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Combining rigour with relevance: A novel methodology for testing Chinese herbal medicine

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ABSTRACT

Background: There is a need to develop an evidence base for Chinese herbal medicine (CHM) that is both rigorous and reflective of good practice. This paper proposes a novel methodology to test individualised herbal decoctions using a randomised, double blinded, placebo controlled clinical trial.

Method: A feasibility study was conducted to explore the role of CHM in the treatment of endometriosis. Herbal formulae were pre-cooked and dispensed as individual doses in sealed plastic sachets. This permitted the development and testing of a plausible placebo decoction. Participants were randomised at a distant pharmacy to receive either an individualised herbal prescription or a placebo.

Results: The trial met the predetermined criteria for good practice. Neither the participants nor the practitioner-researcher could reliably identify group allocation. Of the 28 women who completed the trial, in the placebo group ($n = 15$) 3 women (20%) correctly guessed they were on placebo, 8 (53%) thought they were on herbs and 4 (27%) did not know which group they had been allocated to. In the active group ($n = 13$) 2 (15%) thought they were on placebo, 8 (62%) thought they were on herbs and 3 (23%) did not know. Randomisation, double blinding and allocation concealment were successful and the study model appeared to be feasible and effective.

Conclusion: It is now possible to subject CHM to rigorous scientific scrutiny without compromising model validity. Improvement in the design of the placebo using food colourings and flavourings instead of dried food will help guarantee the therapeutic inertia of the placebo decoction.

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1. Introduction

1.1. Current status of Chinese herbal medicine

Chinese herbal medicine (CHM) has been practised in East Asian countries for over 2000 years. CHM is taught as an undergraduate course at 47 Chinese universities and is investigated at 139 Traditional Chinese Medicine (TCM) research institutes. In 2008 there were 218,044 registered TCM doctors practising in the 3063 hospitals in China. The gross value of CHM products in China in 2008 was estimated to be 216.65 billions RMB (\$31 billion dollars) accounting for over a quarter of the total expenditure on all medicines (MOH, 2010; SATCM, 2010). Globally the herbal medicine market is growing at an average of 13% per annum and was estimated to have reached \$40 billion in 2006 (Kaphle et al., 2006).

Currently there are no precise figures on the number of CHM practitioners operating in the UK or the extent of the CHM market.

The two main CHM registers in the UK contain over 1100 members but this does not include unregistered practitioners working in high street retail outlets. According to a recent survey of 2032 UK adults (MORI, 2008), conducted for the Medicines and Healthcare products Regulatory Agency (MHRA) 5% of the adult population (approximately 2.5 million) has already used CHM.

These figures point to the substantial role of CHM within China and the developing role of CHM in contemporary health care globally and in the UK. The need for rigorous research methodology to evaluate safety and effectiveness is therefore self-evident. This paper focuses on the methodological development of fastidious randomised controlled trials.

1.2. Chinese herbal medicine (CHM)

CHM typically involves the use of herbal formulae of between 10 and 20 separate herbal ingredients selected from a *Materia Medica* of several thousand herbs that are prepared either as a boiled decoction, as dried herbal extracts, or taken as pills. Diagnostic and therapeutic treatment principles are framed according to the traditional Chinese understanding of pathological processes. Best practice of CHM is usually considered to require the use of individualized herbal decoctions that are adapted to address the

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particular needs and the changing clinical presentations of each patient (Bensky and Gamble, 1986). This makes CHM a dynamic and highly responsive system of medicine that resonates strongly with the increasing emphasis within bio-medicine for the use of both combination therapies to achieve optimum benefits and individualised treatments to take into account genetically variable responses to modern drugs.

