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Efficacy and safety of topical *Matricaria chamomilla* L. (chamomile) oil for knee osteoarthritis: A randomized controlled clinical trial

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ABSTRACT

Objective: To assess the efficacy and safety of topical *Matricaria chamomilla* (Chamomile) oil in patients with knee osteoarthritis.
Method: Patients were randomized and treated with topical chamomile oil, diclofenac or placebo, 3 times/day for 3 weeks. They were allowed to use acetaminophen as analgesic. The patients were asked about their total acetaminophen use. Moreover, they were assessed in the terms of pain, physical function and stiffness by using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire at the enrolling and weekly.
Results: Chamomile oil significantly reduced the patients' need for acetaminophen ($P = 0.001$) compared with diclofenac and placebo. However, there were no significant differences in WOMAC questionnaire domains. The patients did not report any adverse events by using chamomile oil.
Conclusion: Chamomile oil decreased the analgesic demand of patients with knee osteoarthritis. In addition, it may show some beneficial effects on physical function, and stiffness of the patients.

1. Introduction

Osteoarthritis (OA) also known as degenerative arthritis is a progressive joint disease which affects joint cartilage, synovium, subchondral bone and surrounding tendons and ligaments [1]. The WHO Rheumatic Disease Panel made an estimation of 10% for OA in the world's population aged 60 years and more [2].

Knee osteoarthritis is one of the leading causes of pain, physical dependency and impaired mobility in the elderly [3,4]. According to the severity of the disease, there are several therapeutic options for knee OA, from non-pharmacologic modalities to pharmacologic treatments and surgical procedures [5]. Non-pharmacologic treatments (e.g. educational programs, exercise, and physical therapy) are underestimated by many physicians and underutilized by patients [6]. In addition, surgery has remained as the last option and rejected by many patients [7]. Therefore, medications (especially analgesics) are the most prevalent prescriptions for the knee OA [8]. However, analgesic's adverse effects and patient's co-morbidities, such as ischemic heart disease and gastric upset, are considered as important limitations for this therapeutic option [9]. Thus, other safe and efficient treatments are needed.

Today, Traditional Medicine (TM) is a medical system appreciated by general population and especially by patients who suffered from chronic diseases [10]. Above the mentioned limitations for treatment lines in knee OA, along with common reasons for use of TM (e.g. easy accessibility, lower cost and its natural origination [11]) directed these patients to use TM [12]. However, the efficacy and safety of many of these modalities have not yet been elucidated clearly.

According to the most famous Traditional Persian Medicine

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(TPM) textbooks, chamomile, which is known as *Matricaria chamomilla* L. (Asteraceae or Compositae) oil can demonstrate several therapeutic effects. For example, in *The Canon of Medicine,* which was written by *Ibn-e-Sina* or Avicenna (980–1037 AD) [13], chamomile oil has been highlighted as a tonic for the nervous system [14]. Also, chamomile oil was being prescribed for different joint pains such as knee pain [15]. In addition, chamomile has been used for alleviating rheumatic and arthritis pain by different TMs [16]. Chamomile is a rich source of terpenoids and flavonoids [17] and can possess anti-inflammatory, antioxidant [18] and anti-nociceptive [19] effects.

In addition, chamomile is a safe medicinal herb, and especially there were several reports on its external use for a variety of diseases on different sites of the human body [20]. In addition, Chamomile is listed on the "FDA's generally recognized as safe" herbs [21].

Therefore, according to the aforementioned effects of the chamomile in TPM and the current literature, this study was designed to assess the efficacy and safety of topical chamomile oil in knee OA.

2. Materials and methods

2.1. Study design

The study was designed as a three-arm, blinded, randomized, placebo-controlled clinical trial using a parallel design. In addition, the design and methods have not been changed after the trial's commencement.

2.2. Ethical issues

The study protocol was in compliance with the Declaration of Helsinki (1989 revision) and approved by the Local Medical Ethics Committee of Shiraz University of Medical Sciences (SUMS) with reference number: CT-9376-7366. The trial protocol was registered in Iranian Registry of Clinical Trials database under registration ID: IRCT2015013120885N1. All of the enrolled participants returned their signed informed consent forms.

