DESCRIPTION OF EFFECTIVENESS OF CILOSTAZOL AND ASPIRIN AS ADJUVANT OF DIABETIC FOOT WAGNER GRADE II AND III

(Overview of Erythrocyte Sedimentation Rate)

Pandji Winata Nurikhwan[1], Zairin Noor Helmi[2], Nelly Al Audhah[3]

[1] Medical Education Study Program, Faculty of Medicine University of Lambung Mangkurat Banjarmasin
[2] Departement of Orthopedic Surgery, Faculty of Medicine University of Lambung Mangkurat Banjarmasin
[3] Departement of Parasitology, Faculty of Medicine University of Lambung Mangkurat Banjarmasin

Correspondence's email: pandji.winata@gmail.com

Abstract: Inflammation in patients with diabetic foot will activate platelets and cause aggregation and lead to stasis of blood flow. This inflammation is caused by infection of the diabetic foot. Management of diabetic foot infections in patients is the use of antibiotics. However, the presence of vascularization disorders causing antibiotic delivery to the site of infection to be disrupted so that the process of eradication of infection would be inhibited. One of inflamation markers on patient with diabetic foot is increasing of Erythrocyte Sedimentation Rate (ESRs).The general objective of this study was to determine the efficacy difference between cilostazol and aspirin as an adjuvant to accelerate tissue healing of diabetic foot care Wagner Grade II – III based on erythrocyte sedimentation rate. This study is a descriptive study using the double-blind and randomized pretest-posttest design. A total of 14 samples is obtained by consecutive sampling. The results showed that four patients given cilostazol showed a 35% reduction in ESR and ten patients were given aspirin showed a 35% reduction in ESR. It can be concluded giving cilostazol and aspirin as adjuvant diabetic foot Wagner II and III showed a decrease in ESR.

Key words: erythrocyte sedimentation rate, diabetic foot, cilostazol, aspirin.

INTRODUCTION

The incidence of diabetic foot treated at Hasan Sadikin Hospital in 2003 ranged from 44% of the overall Diabetes Mellitus (DM) treated patients (1). The incidence of chronic ulcers in diabetic feet is around 15% according to the American College of Foot and Ankle surgeon (ACFAS) (2). Recurrent trauma in diabetic patients with neuropathy leads to abrasion, ulcers, cellulitis to foot ulcers that are often unnoticed or complained of not getting pain. Often the wound does not heal on its own, otherwise it increases the weight of the ulcer that does not heal (3). This occurs due to decreased quality of soft tissue, secondary to the increase in blood sugar levels are not controlled in a long time. This causes the occurrence of diabetic foot trials, such as, (1) secondary dyslipidemia of fatty blood profiles, decreased HDL / LDL ratio and elevated levels of triglyceride (2) macroangiopathy in the form of fatty deposits in blood vessel wall (atherosclerosis), and (3) microangiopathy of stasis and thrombosis (4).

Medical management as an adjuvant in the management of diabetic foot is still a new innovation, in the diabetic foot management guideline of ACFAS, there is no medical recommendation as adjuvant of diabetic foot management. Apart from the antibiotics used for infection management (2). However, for the management of similar abnormalities in Peripheral Arterial Disease (PAD) some vasodilator and anti-aggregation drugs of platelets have been used, including pentoxifylline, clopidrogel and the latter cilostazol. Cilostazol is a approved drug by Food and Drug Administration (FDA) for management of claudication intermittent in peripheral arterial disease (Peripheral Arterial Disease). Cilostazol works by increasing the activity of cyclic Adenosine Mono-phosphate (cAMP) found in smooth muscle tissue, platelets, and endothelial cells, inhibits platelet activation and aggregation, and causes vasodilation. Cilostazol also improves blood lipid profile by increasing HDL levels and lowering blood triglyceride levels. Even in the study of Ahn et al (2001) it was demonstrated that administration of cilostazol for 1 year may decrease the thickness of the intima tunica in the carotid artery (5).

