Short-term Effectiveness of Nexala® in the Treatment of Patients with Gonarthrosis and Coxarthrosis

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ABSTRACT

Objectives We have evaluated the short-term safety and effectiveness of Nexala® in patients with gonarthrosis and coxarthrosis; Nexala®, a formulation containing Theracurmin®（highly bioavailable curcumin）, Akbamax®（enriched boswellic acid extract）and Vitamin D3（Cholecalciferol）.

Methods 30 patients were selected, 20 were recruited and all 20 completed the study. Treatment with Nexala® was well tolerated and did not produce any adverse effects.

Results The formulation of Nexala®（2 capsules x day）reduced pain, stiffness and improved functionality significantly（$P<0.0001$）after a 28-day period of continuous treatment measured by WOMAC and the Lequesne Index.

Conclusions Nexala® shows great potential for the treatment of patients with arthrosis; its short-term effectiveness as well as its tolerability profile makes it an ideal candidate when we need to decrease pain and inflammation and improve functionality in patients with gonarthrosis and coxarthrosis.

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KEY WORDS Highly bioavailable curcumin, Enriched boswellic acid extract, Cholecalciferol, Osteoarthritis

INTRODUCTION

Arthrosis, also known as degenerative joint disease, is a slow and progressive process that affects millions of people worldwide; it usually occurs when joint structures are abnormal or the joint is subjected to a very high level of stress causing cartilage breakdown, synovial proliferation, inflammation, pain, and stiffness of the joints.[1,2)] It is estimated, for example, that in the USA it affects more than 27 million people, being the main cause of physical disability, as well as a significant loss in the quality of life of elderly patients worldwide.[3)] Generally, these types of conditions are chronic and are treated with analgesics and non-steroidal anti-inflammatory drugs（NSAIDs）, but unfortunately, there is no ideal and definitive treatment that does not cause adverse gastrointestinal and/or cardiovascular effects of this class of products, especially in the long term.[4,5)] For this reason, it is necessary to have drugs that not only reduce joint pain and inflammation, but also help to slow down the progression of the disease.

There are a growing number of products on the market with analgesic, anti-inflammatory and carti-

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lage-protective action and which also offer a better safety profile than offered so far by the usual treatments. In this respect, one of these natural agents is curcumin, a polyphenol from the Curcuma Longa (Turmeric), which has been used since ancient times. Due to its anti-inflammatory and antioxidant properties, it regulates several biochemical and molecular pathways, including transcription factors, cytokines, enzyme and genes that regulate cell proliferation, apoptosis.[6)]

Different studies have reported effects comparable to NSAIDs and related to the suppression of prostaglandin synthesis, through inhibition of cyclooxygenase-2 (COX2),[7)] as well as an important mechanism for inhibiting the activation of Nuclear-factor kappa-beta (NF-κB)[8)]; in addition, curcumin has also been reported as an important inhibitor of inflammatory and catabolic mediators of chondrocytes.[9)] Another interesting aspect is the lack of side effects, which makes it a very interesting compound. In addition, its lack of or absence of bioavailability in blood, which has always been the battle horse, is now being improved and improved curcumin compounds, so-called high bioavailability curcumin compounds, able to reach target cells are being developed.[10)] To overcome this problem, Theravalues Corporation (Tokyo, Japan) has developed a compound called Theracurmin®, which has improved its bioavailability by more than 27 times the normal curcumin.[11)] When compared with other formulations of the so-called high bioavailability curcumins, it is worth noting how their absorption is much higher than the same, and it has been seen how Theracurmin® bioavailability is due to its size (nanoparticles (over 350 nm) submicron colloidal, its high dispersibility, its low aggregability and its high-water solubility. All these features make this a very interesting compound because of its formulation and the clinical benefits it can provide, especially to patients affected by arthrosis, arthritis and other types of diseases related to ageing and inflammatory bowel problems.[11,12)] Another interesting compound, because of its anti-inflammatory, analgesic, and anti-arthritic effects, is the boswellic acids from Boswellia Serrata.[13,14)] Its main active ingredient, 3-*O*-Acetyl-11-keto-beta-Boswellic Acid (AKBA) is a potent inhibitor of 5-Lipooxygenase (5-LOX), the key enzyme in the biosynthesis of leukotrienes in the inflammatory cascade.[15,16)] Akbamax® is a new formulation of Arjuna Natural Extracts LTD, from Boswellia Serrata, in which only those boswellic acids with beneficial effects for the patient have been selected and furthermore, they have been enriched by up to 5 times compared to other commercially more common and/or usual preparations, and those less beneficial (e.g. β-Boswellic) have been eliminated. The beneficial effects of Boswellic acids not only derive from their inhibition of 5-LOX, but also from the inhibition of different matrix metalloproteins in primary chondrocytes, in addition to improved recovery of glycosaminoglycans (GAGs) in human chondrocytes induced by pro-inflammatory cytokines,[17)] and all this, with a good level of safety and with hardly any secondary effects, which is why it is another of those interesting compounds in patients affected by arthrosis, arthritis and with inflammatory intestinal problems.[18)] Vitamin D provides us with more positive information every day about its use in arthrosis, as it has been shown to reduce pain and improve joint functionality.[19)] Also, hypovitaminosis D has been found to be associated with an increased risk of gonarthrosis.[20)] Different studies have determined its beneficial effect in patients with vitamin D deficiencies, in which it has been shown that calcium absorption increased by up to 65% after intake. In addition, it stimulates remodelling and plays a protective role on osteoblasts. For these reasons, and although there is still some controversy about it, different reports indicate that supplementing with 600-700 IU has been associated with a 23-26% improvement in bone health, especially in the elderly. Another longitudinal study by Zhang, et al: 2014,[21)] shows that individuals with vitamin D deficiency are associated with a significant increase in progression of the risk of osteoarthritis; the same study confirms that patients who were supplemented with vitamin D did not progress in their knee arthrosis, unlike those who were not supplemented.

