Effect of Sidaguri (*Sidarhombifolia L*) on C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in osteoarthritis patients

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Abstract. Osteoarthritis (OA) is degenerative and inflammatory joint diseases. Management of OA, until now limited only to overcome the pain, inflammation, and improvement of joint function with medication in the form of NSAIDs that have many side effects. Damage to cells due to the stimulus will free various mediators or substances inflammation such as prostaglandin, IL-6, TNF-α and nitric oxide. Sidaguri plant (*Sidarhombifolia* L) has anti-inflammatory activity by inhibition of nitric oxide. The mechanism of action Meloxicam, like other NSAIDs, may be associated with the inhibition of prostaglandin synthetase (cyclo-oxygenase). One of the markers of the inflammatory process is CRP and ESR. We tested 50 patients divided into two groups, patients who get Meloxicam and Sidaguri (n = 25) and patients who get Meloxicam and placebo (n = 25). There were significant changes before and after therapy with p-value<0.0001.

1. Introduction

Osteoarthritis (OA) defined by the American College of Rheumatology (ACR) is a collection of conditions that affect the joints with signs and symptoms associated with the destruction of articular cartilage integrity.[1,2] Osteoarthritis mainly concerns them in middle and advanced age and will become a health problem in the community as the life expectancy increases. WHO estimates that 10% of the population aged over 60 years develop the disease, whereas 12.1% of population 25 to 75 years in the United States have signs and clinical symptoms of OA.[3] OA is a disease with the highest prevalence in our community group and the second most common cause of disability in elderly in western countries.

Biological and mechanical disturbances will lead to impaired synthetic balance and cartilage damage. Inflammation will aggravate it, whereas the inflammatory process involved various mediators.[4] The inflammatory response triggers an enzymatic sequence that ends destruction to joints.[5] The inflammatory process will affect the onset of pain. Assessment of pain that is widely used is the Visual analog scale (VAS). Pain scale 1-3 means mild (can still be arrested, uninterrupted activity) and treated with non-opioid analgesics ± adjuvant therapy, 4-6 means moderate (disturbing physical activity) and treated with non-opioid analgesia with weak opioid analgesics (second level opioids) with or without Adjuvant therapy, 7-10 pain scale means severe pain (cannot do activity

independently) and treated with strong opioid analgesics (level three opioids) with or withoutadjuvant therapy.[6]

Management of OA is currently being done more to treat pain, inflammation, and improvement of joint function (drugs modification). Drugs to overcome pain in OA are NSAIDs. Also, NSAIDs are unable to alter the natural course of OA disease.[7]

Meloxicam is a non-steroidal anti-inflammatory (NSAID) that has anti-inflammatory, analgesic, and antipyretic. The mechanism of action Meloxicam, like other NSAIDs, may be associated with the inhibition of prostaglandin synthetase (cyclo-oxygenase).[8,9]

The concentration of CRP can increase up to 100 times.[10] CRP is an inflammatory marker produced and released by the liver under stimulation of cytokines such as IL-6, Interleukin 1 (IL-1), and Tumor Necrotizing Factor α (TNF-α).[10] Colchicine can inhibit the production of CRP while immunosuppressive drugs such as corticosteroids and others or anti-inflammatory drugs (Non-Steroid Anti-Inflammation Drug) cannot inhibit its secretion.[11]

ESR is a non-specific test. The rate may increase during acute inflammatory processes, acute and chronic infections, tissue damage (necrosis), rheumatoid, collagen disease, malignancy and physiological stress conditions (e.g. pregnancy).[12]

According to the Minister of Health Decree in the National Health System (SKN) stating that the development and improvement of traditional medicine must continue to obtain high quality, safe, and widely used for self-treatment and formal health services.[13]

Sidaguri plant (*Sidarhombifolia L*) has anti-inflammatory activity by inhibition of nitric oxide.[14] In another study, it was found that the active compound β-sitosterol that resembles hydrocortisone and oxyphenbutazone in Sidaguri plants has anti-inflammatory activity.[15]

2.Methods

2.1. Patient Selection

The research was conducted in a clinical trial with parallel design method with treatment group and control group independently and randomized; the sample was taken by total sampling technique, starting from April 2017 until October 2017. Samples to be used in this study were all patients with the diagnosis of Osteoarthritis at Haji Adam Malik Hospital Medan and in Prof. Dr. Boloni hospital Medan. Blood sampling was performed at the cubital fossa area of the study subjects for CRP, ESR, renal function test (RFT), and liver function test (LFT) examinations one day before getting treatment and 30 days later. A randomizeddouble blind method was obtained to obtain treatment groups receiving Sidaguri extract (*SidaRhombifolia* L) with meloxicam and a control group that received placebo-containing drugs with Meloxicam in simple random sampling with some sealed envelopes that were not transparent and given odd and even numbers on the rolled of paper in it.