Erythrocyte sedimentation rate (ESR) serves to measure the rate of red plasma deposition in the plasma (mm / hr). ESRs are found to increase during acute inflammatory / inflammatory processes, acute and chronic infections, tissue damage (necrosis), collagen disease, rheumatoid, malignancy, and physiologic stress conditions (e.g. pregnancy). When done repeatedly, the rate of sedimentation of blood can be used to assess the course of diseases such as tuberculosis, rheumatic fever, arthritis and nephritis. Erythrocyte sedimentation rate (ESR) rates indicate an active lesion, an increase in ESR compared to the previous one indicates a widespread process, while a decreasing ESR compared to the previous one indicates an improvement. Bendes and Neves, in a study in 2012 showed that the levels of ESRs could be used as markers infection of the diabetic foot

(6). Based on guideline issued by ACFAS, pharmacological management used to overcome infection in diabetic foot is by using antibiotic (7). Antibiotics used in Diabetic Foot Polyclinic of Ulin Hospital Banjarmasin is broad-spectrum antibiotic and given for 7 days in a row. However, in diabetic foot patients there is a vascularization disorder in the form of macroangiopathy and microangiopathy. Disorders of vascularization will cause blood flow to the foot becomes disturbed so that antibiotic delivery to the site of infection will be difficult. The infection of germs that cause infection will be slower so that the decrease in the level of ESR will be longer (8). Aspirin is the main drug used by the Diabetic Foot Polyclinic of Ulin Banjarmasin Hospital in dealing with vascularization disorders in diabetic patients. Aspirin is a drug that belongs to Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). This drug works by inhibiting the formation of thromboxane A2 (TXA2) present in platelets. This will lead to thrombocyte aggregation resistance (9).

RESEARCH METHODS

This research design is a descriptive study using double blind method and randomized pretest - posttest design. Diabetic Foot Polyclinic of Ulin Banjarmasin Hospital from July to October 2013. The subject of this research is diabetic foot patient of Wagner with Grade II and III. The number of research samples of 14 patients is divided into 2 groups, namely aspirin and cilostazol. Conditions of research subjects are getting standard treatment in the form of hypoglycemic drugs, antibiotics, and open wound care. Required research materials include 100 mg cilostazol and aspirin. ESR examination using Westergren tube, EDTA vacuum cleaner tube, and 1 cc injection syringe. The research procedure includes 6 stages. First, the research was done after getting approval from the Research Ethics Committee of the Faculty of Medicine, University of Lambung Mangkurat. Second, the research permit will be submitted to the Diabetic Foot Polyclinic of Ulin Banjarmasin Hospital. Third, the sample selection is done by using consecutive sampling method. Any patient who meets the inclusion and exclusion criteria will be given an explanation of the intent and purpose of the study, then the patient will be asked to sign the form of an informed consent as evidence that the patient has been willing to serve as a sample of the study. The study sample was then divided into two treatment groups. The division of groups is done randomly using the help of computer programs. Fourth, samples in the aspirin group will be given an aspirin dose of 80mg taken once daily for 7 days, while in the cilostazol group will be given cilostazol doses of 100 mg taken twice daily for 7 days. Fifth, patients in each group measured the ESR on day 0, before treatment was given. Sixth, after the patient was given treatment, each patient on the treatment group performed again ESR measurements on day 7. How to analyze the research data: data collected by measuring ESR in diabetic foot patient of Wagner grade II and III on day 0, 7. Data then tabulated and counted.

RESULTS AND DISCUSSION

Research on the difference in effectiveness between cilostazol and aspirin on the rate of erythrocyte sedimentation rate as a diabetic foot adjuvant according to Wagner grade II and III has been implemented in July - October 2013 with a sample of 14 people. The results of this study are presented in Figure 1 to 5.

