

# 変形性膝関節症治療のための関節内注入合成潤滑剤用ポリエチレングリコールの in vivo での評価

## In vivo trial of Polyethylene Glycol (PEG) as an Artificial Intra-articular Lubricants for Osteoarthritis of the Knee

小林正典\*

Masanori Kobayashi

### Summary

Although the clinical effect of intra-articular administration of the Hyaluronic Acid (HA) for the treatment of osteoarthritis knee joint has been widely recognized, the efficacy of mechanical tribology function of HA as a viscosupplementation to joint lubrication has not yet been confirmed.

To examine in vivo the effects of enhancement of tribology function of joint lubricant for the treatment of osteoarthritis, high viscous Polyethylene Glycol (PEG) was synthesized as an artificial lubricant, and animal experiment was performed. Experimental osteoarthritis models of the both of knee joints of three rabbits were induced by meniscectomy and cartilage defects. These animals were subjected to monthly intra-articular cartilage injection of PEG lubricant to one side knee joint ( another side was not injected as a control knee ), and were sacrificed at 3 month after operation. The extracted knee joints were evaluated macroscopically and histologically.

As a results, the PEG injected knees had a tendency to demonstrate less damage of articular cartilage compared with the control group. This finding indicated that the development of mechanical lubricant system by PEG for the preventing of articular cartilage wear could have potential to be one of effective treatment for arthritis.

キーワード : 関節内注入、 ポリエチレングリコール、 変形性関節症、 トライボロジー

Keywords : Intra-articular administration, Polyethylene Glycol (PEG), Osteoarthritis, Tribology

### 1. INTRODUCTION

Osteoarthritis (OA), the most common form of arthritis, is a chronic disease characterized by the slow degradation of cartilage, pain and increasing disability. The disease can have an impact on several aspects of a patient's life, including function and activities of daily life, relationships, economic status, body image and emotional wellbeing<sup>1,2)</sup>.

Orthopedic procedures are important in the management of OA and should not be reserved only for late severe disease.

Although Total knee arthroplasty (TKA) is representative procedure for OA knee associated with severe deformity, current conservative therapies for moderate OA are drug therapy, physical therapy, muscle exercise, and therapy and rehabilitation. These goals of most patients is the relief of

---

\* 工学部総合機械工学科

pain and localized stiffness, as well as the prevention of deformity and associated limitation of motion.

As another treatment of OA knee joint, the intra-articular injection method of high-molecular-weight hyaluronic acid (HA) has recently become more widely accepted for relief from pain. HA is responsible for the viscoelastic properties of synovial fluid, a highly viscous fluid. Its mechanism of action includes two types: one involves the biomechanics system, the enhancement of articular lubrication and fluid viscosity, while the other involves the biological and biochemical system, the inhibition of inflammatory agents such as PGE<sub>2</sub>, NO and the suppression of proteoglycan from cartilage matrix<sup>3-5</sup>.

This concept of the intra-articular injection of hyaluronic acid for OA is also reasonable given the tribology theoretical background; however, hyaluronic acid is easily degraded in articular joints according to recent studies. Therefore, new materials with excellent biocompatibility, durability, rheology and lubricative function are desired instead of hyaluronic acid.

Against this background, we have synthesized and developed Polyethylene Glycol (PEG) sol as a new intra-articular lubricant for medical treatment for OA knee<sup>6</sup>.

In present study, the efficacy of this PEG lubricant has been accessed by the animal experiment using the rabbits.

## 2. Materials and Methods

### 2.1 Materials

#### 2.1.1 The fabrication and characteristics of PEG lubricant

PEG is a polymer with the chemical formula HO-(CH<sub>2</sub>CH<sub>2</sub>OH) n-H, which refers to a chemical compound composed of repeating ethylene glycol units as shown in Fig.1. It has long been manufactured industrially and utilized in many applications, such as nonionic surfactants, lubricants, as an intermediate for urethane composition, adhesives and cosmetics.

Furthermore, PEG is non-toxic and biocompatible material, PEG is thus also used for bio-related applications, such as pharmaceutical formulations, aqueous two-phase partitions, as a precipitant for plasmid DNA isolation, protein crystallization and cell fusion. We have also paid attention this advantage, attempted to synthesized the PEG lubricant.

