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Randomized, Double-Blind, Double-Masked, Parallel Group Clinical Study to Compare the Effectiveness of Diclofenac Potassium 150 mg, LP OD, vs Diclofenac Potassium 50 mg, TID, Three Times a Day, in Knee Osteoarthritis

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Abstract

Background: Osteoarthritis is a chronic disease associated with pain, inflammation, stiffness and synovial effusion, with progressive functional limitation, compromising quality of life. It progressively leads to loss or decrease in joint function. Pharmacological and non-pharmacological therapy seeks symptomatic management, complicated by a lack of adherence. After acetaminophen, non-steroidal anti-inflammatory drugs such as diclofenac are the most widely used medications. **Objectives:** The primary objective compared the analgesic effect of diclofenac 150 mg once daily vs. 50 mg three times daily in patients with knee osteoarthritis. The secondary objective assessed changes in quality of life. **Method:** One group received diclofenac 150 mg OD with placebo TTD. Another group received placebo OD and 50 mg active diclofenac (reference) TTD, both for 30 days. The evaluation of pain was carried out by a visual analog scale (VAS), at the beginning, 2, 3, 4, 15 and 30 days, quality of life (the WOMAC scale) and adverse effects, at 15 and 30 days. **Results:** Pain decreased significantly on days 15 and 30, compared to day 0, in both groups, without differences between groups. The total results in the WOMAC scale showed a very marked improvement at 15 and 30 days, without differences between groups. The most frequent adverse effects were constipation 6% in the reference group, and gastric discomfort 30.3% in the reference group vs 28.1%, in the Test group. **Conclusions:** Prolonged-release

diclofenac 150 mg OD is as effective as diclofenac 50 mg TID for the treatment of patients with knee osteoarthritis.

Keywords

Knee Osteoarthritis, Diclofenac, Visual Analog Scale, WOMAC Scale

1. Introduction

Osteoarthritis is a chronic disease where cartilage damage and inflammation of the synovial membrane combine with sudden crises of pain, inflammation, stiffness and synovial effusion. It is the most common of joint diseases, which progressively leads to a loss or decrease in joint function. This entity can affect 85% of the 70-year-old population and 20% of the general population [1].

In this pathology, pain and inflammation converge as main symptoms; its therapy is focused on pharmacological and non-pharmacological treatments, aimed at symptomatic management [1].

The aging of the population, and obesity, are the greatest risk factors for osteoarthritis, which gradually increases after the age of 30, and can reach up to 80% around the age of 65 and even 95% at older ages [2].

It occurs primarily in weight-bearing joints, such as the hip and knee, because they are sites exposed to joint overload, trauma, biomechanical alterations, or infection, not to mention the important role of heredity [3].

It presents with pain and progressive functional limitation; it constitutes, in addition to a usual reason for medical consultation with the consequent high costs for its care and treatment, a frequent cause of deterioration in the quality of life (QoL) [4].

There are studies that show that, in people with symptomatic osteoarthritis, up to 50% of them suffer some degree of disability [5].

After acetaminophen, nonsteroidal anti-inflammatory analgesics (NSAIDs) are the most frequently used medications in patients with osteoarthritis [6].

In order to assess the safety and efficacy of diclofenac, a Network Meta-Analysis (NMA) was performed in patients with osteoarthritis [7], in which randomized controlled trials (RCTs) of diclofenac, lasting at least 4 weeks for the treatment of osteoarthritis (OA), were identified from 'legacy' studies conducted by Novartis, but not published in a peer-reviewed journal or included in any previous conjoint analysis. Nineteen RCTs (5030 patients) were included, 18 of which were double-blind and one single blind. All studies were conducted before cyclooxygenase 2 (COX-2) inhibitors were marketed. The data allowed a robust comparison of efficacy between diclofenac and ibuprofen. Diclofenac 150 mg/day was more effective than ibuprofen 1200 mg/day and probably had favorable results for pain relief compared to ibuprofen 2400 mg/day [7].

Diclofenac has a systemic absorption directly proportional to the dose within the range of 25 to 150 mg. Multiple-dose administration produces absorption

characteristics that are similar to those observed after a single administration [8] [9] [10] [11] [12]. The absolute bioavailability of 90 ± 11.6% after oral administration of a single 50-mg dose of $^{[14C]}$Diclofenac suggests that diclofenac undergoes first-pass metabolism with approximately 60% of the ingested dose reaching the systemic circulation [10] [11] [12].

