Danqi Piantang Jiaonang (DJ), a Traditional Chinese Medicine, in post-stroke recovery

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SX led the development of DJ in China and is responsible for the integrity of the clinical data.

All authors contributed towards the writing of the manuscript.

Statistical analysis was performed by EC.

Conflicts of Interest :

CC, NVR, RNG, BPLC have received a grant from the National Medical Research Council of Singapore to conduct a randomized double blinded placebo-controlled clinical trial of DJ in acute stroke.

SX is a member of the Scientific Advisory Board and a shareholder of Moleac which owns the commercial and intellectual property rights of DJ outside China. DP is a shareholder and an employee of Moleac. CL served as an employee of Moleac until July 2006.

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ABSTRACT (248 words)

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Chinese medicine (TCM) widely used in China to improve recovery after stroke, has been compared to another TCM in two unpublished randomized clinical trials. The results of these studies were pooled and re-analysed to assess efficacy and safety.

Methods: 605 subjects were randomized in two randomized double blinded controlled trials to receive either DJ or Buchang Naoxintong 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 TCM standards for diagnosis of apoplexy, and 3) Diagnostic Therapeutic Effects of Apoplexy (DTER) score ≥ 10.

Results: The functional outcome, measured by the Comprehensive Function Score component of the DTER scale showed a statistically significant superiority of DJ over the control treatment group (RR = 2.4, 95% CI= 1.28, 4.51; p=.007). Tolerance was excellent in both groups.

Conclusions: The pooled analysis of 2 unpublished trials of DJ, a TCM currently approved in China to improve neurological recovery after stroke, shows the good tolerability and superiority of DJ over another TCM also approved for stroke. A large double blind randomized clinical trial is required to further assess the safety and efficacy of DJ.

KEY WORDS

Cerebral Infarct

Traditional Chinese Medicine

Randomized Controlled Trials

Stroke recovery

INTRODUCTION

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-analysis[3] 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 since only 3 were randomized, double blind and placebo controlled whilst 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 since pharmacological studies have demonstrated some TCM to have antioxidant, anti-inflammatory, and anti-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 FDA 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 re-analyze clinical data from two 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. 200 subjects were randomized in the first study and 405 in the second. Both studies had similar designs that are described below.

Patients

Stroke in- or out-patients 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 Pharmaceutics Examination Centre of the State Food and Drug Administration and by each individual institution's Ethics Committee.

Inclusion Criteria

Patients were eligible if they (I) were between 18 to 70 years old, (II) were diagnosed with ischemic stroke according to Western Medicine diagnosis standards in China[8] and (III) met the requirements of the TCM standards for diagnosis of apoplexy[9], (IV) had a Diagnostic Therapeutic Effects of Apoplexy (DTER) score ≥ 10 (Table 1) (V) were at the restoration stage according to TCM criteria (i.e. between 15 days and six months after the onset of symptoms), and (VI) 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 ischaemic 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 tumours, atrial fibrillation, other clinically significant systemic diseases or were pregnant and lactating women.

Stratification and randomization

In the two randomized trials, eligible patients were randomized after stratification according to whether their condition was mild, moderate or severe, utilizing the patients' score on the DTER (Table 1). A DTER score of 10-13 was classified as mild, 14-26 as moderate, and 27-34 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 pre-generated 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 centre. 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 paper 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 two 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.

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 two 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 two 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 one month in the comprehensive functions score. The neurological deficit score (obtained by adding the first seven sub-scores of the DTER scoring system) and each of its individual seven components were also analysed. Safety was evaluated by the pooled analysis of serious and non-serious adverse events and of laboratory evaluations, collected in the two randomized trials.

Statistical Methods

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

The neurological deficit score, obtained by adding the first seven sub-scores of the DTER and individual sub-scores - 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 to 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.100 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 Dec 10th 1999 till July 20th, 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 below.

Effects on functional outcomes (figure 1)

Functional outcome was assessed using the Comprehensive Function Score component of the DTER scale. (Table 1) The scores were dichotomized into two categories: 0 versus 2-8. 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 one month than those randomized to the control treatment group (RR = 2.4, 95% CI= 1.28, 4.51; p=.007).

