The Efficacy of Plygersic Gel for Use in the Treatment of Osteoarthritis of the Knee

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Objective: *An evaluation of the efficacy of the combination of ginger (Zingiber officinale) and plai (Zingiber cassumunar) gel for the treatment of osteoarthritis of the knee using 1% diclofenac gel as a comparator.*
Material and Method: *A double-blind, randomized, controlled trial of the combination of 4% ginger and plai extract in a gel (Plygersic gel) as compared with a 1% solution of diclofenac in patients with osteoarthritis knees. The number of participants in each group totaled fifty. The length of treatment was a 6 week period. The efficacy of the drugs was monitored by using the Knee Injury and Osteoarthritis Outcome Score (KOOS). The t-test was used to compare the scores before and after treatments in each group. The repeated ANOVA was used to compare the scores between the two groups.*
Results: *Both Plygersic gel and diclofenac gel could significantly improve knee joint pain, symptoms, daily activities, sports activities and quality of life measured by KOOS following 6 weeks of treatment. In the repeated ANOVA, there were no differences in the results between the Plygersic and diclofenac gel groups.*
Conclusion: *Plygersic gel relieves joint pain and improves problematic symptoms and improves the quality of life in osteoarthritis knees during a 6 week treatment regimen with no differences to the 1% Diclofenac gel group.*

Keywords: *Ginger, Zingiber officinale, Plai, Phlai, Zingiber cassumunar, Topical gel, Osteoarthritis.*

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Osteoarthritis (OA) is the most common musculoskeletal disorder affecting synovial joints and is a major cause of pain and physical disability in older adults[1]. The prevalence of osteoarthritis in Thailand is at 11.3%[2]. The most widely used drugs in OA are NSAIDs and acetaminophen for pain relief and relief of other problematic symptoms[3]. Oral NSAIDs are associated with a number of adverse reactions. These include gastrointestinal problems, hepato-renal and cardiovascular toxicity[4]. Using topical NSAIDS in replacement of the oral forms have shown to provide similar results without serious adverse reactions[5-7]. In addition, topical NSAIDs are also preferred to oral forms for the reasons of; direct access to the target site, convenience, the resulting improved patient compliance and may help to reduce the overall cost of treatment[8]. In England, topical NSAIDs are first-line treatments for osteoarthritis rather than the consideration of oral NSAID use[9]. In the US, 1% diclofenac sodium gel has been approved for the treatment of pain in OA and other musculoskeletal injuries[10]. It has also been used as an alternative to acetaminophen, oral NAIDs, Tramadol and intra-articular corticosteroid injections[3].

Presently, treatment of OA with herbal medicines has become an attentiveness[11]. In Thailand, Ginger (*Zingiber officinale*) and plai (*Zingiber cassumunar* Roxb) has been used for treating musculoskeletal pain as a traditional choice. In *in vitro* studies, ginger and plai has been shown to block the formation of inflammatory mediators such as thromboxane, leukotrienes and prostaglandins[12-20]. In *in vivo* studies, ginger extract has shown significant effects on reducing symptoms of OA of the knee[21,22]. The major side effect of oral ginger is heartburn and gastrointestinal disturbances similar to the side effects of oral NSAIDs[21]. To avoid these side effects, the topical forms are considered preferable to the oral forms.

Plygersic gel (Fig. 1) is manufactured by the Thailand Institute of Scientific and Technological Research (TISTR) with the goal of encouraging the use of Thai herbs as forms of medication. Plygersic gel

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Fig. 1 Plygersic gel

contains extract of ginger and plai by the ratio of about 4% by weight. From a study conducted by TISTR, ginger extract is a more potent anti-inflammatory when compared to Plai but, has a shorter duration in its anti inflammatory properties. The mixing of the two components should have a synergistic effect on the anti inflammatory properties without the necessity of increasing the dosages. In animal studies, Plygersic has shown to reduce inflammation in adjuvant induced arthritis in rats[23]. However; there have been no clinical trials in OA in humans to this time. In our present study, the efficacy and side effects of combinations of plai and ginger gel (Plygersic) for the treatment of osteoarthritis of the knee was evaluated by comparisons with 1% Diclofenac gel.