The control of many chronic diseases, such as osteoarthritis, in which it is necessary to make changes in lifestyle, diet, or permanent pharmacological treatment, is sometimes difficult to achieve [13].

Among the causes identified that can influence the lack of adherence, it is worth mentioning the complexity of the treatment (several doses per day, difficult schedules to comply with), and the fear of side effects [14].

The advancement of new galenic formulation techniques has allowed the development of pharmaceutical products, which, while maintaining a known range of effectiveness, offer advantages in relation to conventional forms, such as less frequent administration, as occurs in extended-release forms.

In Venezuela, LETI Group, through its company Biocontrolled, has developed a new formulation of 150 mg of potassium diclofenac, which releases 50 mg in the first hour and 100 mg delayed (dual action), with the intention of accelerating the onset of pain relief (**Figure 1**).

Taking this into consideration, this study is carried out in order to compare the efficacy of diclofenac potassium LP 150 mg, administered once a day, versus diclofenac potassium 50 mg immediate-release tablets, TID, to evaluate its efficacy in pain and quality of life in patients with knee osteoarthritis.

2. Materials and Methods

A randomized, double-blind, double-dummy, parallel group study was carried out.

The patients signed the informed consent to participate in it, and the protocol was approved by an Institutional Ethics Committee and by the country's Health Authorities.

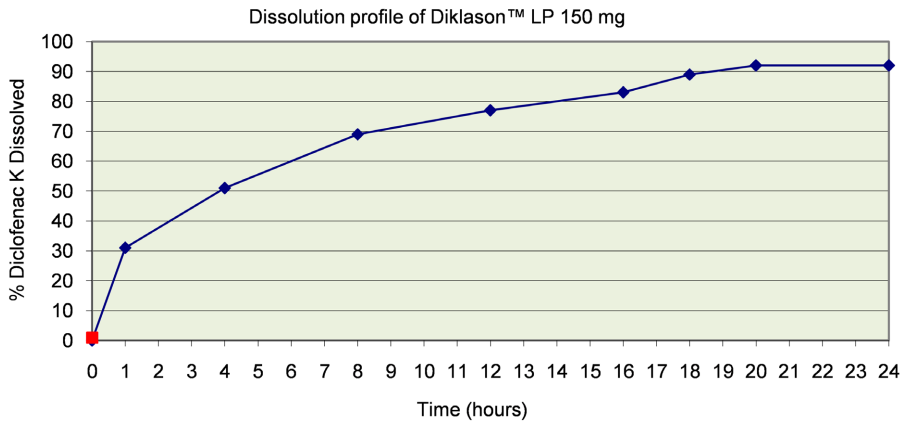

Figure 1. Dissolution profile of prolonged release diclofenac.

2.1. Inclusion Criteria

1) Patients of both sexes diagnosed with osteoarthritis of the knee were admitted according to the criteria of the American Society of Rheumatology [15].

2) Knee pain and three or more of the following findings:

a) More than 50 years;

b) Morning stiffness less than 30 minutes;

c) Crepitation, bone pressure pain, bone hypertrophy, lack of joint heat.

3) Class I to class III radiological lesion (Radiological Classification of Osteoarthritis, Kellgren and Lawrence) [16].

2.2. Exclusion Criteria

a) Patients with kidney disorders, liver function disorders or coagulation disorders;

b) Uncontrolled arterial hypertension, poorly controlled diabetes, patients with MI or cerebral stroke, 6 months prior to the start of the investigation;

c) Knee replacement or other intra-articular surgery, arthrocentesis within three months prior to trial;

d) Diagnosis of fibromyalgia, rheumatoid arthritis, ankylosing spondylitis, active gout, or other inflammatory joint disorders other than osteoarthritis;

e) Patients with active gastrointestinal disease: peptic ulcer disease, inflammatory bowel disease (Crohn's disease or ulcerative colitis) or any other disease that, in the investigator's opinion, discourages the use of NSAIDs;

f) Patients with a history of malignant disease;

g) Patients who had received, in the 8 weeks prior to the study, treatment with I. M. or intra-articular steroids, or those who have received intra-articular Hyaluronic Acid;

h) Patients who have received analgesic therapy 24 hours prior to study entry, for short-acting analgesics, and 7 days prior for long-acting analgesics;

i) Patients with hypersensitivity or allergy to NSAIDs;

j) Proven pregnancy, or lactating women.

