Journal of Ethnopharmacology 140 (2012) 555–567

Contents lists available at SciVerse ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jethpharm

Comparison of effectiveness and safety between granules and decoction of Chinese herbal medicine: A systematic review of randomized clinical trials

Hui Luo[a], Qing Li[a], Andrew Flower[b,**], George Lewith[b], Jianping Liu[a,c,*]

[a] Center for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing 100029, China
[b] Center for Research on Complementary and Alternative Medicine, University of Southampton, United Kingdom
[c] The National Research Center in Complementary and Alternative Medicine (NAFKAM), Department of Community Medicine, University of Tromsø, Tromsø N-9296, Norway

ARTICLE INFO

Article history:
Received 17 September 2011
Received in revised form 22 January 2012
Accepted 22 January 2012
Available online 9 February 2012

Keywords:
Chinese herbal medicine
Granules
Decoction
Comparison
Systematic review
Clinical trials

ABSTRACT

Background: The clinical use of Chinese herbal medicine granules is gradually increasing. However, there is still no systematic review comparing the effectiveness and safety of granules with the more traditional method of herbal decoctions.

Method: A literature search was conducted using China National Knowledge Infrastructure Databases (CNKI), Chinese Science and Technology Periodical Database (VIP), China Biomedical Database web (CBM), Wanfang Database, PubMed, and the Cochrane Library until March 10, 2011. Clinical controlled trials (CCTs) including randomized trials (RCTs) comparing the effectiveness and safety between Chinese herbal medicine granules and decoction were included. Two authors conducted the literature searches, and extracted data independently. The assessment of methodological quality of RCTs was based on the risk of bias from the Cochrane Handbook, and the main outcome data of trials were analyzed by using RevMan 5.0 software. Risk ratio (RR) or mean difference (MD) with a 95% confidence interval (CI) were used as effect measure.

Results: 56 clinical trials (n = 9748) including 42 RCTs and 14 CCTs were included, and all trials were conducted in China and published in Chinese literature. 40 types of diseases and 15 syndromes of traditional Chinese medicine (TCM) were reported. Granules were provided by pharmaceutical companies in 13 trials. The included RCTs were of generally low methodological quality: 7 trials reported adequate randomization methods, and 2 of these reported allocation concealment. 10 trials used blinding, of which 5 trials used placebo which were delivered double blind (blinded participants and practitioners). 98.2% (55/56) of studies showed that there was no significant statistical difference between granules and decoctions of Chinese herbal medicine for their effectiveness. No severe adverse effects in either group were reported.

Conclusions: Due to the poor methodological quality of most of the included trials, it is not possible to reach a definitive conclusion whether both Chinese herbal medicine granules and decoctions have the same degree of effectiveness and safety in clinical practice, but this preliminary evidence supports the continued use of granules in clinical practice and research. Standardization of granules and further more rigorous pharmacological, toxicological and clinical studies are needed to demonstrate the equivalence with decoctions.

1. Background

Prolonged boiling or 'decocting' is the earliest and most popular method of preparing herbal medicines in the practice of traditional Chinese medicine (TCM). The composition of herbs within a decoction is flexible and can be revised according to the condition of a patient, defined according to TCM syndrome differentiation and treatment principles. However, decoctions have some disadvantages, such as the difficulties in ensuring quality control of the herbal ingredients, the time and inconvenience they required to prepare, the practical problems relating to their transportation and storage, the difficulty in ensuring

* Corresponding author at: Center for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, 11 Bei San Huan Dong Lu, Chaoyang District, Beijing, China, 100029. Tel.: +86 10 64286757; fax: +86 10 64286760.
** Corresponding author at: Complementary Medicine Research Unit, Dept Primary Medical Care, University of Southampton, Aldermoor Health Centre, Aldermoor Close, Southampton SO16 5ST, United Kingdom.
E-mail addresses: flower.power@which.net (A. Flower), jianping_l@hotmail.com (J. Liu).

0378-8741
doi:10.1016/j.jep.2012.01.031

adequate quality control of the herbal ingredients, and the requirement to consume a large volume of unpleasant tasting medicine. These obstacles can reduce compliance and may interfere with Chinese herbal medicine (CHM) treatment. Historically different kinds of formulation have been developed in response to these shortcomings. These include traditional preparations of *wan* (pills), *san* (powder), *gao* (ointment), *dan* (another type of pill used in TCM) and the modern formulations of granules (*ke li ji*), oral liquids, capsules, tablets, and even injections.

