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Original Articles

A Feasibility Study Exploring the Role of Chinese Herbal Medicine in the Treatment of Endometriosis

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Abstract

Background: Endometriosis is a common and disabling gynecologic condition affecting between 5% and 15% of women of childbearing age. Conventional medical intervention has unpleasant side-effects, and symptoms frequently return after treatment. Preliminary evidence suggests Chinese herbal medicine (CHM) may contribute to the treatment of endometriosis.
Objectives: The aims of this study were to test the feasibility of a novel methodology for investigating individualized decoctions of CHM rigorously and to gather preliminary data on the treatment effect of CHM for a larger definitive trial.
Design: This was a 16-week prospective, double blinded, randomized controlled trial of 40 women with laparoscopically confirmed endometriosis.
Settings: The trial was conducted at a private CHM clinic in Hove (U.K.) and at a National Health Service outpatient clinic in London (U.K.).
Interventions: Participants were initially randomized to either wait-list control (WLC) or treatment groups to receive either individualized CHM decoctions or a therapeutically inert placebo decoction.
Outcome measures: Four 10-cm visual analogue scales (VAS) were used to measure menstrual pain, daily pain, and pain on intercourse and bowel movement; these measurements were recorded weekly. The Endometriosis Health Profile–30 (EHP-30) endometriosis-specific quality-of-life questionnaire was completed at the beginning and at the end of the trial. The Measure Yourself Medical Outcomes Profile (MYMOP) a patient-centered health questionnaire was completed monthly. Liver and renal function was measured at 0, 4, 8, and 16 weeks.
Results: Twenty-eight (28) women completed the trial. High dropout rates led to the suspension of the WLC. Randomization, double blinding, and allocation concealment was achieved successfully. Adjusted mean differences favored the active treatment in the EHP-30 and MYMOP scores. VAS scores favored the active treatment for relief of menstrual pain and the placebo group for reduction of daily pain.
Conclusions: the methodology successfully allowed individualized CHM decoctions to be tested rigorously. There are nonspecific contextual effects from CHM that require further investigation. Provisional data were generated to warrant a larger, more-definitive study.

Introduction

Endometriosis is a common gynecologic condition caused by endometrial cells occurring ectopically and leading to local inflammation, fibrous adhesions, and signature ovarian "chocolate" cysts. Symptoms can be severe and disabling and include dysmenorrhea, noncyclical pelvic pain, pain on bowel movement and intercourse, and infertility. The prevalence of endometriosis is estimated at between 5% and 15% of menstruating women.[1,2] In the United States, the costs for treatment and time taken off from work were estimated at $22 billion per annum.[3]

Conventional medical treatment is either surgical or medical. Surgery is usually laparoscopic and can provide significant short-term relief, but relapse is common.[4,5] Medical treatment involves the uses of nonsteroidal anti-inflammatory drugs (NSAIDs) for pain management and hormonal treatments to reduce levels of endometrial-stimulating hormones. Medical treatments appear to have equivalent benefits[6–9] but are generally characterized by the possibility of unpleasant short- and

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long-term side-effects.[10,11] Such treatments are incompatible with achieving conception and are associated with high rates of relapse once medication is stopped.[12,13] The conventional treatment of endometriosis is far from satisfactory.

Chinese herbal medicine (CHM) has a recorded history of more than 2000 years. Although endometriosis as a distinct clinical entity did not exist until modern surgical diagnosis, there are repeated references in classical CHM literature to the typical signs and symptoms that characterize this condition.[14–16] In China, there have been more than 100 clinical trials exploring the impact of CHM on this disease.[17] The great majority of these trials have been shown to be methodologically flawed, with inadequate randomization and blinding,[18] unclear inclusion criteria, and the use of nonvalidated outcomes measures.[18] However, these trials do provide preliminary evidence to warrant further investigation of the potential role of CHM in the treatment of endometriosis.

CHM is a complex intervention that combines the specific effects of herbal prescriptions (comprised of, typically, between 5 and 15 separate herbal ingredients selected from a materia medica of several hundred commonly used herbs) with contextual effects that emerge out of various aspects of the therapeutic relationship.[19,20] CHM theory emphasizes the need to individualize herbal decoctions according to each patient's disease presentation. Current CHM research tends to test standardized pills or encapsulated powders that can be matched easily by plausible placebos. This, however, does not reflect best practice.[21] To combine clinical relevance with scientific rigor, it is important that trials investigating CHM reflect real-world practice. A feasibility study was designed to test a novel methodology that enabled individualized herbal decoctions to be compared with a placebo decoction in a prospective, double-blinded, randomized controlled trial (RCT), and to pilot the process of evaluating the potential role of CHM systematically in the treatment of endometriosis.

Methods

Figure 1 summarizes the study protocol. All women with a laparoscopically confirmed diagnosis of endometriosis, with relatively stable and measurable symptoms of disease, who were naïve to CHM, and therefore unable to distinguish between active and placebo herbs, were candidates for inclusion in this study. Women who had received surgery, started conventional medical treatment in the previous 3 months, reported other conditions associated with pelvic pain, who had hepatic or renal complications, were pregnant, or were taking any drugs known to interact with CHM were excluded from the trial.

