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Research paper

Incorporating traditional Chinese medicine syndrome differentiation in randomized trials: Methodological issues

Vincent C.H. Chung, PhD[a,b,c,*], Robin S.T. Ho, MPH[a], Xinyin Wu, PhD[a,b,c], Justin C.Y. Wu, MD[b,d]

[a] Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong
[b] Hong Kong Institute of Integrative Medicine, The Chinese University of Hong Kong, Hong Kong
[c] Hong Kong Branch of the Chinese Cochrane Center, The Chinese University of Hong Kong, Hong Kong
[d] Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong

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ABSTRACT

Introduction: In traditional Chinese medicine (TCM), decision on prescription is based on a process called *Bian Zheng Lun Zhi* (syndrome differentiation guided treatment decision). Syndrome differentiation process may not be recognized in conventional standards of randomized controlled trial (RCT), limiting model validity and generalizability of results.
Method: Three major international databases were searched up to July 2016 for articles which discussed how syndrome differentiation, a classical TCM approach in diagnosis, can be incorporated into RCT design.
Results: Four methodological solutions were proposed: (i) Lessons learnt from the design of patient reported outcome questionnaire can inform how a TCM diagnosis instrument can be developed. A proper TCM diagnostic tool with sound psychometric properties can reduce variation in the syndrome differentiation process. (ii) Treatment strategies for a specific TCM diagnosis could be highly diversified. Delphi technique can inform the design of an optimal treatment program by facilitating consensus among experts. (iii) Subgroup analysis is often needed in RCTs recruiting patients with several TCM diagnoses. It is highlighted that investigators should consider whether the design, analysis and context of the trial are robust enough to support a reliable claim of the subgroup effect associated with a particular TCM diagnosis. (iv) Finally, we discuss alternative research and analysis approaches for handling misalignment of Western and TCM diagnoses, including the possibility of unifying TCM syndrome with Western phenotypes using latent class analysis.
Conclusion: Further methodological advances are needed for better alignment of classical TCM theories and diagnostic instrument development, as well as in reducing bias during expert consensus processes.

1. Background

Traditional Chinese medicine (TCM) constitutes a significant part of the Chinese health system [1], and it is widely used among Chinese migrants overseas [2]. Major modalities of TCM practice encompass Chinese herbal medicines (CHM), acupuncture and therapeutic massage (*Tuina*). The practice of TCM is statutorily regulated in China, Taiwan, Singapore, Australia and Canada. Under the context of popular use and formal regulation, evaluation of TCM's efficacy and effectiveness has been high on the policy agenda [3]. With the emergence of evidence based medicine movement, the randomized controlled trial (RCT) has become one of the most preferred methods for investigating treatment effect of TCM [4].

Many RCTs were designed to investigate the effect of a fixed TCM treatment on a specific disease diagnosed with a well-defined organic basis. For instance, a recent Cochrane review on the effect of Chinese herbal medicine for osteoporosis has included 99 different fixed herbal formulae [5]. While this approach provides a

Abbreviations: TCM, Traditional Chinese medicine; CHM, Chinese herbal medicines; RCT, Randomized controlled trial; PRO, Patient reported outcome; EFA, Exploratory factor analysis; BCQ, Body Constitution Questionnaire; WHO, World Health Organization; ICTM, International Classification of Traditional Medicine; DHS, Deficiency of both the Heart and Spleen; HYD, Hyperactivity of the fire due to Yin Deficiency; LSF, Liver-qi stagnation transforming into Fire; CMYMOP, Chinese version of the Measure Yourself Medical Outcome Profile; IBS, Irritable bowel syndrome; LCA, Latent class analysis.

* Corresponding author at: 4/F, School of Public Health Building, Prince of Wales Hospital, Shatin, Hong Kong.
E-mail address: vchung@cuhk.edu.hk (V.C.H. Chung).

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straightforward strategy for clarifying TCM treatment effects from an orthodox manner, it does not reflect how TCM is practiced in real life clinical settings [6]. This commentary aims to discuss how trial design can take into account the classical diagnostic features of TCM practice, with a hope that future trial design would reflect the strengths and weaknesses of TCM treatment from a "real world" perspective.

2. Methods

To synthesize current methodological approaches for including classical TCM diagnosis in RCTs, we conducted a literature review by searching MEDLINE, EMBASE and AMED from their inception till July 2016 using the search terms (*Medicine, Chinese Traditional/ OR *Drugs, Chinese Herbal/) AND (syndrome differentiat*.mp. OR syndrome pattern*.mp. OR TCM adj2 pattern*.mp. OR TCM adj2 syndrome*.mp. OR CM adj2 pattern*.mp. OR CM adj2 syndrome*. mp. OR Chinese medicine adj2 pattern*.mp. OR Chinese medicine adj2 syndrome*.mp. OR traditional Chinese medicine adj2 pattern*.mp. OR traditional Chinese medicine adj2 syndrome*. mp.). The generated citations and were screened by two reviewers for eligibility (XYW and RH). Both narrative and empirical articles illustrating the inclusion of TCM diagnosis were included, and disagreement on the eligibility were resolved by a third author (VC). No language restrictions were applied in literature selection. Also, relevant methodological papers were added to enrich the discussion with state-of-the-art epidemiological insights.

