

CLINICAL EFFICACY AND SAFETY OF LYPRINOL[®], A PATENTED EXTRACT FROM NEW ZEALAND GREEN-LIPPED MUSSEL (*PERNA CANALICULUS*) IN PATIENTS WITH OSTEOARTHRITIS OF THE HIP AND KNEE : A MULTICENTER 2-MONTH CLINICAL TRIAL

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Summary

■ **Objective :** To validate the clinical efficacy and safety of Lyprinol[®] (a patented extract from *Perna Canaliculus*), a 5-LOX inhibitor in patients with osteoarthritis.

■ **Methods :** In this multicenter trial, 60 patients with symptomatic osteoarthritis of the knee and hip were included to receive Lyprinol at a dose of 2 capsules twice a day. After a 4- and 8-week treatment period, the following parameters were analyzed: visual analogue scale; Lequesne functional index; global assessment by patients; global assessment by physician; and adverse effects.

■ **Results :** Lyprinol treatment led to significant improvement of the signs and symptoms of osteoarthritis as determined by all efficacy measures. After a 4- and 8-week treatment period, 53% and 80% (respectively) of patients experienced significant pain relief, and improvement of joint function. There was no reported adverse effect during this clinical trial.

■ **Conclusion :** Lyprinol was very effective and is a promising anti-inflammatory product that relieves the signs and symptoms of osteoarthritis, without adverse effect.

Key-Words : Lyprinol - 5-LOX - Anti-inflammatory - Clinical study - Lequesne functional index.

INTRODUCTION

It has been reported that the incidence of arthritis in New Zealand coastal-dwelling Maoris is very low (1). Local physicians suspect that this may be due to their diet that includes raw green-lipped mussels (NZGLM). A number of studies have been conducted for the last 30 years, looking for the active component of the NZGLM in arthritis (1-8). It is now known that NZGLM has 5-6 types of omega-3 polyunsaturated fatty acids (omega-3 PUFAS) (EPA, DHA, DPA, and other sterols); these compo-

nents have synergistic effects that eventually result in anti-inflammatory activity.

Lyprinol is a natural material from NZGLM, extracted by a patented method including supercritical CO₂ extraction (1).

Omega-3 PUFAS are essential fatty acids that are found abundantly in marine organisms, and a few plants. Plant omega-3 PUFAS are poorly absorbed by human GI tract, and large amounts are required, if an anti-inflammatory effect is expected. Omega-3 PUFAS found in marine organisms have the potential to oxidize rapidly after extraction, resulting in a drastic loss of anti-inflammatory activity (6). As a consequence, treatment with unstabilized freeze-dried NZGLM powder has resulted in variable benefits for patients suffering of arthritis. Fortunately, in 1983 Professor T. Kosuge, of

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Shizuoka University Medical School, Japan, developed a method using a fruit acid that prevents the oxidation of omega-3 PUFAS, and patented it (6). That same year, Dr. Theo Macrides, of RMIT, Australia, succeeded in separating and extracting of the anti-oxidant/anti-inflammatory components from NZGLM (4). Then, starting in 1994, farming of NZGLM expanded, and the liquid CO₂ supercritical extraction of the anti-inflammatory components gave birth to Lyprinol.

After many years of pre-clinical/animal and clinical studies, the efficacy of Lyprinol in the treatment of rheumatoid (RA) and osteoarthritis (OA) (3-13), and asthma (14), was demonstrated. We designed and conducted this clinical trial in OA to validate the clinical efficacy and safety of Lyprinol® in Korean patients.

PATIENTS AND METHODS

PATIENTS

Sixty patients with confirmed hip and knee osteoarthritis were enrolled in this study, and 54 completed it. They were recruited in 8 hospitals between May and October 2001. (Seoul National University Hospital: n = 7; Chung Ang University Hospital: n=16; Gyeong Sang University Hospital: n = 4; Chungnam National University Hospital: n = 6; Chonnam National University Hospital: n=5; Kosin University Hospital: n = 5; Yeungnam University Hospital : n = 5; Yonsei Medical Clinic: n = 6). The diagnosis of osteoarthritis of knee and hip was made according to the American College of Rheumatology (ACR) diagnostic criteria (15, 16).

Patients were included with the following (table 1):

- Age: 40-75 years ;
- ACR functional class I, II, III;
- VAS (Visual Analogue Scale measuring the intensity of pain in cm): > 4 ;
- LFI (Lequesne's functional index (17) with a joint mobility scale): > 4 < 17 ;
- No corticosteroids for 4 weeks before inclusion;
- Women who were not pregnant, and used adequate contraception during the trial.