MATERIALS AND METHODS

The purpose of this study was to evaluate the short-term effectiveness of Nexala® in reducing pain, stiffness and functionality in patients with Gonarthrosis and Coxarthrosis.

30 Capsules (Laboratorios Farmolab S. L., Spain) containing: a new formulation of very high bioavailability curcumin (Theracurmin®), a formulation of boswellic acids, which have been enriched (Akbamax®) and Vitamin D3 (Cholecalciferol).

1 Design

The Nexala 30 Capsules formulation contains 90 mg

Theracurmin®, 100 mg Akbamax® and 10 μg of Cholecalciferol. This was an open study under care conditions with the informed consent of each patient. 20 patients decided to agree to enter the study and they signed the informed consent document prior to their participation in the study: 11 of them had Gonarthrosis and 9 patients had coxarthrosis. The study was carried out at the Mittelmeer Klinik by its trauma unit. The treatment for the patients was provided by Laboratorios Farmolab S. L. The 20 patients were evaluated in 2 visits, one at the beginning（day 0）and one at the end（after 28 days of treatment）.

The studies were conducted in accordance with the principles of the Declaration of Helsinki（2013）. This is an observational clinical study conducted with patients from the usual practice clinic who attended the Mittelmeer Klinik. The study protocol was carried out and approved by the Mittelmeer Klinik Scientific Committee and all patients included gave their authorization and consent to participate in the study.

2 Patients

The type of patients to be included were patients of both sexes, over 18 years of age, medically stable, with moderate long-term arthrosis evidenced by narrowing of the medial joint space or inflammation; patients with a severe form of arthrosis evidenced by radiological findings, with restricted mobility, breastfeeding mothers, patients with a history of rheumatoid or reactive arthritis, or clinical findings of significant systemic disease, drugs or alcohol, malnutrition or any other condition that could alter or affect the conduct of the study were excluded from this study. In total, 30 patients were selected and 20 were included in the study; 11 patients had a previous diagnosis of gonarthrosis and 9 patients had a previous diagnosis of coxarthrosis, each patient was assigned a number and all patients were included in the same treatment group.

