

# Korean Multi-Centre Study of Lyprinol For Patients With Osteoarthritis of the Hip and Knee (English Translation)

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## 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 : Multicenter Clinical Trial with a 2 Months Treatment Period

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### - Abstract-

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

**Methods** : In this multicenter trial, 54 patients with symptomatic osteoarthritis of the knee and hip were to receive Lyprinol at a dose of 2 capsules twice a day. After 4 and 8 weeks treatment period, the following parameters were analyzed ; Visual analogue scale, Lequesne index, Global assessment by patients, Global assessment by doctors and Adverse effects.

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

**Conclusion** : Lyprinol was very effective and promised anti-inflammatory material to relieve the signs and symptoms of osteoarthritis without adverse effect.

**Key Words** : Lyprinol, LOX, anti-inflammatory, visual analogue scale, Lequesne index.

## Introduction

It is well known that the incidence of arthritis in coastal dwelling Maoris is very low. The epidemiological study showed that it is due to their dietary behavior of taking fresh green lipped mussel. A number of scientists conducted various researches over 20 years in order to find out which component in green lipped mussel has therapeutic effects on arthritis. The research revealed that green lipped mussel has 5 or 6 kinds of Omega-3 Poly Unsaturated Fatty Acids (EPA, DHA, DPA, and other sterols) and these components have synergistic effect that lead to anti-inflammatory action.

Lyprinol is a novel natural material, which is concentration of anti-inflammatory component, extracted by patented method from green lipped mussel that is native only in New Zealand.

Omega -3 polyunsaturated fatty acids are essential fatty acids and are found abundantly in marine organism and a few plants are known to have some. But small in quantity Plant extracted Omega -3 unsaturated fatty acids are poorly absorbable in human GI tract and the necessary amount to have desirable anti-inflammatory effect are quite large. Therefore the consumption of plant extracted fatty acids for therapeutic purpose is not realistic. The Omega-3 polyunsaturated fatty acids found in marine organism oxidize rapidly after their death and anti-inflammatory effects are reduced drastically. So the selective extraction of anti-inflammatory components and prevention of oxidation has been extremely difficult. -1 Thus the intake of dried powder of New Zealand green lipped mussel (Seatone) had little effect on patients with arthritis.

Then in 1983, Dr. Kosuge of Shizuoka University, Medical School, developed a method of freeze drying of mussel that prevent the oxidation of Omega-3 and it was patented.----10

In the same year, Dr. Theo Macrides of Australia succeeded in separation and extraction of anti-oxidant, anti-inflammatory components from green lipped mussel----13

Then from 1994, the farming of green lipped mussel became very active, and the development of the extraction method of anti-inflammatory components from the mussel lead to the birth of Lyprinol.

After 3 years of pre-clinical study (animal study) and clinical study, the excellent efficacy of Lyprinol in treatment of Rheumatoid arthritis, Osteoarthritis and Asthma was proved. Now it became one of the most selling OTC products in Europe, U.S.A., Oceania, and South East Asia. Thus the authors of this report began this study in order to validate the clinical efficacy and safety of Lyprinol which is launched in Korea in April 2001.

## Patients and Methods

### 1. Patients

The 54 patients with hip and knee osteoarthritis was included in this study who visited 8 hospitals between May and October 2001. (Seoul National University Hospital: 7 patients, Chung Ang University Hospital: 16 patients, Kyung Sang University Hospital: 4 patients, Chungnam University Hospital: 6 patients, Chonnam University Hospital: 5 patients, Kosin University Hospital: 5 patients, Youngnam University Hospital: 5 patients, Yonsei Medical Clinic: 6 patients). The diagnosis of osteoarthritis in knee and hip joint were made in accordance with the American College of Rheumatology's diagnosis criteria. The selection of patients were made by following criteria and possibly pregnant patients were excluded.

- 1) Age: between 40 and 75.
- 2) ARA (American College of Rheumatology) Functional class I, II, III.
- 3) VAS (Visual Analogue Scale) : above 4.
- 4) LFI (Lequesne's functional index) : above 4 below 17.
- 5) No administration of any kind of steroid preparation before 4 weeks of commencing the clinical trial.

In case of new patients

- 6) Global assessment grade by patients : poor or very poor.
- 7) Global assessment grade by doctor : poor or very poor.

In case of patients who had taken NSAID before.

- 8) After stop taking NSAID, LFI had increased over 2.
- 9) Global assessment grade by doctor and patient deteriorate 1 grade or more after stop taking NSAID.
- 10) Longer than 2 days of drug washout period of Analgesic and Anti-inflammatory agent.

### 2. Methods

This study was designed to validate the efficacy of Lyprinol, which has proven its efficacy in overseas clinical trial. This study was an open clinical trial. All the selected patients heard detailed information of Lyprinol and signed on informed consent. Participating patients took 4 capsules a day (2 in the morning, 2 in the evening).

The efficacy was assessed at 4 weeks and 8 weeks later respectively and following criteria was used to assess.

