

Original Article

COMPARISON OF PAIN SCORE IN OSTEOARTHRITIS PATIENTS TREATED WITH A COMBINATION OF DIACEREIN AND MELOXICAM AND MELOXICAM ALONE

NI MADE OKA DWICANDRA^{a*}, ANTONIOUS ADJI PRAYITNO SETIADI^b

^aPharmacy Department, Institute of Health Sciences Medika Persada Bali, Denpasar, Bali, Indonesia, ^bDepartement of Clinical Pharmacy, Pharmacy Faculty, University of Surabaya, Surabaya, Jawa Timur, Indonesia
Email: okadwicandra@gmail.com

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ABSTRACT

Objective: Osteoarthritis (OA) is a progressive chronic disease with the loss of articular cartilage. In managing OA, inadequate pain relief (IPR) often occurs, particularly with a single non steroidal anti-inflammatory drugs (NSAIDs) therapy. In this research, pain outcome of OA patients treated with a combination of diacerein and meloxicam vs meloxicam alone was evaluated.

Methods: This research was conducted at rumah sakit umum daerah (RSUD) Dr. Mohammad Soewandhie Surabaya by using randomized controlled trial (RCT) design. Pain outcome was evaluated by pain intensity and area under the curve (AUC) of pain score in week 0-4th.

Results: There were a significantly different ($p < 0.05$) in pain intensity seen in 3rd and 4th weeks after treated with a combination of diacerein and meloxicam, and with meloxicam only. However, there were no different in AUC pain score between combination and single therapy.

Conclusion: Combination therapy of diacerein and meloxicam was more effective than meloxicam alone. A significant effect of a combination therapy of diacerein and meloxicam occurred at 3rd weeks. The prolong study in order to get the differences in AUC pain score are needed.

Keywords: Osteoarthritis, Diacerein, Meloxicam, Pain intensity

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INTRODUCTION

Osteoarthritis (OA) is a progressive chronic disease that was characterized by loss of articular cartilage [1]. World Health Organization data showed that OA is still one of the ten most diseases that caused disability in developed countries. Prevalence of radiological knee OA in Indonesia was 15.5% in men and 12.7% in women between 40-60 y of age [2].

Osteoarthritic pain is a chronic pain. Its remission for longer period is difficult [3]. Osteoarthritis and pain symptom experienced by patients have bad effects. Walking limitations have an impact on activities of daily living, which 11% of patients need assistance to do personal care [1]. Osteoarthritis patients also have limitations to work [4]. A disability that occurs in OA patients is associated with greater depression [5]. However, in its management, inadequate pain relief (IPR) was occurred in 54-64% of patients. Satisfaction and quality of life become worse because of IPR [6-8].

Among the study of OA therapy, non steroidal anti-inflammatory drugs (NSAIDs) are the most widely prescribed medication [6-8], but they often cause a dissatisfaction in the treatment of pain [9]. The inability of NSAIDs in overcoming the pain can be caused by the analgesic ceiling effect. In addition, OA is a complex process involving a variety of mechanisms [9]. The combination of analgesics that works by different mechanism may lead to a synergistic effect in the treatment of OA [10, 11]. Non steroidal anti-inflammatory drugs also do not affect the underlying pathogenesis of the disease [12], so they have a minimal role in modifying the course of the disease and improve the quality of life.

A combination drug that can be offered to overcome OA is diacerein and meloxicam. Diacerein is an interleukin 1(IL-1) inhibitor developed for the treatment of OA. Diacerein has efficacy in terms of functional manifestations and structural components of OA [13-15]. It plays an important role in cartilage degradation and stimulation of nociceptive pathways. This mediator shows potent bioactivity in inhibiting synthesis of extracellular matrix (ECM), promoting cartilage damage, and suppressing the expression of an important component of ECM in chondrocytes [16].