Material and Method

The present study was approved by the Ethical Committee of the Faculty of Medicine, Thammasat University. Between March 2010 and September 2010, One hundred patients in Khai Bang Rachan Hospital in the Singburi Province, who were diagnosed with osteoarthritis, were randomly selected to receive the treatments. The diagnosis of osteoarthritis was based on the clinical criteria of osteoarthritis as specified by the American Rheumatism Association (ARA)[24].

All patients completed informed consent forms and were informed of the risks of the present study. These include an increase in symptoms and possible adverse effects, as mentioned previously, from the use of ginger and plai. The demographics of the patients were recorded. The roentgenograms of both knees of all patients were performed to stage the degrees of their osteoarthritis by Kellgren-Lawrence grading scale[25] (Grade 0 = Normal; Grade 1 = Possible osteophytes, Doubtful narrowing of joint space; Grade 2 = Definite osteophytes, Absent or questionable narrowing of joint space; Grade 3 = Moderate osteophytes, Marked narrowing of joint space, Severe sclerosis, Possible deformity; Grade 4 = Large osteophytes, Marked narrowing of joint space, Severe sclerosis, Definite deformity).

The patients were randomly selected to the Plygersic gel group and the Diclofenac gel group. The Plygersic group received Plygersic gel with application of a 1 gm solution 4 times a day for two months. The Diclofenac group also received the identical tube containing a 1% Diclofenac sodium gel applied by the same method.

On physical examination, the patients exhibited no obvious deformities of the knees and had no surgical procedures of the lower extremities in the six months prior to treatment. At the study's entry, treatment with analgesics and NSAIDs were discontinued for two weeks before starting this regimen. During the treatment, paracetamol, 500 mg, 2-4 tabs per day, was allowed for the occurrence of severe pain.

The evaluation of the results of the treatment were by physical examinations and Knee injury and Osteoarthritis Outcome scores using the (KOOS) questionnaire[26] at the start of treatment, after two weeks, after four weeks and after six weeks of treatment. The KOOS is a 42-item, self-administered, self-explanatory questionnaire in five separately scored subscales; nine items addressing pain and seven items addressing other symptoms. Function in Daily Living (ADLs consisted of 17 items), function in sports and recreation (Sport/Rec totaling five items) and their quality of life (QOL) in relation to knee function with four items. Scores are interpreted in a 0-100 scale, with zero representing extreme knee problems and 100 representing no knee problems. The KOOS is an extension of the Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) and can be converted to WOMAC scores[27].

Adverse reactions were recorded during follow-up appointments and routine Complete Blood Count (CBC), Urine Analysis (U/A) and blood chemistry

test (FBS, BUN, Cr, SGOT and SGPT) values were also recorded.

Results

The effectiveness of plygersic gel

Of the 100 patients initially enrolled in the study, 50 in the Plygersic group and 50 in the Diclofenac gel group, one patient in the Plygersic group dropped out of the present study due to an adverse skin reaction (Fig. 2). Ninety-nine of the patients completed the study and reported for testing at the periods in the beginning, at two weeks, four weeks and at the six week evaluation period. The baseline characteristics of the patients who completed the study are shown in Table 1. There are no statistical differences between the two groups by t-test (Table 1). The mean of the KOOS values in the five categories of KOOS at the baseline, two week, four week and six week follow-up periods after treatment demonstrated an improvement starting from two weeks into their therapies for both groups (Fig. 3). The paired t-test results demonstrated significant improvement of KOOS in the five items in both the Plygersic gel and Diclofenac gel groups when compared at the initiation of treatments and following six weeks of treatments ($p < 0.01$) (Table 2, 3). Comparing the results of the treatments between Plygersic and Diclofenac gel, there were no statistical differences between the two groups in the repeated ANOVA scores (Table 4).