Effects on recovery of neurological deficits (figure 2)

The Neurological deficit score was obtained by adding the first seven sub-scores of the DTER (Table 1). The trend in the pooled analyses was in favor of DJ but the result was not statistically significant (WMD = 0.22, 95%, CI = -0.11, 0.56; p=.18) (Figure 2).

Effect on motor scores

The first seven sub-scores were analyzed individually. Most of these separate motor function pooled analyses showed an advantage in those subjects randomized to the DJ treatment group compared to the control treatment group. Specifically, DJ statistically significantly decreased the scores at one month for the two domains of upper limb (WMD = -0.43, 95%, CI = -0.73, -0.12; p .006) and distal lower limbs (WMD = - 0.32, 95%, CI = -0.59, -0.06; p=0.02) as compared to the active control. A numerical decrease in the score for lower limb, facial and distal upper limb functions were observed but was 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 two cases of nausea and vomiting in subjects receiving DJ. Blood cell count, renal function (blood and urine testing) and 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.

Whilst the use of DJ in post-stroke 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 interepretation of the results. However, BNJ is an approved TCM for stroke, is widely used and 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 randomization. This may had led to a bias due 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 of rapidly growing health system and economic importance[11]. Whilst 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 as it may then open up the 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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Table 1 Diagnostic Therapeutic Effects of Apoplexy scoring system

1 - Visual fields / eye symptoms	**2 - Facial movement / Facial paralysis**	**3 - Upper limb paralysis**
0 = No visual loss 2 = Partial visual loss due to eyes hung upwards 4 = Eyes' deviation	0 = Normal facial movement, no asymmetry 1 = Partial facial paresis 2 = Complete facial 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	**5 - Lower limb paralysis**	**6 - Toe 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	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	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	**8 - Comprehensive functions**	
0 = No aphasia 1 = Mild aphasia with unclear pronunciation 3 = Moderate aphasia with incomplete sentence 4 = Important aphasia with unclear words 6 = Severe aphasia	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	

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 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%)

Caption for Figure 1

Figure 1 Effect on functional outcome at 1 month†

† Favorable functional outcome is defined as a score of 0 (able to take care of oneself and speak freely) versus any higher score according to the Standards for Evaluating the Diagnosis Therapeutic Effects of Apoplexy scoring system-comprehensive function sub-score (as defined in table 1)

Caption for Figure 2

Figure 2 Effect on neurological deficits at 1 month†

† The Neurological deficit score was obtained by adding the first seven sub-scores of the Standards for Evaluating the Diagnosis Therapeutic Effects of Apoplexy scoring system (as defined in table 1).

Figure 1 Effect on functional outcome at 1 month

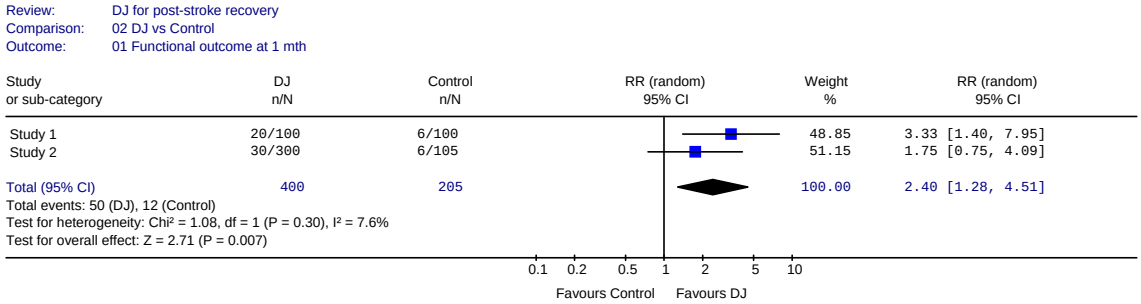

Figure 2 Effect on neurological deficits at 1 month