THE EFFECTIVENESS AND SAFETY OF INTRA-ARTICULAR INJECTION OF ACTOVEGIN IN OSTEOARTHRITIS OF THE KNEE : A PHASE TWO CLINICAL TRIAL

Mr. Somsak Kuptniratsaikul

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science in Health Development
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ประสิทธิผลและความปลอดภัยของยาฉีด Actovegin เข้าข้อเข่าในการรักษาผู้ป่วยข้อเข่าเสื่อม: การศึกษาทางคลินิกระยะที่ 2

นายสมศักดิ์ คุปต์นิรัติศัยกุล

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาการพัฒนาสุขภาพ
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Thesis Title	The Effectiveness and Safety of Intra-articular Injection of Actovegin in Osteoarthritis of the Knee : A Phase Two Clinical Trial
By	Mr.Somsak Kuptniratsaikul
Field of Study	Health Development
Thesis Advisor	Associate Professor Tawechai Tajapongvorachai
Thesis Co-advisor	Professor Visanu Thamlikitkul

Accepted by the Faculty of Medicine, Chulalongkorn University in Partial Fulfillment of the Requirements for the Master's Degree

……Dean of the Faculty of Medicine

(Professor Pirom Kamol-Ratanakul, M.D., M.Sc.)

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(Professor Kammant Phanthumchinda , M.D., M. Sc.)

…….. Thesis Advisor

(Associate Professor Tawechai Tajapongvorachai, M.D., M. Sc.)

…….. Thesis Co-advisor

(Professor Visanu Thamlikitkul, M.D., M. Sc.)

…….. Member

(Assosiate Professor Pibul Itiravivong , M.D.)

…….. Member

(Assist. Prof. Somrat Lertmaharit, M. Sc., M. Med. Stat.)

สมศักดิ์ คุปต์นิรัติศัยกุล : ประสิทธิผลและความปลอดภัยของยาฉีด Actovegin เข้าข้อเข่าในการรักษาผู้ป่วยข้อเข่าเสื่อม: การศึกษาทางคลินิกระยะที่ 2 (THE EFFECTIVENESS AND SAFETY OF INTRA-ARTICULAR INJECTION OF ACTOVEGIN IN OSTEOARTHRITIS OF THE KNEE : A PHASE TWO CLINICAL TRIAL) อ. ที่ปรึกษา : รศ.นพ. ทวีชัย เตชะพงศ์วรชัย, อ.ที่ปรึกษาร่วม : ศ.นพ.วิษณุ ธรรมลิขิตกุล. 47 หน้า ISBN : 974-53-1081-6

ความเป็นมา : Actovegin เป็นสารที่ได้จากการสกัดเอาโปรตีนออกจากเลือดลูกวัว ด้วยวิธีการกรองอย่างละเอียดอ่อน (Ultrafiltration) และได้มีการนำยาชนิดนี้มาใช้ทางคลินิค มีรายงานผลการรักษาเบื้องต้นมาแล้ว คือผลของการฉีดยานี้เข้าข้อเข่าเพื่อการรักษาข้อเข่าเสื่อมแต่การศึกษานั้นมีข้อจำกัดในแง่จำนวนตัวอย่าง **วัตถุประสงค์**: เพื่อศึกษาประสิทธิภาพและผลข้างเคียงของการใช้ Actovegin แบบฉีดเข้าข้อเพื่อรักษาข้อเข่าเสื่อม รูปแบบวิจัย : การศึกษาเปรียบเทียบก่อนและหลังการใช้ยา **วิธีการ**: ผู้ป่วยข้อเข่าเสื่อม จำนวน 44 คน ซึ่งไม่ได้ผลจากการรักษาแบบอนุรักษ์ ด้วยวิธีการรับประทานยาและกายภาพบำบัดแล้ว ผู้ป่วยเหล่านี้จะได้รับยา Actovegin ฉีดเข้าข้อเข่าติดต่อกัน 2 ครั้งห่างกัน 1 สัปดาห์ **การวัดผล**: บันทึกระดับความเจ็บปวดในตารางแสดงความเจ็บปวด (VAS), ระยะเวลาจนกระทั่งอาการเจ็บของข้อเข่าลดลง, เส้นรอบวงของข้อเข่า, ผลการรักษาในภาพรวมและระดับความพึงพอใจของผู้ป่วย รวมทั้งผลข้างเคียงของยาที่เกิดขึ้น **ผลการวิจัย**: พบความแตกต่างของระดับความเจ็บปวดโดยรวมอย่างมีนัยสำคัญทางสถิติ ระหว่างก่อนและหลังได้รับการรักษาด้วยการฉีดยานี้เข้าข้อเข่าในทุกมิติของการวัด ยกเว้นการปวดเข่าในอิริยาบถพักเข่า ผลของการรักษาที่ดีขึ้นโดยระดับความเจ็บปวดข้อเข่าลดลงนี้สอดคล้องกันกับผลของระดับความพึงพอใจของผู้ป่วย และการประเมินผลการรักษาโดยภาพรวม ซึ่งระดับความพึงพอใจและการประเมินผลการรักษาโดยภาพรวมในสัปดาห์ที่หนึ่งและสองไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติ แสดงว่าประสิทธิภาพของยานี้เกิดขึ้นตั้งแต่สัปดาห์แรกหลังฉีด โดยสอดคล้องกับระยะเวลาที่ผู้ป่วยประเมินว่ามีอาการปวดลดลง (เฉลี่ย 6.3 วัน) การศึกษานี้ไม่พบความแตกต่างทางสถิติของเส้นรอบวงข้อเข่าก่อนและหลังฉีดยา ส่วนผลข้างเคียงของยาพบเพียงร้อยละ 7.5 - 9.4 ซึ่งเป็นผลข้างเคียงที่ไม่รุนแรง **สรุป**: การฉีดยา Actovegin เข้าข้อนี้สามารถลดอาการปวดได้และมีผลข้างเคียงน้อย อย่างไรก็ตามควรมีการศึกษาเพิ่มเติมในแง่ของความคุ้มทุน รวมทั้งรูปแบบการวิจัยอื่นเพิ่มความมั่นใจในประสิทธิภาพของการรักษา

สาขาวิชา การพัฒนาสุขภาพ ลายมือชื่อนิสิต .....

ปีการศึกษา 2547 ลายมือชื่ออาจารย์ที่ปรึกษา .....

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KEY WORD / KNEE OSTEOARTHRITIS / ACTOVEGIN / INTRA-ARTICULAR INJECTION / SAFETY / EFFICACY

SOMSAK KUPTNIRATSAIKUL : THE EFFECTIVENESS AND SAFETY OF INTRA-ARTICULAR INJECTION OF ACTOVEGIN IN OSTEOARTHRITIS OF THE KNEE : A PHASE TWO CLINICAL TRIAL THESIS ADVISOR : ASSOC. PROF. TAWECHAI TEJAPONGVORACHAI, THESIS COADVISOR : PROF. VISANU THAMLIKITKUL, 47 pp. ISBN : 974-53-1081-6

Background: Actovegin is a protein-free hemodialysate derived from calf blood and product essentially by ultra filtration. Clinical use and outcomes of the treatment of Actovegin for osteoarthritis was reported in a recent study which was a case series of intra-articular injection. It did not show any side effects due to small sample size. Objective: To study the effectiveness and side effect of intra-articular injection of Actovegin for the treatment of knee osteoarthritis. Study design: Comparative study design (before and after design). Materials and Methods: Forty-four patients with knee OA failed to conservative treatment were recruited into the study receiving Actovegin for 2 consecutive weeks. Outcome measured: The visual analog scale (VAS) pain, the duration for pain to resolve, global assessment and patient's satisfaction of effect, adverse effects and joint effusion assessment were employed as measurement of the outcomes. Results: There were statistically significant difference between before and after in all dimensions of VAS pain except pain at rest. These results corresponded to the patient's satisfaction and patient's global assessment. There were no statistically significant difference of the patient's satisfaction and patient's global assessment between week 1 and week 2. It might indicate the effect of Actovegin injection could be detected since the first week. These results corresponded to the duration to pain resolve (mean 6.3 days). There were no difference of the knee circumference before and after injection. Although the adverse effects of this present study ranged from 7.5 - 9.4%, those were minor such as effusion, inflammation or persistent pain. Conclusion: The present study revealed positive results of intra-articular injection of Actovegin. Further study in other perspective such as randomized control trial, cost effectiveness and details of economic study should be performed.