3 Evaluation of effectiveness

The effectiveness of the Nexala® treatment was assessed using the WOMAC（Western Ontario and McMaster Universities Osteoarthritis Index）and Lequesne Index scales.[22,23] In the evaluation, and depending on the type of arthrosis presented by each patient, two scales were assessed, one being the specific questionnaire for arthrosis WOMAC, which informs us about the patient's pain, stiffness and functionality, and is considered a good tool for assessing the activity of the disease in patients diagnosed with arthrosis, and the other being the Lequesne assessment scale or Index in its two variants; Patients presenting gonarthrosis did the Lequesne Index variant of the Knee and those presenting Coxarthrosis did the Lequesne Index variant of the Hip. The Lequesne Index allows us to measure the repercussions of pain and also the functionality of both gonarthrosis and coxarthrosis, as well as helping us to establish a good correlation between the two scales used and therefore obtain more reliable results.[24]

Table 1　Basal characteristics

Characteristics	Gonarthrosis	Coxarthrosis
Female Male	9（81.8%） 2（18.2%）	7（77.8%） 2（22.2%）
Age	63.6±12.4	71.1±10.9
WOMAC Score（DE average）*	53.8（25.8）	59.3（17.6）
Lequesne Funcional Index（DE average）**	12.4（4.6）	14.2（2.0）

*0.6717 and **0.2695 respectively indicating homogeneous groups without statistical significance

4 Statistical analysis

Statistical analysis of the data was performed using the one-way ANOVA method to analyse effectiveness data to determine statistically significant differences in the treatment group and in the treatment time. The evaluations used included tests performed by patients at the beginning of the treatment and after 28 days of treatment.

$P<0.05$ was considered to indicate a statistically significant difference. All data were analysed by an independent external company to the centre where the study was conducted（SAIL-Biometry 08027 Barcelona）.

RESULTS

1 Basal characteristics

The basal characteristics of the patients are shown in **Table 1**. There were no significant differences between the groups of patients as indicated by the Mann-Whitney *U* analysis. Nexala® was evaluated at a dose of two capsules per day, so the patients took a total dose of 700 mg/day.

2 Clinical effectiveness

Data on the evolution of pain, stiffness, and functionality through the WOMAC and the Lequesne Index are

Table 2　Total results and subscales

Parameter and Treatment	Basal median	Median day 28	% Change	*P*-value
WOMAC TOTAL Score Nexala®	59.5	24.0	−54.8（−66.7; 5.4）	＜0.0001
WOMAC PAIN Scale (min/max)	13.0（3.0; 19.0）	5.0（2.0; 11.0）	−57.7（−75.0; 25.0）	＜0.0001
WOMAC STIFFNESS Scale (min/max)	4.5（1.0; 8.0）	2.0（1.0; 4.0）	−50.0（−66.7; 0.0）	＜0.0001
WOMAC FUNCTIONALITY Scale (min/max)	44.5（7.0; 66.0）	17.0（1.0; 39.0）	−52.6（−85.7; 0.0）	＜0.0001
LEQUESNE TOTAL Score	13.3	5.3	−55.2（−71.4; 0.0）	＜0.0001
LEQUESNE PAIN Scale (min/max)	5.5（3.0; 8.0）	2.5（1.0; 6.0）	−50.0（−71.4; 0.0）	＜0.0001
LEQUESNE Max Walking Dist (min/max)	3.0（1.0; 7.0）	1.0（1.0; 6.0）	−58.3（−80.0; 0.0）	＜0.0001
LEQUESNE Daily Life Activities (min/max)	4.0（2.0; 8.0）	2.0（1.0; 4.5）	−52.3（−69.2; 0.0）	＜0.0001

shown in **Table 2.**

At the end of the study, statistically significant reductions（$P<0.0001$）were produced in all the parameters analysed, pain, stiffness, and functionality, both in the analysis carried out through the WOMAC, and in that carried out with the Lequesne Index, evaluating the initial situation and the one obtained on the 28th day of treatment. It is interesting to note that the values obtained between the two scales show a very similar correlation, which indicates good consistency when evaluating the results.

When analysing the medians of the total questionnaires we can see that Nexala® starts in the WOMAC with a median of 59.5 and on day 28, the median obtained is 24.0, which indicates a change percentage of −54.8%; the Lequesne Index the basal median was 13.3 and on day 28 of treatment the median obtained was 5.3, which represents a change percentage of −55.2%.

3　Pain assessment（Fig. 1）

Analysis of the corresponding total pain subscales（all patients with arthrosis included）shows clear statistical significance with a $P<0.0001$ at the end of treatment, obtaining a change percentage on the WOMAC scale of a median of −57.7% and on the Lequesne Index, a median of −50%. When analysing the results in patients with Gonarthrosis and Coxarthrosis, we see how the improvement is very significant（$P<0.0001$）and change percentages that are situated in the WOMAC pain Subscale in patients with Coxarthrosis at −50% and −58% for patients with Gonarthrosis; in the Lequesne Subscale Pain Index of patients with Coxarthrosis it was −60% and −50% for patients with Gonarthrosis. Nexala® shows its effectiveness in reducing pain, regardless of the type of arthrosis of the patient.