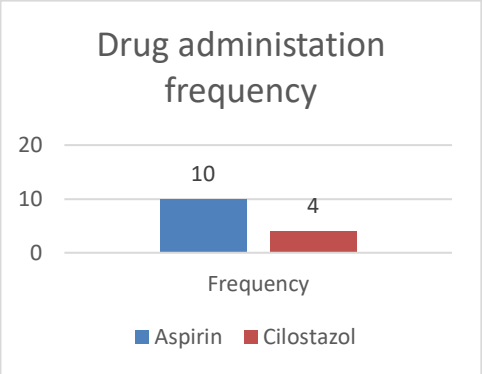

Figure 1. Distribution of drug administration

No	Patient ID	Age (yr)	Wagner Classification
1	P1	43	3
2	P2	52	2
3	P3	63	2
4	P4	65	2
5	P5	52	2
6	P6	44	2
7	P7	50	2
8	P8	45	2
9	P9	61	2
10	P10	60	3
11	P11	54	2
12	P12	45	2
13	P13	58	
14	P14	58	2

Figure 2. Patient Characteristic

Patient ID	ESR count before Treatment (mm/hr)	ESR count after Treatment (mm/hr)	Reduction	Drug use	Antibiotic Use before Treatment
P1	140	90	36%	A	Yes
P2	45	30	33%	A	No
P3	61	121	-98%	A	Yes
P4	89	50	44%	A	No
P5	122	118	3%	A	Yes
P6	131	70	47%	A	No
P7	14	12	14%	A	No
P8	45	30	33%	A	No

P9	67	33	51%	A	Yes
P10	107	70	35%	A	No
P11	111	95	14%	C	Yes
P12	58	27	53%	C	Yes
P13	12	12	0%	C	Yes
P14	95	60	37%	C	No

Figure 3. Patient ESR results, percent reduction, drug used, and antibiotics used.
A = Aspirin; C = Cilostazol, ESR = Erythrocyte Sedimentation Rate

