Establishing Evidence for Chinese Medicine: a Case Example of Irritable Bowel Syndrome

Alan Bensoussan

Chinese Medicine Unit, College of Social and Health Sciences, University of Western Sydney, Australia

Key Words
Chinese herbal drugs; evidence-based medicine; individualization of treatment; irritable bowel syndrome

Traditional Chinese medicine (TCM) is now used by a broad cross-section of the western community. It offers some attraction because it provides new options for treatment, an individualized approach, and potentially avoids use of harsh drugs or surgery. However, despite this growing popularity there is debate as to its evidence base. Few TCM trials have been performed in the West, and previous Chinese TCM trials have been perceived to lack methodological rigour. Establishing and applying stronger clinical trial methodologies in TCM is imperative for its integration with modern medicine and achieving the end goal of creating options for patient care. A clinical trial was designed using a variety of approaches to promote methodological rigour whilst allowing the flexibility required in TCM practice. Irritable bowel syndrome (IBS) was selected as the disease focus, creating the possibility of tailoring TCM treatments to the variable clinical presentations of IBS. Patients were randomised to receive individually tailored treatment (n=38), a standard Chinese herbal formulation (n=43), or placebo (n=35) for 16 weeks. Patients, gastroenterologists, and herbalists were all blinded as to treatment group. Both standard and individually tailored treatments were significantly more effective than the placebo treatment on all key outcome measures. However, this study failed to confirm the added value of tailoring treatments. Chinese herbal formulations individually tailored to the patient proved no more effective than the standard treatment on all measures. Nevertheless, the trial demonstrates it is possible to test individualisation of treatment whilst adhering to conventional trial protocols. Clinical trials can be designed that accommodate nuances of TCM practice. This study also shows Chinese herbal medicine may offer assistance to some patients with IBS and may prove as effective as current pharmaceutical approaches. Further validation of TCM interventions is required. [Chin Med J (Taipei) 2001;64:487-492]

Received: March 28, 2001; Accepted: August 6, 2001.
Correspondence to: Dr. Alan Bensoussan, Head, Chinese Medicine Unit, College of Social and Health Sciences, University of Western Sydney, Locked Bag 1797, Penrith South DC, NSW 1797 Australia. Fax: +61-2-9773-0998; E-mail: a.bensoussan@uws.edu.au
The recent push to apply the principles of evidence-based medicine to TCM is important. Evidence-based medicine (EBM) demands that doctors make decisions about treatments based on good quality evidence, and not simply their personal experience, or the “ex pert” opinion of their colleagues. For clinicians to feel comfortable in recommending a particular TCM approach an acceptable standard of evidence must be demonstrable. What then in TCM is “best evidence” and how is it applied? Best evidence usually means making sure, when possible, that treatments have been rigorously tested in independent, sound, long-term studies. The question that is often asked is whether “long history of use” in TCM can in any circumstances represent good quality evidence.

The rules of EBM privilege certain kinds of evidence as having more weight. Table 1 summarizes the principal levels of evidence as they apply to the clinical evaluation of interventions.

The number of clinical trials of CHM reported in the English literature is small. English language evidence on treatment outcomes with CHM is principally at Level 2 or below. There is good preliminary evidence that demonstrates CHM may offer help in chronic hepatitis C, atopic eczema and now, irritable bowel syndrome. There is also weaker, but important, evidence in a number of other clinical areas, including pain management, anxiety, insomnia, cancer, vestibular disturbance, diabetes, respiratory infections, alopecia, dyspepsia and apoplexy. Although there are some strong studies, overall, the clinical trial evidence reported in English language medical journals is patchy and generally weak.

