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N-of-1 trials in China☆

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Current situation

Summary

Context: The N-of-1 trial design (randomized and blinded single-patient trials) has been popular abroad for 25 years or more. Many papers using the N-of-1 trials have been published in international medical journals.

However, little is known about this methodology in China. Our purpose is to describe the current status of N-of-1 trials in China, to explain why they have not been more widely used, and to suggest a roadmap for the development of N-of-1 trials, especially for the study of Traditional Chinese Medicine (TCM).

Methods: An electronic search was conducted using the Chinese Biological Medicine Database (CBM) and China National Knowledge Infrastructure (CNKI) with the keywords ''N-of-1 trial, single case OR individual patient AND randomized''. We also searched PubMed. The Chinese Science Citation Database (CSCD) as a citation was searched at last.

Results: 23 studies were retrieved from CBM and 34 from CNKI. There were 13 papers about N-of-1 trials in CBM and 17 in CNKI. Only 3 studies were rigorously designed (i.e., using randomization, control periods and blinding). The other 8 papers were descriptive and review articles, most of which were in TCM. One review was published in SCI-E and one in MEDLINE. Three papers were found in CSCD as citations. Only one of the retrieved studies was funded.

Conclusions: While N-of-1 trials may offer a good tool to individualize clinical care and enrich TCM clinical research, they have not been widely used to date. To spur the development of this method, we would like to suggest three points. First, the Chinese government should endorse and sponsor N-of-1 studies. Second, researchers and physicians should be systematically trained in the method. Third, thorough considerations on trials allow better research and focus on the patients' needs.

Background

For the last few decades, the randomized controlled trial (RCT) has been recognized as the most useful study design to evaluate the effectiveness of treatments, as it provides information on the average effect of a treatment across a population.[1] However, some diseases and treatments are difficult to adapt to the RCT method. For example, information

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about a treatment derived from an RCT may not necessarily be applicable to each individual patient. It is possible that drugs that have significant treatment effects in experiments may not be appropriate for some types of patients (perhaps those who have more vague symptoms or more poorly defined diseases and may fall outside the strict criteria used in RCTs). Similarly, the studied patient population, stage of disease or outcomes that are measured in an RCT may not be relevant to general community settings. In some circumstances, large-scale randomized controlled trials may be available to only a minority of patients with a particular condition.[2] An RCT may be considered just a ''trial'', rather than a ''trial of treatment''.

The N-of-1 trial[3–7] has become accepted as a method of studying therapy in the developed world. Following on from its use in experiments of psychology and psychiatry for nearly 40 years,[8,9] the concept of the N-of-1 trial was introduced to medicine by investigators at McMaster University in Canada in 1986.[4,7] The study design has become popular for evaluating the efficacy of interventions, improving prescribing, investigating new drugs and making the best decisions for individual patients, although these trials are not currently widespread in healthcare and the design is said to be under-exploited.

In N-of-1 trials, a patient acts as his/her own control in a study comparing the efficacy of a treatment with placebo or another treatment. The principle of this trial is to identify the best treatment for an individual patient, formalizing a 'trial of treatment' by using blinding and multiple crossover periods.[10] The trial design is systematic and can solve some problems that cannot be answered by parallel groups in randomized controlled trials. N-of-1 trials can be used for patients with chronic conditions where individual responses to medication are variable, and where treatment decisions are frequently chosen based on informal trials of therapy. The N-of-1 trial has a long tradition in behavioral interventions.[11] Compared to RCTs, N-of-1 trials of a single person may improve the certainty of a treatment decision for that person. A series of such trials may permit more general inferences to be drawn about a treatment in the population[12]; because more precise information is collected about each individual in the series, an estimate of the population treatment effect may often require a smaller sample size than would be needed for a traditional RCT.

Traditional Chinese Medicine (TCM) is characterized by individualized diagnosis and treatment under the guidance of its holistic concept; the same disease in different individuals may have different treatments under TCM. RCTs cannot easily give consideration to individual treatment plans for patients that have the same disease.

The concept of the N-of-1 trial is that a clinician and patient can take part in the treatments and determine which of the treatments is more likely to work best for him/her over the long term. In the trial process, the opinion of the patient is of vital importance, which follows the principle of being patient-centered. N-of-1 trials can broadly focus on improving the quality of communication between providers and patients as a way of improving the overall standard of care.

An N-of-1 trial and the inherent principles of TCM both focus on individualized treatment, and the individualized choice of relevant outcome measures.

The N-of-1 trial in research has many advantages and has been used in developed countries such as the US,[13] Australia,[14] and Canada,[6] and is used in the setting of many diseases such as pulmonary and cardiovascular diseases. Many of these trials have recently used commercial post-trial questionnaires indicating universal acceptability. However, little has been documented about how patients experience N-of-1 trials in China, although the trials have been performed in medicine for over a decade in clinical research.

In this article, we report the current development of the N-of-1 trial in China, commenting upon the reasons N-of-1 trials have not been vigorously developed in China, and we conclude with an argument that researchers in TCM should use this trial method more widely to facilitate modern TCM clinical care and to produce evidence that accounts for the heterogeneity of TCM effects.[15]

Methods

An electronic search was conducted of the main Chinese medical databases—CBM (Chinese Biological Medicine Database) (1978-2011.12) and CNKI (China National Knowledge Infrastructure) (1994-2011.12) with the keywords ''N-of-1 trial, single case'' OR ''individual patient'', AND ''randomized''. We also searched for relevant citations in the databases of Hang Kong, Tai Wan and Macao from the PubMed.

Results

23 and 34 studies were retrieved from the CBM and CNKI databases respectively, of which there were 13 papers that referred to the N-of-1 trial or that mentioned a trial with a single subject design in CBM and 17 in CNKI. After removing duplicates, 6 studies used a single case experiment design (regardless of methods); only 3 studies were strictly designed using randomization, controls and blinding. The other 8 papers were descriptive papers or reviews (Fig. 1).

The 6 trials from our search cannot properly be considered N-of-1 trials. The authors reported these trials as ''single case experiments'', but these trials did not include patients acting as their own control where the study compared the efficacy of a treatment with either a placebo or another treatment. They were really case reports. The 6 trials had a range of settings such as rehabilitation medicine and functional recovery, behavioral language treatment, stroke, brain injury, hepatic myelopathy and aphasia; these trials included 20 patients.

We did identify 3 studies with robust designs[16–18] and 8[19–26] reviews about N-of-1 trials. In the 3 studies with robust designs, each studied TCM[16–18] with or without acupuncture,[16] for the chronic diseases—myelosuppression,[17] spinal injury[16] and hypertension.[18] Among the reviews and background papers, 6 reviews[21–26] were applicable to methods used to carry out N-of-1 trials in TCM, of which one specifically focused on tumors.[23] All authors of the 8 reviews gave details about the conception, the benefits compared to RCTs, the applicable conditions to be considered when selecting a disease for study, and the practical trial procedures. Fig. 1 shows the process of selection of studies.