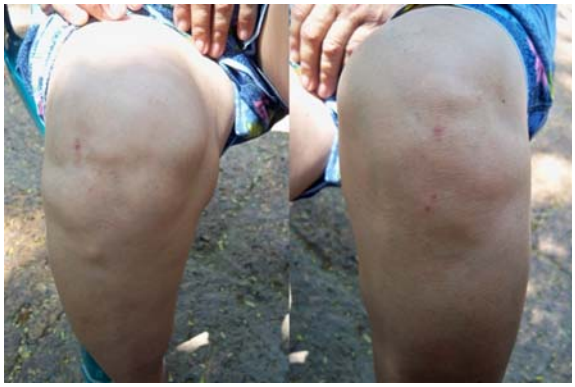

Fig. 2 Contact dermatitis in the Plygersic group's patient who was released from the study

Adverse events

During the present study, (initial, 2, 4, 6 weeks) none of the patients in either group had shown abnormal laboratory values (CBC, Urine analysis, BUN, Cr, SGOT, SGPT). From clinical assessments; all patients, with the exception of the patient in Plygersic gel group who had to be removed, had shown a reaction to either of the drugs (Fig. 2). This patient's reaction was diagnosed as a contact dermatitis and the patient received topical corticosteroids for a period of one week with the resulting resolution of symptoms.

Discussion

The present study is the first recorded clinical trial of the topical use of extract components from ginger (*Zingiber officinale*) and plai (*Zingiber cassumunar* Roxb) for the treatment of OA. The active components from ginger are 6-gingerol and 6-shogaol. The 6-gingerol has shown to reduce edema in rat's paws that was induced by the use of carrageenin[28]. The 6-shogaol has demonstrated that it had a more potent anti inflammatory effect than ibuprofen when used in the treatment of monosodium urate crystal-induced inflammation in mice[29]. The active components obtained from plai are cassumunarins and (E)-1-(3, 4-dimethoxyphenyl) butadiene (DMPBD). The cassumunarins has shown that it could reduce inflammation that was induced with 12-o-tetradecanoylphorbol 13-acetate in rats[18]. The (E)-1-(3, 4-dimethoxyphenyl) butadiene (DMPBD) has shown its ability to inhibit cyclooxygenase and lipoxygenase in arachidonic acid

Table 1. Base line characteristics of patients in Plygersic and Diclofenac groups

	Plygersic gel	Diclofenac gel	p-value
M:F	44:5	41:9	
Age (year) Mean(SD)	57.94 (9.673)	58.26 (9.066)	0.865
Height (cm) Mean(SD)	154.26 (6.73)	155.08 (5.99)	0.526
Weight (kg) Mean(SD)	62.31 (12.43)	65.70 (16.20)	0.346
BMI Mean(SD)	26.25 (5.16)	27.63 (5.56)	0.204
Duration of symptoms (year) Mean (SD)	3.65 (2.09)	3.80 (3.34)	0.816
Kellgren-Lawrence Grade Mean (SD)	2.02 (0.75)	2.26 (0.83)	0.128