Field of study HEALTH DEVELOPMENT Student's signature .....

Academic year 2004 Advisor's signature .....

Co-advisor's signature .....

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CHAPTER I

INTRODUCTION

RATIONALE AND BACKGROUND

Osteoarthritis (OA) is the most common degenerative joint disorder, resulting in significant morbidity and health care expense(1). It causes pain and dysfunction in 20% of elderly persons(2). It can affect any joint containing hyaline cartilage, troublesome symptoms occur most often in the weight-bearing joints of the lower extremities(3). Osteoarthritis of the knee, the most commonly affected, can be found in one third of the population between the ages of 63 and 94 years(4). A prevalence of knee pain from a recent survey of musculoskeletal disorders in Greater Manchester, was between 21-35% in men and women aged 45 or over (5). Another study from Thailand revealed the prevalence of knee OA in the community of Bangkok ranged from 34.5 - 45.6% (6). Physical disability arising from pain and loss of functional capacity reduces quality of life and increases the risks of further morbidity and mortality (7).

The pathophysiologic deficits of knee OA are associated with joint instability(8), reduction of joint range of motion(ROM) (9), and disuse atrophy of quadriceps muscle(10) which finally produced clinical concern of pain, decreased activity and physical deconditioning which, in turn, attenuate the ability to carry out activities of daily living(10,11). The pathogenesis of primary human osteoarthritis is unknown. It has been suggested that hypoxia caused by reduced subchondral blood flow plays a central role in the development of tissue damages in osteoarthritis (12).

Most treatment interventions are aimed at reducing pain with sorts of mean such as conservative physical interventions, enteral analgesics and non-steriodal

anti-inflammatory drugs (NSAIDs), and surgical correction. NSAIDs are the commonest symptomatic treatment for OA but have major adverse effects(13) and might even worsen the osteoarthritic process(14). There is also some evidence that NSAIDs may be overused(15). The cost and risks associated with surgical correction make it a later resort for most patients. Not only enteral but also parenteral administration of NSAID(16), steroid (17,18), viscosupplementation (19-22), cytokine substance (22-24), somatostatin (25) and glucosamine salt (26) were employed for the treatment.

Even though injection therapies are more invasive and sometime more expensive than oral NSAID, it can be an alternative prior to surgery which is considered very invasive and unpleasant to many senior subjects. That is a good explanation of their indication for certain group of OA knee patients who refuse surgical treatment even conservative treatment failure.

REVIEW OF LITERATURES

Osteoarthritis of the knee is a common rheumatologic disease characterized by pain, stiffness and decreased range of motion (4, 27). It is a major cause of morbidity, physical limitation and increased health care utilization, including total joint arthroplasty, especially in the elderly. The progressive erosion of articular cartilage, leading to joint space narrowing, subchondral sclerosis, marginal osteophyte formation, subchondral cysts and synovial inflammation, characterizes the disease process. The aims of treatment concern about disabling aspects of OA, varied from pain to physical and emotional deficits (1).

Nowadays there is no cure for OA, (28, 29) so treatment is primarily focused on managing the condition by minimizing morbidity. Current recommendations, including guidelines published by the American College of Rheumatology, focus on the relief of pain and stiffness and maintenance or improvement in functional status as

important goals of therapy (30). There are several strategies to relief pain and improve functions.

Moreover humoral aspects were being discussed in the initiation of arthritis. The effects of the proteolytic enzyme elastase on the cartilage of knee joints in rabbits have been investigated and there was clear evidence of elastase having severe destructive effects on cartilage (31). To prevent the initiation of cartilage damage by humoral factors, early elimination of the pathological intra-articular effusion was necessary.

Intra-articular injections of numerous pharmacological agents were introduced and reported in literatures of their advantages and drawbacks for osteoarthritis. Moens and colleagues (16) reported alternative route of administration of NSAID in 1986, this kind of technique is not commonly used currently.

Hyaluronate is another suitable agent for intra-articular injection for knee OA. In 1971, Rydell and colleagues reported an early study effect of intra-articular injection of hyaluronate which is a content of articular molecular structure (22). Namiki and colleagues (32) reported in 1982 of 45 knees study in 40 patients and suggested that the beneficial effects of hyaluronic acid may be attributable to improved lubrication of the affected joint, to normalization of synovial fluid production by the action of hyaluronic acid on synovial tissue, and / or to the improvement of the intra-articular environment by the contribution of hyaluronic acid to the rebuilding of the barrier that protects the synovial membrane and articular surface.

Moreover studies of hyaluronate injection revealed promising results (10). The proposed mechanisms of action of hyaluronate also resulted from the physical properties of hyaluronic acid, as well as from its anti-inflammatory, anabolic, local analgesic, and chrondroprotective effects (19, 33). Even with many reports of the advantage of hyaluronate injection, some adverse effect of intra-articular hyaluronate

injection include aseptic acute arthritis, which develops within hours after injection were reported (19,21). Furthermore, the medication is relatively expensive so both the cost-benefit aspects and the long-term effects of the medication is necessary to provide insights into (19). Several of other pharmacological products such as somatostatin and glucosamine salt were also reported of favorable outcomes to the disease but no sufficient consecutive reports to confirm those benefits (25, 26).

Actovegin is an interesting active medicine. It is a protein-free hemodialysate derived from calf blood and product essentially by ultrafiltration. It has been used for more than 25 years as remedy of brain circulation and metabolism in human. The clinical usage of this product has been extended to other several aspects (34) such as myopathy, brachial plexus injury, placental insufficiency, stage IV chronic arterial occlusion, acute traumatic ischemia, gastric and duodenal ulcer, DM, CTS. In addition, it was also employed in the treatment of Achellis tendonitis (35).

Its pharmacological effects have been the subject of several studies (36-38). Actovegin's mechanism of action is expressed as an effective stimulation of glucose transporter, similar to the effect of insulin (39). De Groot and colleague (36) performed an experiment with the aim of investigating Actovegin 's protective effect against anoxia in hepatocyte. Liver-cell cultures were maintained under anoxic conditions for over 8 hours, and application of Actovegin increased the survival rate of approximate 10% (an aerobic control) to 80%. At concentrations above 1 mg/ml the extract produced marked protection. At 4 hour of anaerobic incubation at 37 degrees C, only 20% of cells were damaged as compared to 50% of the anaerobic control incubation (36).

Concerning the frequency and severity of undesired drug effects (UDE), 208 of degree I and II were reported from 44 clinical studies with parenteral application of Actovegin, conducted by order of Nycomed Arzneimittel GmbH. This corresponds to a frequency of 6% in a total of 3,458 patients treated with Actovegin, compared to the

rate of 3.3% obtained in the placebo groups (34). Those commonly reported UDE of Actovegin included dizziness, headache, heat sensations, nausea and reddening of skin. In addition, Kanowski reported that Actovegin had the relatively low rate of side effects and suggested this drug to be a very favorable benefit-risk ratio (39). The results of another recent study which is a case series of intra-articular injection did not show any side effects but that might be due to the small sample size (40).

Concerning the pathogenesis of primary human osteoarthritis, it is unknown and has been suggested that hypoxia caused by reduced subchondral blood flow plays a central role in the development of tissue damages in osteoarthritis. This hypothesis was investigated using an in situ technique based on mass spectrometry to measure subchondral pO_2 and pCO_2 in both femoral heads of patients with late stage unilateral osteoarthritis and the normal opposite hip. Intraosseous pressure was recorded and lactate concentrations and pH were measured in blood samples obtained from the two femoral heads. The subchondral pO_2 in the diseased hip was significantly lower than pO_2 in the normal hip (43 torr versus 63 torr). The intraosseous pressure was significantly higher in the diseased than in the normal hip. The lactate concentration showed a 50% increase in the diseased hip. There were no differences in pCO_2 and pH between the two locations (12).

The pharmacological effects of Actovegin against anoxia seemed to reverse the process of OA and the researcher would like to confirm this effect.

CHAPTER II

RESEARCH DESIGN

RESEARCH QUESTIONS

Primary research question

What was the mean change of pain score of patients (before & after) receiving intra-articularly injection of Actovegin?

Secondary research questions

1) What was the mean duration of the symptom of knee pain resolved (measure in days) with intra-articularly injection of Actovegin?

2) What was the global assessment of improvement of the patients who receive intra-articularly injection of Actovegin?