Newly diagnosed patients (novice; no previous treatment with NSAIDs):

- Global assessment grading by patient: poor or very poor;
- Global assessment grading by physician: poor or very poor.

Patients previously treated with NSAIDs:

- LFI increased >2, after discontinuing NSAID;
- Global assessment grading by doctor and patient: deterioration of >1 grade discontinuing NSAID;
- > 2-day drug washout period of analgesic and/or anti-inflammatory medication.

METHODS

This study was an open clinical trial, using the patient's symptoms at inclusion as baseline. All patients were given full information on Lyprinol, and signed an informed consent form. Patients were instructed to take 4 capsules daily (2 in the morning, 2 in the evening) of Lyprinol (Pharmalink International Ltd., Hong Kong).

The efficacy was assessed at 4- and 8-week respectively, and the following criteria were used:

- VAS (measured in cm);
- LFI (Joint mobility being the most important component);
- Patient's Global Assessment: 5 grades (much improved; improved; no change; worse; much worse). Only "much improved" and "improved" grades were accepted as positive response;
- Physician's Global Assessment: 5 grades, identical to patient's, with same conclusions.

Since there has not been any reported adverse effect attributable to Lyprinol for the last 5 years, the evaluation of safety was limited to reports of abnormal symptoms by patients; we did not conduct any laboratory tests.

STATISTICAL ANALYSIS

The authors analyzed the following: VAS, LFI, and Global Assessments; we considered as meaningful a P value < 0.05. A paired t-test was performed by comparing the difference between before and after administration to assess the efficacy of Lyprinol in respect to VAS and LFI.

The global assessments by physicians and patients were analyzed by Chi-square test to check any subjective and/or objective difference on the scales of improvement of symptoms.

Gender	Age (yrs)	Wt(kg)	VAS (cm)	LFI	Global assessment			
					Physician		Patient	
M	F				Poor	Very poor	Poor	Very poor
2	52	61	62	6.1	13	31	24	30

Table 1 : aseline characteristics of the patients: VAS(cm): visual analog scale; LFI: Lequesne's functional index. Total (N = 54).

RESULTS

PATIENTS

60 patients were included in this clinical trial, and 54 completed the trial. The 6 drop-outs included: violation of protocol = 2; missed appointments = 3; intercurrent illness = 1.

Of the 54 patients, 11 patients completed the 4-week trial only (diverse reasons were put forward, though none related to Lyprinol), while the remaining 43 completed the 8-week trial. All patients were females, but 2. The average age was 61, and average body weight was 62.2 kg.

Average duration of osteoarthritis (OA) was 6.4 years. All patients had knee OA, except 1 who had hip OA. According to ACR criteria, 40 patients were class II, and 14 were class III.

EFFICACY OF LYPRINOL

n Evaluation of improvement of pain: the improvement of pain was evaluated by VAS. The average VAS before administration of Lyprinol was 6.1 cm; after 4 weeks of treatment, the average VAS was reduced to statistically meaningful 4.9 cm. ($p < 0.05$).

Among the 43 patients who completed the 8 weeks trial, the average VAS was 6.4 cm before treatment; after 4 weeks it was 5.3 cm, and 8 weeks later it was reduced to 3.9 cm. Therefore the prolonged treatment was associated to an improved reduction of pain. ($p < 0.05$) (figure 1).

■ The evaluation of improvement of joint function (Lequesne functional index; LFI) : the evaluation of improvement of joint function after treatment was evaluated by LFI. The LFI before treatment was 13.04 ± 3.38 , and after 4 weeks treatment it was reduced to 10.56 ± 3.23 ($p < 0.05$). The LFI of 43 patient who completed the 8 weeks trial was 13.67 ± 3.23 before treatment; after 4 weeks of treatment it was reduced to 11.35 ± 2.73 , and after 8 weeks of treatment it was reduced to 8.63 ± 2.85 ($p < 0.05$).

Therefore the prolonged intake of Lyprinol resulted in a more significant reduction of Lequesne functional index (LFI) (figure 2).

■ Global assessment by patients: the patients were asked to fill the questionnaire before and after the treatment for global assessment. After 4 weeks of treatment with Lyprinol, 57% of patients mentioned that they felt improvement (improved: 27/54; very improved: 4/54), while 43% (23/54) felt no improvement.