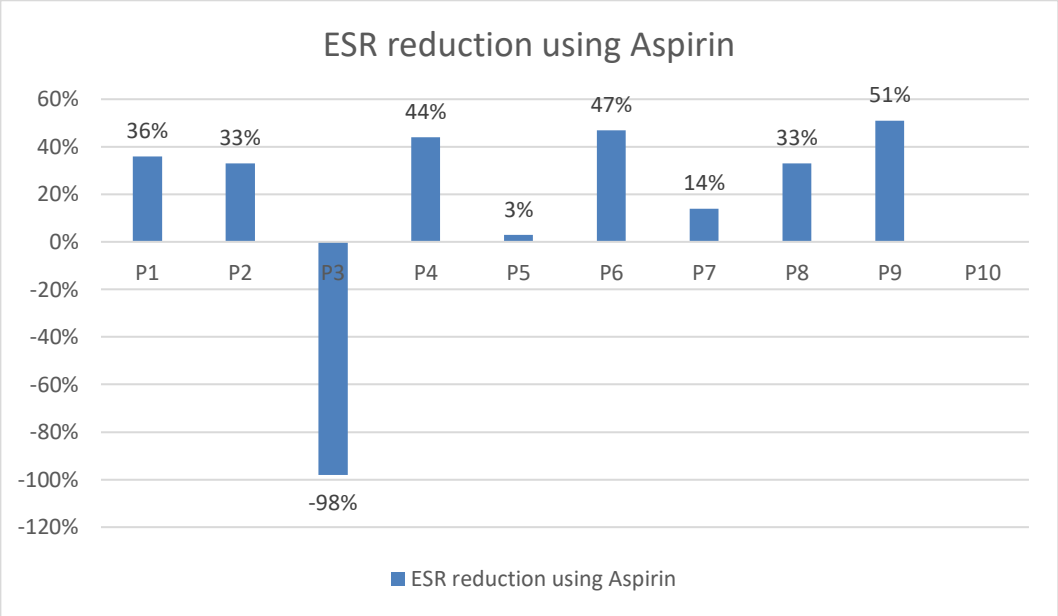

Figure 4. Results of ESR Patients Treated with Cilostazol

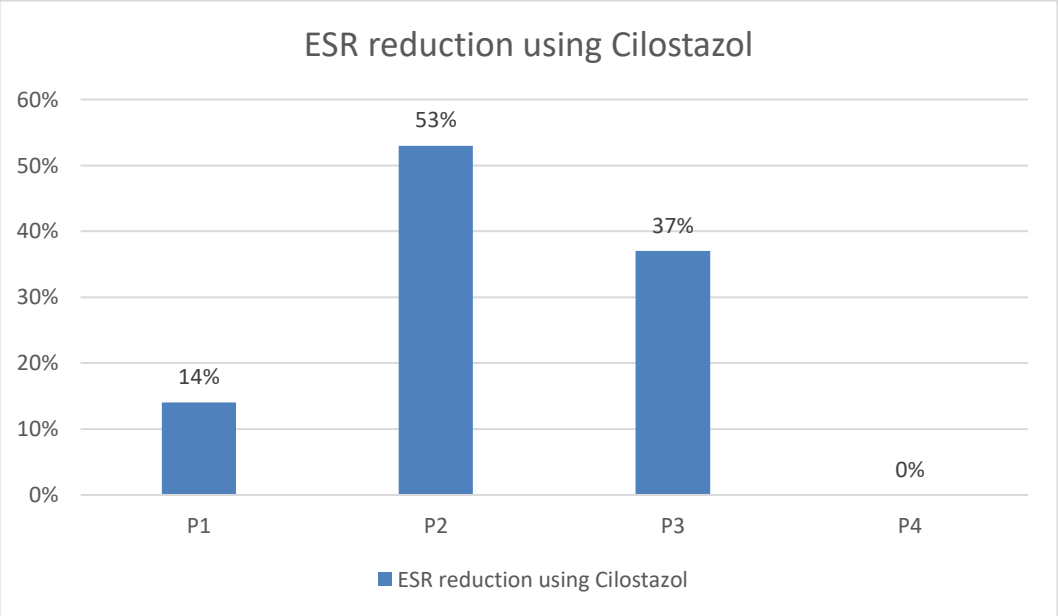

Figure 5. Results of ESR Patients Treated with Cilostazol

Based on the above data, in the cilostazol group there was improvement with mean of 35%. It can be said that administration of cilostazol as adjuvant in diabetic foot patients is effective in the process of eradication of bacteries. This statement is reinforced by Reilly et al (2001) that cilostazol works by increasing the cAMP activity present in smooth muscle tissue, platelets and endothelial cells leading to inhibition of platelet activation and aggregation, and vasodilation (10). This causes the flow distribution of antibiotic drugs to the tissue increased so as to accelerate eradication of bacteria and repair of wounds in diabetic foot caused by the presence of macrongiopathy and microngiopathy.

The aspirin group improved with an average of 35%. This improvement occurs with the mechanism of action of aspirin as an antiplatelet drug that inhibits platelet aggregation (11), by helping the blood flow to the periphery and distribution of antibiotics in patients diabetic foot become more smoothly so that eradication of bacteria that accelerate wound healing. Guo and DiPietro explain that wound healing can also be influenced by drug administration, for example steroid and NSAIDs (aspirin).

Patients who received diabetic foot care included in Wagner II and III criteria were given antibiotic drugs. The drug given by the physician on duty is a 3rd generation cephalosporin antibiotic. At the time of this study the drug was given for 1 week simultaneously with the giving of free variable. This drug serves to eliminate the bacteria contained in the wound so that wound healing can occur more quickly. The parameter used to determine the likelihood of a decrease in infection is a decrease in the ESR which is one of the markers of infection.

In the group of patients who were given aspirin, found an increase

in levels of ESRs, namely Tn. R. On day 0, the patient's ESR shows a figure of 61 mm / hr, and after day 7, the patient's ESR increases to 121 mm / hr. This increase may be due to antibiotic resistance so that inflammation persists and becomes widespread.

In the cilostazol group of patients, the patient's ESR on behalf of Ny. R is still within normal limits despite having an ulcer with a grade of Wagner II. Researchers believe this is because at the time of patients experiencing Wagner II ulcers, patients immediately make a visit to the hospital to get treatment so that inflammation has not occurred systemically in improving the ESR.

