Effect of Kuanxiong Aerosol (宽胸气雾剂) on Patients with Angina Pectoris: A Non-inferiority Multi-center Randomized Controlled Trial

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ABSTRACT Objective: To evaluate the effect and safety of Kuanxiong Aerosol (宽胸气雾剂, KA) on patients with angina pectoris. Methods: Block randomization was performed to randomly allocate 750 patients into KA (376 cases) and control groups (374 cases). During an angina attack, the KA group received 3 consecutive sublingual sprays of KA (0.6 mL per spray). The control group received 1 sublingual nitroglycerin tablet (NT, 0.5 mg/tablet). Log-rank tests and Kaplan-Meier estimations were used to estimate the angina remission rates at 6 time-points after treatment (1, 2, 3, 4, 5, and >5 min). Logistic regression analysis was performed to observe the factors influencing the rate of effective angina remission, and the remission rates and incidences of adverse reactions were compared for different Canadian Cardiovascular Society (CCS) classes of angina. Results: The 5-min remission rates in the KA and control groups were not significantly different (94.41±9.64%, P>0.05). The angina CCS class significantly influenced the rate of remission (95% confidence interval = 0.483–0.740, P<0.01). In the CCS subgroup analysis, the 3- and 5-min remission rates for KA and NT were similar in the CCS I and II subgroups (P>0.05), while they were significantly better for KA in the CCS II and III subgroups (P<0.05 or P<0.01). Furthermore, the incidence of adverse reactions was significantly lower in the KA group than in the control group for the CCS II and III subgroups (9.29% vs. 26.22%, 10.13% vs. 20.88%, P<0.05 or P<0.01). Conclusions: KA is not inferior to NT in the remission of angina. Furthermore, in CCS II and III patients, KA is superior to NT, with a lower incidence of adverse reactions. (Registration No. ChiCTR-IPR-15007204)

KEYWORDS Kuanxiong Aerosol, angina pectoris, Canadian Cardiovascular Society classification of angina, randomized controlled trial, Chinese medicine

Nitroglycerin preparations are widely used in clinics, and have consistently been recommended by domestic and international clinical guidelines for the treatment of angina pectoris caused by coronary heart disease (CHD). However, nitroglycerin treatment can lead to drug tolerance, and has relatively strong vasodilative effects. As a result, nitroglycerin can lead to adverse reactions, such as headaches and hypotension. The advantages of...
treating angina using Chinese medicine (CM) are related to its syndrome differentiation and treatment, holistic regulation, focus on qi and blood relationship, and maintenance of the body's balance of yin and yang. However, CM dripping pill preparations that are commonly available on the market, such as Suxiao Jiuxin Pills (速效救心丸, a quick-acting drug with cardioprotective effects), have a relatively slow onset, and are unable to achieve a rapid therapeutic effect. Conversely, CM aerosols have several advantages, including rapid onset, portability, ease of use, and low toxicity. Hence, aerosols have become the preferred option for the treatment of cardiovascular emergencies.

The main treatments for angina in CM are Fangxiang Wentong (FXWT, aromatic herbs used to warm and unblock the meridian) and Xuanbi Tongyang (eliminates stagnation to activate yang). In the 1970s–1980s, 2 famous CM doctors from the China Academy of Chinese Medical Sciences, Prof. GUO Shi-kui and Academician CHEN Ke-ji, were presented with the Ministry of Health First-Grade Achievement Award for their work evaluating the clinical efficacy of Kuanxiong Aerosol (宽胸气雾剂, KA) in the treatment of angina. KA is a prescription based on the traditional principle of FXWT, and has been shown to have similar efficacy in alleviating angina to domestic nitroglycerin tablet (NT). Subsequently, a number of clinical trials have followed, which showed that KA has valuable clinical applications in alleviating acute angina.

Our research group has previously performed a multi-center, randomized, controlled trial (RCT) with domestic NT as control to evaluate the fast-acting effect and safety of KA. The results demonstrated that KA was not inferior to NT in rapidly relieving angina, and improving ischemic electrocardiogram (ECG) changes. Furthermore, KA had better tolerability than NT in clinical application. Nevertheless, the study did not analyze the possible factors that could influence the effect of KA in the treatment of angina. Therefore, the present study employed unconditional logistic regression to further analyze the objective factors that could influence the remission rate of angina. In addition, subgroup analysis was performed to evaluate the therapeutic effect of KA for different Canadian Cardiovascular Society (CCS) classes of angina.

METHODS

Diagnostic Criteria

Western Medicine Diagnostic Criteria

The Western medicine (WM) diagnostic criteria for stable and unstable angina were based on the "Guideline for Diagnosis and Treatment of Patients with Chronic Stable Angina" and "Guideline for Diagnosis and Treatment of Patients with Unstable Angina and Non-ST-segment Elevation Myocardial Infarction" published in 2007.

CM Syndrome Differentiation Criteria

CM syndrome differentiation was referred to the "Guiding Principles for the Clinical Study of New Chinese Medicines".

Inclusion Criteria

Patients were included if they met all the following criteria simultaneously: (1) WM diagnostic criteria and CM syndrome differentiation criteria [Xin (Heart) blood stasis syndrome or qi stagnation and blood stasis syndrome or cold-coagulation and blood-stasis syndrome]; (2) aged 30–75 years old; (3) signed the written informed consents voluntarily; (4) angina attack occurrence was at least 3 times per week before enrollment.

Exclusion Criteria

Patients were excluded if they met any of the following criteria: (1) pregnancy or breast-feeding women; (2) participating in other clinical subjects at the same time; (3) with alcohol allergy, nitrates prohibited and careful use; (4) with cognitive impairment, unable to cooperate; (5) with serious liver damage, kidney function or mental disorder; (6) with severe cardiopulmonary dysfunction and malignant arrhythmia.

Rejection Criteria

Patients were rejected if they (1) did not experience any angina attacks during the week after enrollment; (2) did not take their medication, or did not have test records.

Estimation of Sample Size

A statistical non-inferiority test was used to estimate the required sample size. The number of cases was based on a 1:1 ratio of the test drug to the control. The following formula was used.