A Randomized Controlled 24-week Trial to Evaluate the Efficacy and Safety of Bi Qi Capsule for the Treatment of Knee Osteoarthritis

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Research

Keywords: Bi Qi capsule, Knee osteoarthritis, randomized controlled trial

Posted Date: February 28th, 2020

DOI: https://doi.org/10.21203/rs.2.24688/v1

Abstract

Objective: To evaluate the efficacy and tolerability of Bi Qi capsule in knee osteoarthritis.

Patients and methods: An open-label, 24-week, parallel randomized controlled trial conducted between October 2016 to October 2018. Patients with knee osteoarthritis were randomly assigned 1:1 to receive Bi Qi capsule (1.2g, twice a day) and Calcitriol capsule (0.25ug, once a day). Western Ontario and McMaster Universities Osteoarthritis (WOMAC) was the primary outcome, including pain, stiffness, and function subscale scores. Secondary outcome measures were visual analogue scale (VAS) score for the patients assessment of pain, bone mineral density (BMD), patient's assessment of function using the Health Assessment Questionnaire (HAQ). Safety was assessed by recording adverse events (AEs).

Results: 100 patients were included in the study. 15(15%) patients discontinued the study because of lack of efficacy, adverse events and loss of follow up. At the end of the treatment ,the decrease in WOMAC total score was -8.7(4.9) and -5.4(5.6) and improvement of WOMAC function was -4.88(3.6) and -2.70(3.86) in the Bi Qi group and the controlled group, respectively (p□0.01). The improvement in BMD of left femoral neck was 0.05(0.2) and -0.01(0.04) , improvement in T score of left femoral neck was 0.15(0.5) and -0.05(0.3) in the Bi Qi group and the controlled group, respectively (p□0.01). No significant difference was observed between treatment groups for changes in WOMAC pain, WOMAC stiffness, VAS, BMD of lumbar spine, T score of lumber spine and HAQ over 24 weeks. Two adverse events were reported in Bi Qi group: facial edema (n=1), nausea (n=1) and one adverse events was reported in controlled group: lip swelling (n=1). All these adverse events were mild and could be alleviated after withdrawing treatment.

Conclusion: It can be concluded that Bi Qi capsule was found to be effective and safe in reducing WOMAC total score, improving WOMAC function and BMD in individuals suffering from KOA.

1. Introduction

Osteoarthritis (OA) refers to a syndrome of joint pain accompanied by functional limitation and reduced quality of life [1]. The pathology of OA involving the cartilage degradation, bone remodeling, osteophyte formation and synovial inflammation leading to pain, stiffness, swelling and even loss of normal joint function[2]. OA is the most common form of arthritis, affecting an estimated 302 million people worldwide, the most commonly of which is knee osteoarthritis (KOA) [3].There are currently no effective disease-modifying remedies available to treat KOA. Oral non-steroidal anti-inflammatory drugs (NSAIDs) are strongly recommended for patients with KOA but only short-term and intermittent use because potential adverse of gastrointestinal, cardiovascular system. Other oral pharmacological agents such as glucosamine, chondroitin sulfate are strongly recommended against in patients with KOA because discrepancies in efficacy [4].Thus, complementary and integrative therapies are favored in treatment of KOA. In fact, a growing number of patients with chronic musculoskeletal pain report utilizing such therapy, specifically traditional Chinese medication (TCM) [5].

Bi Qi capsule is a TCM preparation for treatment arthritis including RA and KOA. It is composed of many natural products as follows: The dried fruit of *Strychnos nux-vomica* (Ma qian zi), the dried body of *Pheretima aspergillum* (Di long), the root of *Codonopsis pilosula* (Dang shen), the sclerotia of *Poria cocos* (Fu ling), the rhizome of *Atractylodes macrocephala* (Bai zhu), the root and rhizome of *Glycyrrhiza uralensis* (Gan cao), the rhizome of *Ligusticum wallichii* (Chuan xiong), the root and rhizome of *Salvia miltiorrhiza* (Dan shen), the root and rhizoma of *Panax notoginseng* (San qi) and the root of *Achyranthes bidentata* (Niu xi)[6]. Bi Qi capsule is widely used in treating KOA in China because of its good clinical efficacy. For example, a six-week clinical study involving 221 participants compared the Bi Qi capsule to Teng Huang Jian Gu pill (another Chinese patent), it concluded that Bi Qi capsule was better in improving the Visual Analogue Scale (VAS) score and Hospital for Special Surgery Knee Score (HSS) score than the control group [7]. Another non-randomized controlled trial involving 86 participants of KOA reported the Bi Qi capsule was superior to diclofenac tablets in improving total effectiveness after 84 days (12 weeks) [8]. But it is still insufficient evidence available to demonstrate the efficacy of Bi Qi capsule of high quality with a randomized design. For this reason, we conducted a randomized controlled clinical trial primarily to evaluate the efficacy and safety of Bi Qi capsule in KOA.

