarct.

Results

Baseline Characteristics

A total of 40 subjects were recruited in this study. The active and control groups had similar baseline characteristics (table 1). In general, the patients were young-elderly, predominantly male, Chinese, with moderately severe stroke, recruited 2 weeks after stroke. The higher proportion of males and shorter time interval between stroke onset and recruitment in the placebo group compared to the active group were not statistically significant.

Patient Flowchart

All 40 subjects were included in the final analysis: 20 received Neuroaid, and the other 20 placebo (fig. 1). Thirty-two subjects completed the study, 15 in the Neuroaid group and 17 in the placebo group; 3 patients in the Neu-

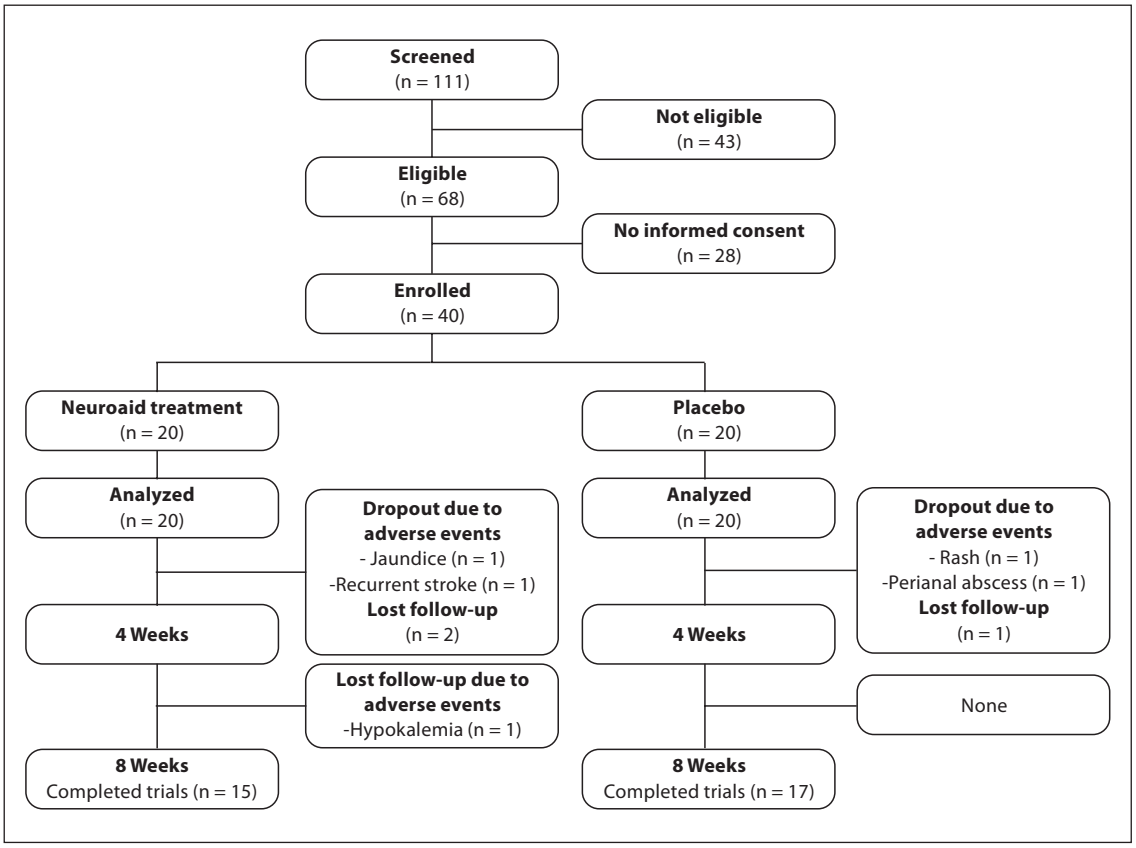


Fig. 1. Patient flowchart.

roaid group and 1 in the placebo group were lost to follow-up at 8 weeks, 3 patients in the Neuroaid group and 2 in the placebo group were withdrawn for safety reasons.

Patient compliance information was available for 39 subjects. Of these, only 1 subject in the placebo group was reported to be noncompliant with the treatment regimen.

Efficacy Results

None of the primary or secondary outcomes was statistically significant between the Neuroaid group and the control group, probably due to the small sample size. However, overall, at 8 weeks the FMA scores were higher in the Neuroaid group and the FIM scores were higher in the placebo group. The NIHSS scores were similar in both groups (table 2). Using repeated-measures tests, the treatment effect was not significant over time although the trend towards the Neuroaid treatment was seen at 8 weeks ($p = 0.40$) (fig. 2a).

Exploratory Analysis

The exploratory analysis was based on the FMA as it has been shown to be the relevant scale to detect changes over time for patients after stroke rehabilitation [12]. Additionally, as all the trends were increasing over time, we also focused our analysis on the scores at 8 weeks.