- 1) Visual Analogue Scale
- 2) Lequesne's Functional Index
- 3) Patients' Global Assessment : 5 Grade of (Much improved, Improved, No Change, Poor, Very Poor). Only much Improved and Improved Grade was accepted as positive response.
- 4) Doctors' Global Assessment : 5 Grade of (Much Improved, Improved, No Change, Poor,

Very Poor). Only Much Improved and Improved Grade was accepted as positive response.

Since there has not been a reported case of adverse effect of Lyprinol for last 5 years, the evaluation of safety was limited to only when a patient reports any abnormal symptoms, and there has not been regular additional laboratory examination other than physical examinations.

### 3. Statistical Analysis

Paired t-test was performed by comparing the difference between before and after administration to assess the efficacy of Lyprinol. The author analyzed those variables i.e. V.A.S., L.F.I., and Global Assessments, and analyzed the statistics meaningful only when the p value less than 0.05

The global assessments by doctors and patients were analyzed by chi-square test to see if there are any subjective and objective disagreement on the scales of improvement of symptoms.

## **Results**

### 1. The Characteristics of Patients

60 patients participated in this clinical trial, and among them the 54 patients lasted until the end of the studies, excluding 6 drop out patients (violation of protocol : 2 patients, fail to appear for regular check up: 3 patients, other disease reported : 1 patient)

Among the 54 patients, 11 patients participated for 4 weeks trial only, and the remaining 43 patients continued to complete the 8 weeks trial. All the patients were females except 2 male patients. The average age of patients were 61 years, and average body weight were 62.2 kgs. Average duration of arthritis were 6.4 years. Except 1 case of hip arthritis, all patients had knee arthritis. The number of patients according to the American College of Rheumatology, Class II patients were 40, and Class III patients were 14.

### 2. The Therapeutic Efficacy of Lyprinol

#### 1) The evaluation of improvement of pain:

The evaluation of improvement of pain was evaluated by Visual Analogue Scale. The average VAS before the administration of Lyprinol was 6.1 cm and after 4 weeks of treatment, the average VAS was reduced to statistically meaningful 4.9 cm. (p= 0.00).

Among those 43 patients who completed the 8 weeks trial, the average VAS was 6.4 cm before treatment. After 4 weeks, it became 5.3 cm, and 8 weeks later it was reduced to 3.9 cm. So it shows that the longer intakes of Lyprinol lead to better improvement of pains (p= 0.00) (Fig. 1).

#### 2) The evaluation of improvement of joint function (Lequesne Functional Index):

The evaluation of improvement of joint function after treatment was evaluated by the Lequesne Functional Index (LFI). The LFI before the treatment was  $13.04 \pm 3.38$ , and after 4 weeks

treatment, it was reduced to  $10.56 \pm 3.23$  ( $p=0.00$ ). The Lequesne Index of 43 patient who completed the 8 weeks trial was  $13.67 \pm 3.23$  before treatment. After 4 weeks treatment, it was reduced to  $11.35 \pm 2.73$ , and after 8 weeks treatment, it was reduced to  $8.63 \pm 2.85$ . ( $p=0.00$ ). The continuous intake of Lyprinol made more meaningful reduction of Lequesne Index. (Fig. 2)

### 3) Global assessment by patients:

The patients were asked to fill the questionnaire before and after the treatment for the global assessment by patients themselves. The results show that after 4 weeks treatment with Lyprinol, 57% of the patients replied that they felt improvements (improved : 27/54, very improved:4/54) And 43% (23/54) of patients replied with no improvements.

The assessment by the 43 patients who completed 8 weeks treatment, the improvement rate was 87%, (improved 13/43, very improved 23/43). The continuous intake of Lyprinol had better result on osteoarthritis. (Fig. 3)

### 4) Global assessment by doctors:

The doctors were asked to fill the questionnaire after 4 weeks treatment, and after 8 weeks of treatment on the clinical improvement of their patients with osteoarthritis.

The results showed that after 4 weeks of treatment, improvement rate was 57% (improved : 27/54, very improved 4/54) and 43% (23/54) of patients replied with no improvements.

In the assessment on the 43 patients who completed 8 weeks treatment, the improvement rate was 90% (39/43). The continuous intake of Lyprinol had better result on osteoarthritis. (Fig. 4.)

5) The analysis of the discrepancy between the global assessments by doctors and by patients. No meaningful discrepancy was observed between the assessment by doctors and assessment by patients. ( $p=0.00$ )

## 3. Adverse Reaction

During the 8 weeks of trial period, there was not any kind of adverse reaction reported. 2 patients reported temporary worsening of arthritis pain after 2 or 3 days of the commencement of the trial but it disappeared spontaneously. So Lyprinol could be taken continuously.