2. Methods

2.1 Study design

This was a single-site, two parallel-group, randomized controlled clinical trial of 24-weeks duration to assess the efficacy and safety of Bi Qi Capsule in patients with knee osteoarthritis in the Guangdong Provincial Hospital of Chinese Medicine from October 2016 to October 2018. The severity of KOA ranged from grade 1 to grade 3 by Kellgren-Lawrence system [9]. The study was approved by the institutional ethical review board. This trial was registered with ClinicalTrails.gov (IPR16009029).

The manuscript was in accordance with the populated CONDORT checklist (see Additional file 1) and flow diagram (see Additional file 2).

2.2 Setting and participants

Inclusion Criteria All participants were recruited from Guangdong Provincial Hospital of Chinese Medicine. To be eligible for this trial, patients had to meet the following criteria (1): 18-65 years of age;(2) diagnosed with KOA according to American College of Rheumatology criteria [10] with radiographic confirmation at screening by the radiologist (Kellgren-Lawrence score ≥4).

Exclusion Criteria Patients were excluded if they (1) had evidence of specific joint safety conditions (e.g., rapidly progressive KOA, osteonecrosis, bone tumor, bone tuberculosis); (2) combined with other diseases that could affect the efficacy assessment (e.g., rheumatoid arthritis, spondyloarthritis, gout); (3) had a history of trauma or surgery on knee; and pregnancy or breastfeeding; (4) had other conditions which made them ineligible for the study treatment. All patients provided written informed consent prior to study enrollment.

2.3 Study treatment

A computer-generated randomized code was used to assign patients with KOA in a 1:1 ratio to receive oral Bi Qi Capsule (1.2g, twice a day) (group A); Calcitriol capsule (0.25ug,once a day) (group B). Celecoxib (0.2g, once or twice a day) was permitted to take orally for up to 7 days for the patients who had a VAS for pain over 4 (cm) but not within 48 hours of a study visit. Study visits were scheduled for week 4, week 12 and week 24, during which safety and efficacy assessments were performed.

2.4 Outcomes and measurements

The primary efficacy end points were the change from baseline to week 24 in Western Ontario and McMaster Universities Osteoarthritis (WOMAC), including pain, stiffness, and function subscale scores [11]. Secondary outcome measures were VAS score for the patients assessment of pain, bone mineral density (BMD),patient's assessment of function using the Health Assessment Questionnaire (HAQ).The hematology (full blood count), biochemistry indices (alanine aminotransferase, aspartate aminotransferase, creatinine, urea nitrogen), routine urine test and electrocardiogram were recorded at baseline and after 4,12,24 weeks of treatment.

2.5 Statistical analysis

A full analysis set (FAS) was used to evaluate the baseline data, and a per-protocol (PP) analysis was performed to assess the efficacy and safety of the two treatments. The ITT analysis included all participants who received treatment for at least 4 weeks. The PP analysis included the participants who finished 24 week observation without violation of treatment. Continuous data are presented as mean (SD). Categorical data are presented as numbers (n) or proportions (%). Differences between groups were analyzed for significance using a one-way analysis of variance F test or a non-parametric test (continuous data) and χ^2 test (categorical data). The WOMAC, VAS and HAQ scores were analyzed using repeated measures Analysis of Variance (ANOVA) with post hoc between multiple comparisons. All analysis was computed using SPSS statistics V.17.0.