Although diacerein can contribute to overcoming the problem of OA, some studies are still debating its benefit. Several randomized controlled trials (RCTs) and meta-analysis studies showed the benefits of diacerein in the treatment of OA and others studies in the Cochrane library declared the absence of significant benefit of diacerein [13, 17-22]. Diacerein was reported having slow-acting properties. The long onset of diacerein cause pain management with diacerein must be combined with other analgesics, such as NSAIDs during the first month of treatment [14]. One of the NSAIDs that can be used is meloxicam that showed benefit in overcoming the pain of OA and rheumatoid disorder [23-26]. Meloxicam has a long half-life (20-24 h) so the using frequency was lower and easier for patients [27]. Based on the above, pain outcomes of OA patients receiving combination therapy of diacerein and meloxicam, and meloxicam alone were compared in this study.

MATERIALS AND METHODS

Study design

This was an open-label, RCT study. The study was conducted during the period January 2016-March 2016 at rumah sakit umum daerah (RSUD) Dr. Mohammad Soewandhie Surabaya. The patient was provided written informed consent. The study was approved by Badan Koordinasi Pendidikan RSUD Dr. Mohammad Soewandhie Surabaya and Badan Kesatuan Bangsa, Politik, dan Perlindungan Masyarakat Kota Surabaya with approval number 070/2554/436.7.8/2016. The consecutive sampling method was used to get participant.

Before intervention was started, screening visit was conducted to determine who will be included in the randomization. At the time of screening, washout was conducted for the analgesic that was used by patients. The washout period was conducted over $5 \times t_{1/2}$ of the drug. If patients experienced pain during the washout period, the patients would be given rescue medication (paracetamol 500 mg, maximum 4 g/d). After a washout period, and the patient experienced pain at least 24 h with scale ≥ 4 , randomization was conducted with blocked randomization method.

Participants in the study were divided into two groups, to receive the combination of diacerein (Artoflam®) 50 mg once daily and

meloxicam 15 mg once daily or to receive meloxicam 15 mg once daily. Drug administration was conducted for 4 w. Follow-up was done every week. Patients were asked to record date and a missed dose, other drugs taken, and changes in the drugs taken. Patients were asked to return the blister of drugs that have been taken and the rest of the drug (both drugs from our study or other drugs consumed by the participant).

Compliance was calculated by comparing the actual amount of drug taken with drugs should be taken during the treatment period. Patients who missed >20% of the drugs were categorized as non-compliant. Patients were discontinued from the study if there were any violation in the criteria of the study, non-compliance with the study protocol, or the incidence of severe side effects.

Patient

The population was outpatients of the orthopedy clinic in RSUD Dr. Mohammad Soewandhie Surabaya. Patients were eligible for the study if they were diagnosed with OA knee by orthopedic specialists, 18-75 y old, had moderate pain when they did not use analgesic (pain score ≥ 4 with 0-10 scale), body mass index (BMI) ≤ 39 kg/m², and agreed to follow the study by signing an informed consent. The definition of knee OA in this study is OA that met clinical criteria and radiological criteria based on Indonesian Rheumatism Association [2].

Exclusion criteria were patient with malignancy; pregnant or using hormonal contraceptive; bleeding disorder or using anticoagulant, or aspirin with daily dose more than 325 mg; uncontrolled hypertension (diastolic >95 or systolic >165), heart failure, or unstable angina; liver and kidney disorder (creatinine clearance ≤ 30 ml/min that was calculated with Cockcroft-Gault formula); psychiatric disorders, using antidepressants, anticonvulsants, antipsychotics, sedatives, or muscle relaxant; drug dependency, drug abuse, or alcohol abuse (≥ 3 glasses/d); history of allergy with drug used in this study; reading, hearing, and speaking inability.

Evaluation of pain outcome

Pain intensity was measured by a combination of Wong Backer Face Rating Scale (WBFPRS) and numeric rating scale (NRS) tools (fig. 1).

Patients were asked to circle one number between 0 and 10 that was the most appropriate to describe the intensity of their pain. Pain intensity was assessed at baseline and every week until the 4th w. The area under the curve (AUC) of pain intensity on each subject was calculated up to 4 w of observation using trapezoidal rule.