After a lengthy process, ethical and Medicines and Healthcare products Regulatory Agency (MHRA) approval was granted (EudraCT 2005-003311-67), and the trial commenced in October 2006 and concluded in August 2008.

Initial recruitment was through a specialist endometriosis treatment center in Worthing Hospital, in the United Kingdom, and later via a network of general practitioners in the London area. Both recruitment methods proved to be completely unsuccessful. Fortunately, at the same time as these National Health Service (NHS) pathways were being explored, details of the trial were publicized on the website of Endometriosis UK—the national charity for women with endometriosis. This led to the first few self-referred participants being accepted into the trial in November 2006. Additional publicity from local and national media eventually enabled 40 self-referred women to be recruited by the end of the trial. All women provided written consent prior to their inclusion in the trial.

The trial was based in a Chinese medicine clinic in Hove, United Kingdom, and at The Gateway clinic in South London, United Kingdom, which is an NHS clinic offering acupuncture and herbal medicine.

Monthly consultations took place with the practitioner–researcher (a member of the U.K. Register of Chinese Herbal Medicine with more than 15 years of clinical experience) and lasted 20–30 minutes. Clinical practice guidelines for the trial were developed after conducting a systematic review of the available literature[21] and by a Delphi process used to develop an expert consensus on good practice.[21] For this trial, good practice was defined as a consistent CHM approach, with a clear and demonstrable professional consensus, and preliminary evidence of effectiveness.

Women were initially randomized either to a wait-list control (WLC) group or to a treatment group that was subsequently randomized to active or placebo interventions. The aim of the WLC group was to provide a way of comparing the natural history of the disease with either the contextual (placebo) or combined contextual and specific (verum) effects of treatment. The duration of the trial was 16 weeks, with a 4-week run in period to establish stable and measurable levels of endometriosis-related pain. After 16 weeks, women allocated to the WLC group were eligible to join the treatment arms of the trial. Women in the active group received individualized herbal formulations of between 10 and 15 herbs selected from the Chinese materia medica, with a daily dosage amounting to between 150 g and 250 g. A month's supply of herbs was soaked in 9 L of water for 40 minutes and then cooked for 1 hour using pressurized herb cooking machines that are commonly used in Chinese hospitals. The precooked herbs were then dispensed as individual dosages of 180 mL (taken two times per day) in sealed plastic packets. Subjects who were to received placebo herbs were given packets that looked identical to the ones containing active treatment herbs, which were produced according to the same procedure as the active herbs but contained a decoction made from commonly available dried foods and culinary herbs (see Box 1). A group of Western herbal practitioners had previously agreed that the placebo formulation did not contain ingredients that were known to have therapeutic action for the treatment of endometriosis. Prior to the trial, the placebo was tested on CHM-naïve volunteers and found to be as plausible as CHM in terms of taste and appearance.

All herbs were supplied by Balance Healthcare, a company that conformed to high standards of good dispensary practice as defined by the Register of Chinese Herbal Medicine Approved Supplier scheme. Placebo dried foods and culinary herbs were supplied by Sleaford Quality Foods. Herbs and placebo foods were sent to a second herbal dispensary, where they were precooked and collected or sent to participants by mail.

The primary objectives of the trial were: to (1) assess the feasibility of this new methodology for testing CHM; (2) to estimate the specific and contextual effects of CHM in relieving endometriosis-related pain and in improving quality of life; (3) to establish the size and standard deviation of the

Box 1. Contents of Herbal Placebo

- Chicory (*Cichorium intybus*)—15 g
- Lemon verbena (*Aloysia triphylla*)—15 g
- Coriander (*Coriandrum sativum*)—3 g
- Cabbage (*Brassica oleracea*)—10 g
- Sweet corn (*Zea mays* var. r*ugosa*)—10 g (replaced by puy lentils [*Lens culinaris*])—10 g)
- Turnip (*Brassica rapa* var. *rapa*)—10 g
- Peas (*Pisum sativum*)—10 g
- Leek (*Allium ampeloprasum* var. *porrum*)—5 g

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 a 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 (Derived from Chevalier A. The Encylopaedia of Medicinal Plants. London: Dorling Kindersly, 1996).

treatment effect using CHM in the management of endometriosis; and (4) to use these data in the design of an adequately powered, more definitive, future study.

Three outcomes measures were selected for the trial. Four 10-cm visual analogue scales (VAS) were used to measure weekly variations in menstrual pain, pain on intercourse, pain on bowel movement, and daily pain. The Measure Your Own Medical Outcomes Profile (MYMOP), a validated patient-centered questionnaire, was completed once per month to allow participants to identify two symptoms that bothered them most and an activity restricted by endometriosis, and to rate their level of well-being using a 1–7-point Likert scale. The Endometriosis Health Profile–30 (EHP-30), an endometriosis-specific quality-of-life questionnaire (QoL) was completed at the beginning and the end of the trial. The VAS scores and the EHP-30 were primary outcomes at the start of the trial. A reduction of 30% in a VAS score,[22] a 1 or more point change in the 7-point Likert scale used for MYMOP,[23] and an effect size of ≥ 0.5 in the EHP-30[24] were regarded as clinically important reductions of symptoms.