3. Results

3.1 Trial Population

Patients were recruited from the Outpatient Department of Rheumatology in Guangdong Provincial Hospital of Chinese Medicine over a 2-year period from October 2016 to October 2018. One hundred and ten patients were examined by the rheumatologists for KOA and were assessed for eligibility to enter the study according to the inclusion and exclusion criteria. One hundred participants met the inclusion criteria, of which 50, 50 were randomized into the treatment group (group A, Bi Qi capsule 1.2g twice a day) and controlled group (Group B, Calcitriol capsule 0.25ug once a day) separately. A total of 10 patients were lost to follow-up by the end of 24-treatment (5 patients in the group A and 5 in the group B).

2 patients in group A and 1 patient in group B withdrew from the trial because of the adverse events. And 2 patients in group A dropped out because of lacking efficacy and protocol violation (Figure.1).

Figure 1 Flowchart of the participants

Baseline demographic and clinical characteristics, including gender, age, body mass index (BMI), Kellgren-Lawrence score, WOMAC, VAS for pain, BMD and Health Assessment Questionnaire (HAQ) were not significant different between group A and B (Table 1).

Table 1 Baseline patient characteristics (FAS analysis)

characteristics		Group A(n=50)	Group B(n=50)	*P* value
Gender, No (%)	Female	14(28)	10(20)	0.24
	Male	36(72)	40(80)	
Age (years)	Mean(SD)	59.8(5.8)	57.22(7.5)	0.06
	Range	42-70	39-72	
BMI(kg/m^2)	Mean(SD)	23.5(4.2)	23.6(4.1)	0.29
WOMAC	Mean(SD)	13.6(7.2)	11.4(5.5)	0.11
VAS for pain(cm)	Mean(SD)	5.1(1.7)	4.9(1.8)	0.79
HAQ	Mean(SD)	2.1(1.7)	1.9(2.0)	0.35
Lumbar spine BMD (g/cm^3)	Mean(SD)	0.9(0.2)	0.9(0.2)	0.36
Lumbar spine T score	Mean(SD)	-1.3(1.5)	-1.2(1.3)	0.32
Left femoral neck BMD (g/cm^3)	Mean(SD)	0.7(0.2)	0.7(0.1)	0.43
Left femoral neck T score	Mean(SD)	-1.4((1.1)	-1.3(1.1)	0.61
Radiographic stage	I	10	12	0.282
	II	29	30	
	III	11	8	

FAS full analysis set

3.2 Efficacy Assessment

The baseline mean WOMAC total scores were found to be comparable between the two groups ($p > 0.05$). The WOMAC total score showed a significant and progressive reduction in the group A at week 24 compared with the group B, with a reduction of 8.7 points in group A and 5.4 points in group B ($p = 0.011 < 0.05$). The change sores of WOMAC total scores from baseline to week 24 were statistically significant in groups A compared with group B ($p < 0.001$). Within the groups, a significant reduction in WOMAC total scores was observed in both groups ($p < 0.001$). The mean WOMAC pain scores and stiffness scores in both groups was comparable at the baseline visit. Although a tendency of reduction in WOMC pain and stiffness scores was observed, there was no significant differences between the group A and group B at every visit time point ($p > 0.05$). Within the groups, a significant reduction in WOMAC pain score was found from the week 4 in both groups ($p < 0.001$), a significant reduction in WOMAC stiffness score was observed from the week 4 in group A and week 12 in group B ($p < 0.05$). For the WOMAC physical function, there was a significant difference from week 4 in group A and week 12 in group B within the groups ($p < 0.001$).A significant difference was observed between the two groups at week 24 ($p < 0.001$) (Table 2,4 and Figure.2). The baseline mean BMD of lumbar spine and left femoral neck, the mean T score of lumbar spine and left femoral neck were found to be comparable between the two groups ($p > 0.05$). The BMD of left femoral neck showed a significant improvement in the group A at week 24 compared the group, with an improvement of 0.05 in group A and -0.01 in group B ($p < 0.01$). Also, there was a significant difference between the two groups for the T score of left femoral neck at the end of treatment, with an improvement of 0.15 in group A and -0.05 in group B ($p < 0.05$). There was no significant difference between group A and group B for the BMD and T score of lumbar spine ($p > 0.05$). The mean VAS and HAQ scores in both groups were comparable at the baseline visit. Although there was also a tendency of both outcome measures in the two groups, no significant difference was found between the group A and group B at each visit and no significant difference was observed for change scores of VAS and HAQ between the two groups ($p < 0.05$) (Table 3,4).