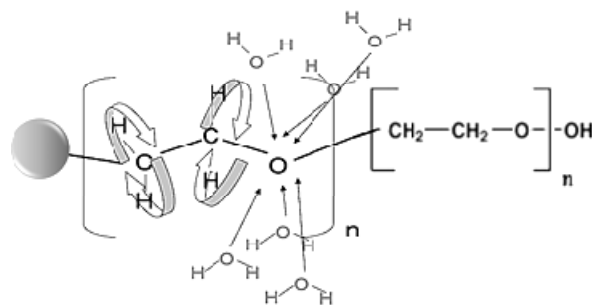


Fig.1 The polyethylene glycol (PEG) molecular structure.

As an artificial lubricant, PEG (molecular weight: 2 million) powder was prepared, dissolved in distilled water, heated and synthesized to 6wt.% PEG hydrate sol material, as shown in Figure 2.

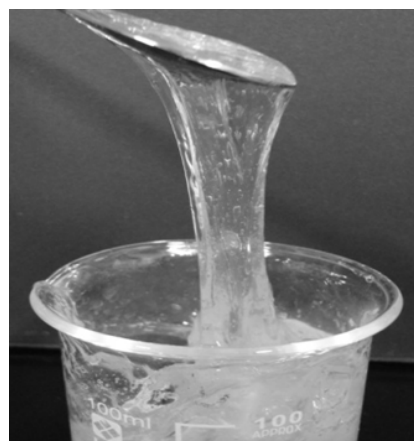


Fig.2 Polyethylene glycol (PEG) lubricant. (PEG 6 wt% sol)

This water glycol hydraulic fluid has a three-dimensional network structure with H<sub>2</sub>O molecules and high viscoelasticity.

#### 2.1.2 Viscosity of PEG lubricant

The measured viscosities of this PEG lubricant and human synovial fluid are shown and compared in Figure 3. PEG lubricant has high viscosity (about 280 dPa·st) compared with synovial fluid, and shows non-Newtonian fluid changes depending on the shear rate.

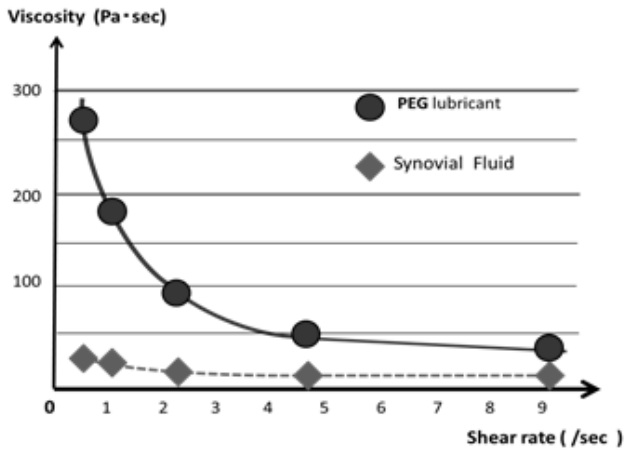


Fig.3 The Correlation of the viscosity and Shear rate of two kinds of lubricants (PEG lubricant and human synovial fluid)

## 2.2 Method

### 2.2.1 knee OA model of rabbits

Prior to an experiment on intra-articular injections of PEG, knee OA model rabbits were prepared by a surgical procedure producing a cartilage defect in the femoral condyle and meniscectomy, followed by three months of postoperative progress.

As shown in Figure 4, the rabbits knee joints of these experimental rabbits exhibit features reflecting the early appearance of osteoarthritis, such as progressive cartilage wear of the tibia and femoral cartilage defect (shown by arrows).

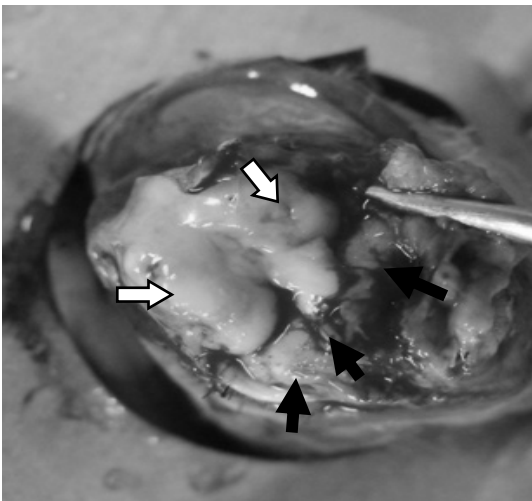


Fig.4 Macro-appearance of Osteoarthritis (OA) model of the knee joint of rabbits

### 2.2.2 In vivo trial of intra-articular lubricants for osteoarthritis of the knee

While PEG lubricant was injected into one knee joint once a month for three months, the other side, used as a control, was not injected; after that the rabbits were then sacrificed, and the cartilage of the knee was examined macroscopically and histologically.

