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Efficacy and tolerability of an aqueous extract of roots and leaves of *Withania somnifera* in a randomized, double-blind, placebo-controlled clinical study in patients with knee joint pain and discomfort

G.S.H. Ramakanth*, C. Uday Kumar, P.V. Kishan, P. Usharani

Dept. of Clinical Pharmacology & Therapeutics, Nizam's Institute of Medical Sciences (NIMS), Hyderabad, India

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ABSTRACT

Background: Root extracts of *Withania somnifera* (Ashwagandha) are known to possess analgesic, anti-inflammatory and chondroprotective effects. An aqueous extract of roots plus leaves of this plant has shown to yield higher percentages of withanolide glycosides and, accordingly, may possess better analgesic, anti-inflammatory and chondroprotective effects than root alone extracts.
Objectives: To evaluate efficacy and tolerability of a standardized aqueous extract of roots plus leaves of *W. somnifera* in patients with knee joint pain and discomfort.
Material and methods: Sixty patients with knee joint pain and discomfort were randomized in a double-blind manner to *W. somnifera* 250 mg, *W. somnifera* 125 mg and placebo, all given twice daily. Assessment was done by Modified WOMAC, Knee Swelling Index (KSI), Visual Analogue Scale (VAS) at baseline and at the end of 4, 8, 12 weeks. Tolerability was assessed by incidence of adverse effects in treatment groups. Student's 't' test and ANOVA were used to compare mean change from baseline within and between the study groups. A $p < 0.05$ was considered significant.
Results: At the end of 12 weeks, compared to baseline and placebo, significant reductions were observed in mean mWOMAC and KSI in *W. somnifera* 250 mg ($p < 0.001$), *W. somnifera* 125 mg ($p < 0.05$) groups. VAS scores for pain, stiffness and disability were significantly reduced in *W. somnifera* 250 mg ($p < 0.001$), *W. somnifera* 125 mg ($p < 0.01$) groups. *W. somnifera* 250 mg group showed earliest efficacy (at 4 weeks). All treatments were well tolerated.
Conclusions: Both the doses of an aqueous extract of *W. somnifera* produced significant reduction in outcome variables, with the 250 mg group showing significantly better response. In addition, the therapeutic response appears to be dose-dependent and free of any significant GI disturbances.

1. Introduction

1.1. Background

Knee joint pain and discomfort are the most prevalent of the chronic rheumatic symptoms and is a leading cause of disability in most countries worldwide [1].The prevalence of joint pain and discomfort due to osteoarthritis (OA) increases with age and more so with female gender, though males are also affected. OA contributes to a higher disease burden in men below the age of 50 and in women over the age of 50 [2]. Most of the disability arising due to OA is due to involvement of hip and knee joints [3]. Knee OA is likely to become the fourth most important global cause of disability in women and eighth most important in men [4].

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs for the symptomatic treatment of pain in OA. However, NSAIDs are associated with serious gastrointestinal adverse effects which limit their use in many patients [5,6]. Other drugs like opioids and non-opioid analgesics and intra-articular steroids may not be effective in all patients [5,6].

* Corresponding author.
E-mail address: grkclinpharma@gmail.com (G.S.H. Ramakanth).
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Hence, there is a specific need for effective and safe drugs in the treatment of OA.

Herbal medicines have been explored for their usefulness in OA for a long time. *Withania somnifera* (Ashwagandha), a plant belonging to the family Solanaceae, is widely used in Ayurvedic medicine for this purpose. It is an ingredient in many formulations prescribed for a variety of musculoskeletal conditions (e.g., arthritis, rheumatism), and as a general tonic to improve overall health [7]. Roots of the plant reportedly exhibit anti-inflammatory, anti-tumour, anti-stress, antioxidant, immunomodulatory, haematopoietic and rejuvenating properties [8]. There is evidence of effectiveness of *W. somnifera* in various rheumatologic conditions due to its anti-inflammatory properties [9]. In a randomized, double-blind, placebo-controlled, cross-over study in patients with OA, treatment with roots of *W. somnifera* produced a significant drop in severity of pain and disability score. It also acts as an analgesic that soothes nervous system from pain response [10]. Chemical composition of *W. somnifera* extracts vary widely depending on which part of the plant is used as well as the extraction solvent and procedure, and thus different extracts are expected to elicit different clinical response. Sensoril® is an aqueous extract of *W. somnifera* roots plus leaves and contains withanolide glycosides, Withaferin-A and oligosaccharides as the major components. There are very few human studies evaluating the effects of *W. somnifera* root extracts, in combination with other herbal products, in patients with symptoms of knee joint pain and disability and there are no human studies reported with an aqueous extract of roots plus leaves of *W. somnifera*.