Fig. 1: Combination of WBFPRS and NRS tools

Statistical analysis

Data were analyzed with per protocol method. Normality test was analyzed with Shapiro-Wilk test. Data followed a normal curve if $p > 0.05$. Homogeneity test was done by Levene's test. Data were homogeneous if $p > 0.05$. Pain intensity was analyzed using the following method.

1. Paired-sample t-test or Wilcoxon signed rank test was used to compare the efficacy of each group with baseline.
2. Independent-samples t-test or Mann-Whitney U test was used to compare the efficacy between the group receiving combination of diacerein and meloxicam, and meloxicam alone

For all test, data between different groups were significant if $p < 0.05$

RESULTS

A total 68 subject were included in this study. Six subjects were excluded as they used others analgesics, had low compliance, experienced adverse drug reaction (ADR) that could not be tolerated, consumed other OA drug, and experienced getting worse pain. The remaining 62 patients completed the study and included in the analysis (fig. 2.)

Table 1: Demographic and clinical characteristics of participant

No	Patients characteristics	Combination of diacerein dan meloxicam (N=30)	Meloxicam alone (N=32)	p	
1	Gender	Female Σ (%)	24 (80.0%)	25 (78.1%)	1.000
		Male Σ (%)	6 (20.0%)	7 (21.9%)	
2	Age	≥ 60 y	16 (53.3%)	18 (56.3%)	1.000
		<60 y	14 (46.7%)	14 (43.8%)	
		mean \pm SD (y)	61.13 \pm 8.53	60.41 \pm 7.69	
3	BMI	Normal weight Σ (%)	11 (36.7%)	6 (18.8%)	0.136
		Overweight Σ (%)	13 (43.4%)	13 (40.6%)	
		Obese Σ (%)	6 (20.0%)	13 (40.6%)	
4	Pain intensity	mean \pm SD	5.93 \pm 1.51	6.19 \pm 1.42	0.498
5	WOMAC score	Pain (mean \pm SD)	8.07 \pm 3.42	8.81 \pm 3.04	0.660
		Stiffness (mean \pm SD)	3.90 \pm 2.20	4.06 \pm 1.70	0.971
		Physical function (mean \pm SD)	31.70 \pm 11.74	34.34 \pm 10.15	0.346
		Total (mean \pm SD)	43.67 \pm 15.63	47.22 \pm 13.15	0.339
		Menopausal status	Menopause Σ (%)	20 (83.3%)	24 (96.0%)
7	OA grade	Not menopause Σ (%)	4 (16.7%)	1 (4.0%)	0.212
		1 Σ (%)	2 (6.67%)	0 (0.0%)	
		2 Σ (%)	8 (26.7%)	19 (59.4%)	
		3 Σ (%)	16 (53.3%)	8 (25.0%)	
		4 Σ (%)	4 (13.3%)	5 (15.6%)	
8	Duration of OA	≥ 5 y Σ (%)	2 (6.7%)	1 (3.1%)	0.607
		<5 y Σ (%)	28 (93.3%)	31 (96.9%)	
		mean \pm SD (years)	1.13 \pm 1.80	0.75 \pm 1.92	
9.	Involved joints	Unilateral	15 (50.0%)	12 (37.5%)	0.462
		Bilateral	15 (50.0%)	20 (62.5%)	

N: sample size, BMI: body mass index (normal weight ≥ 18 kg/m² and <25 kg/m²; overweight ≥ 25 kg/m² and <30 kg/m²; obese ≥ 30 kg/m²), WOMAC: The Western Ontario and McMaster Universities Arthritis Index