## **Discussion**

The purpose of this clinical trial was to validate the efficacy and safety of a natural substance, Lyprinol, which has proven therapeutic effects on arthritis. Lyprinol is marketed in over 20 countries in the world, and its efficacy has been proved by numerous clinical trials.<sup>1,2,3,4,5,7,,11.</sup>

An English clinical trial on osteoarthritis patients reported that over 70% patients improved their symptoms, and the authors of this trial wanted to investigate whether those results could be achieved from Korean patients. <sup>1,7, 11.</sup>

In the recent trend of alternative medicine gets more attention ever before, this clinical trial is a worthwhile scientific verification of an alternative medicine.

This clinical trial had been conducted in 8 university hospitals and medical clinics for 8 weeks, and the results showed no adverse effect and excellent therapeutic effect. All the symptoms of osteoarthritis got positive response to Lyprinol : over 50% patients for 4 weeks treatment, and over 80% patients for 8 weeks treatment. The grade of pain (visual analogue scale) and functional difficulty (Lequesne index) were reduced meaningfully as the global assessments got better.

What is noticeable in this 8 weeks clinical trial is that the Lyprinol administration period shorter than a month gets not so impressive improvement of symptoms, but over 2 month period of extended treatment get drastic anti-inflammatory effect.

The ratio between Omega 6 and Omega 3 in human cell membrane is 6 to 1. And this dominant Omega 6 polyunsaturated fatty acid become substrates that produce various inflammation mediating factors. 2, 15.

The substitution of cell membrane that is Omega 3 dominant takes 3 or 4 weeks time, thus the therapeutic effect of Lyprinol does not takes place immediately after the administration, and over a month period of extended treatment makes noticeable therapeutic effect. And stopping of administration leads to termination of this effect.

Lyprinol is manufactured from green lipped mussel which is native only in clean seas of New Zealand. The mussel is processed by patented freeze drying and lipid extraction method, and from this lipid, the concentrated extract of supernatant of anti-inflammatory component is encapsulated. The benefits of taking Lyprinol are various, and its effects on numerous inflammatory diseases and circulatory disease are well proven. Lyprinol is effective in treating not only arthritis, but also good for bronchial asthma, caused by the inflammation in respiratory tract, and those cardiovascular diseases such as arrhythmia or ischemic heart disease. 5,6, 12.

Lyprinol is a natural substance which is a group of omega -3 poly unsaturated fatty acid, and has extremely complex biochemical structures. It is known that the anti-inflammatory property of Lyprinol is synergistic interaction of 4 or 5 different omega -3 polyunsaturated fatty acids. In addition to eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA), there are 2 or 3 other fatty acids with unknown chemical structures in Lyprinol. 15.

It is known that the mode of action of Lyprinol is having anti-inflammatory property by inhibiting Lipoxygenase pathway, that is responsible enzyme in the process of Arachidonic acid metabolism. 4,8,16. Also Lyprinol share some property that is similar to those of COX-2 inhibiting agents, so the all properties of Lyprinol are not understood fully. Lyprinol inhibits Lipoxygenase (LOX) that metabolize Arachidonic acid in cell membranes to Leukotriens, and thus inhibits the chemotaxis of neutrophil by Leukotriens, and it leads to the improvement of arthritis symptoms such as pain, swelling, stiffness, and fever.

Lyprinol was reported that in the study of artificially induced arthritis in Wistar rats, it is much more effective in inhibiting the swellings than the same dose of Indomethacin. 16

And it also inhibits bronchial spasm, and can be used to ameliorate the symptoms of asthma patients. 5. It is well known that Leukotriens have strong bronchoconstricting property.

Moreover Lyprinol seems to have property that inhibits Cyclooxygenase (COX-2), and it eventually inhibits the production of TXA2 and PGE2, and thus protect arteriolar and capillary in cavum articulare from infarction caused by thrombus, and help the supply of blood to the damaged joints, and protects cardiovascular system.

Therefore it is safe to say that Lyprinol is the first clinically proven LOX inhibitor, without any adverse effect. There have been a couple of LOX inhibiting agents developed, they all failed to pass phase I clinical trial because of their unbearably high toxicity. Lyprinol is the only LOX inhibitor developed so far.

There has not been any reported case of adverse effects related to Lyprinol since its launch of 5 years ago. So Lyprinol is very effective and safe material that a patient can freely take without a prescription from a doctor. Moreover Lyprinol can be taken in large amount without any concern about toxicity, the mega dose therapy can be applied to increase the therapeutic effect, and it is quite safe to be taken along with other anti-inflammatory agent (such as steroids, NSAIDS, etc.) without concerning the drug interactions. It helps other agents. From now on, Lyprinol will be welcomed by numerous arthritis patients as a safe and effective treatment.

## Conclusion

Lyprinol is natural anti-inflammatory material which is omega 3 polyunsaturated fatty acids, extracted from freeze dried New Zealand green lipped mussel. We conducted a clinical trial with 54 osteoarthritis patients for 8 weeks, and the results showed that over 80% patients had positive response, and there was no adverse reaction. So Lyprinol is safe to take and the therapeutic effects are excellent.

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