Role of diacerein in pain intensity and functional status in patients with knee osteoarthritis

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ABSTRACT

Background: Inflammation is an important mechanism in the pathogenesis of osteoarthritis (OA). Proinflammatory mediators, especially interleukin-1β (IL-1β), play a significant role in the occurrence of joint inflammation, which lead to pain and limitation of daily activities. As an anti–IL-1β, diacerein is therefore have potency to reduce pain and improve functional status of OA patients.

Objective: To evaluate the role of diacerein in pain intensity and functional status of knee OA patients.

Methods: This is a pre-post study without control group using consecutive sampling conducted at rheumatology outpatient clinic at the Cipto Mangunkusumo General Hospital, Jakarta from January until May 2006. At the first visit, all patients underwent assessment of pain intensity (using visual analog scale (VAS)) and functional status (Lequesne algofunctional index) to obtain baseline data. We also performed knee radiograph examination to evaluate joint damage based on the Kellgren-Lawrence classification. Measurement of IL-1β level in synovial fluid was performed using enzyme-linked immunosorbent assay, with a minimum detectable value of 3.9 pg/mL. Diacerein was administered with a dose of 50 mg, given orally twice a day for 2 months. Follow-ups were done in the first, second, and eighth week after the administration of diacerein. In the eighth week we repeated the measurement of IL-1β level.

Results: Thirty three patients were enrolled in this study, most (78.8%) of them were female. The majority (81.8%) belong to the 50- to 70-year-old age group. More than half of the patients (54.5%) had detectable IL-1β level. The median baseline VAS score was 65.00 (range 25–100) while the median baseline Lequesne score was 11.00 (range 1.5–21.0). The statistical analysis showed a significant decrease in VAS at the first (p = 0.000), second (p = 0.000), and eighth week (p = 0.000). Lequesne index score was also decrease significantly at the first (p = 0.000), second (p = 0.000), and eighth week (p = 0.000) of treatment. We found no significant correlation of IL-1β level with VAS and Lequesne algofunctional index scores.

Conclusions: Among the patients in this study, there were significant decrease in pain intensity and disability after the administration of diacerein.

Osteoarthritis (OA) is one of the muskuloskeletal diseases that has become the concern of the World Health Organization because it affects the social and mental function and the quality of life of the patients. It is estimated that 10% of the world population older than 60 years old suffers from OA.[1]

The concept of inflammation as the pathogenesis of OA, a fact that is supported by many studies, has also become major concern. Several proinflammatory mediators have been known to be involved in the pathogenesis of OA, the most important of which are tumor necrosis factor α (TNFα) and interleukin (IL)-1β.[2] Studies by Martel-Pelletier et al[3,4] and Firestein et al[5] have found the presence of IL-1β, TNFα, dan IL-1–receptor antagonist (IL-1RA) in the synovial tissue of OA patients. Smith et al[2] in his study by using arthroscopy found increase in cell wall thickness, vascularization, infiltration of inflammatory cells, IL-1β, and TNFα in joint cartilage in accordance with the severity of OA. Interleukin-1β and TNFα have the ability to increase their secretion and trigger chondrocytes to secrete IL-8, IL-6, and leukocyte inhibitory factor (LIF), therefore indreasing the production of protease and prostaglandin E2. Interleukin-1β also inhibit the synthesis of aggrecan, an important component of joint cartilage matrix.[2,3,6]

Both the degeneration and inflammation process will eventually disturb joint integrity and cause complaints of pain, limitation in joint range of movement, muscle atrophy, decrease in strength and endurance of muscle, deformity, and joint instability. Diacerein, an anthraquinon derivate, and its metabolite, rhein, shows strong in vitro inhibitory action against cytokines (particularly IL-1β in synovium) and chondrocytes which affect the cartilage degradation. Besides, diacerein has also been shown to decrease the bioactivity of IL-1 receptor in vitro. From studies we know that diacerein have both symptoms-modifying effects and structure-modifying effects.[7–9] In this study we aim to investigate the IL-1β level in synovial fluid of OA patients and its correlation with pain intensity, radiographic joint damage, and Lequesne algofunctional index.

METHODS

This study used a pre-post design without control group. Samples were collected using consecutive sampling method at rheumatology outpatient clinic at the Cipto Mangunkusumo General Hospital,

Jakarta from January until May 2006. The inclusion criteria were osteoarthritis patients who fulfilled the American College of Rheumatology criteria[10] for knee osteoarthritis (knee pain and at least 1 of the following: age >50 years, morning stiffness <30 minutes, and crepitus on active motion plus osteophytes); had not received analgesics, nonsteroidal anti-inflammatory drugs, steroids, or traditional remedies for at least one week; had not received chondroitin sulphate, glucosamine sulphate, or intra-articular corticosteroid injection for at least one month; and was not receiving hormone-replacement therapy. Patients with history of knee trauma or surgery, signs of active inflammation of the knee, congenital deformity of the knee, paraparesis, impairment of kidney (creatinine clearace test <30 mL/min) and liver function, and to whom articular injection were contraindicated were excluded from the study. All patients agreed to participate and signed informed consent. The study was approved by the Ethical Committee of the University of Indonesia School of Medicine.

