



Communication

Treatment of Chronic Pain in Patients with Osteoarthritis of the Hip and Knee with a Combination of Hydroxytyrosol, Omega 3 Fatty Acids and Curcumin: Results of a Pilot Study

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Abstract: Chronic pain is the most common symptom of osteoarthritis and is very often accompanied by limitations in the performance of activities of daily living and has a negative impact on patients' quality of life. It is estimated that 14% of the elderly population routinely use NSAIDs for pain management, not without serious adverse effects. **Objective:** We aimed to test the efficacy and possible side effects of OliminaDol (encapsulated combination of purified hydroxytyrosol, omega-3 fatty acids and curcumin) in the treatment of chronic osteoarthritis pain. Seventy-four patients with a diagnosis of osteoarthritis who had chronic pain were selected. The therapeutic intervention consisted of self-administering one capsule of the supplement every 12 h for 30 days. A visual analogue scale (VAS) was used for pain assessment. The efficacy was assessed by comparing the means of pain intensity at baseline and at the end of treatment. The data on the National Cancer Institute (NCI-CTCAE) version 4 criteria were also analyzed. **Results:** Thirty-six patients were evaluable for the primary objective. The mean value + standard deviation of pain intensity measured by the VAS scale at day +1 was 5.78 + 0.15 and the mean value of pain 30 days after initiation of treatment was 4.19 + 0.22. There was a decrease in pain intensity of 1.63 + 2.28 with $p = 0.000$. A total of 27 patients (75%) had pain reduction and in 19 of them (52.7%), the difference was greater than 2 points on the VAS scale. OliminaDOL administration was associated with very few and insignificant side effects, notably constipation in two patients (5.4%) and a fishy taste in three patients (8.1%). **Conclusions:** The administration of OliminaDOL produced a significant decrease in the mean value of pain intensity without side effects. These results, together with other published studies, demonstrate the possibility that some supplements, or a combination of them as in our case, can be an alternative for the treatment of chronic pain.



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1. Introduction

Chronic pain is prevalent in all parts of the world and accounts for 20% of primary care visits, 12% of all prescriptions and more than USD 100 million in direct and indirect costs [1]. Moreover, pain-related costs exceed those of other conditions such as cancer, cardiovascular disease and diabetes [2].

Although pain is one of the most common symptoms, it cannot always be labeled as chronic pain [3,4]. It is the most common symptom of osteoarthritis and is very often accompanied by limitations in the performance of activities of daily living and has a negative impact on patients' quality of life [5,6]. It has been estimated that approximately

27 million adults suffer from osteoarthritis in the United States, 8.5 million in the United Kingdom and 7 million in Spain [7–10].

In 1971 Vane J et al. [11,12] suggested that blockade of cyclooxygenase could inhibit the conversion of arachidonic acid to proinflammatory prostaglandins that mediate the inflammatory response to pain and inflammation. Since then, non-steroidal anti-inflammatory drugs (NSAIDs) have become the drugs of choice for the treatment of pain with an inflammatory component. It is estimated that 14% of the elderly population routinely use NSAIDs for pain management [13], not without serious adverse effects, including digestive manifestations such as bleeding and gastric ulceration. In 3% of patients, this is a serious complication that results in more than 100,000 hospitalizations and about 16,500 deaths per year, exceeding the estimated cost of treating these complications by more than USD 1.5 billion annually [14]. NSAIDs are a major cause of morbidity and mortality, as noted by several regulatory agencies [15]. For this reason, there is a need to identify new treatments for chronic osteoarthritis pain that are safe and inexpensive. Recently, non-pharmacological anti-inflammatory agents have begun to be used as an alternative to NSAIDs.

The hypothesis of our work is that the encapsulated combination of purified hydroxytyrosol, omega-3 fatty acids and curcumin, called OliminaDol, is effective in the treatment of chronic osteoarthritic pain, and to this end, we present this prospective single-arm study. Purified hydroxytyrosol extracted from olive fruit [16–18], which has demonstrated several important antioxidant and anti-inflammatory effects [19,20], is capable of reducing various pro-inflammatory cytokines such as tumor necrosis factor (TNF-alpha), as well as interleukin 1 (IL-1) and interleukin 6 (IL-6) produced by leukotrienes [21–24]. Moreover, it has an antinociceptive and analgesic effect by inhibiting cyclooxygenase-2 (COX-2) activity and neuromodulating gamma-aminobutyric acid (GABA) receptors, as well as opioid receptors [25–28]. Omega-3 fatty acids, found in the oil of certain fish, have been shown to be useful in reducing inflammation and the microenvironment that promotes cartilage degradation [29–33]. Omega-3 acids (EPA and DHA) can compete with pro-inflammatory interleukins (IL-1, IL-6, IL-12) and TNF-alpha. The role of omega-3 fatty acids in gut microbiota homeostasis suggests that an adequate intake with an appropriate ratio of EPA and DHA is of vital importance to regulate the anti-inflammatory and antinociceptive component to control chronic pain [34–38]. Finally, curcumin, a bioactive component of turmeric roots, is composed of polyphenols called curcuminoids, which have antioxidant effects and have been found to be effective in the treatment of chronic pain [39–43]. They have recently been used in the treatment of musculoskeletal pain, especially the pain associated with osteoarthritis [44,45], with a meta-analysis also showing a favorable effect [46].