2. Objectives

To evaluate the efficacy and tolerability of a standardized aqueous extract of roots plus leaves of *W. somnifera* using Modified WOMAC index score, pain relief as assessed by Visual Analogue Scale (VAS) and changes in Knee Swelling Index (KSI) in patients with pain and discomfort of knee joint.

3. Methods

3.1. Study design

The study was a prospective, randomized, double-blind, placebo-controlled trial with 1:1:1 allocation ratio of the participants in to the 3 study groups. The study was approved by the local Institutional Ethics Committee.

3.2. Study participants

3.2.1. Eligibility criteria

The patients were screened for their eligibility to participate in the study during the screening visit (Visit 1).

a. Inclusion Criteria

Patients with knee joint pain and discomfort of either gender aged between 40 and 70 years, for at least 6 months duration and meeting the American Rheumatology Association (ARA) functional class I to III and who recorded baseline pain scores of at least 40 mm on the VAS monitored at baseline visit were enrolled. Patients who discontinued all current analgesic therapy, including NSAIDs, over the counter pain medications and topical analgesics for 7–10 days prior to the start of the study were randomized into the study.

b. Exclusion Criteria

Patients with severe OA (ARA functional class IV), on alternative system of medicine, any psychiatric disorder or who have been using systemic/intra-articular steroids within 12 weeks of study and hyaluronic acid in the last 9 months, or potential candidates for imminent joint replacement and patients with uncontrolled hypertension or diabetes, hepatic or renal impairment, pregnant or lactating females, or with a recent trauma of the involved knee were excluded from the study.

3.3. Study interventions

The study medications included capsules of *W. somnifera* in the strengths of 125 mg and 250 mg and identical placebo capsules, supplied by Natreon, Inc, New Jersey, USA.

A *W. somnifera* capsule consists of standardized aqueous extract of roots and leaves of *W. somnifera* (Sensoril®) containing not less than 10% Withanolide glycosides, not less than 32% oligosaccharides and not more than 0.5% of Withaferin- A and is standardized by HPLC (Fig. 1). The excipients used in these capsules include microcrystalline cellulose, croscarmellose sodium, silicon dioxide, magnesium stearate and gelatin from the capsule shell.

3.4. Study procedure

The study was conducted in the Department of Clinical Pharmacology and Therapeutics. The patients were randomized by the principal investigator using a computer generated simple randomization sequence with a block size of 20 patients per group. Case record numbers and sequentially numbered containers were used for random allocation sequence. The study was performed in a double-blinded manner, with both the study patients and the investigator blinded to study interventions. The participant flow chart is shown in Fig. 2.

A run-in period was allowed between screening visit (Visit 1) and randomization visit (Visit 2) to ensure that the were weaned off all medications 7–10 days prior to randomization. At the baseline/randomization visit (Visit 2, Day 0), all eligible were randomized to receive either *W. somnifera* 250 mg or *W. somnifera* 125 mg or identical placebo capsules for 4 weeks, with one capsule of the study medication to be taken twice daily after food with a glass of water. Paracetamol 650 mg tablets were used as and when required as rescue medication. The subsequent visits were scheduled at 4 weeks interval (Visit 3-after 4 weeks of treatment initiation, Visit 4 -after 8 weeks of treatment initiation and Visit 5- after 12 weeks of treatment initiation). The study and rescue medications were dispensed at visits 2, 3 and 4 and compliance to study medications was checked by pill count method during the subsequent visits. The total duration for which the patients received study medications was 12 weeks.

All the efficacy variables, pill count, use of rescue medication and Physician's Global Assessment were evaluated in the subsequent visits. Adverse reactions/serious adverse effect (ADR/SAE) monitoring was done throughout the course of study. Safety lab were done before and after treatment and as and when required.

3.5. Outcomes

The primary outcome measure was percentage change in the Modified Western Ontario and McMaster University Osteoarthritis Index (mWOMAC, Ref. www.copcord.org/images/WOMAC.pdf) score at the end of 12 weeks from baseline.

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