4　Stiffness assessment（Fig. 2）

The stiffness assessment is carried out by the WOMAC stiffness subscale, which helps us to determine the immediate situation of the patient by having to tell us what their situation is during the two days prior to their entry into the study. Analysis of the data obtained after 28 days of treatment indicate that there is a statistically significant improvement（$P<0.0001$）with Nexala® in terms of stiffness, with change percentages of the median of −50% in all patients and by patient group of −60% in patients with coxarthrosis and −50% in patients with gonarthrosis.

5　Functionality assessment（Fig. 3）

Another aspect that we find very interesting to highlight is the evolution of the functional capacity, for this, we use the WOMAC in its functionality section, as well as the Lequesne Index in its maximum walking distance sections and the daily life activities section. All these indicators allow us to evaluate the degree of functionality and its evolution with greater precision, and we can observe how there is a statistically significant improvement（$P<0.0001$）in the overall number of patients with a change percentage of the median of −52.5% at day 28 of treatment, and by patient group of −51.5% in patients with coxarthrosis and −64.6%

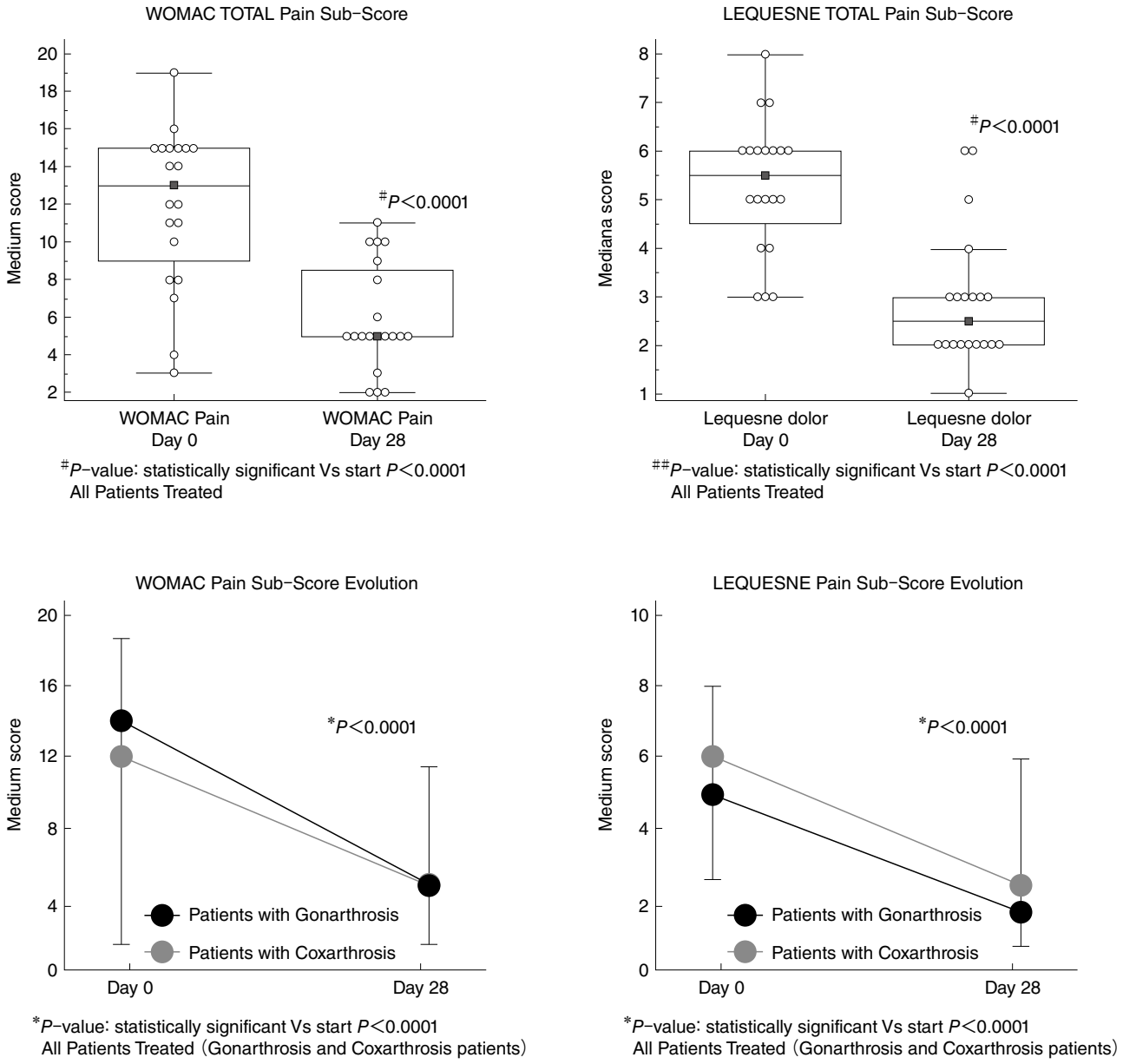