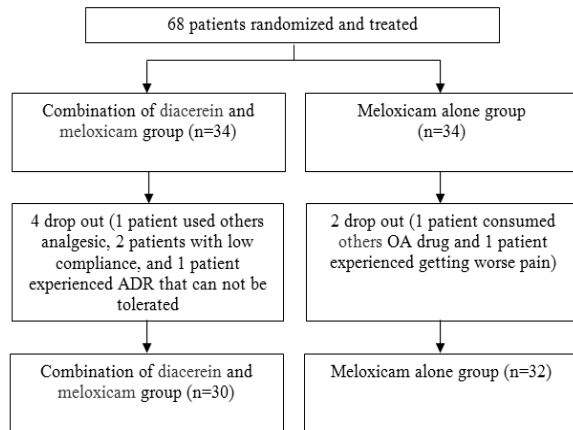


Fig. 2: Study design

The demographic and baseline clinical characteristics of patients were shown in table 1. The two treatment groups were similar with regard to demographic data and baseline clinical characteristic.

Pain outcome evaluation

Pain score decreased significantly in all groups when compared to the baseline values of each group ($p < 0.05$) after 4 w therapies (table 2).

Table 2: Statistical analysis results of pain intensity difference in pre and post treatment

No	Groups	Pain intensity	N	mean±SD	Sig
1	Combination of diacerein and meloxicam	Pre treatment	30	5.93±1.507	0.001*
		Post treatment	30	3.03±1.098	
2	Meloxicam alone	Pre treatment	32	6.19±1.424	0.001*
		Post treatment	32	3.81±1.615	

N: sample size, Sig: significance, SD: Deviation standard, *: $p < 0.05$

Table 3: Statistical analysis results of pain intensity difference between combination of meloxicam and diacerein, and meloxicam alone

No	Time of follow-up	Combination of diacerein dan meloxicam		Meloxicam alone		Sig
		mean±SD	CI 95%	mean±SD	CI 95%	
1.	Week 0	5.93±1.51	5.37-6.50	6.19±1.42	5.67-6.70	0.498
2.	Week 1	4.83±1.60	4.24-5.43	5.34±1.52	4.80-5.89	0.093
3.	Week 2	4.17±1.60	3.57-4.76	4.69±1.66	4.09-5.28	0.101
4.	Week 3	3.37±1.25	2.90-3.83	4.19±1.67	3.58-4.79	0.031*
5.	Week 4	3.03±1.10	2.62-3.44	3.81±1.62	3.23-4.39	0.035*
6.	AUC	16.85±5.22	14.90-18.80	19.22±5.97	17.0-21.37	0.064

SD: Deviation standard, CI 95%: Confident Interval 95%, *: $p < 0.05$

In this study, the combination of meloxicam and diacerein were significantly effective to reduce pain intensity after 4 w. There were no studies that accessed the efficacy of the combination of meloxicam and diacerein. However, there was a similar study conducted by Gupta *et al.* (2012). In that study, 50 mg diacerein and other NSAIDs (diclofenac 75 mg/d), showed significantly different pain scores compared with baseline (after 16 w of therapy) [29]. Randomized controlled trial studies by Shafshak *et al.* (2012) showed administration diacerein (100 mg/d) and diclofenac giving the difference of pain intensity in the pre and post treatment, both at 1 mo ($p = 0.033$) and 2 mo ($p = 0.001$) therapy [30]. A significant reduction effect in pain intensity after 4 w follow-up in this study was supported by the results of the other literature, which said that effects of diacerein appear 2-4 w after therapy, and were significant after 4-8 w [20]. Meloxicam reaches significant effects as an analgesic in 2nd-4th w [27].

Diacerein therapeutic effect on OA based on its ability to inhibit pain and also its affect on the structural components of the joint [15].

In the first week until 2nd w, the difference of pain score between the combination of meloxicam and diacerein, and meloxicam alone could not be seen. Those differences were seen at 3rd weeks ($p < 0.05$). This difference was stable at the end of follow-up (4th w). There was no significant difference in AUC of pain intensity (table 3).

DISCUSSION

This study was designed to assess the efficacy of combination diacerein and meloxicam, and meloxicam alone. In addition, this study was designed to compare the efficacy of combination diacerein and meloxicam, and meloxicam alone after 4 w of therapy.