Table 2 WOMAC subscales of the two groups at each visit (PPS analysis), Mean (SD)

Measures	visit	Group A(n=40)	Group B(n=44)	*P* value
WOMAC	0w	12.7(5.9)	11.3(5.8)	0.28
	4w	9(5.1)	9.6(4.8)	0.60
	12w	5.96(3.9)	7.4(4.1)	0.10
	24w	4.0(2.9)	5.9(3.7)	0.01
WOMAC pain	0w	4.0(2.0)	3.6(1.8)	0.25
	4w	2.7(1.9)	3.0(2.0)	0.41
	12w	1.7(1.4)	2.1(1.5)	0.16
	24w	1.3(1.1)	1.6(1.2)	0.29
WOMAC stiffness	0w	1.5(0.8)	1.5(1.2)	0.77
	4w	1.2(0.9)	1.2(1.2)	0.81
	12w	0.8(0.9)	1.0(1.0)	0.33
	24w	0.6(0.7)	0.8(0.9)	0.19
WOMAC function	0w	7.2(4.4)	6.3(4.1)	0.36
	4w	5.2(3.2)	5.4(2.9)	0.81
	12w	3.5(2.4)	4.3(2.5)	0.15
	24w	2.3(1.8)	3.6(2.4)	0.01

PPS per protocol set

Table 3 VAS and HAQ subscales of the two groups at each visit (PPS analysis), Mean(SD)

Measures	visit	Group A(n=40)	Goup B(n=44)	*P* value
VAS for pain (cm)	0w	4.9(1.7)	4.9(1.8)	0.80
	4w	4.1(1.7)	4.2(1.6)	0.93
	12w	3.6(1.4)	3.5(1.5)	0.93
	24w	2.7(1.3)	2.9(1.5)	0.47
HAQ	0w	1.9(1.7)	1.8(1.9)	0.74
	4w	1.5(2.4)	1.4(1.7)	0.88
	12w	0.7(1.0)	2.1(1.5)	0.37
	24w	0.4(0.7)	0.7(1.3)	0.11
Lumbar spine BMD (g/cm^3)	0w	0.9(0.2)	0.9(0.2)	0.36
	24w	0.9(0.1)	0.9(0.2)	0.57
Lumbar spine T score	0w	-1.3(1.5)	-1.2(1.3)	0.32
	24w	-1.4(1.6)	-1.2(1.2)	0.44
Left femoral neck BMD (g/cm^3)	0w	0.7(0.2)	0.7(0.1)	0.43
	24w	0.7(0.1)	0.7(0.1)	0.78
Left femoral neck T score	0w	-1.4((1.1)	-1.3(1.1)	0.61
	24w	-1.3(1.1)	-1.4(1.1)	0.78

PPS per protocol set

Table 4 Change scores of clinical measures of the two groups from baseline to 24w (PPS analysis), Mean (SD)

Measures	group	n	Mean(SD)	*P* Value
WOMAC	Group A	40	-8.7(4.9)	0.01
	Group B	44	-5.4(5.6)	
WOMAC pain	Group A	40	-2.8(2.0)	0.09
	Group B	44	-2.0(1.7)	
WOMAC stiffness	Group A	40	-0.98(0.9)	0.11
	Group B	44	-0.66(1.3)	
WOMAC function	Group A	40	-4.88(3.6)	0.01
	Group B	44	-2.70(3.9)	
VAS for pain (cm)	group A	40	-2.3(1.4),-2	0.37
	Group B	44	-2.0(1.7),-2	
HAQ	group A	40	-1.6(1.5),-1.5	0.16
	Group B	44	-1.1(1.3),-1	
Lumbar spine BMD (g/cm^3)	group A	40	-0.02(0.07)	0.31
	Group B	44	-0.004(0.05)	
Lumbar spine T score	group A	40	-0.06(0.5)	0.60
	Group B	44	-0.07(0.3)	
Left femoral neck BMD (g/cm^3)	group A	40	0.05(0.2)	0.007
	Group B	44	-0.01(0.04)	
Left femoral neck T score	group A	40	0.15(0.5)	0.026
	Group B	44	-0.05(0.3)	

PPS per protocol set

Figure 2 Change from baseline to Week 24 in WOMAC total score, WOMAC pain, WOMAC stiffness, WOMAC function at each visit

3.3 Safety Assessment

There were no significant abnormal changes in hematology, hepatic and renal functions at the end of treatment (Table 5). Two adverse events were reported in group A: facial edema (n=1), nausea (n=1) and

one adverse events was reported in group B: lip swelling (n=1). All these adverse events were mild and could be alleviated after withdrawing treatment.