In addition liver (alanine transferase) and renal (serum creatinine) tests were conducted at 0, 4, 8, and 16 weeks using the validated Reflotron desktop analyzer.[25]

As this trial was a feasibility study and there was no measurement of the extent and standard deviation of the effect size of these outcomes, no *a priori* power calculation of numbers needed to treat was possible.

Randomization

A computer-generated random numbers table was used for both phases of randomization to provide an irregular block allocation sequence prior to the trial. Block randomization was selected, because it ensured that there would relatively equivalent numbers in the groups even if full recruitment was not possible. The use of random blocks comprising 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. To ensure optimum allocation concealment, these envelopes were opened by an employee at the herbal dispensary based at a distant site in Oxfordshire, United Kingdom. An opaque white envelope was used for the initial randomization to treatment or wait-list arms. This allocation was conveyed by telephone to the practitioner–researcher who then assigned each participant to a group. A second randomization took place at the dispensary using opaque brown envelopes that divided participants into either active or placebo arms. This information was not presented to the practitioner or the participant until after the conclusion of the whole trial. 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.

After completion of the run-in period, the trial proper commenced. Herbal prescriptions were e-mailed to the designated employee at the dispensary who then instructed the herbal packers to prepare either an active or a placebo prescription. Active and placebo herbs were then packaged identically, using an opaque muslin bag that was sent to the Hove clinic dispensary to be cooked and prepared into single-dose packets. Participants were asked not to show their herbs to the practitioner or to other women involved in the trial.

Statistical analysis

As a result of the small initial sample size and the considerable amount of missing data, it was decided to use descriptive rather than analytical statistics to report details of the trial. Stata version 9 (StataCorp, 2005, College Station, TX) was used to calculate adjusted mean differences between the groups. However, performing sophisticated statistical tests such as analysis of covariates, with such small sample sizes was considered to be inappropriate and misleading. An assessment of clinically important changes after 16 weeks of treatment was made for both groups and a comparison was made of the adjusted mean differences between the two groups. An aggregation of scores from the run-in period was used to provide baseline data for the VAS outcomes and data from week 0 were used for MYMOP and EHP-30.

Results

Recruitment

A CONSORT [Consolidated Standards of Reporting Trials] diagram (Fig. 2) shows the recruitment pathway for the 158 women who expressed an interest in taking part in the trial.

By December 2007, 7 of 13 (54%) of the women in the WLC had dropped out. As a result, the WLC control group was suspended. The total dropout percentage from the trial was 22.5%.

Baseline characteristics

The groups were comparable in terms of age and duration of illness. However, the active treatment group comprised a greater proportion of women with more-severe symptoms of endometriosis. In addition, 5 of the 13 (38.5%) women in the active group experienced pain, despite taking hormonal medication, compared to 2 of 15 (13.3%) women in the placebo group. (See Table 1)

Blinding

When "guessing which treatment they had" 53% ($n=8$) of women in the placebo group thought they were on active

