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The Effect of 2% Topical Mupirocin Cream on Biofilm Growth in Double Lumen Catheters in Hemodialysis Patients

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ABSTRACT

Double lumen catheter is a known risk factor for Staphylococcus aureus infection and bacteraemia in haemodialysis patients. The objective of this study was to determine the effectiveness of topical 2% mupirocin cream in lowering the growth of the biofilm at the Haemodialysis Installation of Dr. Soetomo Hospital Surabaya. Our research was an analytical quasi-experimental which subject divided into 2 groups equally, control and mupirocin group. Biofilms catheter was examined by tube test method with a nephelometer. Positive biofilm results if ≥0.36 MF, negative if >0.36 MF. Our research was obtained men (37%) and women (63%) with median age 51.3 (20-73 years). The mean duration of catheter insertion was longer in control than in the mupirocin group, 65.16 and 49, respectively (p = 0.005). There were positive biofilm growth results in both groups, 8 subjects (42%) in control group and 3 subjects (16%) in the mupirocin group, respectively. There was significant differences in the growth of biofilm between the two groups (p = 0.036; rd = 26%). Topical 2% mupirocin cream applied to the exit site CDL significantly reduced the biofilm growth in haemodialysis patients.

Keywords: Haemodialysis, double lumen catheter, CDL.

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INTRODUCTION

Chronic kidney disease (CKD) is rapidly becoming recognized as a major health, social and economic problem in Indonesia.(1) Hemodialysis is effectively treatment modality in maintained long survival rates and patient's life with CKD.(2) Nowadays, the central venous insertion has become a primary technique for establishing rapid access for hemodialysis in acute renal impairment patients who need immediate hemodialysis or CKD patients whose permanent vascular access cannot be used(3–5). Based on the 2011 US Renal Data System, more than 370,000 patients are undergoing routine hemodialysis. Eighty percent of these patients undergo hemodialysis catheters as the first dialysis vascular access.(6) Some reasons for using central venous insertion include loss of permanent dialysis access, delayed referral for dialysis initiation, waiting for the maturation of arteriovenous fistula (AV shunt), and limited access options in patients with severe vascular peripheral disease.(7,8)

Catheter-Related Bloodstream Infection (CRBSI) is a major cause of morbidity and mortality among patients with central venous insertion for hemodialysis.(7) The microorganisms that cause vascular access infections generally originate from the patient's skin. Gram-positive bacteria are the most common cause of CRBSI. The most commonly found gram-positive bacteria are Staphylococcus aureus (23.5%) and Staphylococci coagulase-negative (23.5%).(9–11) Acute infections due to the bacterium cause marked inflammation.(12) Complications that can be caused by CRBSI include infective endocarditis, sepsis, pulmonary embolism, and abscesses. So it can be concluded that CRBSI is strongly associated with mortality, hospitalization and poor prognosis.(7)

Biofilm is a bound of microorganisms that are attached to a solid surface. The solid surface can be either biotic or abiotic tissue.(13,14) The form of biofilm is a form of defense from microorganisms against physical, chemical, and biological threats. Pathogenic bacteria can form biofilm and cause disease by fighting off the immune system and creating a bacterial resistance to antibiotics.(15) Medical devices are a good place for biofilm to grow. Catheter double lumen (CDL), is a medical device that is often used in hemodialysis patients.(16) It has been reported that biofilm formations are more extra luminous in CDL installation less than 10 days, but in CDL installations above 30 days, biofilm formations are more intralumen.(17) The role of biofilms in intervascular catheters in the incidence of CRBSI is well known.(18) The incidence of antibiotic resistance in infections associated with medical devices is increasing, especially those caused by biofilm-producing bacteria.(19)

The treatment of infection still becomes problem until nowadays. Antibiotics are commonly used to treat the infectious diseases caused by *S. aureus*.(20) Mupirocin reversibly binds to isobutyl-tRNA synthetase and inhibits bacterial protein synthesis. Therefore, this drug is bacteriostatic, an antibiotic that works by inhibiting bacterial growth and multiplication. Mupirocin activity mainly works against Gram-positive bacteria, specifically Staphylococcus and Streptococcus. However, the mupirocin can also fight certain Gram-negative bacteria, including Hemophilus influenza and Neisseria gonorrhoeae, and also against Gram-negative bacilli and other anaerobes, although not as active as Gram-positive bacteria.(21) The previous study showed that using topical antibiotic ointments at the site of CDL insertion showed a 75-93% success in reducing the risk of CRBSI. The use of mupirocin in hemodialysis patients also reduces the level of bacteremia by Staphylococcus aureus by 78%.(17) Elimination of biofilms on intravascular catheters is a challenge for practitioners. The biofilm picture in the form of a microbial community is the first step in planning and evaluating the effectiveness of

therapy.(22) The objective of study was to determine the effectiveness of topical 2% mupirocin cream in lowering the growth of the biofilm at the Hemodialysis Installation of Dr. Soetomo Hospital Surabaya.