Fig. 1　Pain assessment

Top box plots pain scale analysis. Bottom analysis scales of pain by pathology.

in patients with gonarthrosis.

6　Maximum walking distance（Fig. 4）

The evolution of the maximum walking distance is done through the Lequesne Index in the corresponding subscale, taking into account the maximum distance a patient can walk initially and after 28 days of treatment. The score goes in the opposite direction, therefore, the higher the score, less is the distance the patient can walk and the positive evolution would indicate a decrease in the score. The results show a clear improvement, being statistically significant（$P<0.0001$）the change produced after the treatment in which it can be observed how the median of the patients at the beginning of the study was at a distance of 500–900 meters, or in other words could walk for a maximum of 8–15 minutes, to reach a maximum walking distance of more than 1 km at the end of the study with slight limitations. If we make this same analysis according to the group of patients, on the one hand we see how patients with coxarthrosis could initially walk a maximum of 300–500 meters and at the

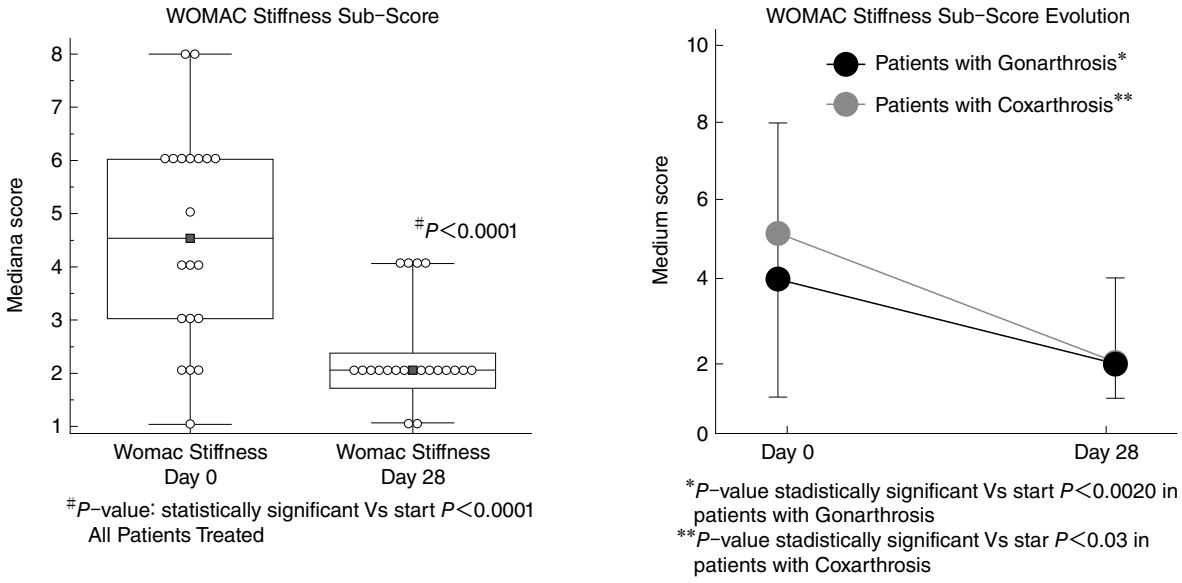

Fig. 2　Stiffness assessment

Left box plot stiffness analysis. Right stiffness evolution analysis by pathology.