Since granules may retain the advantages of decoctions and also address the problems of quality control, preparation, and administration that occur with decoctions, their use has increased dramatically both within China and other Asian countries and regions. In Taiwan, Japan and South Korea research into granules began in the 1970s, and has led to rapid growth in this sector of the herbal market. In Japan, more than 400 kinds of granules have been developed, 148 Kampo granule herbal drugs were covered by National Health Insurance Fund, and 86% of Japanese medical doctors use granules in their clinical practice (Edwin Lowell and Nobuo, 2004). In South Korean, more than 300 kinds of concentrated granules have been developed and are now covered by health insurance (Zhang et al., 2000). Compared with Taiwan, Japan and South Korean, the mainland of China's research and development in this field has been relatively slower. Although Chinese herbal medicine granules were first included in the 1977 edition of Chinese Pharmacopoeia (zhong guo yao dian) (Yuan, 1999), these 'granules' were developed from patent medicine formulations and did not include single herbal granules that could be used for individualized prescriptions. Until 1987, the Chinese Ministry of Health required the reform of TCM formulations in order to improve their effectiveness and to ensure adequate protection for endangered Chinese medicinal plants. Therefore, after their initial production and a period of evaluation about 4 years, Chinese manufactured granules for individualized prescriptions were first produced in 1992, and the first group of herbal pharmaceutical companies producing granules were officially approved by the Chinese State Administration of TCM in 1993. Currently, Chinese pharmaceutical companies have developed more than 600 kinds of individual herb granules and 200 kinds of herbal formulae, which have been widely used in clinical practice (Jia and Zhang, 2005; Li, 2006; Ltd, 2011). Granules were covered by basic medical insurance in Beijing in April 2009.

With the development and wide use of granules, their effectiveness and safety have become an increasing focus for research. How do the effectiveness and safety of granules' compare with decoctions? Can granules be used as a substitute to traditional decoctions? There is considerable confusion and uncertainty in both herbal medicine producers and consumers in regard to these issues (Zhao, 1996; Yuan, 1999; Cheng, 2000; Xia, 2000; Li and Chen, 2010). Within a complex Chinese herbal formula, a variety of chemical reactions may occur during preparation. Differences in the detail of manufacture (boiling, desiccation and granulation) may affect dissolution rates and change the proportion of available compounds within a formula (Yuan, 1999; Zhang and Jiang, 2005; Yu et al., 2010). There is some chromatographic evidence that contents of constituents and active components in a herbal decoction may exhibit a different high-performance liquid chromatography (HPLC) fingerprint chromatogram to those found in an identical mixture of granules dissolved in boiling water (Chen et al., 2006; Ma et al., 2006). In addition, in China the price of granules is higher than dried Chinese herbs used in decoctions and this has limited the use of granules (Zhang and Jiang, 2005; Li, 2006; Liu, 2008; Li and Chen, 2010). In the West the converse is true and powders are considerably cheaper to use than decocted herbs.

In response to this confusion clinical studies comparing the effectiveness and safety of decoctions and granules have been published over the previous 3 decades, but no systematic review of these studies has been published. The aim of this current review is to examine these data to evaluate the effectiveness and safety of granules in comparison with decoctions, in order to address this confusion.

2. Materials and methods

2.1. Search strategy

A search strategy was designed to search all the available literature. We searched the Chinese National Knowledge Infrastructure Databases (CNKI) (1979–2011), the Chinese Science and Technology Periodical Database (VIP) (1989–2011), the Chinese Biomedical Database web (CBM) (1978–2011), the Wanfang Database (1985–2011), PubMed (1966–2011), and the Cochrane Library (Issue 3, 2011). All the searches ended at 10th March 2011. There was no limitation on language or publication type. The search terms included "decoction" and "granules". Two authors (Luo and Li) conducted the literature search independently. Articles were screened according to the title and then selected after abstracts were read. The full text was downloaded if the study met the inclusion criteria.

2.2. Inclusion criteria

Studies meeting the following three criteria were included in this review: (1) Type of studies: randomized controlled trials (RCTs), clinical controlled trials (CCTs). (2) Type of interventions: the study was designed to compare the effectiveness and safety of granules and decoctions, or if the clinical trial included more than two kinds of interventions, at least of which one was a decoction group and the other one was granule group. (3) The proportions of herbal medicine composition in the decoction and granules were the same.

2.3. Exclusion criteria

The following kinds of studies were excluded: (1) Multiple publications reporting the same data of patients. (2) Lack of basic information on participants or interventions. (3) Inconsistency in intervention between treatment and control group. (4) Interventions for external use.

2.4. Assessment methods

2.4.1. Searching for studies

Searching for studies was carried out by using criteria from the Cochrane Reviewers' Handbook 5.0.2 (Higgins and Green, 2009): (1) Search results from different databases were imported into the document management software Note Express 2.0; (2) Repeated and non-relevant studies were rejected by screening the title and abstract; (3) The full text of studies of potential relevance to the review were downloaded. (4) Repeated studies and publications were removed. (5) In instances of missing information the main researcher of the study was contacted for clarification. (6) Studies for inclusion were identified according to the inclusion criteria. (7) Finally a decision was made whether or not to include the study. Steps 1–5 were carried on by Luo, 6–7 steps were carried on by Luo and Li independently. They also cross checked the results with each other. Disagreements were resolved by discussion or submitting to the third researcher (Liu).