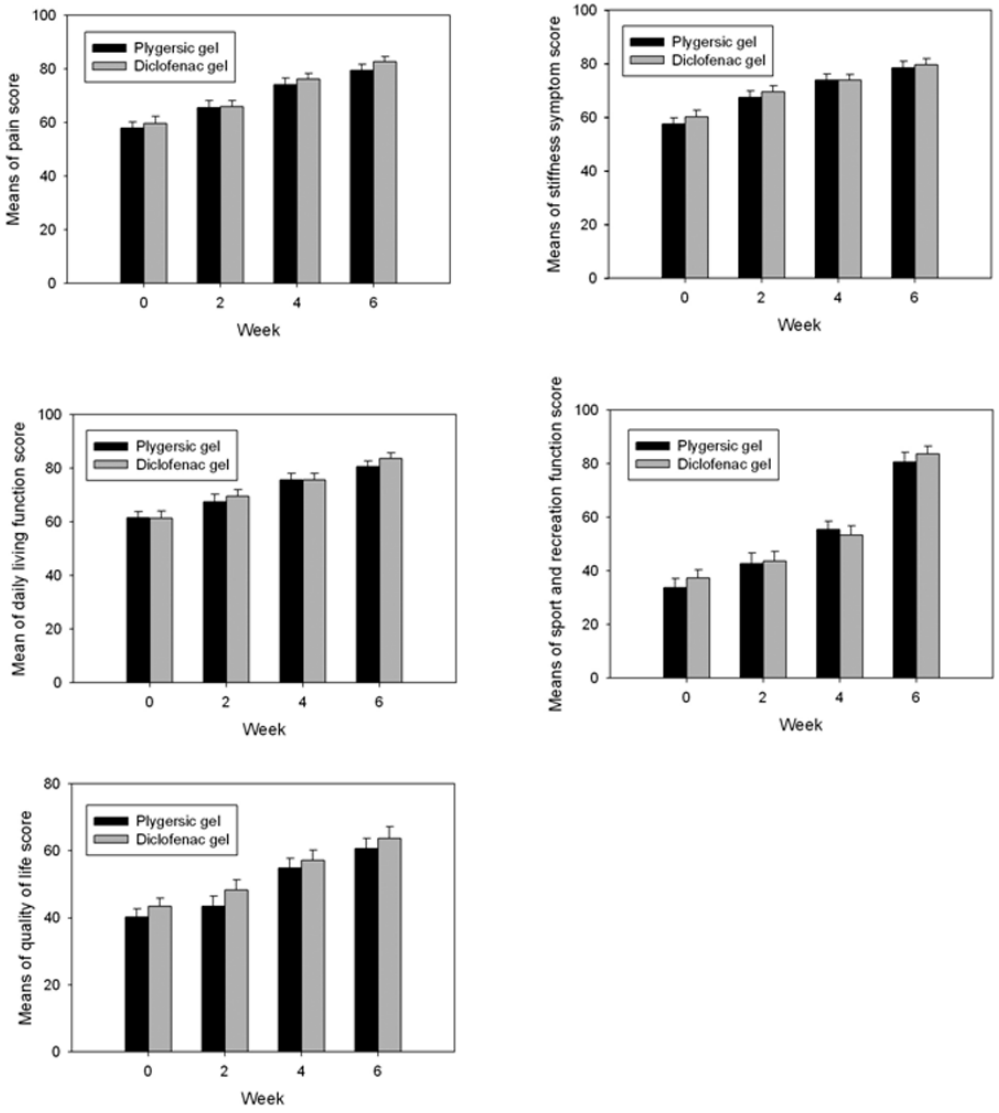

Fig. 3 The mean scores of pain, stiffness symptoms, daily living function, sport and recreation and quality of life of KOOS in the Plygersic and Diclofenac groups

Table 2. The comparison of the mean KOOS in Plygersic group at initiation and at 6 weeks of treatment by the paired t-test

	Base line	At 6 week	p-value
Symptom score	57.44 (17.10)	78.50 (16.58)	< 0.001
Pain score	57.82 (15.82)	79.36 (16.63)	< 0.001
Daily living score	61.58 (15.70)	80.46 (15.26)	< 0.001
Sport and recreation score	33.78 (23.95)	59.08 (20.07)	< 0.001
Quality of life score	40.28 (16.37)	60.66 (21.36)	< 0.001

metabolism[15-17]. The only previous study using plai gel for musculoskeletal problems was done in athletes with ankle sprain injuries. The use of plai gel (14% of plai oil) has shown the ability to reduce signs and symptoms of inflammation within 7 days[30].

In vitro studies, NSAIDs have the ability to

Table 3. The comparison of the mean KOOS in the Diclofenac group at initiation and at 6 weeks of treatment by the paired t-test

	Base line	At 6 week	p-value
Symptom score	60.16 (18.05)	79.60 (15.61)	< 0.001
Pain score	59.61 (18.47)	82.56 (14.61)	< 0.001
Daily living score	61.38 (18.92)	83.53 (14.91)	< 0.001
Sport and recreation score	37.30 (21.27)	63.20 (26.87)	< 0.001
Quality of life score	43.44 (16.87)	63.77 (23.74)	< 0.001

Table 4. The comparison of the mean KOOS between the Plygersic and Dicofenac groups by the repeated ANOVA

	F-test	p-value
Symptom score	0.359	0.551
Pain score	0.552	0.459
Daily living score	0.235	0.629
Sport and recreation score	0.178	0.674
Quality of life score	1.181	0.280

penetrate and absorb into the dermis and has demonstrated the anti-inflammatory effect by the inhibition of cyclo-oxegenase[31]. With application via the topical route, the subcutaneous and muscular concentration of NSAIDs was higher than the concentrations in plasma but lower concentrations were available to synovial tissue[32]. Since, the OA is not exclusively a disorder of articular cartilage; multiple components of the joints are adversely affected by OA. These include peri-articular bones, synovial joint linings and supporting soft tissues[33]. The higher concentration of NSAIDs in soft tissues around the knee may reduce the inflammation and pain in these structures leading to improvements as shown in several clinical studies on the use of topical NSAIDs[5,6]. Because the anti-inflammatory effects of compounds from plai and ginger have shown to be similar to NSAIDs, theoretical consideration allows the bridging of these mechanisms of action to Plygersic gel. However, further studies should be carried out to measure the absorption of ginger and plai components by soft tissues.