3) What was the satisfaction rate of the patients who receive intra-articularly injection of Actovegin?

4) What were the adverse effects of intra-articularly injection of Actovegin?

5) Could intra-articularly injection of Actovegin alleviate the joint effusion in the OA patient?

OBJECTIVES

Primary objective

To evaluate the effectiveness of intra-articularly injection of Actovegin for the treatment of primary knee OA in term of pain VAS score reduction particularly in whom was unresponsive to NSAID regimen.

Secondary objectives

1. To evaluate the mean duration of the symptom of knee pain resolved (measured in days) after receiving the intra-articularly injection of Actovegin in whom was unresponsive to NSAID regimen.
2. To evaluate the patients' global assessment of improvement after receiving the intra-articularly injection of Actovegin in primary knee OA.
3. To evaluate the patients' satisfaction rate after receiving the intra-articularly injection of Actovegin in primary knee OA.
4. To evaluate the adverse effects of intra-articularly injection of Actovegin for the treatment of primary knee OA.
5. To evaluate the degree of joint effusion after intra-articularly injection of Actovegin for the treatment of primary knee OA.

RESEARCH HYPOTHESIS

The mean difference of pain score in patients with knee OA after receiving Actovegin intra-articularly injection was different from prior to injection.

Statistical hypothesis

Null hypothesis: $\mu_{Before} - \mu_{After} = 0$

Alternative hypothesis: $\mu_{Before} - \mu_{After} \neq 0$

μ_{Before}: mean of pain VAS in patients with knee OA before receiving intra-articularly injection of Actovegin

μ_{After} : mean of pain VAS in patients with knee OA after receiving intra-articularly injection of Actovegin

CONCEPTUAL FRAMEWORK

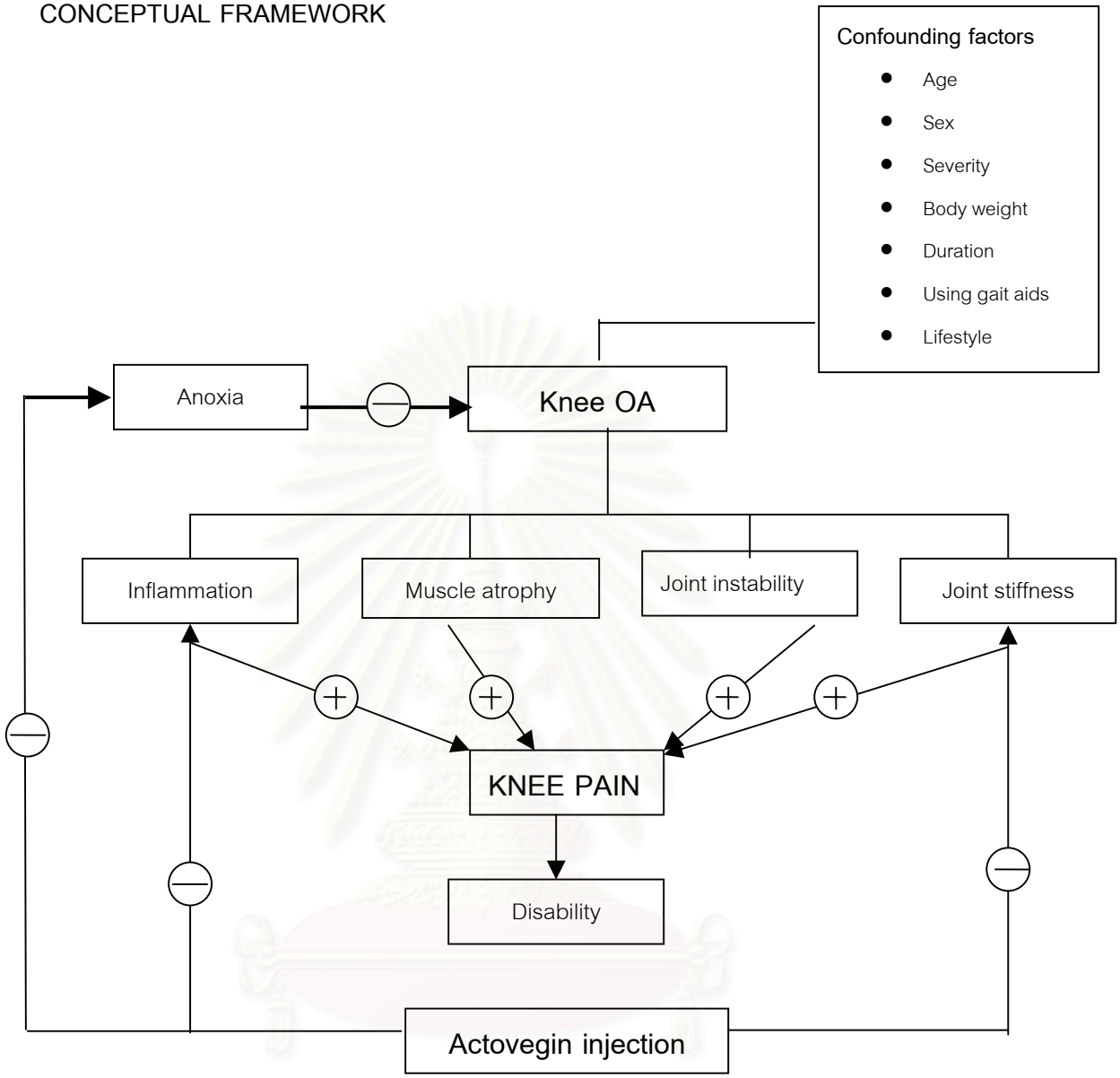

Figure 2.1 Conceptual framework demonstrates factors influencing pain elicited from disease of knee osteoarthritis

OPERATIONAL DEFINITIONS

Knee osteoarthritis

Diagnostic criteria were based on American College of Rheumatology classification: (41) Knee pain and radiographic osteophytes and at least 1 of the following 3 items

1. Age > 50 years
2. Morning stiffness < 30 minutes in duration
3. Crepitus on motion

Fail to conservative treatment

The patients were considered fail to conservative treatment when there were severe and persistent pains after

- full recommended dosages of NSAID including rehabilitation program were prescribed and administrated adequately
- any undesired effect of conservative treatment causing the patients to cease their treatment

RESEARCH DESIGN

This study was designed as a comparative study design (before and after design) to answer the primary research question.

CHAPTER III

RESEARCH METHODOLOGY

POPULATION AND SAMPLE

Target population

The patients with primary knee osteoarthritis with grade II-III of Kellgren & Lawrence criteria.

Study population

All of the patients diagnosed as knee osteoarthritis and failed to conservative treatment in out-patient clinic, Department of Orthopedics, Chulalongkorn Hospital were recruited in this study.

Eligibility criteria

Inclusion criteria

- Patients' age more than 50 years old
- Both sex
- Fail to conservative treatment
- Patient who could not tolerate medical treatment
- Patient who accepted intra-articular injection
- Pain VAS on level walking more than or equal to 5
- Patients grade II-III of Kellgren and Lawrence criteria

Exclusion criteria

Patients who had one or more of the following criteria were excluded from the study

- Secondary causes of knee OA
- Severe joint instability or severe deformity (grade IV Kellgren and Lawrence)

- History of intra-articular injection within 6 months
- Bleeding tendency
- History of allergy to calf protein

Sample size

Sample size calculation was based on the ability to detect a clinically important difference of mean of pain score between before and after injection. The equation for sample size estimation of two independent means was

$$n = \frac{\sigma^2 [Z_{\alpha/2} + Z_{\beta}]^2}{d^2}$$

α = 0.05 (type 1 error)

β = 0.10 (type 2 error)

$Z_{\alpha/2}$ = 1.96 (two-tailed)

Z_{β} = 1.28 (power of the test is 90%)

d = mean of each pair pain VAS change in pilot group

σ^2 = variance of pain VAS change in pilot group

From literature review, there was only one article studied the effect of Actovegin which measured pain VAS as a primary outcome of treatment in knee OA (40). There was only one treatment group. The mean and SD of pain VAS of before, after treatment and mean difference were 70.0 $\pm$ 21.2, 42.6 $\pm$ 24.1 and 27.4 $\pm$ 20.2 respectively. To use the α equal to 0.05 (two-tailed), the power of this study is 90%, the number of subjects was 5.7.