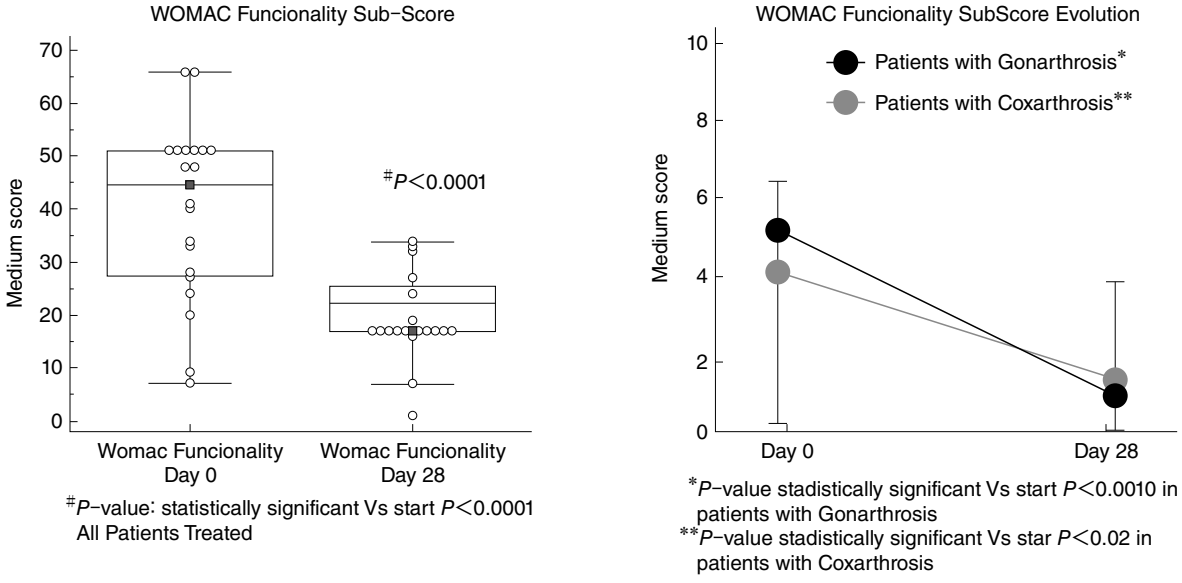

Fig. 3　Functionality assessment

Left box plot functionality analysis. Right functionality scales evolution analysis by pathology.

end of the study they could walk around 1 km, which is a statistically significant difference of a $P<0.02$, and patients with gonarthrosis, initially could walk a maximum of 500–900 meters and at the end of the study they could walk more than 1 km, with slight distance limitation, which is a statistically significant difference of a $P<0.02$.

7　Daily life activities（Fig. 5）

It is interesting to observe how their quality of life improves in a statistically significant way both in the total number of patients（$P<0.0001$）, and in each group of patients（$P<0.0020$ for patients with gonarthrosis and $P<0.02$ for patients with coxarthrosis）. In short, patients with gonarthrosis could go up and down stairs better, bend over and improve their walk on less stable surfaces, and on the other hand, patients with coxarthrosis improved in aspects such as bending over, going up and down stairs, as well as in matters related to getting into and out of a car more comfortably.