2.3. Evaluations

The primary endpoint was pain at baseline (baseline), 2, 3, 4, 5 days, and 30 days. The secondary objectives were to evaluate the quality of life through the WOMAC scale at 0, 15 and 30 days.

The evaluation of pain intensity (Pain Intensity/PI) was performed using the Visual Analog Pain Scale (VAS: 0 - 10), in the two study groups (Group A or B), where 0 is the total absence of pain and 10 is the maximum possible pain. It was measured immediately before the administration of study drugs (time 0, baseline) and at 15 and 30 days. The evaluation of quality of life was evaluated using the WOMAC questionnaire, in the same periods of time [17] [18].

Patients received one of two blinded clinical supply boxes (treatments) during the study: a) a group with diclofenac potassium 150 mg PL OD (active) and dic-

lofenac potassium 50 mg TID (placebo); b) diclofenac potassium 50 mg TID (active) and diclofenac potassium 150 mg LP (placebo).

2.4. Statistic Method

The sample size calculation was performed, establishing that to detect a difference of 1.2 on the VAS scale with an accuracy of 99%, a minimum of 30 patients per group was needed.

The VAS scale and the WOMAC scale were analyzed within the group (before and after) using the Wilcoxon Rank scale and between groups using the McWhitney Rank scale.

3. Results

The groups were similar at the beginning of treatment in age, weight, height, BMI, duration of osteoarthritis and there were fewer severe cases of left knee osteoarthritis in the test group. (Table 1, Table 2)

There was a significant decrease in pain measured by VAS 0 - 10 in both groups, with no difference between them at any time of evaluation during the treatment period. (Table 3, Figure 2)

Table 1. Description of the evaluated population.

Parameter	Reference (n = 33)	Test (n = 32)	P between groups
Sex f/m	28/5	22/10	0.00
Menopausal women	76%	60%	0.00
Age	61.5 ± 7.1	58.4 ± 7.3	0.09
Duration of osteoarthritis (years)	8.7 ± 10.4	7.3 ± 7.5	0.54
Weight	76.5 ± 14.8	78.8 ± 12.6	0.65
Height	1.6 ± 0.1	1.6 ± 0.1	0.46
IMC	30.2 ± 6.4	32.9 ± 16.5	0.39
SBP	127.6 ± 7.5	127.9 ± 7.8	0.86
DBP	79.5 ± 5.1	82.4 ± 8.8	0.11
Background	Arterial Hypertension 79% Diabetes 9% Cervical osteoarthritis 3% GI Reflux 3%	Arterial Hypertension 75 %	

Table 2. Affected knee.

	Left			Right		
Radiological class	I	II	III	I	II	III
Reference	29.2%	50.0%	20.8%	23.3%	63.3%	13.3%
Test	44.0%	52%	4.0%	40.91%	54.5%	4.6%
P				0.00	0.84	0.86

Table 3. Evolution of pain.

VAS 0-10						
VAS	**Base**	**Day 2**	**Day 3**	**Day 4**	**Day 15**	**Day 30**
Reference	6.17 ± 2.48	4.05 ± 2.41	3.00 ± 1.97	2.70 ± 2.04	2.55 ± 2.28	1.92 ± 2.72
P from base		0.00	0.00	0.00	0.00	0.00
Test	5.95 ± 2.08	4.10 ± 2.15	2.95 ± 1.68	2.50 ± 1.82	2.29 ± 1.97	1.55 ± 1.99
P from base		0.00	0.00	0.00	0.00	0.00
P between groups	0.709	0.754	0.861	0.805	0.854	0.954

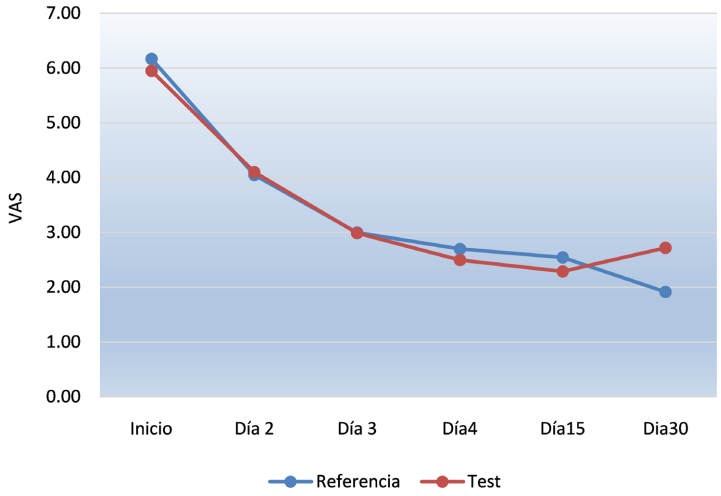

Figure 2. Evolution of the VAS.