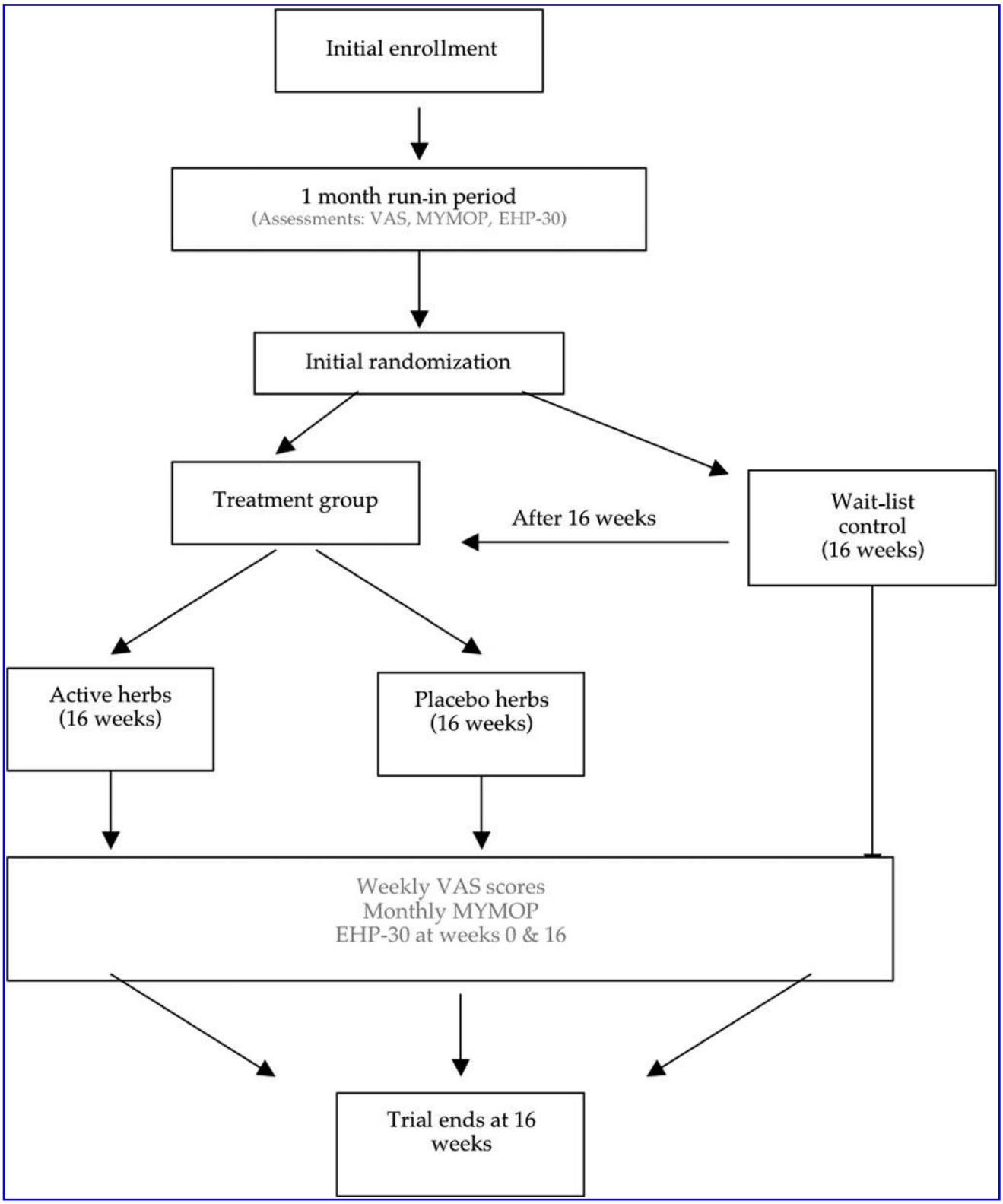

FIG. 1. Protocol summary. VAS, visual analogue scale; MYMOP, Measure Your Own Medical Outcomes Profile; EHP-30, Endometriosis Health Profile–30.

herbs, compared to 62% ($n=8$) in the active group. The practitioner was also unable to identify correctly which groups the women had been assigned to. The inability of the participants and practitioner to identify reliably which group they had been allocated to indicates the placebo decoction was plausible and that the methodology used to ensure double blinding and allocation concealment during the trials was successful.