VAS pain(pre) = 70.0 $\pm$ 21.2

VAS pain(post) = 42.6 $\pm$ 24.1

mean difference = 27.4 $\pm$ 20.2

$$n = \frac{(20.2)^2 [1.96 + 1.28]^2}{[27.4]^2} = 5.7$$

The number of calculated sample size in this study was as small as 5.7. The reason was that the standard deviation of mean difference of the previous study was so narrow as compared to the very wide mean difference. Even though a very small number of sample size calculation, the author considered at least number of sample size for normal distribution. In this study, 30 cases were the appropriate sample size. When considered 25% drop out rate, the number of sample size would be 40 as shown below.

$$n = \frac{30}{(1 - 0.25)} = 40$$

INTERVENTION

Patients were asked to discontinue all current OA medications but only tramadol as a rescue medication and were scheduled to return at the end of first and second week. They were interviewed for demographic and baseline data. They received intra-articularly injection of actovegin once a week for two times. Subjects had no other treatment except tramadol which researcher prescribed for pain relief. They were asked to bring medicine back at follow up period to count for the rest. In addition, they were expected to report undesired effects happened after injection (potential adverse effects). Pain visual analog scale improvement indicated by subject was brought to researcher in two weeks follow up.

SAFETY MEASURES

The study protocol was terminated if one of the following happened

- Serious adverse event occurred.
- Patients decided to withdraw from the study.
- Patients got much improved.

DATA COLLECTION

After all subjects signed the informed consent form, they were interviewed about their baseline characteristics, and asked to complete the questionnaire including VAS on different activities. At the end of the first and second week, they completed the questionnaire, including complications occurred, their satisfaction and the overall improvement. Participants were asked to record overall pain score everyday. If the overall pain came down to 35% from the baseline, that meant the date for pain resolved (42).

Patients' global assessment of the treatment

At the end of the first and second weeks, the patient was asked to rate his/her global assessment of the SWD treatment which were a 6-categorical scale, i.e. complete recovery, much improved, moderately improved, slightly improved, no different, or getting worse.

Patients' satisfaction to the treatment

At the end of the first and second week, the patient was asked to rate his/her satisfaction to the SWD treatment which were a 5-categorical scale, i.e. very satisfied, moderately satisfied, little satisfied, indifferent, or unsatisfied.

Safety monitoring

The patient was asked to report to the therapist regarding any symptoms occurring after injection. Adverse events of actovegin, e.g. dizziness, headache, heat sensations, nausea and reddening of skin, were evaluated at the first and second-week follow up.

MEASUREMENT

All of the measured variables including administrative variables, baseline variables, efficacy variables, and safety variables were tabulated in table 3.1.

Table 3.1 Summary of measured variables

Administrative variables		
■ Name		
■ Identification no.		
■ Telephone no.		
Baseline variables / Covariates		
■ Age (yr)	Continuous numerical	Mean ± SD
■ Sex	Dichotomous categorical	N (%)
■ Body mass index (kg/m^2)	Continuous numerical	Mean ± SD
■ Education level	Ordinal categorical	N (%)
■ Duration of disease (yr)	Continuous numerical	Mean ± SD
■ Affected side	Nominal categorical	N (%)
■ Activity level	Nominal categorical	N (%)
■ Severity score	Continuous numerical	Mean ± SD
Efficacy variables		
■ Pain on level walking	Continuous numerical	Mean ± SD
■ Pain on going up and downstairs	Continuous numerical	Mean ± SD
■ Pain at night	Continuous numerical	Mean ± SD
■ Pain at rest	Continuous numerical	Mean ± SD
■ Pain on weight bearing	Continuous numerical	Mean ± SD
■ Knee circumference	Continuous numerical	Mean ± SD
■ Patient's global assessment	Ordinal categorical	N (%)
■ Patient's satisfaction	Ordinal categorical	N (%)
Safety variables		
■ Adverse events	Nominal categorical	N (%)

CHAPTER IV

DATA ANALYSIS

GENERAL CONSIDERATIONS

The statistical analysis was focused on the detection of significant differences between pre and post injection with respect to the overall VAS.

All tests of hypotheses were conducted at the two-sided, and 0.05 level of significance.

The statistical analysis was performed using SPSS for windows, release11.0.1 (SPSS, Inc).

PLAN FOR STATISTICAL DATA ANALYSES

Baseline characteristics

The study subjects were examined for their baseline characteristics and demographic data were described as descriptive data.

Efficacy analyses

Statistical analysis was performed to compare the outcomes between the pre and post treatment groups. The mean and SD of pain VAS before and after injection were computed with 95% confidence interval. The statistical analysis was summarized in Table 4.1. Since the primary outcome (VAS) was the continuous variable and the difference was normally distributed, parametric test (paired t-test) was used to compare the mean of difference of pain VAS before and after injection.

For the secondary outcomes, the patient's global assessment and satisfaction index of week 1 and week 2 were analyzed by Mc Nemar test.

Safety analyses

The frequencies of adverse events were presented with descriptive statistics. Test of statistical hypothesis was not applied because the adverse events were expected to occur in very low frequency.

Table 4.1 Summary of statistical analysis

Variables	Statistical test
Primary efficacy variable	
■ Overall pain score	Paired t-test
■ Pain on level walking	Paired t-test
■ Pain on going up and downstairs	Paired t-test
■ Pain at night	Paired t-test
■ Pain at rest	Paired t-test
■ Pain on weight bearing	Paired t-test
Secondary efficacy variables	
■ Patient's global assessment of effect (wk 1 vs. wk 2)	Mc Nemar test
■ Patient's satisfaction to treatment (wk 1 vs. wk 2)	Mc Nemar test
■ Knee circumference	Paired t-test
Safety variables	
■ Adverse events	No statistical test

CHAPTER V

ETHICAL CONSIDERATION

GENERAL CONSIDERATION

This study was conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki. This study was approved by the ethical committee of Faculty of Medicine, Chulalongkorn University.

Prior to recruitment into this study, the patients were thoroughly informed about the following items:

1. Objectives of the study
2. The information about details of the interventions
3. Treatment outcomes and potential side effects
4. The patients' right to withdraw from the study without interference with their proper medical care.

A signed informed consent was obtained from the patient without enforcement. (For consent form, see APPENDIX C).

SPECIFIC CONSIDERATION

The complications of the treatment regimens such as dizziness, headache, heat sensations, nausea and reddening of skin were carefully detected. To beware for these potential complications, close observation for one hour after injection was performed. The patients were allowed to call the principal investigator at anytime in case of adverse effects occurred.

CHAPTER VI

RESULTS OF THE STUDY

FLOW OF STUDY PARTICIPANTS

Figure 6.1 demonstrated flow of study participants. Forty-four were enrolled. Forty patients came back for first visit: 4 cases were lost to follow up (2 cases due to inaccessible and 2 cases due to economic problems). Only thirty-two subjects came back for second visit. There were 8 cases dropped out from the study; 6 cases were due to much improved and 2 cases were due to getting worse. The characteristics of all lost cases were similar to those of included cases. Therefore, data of 40 and 32 cases were finally included in the first and second week analysis.

BASELINE AND DEMOGRAPHIC DATA

Table 6.1 demonstrated baseline and demographic data of the patients. Data of the subjects were presented on their baseline characteristics.

The data variables of the subjects were summarized as mean, SD, minimum, maximum as follows: age (58.55 $\pm$ 11.22 yr), sex (female: 37 (84.1%), body mass index (27.46 $\pm$ 4.34 kg/m^2), education level (Illiterate: 4.5%, primary school: 72.7%, secondary school: 13.6%, university: 9.1%), duration of disease (38.89 $\pm$ 58.11 months), affected side (right: 22(50%), lifestyle (sedentary: 22.7%, active life: 29.5%, still working: 29.5%, agriculture: 15.9%, household shore: 2.3%), and baseline severity score (14.45 $\pm$ 4.09).

EFFICACY OUTCOME

Change from baseline of average pain score and pain score on different activities after 1-week and 2-week of Actovegin injection treatment were normally distributed, which were confirmed by Kolmogorov-Smirnov test (average pain score reduction at 1 and 2 week: p = 0.139 and 0.147, pain at level walking reduction at 1 and 2 week: p = 0.194 and 0.149, pain on going up and down stair reduction at 1 and 2 week: p = 0.185 and 0.184, pain at night reduction at 1 and 2 week: p = 0.155 and 0.150, pain at rest reduction at 1 and 2 week: p = 0.243 and 0.209 , pain on weight bearing reduction at 1 and 2 week: p = 0.219 and 0.144). Therefore, the comparison of average pain score and pain on different activities between before and after the treatment were performed by parametric test (paired t-test).