2.2. Diagnosis of Osteoarthritis

We diagnose OA with clinical manifestations and radiography. In the early stages, the radiographs can be normal, but the narrowing of the joint space is evident when the articular cartilage disappears. Also, the characteristics are subchondral bone sclerosis, subchondral cyst, and osteophytosis.[7,16]

2.3. Definition of Inflammation

Damage to cells due to the stimulus will free a variety of mediators or inflammation substances including histamine, bradykinin, kallidin, serotonin, prostaglandin, IL-6, IL-1, TNF-α, leukotriene and nitric oxide.[17]

2.4. Inclusion criteria and exclusion criteria

Inclusion criteria, subjects aged over 40 years of both men and women who suffer from osteoarthritis disease with VAS ≥ 4, with no impaired liver and kidney function and other causes of inflammatory reaction. Against some subjects conducted explanations and asked to provide informed consent

(informed consent) to follow the research and approved by the Research Ethics Committee Medical Field FK USU.

2.5. Statistical Methods

To display epidemiological data the subject of research used tabulation to show the descriptive picture. Data were processed and analyzed using SPSS Version-17 program with p <0.05 significance.

3.Result

This study followed 50 patients who met the inclusion criteria, the patients divided into two groups: the group with Meloxicam with Sidaguri (n=25) and the Meloxicam group with placebo (n=25).The number of male patients with Meloxicam therapy and placebo was 9 (69.2%), while the number of male patients with Meloxicam and Sidaguri was 4 (30.8%). The number of female patients with Meloxicam and placebo was 16 (43.2%), while the number of female patients with Meloxicam and Sidaguri therapy was 21 (56.8%). The chi-square test obtained p-value = 0.107. (Table 1)

Table 1. Basic characteristics.

Characteristics		Therapy		P-Value
		Meloxicam& Placebo (MP)	Meloxicam&Sidaguri (MS)	
Gender	Male	9 (69.2%)	4 (30.8%)	0.107
	Female	16 (43.2%)	21 (56.8%)	
Age		58.92 ±10.43	59.64 ± 11.39	0.817

From the statistical test, the laboratory results of CRP, liver function, renal function and ESR before and after Meloxicam and placebo administration were found to improve after drug treatment with p-value <0.0001. (Table 2)

Table 2. Significance test differences in laboratory results based on Meloxicam and placebo therapy.

Variable	Mean	n	Standard Deviation	P-Value
ESR-PRE	23.56	25	4.321	<0.0001
ESR-POST	22.36	25	3.774	
CRP-PRE	0.908	25	0.271	<0.0001
CRP-POST	0.844	25	0.252	
SGOT-PRE	19.32	25	4.862	<0.0001
SGOT-POST	23.96	25	4.971	
SGPT-PRE	21.32	25	7.482	<0.0001
SGPT-POST	26.68	25	7.548	
UREUM-PRE	30.724	25	17.435	<0.0001
UREUM-POST	37.72	25	18.151	
CREATININ-PRE	0.8492	25	0.235	<0.0001
CREATININ-POST	1.024	25	0.238	

From the statistical test, the laboratory results of CRP, liver function, renal function and ESR before and after Meloxicam and Sidaguri administration were found to improve after drug treatment with p-value <0.0001. (Table 3)

Table 3. Significance test differences in laboratory results based on Meloxicam and placebo therapy.