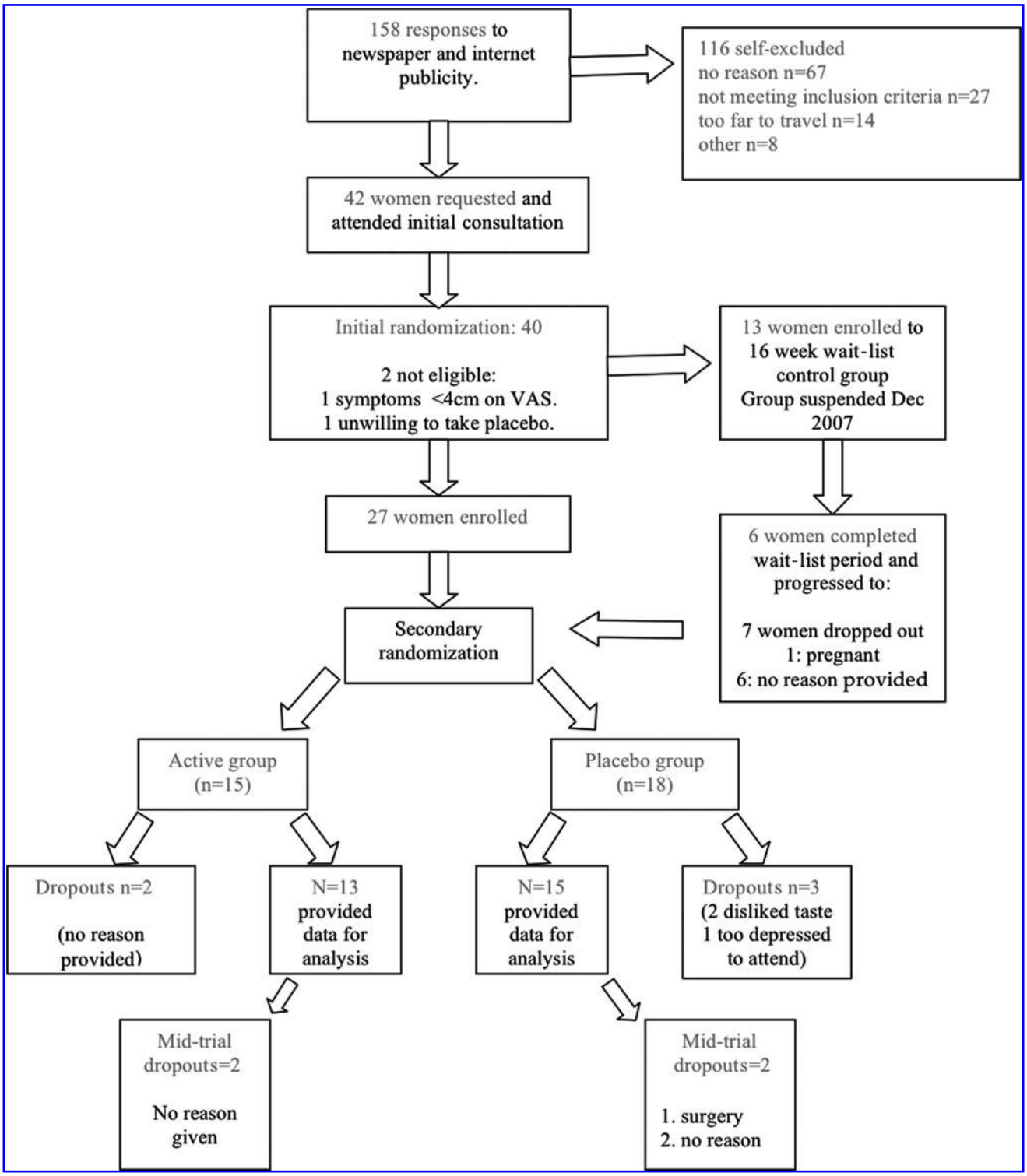

FIG. 2. Flow chart of participants from referral through to randomization (CONSORT [Consolidated Standards of Reporting Trials] diagram). VAS, visual analogue scale.

Missing data

There was a considerable increase in missing data as the trial progressed. This was most apparent in the weekly VAS scores. The MYMOP questionnaire provided a more consistent level of responses in both the active and placebo groups than for the other two outcomes.

Outcomes

VAS scores. Both groups experienced a reduction in the severity of symptoms in all four of the VAS scores. Clinically important changes (>30% change) were reported for period pain (35.1%) and pain on intercourse (55.2%) in the active group; and for pain during sexual activity (76.5%) and daily pain (35.6%) in the placebo group. (See Table 2).

Table 1. Baseline Characteristics of the Active and Placebo Groups

Group	*Placebo*	*Active*
Number	15	13
Average age (range)	35.7 years (24–50)	33.2 years (21–44)
SD	8 years	7.2 years
Duration (range)	12.6 years (2–29)	11.2 years (3–20)
SD	8.9 years	5.8 years
Relationship status	7 (47%)	5 (38.5%)
Single	6 (40%)	5 (38.5%)
Cohabiting or married	2 (13%)	3 (23%)
Missing	2 (13%)	5 (38.5%)
Number (%) using hormonal medication		
Pretreatment (weeks 0–3)		
Mean VAS scores (SD): *(Number of respondents)*		
Period pain	6.8 (1.9) *(12)*	6.6 (2.4) *(11)*
Pain during sex	3.1 (2.65) *(7)*	5.2 (2.9) *(6)*
Pain on bowel movement	3.2 (2.3) *(12)*	4.9 (3.4) *(9)*
Daily pain	4.0 (2.2) *(13)*	4.9 (2.3) *(10)*
Number (and %) of women with severe pain before Tx:		
Period pain VAS >7	9 (60 %)	9 (69.2%)
Pain during sex VAS >5	2 (13.3%)	4 (30.7%)
Pain on bowel movement VAS >5	3 (20%)	5 (38.5%)
Daily pain >VAS 5	3 (20%)	6 (46.2%)

SD, standard deviation; VAS, visual analogue scale; Tx, treatment.

MYMOP scores. Clinically important changes were observed in all scores in the active group and in all scores, except Well-being, in the placebo group. In the active group the adjusted mean difference between weeks 0 and 16 all showed clinically important changes of >2 points in the Likert scale.[25] The adjusted mean differences favored the active group in all the MYMOP scores. (See Table 3).

The EHP-30. Both groups showed an improvement in all domains of the EHP-30. With the exception of social support in the placebo group (0.32) all these changes were clinically important (>0.5 point change). In the active group all the scores showed a clinically large change (>0.8 point change) while, in the placebo group, this was the case for control, emotional well-being, and self-image. (See Table 4).

Adverse events. There were no serious adverse events during the trial. In the placebo group, there were 2 cases of mild transient increases in alanine transferase (ALT) (levels of 56 and 41), coinciding with slightly increased use of paracetamol-based analgesia. Both of these returned to normal within a month. One (1) woman in the placebo group started the trial with a slightly raised creatinine level (89 g/dL) that, by the end of the trial, was reduced to 68 g/dL, which may have been the result of reduced requirements for analgesia. There were no elevated results on liver or renal function tests in the active treatment group.

