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Danqi Piantang Jiaonang (DJ), a Traditional Chinese Medicine, in Poststroke Recovery

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Background and Purpose—Stroke is a leading cause of death and disability worldwide. Despite improvements in acute stroke treatment, many patients only make a partial or poor recovery. Therefore, there is a need for treatments that would further improve outcome. Danqi Piantang Jiaonang (DJ; NeuroAid), a traditional Chinese medicine widely used in China to improve recovery after stroke, has been compared with another traditional Chinese medicine in 2 unpublished randomized clinical trials. The results of these studies were pooled and reanalyzed to assess efficacy and safety.

Methods—Six hundred five subjects were randomized in 2 randomized double-blinded, controlled trials to receive either DJ or Buchang Naointong Jiaonang. Subjects were treated for 1 month. Inclusion criteria were: (1) patients with recent (from 10 days to 6 months) ischemic stroke; (2) patients satisfying Western diagnostic standards for stroke and traditional Chinese medicine standards for diagnosis of apoplexy; and (3) Diagnostic Therapeutic Effects of Apoplexy score ≥ 10 .

Results—The functional outcome, measured by the Comprehensive Function Score component of the Diagnostic Therapeutic Effects of Apoplexy scale, showed a statistically significant superiority of DJ over the control treatment group (relative risk, 2.4; 95% CI, 1.28 to 4.51; $P=0.007$). Tolerance was excellent in both groups.

Conclusions—The pooled analysis of 2 unpublished trials of DJ, a traditional Chinese medicine currently approved in China to improve neurological recovery after stroke, shows good tolerability and superiority of DJ over another traditional Chinese medicine also approved for stroke. A large double-blind randomized clinical trial is required to further assess the safety and efficacy of DJ. (*Stroke*. 2009;40:00-00.)

Key Words: cerebral infarct ■ randomized controlled trials ■ stroke recovery ■ traditional Chinese medicine

Stroke is a leading cause of death and disability worldwide.¹ Despite improvements in acute stroke care—stroke unit care, thrombolysis in appropriately selected patients, and early and sustained antiplatelet therapy—many patients only make a partial or poor recovery after stroke and the major burden of stroke is chronic disability.² Therefore, there is a need for treatments that would further improve outcome.

Clinical research performed in China based on traditional Chinese medicine (TCM) has the potential of suggesting new treatments for cerebral infarction. Currently, there are more than 100 TCM agents used clinically in China for stroke with the approval of the Chinese National Drug Administration.³ However, these have limited acceptability outside China due to unfamiliarity with TCM where the concept of stroke is quite different in many ways from that held by Western medicine.

Moreover, there is a lack of availability of the evidence for the efficacy and safety of TCM. A recent meta-analysis³ of

TCM for ischemic stroke only found clinical trial reports for 59 TCM and concluded that the methodological quality of most included trials was poor because only 3 were randomized, double-blind, and placebo-controlled, whereas only 2 had long-term outcome assessments. Nevertheless, most studies reported neurological improvement with little heterogeneity in effect size. Although this may be a result of admission, selection, reporting, or publication bias, it is clear that further large, well-designed trials are necessary because pharmacological studies have demonstrated some TCM to have antioxidant, anti-inflammatory, and ant glutamate effects.⁴ TCM can dilate blood vessels, suppress platelet aggregation, protect against ischemic reperfusion injury, and enhance the tolerance of ischemic tissue to hypoxia.⁵

Danqi Piantang Jiaonang (DJ) is a TCM marketed in China as Danqi Piantan Jiaonang and internationally as NeuroAid. It was registered in China by the Sino Food and Drug Admin-

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Table 1. Diagnostic Therapeutic Effects of Apoplexy Scoring System