Effectiveness of the treatment between week 0 vs. week 1 and week 0 vs. week 2 were demonstrated in Table 6.2 and 6.3. The change from baseline in average pain score were 1.48 $\pm$ 2.51 and 2.27 $\pm$ 2.76, p = 0.001 and<0.001 for week1 and week 2 respectively. The detail of pain score reduction in certain activities were as of the followings; pain reduction on weight bearing were 1.64 $\pm$ 3.06 and 2.03 $\pm$ 3.30, p = 0.002 for both week1 and week 2, pain reduction on going up and downstairs were 2.01 $\pm$ 3.02 and 3.20 $\pm$ 3.52, p < 0.001 for both week1 and week 2, and pain on level walking were 2.01 $\pm$ 3.02 and 2.93 $\pm$ 3.15, p<0.001 for both week 1 and week 2. These pains on activities were improved statistically significant in both week 1 and 2 follow up. However, the pain reduction at rest was 0.34 $\pm$ 3.03 and 0.78 $\pm$ 2.57, p = 0.502 and =0.106 for week1 and week 2 respectively. These pain reduction at rest revealed no statistical significance in neither week 1 nor 2 follow up while the pain reduction at night were 1.28 $\pm$ 4.30 and 2.25 $\pm$ 4.67, p = 0.078 and =0.01 for week1 and week 2 respectively. This pain reduction at night was statistically significant in only week 2 but not in week 1.

The secondary efficacy outcomes of the present study comprised knee circumference, global assessment index, patient's satisfaction index, duration of pain resolved, and adverse events. Because change from baseline of knee circumference

reduction after 1-week and 2-week of Actovegin injection treatment revealed normal distribution, which was confirmed by Kolmogorov-Smirnov test: p = 0.177 and 0.186 at week 1 and week 2 respectively, the parametric test (paired t-test) was employed. There was no statistically significant difference of knee circumference between before and after treatment.

Regarding the secondary outcomes, the global assessment index in week 1 and week 2 were shown in Table 6.4. The improved group (much, moderately and slightly improved) compared to the non improved group was 74.4%: 25.6%, week 1; 90%: 10%, week 2 respectively). The numbers of improved and not-improved groups in week 1 and week 2 was analyzed by Mc Nemar's test (Table 6.5). Considering the patients' satisfaction index of treatment, the satisfied groups (little, moderately and very satisfied) were 79.5% and 93.1% in week1 and week 2 respectively (Table 6.6). The numbers of satisfied and unsatisfied groups in week 1 and week 2 was also analyzed by Mc Nemar's test (Table 6.7). Table 6.8 revealed the duration of pain resolved after first injection which was 6.27 $\pm$ 4.34 days, with ranged from 1 to 14 days.

SAFETY OUTCOME

The adverse events of Actovegin injection intra-articularly were demonstrated in Table 6.9. The adverse events ranged from 7.5 - 9.4%. All of the adverse events were inflammation, persistent pain and more disabled in the following day, which could be resolved in a few days. There was no serious adverse event at all.

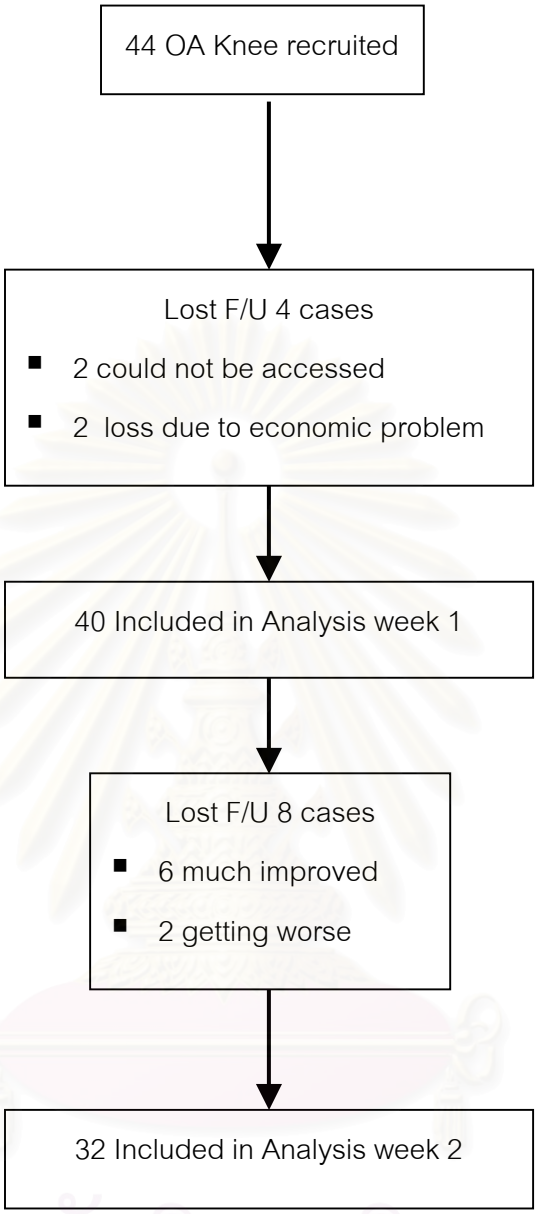

Figure 6.1 Flow of study participants

Table 6.1 Baseline characteristics of the patient

Characteristics	mean	SD	min	max
Age (yr)	58.55	11.22	47.0	81.0
Sex (female)	37(84.1%)			
Body mass index (kg/m^2)	27.46	4.34	18.36	37.66
Educational level				
Illiterate	2 (4.5%)			
Primary school	32 (72.7%)			
Secondary school	6 (13.6%)			
University	4 (9.1%)			
Duration of disease (mo)	38.89	58.11	1.0	240.0
Affected side (right)	22(50%)			
Activity				
Sedentary	10 (22.7%)			
Active life	13 (29.5%)			
Still working	13 (29.5%)			
Agriculture	7 (15.9%)			
Household shore	1 (2.3%)			
Severity score (0-24)	14.45	4.09	5.5	22.5

Note: Data were mean, SD, minimum, maximum or n (%)

Table 6.2 Pain score on different activities, average pain score and knee circumference compared between week 0 and week 1

Efficacy variables	Score at week 0	Score at week 1	Mean difference ± SD	95% confident interval		P-value[@]
				lower	upper	
Pain on level walking	6.96 ± 1.97	5.05 ± 2.71	1.91 ± 3.17	0.85	2.96	0.001*
Pain on going up and downstairs	7.58 ± 1.75	5.57 ± 2.50	2.01 ± 3.02	1.01	3.02	<0.001*
Pain at night	4.92 ± 3.35	3.64 ± 2.97	1.28 ± 4.30	-0.15	2.72	0.078
Pain at rest	2.60 ± 2.85	2.26 ± 2.37	0.34 ± 3.03	-0.67	1.35	0.502
Pain on weight bearing	5.74 ± 2.80	4.10 ± 2.95	1.64 ± 3.06	0.62	2.67	0.002*
Average pain score	5.59 ± 1.75	4.11 ± 2.36	1.48 ± 2.51	0.64	2.32	0.001*
Knee circumference	42.09 ± 4.82	41.97± 5.19	0.12 ± 1.41	-0.34	0.58	0.607

Note: @ Paired t-test

* Statistically significant

Table 6.3 Severity score, pain score on different activities, average pain score and knee circumference compared between week 0 and week 2

Efficacy variables	Score at week 0	Score at week 2	Mean difference ± SD	95% confident interval		P-value[@]
				lower	upper	
Severity score	14.42 ± 3.93	10.53 ± 6.07	3.89 ± 4.71	2.22	5.56	<0.001*
Pain on level walking	7.12 ± 2.13	4.18 ± 2.79	2.93 ± 3.15	1.76	4.11	<0.001*
Pain on going up and downstairs	7.73 ± 1.84	4.53 ± 2.76	3.20 ± 3.52	1.89	4.51	<0.001*
Pain at night	4.77 ± 3.56	2.52 ± 2.61	2.25 ± 4.67	0.58	3.92	0.010*
Pain at rest	2.77 ± 3.10	1.98 ± 2.77	0.78 ± 2.57	-0.18	1.74	0.106
Pain on weight bearing	5.87 ± 3.06	3.83 ± 3.15	2.03 ± 3.30	0.80	3.26	0.002*
Average pain score	5.69 ± 1.92	3.42 ± 2.47	2.27 ± 2.76	1.24	3.31	<0.001*
Knee circumference	42.15 ± 4.84	41.85 ± 4.85	0.29 ± 1.34	-0.20	0.78	0.237