3. Main text

3.1. Concept of syndrome differentiation in traditional Chinese medicine

In TCM practice, clinical decision making is based on a process called *Bian Zheng Lun Zhi* (syndrome differentiation followed by treatment procedures). Syndrome differentiation is a classical diagnostic procedure guided by TCM theories. It entails the collection of diagnostic information by observation, listening, questioning, and pulse analysis. This information is then analyzed according to TCM theory (i.e. the syndrome differentiation process), followed by choices of treatment strategies based on the syndrome [6]. For example, when the syndrome differentiation process suggests that a patient is *Qi* deficient, treatment should be directed towards the nourishment of *Qi* using herbal formulae, acupuncture or *Tuina*.

The syndrome differentiation process may not be recognized in conventional RCT settings [7]. For instance, in trials included in the Cochrane review mentioned above, a fixed formula is given to osteoporotic patients randomized to treatment group regardless of their TCM diagnosis [5]. This approach is considered to have limited model validity as it does not reflect routine TCM practice [8], and from a classical point of view the lack of syndrome differentiation may lead to inappropriate patient selection and underestimation of treatment effect [7].

3.2. Improving model validity of TCM trials by incorporating syndrome differentiation: challenges and opportunities

The incorporation of syndrome differentiation process in TCM RCT has been proposed as a potential solution for improving model validity [9]. One of the possible approaches is to individualise TCM therapies for each patient randomized to treatment group. For example, in a three-arm RCT investigating the effect of Chinese herbal medicine for irritable bowel syndrome (IBS), patients were randomized into: (i) individualised treatment group in which patients received tailored herbal formulae according to their syndrome differentiation result; (ii) standardized herbal treatment group which patient received a fixed formulae; and (iii) placebo. Results showed that only patients randomized to the individualised treatment group benefited from sustained improvement [10]. A further example can be found in Appendix A. This approach allows high model validity, but whether the results are replicable in other settings remains doubtful, due to variation in syndrome differentiation – treatment decision process among TCM practitioners. In an evaluation of inter-observer agreement between TCM practitioners on the management of IBS, significant variations in syndrome differentiation and subsequent treatment decision were observed [11]. This implies that RCT results from such individualised approach may carry limited external validity [12]. To address this shortcoming, TCM trial designers can specify how the whole syndrome differentiation – treatment decision process will be implemented in the trial protocol.

The template for intervention description and replication (TIDieR) provides a comprehensive guide and checklist for designing such a protocol, in which detailed description on the following are recommended: *Why, What, Who provided, How, Where, When and How much, Tailoring, Modification and How well* [13]. The "Tailoring" item is particularly relevant as it highlights what should be pre-specified to allow replication of syndrome differentiation – treatment decision process. Essentially, an algorithm for categorizing patient into a particular TCM diagnosis, and their corresponding treatment regime should be provided. Diagnostic variation between practitioners is a major barrier in devising a replicable algorithm [14] and strategies for tackling this problem are needed. In a systematic review on strategies for reducing inter-rater variability among healthcare professionals, the use of diagnostic instrument is considered to be one of the best approaches [15]. This leads us to a discussion on how a diagnostic tool for assisting TCM syndrome differentiation should be developed [16].

3.3. Linking TCM and conventional western diagnoses by measurement scales: lessons learnt from the development of patient reported outcome instruments

TCM diagnosis derived from the process of syndrome differentiation can be linked with conventional Western diagnosis. TCM questionnaires measuring practitioner observation, listening, questioning, and pulse analysis can be developed and validated among a representative sample of patients who fulfill the criteria of Western diagnosis. The initial process would resemble the development of patient reported outcome (PRO) instrument, in which key concepts relating to a particular TCM diagnosis can be summarized comprehensively via literature review, focus groups and interviews with patients and TCM practitioners. Building on these qualitative data, researchers can devise questionnaire items using Delphi technique and pilot it among patients using cognitive interview techniques. These steps will ensure the face and content validity of the TCM diagnostic instrument [17,18].

Next, the instrument can be administered to a representative sample of patients. Using the resultant dataset, construct validity of the instrument can be evaluated by factor analysis. Exploratory factor analysis (EFA) allows the identification of items that define the TCM diagnostic construct, and confirmatory factor analysis can test whether the items developed in EFA fits with the actual data. In addition, by examining the convergence between instrument-derived results with a diagnosis agreed by a TCM expert panel, criterion validity of the instrument can be assessed. Finally, test-retest reliability and internal consistency of the instrument should be evaluated [19].

For example, a Body Constitution Questionnaire (BCQ) was developed to measure Yin deficiency in a two step process. The

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