## 3. Result

### 3.1 macroappearance

Figure 5 shows the macroappearance of the articular cartilage in knees of the control group and the PEG-injected group (PEG group). In the PEG group, there were no significant changes in the cartilage in both femur and tibia compared with the cartilage before injection. In contrast, apparent erosion and some progression of deformation, including cartilage defect (arrows), were observed in the tibial cartilage of the control group, as shown in Fig. 5 (a)-2.

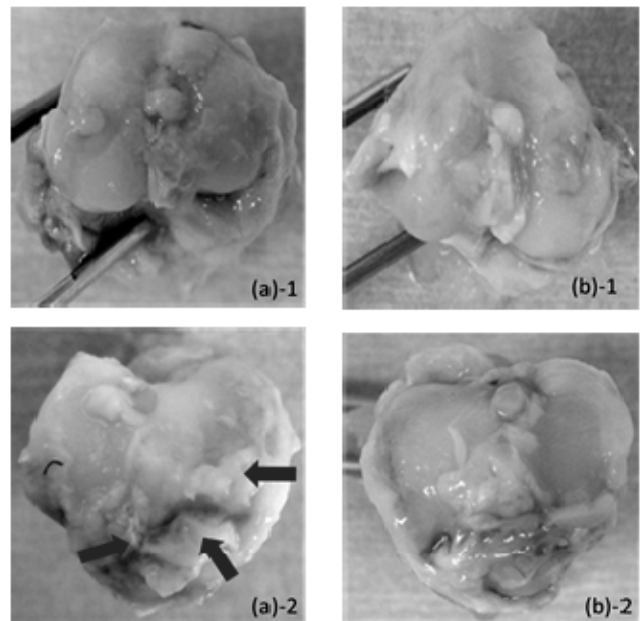


Fig.5 Micro photographs of rabbits knee joints for 3months under PEG injection

- |                         |                        |
|-------------------------|------------------------|
| (a)-1 femoral cartilage | (a)-2 tibial cartilage |
|                         | in Control group       |
| (b)-1 femoral cartilage | (b)-2 tibial cartilage |
|                         | in PEG group           |

### 3.2 Histological finding

Figure 6 shows the results of the histological photographs of tibial articular cartilage. Although partial mild disturbance is observed on the cartilage surface in the PEG group, the cartilage surface itself is maintained. In contrast, in the control group, the cartilage is in a poor state, with thinning and partial delamination.

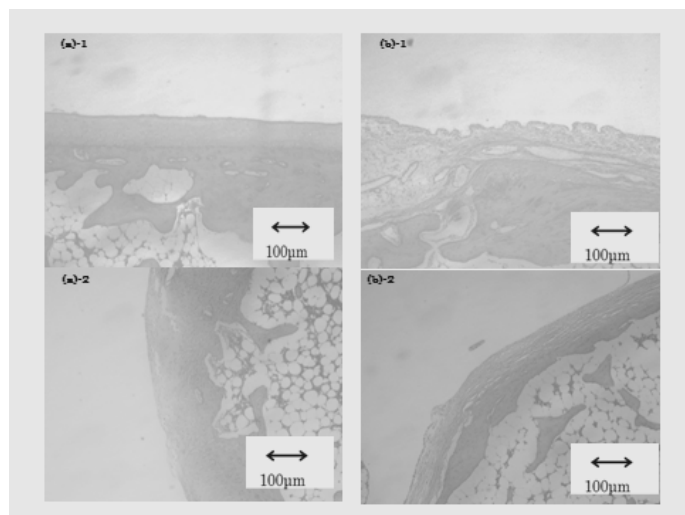


Fig 6. Histological photographs of rabbits knee joints for 3 months under PEG injection

(a)-1 femoral cartilage      (a)-2 tibia cartilage  
in Control group  
(b)-1 femoral cartilage      (b)-2 tibia cartilage  
In PEG group

### 4. Discussion

According to the pathophysiology of osteoarthritis of knee joints, OA is characterized by the slow degradation of cartilage over several years. In normal cartilage, a delicate balance exists between matrix synthesis and degradation; in contrast, OA cartilage degradation exceeds the rate of synthesis or regeneration. The balance is affected and regulated by several factors, such as age and weight.