Compliance. Compliance in taking the herbal decoction was assessed during each consultation. Women who had difficulty taking the recommended dose of the herbs were advised to halve the dose, flavor it with apple juice, and take the herbs after eating food. This is the same procedure that would be applied during routine clinical practice and, thus it conformed to the pragmatic nature of this trial. Only 2 women dropped out of the trial, because they were unable to tolerate the taste of the herbs, and both of the women were in the placebo arm.

Power calculation. A power calculation using nQuery Advisor software was conducted using the standard deviations derived from this trial. To have 90% power to detect a statistically significant ($p<0.05$) and a clinically important 1-point difference in VAS scores between 2 groups, there would need to be 113 women in each group. This figure will be used to inform recruitment in a proposed larger and more definitive study.

Discussion

Overall the VAS, MYMOP, and EHP-30 outcome measures favored the active treatment group. There were no serious adverse reactions reported during the trial or any abnormal liver or renal function test results in women taking the active CHM. For VAS scores, both groups showed clinically relevant reductions in pain on intercourse. A relevant reduction in period pain, the most common symptom of

Table 2. Adjusted Mean Differences of VAS Scores at 16 Weeks

Outcomes	*Group (Number providing data (n))*	*Adjusted mean at week 16*	*Adjusted mean difference b/n baseline and week 16 (SD)*	*Clinically important change*	*Adjusted mean difference b/n groups (95% CI)*
VAS				**> 30 % change**	
Period pain	Placebo ($n=5$)	5.59	−1.14 (2.29)	No (17%)	−1.22 to −4.37 1.97)
	Active ($n=7$)	4.36	−2.36 (2.22)	Yes (35.1%)	
Pain during sex	Placebo ($n=3$)	0.31	−3.74 (1.62)	Yes (76.5%)	0.77 to −2.08 3.62)
	Active ($n=5$)	1.08	−2.98 (1.56)	Yes (55.2%)	
Pain on bowel movement	Placebo ($n=5$)	2.94	−0.96 (2.61)	No (24.6%)	0.08 to −3.45 3.62)
	Active ($n=7$)	3.02	−0.88 (2.51)	No (22.7%)	
Daily pain	Placebo ($n=6$)	2.84	−1.57 (2.35)	Yes (35.6%)	0.74 to −2.10 3.57)
	Active ($n=7$)	3.57	−0.83 (2.32)	No (18.9%)	

VAS, visual analogue scale; b/n, between; SD, standard deviation; CI, confidence interval.

Table 3. Adjusted Mean Differences of MYMOP Scores at 16 Weeks

MYMOP				*> 1 pt. change*	
Symptom 1	Placebo ($n=10$)	2.51	−1.57 (1.96)	Yes	−0.58 to −2.55 1.39)
	Active ($n=8$)	1.93	−2.15 (1.97)	Yes	
Symptom 2	Placebo ($n=10$)	2.77	−1.51 (1.90)	Yes	−0.89 to −2.9 1.13)
	Active ($n=8$)	1.87	−2.41 (1.93)	Yes	
Activity	Placebo ($n=9$)	2.42	−1.50 (1.69)	Yes	−0.69 to −2.60 0.94)
	Active ($n=8$)	1.74	−2.19 (1.71)	Yes	
Well-being	Placebo ($n=10$)	2.67	−0.95 (1.93)	No	−1.06 to −3.09 0.96)
	Active ($n=7$)	1.60	−2.01 (1.97)	Yes	

MYMOP, Measure Your Own Medical Outcomes Profile;

endometriosis, was only apparent in the active group. Although both groups showed clinically important changes in MYMOP scores, the average improvement for the active scores was 2.2 compared to 1.4 in the placebo group. In the EHP-30, four of five domains favored the active treatment group. While the generalizability of these findings are undermined by the wide confidence intervals which crossed the null and the small sample size, these findings suggest a possible difference between active and placebo treatments that might become significant in an adequately powered study. Importantly, the outcomes also suggest a nonspecific contextual effect of CHM that may emerge from the nonherbal components of CHM treatment, such as the therapeutic relationship. These components have been widely ignored in existing CHM research and require further investigation using methods such as comparing placebo treatment with a wait-list control group and by applying qualitative methodologies to provide a deeper exploration of the experience of undergoing CHM treatment.

This trial was a feasibility study testing a novel methodology for investigating CHM research and was not powered to clarify definitively whether CHM has specific efficacy as a treatment for endometriosis. Data from this trial have been used in a power calculation to define numbers required for a more definitive study. This trial has, for the first time, established the feasibility of investigating individualized CHM decoctions within a double-blinded RCT. Randomization, blinding, and allocation concealment were achieved successfully, and refined versions of this methodology can be adopted by other researchers seeking to reproduce and test rigorously the real-world practice of CHM.

Limitations of this study

Selection bias. It is only possible to speculate on the reasons why there was no recruitment from NHS sources. Consultants and general practitioners may have been too busy, and this may have been coupled with some distrust of CHM after a few high-profile cases of adverse events from CHM.[26,27] The lack of adverse events in this study should contribute toward easing concerns about the safety of CHM.