1-Visual fields/eye symptoms 0=No visual loss 2=Partial visual loss due to eyes hung upward 4=Eye deviation	2-Facial movement/facial paralysis 0=Normal facial movement, no asymmetry 1=Partial facial paresis 2=Complete facial paralysis	3-Upper limb paralysis 0=No drift 1=Weakness in raising arm 2=Ability to hold/raise the arm over the shoulder 4=Inability to hold/raise the arm over the shoulder 5=Slight movement of the arm 6=No movement of the arm
4-Finger paralysis 0=Normal movement 1=Weakness in moving fingers 2=Partial movement only: able to clench the fist and extend the fingers partially 4=Slight movement of the fingers only 5=Complete paralysis of the fingers	5-Lower limb paralysis 0=No drift 1=Ability to raise/hold the leg by more than 45° 2=Inability to raise/hold the leg by more than 45° 4=Horizontal movement only 6=Slight movement or no movement	6-Toe paralysis 0=Normal movement 1=Weakness in moving toes 2=Partial movement/stretch of the toes 4=Slight movement of the toes only 5=Complete paralysis of the toes
7-Best language 0=No aphasia 1=Mild aphasia with unclear pronunciation 3=Moderate aphasia with incomplete sentence 4=Important aphasia with unclear words 6=Severe aphasia	8-Comprehensive functions 0=Able to take care of oneself and speak freely 2=Live independently and able to do some simple work with some incomplete function 4=Able to walk and take care of oneself but must be helped partially 6=Able to stand and take a step but must be taken care of at all times 8=Confined to bed	

istration in 2001 after being evaluated in clinical trials, which are only partly published in the Chinese medical literature.⁶ DJ is widely available in China and is a hospital prescription reimbursed through health coverage. In 2006, DJ was selected by the Chinese Ministry of Science and Technology for the Key Technologies Research & Development program, aimed at promoting development of the most promising Chinese innovations.⁷ Buchang Naoxintong Jiaonang (BNJ) is an approved TCM for stroke, which is widely used. The aim of the present study is to pool and reanalyze clinical data from 2 unpublished trials of DJ known to the investigators.

Methods

Two randomized clinical trials comparing the efficacy and safety of DJ and BNJ, a TCM approved by the Sino Food and Drug Administration, in subjects with recent ischemic stroke, are included in this pooled analysis. Two hundred subjects were randomized in the first study and 405 in the second. Both studies had similar designs that are described subsequently.

Patients

Stroke in- or outpatients were recruited from 6 participating institutions (Heilongjiang and Changchun TCM Universities, Shanxi, Anhui, Henan, and Liaoning Traditional Chinese Medicine Institutes). The protocol was approved by the New Pharmaceuticals Examination Centre of the State Food and Drug Administration and by each individual institution's ethics committee.

Inclusion Criteria

Patients were eligible if they (1) were between 18 and 70 years old; (2) were diagnosed with ischemic stroke according to Western medicine diagnosis standards in China⁸; (3) met the requirements of the TCM standards for diagnosis of apoplexy⁹; (4) had a Diagnostic Therapeutic Effects of Apoplexy (DTER) score ≥ 10 (Table 1) (5) were at the restoration stage according to TCM criteria (ie, between 15 days and 6 months after the onset of symptoms); and (6) provided signed informed consent.

The Western medicine diagnosis standards followed the "Key Points for Diagnosing Cerebrovascular Diseases" modified in the 4th National Cerebrovascular Disease Seminar by the China Medical Society in 1995.⁸ Details of the DTER scoring system are provided in Table 1.

Exclusion Criteria

Patients with transient ischemic attacks, lacunar infarcts, or infarction of the basilar artery system were excluded from the study. Patients were also excluded from the study if they had other intracranial pathologies such as intracranial tumors, atrial fibrillation, other clinically significant systemic diseases, or were pregnant and lactating women.

Stratification and Randomization

In the 2 randomized trials, eligible patients were randomized after stratification according to whether their condition was mild, moderate, or severe, using the patients' score on the DTER (Table 1). A DTER score of 10 to 13 was classified as mild, 14 to 26 as moderate, and 27 to 34 as severe. Study centers were requested to target recruitment of approximately 20% mild, 60% moderate, and 20% severe cases.

Randomization numbers were generated by computer. Randomization numbers were pregenerated and placed in sealed envelopes. A serial number was given to each envelope according to the sequence of allocation of the randomized number. Each envelope was then opened in sequence according to the admission sequence of the subjects at the respective study center. Subjects were randomized into treatment or control groups according to the randomized number in the envelope.