Martinez N et al. have previously reported that the combination of purified hydroxytyrosol with omega-3 fatty acids and curcumin produces a decrease in inflammatory markers in breast cancer patients and improves chronic pain induced by aromatase inhibitors [47].

2. Materials and Methods

Design: This was a prospective, open-label, single-arm, cohort, pilot clinical study to test the efficacy of OliminaDol in the treatment of chronic osteoarthritis pain. The study followed the STROBE checklist. The protocol and informed consent were approved by the Ethics Committee of the Hospital Virgen de la Luz (Cuenca) (Approval code: 2019/E0219) and the guidelines of good clinical practice and the Declaration of Helsinki were followed.

Selection of participants: Individuals over 18 years of age with a diagnosis of osteoarthritis who had chronic pain (with “maximum pain” in the previous 24 h) greater than 4 on the visual analogue scale (VAS) of pain, and who agreed to participate in a study of self-administration of oral dietary supplements for a period of 30 days were included. A visual analogue scale (VAS) consisting of a 10 cm line with marks from 0 (no pain) to 10 (maximum pain imaginable or unbearable pain) was used for pain assessment, where the patient marks the place they consider the most appropriate for the degree of pain presented [48–52]. Inclusion criteria were as follows: patients with “maximum pain” in the

last 24 h that was greater than or equal to 3 on the visual analogue pain scale (VAS), with a diagnosis of hip and knee osteoarthritis, age above 18 years and signed consent to receive the study treatment, able to self-administer food supplements orally without supervision for a prolonged period of time. Exclusion criteria were pregnancy or lactation, as well as any condition requiring the use of systemic corticosteroids or other immunosuppressive agents, patients with a known immunodeficiency such as HIV or severe uncontrolled infection, and routine use of step 3 or higher analgesics.

Treatment and performance of the study: The therapeutic intervention consisted of administering one capsule of the supplement every 12 h for 30 days. Each capsule of OliminaDOL contains 460 mg of eicosapentaenoic acid (EPA) and decosahexanoic acid (DHA) oil, 125 mg Hytolive powder (12.5 mg hydroxytyrosol) and 50 mg curcumin extract (47.5 mg curcuminoids). Thirteen patients also took NSAIDs during the trial. To assess the impact of OliminaDOL on pain, the patients completed the VAS pain scale together with the doctor at the first visit. Due to the effects of the pandemic since March 2020 and the difficulty of patients to go to the Health Centre, the second pain assessment was carried out by telephone 30 days after starting treatment, and adverse effects related to the administration of OliminaDOL were also noted [52].

Objectives and statistical analysis: The primary objective was assessed by comparing the means of pain intensity at baseline and at the end of treatment. The statistical test used was Student's *t*-test for paired samples. A *p*-value < 0.05 was considered statistically significant. Data on possible side effects, assessed according to the National Cancer Institute (NCI-CTCAE) version 4 criteria, were also analyzed.

3. Results

Between October 2021 and March 2022, 74 patients seen in two Primary Care Health Centers in Cuenca were included in the study. The selected patients had chronic pain with an intensity of more than 4 on the VAS scale.

Of the 74 patients, 36 had pain resulting from osteoarthritis and met all the inclusion criteria and were the reason for the present study. The clinical characteristics of the patients and their associated comorbidities are shown in Table 1. The sample population had a mean age of 74 years (range 42–89), and consisted of 26 females (72.2%) and 10 males (27.8%). The most frequently associated comorbidities were hypertension (18 patients), diabetes (9 patients), dyslipidemia (15 patients) and obesity (9 patients). Osteoarthritis was located in the knee in 20 cases, in the hip in 12 cases and in both joints in 5.

Table 1. Age and gender are expressed as the mean (range) and comorbidities are expressed as an absolute value and (relative) value.

Patient Characteristics (<i>n</i> = 36)	
Age	73.44 (42–89)
Gender:	
Male	26 (72.22)
Female	10 (27.78)
Comorbidities:	
Hypertension	18 (50%)
Obesity	9 (25%)
Diabetes	9 (25%)
Dyslipidemia	15 (41.67%)

All 36 patients were evaluable for the primary objective. The mean value + standard deviation of pain intensity measured by the VAS scale at day +1 was 5.78 + 0.15 and the mean value of pain 30 days after initiation of treatment was 4.19 + 0.22. There was a decrease in pain intensity of 1.63 + 2.28 with a *p* (Cohen D test) of 1.4664. A total of 27 patients (75%) had pain reduction and in 19 of them (52.7%), the difference was greater than 2 points on the VAS scale. The reported adverse effects are shown in Table 1. OliminaDOL administration

was associated with very few and insignificant side effects, notably constipation in two patients (5.4%) and a fishy taste in three patients (8.1%).