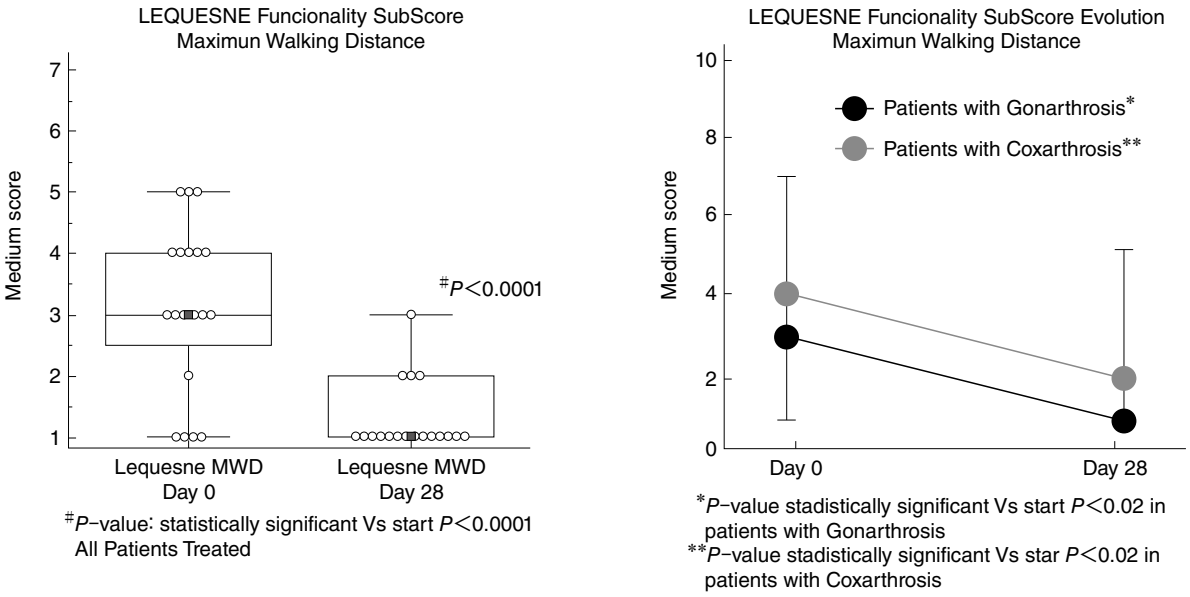

Fig. 4　Maximum walking distance

Left box plot maximum walking distance（MWD）analysis. Right MWD analysis evolution by pathology.

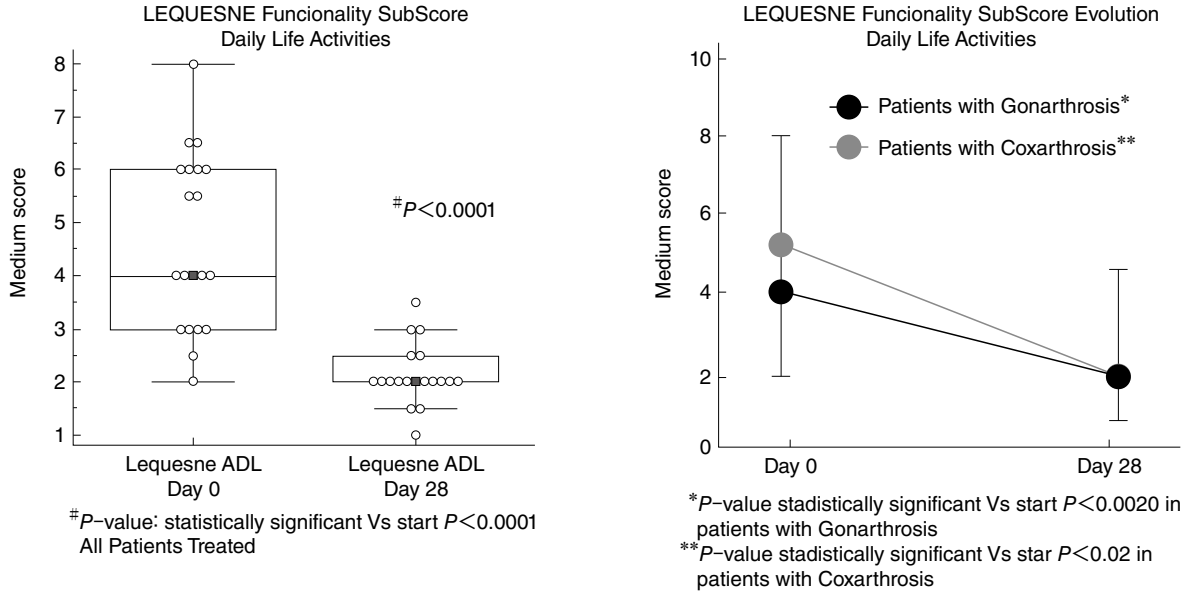

Fig. 5　Daily life activities

Left box plot Daily Life Activities（ADL）analysis. Right ADL evolution analysis by pathology.

8　Safety

Regarding the study safety it was evaluated by patient clinical conditions following the first week and at the end of the study（at 28th day）. A complete clinical assessment directed to evaluate the present of sings adverse events, like vomiting, nausea, bloating, diarrhoea, discomfort, etc., mainly intestinal signals were conducted. There were no adverse events reported in the study all patients that started the study concluded the 28 days of treatment without any side effect confirmed under the patient assessment performed.

DISCUSSION

In this study, the safety and efficacy of oral rehydration of Nexala, which comprises THERACURMIN®, Akbamax®, and Vitamin D, was investigated in patients with osteoarthritis（OA）of the hip and knee.