Subjects as well as investigators and pharmacists were blinded to the allocation. The password for the randomization envelope for each subject was kept by the sponsor and a designated researcher.

For simplicity, the BNJ treatment group is later referred to in this article as the "control group."

Interventions

Subjects were randomized to receive either DJ or BNJ, which served as a control, in a 1:1 ratio in the first study of 200 subjects and in a 3:1 ratio in the second study of 405 subjects. BNJ was used as no placebo was allowed in accordance with the Chinese guidelines governing TCM clinical research.

DJ was developed by the No. 1 Hospital attached to the Tianjin TCM Institute for treating apoplexy with qi deficiency and blood stasis during the recovery phase. It consists of a dry extract of 14 components, the 2 main ingredients being Radix Astragalus (Huangqi) and Radix Salviae miltiorrhizae (Danchen). The respective raw materials were processed into a dry extract, which was then used to fill a hard gelatin capsule. Dextrin, an inert pharmaceutical excipient, was added to the dry extract to make up the weight of each capsule to 0.4 g.

Table 2. Baseline Characteristics

Groups	DJ (n=400)			Control (n=205)		
Male, n (%)	232 (58%)			136 (68%)		
Mean age and range, years	59.2 (31–70)			58.8 (30–70)		
Time from stroke onset to treatment initiation, n (%)	15–60 days 255 (64%)	61–120 days 83 (21%)	121–180 days 62 (16%)	15–60 days 136 (66%)	61–120 days 44 (21%)	121–180 days 25 (12%)
Stroke severity DTER score, n (%)	Mild 10–13 n=85 (21%)	Intermediate 14–26 n=252 (63%)	Severe 27–34 n=63 (16%)	Mild 10–13 n=40 (20%)	Intermediate 14–26 n=121 (59%)	Severe 27–34 n=44 (21%)

BNJ was produced by the Xianyang Buchang Medicines Co, Ltd. Both the investigational drug and the control drug were provided by Tianjin Shitian Medicines Co, Ltd. Subjects took 4 capsules after each meal, 3 times per day for 4 weeks.

Data Management

We compiled an electronic database consisting of data from individual subjects in the 2 eligible trials. Data included baseline characteristics, the allocated treatment medication, scores as defined by the DTER scoring system (Table 2) as well as adverse events and laboratory evaluations. Data were checked for completeness and internal consistency with subjects' records.

Objectives and Outcome Measures

The 2 Chinese studies compared the efficacy of DJ as measured by the DTER scoring system with that of BNJ and also compare their safety profiles.

Likewise, the primary outcome measure of this pooled analysis was the improvement at 1 month in the comprehensive functions score. The neurological deficit score (obtained by adding the first 7 subscores of the DTER scoring system) and each of its individual 7 components were also analyzed. Safety was evaluated by the pooled analysis of serious and nonserious adverse events and of laboratory evaluations collected in the 2 randomized trials.

Statistical Methods

Because statistical analyses in the Chinese studies were performed on nonstandard outcome measures likely to be unfamiliar to Western-trained physicians, we have extracted data from these 2 randomized studies, pooled the data together, and reanalyzed using the random effects model.¹⁰ The comprehensive functions score was dichotomized into 0 versus 2 to 8, which may be compared with a 0 to 1 versus 2 to 5 dichotomy on the modified Rankin scale, although no formal validation studies have been conducted. The probability of improvement in the DJ treatment group compared with the control group was quantified as a relative risk.

The neurological deficit score, obtained by adding the first 7 subscores of the DTER and individual subscores—evaluating language function, facial paralysis, visual symptoms, upper and lower limb paralysis, upper and lower distal limb paralysis—were treated as continuous variables. Improvement in the DJ compared with the control group was quantified by the difference in mean scores.