4. Discussion

Osteoarthritis is the most common musculoskeletal disease and mainly affects the joints of the hands, spine, hips and knees, as seen in our series [53–55]. It is not currently regarded as a passive degenerative disorder, but as an active process in which there is an imbalance between the destruction and repair of joint tissues. The onset of symptoms is usually insidious and intermittent, gradually increasing over time until it becomes persistent. The most commonly associated risk factors are older age, female sex and obesity.

The basic treatment of osteoarthritis includes moderate exercise, weight loss and the use of pain control drugs such as analgesics (paracetamol, codeine) and NSAIDs [13,14]. However, the presence of previous comorbidities and the potential occurrence of serious adverse effects do not allow for continued use in many cases.

There is increasing evidence that dietary habits have a positive influence on health and quality of life, and that non-pharmacological anti-inflammatory agents (dietary supplements) prescribed by physicians can be very useful without adverse effects [56].

These dietary supplements act by interfering with the complex pathophysiological pathways of chronic osteoarthritis pain, either in the transduction of the mechanical stimulus into pain or in the conduction of this stimulus through spinal pathways or in cortical modulation that may be modified by psychological or genetic factors [22,24]. Among the dietary supplements that have proven useful in rheumatic diseases (osteoarthritis and rheumatoid arthritis) for their anti-inflammatory and analgesic benefits are hydroxytyrosol, omega-3 acids and curcumin, of which there is already favorable evidence for the treatment of musculoskeletal pain induced by aromatase inhibitors in breast cancer patients [47].

Of particular relevance when using the same supplements and at the same dose is the work of Martínez N et al. in patients with breast cancer, who had chronic musculoskeletal pain of inflammatory origin due to the use of aromatase inhibitors [47]. In this study, there was a decrease in the BPI (Brief Pain Inventory) worst possible pain score of 1.6 ($p = 0.011$), corresponding to a 21.5% decrease, after 30 days of treatment. The mean baseline value of pain severity, as measured by the BPI score, had a decrease of 1.2 points ($p = 0.08$) after 30 days of treatment.

In our study of 36 patients with osteoarthritis, we observed that the administration of OliminaDOL produced a significant decrease in the mean value of pain intensity, as measured using the VAS scale, from 5.78 ± 0.15 to 4.19 ± 0.22 ($p = 0.00$). Although this is a pilot study, we consider our results satisfactory because the magnitude of the decrease 1.59 ± 1.48 was significant and because a decrease of at least 2 points on the VAS scale occurred in 19 patients (52.7%).

These results, together with other published results, demonstrate the possibility that some supplements, or a combination of them as in our case, can be an alternative for the treatment of chronic pain. These include the work of MacFarlane L et al. [57] in a randomized study using vitamin D and omega-3 acids; Maroon JC et al. [58], who treated patients with chronic back pain with omega-3 acid as an alternative to NSAIDs; Tshongo C et al. [59], who treated patients with rice yeast as an alternative to NSAIDs; Tshongo C et al. [60], who treated patients with statin-induced myalgia with red rice yeast and olive extract; Dima R et al. [60] who reviewed low level laser therapies for pain control in osteoarthritis; and Flynn D et al. [61] who considered non-pharmacological treatments for musculoskeletal pain.

Natural dietary supplements do not usually have side effects, especially at the doses used. In our study, we only found constipation in two patients (5.4%) and changes in taste with a fishy flavor in three patients; this absence of serious side effects corroborates the data found by Martínez N et al. [47].

Among the limitations of this study is the absence of a comparator group, although for studies in which the primary objective is pain intensity, the patient himself can be

the control in the baseline situation, as was used in other trials [52]. In addition, the SARS-CoV-2 pandemic had limited patient visits to their Primary Care Health Centre and in this sense, a number of patients smaller than initially planned was eventually chosen (although enough to give proper statistical power) to protect vulnerable patients (due to age, obesity, multiple pathologies).

The last limitation is related to the characteristics of osteoarthritis patients in primary care, which did not allow us to carry out a washout period of previous medication in all patients (13 patients were receiving some analgesic during the study period); in these patients, it was difficult to withdraw the analgesic medication they had been receiving for long periods of time, even if the response has not been totally satisfactory. Thus, we believe that a treatment such as OliminaDol, which helps to reduce the intensity of pain, could help to suspend or de-escalate the previous pharmacological treatment and thus avoid its adverse effects.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki. The study was carried out during the SARS-CoV2 pandemic, for this reason the recruitment and obtaining of the informed consent was carried out through telephone interviews.

Informed Consent Statement: Patient consent was waived due to the study being carried out during the SARS-CoV2 pandemic; for this reason, the recruitment and obtaining of the patient consent was carried out through telephone interviews. The study has the approval of the research ethics committee as shown in the attached document.

Data Availability Statement: The data are accessible to any interested researcher by contacting the corresponding author, Lopez Robledillo.

Conflicts of Interest: The authors declare no conflict of interest.

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