In this study, meloxicam 15 mg/d has proven effective to give a significant difference in the pain intensity between pre and post treatment after 4 w of therapy. Efficacy of meloxicam in overcoming pain in OA was supported by RCT study by Lund *et al.* (2000). That study showed that meloxicam 15 mg/d was significantly more effective to reduce pain than placebo after 3 w of treatment [24]. Randomized controlled trial study by Yocum *et al.* (2000) also showed the benefits of meloxicam 15 mg/d in patients with hip or knee OA compared to placebo. After 12 w of therapy, there were differences in pain intensity when moved ($p < 0.01$) and pain at rest ($p \leq 0.001$) [23]. The effect of meloxicam in reducing the pain intensity was caused by inhibition the cyclooxygenase (COX) enzyme. The COX-2 enzyme plays a role in the synthesis of prostaglandins, which were the mediators of pain [28].

Diacerein activities were caused by its ability to inhibit IL-1. In the chronic inflammatory process, such as the OA, cells were under pressure and produced cytokines such as IL-1, IL-6, tumor necrosis factor- α (TNF- α) which can cause damage to cells and phospholipids membrane release [14]. In structural components, IL-1 plays an important role in cartilage degradation [16].

When it is linked to the response to pain, mechanism of action of IL-1 β able can up-regulate of pro-nociceptive mediators, such as nerve growth factor (NGF), which was known as a neurotrophic factor that played an important role in the process of pain. Interleukin 1 β can signal through a signal cascade that leads to the release and/or activation of nociceptive molecules such as prostaglandins, IL-6, substance P, and matrix metalloproteinase 9 (MMP 9). The action of IL-1 β may also occur directly on nociceptors. The receptor for IL-1 is expressed in sensory neurons. Interleukin-1 β can modulate neuronal accessibility to affect neuronal receptors such as sodium channels, gamma-aminobutyric acid (GABA), and n-methyl-d-aspartate (NMDA) receptors [31]. With a complex mechanism,

diacerein can reduce the intensity of pain and prevents further cartilage damage.

When it was compared with meloxicam alone, the combination of meloxicam and diacerein showed no significant difference in pain intensity at 1st and 2nd w. It could be caused by the onset of diacerein which was achieved at 2nd to 4th w after administration. The difference in pain intensity on both of groups can be observed at the 3rd week 4th weeks. Meloxicam alone group had greater pain intensity than its combination with diacerein.

When they were compared using AUC parameters, the combination of meloxicam and diacerein and meloxicam alone did not show a significant difference. Area under the curve data is the result of merging the intensity of pain from time to time. Pain intensity data can be transformed to the AUC to access the benefits of analgesic [32]. Compared with measurements at the end of study (EOS), the results of trials using the AUC provide smaller effect estimation but better precision. Area under the curve values gives the possibility to maintain the distinction treatment group by calculating the exact onset and offset of action of the drug. Trial with the rapid acting drug showed that AUC was more sensitive than EOS to detect treatment differences [33]. Analysis of the AUC was more stable and sensitive to see the interpatient difference than other measurements. Area under the curve described the cumulative response of an intervention, but did not provide information about the onset of analgesic effect [34].

Despite they have the different working mechanism and can support each other, the addition of diacerein to meloxicam therapy provided no significant difference in AUC of pain intensity. Several other studies supported the insignificant outcomes of pain intensity between the combination of diacerein and meloxicam with meloxicam alone. The results of this research were supported by a similar study conducted by Gupta *et al.* (2012). In that study, diacerein 50 mg in combination with other NSAIDs (diclofenac 75 mg) per day has shown significant differences in pain scores after 16 w of therapy compared with NSAIDs alone. That study did not explain the differences in pain scores over time between the combination group and single group. So, it was not known when these differences began to appear [29]. If it was assumed differences emerged at week 16th, the longer observation was needed in order to see the effect of the combination of meloxicam and diacerein.