CHM is also a complex intervention that frequently incorporates dietary and lifestyle advice and may be used in conjunction with acupuncture, massage and meditation techniques. It uses herbal products, some of which contain highly active compounds. The development of drugs from Chinese herbs such as ephedrine from Ma Huang (*Radix Ephedra sinensis*), artemisinin from Qing Hao (*Herba Artemisiae annuae*) and tamiflu from star anise (*Fructus Illicium verum*) are just a few examples of how some of these active compounds have been refined into conventional medicines. Recent research has demonstrated the effectiveness of an individual herb Lei Gong Teng (*Radix Tripterygii wilfordii*) in the treatment of rheumatoid arthritis (Goldbach-Mansky et al., 2009) and herbal combinations in the treatment of irritable bowel syndrome (Bensoussan et al., 1998), atopic eczema (Sheehan and Atherton, 1992) and as an adjunctive treatment in leukaemia (Wang et al., 2008). In addition it has been estimated that there are over 17,000 clinical trials on CHM in East Asian medical journals (Tang et al., 1999; Wang et al., 2007) although the reliability of many of these studies is questionable owing to a lack of methodological rigour and apparent publication bias (Tang et al., 1999).

CHM has also been responsible for a number of adverse reactions. Adulteration with steroids in skin creams (Keane et al., 1999), the tragic use of nephrotoxic Aristolochia species (Nortier et al., 2000), and rare instances of idiosyncratic liver toxicity (Perharic et al., 1995) make quality control and statutory professional regulation important public health issues and have left many conventional physicians understandably suspicious of the safety of CHM.

There is then a clear need to investigate both the effectiveness and the potential adverse effects of CHM so that it can be assessed in a rational and consistent manner, free from the positive bias of its exponents and the prejudice of those who believe it is dangerous quackery (Colquhoun, 2009).

Our main methodological question is how to preserve the integrity of this complex intervention whilst subjecting it to a rigorous scientific investigation?

1.3. Whole systems research

CHM requires a pragmatic 'whole system' (Verhoef et al., 2004) research methodology that takes into account both the individualized nature of the treatment and recognizes the therapeutic importance of the non specific components of an intervention such as the patient-practitioner relationship, the unique philosophical and linguistic basis that underpin different forms of therapy and the lifestyle recommendations frequently made during a consultation. These factors may be integral to the therapeutic benefits obtained and should not be seen as unwanted 'confounders' to be 'controlled' away by fastidious research design.

This 'whole systems' approach requires the construction of a broad portfolio of evidence that uses a variety of quantitative and qualitative methodologies. One component of this portfolio will be randomized controlled trials (RCT's). The limitations of RCT's are being increasingly recognized (Rawlins, 2008; MacPherson et al., 2009). Nevertheless they still have a vital role in establishing the 'efficacy' of a particular intervention. The challenge has been to develop a methodology that ensures internal and external validity but also achieves 'model validity' (Lewith et al., 2002).

Up until now the use of strong tasting individualised herbal decoctions has made it difficult to apply the double-blind placebo controlled RCT to the best practice of CHM. Instead CHM research tends to adapt clinical practice to conform to the requirements of existing research designs and use standardized preparations of pills or encapsulated powders. However this represents a distortion of 'real world' practise and compromises the relevance of this work.

This paper now reports on the development of a novel methodology to investigate the role of CHM in the treatment of endometriosis that involved three main phases. The first phase involved defining good practice, the second required the design of a plausible placebo for herbal decoctions and the third involved the application of this approach in a double-blinded RCT using individualised CHM.

2. Methods

2.1. Phase I: ensuring clinical relevance; defining good practice

CHM has evolved over hundreds of years and across thousands of miles into a highly pluralistic system of medicine (Scheid, 2002). It does not have (or particularly recommend) the kind of tight clinical guidelines currently being developed within the culture of Western medicine. However, a key component of this research project has been to develop a methodology to locate a nexus of shared and consistent approaches to the CHM diagnosis and treatment of disease. This can then be used in clinical research to ensure that the CHM subjected to scientific scrutiny is representative of an agreed standard of good practice.

For the purposes of this trial exploring CHM and endometriosis there were four main sources used to establish clinical consensus. The first involved reflective practice from the practitioner conducting the research. The second used a modified Delphi process to generate professional consensus from a group of 11 experienced practitioners in CHM gynaecology. Delphi is an iterative process that uses several rounds of questionnaires, interspersed with summarized information and opinions feedback derived from earlier responses, to generate expert consensus (McKenna, 1994). The third process reviewed historical data relating to the treatment of endometriosis from the Chinese cannon that were available in the English language. Finally a Cochrane systematic review was conducted of the 110 clinical trials using CHM in the treatment of endometriosis (Flower et al., 2009). Using these four methods of data collection and analysis it was possible to develop broad clinical practice guidelines. A more complete account of this consensus developing process is presented elsewhere (Flower et al., 2007).