Subgroup Analysis

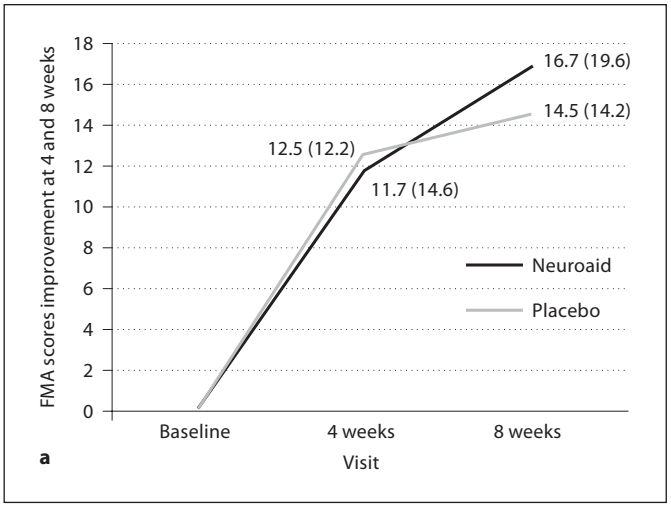
We observed that the Neuroaid group performed better than the placebo group when the severity of the stroke was high; this difference increased at the later stage of the study (+58% higher improvement at 8 weeks in the Neuroaid group in severe cases, $p = 0.36$) (table 3).

Additionally, we observed a very strong tendency of a better recovery in posterior circulation infarction (POCI) patients receiving Neuroaid both at 4 weeks and 8 weeks (respectively $p = 0.15$, $p = 0.23$) (table 3). Since the FMA scores at baseline differed in both groups (43.3 in the Neuroaid group vs. 82 in the placebo group), we compared the recovery of the POCI patients in the Neuroaid

Table 2. Outcome results showing improvement at 4 and 8 weeks

Characteristics	Neuroaid group (n = 20)	Placebo (n = 20)	p value
FMA improvement (ref. baseline)			
By 4 weeks	11.7 ± 14.6	12.5 ± 12.2	0.84
By 8 weeks	16.7 ± 19.6	14.5 ± 14.2	0.68
NIHSS improvement (ref. baseline)			
By 4 weeks	–2 ± 1.9	–1.9 ± 2.5	0.89
By 8 weeks	–2.4 ± 2.0	–3 ± 3.3	0.49
FIM improvement (ref. baseline)			
By 4 weeks	13.6 ± 11.9	19.95 ± 15.5	0.17
By 8 weeks	14.7 ± 11.5	22.6 ± 16.3	0.12

FMA, NIHSS and FIM scores measured at baseline, and at 4 and 8 weeks. The improvement was calculated by numerical difference between the score at baseline and the one at 4 or 8 weeks. Values presented are means ± SD.



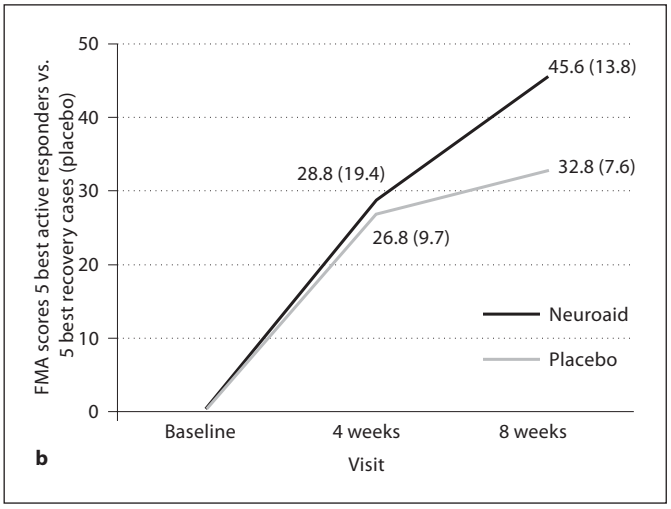


Fig. 2. FMA outcome results: repeated-measures analyses (**a**: n = 40; **b**: n = 10, i.e. the 5 best-recovered in both groups), with means (standard deviations).

group with the recovery achieved by the overall population of the placebo group (43.3 for the POCI Neuroaid group vs. 48.4 for the placebo group at baseline) and also found it to be higher (23.75 vs. 12.5 at 4 weeks, p = 0.35; 26.25 vs. 14.5 at 8 weeks, p = 0.39).

Other characteristics at baseline were shown to have no influence on the results.