All patient underwent assessment of pain intensity and functional status at the first visit to obtain baseline data. In addition, we also measured the IL-1β level in synovial fluid. The pain intensity was assessed using visual analog scale (VAS). Functional status was assessed based on the Lequesne algofunctional index, with scores classified as follows: 1–4 represented mild, 5–7 represented moderate, and scores ≥8 represented severe disability. The level of IL-1β in synovial fluid was measured using enzyme-linked immunosorbent assay (Bender Medsystem, Vienna, Austria) with a minimum detectable value of 3.9 pg/mL. Diacerein was administered with a dose of 50 mg, given orally twice a day for 2 months. Follow-ups with assessment of pain intensity and functional status were done in the first, second, and eighth week after the administration of diacerein. In the eighth week we repeated the measurement of IL-1β level and performed a radiographic examination of the knee to evaluate joint damage based on the Kellgren-Lawrence classification. The comparison of VAS and Lequesne score at baseline and subsequent follow-ups were analyzed using paired T-test or Wilcoxon's test as appropriate. Correlation of IL-1β level with VAS score, Lequesne score, and Kellgren-Lawrence scale were analyzed using Pearson's or Spearman's test as appropriate.

RESULTS

Table 1 shows that the prevalence of OA among the patients was higher in women (80.6%). The majority of patients were in the 50- to 70-years-old age group. There were 7 patients with knee joint effusion and 6 patients with knee deformity. We also found that there were 8 patients who were undergoing rehabilitative therapy in the last 2 months. From 33 patients, 18 (54.5%) had detectable baseline IL-1β level. Twelve patients had their IL-1β level measured at week 8. Among these, only two had detectable baseline IL-1β level (4.917 pg/mL and 16.679 pg/mL), but all had detectable IL-1β level at week 8 and showed increase in IL-1β level compared with their baseline level. Most of the patients (94%) had severe disability according to Lequesne score. Patients with 2nd degree joint damage according to the Kellgren-Lawrence score have the greatest proportion (33.3%), followed by 9 patients (27.3%) who had 1st degree joint damage.

Table 1 Characteristics of patients (N = 33)

Characteristics	n (%)
Sex	
Male	7 (21.2)
Female	26 (78.8)
Age	
<50	3 (9.1)
50–70	27 (81.8)
>70	3 (9.1)
Baseline IL-1β level, pg/mL	
<3.9	15 (45.5)
≥3.9	18 (54.5)
Baseline Lequesne algofunctional index score	
1–4	1 (3.0)
5–7	1 (3.0)
8	31 (94.0)
Kellgren-Lawrence score	
0	0 (0)
I	9 (27.3)
II	11 (33.3)
III	8 (24.2)
IV	5 (15.2)
Knee joint effusion	7 (19.4)
Knee deformity	6 (16.7)

Figure 1 shows the VAS and Lequesne algofunctional index scores at baseline and during the follow-ups. There was a trend that these scores were decreasing during the follow-ups, and from analysis (presented in table 2) we found that the decrease was statistically significant.
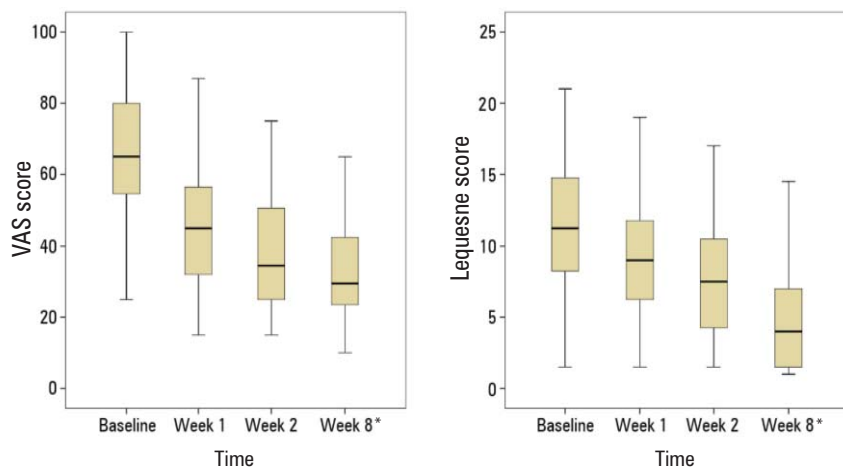
Figure 1 Median value with interquartile range (boxes) and range (whiskers) of visual analog scale (VAS) and Lequesne algofunctional index scores at baseline and during the follow-ups. Median VAS score at baseline, first, second, and eighth week was 65 (range 25–100), 45 (range 15–87), 35 (range 15–75), and 29.5 (range 10–65), respectively. Median Lequesne score at baseline, first, second, and eighth week was 11 (range 1.5–21.0), 9 (range 1.5–19), 7.5 (range 1.5–17), and 4 (range 1–19), respectively.