Results

Recruitment and Subjects' Flow

In the first study, 201 subjects were enrolled initially. One subject was subsequently excluded and not randomized due to the administration of concomitant medication. One hundred subjects were randomized to the DJ treatment group and 100 to the control group. In the second study, 405 subjects were enrolled, 300 subjects allocated to the DJ treatment group and 105 subjects to the control group. Thus, in total, 605 subjects were randomized by 6 hospitals in China from December 10, 1999, until July 20, 2000, with 405 subjects

randomized to the DJ treatment group and 205 subjects to the control group. No subjects were withdrawn or lost to follow-up.

Characteristics of Subjects

Baseline characteristics are indicated in Table 2. There was no difference at baseline between the DJ and control group in gender, age, time from stroke onset, or stroke severity.

Efficacy Results

The results of the pooled analysis are summarized subsequently.

Effects on Functional Outcomes

Functional outcome was assessed using the Comprehensive Function Score component of the DTER scale (Table 1). The scores were dichotomized into 2 categories: 0 versus 2 to 8. Both studies showed an advantage to DJ and the pooled analysis suggested that subjects receiving DJ were more likely to achieve a good functional outcome at 1 month than those randomized to the control treatment group (relative risk, 2.4; 95% CI, 1.28 to 4.51; $P=0.007$; Figure 1).

Effects on Recovery of Neurological Deficits

The neurological deficit score was obtained by adding the first 7 subscores of the DTER (Table 1). The trend in the pooled analyses was in favor of DJ, but the result was not statistically significant (weighted mean difference, 0.22; 95% CI, -0.11 to 0.56 ; $P=0.18$; Figure 2).

Effect on Motor Scores

The first 7 subscores were analyzed individually. Most of these separate motor function pooled analyses showed an advantage in those subjects randomized to the DJ treatment group compared with the control treatment group. Specifically, DJ statistically significantly decreased the scores at 1 month for the 2 domains of upper limb (weighted mean difference, -0.43 ; 95% CI, -0.73 to -0.12 ; $P=0.006$) and distal lower limbs (weighted mean difference, -0.32 ; 95% CI, -0.59 to -0.06 ; $P=0.02$) as compared with the active control. A numeric decrease in the score for lower limb, facial and distal upper limb functions was observed but not statistically significant. No significant effect was observed on visual and language functions.

Safety Results

The clinical trials reported no severe adverse events and only 2 cases of nausea and vomiting in subjects receiving DJ. Blood cell count, renal function (blood and urine testing), and

Review: DJ for post-stroke recovery
 Comparison: 02 DJ vs Control
 Outcome: 01 Functional outcome at 1 mth

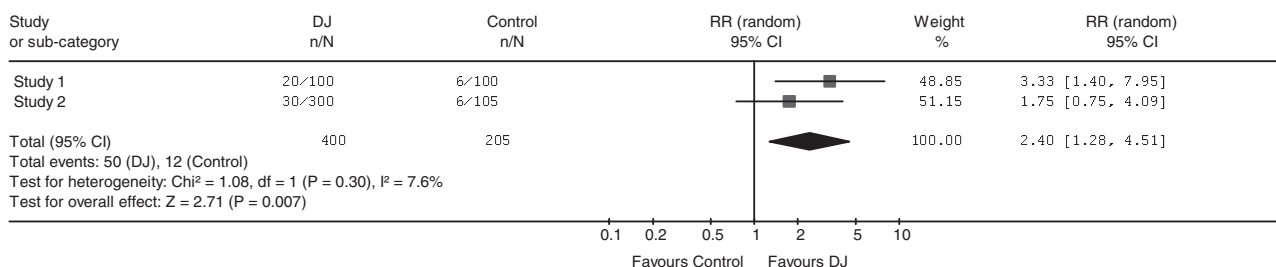


Figure 1. Effect on functional outcome at 1 month. Favorable functional outcome is defined as a score of 0 (able to take care of one-self and speak freely) versus any higher score according to the Standards for Evaluating the Diagnosis Therapeutic Effects of Apoplexy scoring system comprehensive function subscore (as defined in Table 1).

liver function were measured and no abnormal changes were observed.