Considering that biomechanical stress also belongs to this group of factors, it would be highly effective for the medication and prevention of osteoarthritis to improve the biomechanical and tribological circumstances of the cartilage in knee joints by the use of an appropriate lubricant. This experimental result supports this concept.

Moreover, PEG mixed synovial fluid exhibited the best

result. As this mechanism, interaction between the PEG molecules and proteins in the synovial fluid is also suspected. It is well known that these proteins in the synovial fluid, especially albumin, have a very important role in boundary lubrication in synovial joints<sup>7</sup>. The protein molecules can adsorb on cartilage surface as a wear-protective layer and form an excellent lubrication system. On the other hand, since PEG molecules are also organic compounds having a hydroxyl group at one or both ends of the molecules<sup>8</sup>, boundary lubricating film would be formed between lubricant surfaces<sup>9,10</sup>. The improved lubrication mode by two different types of functional lubricant might prevent OA progression, although the details of the mechanism involved are unclear.

The results of our in vivo study strongly suggested that a lubricant involving a mixture of PEG hydraulic fluid and synovial fluid could effectively protect against OA progression in the knee joint. Though further study regarding the details of the lubrication mechanism of synovial fluid mixed with PEG is necessary, in future, by modifying other functional compounds at one or both ends of the PEG molecules, even better intra-articular injection of PEG lubricant could be developed for OA treatment.

### 参考文献

- 1) Hayashi, K., Ishii, Y., Ninomiya, S., Takaoka, K. and Nakamura, T. (1997) Orthopedic Surgery, 48 No.8 . (Nankoudo Co.,Ltd., Japan).
- 2) Moskowitz, R.W., Howell, D.S., Golgberg, V.M. and Mankin, H.J. (1992) Osteoarthritis / Diagnosis and medical / Surgical Management, 2nd..Ed. (W.B.Saunders .Co., USA).
- 3) Moreland, L. W. (2003). Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis : mechanisms of action, Arthritis Res Ther., 5, pp. 54–67.
- 4) Goto, M., Hanyu, T., Yoshino, T., Matsuno, H., Shimizu, M., Murata, N., Shiozawa, S., Matsubara, T., Yamana, S. and Matsuda, T. (2001) Intra-articular injection of hyaluronate (SL-6601D) improves joint pain and synovial fluid prostaglandin E2 levels in rheumatoid arthritis : A multicenter clinical trial. Clin.Exper.Rheum. 19. pp.377-383.
- 5) Neustadt, D.H. (2003) Long-term efficacy and safety of intra-articular sodium hyaluronate (Hyalgen) in patients with osteoarthritis of the knee.

- Clin.Exper.Rheum. 21. pp.307-311.
- 6) Kobayashi, M., Ohashi, A. and Hyon, S.Y. (2013) Assessment of Polyethylene glycol as an Intra-articular Injection for Osteoarthritis of Knee joint. Japan.J.Clinic.Biomech., 33, pp. 231–36.
  - 7) Murakami T, Higaki T. (1994) Role of Constituents in Synovial Fluid and Surface Layer of Articular Cartilage in Joint Lubrication (Part 2)-The Boundary Lubricating Ability of Proteins. Tribologist. 40(7) 598-604.
  - 8) Nagasaki, Y. (2011) Construction of a densely poly(ethylene glycol)-chain-tethered surface and its performance. Polymer Journal. 43 pp.949-958.
  - 9) Sakurai, T. (1991) Tribology Series 1, 2nd Ed. (Saiwai-Press, Japan).
  - 10) Okabe, H., Masuko, M and Sakuai, K. (1981) Dynamic behavior of Surface-Adsorbed Molecules under Boundary Lubrications. Trans. ASLE. 24. pp.467-473.