*One patient did not return for follow-up.

Table 2 Statistical analysis of visual analog scale (VAS) and Lequesne algofunctional index (Leq) scores at baseline and during the follow-ups

	VAS week 1	VAS week 2	VAS week 8	Leq week 1	Leq week 2	Leq week 8
VAS baseline	0.000	0.000	0.000			
Leq baseline				0.000	0.000	0.000

Data are presented as p value.

Table 3 shows the correlation of IL-1β level with VAS and Lequesne algofunctional index score at baseline and at week 8. From statistical analysis, we found no significant correlation of IL-1β level with VAS and Lequesne index score.

Table 3 Correlation of interleukin-1β (IL-1β) level with visual analog scale (VAS) and Lequesne algofunctional index (Leq) scores at baseline and at week 8

	VAS baseline	VAS week 8	Leq baseline	Leq week 8
IL-1β baseline	0.398 (0.102)		0.055 (0.829)	
IL-1β week 8		0.016 (0.961)		0.160 (0.620)

Data are presented as r (p value).

We also analyzed the correlation of the IL-1β with the Kellgren-Lawrence score. We found no significant correlation of both the baseline IL-1β level (r = 0.182, p = 0.484) or IL-1β level at week 8 (r = 0.335, p = 0.287) with the Kellgren-Lawrence score.

DISCUSSION

In this study we found that the majority of the patients were women. This is in line with data from World Health Organization (WHO) that shows higher tendency of OA in women (female to male ratio of 2.95:1.71). Estrogen is believed to play a role in this discrepancy.[11] Administration of estrogen to premenopausal women was reported to decrease the production of IL-1β and in a cohort study was shown to slow the progressivity of OA.[12]

Because the measuring kit we used in this study was only able to detect IL-1β level at 3.9 pg/mL or higher, we could not determine valid mean, median, or standar deviation values of IL-1β level. Previous studies have used different measuring kit with different reference ranges.[13–16] At the time of this study there has not been data of a normal range of IL-1β in human. Pelletier et al[17] reported a range of 0.3±0.04 pg/mL in healthy dogs. Another study have reported involvement of IL-1β in inflammation process, indicated by increase in its level in synovial fluid, with no reference ranges.[2] It is also important to consider some characteristics of cytokines that may affect the result of IL-1β level measurement in this study. Cytokine has a high affinity to its ligand, is prone to oxydation, and has a dynamic characteristics inside the body; thus estimation of its level would be more accurate if measurement is performed more than once.[18–20]

From the T-test analysis we found significant decrease in the VAS and Lequesne score during the follow-ups. This result is in line with a study by Nguyen et al[21] which had shown effect of diacerein in reducing pain in OA patients. In a 3-year study by Dougados et al,[22] diacerein also had shown an effect in reducing Lequesne algofunctional index of hip OA patients.

Interleukin-1β play a role in causing pain in OA through a cascade involving cyclooxygenase-2 and nitric oxyde synthase, which will increase prostaglandin E2 level, a major inflammatory mediator in nociceptor sensitization.[4,23,24] From statistical analysis we found no significant correlation of IL-1β level with VAS and Lequesne algofunctional index scores. The result of this study differs from several other studies who investigated the correlation of functional status and inflammatory parameter, such as a study by Kertia et al[23] who found significant correlation of Lequesne algofunctional index with malondialdehyde as well as leukocyte and macrophage count in synovial fluid. Ranitya et al[25] reported increased serum hyaluronic acid level, with significant correlation with Lequesne algofunctional index. Garnero et al[26] in their study found correlation of biochemical marker of synovitis in OA with the Western Ontario and McMaster Universities Arthritis Index and joint damage. The nonsignificant correlation we found in the study may be due to the small sample of detectable baseline IL-1β level or high drop-out rate. It is also important to consider that evaluation of Lequesne algofunctional index consists of other parameter such as joint deformity and this may contribute to the nonsignificant correlation.

We found no significant correlation of the IL-1β level with the Kellgren-Lawrence score. This is in line with the result of a studies by Brenner et al[27] who reported no significant correlation between synovial membrane cytokines level and Kellgren-Lawrence score and Fraenkel et al[12] who reported no significant correlation between cytokine produced by mononuclear cells and the Kellgren-Lawrence score.

CONCLUSIONS

There was a significant decrease of the pain intensity and disability after the administration of diacerein among patients in this study from the first to eighth week of treatment. Concerning correlation of IL-1β level in synovial fluid with the pain intensity and disability, future study with larger sample size and inclusion of a control group is needed in order to draw more definitive conclusions.

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