In contrast, a vast number of clinical studies are reported in the Chinese medical literature. Three snapshot reviews have been undertaken of some of the clinical trials published in key Chinese journals. Each review has concluded the same: in most cases Chinese studies failed to demonstrate methodological rigor or to report sufficient methodological detail in order to adequately evaluate the trials. The perceived weaknesses include:

Publication bias
The majority of reviewed trials demonstrated the superior effectiveness of CHM in comparison with placebo or western medicine. One Medline search of clinical trials from 1966 to 1995 revealed that no trial published in China found a test treatment to be ineffective. Publication bias might be an explanation.

Poor randomization
The method is often inadequately described. Claims for randomization are often in conflict with group sizes: 239/80, 83/18, 100/100/100 and 841/841 have been reported. Lack of attention to blinding
Placebo is too infrequently used; comparison with western medicine or another TCM does not eliminate the placebo effect of CHM. Practitioners are seldom blinded.

Outcomes measures were poorly defined
This applies particularly to subjective measures, a problem exacerbated by the lack of blinded observers.

Weak statistical analyses
Compliance and follow-up are infrequently reported. Intention-to-treat analysis is rarely performed. Hence, so far as concerns the volume of clinical trials reported in the Chinese medical journals, these trials in general have been per ceived as not meeting high methodological standards to be broadly acceptable to the western medical community. The ab-

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Nature of investigation of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SR (with homogeneity) of RCTs or individual RCT (with narrow confidence interval)</td>
</tr>
<tr>
<td>2</td>
<td>SR (with homogeneity) of cohort studies or individual cohort study (including low quality RCT; eg., &lt;80% follow-up) or outcomes research</td>
</tr>
<tr>
<td>3</td>
<td>SR (with homogeneity) of case-control studies or individual case-control study</td>
</tr>
<tr>
<td>4</td>
<td>Case series (and poor quality cohort and case-control studies)</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research of ‘first principles’.</td>
</tr>
</tbody>
</table>

SR = systematic review, RCT = randomised controlled trial. (Adapted from Centre of Evidence-Based Medicine, Oxford University web page: http://cebm.jr2.ox.ac.uk/).
sence of appropriate controls in Chinese clinical trials is surprising given the first mention of a controlled study occurred in 1061 AD, in the Bencao Tujing (Atlas of Materia Medica). This Song dynasty text states:

In order to evaluate the efficacy of ginseng, find two people and let one eat ginseng and run, and the other run without eating ginseng. The one that did not eat ginseng will develop shortness of breath sooner.

TCM is an integral part of the largest public healthcare system in the world and TCM is increasingly adopted by westerners. Clearly, a large portion of health and human resources are invested in TCM. This makes it all the more important to ensure that this investment represents value for money. Practitioners commit a substantial proportion of their training to the study of TCM theory. Is every thing that is taught in TCM the only thing that practitioners and patients judge to be valid evidence of health gain were strong. What risk-benefit analyses have been undertaken of TCM practice? Clearly, quality clinical investigations are desperately needed to justify in vast medical education and the risks carried by patients.

If high level evidence in TCM is scant why are western consumers going down this path? One answer may lie in the relative differences in perception of quality evidence by consumers and scientists. Consumers may be prepared to try a well-documented herbal for malaria in the first instance, (in Chinese medicine this frequently consists of centuries of documentation of heritages) in preference to a recently marketed medicine. The one that did not eat ginseng will develop shortness of breath sooner.

The nature of TCM itself may be a contributing factor to the scarcity of rigorous clinical trials. In TCM, patients with the same medical diagnosis may each receive very different herbal treatments depending on individual clinical manifestations. This poses additional constraints on the methodological design of clinical research. Re-examination of TCM has two particular requirements that reflect the philosophy of its bases of its practice and that differ from conventional drug trials:

1. Because TCM uses criteria and terminology for diagnosis that differ from Western medicine, TCM and Western medicine are likely to be directed towards different conclusions and treatments for each patient in the trial. Hence, a distinct and parallel diagnostic process is required.
2. Re-examination of signs may be needed to suit treatments that are, by definition, individualized events. Treatment should not only be tailored to the individual but also open to modification at differing stages of the patient’s illness.

