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% vs. 90.64%, 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...
treat the 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

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.