Variable	Mean	n	Standard Deviation	P-Value
ESR-PRE	24.28	25	1.79165	<0.0001
ESR-POST	12.28	25	3.40979	

CRP-PRE	1.224	25	0.23678	<0.0001
CRP-POST	0.664	25	0.14107	
SGOT-PRE	19.28	25	7.67854	<0.0001
SGOT-POST	26.08	25	8.07217	
SGPT-PRE	21.76	25	13.72431	<0.0001
SGPT-POST	29.84	25	12.85392	
UREUM-PRE	22.76	25	11.62712	<0.0001
UREUM-POST	31	25	10.99621	
CREATININ-PRE	0.76	25	0.15748	<0.0001
CREATININ-POST	0.8688	25	0.1518	

The average ESR-Post therapy Meloxicam and placebo are 22.36, while the average ESR-Post therapy Meloxicam and Sidaguri 12.28. Based on t-test result of 2 independent samples, obtained p-value < 0.0001, then there is a significant difference between ESR-Post treatment MP and ESR-Post MS. And the average CRP-Post MP was found to be 0.84, while the average CRP-Post MS was 0.64. Based on t-test result of 2 independent samples, obtained p-value = 0.003 <0.05.Hence there is the significant difference between CRP-Post MP and CRP-Post MS. We obtained a VAS score that decreased in both groups after receiving therapy with p-value = 0.043 (Table 4).

Table 4. Significance test of difference between post-therapy ESR and post-therapy CRP in both groups and VAS score.

Variable	Therapy	n	Mean	Standard Deviation	P-Value
ESR	Meloxicam&Placebo	25	22.36	3.77359	<0.0001
	Meloxicam&Sidaguri	25	12.28	3.40979	
CRP	Meloxicam&Placebo	25	0.844	0.25179	0.003
	Meloxicam&Sidaguri	25	0.664	0.14107	
VAS	Meloxicam&Placebo	25	2.92	0.953	0.043
	Meloxicam&Sidaguri	25	2.36	0.952	

4. Discussion

From this research was found 50 samples divided into two groups, and found the majority of women with OA (43.2% and 56.8%), and age in both groups were not significantly different (58.92 ± 10.43 and 59.64 ± 11.39) with p-value 0.817. The prevalence of OA increases with age because conditions are not reversible.The prevalence of OA rises strikingly with age. Regardless of how it is defined, OA is uncommon in adults under age 40 and highly prevalent in those over age 60. It is also a disease that, at least in middle-aged and elderly persons, is much more common in woman than in men, and sex differences in prevalence increase with age.[18]

We found elevated levels of CRP and ESR in both groups of patients, before receiving therapy with either Meloxicam and Sidaguri or Meloxicam with placebo. After 30 days, there was a decrease in CRP and ESR levels and statistically tested with p-value<0.0001. CRP is one of the indicators of systemic inflammation. Although it is not specific to osteoarthritis, the concentration of CRP can increase up to 100 times.[10,19] CRP levels will decrease sharply when inflammation or tissue damage subsides and within 24-48 hours has reached baseline value again. CRP levels are stable in plasma and are not influenced by diurnal variation.[20] ESR may increase during acute inflammatory processes, acute and chronic infections, tissue damage (necrosis), rheumatoid, collagen disease, malignancy and physiological stress conditions (e.g. pregnancy). ESR is a non-specific test. ESR may increase during acute inflammatory processes, acute and chronic infections, tissue damage (necrosis), rheumatoid, collagen disease.[12]

After statistically tested, the average ESR in patients receiving MP therapy was 22.36 and in the MS-treated group was found 12.28 with p-value <0.0001, which means MS therapy better in lowering ESR than MP therapy. Similarly, in the MP group, CRP levels were found to average 0.844 and in the MS group 0.664 with p-value 0.003, followed by improved clinically by looking at the VAS scores

that decreased with therapy (p= 0.043), which means that there was a better decrease in CRP levels in MS therapy than in the group receiving MP therapy.Some studies mention Sidaguri is also anti-inflammatory. Phytochemical compounds contained in Sidaguri are alkaloids and ecdysteroid which play a role in inhibition of prostaglandin biosynthesis by blocking cyclooxygenase. The active compound of β-sitosterol in the Sidaguri plant also has acted as an anti-inflammatory. Sidaguri plant (*Sidarhombifolia L*) has anti-inflammatory activity by inhibition of nitric oxide.[14] Other compounds suspected to have anti-inflammatory activity in the Sidaguri leaf are flavonoids and saponins.[21]

The limitation of this study was the sample size small, further research requires at least larger samples.

5. Conclusion

The Sidaguri combination with Meloxicam is better in lower levels of CRP and ESR which are markers of inflammation.

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