Best Responders

In order to generate testable hypotheses, we looked at the best responders. We found that the relative improvement of the patients compared to their score at baseline results showed that subjects on Neuroaid were more likely to achieve important recovery as the threshold increased (fig. 2a, 3). While 10 and 9 patients in the Neuroaid and placebo group, respectively, achieved at least 50% progress, 6 in the Neuroaid versus 2 in the placebo group achieved more than 150% progress (p = 0.24) (fig. 3). All the characteristics at baseline of these 8 patients were similar to the overall population except for the severity of their stroke (mean of 14.9 on the FMA at baseline).

More detailed analysis showed that at 8 weeks, the 15 patients with the lowest recovery in both groups had very similar improvement in scores. However, the scores of the 5 best-recovered patients in both groups diverged. These 5 patients were further analyzed and the subjects receiving Neuroaid showed a better recovery (+11% at 4 weeks and +39% at 8 weeks, p = 0.17) than the patients in the placebo group. This difference was not statistically significant but showed a trend towards significance over time. Using repeated-measures tests, similar conclusions could be drawn. While the treatment effect did not show significance over time, a tendency could be observed in the later trial period that Neuroaid enhances the recovery of patients (fig. 2b).

The FIM showed a higher score in the placebo group; however, this difference was nonsignificant. The FIM score is employed to test the functional abilities of stroke survivors and might not be relevant for this study focus-

Table 3. FMA improvement scores per stroke severity (severe, moderate and mild) and site of stroke (ACI, LACI and POCI)

Characteristics	Neuroaid group (n = 20)	Placebo (n = 20)	p value
Stroke severity			
4 weeks improvement (ref. baseline)			
Severe	12.5 ± 16.2	9.9 ± 9.2	0.65
Moderate	22 ± 6.2	20.5 ± 13.1	0.92
Mild	1.3 ± 3.0	1.8 ± 1.3	0.77
8 weeks improvement (ref. baseline)			
Severe	18.9 ± 21.9	12 ± 12.4	0.36
Moderate	27.7 ± 8.0	22.6 ± 15.2	0.61
Mild	1.3 ± 3.8	3 ± 2.9	0.47
Site of stroke			
4 weeks improvement (ref. baseline)			
ACI	11.4 ± 12.1	17.3 ± 12.5	0.24
LACI	5 ± 5.3	13.2 ± 12.0	0.29
POCI	23.8 ± 24.5	0.3 ± 2.9	0.15
8 weeks improvement (ref. baseline)			
ACI	15.6 ± 17.2	18.8 ± 16.1	0.68
LACI	12.7 ± 21.2	15.7 ± 13.2	0.74
POCI	26.3 ± 24.1	1 ± 6.6	0.23

Values presented are means ± SD. ACI = Anterior circulation infarct; LACI = lacunar infarction; POCI = posterior circulation infarct.

Table 4. Number of subjects and respective percentages (in parentheses) in each of the groups of presented adverse events and serious adverse event during the trial

	Neuroaid	Placebo	All
Types and number of AES			
Total number of AES			16
Pain	3 (18)	0	3 (18)
Pruritic rash/pruritus	0	2 (12)	2 (12)
Urinary tract infection	0	2 (12)	2 (12)
Elevated liver enzymes	1 (6)	0	1 (6)
Contusion finger	1 (6)	0	1 (6)
Edema foot	1 (6)	0	1 (6)
Thrombocytopenia	1 (6)	0	1 (6)
Chest discomfort	1 (6)	0	1 (6)
Headache	1 (6)	0	1 (6)
Abdominal discomfort	0	1 (6)	1 (6)
Fall	0	1 (6)	1 (6)
Dyesthesia	0	1 (6)	1 (6)
Types and number of SAES			
Total number of SAES			5
Jaundice	1 (6)	0	1 (6)
Hypokalemia	1 (6)	0	1 (6)
Seizures	1 (6)	0	1 (6)
Recurrent stroke	1 (6)	0	1 (6)
Perianal abscess	0	1 (6)	1 (6)

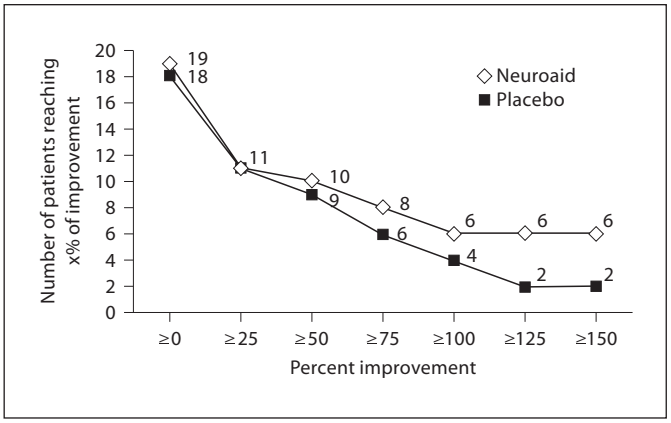


Fig. 3. FMA outcome results in both groups: the relative improvement at 8 weeks compared to baseline. Values present number of subjects reaching each level of improvement.

ing on motor disabilities. Further larger trials are needed to provide conclusive evidence.