But in the 43 patients who completed 8 weeks of treatment, the improvement rate was 87%, (improved: 13/43; very improved: 23/43). Therefore the prolonged intake of Lyprinol gave better results in OA patients (figure 3).

■ Global assessment by physicians: physicians were asked to fill the questionnaire after 4 weeks and after 8 weeks of treatment and assess the clinical improvement of their OA patients.

After 4 weeks of treatment, improvement rate was 57% (improved: 27/54; very improved: 4/54), while 43% (23/54) showed no improvement.

In the 43 patients who completed the 8-week treatment, improvement rate was 90% (39/43). Therefore the prolonged intake of Lyprinol gave much better results in these OA patients (figure 4).

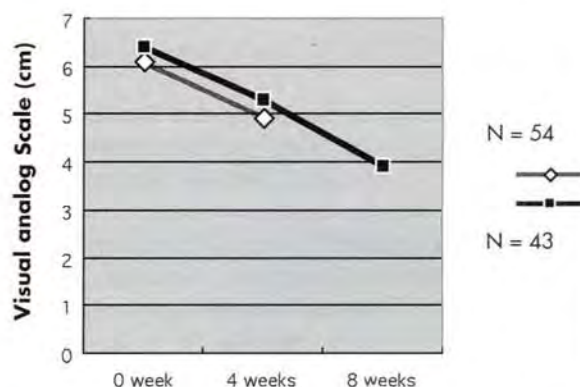


Figure 1 : Change of visual analog scale over the 8 weeks treatment period ($p < 0.05$ by paired t-test).

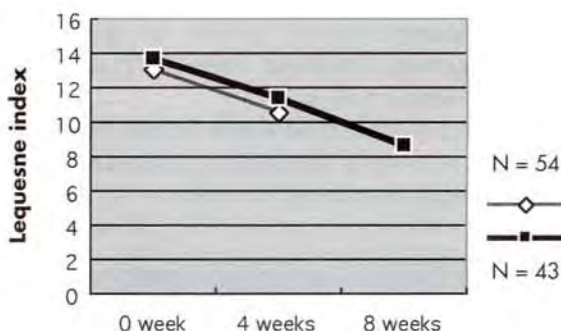


Figure 2 : Change of Lequesne index over the 8 week treatment period ($p < 0.05$ by paired t-test).

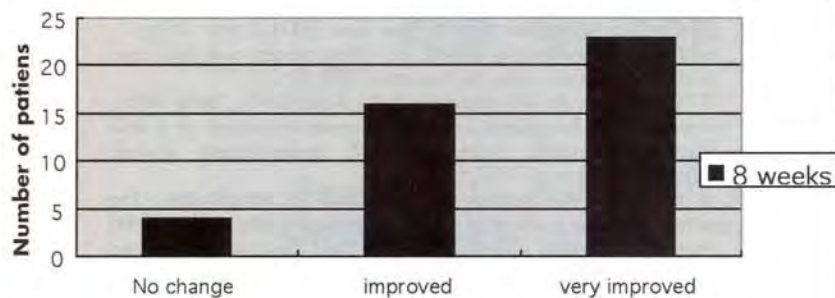


Figure 3 : Global assessment by patients after 8 week treatment period (N=43).

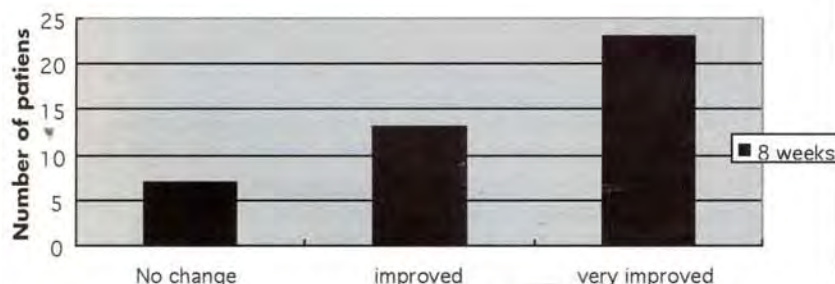


Figure 4 : Global assessment by doctors after 8 week treatment period (N=43).

■ Analysis of discrepancy between global assessments by physicians and by patients:

no meaningful discrepancy was observed between assessment by physicians and by patients ($p < 0.05$).