Table 5 Laboratory parameter at baseline and after 24-week treatment (FAS), Mean(SD)

Laboratory parameter	Group A (n=50) Before treatment	Group A (n=50) After 24 weeks treatment	Group B (n=50) Before treatment	Group B (n=50) After 24 weeks treatment
Total white blood cell count (10^9/L)	6.56(1.69)	6.5(1.6)	6.53(1.18)	6.21(1.60)
Red blood cell count(g/L)	131.76(14.38)	130.32(11.02)	133.5(13.63)	133.02(11.60)
Platelets(10^9/L)	255.44(51.52)	254.34(55.13)	257.58(57.48)	252.8(61.47)
Alanine transaminase(U/L)	18.40(6.66)	19.18(15.70)	19.28(9.08)	18.46(8.89)
Aspartate transaminase(U/L)	19.64(5.43)	22.84(17.53)	19.84(6.08)	19.46(5.84)
Creatinine (umol/L)	69.35(18.65)	68.16(18.78)	69.70(13.10)	70.52(15.29)
Urea nitrogen (mmol/L)	5.16(1.10)	5.80(5.05)	5.45(1.28)	5.27(1.28)
Erythrocyte sedimentation rate(mm/h)	27.76(18.05)	27.96(17.07)	24.12(16.70)	25.50(17.54)
C-reactive protein(mg/L)	3.90(2.72)	3.78(5.99)	3.19(4.98)	2.29(2.84)

FAS full analysis set

4. Discussion

KOA is a chronic and low-grade inflammation, involving mainly innate immune mechanisms. It is well know that inflammatory mediators associated with OA include cytokines, chemokine, growth factors, prostaglandins, nitric oxide, and neuropeptides [12]. Cyclooxygenase inhibitors (e.g., NSAIDS) have been the most commonly recommended medicine in the guideline of KOA but only with time limited use due to its adverse effects [2].Bi Qi capsule was widely used in the treatment of KOA for its efficacy of anti-inflammatory, detumescence, analgesia and improvement of arterial blood flow [13-15].

Previous studies had explained the mechanism of Bi Qi capsule, which could play a protective role in articular cartilage damage and promoted cartilage repair by regulating serum interleukin-1 (IL-1), matrix metalloproteinase-3 (MMP-3) and tissue inhibitor of metalloproteinase-1 (TIMP-1) levels [16]. By regulating the expression of Janus Kinase-3 (JAK-3) and signal transducer and activator of transcription-3 (STAT-3)

in the JAK-STAT singling pathway, Bi Qi capsule suppresses the expression of IL-4,interferon-γ(IFN), IL-1 and other inflammatory cytokines[17]. Joint inflammations, synovial hyperplasia and cartilage destruction can be reduced by up-regulating the express of osteoprotein (OPG), down-regulating the expression of receptor activator of nuclear factor κB ligand (RANKL) and ratio of RANKL/OPG [18].The dried fruit of *Strychnos nux-vomica* is the most important component of Bi Qi capsule. Brucine, a major alkaloid monomer from the dried fruit of *Strychnos nux-vomica*, relieves pain, reduces inflammation, regulates cytokine expression and inhibits the proliferation of synovial fibroblast [19]. It has been reported that the injection of total alkaloids of *nux vomica* cuts down the nitric oxide (NO) and improves the level of superoxide dismutase (SOD) in synovial fluid of KOA on rabbit model. Thus, the repair effect of total brucine on OA cartilage injury may reduce the generation of free radicals by inhibiting lipid peroxidation and increasing the expression of SOD to promote the scavenging of free radicals. It leads to a reduction in free radicals that inhibits chondrocyte apoptosis [20-23]. In addition, it has been demonstrated that cryptotanshinone, brucine and strychnine are the major anti-inflammatory components in the aqueous extract of Bi Qi capsule [24]. Cryptotanshinone not only inhibits the secretion of NO but also suppresses the secretion of interleukin (IL)-6 in lipopolysaccharide (LPS)-induced RAW 264.7 (leukemia cells in mouse macrophage) cells [24].Taken together, these observations strongly suggest that Bi Qi capsule improves affected joints and systemic pathological changes in KOA and inhibits joint damage in participants with KOA, which is in agreement with the result of the present study.