Safety Data

A total of 15 subjects reported 16 adverse events (AEs) during the study: 7 subjects on Neuroaid had 8 AEs, while 8 subjects on placebo had 8 AEs. All AEs were mild (12/16) or moderate (4/16) in severity.

Four serious adverse events (SAEs) were reported in the Neuroaid group (jaundice, hypokalemia, seizures, and recurrent stroke) while 1 SAE was reported in the placebo group (perianal abscess). The SAEs were considered not to be related to the study medication. No deaths were reported.

Two patients in the Neuroaid group left the trial because of SAEs (jaundice and recurrent stroke) compared with 2 patients in the placebo group with AEs (rash and abdominal distension).

All reported AEs and SAEs are presented in table 4.

Discussion

Our study did not detect any statistically significant difference in the effect of Neuroaid on the motor recovery of ischemic stroke patients when starting treatment within a month of stroke onset. These results are probably due to the small sample size. However, some positive trends were noted on exploratory analysis.

The FMA score is a quantitative instrument measuring sensorimotor stroke recovery. Its primary value is the

100-point motor domain. Based on the available evidence, the FMA motor scale is highly recommended as a clinical and research tool for assessing changes in motor impairment following stroke [12]. NIHSS and FIM scores were less appropriate outcome measures in this study focused on post-stroke motor recovery as the NIHSS is a combination of several subscores of which only 4 out of 11 are assessing sensorimotor stroke recovery; the FIM scale is an independence indicator.

Subgroup analysis of severe stroke patients showed a better recovery in the Neuroaid group compared to the placebo group, this tendency increasing at the later stage of the study. In such cases, it is also easier to distinguish the treatment effect from the natural recovery, which tends to be more rapid at first and slower later.

Subgroup analysis also showed a tendency for a better recovery in POCI patients receiving Neuroaid. However, it is difficult to draw any conclusion given the small number of patients involved (n = 7) and the imbalance of the scores at baseline.

We noted the increasing benefit of the treatment over time. Such a hypothesis is consistent with the build-up effect observed in the Neuroaid group, and with the earlier postulate that mechanisms involved in the action of Neuroaid could include neuroplasticity [8], which is time dependent. Brain rehabilitation processes are slow and it takes time to build and grow new neuronal pathways.

Furthermore, the effect of the treatment is significant when there is a potential for recovery, which is also consistent with the hypothesis of natural neuroplasticity mechanisms. Similarly, the 5 best-recovered patients in the Neuroaid group were recovering more than the 5 best-recovered patients in the placebo group, this trend also increasing over time. Thus, a longer treatment duration and longer trial period of follow-up might be more appropriate.

Additionally, the results show a very good safety profile for Neuroaid. Overall the treatment was very well tolerated and none of the adverse events were considered drug-related.

There are some study limitations. The sample size of 40 subjects was not sufficient to draw any conclusion on the efficacy of the treatment. The study itself is an exploratory analysis, with the objective of generating hypotheses for future larger trials. However, trends were observed and results provided estimates for sample size requirements to achieve statistical significance in future studies. The subjects were on average young compared to the average stroke age of 65 years [19]. The profile of the population regarding medical disorders such as hypertension and diabetes was similar to the average profile of stroke patients in Singapore [19]. The duration of the treatment and of this study was shorter versus the duration of other trials assessing the efficacy of Neuroaid after stroke [10]. Most of the trends were strengthening over time when we compared the first and second follow-up. This would suggest that a longer trial period could also be an important criterion for subsequent protocols.

Conclusion

Our study shows that a randomized, double-blind, placebo-controlled trial of a traditional Chinese medicine according to Good Clinical Practice guidelines is possible. Our results suggest that Neuroaid given for 4 weeks to ischemic stroke subjects starting within a month after stroke onset did not statistically significantly facilitate motor recovery. Results also showed that the treatment was safe as an add-on to standard stroke medications.

However, several positive trends could be noted on the FMA score in the Neuroaid group versus the placebo group. Subgroup analysis showed an advantage of the Neuroaid group in the case of severe stroke patients and POCI patients. The overall improvement distribution was also largely favoring the patients in the Neuroaid group with recovery potential.

Trends were increasing over time suggesting that longer treatment duration and trial period are needed to fully observe the treatment effect. Observations support earlier hypotheses of mechanisms around neuroplasticity. A large, randomized, double-blind, placebo-controlled trial on 280 severe stroke patients (power = 0.8, type I error = 0.05, intervention:control = 1:1) would enable to evaluate more definitively the efficacy of Neuroaid in enhancing post-stroke recovery.

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