One aspect of these guidelines related to the means by which CHM was prepared and dispensed. There was a strong consensus that the boiling up of herbal formulae into a decoction was the most potent route for administering CHM. As this was identified as an essential component of good practice the next phase of development involved an exploration of how to incorporate herbal decoctions and, if possible, placebo decoctions into the trial design.

2.2. Phase II: using herbal decoctions

In recent years the traditional practice of preparing herbs as boiled decoctions has received some preliminary validation through chromatographic analysis of different modes of herbal preparation that clearly show decoctions providing a greater number and a higher concentration of available compounds than either pills or powders (Xie, 2006).

Although protracted boiling is an antiquated mode of extraction that can lead to the destruction of heat sensitive active components, CHM practitioners consider that it allows for a powerful synergy between herbal ingredients. Decoctions are also the favoured



Fig. 1. Weighing out dried Chinese herbs.



Fig. 2. Preparing a herbal decoction using modern technology.

method of preparation for the past 2000 years and which still provide the basis for much contemporary clinical practice. It is possible that using modern solvents to extract active compounds from herbs may change the actions of an herb, disturb classical synergies, and alter various buffering systems that effects both the therapeutic effects and the safety of a herb. It therefore seems sensible to use herbal decoctions as part of research into good practice of CHM. Subsequent research into alternative methods of extraction and delivery could then use these data as a baseline measurement for good practice.

There are obvious difficulties involved in researching CHM decoctions. They are strong tasting, time consuming to prepare, and unfamiliar to the Western palate. Compliance can be compromised by these factors. In addition the distinctive taste of herbal decoctions means that it is difficult to prepare a convincing inert placebo decoction. Therefore most clinical research uses either herbal pills or encapsulated herbal powders that are easier to take and more readily mimicked by inert controls (placebos).

Using Donghuayuan decoction machine model (YF40) and packaging machines (YBS250) imported from China it has become possible to pre-cook herbal decoctions and dispense them in sealed, separately packaged, daily dosages (see Figs. 1–3). This obviates the need for any preparation by the patient and leads to both an increased compliance and a more consistent end product. Not only does this facilitate the use of decoctions in clinical research but it also provides a route by which a convincing placebo control could be developed that mimicked the appearance of the active medicine.

Research into these decoction machines suggests that they enable efficient extraction of known active compounds (Jin, 1999; Song et al., 2000) and can demonstrate high levels of stability up to 9 weeks after packaging (Xu et al., 2008). Heat resistant, food quality plastics are used to minimize interactions between the packaging and the decoctions. The main disadvantage to this method of preparation is the additional cost incurred, which may amount to an extra £1/day of treatment.

2.2.1. Developing a herbal placebo

The production of an inert, strong tasting, plausible herbal placebo was challenging and required several stages of development prior to the trial commencing.



Fig. 3. Pre-cooked herb sachets.

Box 1: The herbal placebo

Chicory (*Cichorium intybus*)
 Lemon verbena (*Aloysia triphylla*)
 Coriander (*Coriandrum sativum*)
 Cabbage (*Brassica oleracea*)
 Sweet corn (*Zea mays* var. *rugosa*)-replaced by puy lentils (*Lens culinaris*)
 Turnip (*Brassica rapa* var. *rapa*)
 Peas (*Pisum sativum*)
 Leek (*Allium ampeloprasum* var. *porrum*)

A review of the available literature was conducted to identify precedents that could be used as models for the endometriosis trial. The only evidence that could be found for the use of placebo in research using CHM decoctions occurred in a series of clinical trials conducted in the UK investigating the treatment of atopic eczema (Sheehan and Atherton, 1992). These trials successfully used a placebo decoction made up of culinary and medicinal herbs to match a standardized active CHM prescription for the treatment of atopic eczema. This approach has, to our knowledge, not been replicated perhaps due to concerns over the therapeutic inertia of the 'placebo' herbs used in the trial (hops (*Humulus lupulus*) for example have a sedating effect which could have an impact on stress related eczema). In addition whilst the placebo was plausible the active treatment was a standardized rather than individualized mixture of herbs. For these reasons it was necessary to develop and evaluate a new approach to administering both CHM and a placebo decoction.