The present results have shown that combinations of extract of ginger and plai (Plygersic) and Diclofenac gel have significant improvements in the experience of pain, symptoms of decreased range of motion, improving patient's ADLs, increased sports activities and improved quality of life when measured by the KOOS in the period at 2 through 6 weeks of treatments (Fig. 3, Table 2, 3). The improvements in their pain and other symptoms in the Diclofenac gel group were comparable with the previous studies[5,6]. When comparisons were made between the Plygersic and Diclofenac groups, the improvement of the KOOS over 6 weeks has not shown any significant differences (Table 4). The use of both gels, Diclofenac and Plygersic, did not result in any serious side effects in any clinical observations or laboratory test results. Only one patient out of the 50 from the Plygersic gel group had experienced contact dermatitis to a minimal degree. From our results; Plygersic gel has proven to be effective for the treatment of osteoarthritis of the knee similar to the 1% Diclofenac gel group.

Summary

Plygersic gel (combination of *Zingiber officinale* and *Zingiber cassumunar* Roxb. extract) is as effective as 1% Diclofenac gel and is possibly another option for the treatment of osteoarthritis of the knee.

Acknowledgement

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Potential conflicts of interest

None.

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ประสิทธิภาพของยาไพลเจอร์สิก เจล (Plygersic gel) ในการรักษาโรคข้อเข่าเสื่อม

สัญญาณ เนียมปุก, ภาคภูมิ ศิริอาชาวัฒนา, ธัญวรัตน์ กาจสงคราม

วัตถุประสงค์*: เพื่อศึกษาประสิทธิภาพของยา ไพลเจอร์สิก เจล (เจลผสมที่มีส่วนประกอบของขิงและไพลร้อยละ 4) ในการรักษาข้อเข่าเสื่อม โดยเปรียบเทียบกับ ไดโคลฟีแนค เจล*

วัสดุและวิธีการ*: อาสาสมัครผู้ป่วยโรคข้อเข่าเสื่อมจำนวน 100 คน ได้รับการเลือกแบบสุ่มในการใช้ยาไพลเจอร์สิก เจล และ ไดโคลฟีแนค โดยทั้งสองกลุ่มจะได้รับยาที่อยู่ในหลอดที่มีรูปร่างภายนอกเหมือนกัน โดยใช้ทาที่เข่าวันละสี่ครั้ง ให้ผู้ป่วยทำแบบสอบถาม KOOS (Knee Injury and Osteoarthritis Outcome Score) เพื่อประเมินผลการรักษา และประเมินผลแทรกซ้อนจาก สอบถามอาการ, ตรวจร่างกายโดยแพทย์ และ เจาะเลือดกับตรวจปัสสาวะ ในสัปดาห์แรก สัปดาห์ที่ 2, 4, และ 6 จากนั้นนำผลแบบสอบถามที่ได้มาวิเคราะห์ โดยเปรียบเทียบ ผลของแบบสอบถาม KOOS ก่อนและหลังการรักษาโดยใช้ paired t-test และเปรียบเทียบผลการรักษาระหว่าง ไพลเจอร์สิก เจล และ ไดโคลฟีแนค เจล โดยใช้ repeated ANOVA*

ผลการศึกษา*: ทั้งไพลเจอร์สิก เจล และ ไดโคลฟีแนคเจล สามารถลดอาการของข้อเข่าเสื่อมได้อย่างมีนัยสำคัญ และการเปรียบเทียบผลระหว่างสองกลุ่มไม่มีความแตกต่างกัน*

สรุป*: ไพลเจอร์สิก เจล มีประสิทธิภาพในการลดอาการของข้อเข่าเสื่อมในการรักษา 6 สัปดาห์ โดยผลที่ได้ ไม่แตกต่างจากการใช้ไดโคลฟีแนค เจล*