Note: @ Paired t-test

* Statistically significant

Table 6.4 Patient's global assessment at week 1 and 2

Efficacy variables	Week 1 (n = 39)	Week 2 (n = 29)
Patient's global assessment		
■ Much improved	8 (20.5%)	11 (37.9%)
■ Moderately improved	13 (33.3%)	12 (41.4%)
■ Slightly improved	8 (20.5%)	3 (10.3%)
■ No difference	8 (20.5%)	3 (10.3%)
■ Getting worse	2 (5.1%)	0 (0%)

Note: Data were n (%)

Table 6.5 Patient's global assessment difference between week 1 and 2

Week 1	Week 2		Total	P-value[@]
	Improved	Non-improved		
Improved	20	1	21	.125
Non-improved	6	2	8	
Total	26	3	29	

Note: Data were n

@ Mc Nemar test

Table 6.6 Patient's satisfaction at week 1 and 2

Variables	Week 1 (n = 39)	Week 2 (n = 29)
Patient's satisfaction		
■ Very satisfied	16 (41.0%)	12 (41.4%)
■ Moderately satisfied	14 (35.9%)	12 (41.4%)
■ Little satisfied	1 (2.6%)	3 (10.3%)
■ Indifferent	4 (10.3%)	2 (6.9%)
■ Unsatisfied	4 (10.3%)	0 (0%)

Note: Data were n (%)

Table 6.7 Patient's satisfaction difference between week 1 and 2

Week 1	Week 2		Total	P-value[@]
	Satisfied	Unsatisfied		
Satisfied	21	2	23	.289
Unsatisfied	6	0	6	
Total	27	2	29	

Note: Data were n

@ Mc Nemar test

Table 6.8 Duration to pain resolved after first injection

Outcome	mean	SD	min	max
Duration to pain resolved (days)	6.27	4.34	1	14

Table 6.9 Adverse events of Actovegin

Adverse events	Number of remained subjects	Frequency n (%)
First week adverse event;	40	3(7.5%)
Second week adverse event;	32	3(9.4%)
Adverse event frequency		
■ Rash		0
■ Nausea		0
■ Effusion		2
■ Inflammation		1
■ Persistent pain		2
■ More disabled		3
■ Anaphylaxis		0

Note: Some patients experienced more than one event

CHAPTER VII

DISCUSSION, CONCLUSION AND RECOMMENDATION

DISCUSSION

Baseline characteristics

The main objective of the present study was to assess treatment effect of a kind of protein dialysate of calf blood extraction (Actovegin) on the intensity of pain measured by pain visual analog scale score (PVAS). The most reliable indicator of the existence and intensity of pain is patient self-reporting. These data were reliable according that there was no inter observer variation because all the scores were assessed by the same evaluator (individual patient per se) both before and after intervention. As a result, assessment of pain experience is always subjective and the data obtained can be influenced by psychological (pain experience, pain expectation, cognitive function), social and medical factors (43).

In this clinical trial the baseline variables were included age, sex, body mass index, education level, affected side, lifestyle, severity score (Table 6.1). Because the data of age, body mass index, and severity score were distributed in normal distribution spectrum, it was appropriate to report these data in term of means with standard deviations. The mean age of subjects was 58.55 years with only one case of 81 year old subject which the author believed that there was very little effect on high number of total cases. The average of body mass index of these subjects was 27.46 which were classified as obese group (44). There was evidence of body weight on severity of OA knee (45). The average severity score of the subjects was 14.45. According to the severity score (Lequesne's index), the score ranged from 11 to 13 was categorized into very severe group and the score more than or equal to 14 was extremely severe (46). Therefore, the subjects in this study had extremely severe degree of osteoarthritis. There were more female patients in this study which was corresponded to many studies of prevalence of osteoarthritis patient in general population (47).

Concerning the education level, most subjects graduated from primary school because this study was performed in public hospital.

Effectiveness

In the present study, the effectiveness was estimated from primary outcome, i.e. average pain score improvement, and secondary outcomes, i.e. knee circumference, global assessment index, patient satisfaction index, duration of pain resolved and adverse events.

For the primary outcome, the author planned to analyze the average pain reduction of week 2 from baseline according to the maximum effect of Actovegin on the second week (39). Unfortunately, a considerable number of subjects were withdrawal after the first week; therefore the average pain reduction of week 1 from baseline was also analyzed. The average pain score reduction between week 0 and week 2 (Table 6.3) was statistically significant between before and after intervention with the 95% CI of difference of 1.24 and 3.31. The average pain score reduction between week 0 and week 1 (Table 6.2) revealed similar improvement to that between week 0 and week 2. In the present study, baseline average pain score was 5.69 (before intervention). If we considered in detail of pain improvement in certain activities ;pain on weight bearing, pain on going up and downstairs and pain on level walking, these pains on activities were statistically significant improved in both week 1 and 2 follow up and there was a tendency of dosage time dependent as well. Also the 95% CI of average pain score at week 2 follow up could reach the clinical significant improvement (42) (22-58%), and make global assessment moderately to much improved, and also the high proportion of moderately to very satisfied patients. However, pain at rest revealed no statistically significant in neither week 1 nor 2 follow up. Even though pain at night time revealed statistical significant in week 2 but not in week1, the 95%CI of week 2 was still low (0.58-3.92) and might not be considered clinical significant. A good explanation of these outcomes could be explained by the nature of the disease which is not only mainly degenerative process but also activity aggravation. According to the function of knee as a weight bearing joint, cyclical movement all day long, and also the pain of knee

osteoarthritis could be percept from many kinds of nerve endings, the author postulated that the pain from mechanical stimuli might be alleviated from the effect of the intervention in this study while the pain from chemical stimuli played a high influence on the ultimate pain evaluation (48).

From the results of this study (Table 6.2 and 6.3), there was evidence of pain score reduction in all kind of pain from mechanical loading (e.g. pain on level walking, pain on going up and downstairs, pain on weight bearing). Contrarily, pain without mechanical load (e.g. pain at night and the pain at rest) were not improved significantly. Because of considerable magnitude of visual analog average pain score at the beginning (5.69), the pain improvement could be demonstrated at clinical significant level. Pain visual analog score on varying activities such as pain at level walking, pain on going up and downstairs, pain on weight bearing were rather high magnitude at base line, so it was not so difficult to demonstrate the statistically and clinically significant difference after treatment. On the other hand the pain at night and the pain at rest might be rather more difficult to demonstrate the difference according to the base line magnitude of the pain. As a result of the present study, the author recommended the criteria of patient recruitment in further study as a considerably high magnitude of pain at rest and pain at night time (such as more than 5) to demonstrate a distinguish difference improvement.

Compared to the previous article (40) that reported favorable outcome for the application of Actovegin, it had small sample size, did not categorize pain score on different activities and followed up the patient only one time. The present study conducted with adequate sample size and the proper methodology but needed more degree of strength of evidence such as a double-blinded placebo controlled trial. According to the favorable outcome of the present study, the author encouraged further study of economic dimension which might be more proper as an alternative injection therapy to the osteoarthritis patient.

Considering the change from baseline of knee circumference reduction after 1-week and 2-week of Actovegin injection treatment (Table 6.2 and 6.3), there was

no statistically significantly circumference reduction between before and after the treatment. The author believed that the amount of synovial fluid content intra-articular was so little that it could not be demonstrated by direct measurement by this mean. As a result the author recommended no need for knee circumference measurement as a purpose of synovial fluid volume change in further studies. However that does not mean other purposes such as muscle atrophy which may be measurable.