The rate of sedimentation of blood is influenced by several factors that determine the rapid delay of erythrocyte deposition, such as protein composition, erythrocyte size and shape, and erythrocyte concentration (13, 14, 15). Plasma proteins that accelerate the ESR are acute phase proteins, especially fibrinogen. Other acute phase-related proteins include haptoglobin, ceruloplasmin, α1-acid-glycoprotein, α1-antitrypsin, and CRP. The protein affects the ESR by lowering the erythrocyte negative charge (zeta potential). Zeta potential plays a role to keep the erythrocites away from each other. If the zeta potential decreases, the erythrocytes will form a rouleaux formation (arranged like stacked coins) that can settle faster. Other plasma components that accelerate the ESR are immunoglobulin and cholesterol. While plasma components that slow down ESRs are albumin and lecithin. Large erythrocyte size (macrosite) accelerates precipitation, whereas small size (microsite) slows down precipitation. While irregular erythrocyte form (poikilocytosis, spherocytosis, sickle cell) will inhibit the formation of rouleaux thus slowing the ESR. Low erythrocyte / plasma ratios, as in anemia state accelerate the ESR; while the high erythrocyte / plasma ratio, as in polycythaemia will slow down the ESRs. These factors are the reasons why patients have different percentages in the dereasing of ESR.

Inflammation is a reaction in the tissues of the body primarily played by blood vessels and leukocytes in response to infection, tissue damage (trauma, ischemia, radiation, burns, frost bite, exposure to toxic chemicals), autoimmune diseases (16). During the inflammatory process, macrophages secrete interleukin-1 and interleukin 6 which will stimulate the liver to increase the production of acute phase proteins (17). This increase in acute phase proteins will then accelerate the ESRs and become the basis for the use of ESRs as one of the inflammatory markers. Farnsworth and Paulan (2005) studies suggest an increase in ESRs (> 70 mm / h) in patients with ulcerated diabetic foot (Wagner Grading System) (18). An increase in ESRs with a mean of 104 mm / hr in patients with Diabetic Foot who experienced cellulitis was also found in a study conducted by Kaleta (2001) (19). The use of independent variables (cilostazol or aspirin) is used as a vasodilator so it can help the antibiotic work into the tissues (feet). Researchers can not control the confounding variables that affect the process of improvement, such as patient compliance in taking medication and patient compliance to come to check-up. In addition,

researchers can not control if there are habits of patients, such as smoking. Greenhagen research (2010) states that smoking can increase the risk of DM and peripheral arterial disease, and delay wound healing and ulceration in lower extremities (20). During the study, there were difficulties faced by the researcher, such as the patient could not come according to the schedule specified by the researcher, the researcher also had difficulty in doing the measurement of the wound because the location and shape of the patient's wound were different. This study has limitations, because the samples obtained did not match the expected minimum threshold. So researchers can not perform data analysis to determine the significant effectiveness between cilostazol and aspirin use of wound repair as adjuvant in diabetic feet according to Wagner degrees II and III. Research in Indonesia that examines the effectiveness of cilostazol and aspirin use on wound repair as adjuvant in diabetic feet according to Wagner II and III degree is still small, so hopefully this research can be used as reference for the next research. Herman's study in 2012 conducted at Hasan Sadikin Hospital Bandung examined the effectiveness of cilostazol and placebo as diabetic foot adjuvant Wagner grade II and III (21). in 2011, Hutagalung study in Medan examined the effects of aspirin, cilostazol and clopidogrel on the functional outcome of ischemic stroke patients (22).

CONCLUSION

The conclusion for this study was that the mean ESR before cilostazol drug administration was 69 mm / hr. The mean ESR after cilostazol drug administration was 48.5 mm / hr. The average ESR before aspirin administration was 82.1 mm / hr. The mean ESR after aspirin treatment was 62.4 mm / hr. Giving Cilostazol in four patients showed a mean ESR decrease of 35%. Aspirin administration in ten patients showed a mean decrease of 35%

Suggestions for further research, which can be done research using methods that control variable disrupt, so get more accurate result about difference of effectivity between cilostazol and aspirin to erythrocyte sedimentation rate as adjuvant of diabetic foot according to Wagner grade II and III

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