2.3. Preparation of test drug, placebo and standard drug

Dried *M. chamomilla* flowers were purchased from a local market in Shiraz, southern Iran. The plant sample was identified by a herbalist and a voucher sample (No. 790) has been kept in faculty of pharmacy of SUMS.

Chamomile oil was prepared via traditional direct heat method. At first, 600 gr. of dried flowers was boiled in 3.6 L of water till 1/4 of water remained. Then, powder was removed and the remained water (i.e. aqueous extract of chamomile) was boiled with equal amount of sesame oil. The boiling process continued until all the water was vaporized and oily part remained. The detailed instruction of oil preparation was described earlier [22]. The chamomile oil was poured in 30 ml dark bottles. We used pharmaceutical graded paraffin as placebo, and chamomile oil and placebo were placed in the same containers. Diclofenac gel 1% (BEHVAZAN) in plastic containers was supplied as the positive control medication which was prescribed for the third arm of the study.

2.4. Inclusion and exclusion criteria

Patients (from the Shahid Motahhari Outpatient Clinic, an academic center, affiliated with SUMS) of both sexes, aged between 38 and 65 years old, willing to sign the informed consent form and had no congenital disorders or abnormalities related to their lower extremities were included in the trial. The patients were eligible for inclusion if they had knee OA according to suggested criteria by American College of Rheumatology [23] and had OA grade 1 to 3 according to Kellgren-Lawrence Grading Scale [24].

The exclusion criteria were: serious comorbidities such as liver disorders and renal failure, history of peptic ulcer disease, and dermatologic disorder which affected the surrounding skin of the knees. In addition, the patients were excluded if they had previous surgery for knee replacement or intra-articular steroid injections within 3 months before inclusion in the study or intramuscular steroid injection within the previous month prior. Moreover, the patients who had positive history of hypersensitivity to diclofenac gel, chamomile derived products, were unable to complete data gathering forms (such as cognitive impairment or language problem) and pregnant women were excluded from our study. Patients with coexisting musculoskeletal diseases (including rheumatoid arthritis, septic arthritis, metabolic arthritis, gout and pseudogout, traumatic arthritis and fibromyalgia) were also excluded from the study. In addition, the patients were excluded if they had to use more than 2 g acetaminophen/day or use other analgesics, including injection drugs or other medications such as glucosamine and chondroitin sulfate, during the study period.

2.5. Intervention

The patients were instructed to use their prescribed medication (i.e. chamomile oil, paraffin and diclofenac gel) three times per day, for a period of 3 weeks. They were trained to use the medications on their knee and the surrounding tissues so that it fully covered of skin by the drugs (i.e. 1.5 cc of chamomile oil and paraffin, and a pea size diclofenac). In addition, the patients were advised not to massage the mentioned zone. Patients who affected by knee OA bilaterally, were evaluated, and more severe affected knee included in the study.

All of the participants were allowed to use acetaminophen tablet (500 mg) as the rescue drug, during the trial period. The tablets were supplied for them by the researchers.

2.6. Outcome measures

Need of the participants for supplied analgesic (i.e. acetaminophen tablet 500 mg) was chosen as one of the outcome measures. The patients were evaluated in terms of the number of consumed tablets at the end of the 3rd week.

Moreover, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire, as a self-administered and validated tool [25] was chosen as the other outcome measure. The patients were evaluated by WOMAC in terms of three domains (pain score ranged from 0 (no pain) to 4 (extreme pain); physical function score ranged from 0 (no difficulty) to 4 (the most severe difficulty); also, stiffness score ranged 0 (no stiffness) to 4 (the worst stiffness)). At the beginning of the enrollment and every week during the intervention, the data related to the WOMAC scores were obtained and recorded.

In addition, the patients were asked about any allergic or any adverse reactions at weekly visits.

2.7. Randomization, blinding and concealment of allocation

Eighty four eligible patients were randomly allocated to three parallel groups (i.e. the test drug, placebo and standard drug groups), by the secretary of the clinic, who had been trained and instructed to use a block-randomization list. The list was generated by computer as a non-stratified list, with the same block lengths.

Paraffin was chosen as a placebo which has been packed in the