Initially this involved a consultation process with five expert Western herbal practitioners. A placebo decoction was designed comprising of nine foods and culinary herbs (see Box 1). Lemon verbena and chicory were added to these common foods to introduce a more medicinal, sour and bitter flavour to the decoction. Lemon verbena is an herb that is also used as a popular summer drink and has mildly calming and digestive properties. Chicory can be used as a substitute coffee drink and is described as a mild tonic for the liver and digestive tract (Chevallier, 1996). Whilst it was noted that any herb or food could have some physiological impact, there was a consensus that the herbs and foods that were included in the placebo arm were commonly available in UK shops, free from side effects, and not used in the treatment of endometriosis.

Dried herbs used in the placebo were purchased from Cotswold herbs and dried foods from Sleaford Quality Foods. Dried foods were selected because they could be stored for several months and they resembled the shape, bulk and texture of the active herbs. When cooked the resultant placebo decoction looked similar to the herbs with a strong unpleasant taste. As CHM is renowned for being strong tasting it was important that the placebo decoction was not bland. Prior to commencing the trial eight CHM naïve volunteers were given the placebo decoction and asked to comment on the taste of the "Chinese herbs". There was a consensus that the herbs were 'real' CHM and that the taste was unpleasant!

2.3. Phase III: a feasibility study exploring the role of CHM in the treatment of endometriosis

The next phase in the development process involved the design and implementation of the trial protocol. This required the use of a distant herbal dispensary to ensure secure randomization, blinding and allocation concealment, and the establishment of new regulatory pathways for clinical trials using CHM in the UK.

2.3.1. Randomization, blinding and allocation concealment

The trial design was a prospective double blind RCT with three groups: an active treatment group, a placebo treatment group, and a waiting list control (WLC). By comparing active and placebo groups after the 16 weeks of the trial it was hoped to estimate the specific effects of the CHM intervention. A comparison of the placebo and WLC groups was intended to measure the contextual effects of a CHM intervention. In practice an unacceptably high drop out rate from the WLC group led to this arm of the trial being suspended. A full account of the results of the trial is currently being prepared for publication.

During the course of the trial all participants were seen once a month by a qualified CHM practitioner. A prescription was written and e-mailed to a distant herbal dispensary where randomization to either active or placebo groups was undertaken. Herbs were then packaged in white Muslin bags and sent to a different herbal dispensary with the facilities to prepare pre-cooked herbs in sealed sachets of 150 ml. These were then either collected or sent to trial participants. The daily dosage was 1 sachet taken in the morning and evening.

A computer generated random numbers table was used to provide an irregular block allocation sequence prior to the trial. Block randomization was selected because it ensured that there would be relatively equivalent numbers in the groups even if full recruitment was not possible. The use of random blocks comprising of 4, 6 or 8 participants was chosen so that it would not be possible for the practitioner to discern an obvious and predictable pattern to the randomization. Codes for each group allocation were transferred to sealed opaque envelopes. In order to ensure optimum allocation concealment, these envelopes were opened only at the herbal supplier Kingham Herbs and Tinctures based at a distant site in Oxfordshire. Double blinding was maintained by ensuring that the practitioner did not come into contact with a participant's herbs either at the point of dispensing or any point subsequent to this.

2.3.2. Regulatory obstacles

Prior to this trial the authority regulating clinical trials in the UK—the Medicines and Healthcare products Regulatory Agency (MHRA) had not received any requests to approve a clinical trial using CHM and there was no clear consensus about the legal status or the regulatory requirements relating to this research.

After considerable discussion the MHRA clarified that CHM would be classified as an Investigational Medicinal Product (IMP) requiring a Clinical Trials Authorisation. This was an important clarification of the legal status for CHM used in clinical trials that has implications for all future CHM research in the UK.

Both the MHRA and the local Ethics committee were resistant to the idea of individualised treatments that would change over time. There was confusion owing to the differences between a standardized pharmaceutical product that fitted into the MHRA regulatory (and conceptual) framework and the changing, individualized herbal decoctions involving combinations of 10–15 herbs selected from a *Materia Medica* of several hundred herbs.