All the trial participants were self-referred, and a significant number first heard about the trial from the network of endometriosis self-help networks. It has been noted recently that women attending self-help groups may present with more recalcitrant and treatment-resistant disease than a broader cross-section of women receiving conventional treatment.[28,29] This severity of disease was apparent in the baseline scores of many of the trial participants. This may make the effect size of clinical improvements seen in both the active and placebo groups more interesting and notable. The disproportionate allocation of these participants to the active group may also have skewed the results. Any future trial

Table 4. Adjusted Mean Differences of the EHP-30 at 16 Weeks

	Group (number providing data (n))	*Adjusted mean at week 16*	*Adjusted mean difference b/n baseline and week 16 (SD)*	*Clinical important change*	*Adjusted mean difference b/n groups (95% CI)*
EHP-30				*> 0.5 pt. change*	
Pain	Placebo ($n=7$)	16.7	−6.11 (10.3)	Yes (0.59)	−0.32 to −10.3 9.64)
	Active ($n=11$)	16.4	−6.43 (10.1)	Yes (0.64)	
Control & powerlessness	Placebo ($n=7$)	12.2	−5.76 (5.99)	Yes (0.96)	−1.73 to −8.36 4.67)
	Active ($n=11$)	10.5	−7.49 (5.83)	Yes (1.28)	
Emotional well-being	Placebo (n=7)	10.58	−4.12 (4.28)	Yes (0.96)	−0.37 to −5.15 4.10)
	Active ($n=11$)	10.2	−4.49 (4.16)	Yes (1.08)	
Social support	Placebo ($n=7$)	9.84	−1.48 (4.69)	No (0.32)	−2.71 to −7.67 2.25)
	Active ($n=11$)	6.53	−4.19 (4.52)	Yes (0.93)	
Self-image	Placebo ($n=7$)	4.95	−3.03 (2.86)	Yes (1.06)	0.45 to −2.30 3.21)
	Active ($n=11$)	5.14	−2.57 (2.79)	Yes (0.92)	

EHP-30, Endometriosis Health Profile–30; b/n, between; SD, standard deviation; CI, confidence interval.

investigating CHM for endometriosis should be alert to this potential for selection bias and control for it by stratifying according to disease severity and endeavoring to obtain a broad clinical base for referrals. This will make the results of such a trial more generalizeable.

Missing data and dropout rates. Inexperience of the practitioner–researcher conducting this trial led to considerable missing data. This is particularly true for the VAS scores, which required weekly completion. The small size of the trial, and its status as a feasibility study, meant that it was not considered necessary or desirable to impute missing data using complex statistical modeling techniques. Future trials should investigate the possibility of completing outcomes via the internet and should ensure an adequate auditing system and participant support for data collection throughout the trial.

The high dropout rate from the WLC group also needs to be addressed in any future trial using a similar design. Given the substantial clinical benefits obtained in the placebo group a comparison with a WLC group would be one way of measuring these contextual effects clearly.

Follow-up data were also not available for this trial because of restrictions of time and funding. These data will be an important feature of future research to assess the impact of any CHM intervention on the chronicity of endometriosis.

The herbal placebo. It is possible that the placebo decoction may have had a therapeutic effect. In the development of the protocol for the trial it was anticipated that participants would be preparing their own decoctions. Consequently, it was necessary for the placebo to reproduce the bulk and texture of real herbs. In practice, permission was given for herbs to be precooked and participants did not have any contact with the herbs in their dried form. Future trials aiming to use similar methodology could exclude the risk of therapeutic effect from the placebo by using food coloring and flavoring that have a more-guaranteed pharmacologic inertia.

Conclusions

For the first time, it was possible to conduct a double-blinded RCT using individualized decoctions of CHM. After taking into account the strengths and addressing the weaknesses of the present study, this methodology can now be adopted by other researchers seeking to combine clinical relevance with scientific rigor.

Both active and placebo interventions produced clinically important changes. However, a greater number of outcomes favored the active treatment which suggests there may be a specific effect from CHM. These are only preliminary data that should be interpreted very cautiously, but, given the limitations in the conventional treatment of endometriosis, the clinical benefits suggested by this feasibility study are sufficient to warrant a larger, more definitive trial of CHM.