Randomized controlled trial study by Shafshak *et al.* (2012), in patients receiving diacerein 100 mg/d for 2 mo vs diclofenac vs diacerein, found that in all three groups, there were no significant difference in pain intensity, both at 1 mo ($p = 0.493$) and 2 mo ($p = 0.325$) therapy [30]. Another study by Singh *et al.* (2012) also showed the comparison of addition NSAID (diclofenac) in patients with knee OA who consumed diacerein. The study was conducted for 3 mo. The combination group used diacerein 50 mg/d in the first month, 2 × 50 mg/d in 2nd and 3rd and sustained release diclofenac 75 mg/d from 1st to 3rd mo. Comparison group only used sustained release diclofenac 75 mg/d. After 3 mo, administration of diacerein and diclofenac showed a significant difference in pain intensity compared to diclofenac alone [35]. The difference above was appeared in a longer time (3 mo) compared to our study. That study did not explain about differences in pain scores over time, between the combination group and single group, so it was unknown when these differences were begun. If it was assumed in Singh *et al.* study that differences were shown at the 3rd mo (week 12), we needed longer observation in order to see the different between the combination of diacerein and meloxicam, and meloxicam alone. In addition, that study used different dose every month (50 mg/d of diacerein in the first month, followed by 100 mg/d in the next 2 mo). This dose differences could affect the outcome differences.

The difference of efficacy that was shown at 3rd and 4th w indicated that combination of meloxicam and diacerein had the potential benefits in the treatment of OA. Effect of diacerein was begun at 2nd to 4th w and significant at 4th-8th w [14]. Thus, we need longer observation up to 8 w in order to see the differences in the AUC of pain intensity. The differences in pain intensity between 2 groups become insignificant can be caused by small sample size, so we required the addition of large samples. In addition, different baseline

characteristics among study could influence the results, such as gender, BMI, and duration of suffering from OA.

There were differences in the proportion of men and women in the study conducted by Gupta *et al.* (2012) with our study. Our study was dominated by women (78.1%-80.00%), whereas in the study of Gupta *et al.*, the proportion between male and female was comparable (male: female = 2: 3). Gender was known affecting response to pain experienced. The study that was conducted by Tonelli *et al.* (2011) showed that women had a greater pain intensity than men in patients with osteoarthritis ($p = 0.04$) [36]. Differences in BMI also can contribute to pain intensity difference in OA patients. A study by Oyeyemi *et al.* (2013) showed that BMI influenced the effectiveness of knee OA treatment [37]. The significant differences in pain intensity between the normal weight and overweight ($p = 0.016$) patient and between normal weight and obese patient ($p = 0.005$) was found.

CONCLUSION

Combination therapy of diacerein and meloxicam was more effective than meloxicam alone. A significant effect of a combination therapy of diacerein and meloxicam occurred at 3rd w. The prolong study in order to get the differences in AUC pain score are needed. In addition, the cost-effectiveness analysis was needed to see the benefit of that combination compared with the single therapy.

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AUTHOR CONTRIBUTION

Author, Ni Made Oka Dwicandra, made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data. Co author, Antonious Adji Prayitno Setiadi, participated in drafting the article and revising it critically for important intellectual content.

AFFILIATION

Ni Made Oka Dwicandra

Pharmacy Department, Institute of Health Sciences Medika Persada Bali, Denpasar, Bali, Indonesia

Antonious Adji Prayitno Setiadi

Departement of Clinical Pharmacy, Pharmacy Faculty, University of Surabaya, Surabaya, Jawa Timur, Indonesia

LIST OF ABBREVIATION

AUC: area under the curve, BMI: body mass index, ECM: extracellular matrix, EOS: end of study, GABA: gamma-aminobutyric acid, IL: interleukin, MMP: matrix metalloproteinase, NGF: nerve growth factor, NMDA: n-methyl-d-aspartate, NRS: numeric rating scale, NSAID: non steroidal anti-inflammatory drugs, OA: osteoarthritis, RCT: randomized controlled trial, RSUD: rumah sakit umum daerah, TNF: tumor necrosis factor, WBFrs: wong backer faces rating scale, WHO: world health organization

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CONFLICTS OF INTERESTS

All authors have none to declare

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