Regarding the secondary outcomes, the patient's global assessment showed the improved (much, moderately and slightly) group proportion was far out weight to the non improved one (74.4% : 25.6%, week 1; 90% : 10%, week 2) (Table 6.4). When compared between the numbers of improved and not-improved groups in week 1 and week 2, there was no statistical significance by Mc Nemar's test (Table 6.5). Considering the patients' satisfaction index of treatment, the satisfied groups (little, moderately and very satisfied) were 79.5% and 93.1% in week1 and week 2 respectively (Table 6.6). When compared between the numbers of satisfied and unsatisfied groups in week 1 and week 2, there was no statistical significance by Mc Nemar's test (Table 6.7). Because there were no statistical significant difference of both patient's global assessment and patients' satisfaction index of treatment, this implied the effect of Actovegin could be detected as early as the first week after injection. Concerning other secondary outcome; the mean duration to pain resolved was 6.27 days (ranged from 1 to 14 days) (Table 6.8), which was considered as useful in clinical practice. Because the natural history of osteoarthritis was periodical recurrence, the author planed to extend the follow up period. Unfortunately, the prolong follow up was not feasible, so we could not get those information.

Compliance

Concerning the Actovegin intra-articular injection compliance, the single injection group had better compliance than the double injection group. In the present study, the author found that the patients who refused the second injection were due to either adverse reactions or a high satisfied improvement. In addition the double injection group revealed tendency of both clinical and statistical significant improvement of this

intervention. These outcomes probably implied the strength of relation between the dosage and time to the improvement and corresponded to the study of Kanowski (39) who reported the maximum efficacy of Actovegin at week 2.

Co-intervention

There was no co-intervention in this study because all patients did not have to take any rescue medication at all. This probably implied that the nature of the osteoarthritis was not so serious enough for patients.

Safety

In this study, adverse events occurred in approximately 7.5% and 9.4% of the patients (week 1 and week 2 respectively) (Table 6.9). The common events found in the present study were effusion, inflammation, persistent pain, and more disabled. All these events were not serious and resolved within a few days.

Limitation

This study had some limitations in generalizability, e.g. the results might be applied to subjects with moderate to high pain severity score who were failed to oral medication or physical therapy, but not to the patients with higher degree of osteoarthritis. The compliance in this study also made the limitation as shown by a high drop out rate. This might be due to a considerable invasive procedure of injection. In addition, the outcomes were subjective; therefore this could minimize the strength of the evidence in this present study.

CONCLUSION AND RECOMMENDATION

There was clinical and statistical improvement in pain visual analog score on activity or movement since the first week of intra-articular injection of Actovegin for the treatment of knee osteoarthritis patients. The patients' global assessment and the patients' satisfaction index revealed a high percentage of favorable groups. The duration to pain resolve was 6.3 days. The adverse events ranged from 7.5 - 9.4%.

Therefore, intra-articular injection of Actovegin could be recommended as an alternative treatment in the moderate degree of osteoarthritic patients with moderate to high magnitude of pain severity score and failed to oral medication or physical therapy.

The results of this study are applicable only with this treatment protocol. Stronger evidence-based study such as RCT or other group of high magnitude pain score at rest should be conducted. However, there were varieties of injection therapy protocol for knee osteoarthritis patients. Further studies should be planned to evaluate for the economic dimension which compare to other injection therapy that might impact the cost of treatment.

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APPENDICES

APPENDIX A

SELECTION OF SUBJECTS

Inclusion criteria

Subjects must fulfill all of the following criteria for entrance into the study.

Criteria	yes	no
1. Primary OA knee	☐	☐
2. Age> 50 yr	☐	☐
3. Fail to conservative treatment	☐	☐
4. Patient who can not tolerate medical treatment	☐	☐
5. Patient who accepts intra-articular injection	☐	☐
6. Pain VAS on level walking more than or equal to 5	☐	☐
7. Patients grade II-III of Kellgren and Lawrence criteria	☐	☐
8. Agree to participate in the study and sign consent form	☐	☐

Note: A "NO" for any inclusion criteria is sufficient to exclude the subject.

Exclusion criteria

Subjects fulfilling any of the following criteria will be excluded from the study.

Criteria	yes	no
1. Secondary causes of knee OA	☐	☐
2. Bleeding tendency	☐	☐
3. History of allergy to calf protein	☐	☐
4. History of intra-articular injection within 6 months	☐	☐
5. Severe joint instability or severe deformity (grade IV Kellgren and Lawrence)	☐	☐

Note: A "YES" for any exclusion criteria is sufficient to exclude the subject.

APPENDIX B

คำอธิบาย/คำชี้แจงต่อผู้ป่วยที่เข้าร่วมโครงการ

ผู้ป่วยที่เป็นโรคข้อเข่าเสื่อมหรือผู้แทนโดยชอบธรรมของผู้ป่วยจะได้รับการสอบถามความสมัครใจที่จะเข้าร่วมการวิจัยโดยจะได้รับการอธิบายเกี่ยวกับการวิจัย ผลดีและผลเสียที่อาจจะเกิดขึ้นกับผู้ป่วยจนเป็นที่เข้าใจและหมดข้อสงสัยแล้ว ดังนี้

1. ชื่อโครงการวิจัย

การศึกษาเปรียบเทียบประสิทธิผลและความปลอดภัยของยาฉีดเข้าข้อเข่า Actovegin ในการรักษาผู้ป่วยข้อเข่าเสื่อม

2. ความจำเป็นหรือเหตุผลการวิจัย

ผู้ป่วยโรคข้อเข่าเสื่อมจะมีอาการปวดข้อเข่าจากการอักเสบภายในข้อ ซึ่งมักจะได้รับการรักษาด้วยการใช้ยาต้านอักเสบ และอุปสรรคสำคัญของการใช้ยาต้านอักเสบ คือ ผลข้างเคียงกับระบบทางเดินอาหาร ไม่ว่าจะเป็นอาการแสบท้อง ปวดเสียดท้อง เป็นแผลในกระเพาะอาหาร บางรายมีอาเจียนเป็นเลือด รวมทั้งเรื่องค่าใช้จ่ายหรือราคายาซึ่งค่อนข้างสูง โดยเฉพาะยาต้านอักเสบกลุ่มใหม่ที่มีผลข้างเคียงทางกระเพาะอาหารน้อย กรณีที่การรักษาดังกล่าวข้างต้น ไม่ประสบความสำเร็จแต่ผู้ป่วยยังคงมีอาการปวดเข่าอยู่ จำเป็นต้องรักษาบำบัดด้วยวิธีการอื่นๆ เช่น การฉีด steroid เข้าข้อหรือการผ่าตัดส่องกล้องล้างข้อเข่า หรือแม้กระทั่งอาจจำเป็นต้องผ่าตัดเปลี่ยนข้อเข่า ด้วยเหตุนี้ผู้ป่วยจำนวนหนึ่งซึ่งต้องการหลีกเลี่ยงการผ่าตัดจึงยอมรับวิธีการรักษาด้วยการใช้ยาฉีด ยาฉีดที่มีใช้อยู่ในปัจจุบันมีราคาแพงมาก นอกจากนั้นยังมีผลข้างเคียงอยู่พอสมควรด้วย

Actovegin เป็นยาชนิดหนึ่งที่ใช้ทำการรักษาโรคทางระบบสมอง, การไหลเวียนของเลือด, การบาดเจ็บของเอ็นและกล้ามเนื้อ มีสรรพคุณหลายอย่างเป็นยาที่มีความปลอดภัย ในกรณีดังกล่าวที่ใช้มา และมีฤทธิ์เพิ่มการทำงานของระดับเซลล์โดยการนำออกซิเจนเข้าสู่เซลล์ จึงเป็นสมมติฐานว่าน่าจะบรรเทาพยาธิสภาพของข้อเข่าเสื่อมได้ และเคยมีรายงานการรักษาโรคข้อเข่าเสื่อมด้วยยาชนิดนี้ในผู้ป่วยจำนวน 17 ราย ซึ่งยังไม่พบผลข้างเคียงใดๆ มาก่อน แต่เนื่องจากจำนวนผู้ป่วยยังคงมีจำนวนน้อยจึงต้องการการวิจัยเพิ่มเติมในกรณีนี้

3. วัตถุประสงค์ของโครงการ

เพื่อศึกษาเปรียบเทียบประสิทธิผลของยา Actovegin ในการรักษาผู้ป่วยข้อเข่าเสื่อม

4. ประโยชน์ที่คาดว่าจะได้รับจากการวิจัย

หากการศึกษานี้สามารถพิสูจน์ได้ว่ายา Actovegin มีประสิทธิผลและปลอดภัยในการรักษาโรคข้อเข่าเสื่อม จะทำให้ผู้ป่วยโรคนี้ได้รับการรักษาที่มีประโยชน์ ปลอดภัย และมีราคาถูกกว่าการรักษาด้วยยาฉีดชนิดอื่นที่มีอยู่ในตลาดปัจจุบัน