No difference was observed in the parameters of the WOMAC scale at any time, except for functional disability, which was statistically lower in the test at the beginning and at the end of treatment. (**Table 4** and **Figure 3**)

There was a decrease in pain at 15 and 30 days of the treatment period without differences between the groups. (**Figure 4**)

There was a statistically significant and clinically important decrease in both groups in WOMAC Global Changes throughout the evaluation period. (**Figure 5**)

The most frequent adverse effects were gastric discomfort 30.3% vs 28.1%, reference vs Test (chi^2 0.53), constipation 6% in the reference group.

The efficacy data on pain, evaluated by VAS, were as follows, for the reference product: baseline: 6.17 ± 2.48, day 3: 2.70 ± 2.04, day 15: 2.55 ± 2.28, day 30: 1.92 ± 2.72. For the study drug, diclofenac LP, the values were as follows: basal pain: 5.95 ± 2.08, at day 3: 2.50 ± 1.82, at day 15: 2.29 ± 1.97 and at day 30: 1.55 ± 1.99. In both groups, there was evidence of a significant analgesic effect of the drug, reaching a decrease in the pain scale of 50% on day three of the study (**Figure 2**).

Changes in disability, using the WOMAC scale, could not be compared due to a statistically significant difference at baseline between the two groups. However, when the total results are observed on the WOMAC scale, a very marked improvement can be seen at 15 and 30 days, with no difference between groups.

Table 4. Evolution of the WOMAC results.

WOMAC	Reference	Test	P Intra group -anterior period Ref.	P Intra group -compared to base Ref.	P Intra group -anterior period Test	P Intra group -compared to base Test	P Between Groups
Initial disability	30.18 ± 12.41	25.32 ± 11.19					0.054
Disability 15 days	13.24 ± 11.69	9.90 ± 9.19	0.000	0.000	0.00	0.00	0.200
Disability 30 days	11.33 ± 11.56	5.63 ± 7.47	0.053	0.000	0.00	0.00	0.024
Initial pain	9.09 ± 4.27	7.81 ± 3.89					0.168
Pain 15 days	3.30 ± 2.94	2.58 ± 2.74	0.000	0.000	0.00	0.00	0.228
Pain 30 days	3.07 ± 3.38	2.36 ± 3.26	0.583	0.000	0.65	0.00	0.258
Initial rigidity	3.64 ± 1.83	3.48 ± 1.61					0.500
Rigidity 15 days	1.27 ± 1.31	1.42 ± 1.65	0.000	0.000	0.00	0.00	0.966
Rigidity 30 days	1.14 ± 1.68	1.08 ± 1.26	0.429	0.000	0.084	0.00	0.887
Initial total score	42.91 ± 17.09	36.61 ± 15.81					0.067
Total score 15 days	17.82 ± 15.30	13.90 ± 12.58	0.000	0.000	0.00	0.00	0.141
Total score 30 days	14.00 ± 15.95	7.94 ± 9.80	0.017	0.000	0.01	0.00	0.097

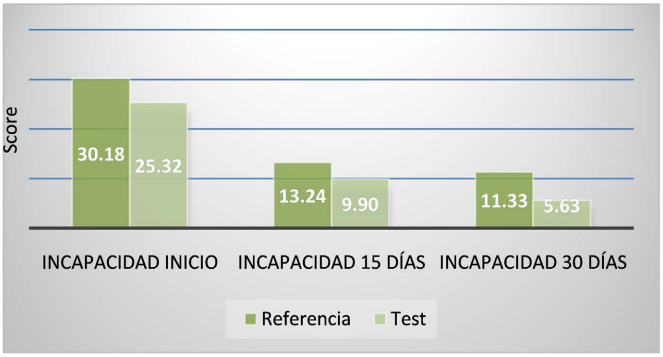

Figure 3. Evolution of WOMAC results: functional disability.