There has been difficulty in adequately evaluating the practice of TCM because of the claimed compatibility between TCM practice (which requires individualization of treatment) and clinical trial methodology (which mandates a degree of standardization). Individualization or tailoring of treatment certainly increases the complexity of clinical trial values. Yet it is important that tailoring is performed in or der not to compromise the trial practice principles. If TCM theories hold any validity then pre sumably patients treated under differing circumstances of these theories will gain benefit beyond the placebo effect, and furthermore, gain some additional value beyond a standard (herbal) treatment.

The remaining derivation of this paper describes a clinical trial of CHM that allowed tailoring of treatment in order to evaluate traditional Chinese medicine theory, yet in a way that re mained rigorous in its clinical observation.5
A trial design— the treatment of irritable bowel syndrome

A clinical trial was designed using a variety of approaches to promote methods of altering TCM practice. Irritable bowel syndrome (IBS) was selected as the disease focus, creating the possibility of tailoring TCM treatments to the variable clinical presentations of IBS. Because IBS has a diverse range of presentations: from diarrhea predominant to constipation predominant. IBS is well suited to testing the funneling effect of tailoring a treatment to improve outcomes.

Gastrointestinal dysfunction is one of the main conditions for which individualized treatment is most effective. In terms of clinical presentation, including drugs, dietary modifications, and counseling.

One hundred sixteen patients were diagnosed with IBS and randomly allocated to three treatment groups: placebo, standard herbal or individualized herbal treatment. Patients were treated for 16 weeks. During the 16-week treatment period, patients were reviewed two-weekly and then monthly by a traditional Chinese herbalist and on two occasions by a gastroenterologist. A two-week run-in period began at randomization to the trial and commencement of treatment was used to reduce the effect of any improvement simply due to a sense of place on the trial. Patients were also followed up 14 weeks after cessation of treatment. Patients, gastroenterologists and herbalists remained blinded throughout the study.

Response to treatment was judged according to a bowel symptom score completed by the patient and by the gastroenterologist, and by other questionnaire items assessing the sense of global improvement, and interference with life activities.

The bowel symptom scale consisted of 100 mm visual analogue scales measuring pain/discomfort, bloating, constipation, and diarrhea.

At the end of the treatment period, active treatment (standard and individualized) was significantly more effective than the placebo treatment. About 70% of patients receiving active treatment stated they had improved during the trial, in contrast to 30% of patients receiving placebo. The degree of improvement in the mean bowel symptom scores was, on average, twice to three times that of patients on placebo (Table 2 and Fig. 1).

Chinese herbal formulations individually tailored to the patient proved no more effective than the standard treatment. Overall, in individualized treatment patients did not perform as well as those on the standard formulation. The standard herbal formulation appeared to be as effective for a wide range of presentations of IBS. However, on follow-up 14 weeks after completion of treatment, the individualized treatment group appeared to better maintain improvement (Fig. 2). Tailoring Chinese herbal treatment may offer better long-term outcomes, but this requires further study.
Treatment outcomes were variable of course. Some patients on active treatment responded very well, some made little or no improvement. Some subjects obtained a response within two weeks, others not until about eight or even ten weeks. (Of course, a number of patients receiving placebo also improved substantially.) Trial IBS patients were generally at the difficult end of the spectrum because their symptoms were severe enough to warrant referral to a specialist, invasive examinations (colonoscopy, endoscopy, and blood tests) and the effort to participate in a long trial. The average duration of the IBS had been of the order of at least five to ten years. These patients were not being especially helped by anything, including dietary changes and medication.

The NNT (number needed to treat) for IBS improvement after 16 weeks of treatment is 2.3 (95% CI 1.6-4.6) for standard treatment and 3.2 (1.8 to 14) for individualized treatment. In recent alosetron (a 5-HT antagonist) studies, the efficacy of alosetron compared with placebo was small, with the percentage of patients responding to the drug being between 7% and 10% greater than those responding to placebo. A benefit of 10% over placebo in diarrhea was the need to treat 10 patients with the drug to achieve one drug-related improvement. Our trial has demonstrated an improved rate for the CHM intervention.