In this 24 weeks trial, the functional outcome at week 24 measured by WOMAC was more favorable among the patients who received Bi Qi capsule (1.2g bid) .WOMAC reduction was chosen as the primary efficacy endpoint in this study as it is widely accepted in osteoarthritis studies. In this clinical study, Group A and Group B showed changes in the WOMAC total score at week 24 compared to the baseline, and the observed changes were 8.7 and 5.4, respectively. Group A showed a statistically significantly better improvement than group B in WOMAC total score reduction. Group A also showed a significant difference with group B for the improvement of WOMAC function, BMD and T score of left femoral neck. No significant difference between group A and group B was found in improving the outcome measures as WOMAC pain, stiffness, VAS for pain, BMD of lumbar spine, T score of lumbar spine and HAQ.

The current study has some limitations. Firstly, this study was an investigator-initiated open-label clinical trial with limited patients. For a completely objective assessment, a double-blind RCT with multi-center, large sample would be necessary in the future. Secondly, our study did not compare results of the Bi Qi capsule to placebo. It will be more convincible to design a group in clinical trial for placebo. Finally, we did not test some biologic markers for explaining the mechanism of the Bi Qi capsule underlying the treatment of KOA, which may be conducted in the ongoing studies.

Conclusions

In summary, our findings provide a clinical evidence for Bi Qi capsule in treating KOA. Bi Qi capsule has better therapeutic efficacy in improving WOMAC total score, WOMAC physical function, BMD of left

femoral neck and T score of left femoral neck than Calcitriol capsule. And the incidence of adverse events was both low in the two groups. Considering both the efficacy and toxicity of Bi Qi capsule, patients taken Bi Qi capsule resulted in a better treatment effect.

Declarations

Additional files

Additional file 1:CONSORT 2010 checklist.

Additional file 2:CONSORT flow diagram.

Ethics approval and consent to participants: This trial was approved by ethical review board of Guangdong Hospital of Traditional Chinese Medicine (B2016-073-01) and was consent to participants.

Consent for publication: This trial was consent for publication.

Data Availability

These data are owned by Guangdong Provincial Hospital of Chinese Medicine. Access to these data will be considered by the author upon request. She can be reached at americaxx@gzucm.edu.cn

Conflicts of Interest None of the authors have conflicts of interest to declare.

Funding

This study was funded by the Science and Technology project of Guangzhou city(No.201710010076), the Key Research Project of Guangzhou University of Chinese Medicine(No.XK2019021),the 1010 project of Guangdong Provincial Hospital of Chinese Medicine(YN10101906),grants from Guangdong Provincial Hospital of Chinese Medicine (No.YN2018ML08).

The design of the study was funded by the Science and Technology project of Guangzhou city (No.201710010076). The collection of study was funded by the Key Research Project of Guangzhou University of Chinese Medicine (No.XK2019021) and the data analysis and interpretation was funded by the 1010 project of Guangdong Provincial Hospital of Chinese Medicine (YN10101906).

Authors' contributions Runyue Huang and Qingchun Huang both contributed to conception and design the study; Xuan xia, Huanrui Wang, Zehao Liu, Xiao cai, Xianghong Chen, Yuan Lv, Xiumin Chen contributed to acquisition of data, or analysis and interpretation of data; Xuan Xia and Runyue Huang have been involved in drafting the manuscript or revising it for important intellectual content; all authors have given approval of the version to be published.

Acknowledgements

The author appreciated the assistance of Jingyao Yan, Jiaqi Wu for their assistance in the execution of this trial and to our Student helpers: Yuting Huang.