ADVERSE REACTIONS

No adverse reaction was reported during the 8 weeks of the trial. 2 patients reported a transient worsening of arthritic pain 2-3 days after the beginning of the trial, but the pain disappeared spontaneously, and Lyprinol was continued.

DISCUSSION

We designed and conducted this clinical trial to validate the efficacy and safety of a natural substance, Lyprinol, which has reported therapeutic effects on arthritis (9-14). A clinical trial conducted in the UK (11) on OA patients reported that over 70% patients had improvement of their symptoms, and we wanted to investigate whether those results could be confirmed in Korean patients.

While alternative medicine gets more attention than ever before, clinical trials are still required as scientific verification of claims.

This open clinical trial was conducted in 8 university hospitals and medical clinics for 8 weeks, and the results showed no adverse effect and excellent efficacy. All the symptoms of OA responded positively to Lyprinol: > 50% patients in the 4-week treatment, and > 80% patients in the 8-week treatment. The grade of pain (VAS) and functional impairment (LFI) were reduced significantly, and patient and physician global assessments improved.

In this trial, the improvement of symptoms after 4 weeks of Lyprinol -although noticeable-, was much less than at the end of the 8 weeks, when a drastic anti-inflammatory clinical effect was observed. An obvious question is whether a further improvement would have been seen if the treatment period had been extended.

Lyprinol is extracted from green-lipped mussels that are farmed only in the pristine clean waters of the Marlborough Sound of New Zealand. Patented freeze-drying, stabilization, and lipid extraction by supercritical CO₂ process the mussels, and this lipid extract with all the anti-inflammatory components is encapsulated (1, 7).

The benefits of taking Lyprinol are many, and its effects on numerous inflammatory diseases are well proven. Lyprinol is effective in treating not only arthritis, but also bronchial asthma, the inflammation of the bronchioles (14, 18).

Lyprinol is a natural mixture of stabilized omega-3 PUFAS, sterol esters and carotenoids that have complex biochemical structures. The anti-inflammatory properties of Lyprinol are due to the synergistic interaction of 4 or 5 different omega-3 PUFAS and other components, e.g. antioxidant carotenoids. In addition to eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA), there are 2 or 3 other fatty acids with different chemical structures in Lyprinol, as well as other ingredients (2).

While the mode of action of Lyprinol, as an anti-inflammatory, is not fully understood, it is known that Lyprinol can inhibit the 5-lipoxygenase (5-LOX) pathway (2). Inhibition of the 5-LOX pathway can lead to a reduction in the leukotriene synthesis (LTs), and thus inhibit the chemotaxis of neutrophils (18), and result in the improvement of arthritic symptoms such as pain, swelling, stiffness and fever (2, 15, 16). LTs are also potent bronchoconstricting substances and their inhibition by Lyprinol may also reduce bronchiolar inflammation and the resulting bronchospasm, and thus

explain the use of Lyprinol in controlling the symptoms of asthmatic adult patients (14). Lyprinol also demonstrates some activities similar to those of COX-2 inhibiting agents. This may result in the eventual inhibition of thromboxane A2 (TXA-2) and prostaglandin E2 (PGE-2), and thus could protect arterioles and capillaries in *cavum articulare* from infarction caused by thrombi, and help the supply of blood to the damaged joints.

Lyprinol, in a study of artificially induced arthritis in Wistar rats, was much more effective in inhibiting swelling than the same dose of indomethacin (3, 7).

Therefore it is safe to confirm that Lyprinol is the first clinically proven 5-LOX inhibitor, without any adverse effect. A couple of LOX-inhibiting agents have been developed, but most failed as medications because of their toxicity.

No serious adverse effects related to Lyprinol have been reported since its launch 5 years ago. Lyprinol is a very effective and safe product that patients can freely take without prescription. Moreover Lyprinol can be taken along with other anti-inflammatory agents (e.g. corticosteroids, NSAIDS, etc.) without fear of drug interaction. Indeed, it may well help and/or complement other medications. Lyprinol is a welcomed addition to the therapy of patients with osteoarthritis.

CONCLUSION

Lyprinol is a natural lipidic anti-inflammatory product, composed of omega-3 PUFAS, extracted from stabilized freeze-dried New Zealand green-lipped mussels. We conducted a clinical trial on 60 enrolled/54 completing the study osteoarthritic patients for 8 weeks, and over 80% patients demonstrated a positive response; there was no adverse reaction. Lyprinol is safe, and the therapeutic effects are excellent.

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