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References

1. Vigano P, Parazzini F, Somigliana E, Vercellini P. Endometriosis: Epidemiology and aet iological factors. Best Pract Res Clin Obstet Gynaecol 2004;18:177–200.
2. Farquhar C. Endometriosis: Clinical review. BMJ 2007;334: 249–253.
3. Simoens S, Hummelshoj L, D'Hooghe T. Endometriosis: Cost estimates and methodological perspective. Hum Reprod Update 2007;4:395–404.
4. Sutton C, Ewen S, Whitelaw N, Haines P. Follow-up on a randomized controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal to moderate endometriosis. Fertil Steril 1997;68:1070–1074.
5. Abbott JA, Hawe J, Hunter D et al. Laparoscopic excision of endometriosis: A randomized, placebo-controlled trial. Fertil Steril 2004;82:878–884.
6. Davis L, Moore J, Kennedy S, Prentice A. Modern combined oral contraceptives for pain associated with endometriosis [Cochrane review]. In: The Cochrane Library, Issue 3:CD001019. Chichester, UK: John Wiley & Sons, Ltd., 2007.
7. Selak V, Farquhar C, Prentice A, Singla A. Danazol for pelvic pain associated with endometriosis [Cochrane review]. In: The Cochrane Library, Issue 2:CD000068. Chichester, UK: John Wiley & Sons Ltd., 2004.
8. Prentice A, Deary AJ, Goldbeck-Wood S, et al. Gonadotrophin-releasing hormone analogues for pain associated with endometriosis [Cochrane review]. In: The Cochrane Library, Issue 2:CD000346. Chichester, UK: John Wiley & Sons, Ltd., 2004.
9. Prentice A, Deary AJ, Bland E. Progestagens and antiprogestagens for pain associated with endometriosis [Cochrane review]. In: The Cochrane Library, Issue 2:CD002122. Chichester, UK: John Wiley & Sons, Ltd., 2000.
10. Bromham DR, Booker MW, Rose GL. Updating the clinical experience in endometriosis—the European perspective. Br J Obstet Gynaecol 1995;102(suppl12):12–16.
11. Sagsveen M, Farmer JE, Prentice A, Breeze A. Gonadotrophin-releasing hormone analogues for endometriosis: Bone mineral density. In: The Cochrane Library, Issue 2:CD001297. Chichester, UK: John Wiley & Sons Ltd., 2003.
12. Vercellini P, Bocciolone L, Vendola N, et al. A gonadotrophin releasing hormone agonist versus a low-dose oral contraceptive for pelvic pain associated with endometriosis. Fertil Steril 1993;60:75–79.
13. Barbieri R, Evans S, Kistner R. Danazol in the treatment of endometriosis: Analysis of 100 cases with a 4-year follow-up. Fertil Steril 1982;37:737–746.
14. Miao SS; Wilms S transl. Essential Prescriptions Worth a Thousand in Gold for Every Emergency [3 vols on gynecology; in Chinese]. Portland, OR: The Chinese Medicine Database, 2007.
15. Yang SZ. The Heart & Essence of Dan-Xi's Methods of Treatment. Boulder, CO: Blue Poppy Press, 1993.
16. Yang SZ, Liu DW. Fu Qing-Zhu's Gynecology. Boulder, CO: Blue Poppy Press, 1995.
17. Flower A, Liu JP, Chen S, et al. Chinese herbal medicine for endometriosis. Cochrane Database Syst Rev 2009; 3:CD 006568.
18. Wang G, Mao B, Xiong ZY, et a1.; CONSORT Group for Traditional Chinese Medicine. The quality of reporting of randomized controlled trials of Traditional Chinese Medicine: A survey of 13 randomly selected journals from mainland China. Clin Ther 2007;29:1456–1467.

19. Lewith G, Brien S, Barlow F, et al. The context and meaning of placebos for complementary medicine. Forsch Komplementmed 2009;16:404–412.
20. Kaptchuk T, Kelley J, Conboy L, et al. Components of placebo effect: Randomised controlled trial in patients with irritable bowel syndrome. BMJ 2008;336:999–1003.
21. Flower A, Lewith G, Little P. Seeking an oracle: Using the Delphi process to develop practice guidelines for the treatment of endometriosis with Chinese herbal medicine. J Altern Complement Med 2007;13:969–976.
22. Farrar JT, Portenoy RK, Berlin JA, et al. Defining the clinically important difference in pain outcome measures. Pain 2000;88:287–294.
23. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimally important change in a disease-specific quality of life questionnaire. J Clin Epidemiol 1994;47:81–87.
24. Jones G, Jenkinson C, Kennedy S. Evaluating the responsiveness of the endometriosis health profile questionnaire: The EHP-30. Quality Life Res 2004;13:705–713.
25. Thue G, Sandberg S. Performance of the Reflotron and the Seralyzer in primary health care. Scand J Clin Lab Investig 1993;53:253–226.
26. Nortier JL, Martinez MCM, Schmeiser HH, et al. Urothelial carcinoma associated with the use of a Chinese herb (*Aristolochia fangchi*). N Engl J Med 2000;342;1868–1692.
27. Perharic L, Shaw D, Leon C, et al. Possible association of liver damage with the use of Chinese herbal medicine for skin disease. Vet Hum Toxicol 1995;37:562–566.
28. Hummelshoj L. Endometriosis Still Takes 8 Years to Diagnose—and Treatment Options Remain Largely Ineffective. Online document at: www.endometriosis.org/press Accessed 15 September 15, 2005.
29. Fagervold B, Jenssen M, Hummelshoj L, Moen MH. Life after a diagnosis with endometriosis—a 15 years' follow up. Acta Obstet Gynecol Scand 2009;88:914–919.

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