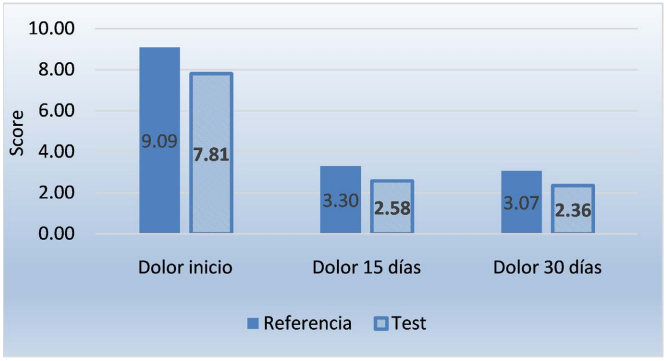

Figure 4. Evolution of WOMAC pain results.

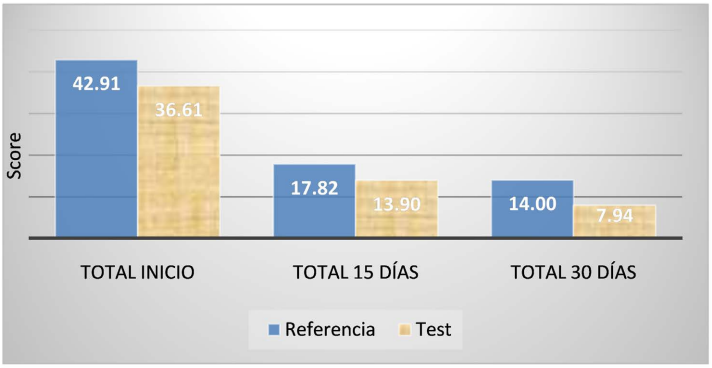

Figure 5. Evolution of the results of the total WOMAC score.

4. Discussion

Osteoarthritis is a chronic disease where cartilage damage and inflammation of the synovial membrane combine with sudden crises of pain, inflammation, stiffness and synovial effusion. This entity can affect 85% of the 70-year-old population and 20% of the general population. [1] It is a pathology which requires chronic treatment, which makes compliance difficult, especially in elderly and polymedicated patients.

The pain and progressive functional limitation constitute a usual reason for medical consultation and frequently causes deterioration in quality of life (QoL) [4]. Its therapy is focused on pharmacological (acetaminophen and NSAIDs) and non-pharmacological treatments, aimed at symptomatic management [1].

The pharmacological treatment of pain in osteoarthritis constitutes a very important challenge for the physician with a great impact on motor function and the consequent disability and deterioration of quality of life. [19] [20].

The control of many chronic diseases, such as osteoarthritis, in which it is necessary to make changes in lifestyle, diet, or permanent pharmacological treatment, is sometimes difficult to achieve. On the other hand, the specific adherence to the pharmacological treatment in this type of diseases is frequently not adequate. In a study published in 2019, carried out in Spain, they evaluated adherence in chronic diseases and the results showed that, in Spanish chronic patients, where approximately three out of four have more than one disease and receive chronic treatments, close to half have poor adherence to treatment. [13]

Reducing the number of daily doses can increase compliance with treatment and improvement of symptoms. A multicenter, randomized, open-label, two-way crossover, phase IV study is the first to evaluate patient preference with a sustained-release paracetamol tablet formulation designed for TID dosing. Compared with standard paracetamol tablets dosed four times daily, the sustained-release formulation was preferred in a 2:1 ratio, provided better overall joint pain relief, resulted in higher levels of satisfaction in subjects with OA of the knee and has the potential to improve patient compliance and, therefore, pain control. [21]

This study allows us to see how the administration of prolonged-release dic-

lofenac potassium at 150 mg, taken once a day, has the same analgesic efficacy in patients with knee osteoarthritis as a dose of diclofenac 50 mg three times a day. Based on this evidence, once a day is much more comfortable for the patient, allowing better adherence to treatment.

Regarding safety, in general, both treatments were well tolerated. The most frequent adverse effects were gastric discomfort 30.3% vs 28.1%, reference vs Test, respectively (chi^2 0.53) and constipation 6% in the reference group.

5. Conclusion

Extended-release diclofenac 150 mg is an effective therapy for the treatment of patients with knee osteoarthritis. Its characteristics and its bioavailability allow a single administration per day vs. the conventional formulation three times a day, with similar analgesic efficacy, which will facilitate better adherence to treatment and will allow better clinical outcomes.

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Conflicts of Interest

Dr. R. Tellez Mendez, Dr L. Cabeza and Dr. J.A. Herrera reveal no conflict of interest. Dr. Maria González Yibirín and Dr. David Rincón Matute work at Laboratorios Leti S.A.V.

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