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Figures

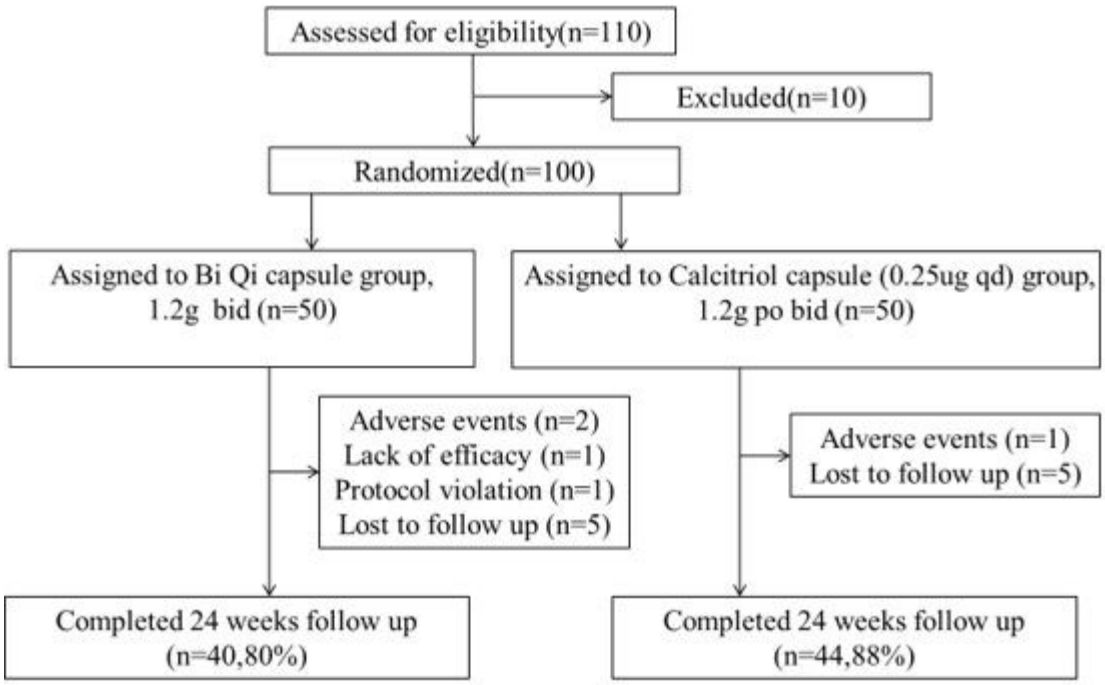

Figure 1

Flowchart of the participants

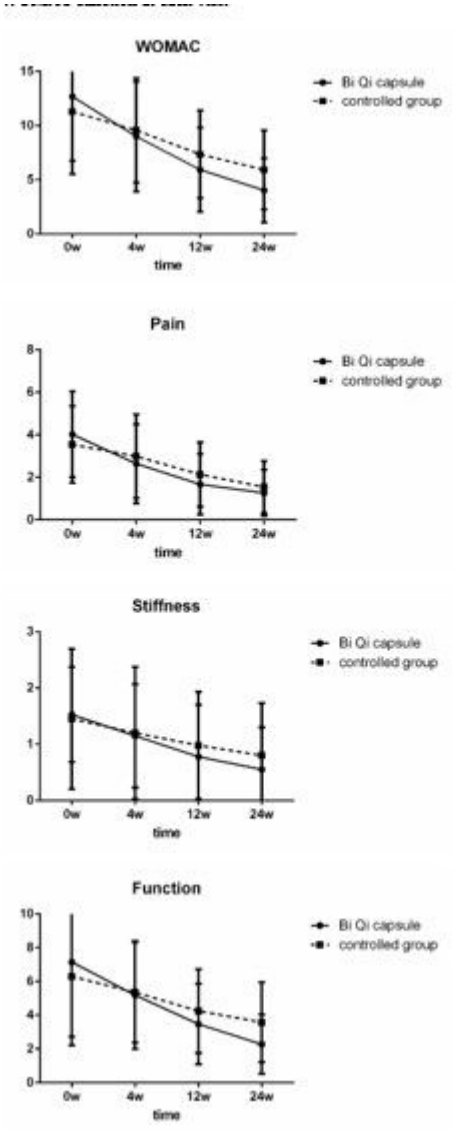

Figure 2

Change from baseline to Week 24 in WOMAC total score, WOMAC pain, WOMAC stiffness, WOMAC function at each visit

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010checklist.doc
- CONSORTflowdiagram.pdf
- ISSMCOREQChecklist.pdf