The assessment of pain, function, and stiffness using the WOMAC showed improvement 28 days after Nexala administration compared with that before administration. In addition, evaluation of stiffness and function using the Lequesne index showed improvement 28 days after administration compared with that before administration.

There are several reports on the effectiveness of curcumin for the treatment of knee OA.

Nakagawa, et al.[25] reported a significant pain reduction in a randomized, double-blinded, placebo-controlled study of 50 patients with knee OA after an 8-week administration of highly bioavailable curcumin. Moreover, celecoxib dependence was significantly reduced in the highly bioavailable curcumin-treated patient group compared with that in the placebo group.

The administration of THERACURMIN® in 45 patients with knee OA for 6 months significantly improved the VAS, JKOM, and JOA items.[26] Treatment of knee OA with curcuminoids and glycosaminoglycans in combination with physical therapy improved the VAS and Lequesne index scores.[27] Treatment with curcuminoids was associated with a significant reduction in the WOMAC, VAS, and Lequesne pain function index scores compared with the placebo.[28] In addition, the use of curcumin complex or its combination with boswellic acid for 12 weeks reduced pain-related symptoms in patients with OA.[29]

The efficacy of boswellic acid-containing products（Boswellina®）and the combination of curcumin C3 Complex® and bioperine in the management of OA has been demonstrated in previous studies, and no adverse events have been reported.[30]

Vitamin D3 has been reported to play a role in the development and progression of OA; vitamin D receptors（VDRs）are expressed in chondrocytes, osteoclasts, and osteoblasts. Vitamin D can reduce bone turnover and cartilage degeneration, thus delaying OA progression.[31,32] When patients with vitamin D-deficient knee OA were administered vitamin D for a year, the WOMAC pain scale and physical activity significantly improved compared with the placebo group 19). In the present study, oral supplementation of Nexala reduced pain in patients with hip and knee OA（**Fig. 1** and **5**）, thereby improving physical function. It was shown to improve significantly. Clinical studies on the effectiveness of curcumin for the treatment of knee OA have reported specific biomarkers. A significant increase in serum superoxide dismutase activity as well as the borderline glutathione concentration and a decrease in malondialdehyde（MDA）were observed.[33] Flexofytol and curcumin extract, significantly decreased serum Coll2-1 levels and tended to decrease CRP levels for 3 months.[34] Belcaro, et al.[35] reported that the treatment group had significantly reduced CRP levels compared with those in the control group. Several *in vitro* studies have partially revealed the molecular mechanisms underlying the anti-inflammatory properties of Boswellia®. These mechanisms include prevention of collagen degradation, inhibition of pro-inflammatory mediators, such as prostaglandins, COX, nitric oxide（NO）, and NF-κB, and downregulation of pro-inflammatory cascades.[36,37]

Vitamin D has been reported to possess anti-inflammatory effects. Vitamin D deficiency is associated with increased inflammation in chronic conditions, including asthma, inflammatory bowel disease, and rheumatoid arthritis（RA）.[38,39] However, in this study, specific biomarkers concern to improved OA condition were not verified. It is considered that changes in anti-inflammatory biomarkers have improved the results from previous studies of the three components（highly bioavailable curcumin, boswella and Vitamin D）. Regarding safety, no adverse events were reported in the evaluation based on the clinical status of patients at the first week and end of the study（day 28）. Therefore, the administration of Nexala was deemed safe under the conditions of use. In this study, the safety and efficacy of Nexala in patients with hip and knee OA was demonstrated. There are 4 main limitations in this study：Short follow-up period（28 days）, the sample size was small（20 cases）, and placebo effects could not be eliminated, and this was an open study.

CONCLUSIONS

In conclusion, Nexala® 30 Capsules, administered twice a day for 28 days, showed a statistically significant improvement（$P<0.0001$）in pain, stiffness, and functional scores, verified through the assessment of the maximum walking distance that the patient with osteoarthritis can perform and the improvement in daily life activities, evaluated through WOMAC and Lequesne Index tests. In addition, this significant improvement occurs in both treatment groups in patients with gonarthrosis and in patients with coxarthrosis. The speed of action is remarkable, as well as the good tolerance, as there are no side effects; in

summary, this study shows a good effectiveness and safety profile of Nexala®. In addition, it also informs us of a rapid analgesic action with Nexala®, establishing a great potential as a useful therapeutic strategy for the management of arthrosis.

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