Blinding

Patient scores on a treatment credibility scale showed that patients remained blinded throughout the trial. Testing the success of blinding was important in this trial because of the added risk of unblinding patients who were receiving tailor-made treatments. To this end all patients had to wait 30 minutes after consultation with the herbalist irrespective of treatment group. This allowed for preparation of the individualized formulas even though the placebo and standard were prepared. If patients couldn’t wait the formula was posted or couriered to them. Further more, our subjects were not a self-selected group with a bias in favor of complementary medicine. Compliance was high. There were no changes in fiber intake or diet generally.

Discussion

Substantial effort was invested in the methodolog-
i cal de sign of the study. The proto col in cluded the fol lowing char ac ter is tics:

1. The herbal med icines used both for stan dard treat ment and for indi vid ual ized treat ment came from a com mon Chi nese herbal pharma copeia.
2. The place bo was ver i fied as indistin guish able in taste and ap pear ance from the Chi nese med i cine.
3. The wait ing time for med i cines was stan dard.
4. The di ag no sis for IBS was stan dard.
5. Stan dard scales were used for IBS symp toms and se ver ity.
6. Pa tients and gastroenterologists scored on the scales in de pend en tly.
7. Pa tients, gastroenterologists and herb al ists were all blinded as to treat ment group.
8. Blinding was ver i fied.
9. Eval u a tors (gastroenterologists) were blinded as to treat ment group.

In terms of our need to de velop a good ev i dence base for TCM, this study shows it is pos si ble to do a rig or ous blinded study that al lows tai lor ing of treat ment with out com pro mis ing tra di tional prac tice. CHM ap pears to of fer ben e fit to some pa tients with IBS. This trial sup ports its con tin ued use in man ag ing IBS and ex plo ra tion of its po ten tial use in other func ti onal dis or ders.

The stan dard Chinese herbal for mu la tion was com plex (20 herbs). It is viewed as a num ber of ac tives work ing to gether, as op posed to one pre cise ac tive con stit u ent. It is not a sed a tive for mula in tra di tional terms, but rather one that is deemed to reg u late and strengthen bowel func tion. It could be pos tu lated that there is a di rect phar ma col og i cal ac tion per haps af fect ing vis ceral hy per sen si tiv ity: one of the cen tral me ch a nisms that ap pears to be dysregu lated in ir ri ta ble bowel syn drome. Whilst it is likely there is a syn ergy be tween cer tain herbs, it is also pos si ble that not all the herbs are ef fi ca cious. The herbs were ad min is - tered as en cap su lated, powder ised raw herbs. This meant there was sub stan tial bulk that had to be de liv - ered (5 cap su les three times per day). An ex tract form is un der de velop ment.

Some gastroenterologists were sur prised by the find ings, oth ers not. Many would pre fer to wait and see till the ac tive has been found, iso lated, con cen - trated and stan dard ized be fore us ing it, al though this may be some time com ing. More im por tantly, treat ment with a sin gle chem i cal is sus pi cious to many. blur ning of the ob vi ous.

Accu mul ating un equiv ocal ev i dence is not easy. This study has shown it is fea si ble to con struct rea son able clin i cal ev i dence with out com pro mis ing the tra di tional prac tice ap proaches in TCM. The trial meth od ology was suc cess ful in its ap pli ca tion and is con sid ered ap pro pri ate for future eva lu a tion of CHM where in di vid u al iza tion of treat ment is con sid ered a core com po nent of prac tice.

The prob lems with clin i cal trial meth odo logy must be ad dressed as an im por tant part of fu ture evalu a tion strat egy of TCM in China, and must in clude re search ers and those re spon si ble for pub li ca tion.

References