Fortunately these difficulties were gradually overcome by supplying the MHRA and ethics committee with the available pharmacological data on the 70 herbs that were most likely to be used in the trial. It was also agreed with the co-ordinator of clinical trials at the MHRA that, as the proposed trial was an investigation of existing routine CHM practice, it constituted a phase 4 not a phase 3 clinical trial. This reduced the cost and the regulatory requirements for the trial and it facilitated final MHRA and ethical approval. These difficulties may be specific to the UK but it is possible that the same unfamiliarity with the CHM model of best practice may also affect the regulatory process for trials using individualised decoctions in other countries.

3. Results

During the trial it was possible to meet the predefined criteria for best practice of CHM. Participants received in depth consultations and were diagnosed according to the categories identified within the consensus guidelines. Participants in the active arm of the trial received individualized herbal decoctions that were adjusted if necessary after each monthly consultation whilst those in the placebo group received identical treatment apart from the delivery of a therapeutically inert decoction.

A distant herbal dispensary was used to randomize trial participants and to ensure adequate blinding and allocation concealment. The effectiveness of this procedure and the plausibility of the placebo were assessed at the end of the trial. Of the 28 women who completed the trial, in the placebo group ($n=15$) 3 women (20%) correctly guessed they were on placebo, 8 (53%) thought they were on herbs and 4 (27%) did not know which group they had been allocated to. In the active group ($n=13$) 2 (15%) thought they were on placebo, 8 (62%) thought they were on herbs and 3 (23%) did not know. The practitioner correctly guessed 5/15 women were on placebo herbs in the placebo group but thought 8 from this group were taking active medication and did not know for 2 individuals. In the active group he thought 5/13 were on herbs, 5 were on placebo, and did not know for 3 participants. In summary neither participants nor practitioner were able to identify treatment allocation and blinding was therefore secure and effective.

4. Discussion

This feasibility trial has proposed and tested a novel methodology to evaluate CHM. A process has been developed to establish a broad consensus on good practice for the management of endometriosis. This relates to diagnostic parameters and treatment including herb selection, treatment principles and the importance of decocted herbs. The legal and ethical requirements for CHM clinical trials in the UK have been clarified. A placebo herbal decoction has been developed that enabled double blinding of both participants and the practitioner-researcher. A method of randomisation has been applied using a distant herbal dispensary that ensures adequate allocation concealment. It has consequently been possible to conduct a double blind placebo controlled RCT using individualized Chinese herbal decoctions for the first time. This has involved rigorous methodology whilst maintaining best practice and model validity for CHM.

Although the placebo decoction was not known to be active in the treatment of endometriosis it was not pharmacologically inert and theoretically could have had some therapeutic effect. Those receiving the placebo decoction during the trial did report considerable improvement in their endometriosis but this could be the result of contextual factors such as the therapeutic relationship established with the herbal practitioner. The next stage in the 'real world' research of CHM requires the development of a placebo decoction of more certain inertia. If there is no need to mimic the bulk and texture of dried herbs, because participants are being supplied with pre-cooked decoctions rather than having to boil their own herbs, then this should be possible using food colourings and flavourings that will already have been extensively tested for safety and pharmacological inactivity. This approach will be developed in a larger, more definitive trial.

The use of pre-cooked decoctions has become increasingly common within China in recent years and is now being introduced into the UK. They facilitate the use of properly prepared herbal decoctions as a form of standard care and as a means of conducting clinical research.

5. Conclusion

The method used during this trial is generalisable to other diseases treated by CHM. In addition, treatment effects from decoctions can now also be compared to effects derived from other methods of administering CHM such as encapsulated herbal powders. This will help to answer key questions within herbal medicine such the optimum method of CHM delivery, questions relating to dosage, and the true value of individualised prescribing. By subjecting traditional notions of 'good practice' to appropriate and relevant research design we can both ensure that CHM is evaluated appropriately and rigorously.

CHM is a rich whole system of medicine with many pharmacologically active medications. It has contributed substantially to western medical pharmacopoeias but at the same time still retains a unique approach that is practiced throughout the world. Given that it almost certainly has a sound pharmacological basis for some of the claims made we must continue to develop increasingly rigorous approaches to its preparation, safety, practice and evaluation.

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