Discussion

The pooled analysis of 2 unpublished trials of DJ, a TCM currently approved in China to improve neurological recovery after stroke, shows the superiority of DJ over another TCM also approved for stroke. Functional outcome as measured by the Comprehensive Function Score component of the DTER scale showed a statistically significant superiority of DJ over the BNJ treatment group. There was also a trend in the pooled analyses in favor of DJ with respect to the neurological deficits score. Tolerance was excellent in both groups.

Although the use of DJ in poststroke recovery appears promising, the data from the Chinese studies are not sufficient for an evidence-based medicine recommendation to change current prescribing or treatment practice. This is due to methodological inadequacies in the studies such as the use of TCM diagnostic criteria for stroke, the lack of placebo control, the broad time interval after onset of stroke, the short treatment period, and the use of outcome measure scales, which are different from those currently widely used in international stroke trials.

The use of BNJ as a control instead of placebo may impact the interpretation of the results. However, BNJ is an approved TCM for stroke, is widely used, and is well tolerated. Hence, it seems less likely that the effect of BNJ on stroke recovery was negative rather than neutral or positive. Another possible confounder may be the wide variation in the time to random-

ization. This may have led to a bias due to patients being at different stages of the natural recovery process.

In the Chinese studies, DJ exhibited a favorable safety profile; there were no serious adverse events recorded and only 2 cases of mild nausea and vomiting. This low rate of adverse events may be due to a combination of the fact that the patients were recruited during their recovery phase when their clinical condition had stabilized and to the method of collection of adverse events in China. However, such a low rate of adverse events again leads clinicians to suspect that the patients selected differ significantly from those recruited in stroke trials in general.

Traditional medicine is widely used globally in both developing and developed countries and is a rapidly growing health system and economic importance.¹¹ Although providers of traditional medicine seek increased recognition and support, many Western-trained professionals have strong reservations about the benefits of traditional medicine. This conflict between “uncritical enthusiasm versus uninformed skepticism” can only be resolved by improving the evidence base from which reliable conclusions can be drawn on the efficacy and safety of traditional medicine. It is vital more efforts are made to identify promising treatments from traditional medicine in a scientifically credible format. Performing well-controlled randomized clinical trials is the only means to ensure that potentially beneficial practices are not neglected nor inadequately evaluated practices promoted.

Establishing whether potential stroke treatment from TCM can be effective and safe through well-designed clinical trials may be considered a priority because it may then open up the

Review: DJ for post-stroke recovery
 Comparison: 02 DJ vs Control
 Outcome: 06 Neurological disorders at 1 mth

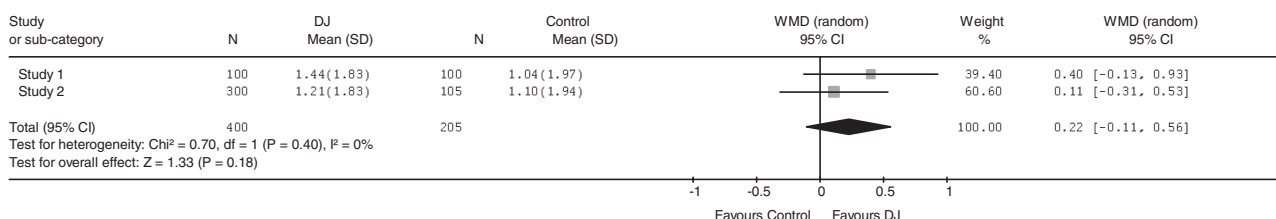


Figure 2. Effect on neurological deficits at 1 month. The neurological deficit score was obtained by adding the first 7 subscores of the Standards for Evaluating the Diagnosis Therapeutic Effects of Apoplexy scoring system (as defined in Table 1).

potential to develop improved treatments based on investigating the active ingredients and mechanisms of actions.

Conclusions

DJ, a TCM drug currently approved in China to improve stroke recovery, has been shown to be well tolerated in this pooled analysis of 2 trials. However, due to various methodological inadequacies, there is a need for a large Phase III double-blind randomized, placebo-controlled trial of DJ and other TCM for stroke recovery before such treatments can be recommended for general clinical use.

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Disclosures

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