5. สิ่งที่จะปฏิบัติต่อท่าน

1. ท่านจะได้รับการตรวจวินิจฉัยว่าเป็นโรคข้อเข่าเสื่อม และรับการเอ็กซเรย์ข้อเข่า เพื่อยืนยันการวินิจฉัย โดยไม่ต้องเสียค่าใช้จ่ายใดๆ เพิ่ม จากนั้นขอให้ท่านหยุดใช้ยารักษาข้อเข่าเดิมทั้งหมดเป็นเวลา 2 สัปดาห์ เพื่อไม่ให้รบกวนยาฉีดที่จะใช้ในครั้งนี้ โดยหากมีอาการปวดข้อท่านสามารถใช้ยาระงับปวดที่เราจะให้ติดตัวไว้ใช้ได้

2. ท่านจะได้รับยาฉีด Actovegin ปริมาณ 10 ซีซี เข้าข้อเข่าเป็นจำนวน 2 ครั้ง ห่างกันหนึ่งสัปดาห์ โดยไม่ต้องเสียค่าใช้จ่าย

3. จะได้รับการนัดหมายให้มาพบแพทย์เพื่อประเมินผลการรักษา ในสัปดาห์ที่ 2

4. ผู้วิจัยจะบันทึกข้อมูลทั่วไปของท่าน เช่น อายุ เพศ โรคประจำตัว และอาการต่าง ๆ รวมทั้งผลการตรวจร่างกายทุกครั้งที่ท่านมารับบริการ

5.หากท่านมีข้อสงสัยใดๆเกี่ยวกับการวิจัยหรือมีผลข้างเคียงจากการรักษาสามารถติดต่อผู้วิจัยได้ที่นายแพทย์ สมศักดิ์ คุปต์นิรัติศัยกุล ภาควิชาออร์โธปิดิกส์ คณะแพทยศาสตร์จุฬาฯ โทร 02-256 4230 หรือหมายเลขโทรศัพท์ 01-668 4924 ตลอด 24 ชั่วโมง

6. การเก็บรักษาข้อมูลเป็นความลับ

ข้อมูลของท่านจะถูกบันทึกและเก็บไว้สำหรับการวิเคราะห์อย่างเป็นความลับโดยที่จะไม่มีการเปิดเผยข้อมูลให้ผู้อื่นทราบเป็นข้อมูลรายบุคคล

7. สิทธิ์ในการถอนตัวจาการการเข้าร่วมในโครงการวิจัย

ท่านมีสิทธิ์ที่จะถอนตัวจากโครงการวิจัยนี้เมื่อใดก็ได้ โดยการถอนตัวจากโครงการของท่านนี้ไม่มีผลต่อการรักษาที่ท่านจะได้รับตามปกติ

ลงนาม.....

(นายแพทย์สมศักดิ์ คุปต์นิรัติศัยกุล)

หัวหน้าโครงการวิจัย

วันที่ ..... มกราคม 2547

APPENDIX C
หนังสือแสดงเจตนายินยอม

การวิจัยเรื่อง การศึกษาเปรียบเทียบประสิทธิผลและความปลอดภัยของยาฉีดเข้าข้อเข่า Actovegin ในการรักษาผู้ป่วยข้อเข่าเสื่อม

วันให้คำยินยอม วันที่..... เดือน..... พ.ศ.....

ก่อนที่จะลงนามในใบยินยอมให้ทำการวิจัยนี้ ข้าพเจ้าได้รับการอธิบายจากผู้วิจัยถึงวัตถุประสงค์ของการวิจัย วิธีการวิจัย อันตราย หรืออาการที่อาจเกิดขึ้นจากการวิจัยหรือจากยาที่ใช้ รวมทั้งประโยชน์ที่จะเกิดขึ้นจากการวิจัยอย่างละเอียด และมีความเข้าใจดีแล้ว

ผู้วิจัยรับรองว่าจะตอบคำถามต่างๆ ที่ข้าพเจ้าสงสัยด้วยความเต็มใจ ไม่ปิดบัง ซ่อนเร้น จนข้าพเจ้าพอใจ

ข้าพเจ้ามีสิทธิที่จะบอกเลิกการเข้าร่วมในโครงการวิจัยนี้เมื่อใดก็ได้ และเข้าร่วมโครงการวิจัยนี้โดยสมัครใจและการบอกเลิกการเข้าร่วมการวิจัยนี้ จะไม่มีผลต่อการรักษาโรคที่ข้าพเจ้าจะพึงได้รับต่อไป

ผู้วิจัยรับรองว่าจะเก็บข้อมูลเฉพาะเกี่ยวกับตัวข้าพเจ้าเป็นความลับ และจะเปิดเผยได้เฉพาะในรูปที่เป็นสรุปผลการวิจัย การเปิดเผยข้อมูลเกี่ยวกับตัวข้าพเจ้าต่อหน่วยงานต่างๆ ที่เกี่ยวข้อง กระทำได้เฉพาะกรณีจำเป็นด้วยเหตุผลทางวิชาการเท่านั้น

ผู้วิจัยรับรองว่าหากเกิดอันตรายใด ๆ อันเนื่องมาจากการวิจัยดังกล่าว ข้าพเจ้าจะได้รับการรักษาพยาบาลโดยไม่คิดมูลค่าตามมาตรฐานวิชาชีพ และจะได้รับการชดเชยรายได้ที่สูญเสียไประหว่างรักษาพยาบาลดังกล่าว ตลอดจนเงินทดแทนความพิการที่อาจเกิดขึ้น

ผู้วิจัยรับรองว่าหากมีข้อมูลเพิ่มเติมที่ส่งผลกระทบต่อการวิจัย ข้าพเจ้าจะได้รับการแจ้งให้ทราบโดยไม่ปิดบัง ซ่อนเร้น

ข้าพเจ้าได้อ่านข้อความดังกล่าวข้างต้นแล้ว และมีความเข้าใจดีทุกประการ และได้ลงนามในใบยินยอมนี้ด้วยความเต็มใจ

ลงนาม..... ผู้ยินยอม

( )

ลงนาม..... ผู้วิจัย

( )

ลงนาม..... พยาน

( )

APPENDIX D

CASE RECORD FORM

Title: The Effectiveness and Safety of Intra-articular injection of Actovegin in Osteoarthritis of the Knee : A Phase Two Clinical Trial

Principal investigator: Somsak Kuptniratsaikul

Record ID ☐☐☐

Protocol…… Date……/……/…….

Baseline data

1. Age.....years
2. Sex ☐ Male ☐ Female
3. Weight.....kg
4. Height……cm
5. BMI……kg/m^2
6. Education level……..
7. Duration of disease……years
8. Affected side ☐ Right ☐ Left ☐ Bilateral
9. Activity level……
10. Duration to pain resolved……

Outcome data

Outcome	Week 0	Week 1	Week 2
11. VAS pain at level walking			
12. VAS pain on stair climbing			
13. VAS pain at night			
14. VAS pain at rest			
15. VAS pain on weight bearing			
16. Average VAS			
17. Knee circumference			

18. Number of Tramadol use……..per 2 weeks

19. Number of injection of actovegin.....times

20. Patients' global assessment score: week 1…… week 2……

21. Patients' satisfaction score: week 1…… week 2……

Global assessment score	Satisfaction score
a. complete recovery b. much improve c. moderately improve d. slightly improve e. no different f. getting worse	1.very satisfied 2. moderately satisfied 3. little satisfied 4.indifferent 5.unsatisfied

22. Adverse effects:	Yes	No
a. Rash	☐	☐
b. Nausea/Vomiting	☐	☐
c. Joint effusion	☐	☐
d. Joint inflammation	☐	☐
e. Persistent pain > 2 hr after injection	☐	☐
f. More disability in the next morning	☐	☐
g. Anaphylaxis	☐	☐

VITAE

Mr. Somsak Kuptniratsaikul was born on the 25th of December, 1960 in Bangkok, Thailand. In 1985, he graduated with M.D. degree from the faculty of Medicine, Chulalongkorn University, Thailand. In 1992, he received Thai Board in Orthopedic Surgery from Medical Council of Thailand. After studying abroad for 1 year in USA, he obtained a certificate of fellowship in Sports Medicine and Arthroscopy from Case Western Reserve University, Ohio in 1993. His present position is Associate Professor in the Department of Orthopedics, Faculty of Medicine, Chulalongkorn University, Thailand.