The Pilot Clinical Study of PG2 Injection on Hemorrhagic Stroke

Background

Astragalus membranaceus (AM) is used to treat stroke for a long time, and a number of studies have shown that AM can reduce cerebral infarction area and has anti-oxidation activity. PG2, a sterile powder of polysaccharides isolated from the root of astragulus (Huang-Chi) for intraveneous injection, has been approved as a botanical drug by TFDA. Hemorrhagic stroke will induce secondary peri-blood clot edema and that may increase intracranial pressure to exacerbate clinical symptom. Therefore, the purpose of the present study was to investigate the efficacy of PG2 on hemorrhagic stroke.

Methods

We, had a double-blind, randomized, placebo-controlled study, enrolled 61 subjects in China Medical University Hospital during March 2011-September 2013。Inclusion criteria was

1. Patients who confirmed diagnosis of first spontaneous hemorrhagic stroke
2. Patients with hemorrhagic stroke in Putamen
3. Patients who admitted to the hospital within 24 hours of onset of hemorrhagic stroke
4. Both Male and Female
5. Age ≥30 and ≤80 years older
6. Patients who signed the informed consent form

And exclusion criteria was

1. Patient with hemorrhage in the area out of Putamen or primary subarachnoid hemorrhage, Arteriovenous malformation (AVM) or brain tumor hemorrhage
2. Patient who performed craniotomy
3. Patient who suffering from cirrhosis, uremia with dialysis, bleeding tendency, severe cardiopulmonary disease or mental disorders would be unable to comply with the study by investigators' decision.
4. Patients have enrolled or have not yet completed other investigational drug trials within 1 month before screening.
5. Female patients are pregnant or breast-feeding

Patients who meet all the criteria above were randomly be divided into the control and treatment groups after the Informed Consent Form (ICF) signed. Table 1 sowed the demographic data of presented study. Each group were treated as follows: 1) control group accepted placebo t.i.w treatment for 14 days from second day of admission, in addition to standard ordinary treatment.; 2) treatment group accepted PG2 t.i.w treatment for 14 days from second day of admission, in addition to standard ordinary treatment. Inflammatory index the TNF-α levels were be measured and clinical symptoms including Glasgow outcome scale (GOS), modified rankin scale (MRS) were be evaluated during this study.

All statistical analyses were based upon intention-to-treat principle. Baseline data were compared between treatment and placebo groups using Student's t test for continuous variables or Chi-square test for

categorical variables. The primary goal of this study was to compare treatment and placebo with respect to scores of functional independence measure, Modified rankin scale, Glasgow outcome scale and Barthel index using Student's t test. The scores of functional independence measure, Modified rankin scale, Glasgow outcome scale and Barthel index at different time points for both treatment and placebo groups were evaluated by generalized linear models with Generalized Estimating Equations (GEE) to consider the within-subject correlation among the repeated measurements. Variables that were imbalanced between groups at baseline were entered into the multivariate generalized linear model with GEE. Safety comparisons were assessed using Chi-square test or Fisher's exact test when it was appropriate. Fisher exact test was used when rare events happened.

RESULT

Safety assessment

All the five SAEs are not relation to the study drug. The first SAE was, the subject had Right ureter ureteroscopic lithotripsy and bladder biopsy, the old disease treatment after the study treatment complete. The second and third SAEs were the subjects hospitalized due to taking rehabilitation. The forth SAEs was the subject died due to heart failure after the study drug treatment complete. And the fifth SAE was left craniotomy with removal of ICH. The 1^{st} , 2^{nd}, and 4^{th} SAEs were placebo group, and the 3^{rd} and 5^{th} SAEs were treatment groups.

Efficacy assessment

The TNF-α levels of treatment group were significantly lower than placebo group in the 7^{th} day 14^{th} days compared to the 1^{st} day of ICH occurred. The *P*-value were 0.004 and 0.04, respectively (Table 2). The correlationship between main outcome, GOS and MRS, and secondary outcome, TNF-α level, were showed on Table 4. The TNF-α level difference between treatment group and placebo group was 20.37 with significantly difference (Table 3). In the 84^{th} days, the GOS in 4-5 of placebo group was 56%, and of the treatment group was 86.4%. In the 84^{th} days, the MRS in 0-2 of placebo group was 56%, and of the treatment group was 81.8% (Table 5, Table 6).

Conclusion

Stroke is the third most common cause of death after heart attack and cancer and has profound negative social and economic effects. The current treatment for complete stroke has limited success in reversing neurodegeneration and restoring premorbid function. Although it is common wisdom that stroke disrupts the BBB, it is not widely realized that the altered BBB in turn affects stroke progression and neuroregeneration. The progression and outcome of stroke is affected by the intricate relationship between the blood-brain barrier (BBB) and tumor necrosis factor α (TNFα). TNFα crosses the intact BBB by a receptor-mediated transport system that is upregulated by CNS trauma and inflammation. Tumor necrosis factor (TNF, cachexin, or cachectin, and formerly known as tumor necrosis factor alpha or TNFα) is an adipokine involved in systemic inflammation and is a member of a group of cytokines that stimulate the acute phase reaction. One of the first indications that TNFα is an important mediator of stroke is the correlation of its expression with stroke damage. TNFα produced by brain parenchymal cells may be beneficial for stroke recovery at certain time points. TNFα were suggested play an important role in tissue regeneration. Both injurious and beneficial roles of TNFα have been proposed for TNFα in the pathogenesis of cerebral ischemia (Meistrell et al., 1997; Pan et al., 1997c; Dziewulska and Mossakowski, 2003). Since TNFα is one of the key players in stroke progression, in the present study, ICH patients who received PG2 injection were significantly reduced the TNFα level.

The modified Rankin Scale (mRS) is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability, and it has become the most widely used clinical outcome measure for stroke clinical trials. The scale runs from 0-6, running from perfect health without symptoms to death. In the data presented here, ICH patients who received PG2 injection were highly improved the ability of daily activities compared with those without received PG2 injection with significantly difference in the 84^{th} day after stroke.

The 'Glasgow Outcome Score' (GOS) is a scale so that patients with brain injuries, such as cerebral traumas can be divided into groups that allow standardised descriptions of the objective degree of recovery. The Glasgow Outcome Score applies to patients with brain damage allowing the objective assessment of their recovery in five categories. This allows a prediction of the long-term course of rehabilitation to return to work and everyday life. Again, here, the data we present showed that ICH patients who received PG2 injection were highly improved the degree of recovery compared with those without received PG2 injection with significantly difference in the 84^{th} day after stroke.

This pilot study have a limitation of poor simple size, however, we would suggest a further more stringent study in PG2 Injection for contributing the beneficent to ICH patients.