METHODOLOGY

Research subjects were CKD patients undergoing routine hemodialysis at the Hemodialysis Installation Hospital Dr. Soetomo Surabaya period November 2018-January 2019 with inclusion criteria of adult age> 18 years, a CDL was just installed for dialysis access, and was willing to sign informed consent. Subject with a history of allergy to topical 2% mupirocin cream was excluded. The research design used was a quasi-experimental method with the post-test only method, non-equivalent control group design. The study protocol was divided into two groups: the standard care group and the standard care group plus mupirocin. The standard group was the group that gets CDL insertion treatment according to the procedure that applies in the Hemodialysis Unit each hemodialysis session. The standard treatment group plus mupirocin was the group that received CDL insertion treatment with 2% mupirocin cream added to the exit site at each hemodialysis session. Some of the confounding factors in the formation of biofilms that we could not control included patients using antibiotic agents both orally and medically during CDL insertion, patients with comorbid infections during CDL insertion, and the length of time CDLs were attached. Criteria for drop out were if a CKD patient was attached CDL is removed before 1 month and more than 3 months and if a CKD patient was attached CDL resigned or cannot continue his involvement from any reason when he is in the process of treatment and observation.

Standard operational for dressing/wound care during the hemodialysis session in the standard care group: Wound care during the hemodialysis session is done by hemodialysis nurses or medical personnel by disinfection at the CDL exit site area using 2% chlorhexidine if there are any contraindications can be used povidone-iodine. The area of disinfection is at least 30 cm, which is applied circularly from the inside out. The application of this disinfectant was repeated 3 times. If a blood clot and crustae are obtained at the insertion site, it can be cleaned using 0.9% NaCl, then cover with sterile gauze. Patients who are still HD 1x / week, CDL exit site treatment is still done every 2x / week by medical personnel. SOP for dressing/wound dressing in the standard treatment group plus mupirocin is not much different in the treatment steps, topical 2% mupirocin cream is applied after the application of disinfectants as in standard care.

Our research subjects were observed for 1-3 months. When the CDL can be removed for any reason, a CDL specimen that is cut using a 5 cm sterile scissor is inserted into the BHI liquid which is then incubated for 24 hours and sent to the Clinical Microbiology Installation of RSUD Dr. Soetomo Surabaya for biofilm examination. Biofilm examination was carried out by experts in the field of microbiology. As for the implementation procedure, namely: as much as 100µ of bacterial colonies taken from primary isolation were bred on TSB media containing 1% glucose. Then incubated for 24 hours at 37°C. The tube containing the broth is then rinsed with phosphate buffer saline (pH 7.3) and then dried. After the tube was dry, the fixation was done by passing the Bunsen flame 3 times, then colored with crystal violet (0.1%). After that, the tube was rinsed with ionized water. The tube was dried in an upside-down position. The interpretation of biofilm results used a nephelometer. Biofilm growth data was categorized as positive and negative. The results of biofilm growth were said to be positive if the result was ≥ 0.36 Macfarland (MF), negative if the result was <0.36 MF.

Data on subject characteristics were presented descriptively namely frequency and percentage for categorical data types. The research data began with the normality test for all general characteristics data of the research subjects with the Shapiro-Wilk test. Statistical analysis of differences in biofilm growth between standard treatment groups plus mupirocin and standard care used independent t-tests. If the data were not normally distributed the test was different by using the Mann-Whitney test. For the difference analysis in biofilm growth results between standard treatments plus mupirocin and standard treatments used the chi-square test. Significance was determined based on $p < 0.05$ with the SPSS 23.0 program.

RESULTS

Subject characteristics in the form of demographic and laboratory characteristics of the research subjects were listed in Table 1. We found that females more than males in the standard care group and standard care group plus mupirocin The median age of both groups did not differ greatly at 51.2 years and 51.3 years, respectivly. The nutritional status assessment was based on BMI calculation. Nutritional status in both groups showed that the majority had normal low nutritional status, 12 patients (63%) and 9 patients (47%), respectivly. The most common underlying cause of kidney failure in this study was due to DM by 17 patients (45%) and hypertension by 14 patients (37%).

Glucose level showed normal values in almost all subjects, however all subjects in this study had anemia (100%). Most of the subjects of this study experienced hypo albumin and uremic which were characterized by increased levels of BUN. The mean albumin level was 3.09 ± 0.47 g / dL (normal 3.4-5.0 g / dL). The mean BUN level was 75.55 ± 41.30 mg / dL (normal 10-20 mg / dL). The site of CDL installation was mostly in subclavia with 33 patients (87%).

Data on the specific characteristics of research subjects are listed in Table 2. These special characteristics data were confounding factors that might affect the results of biofilm growth. The mean length of CDL installed in the standard care group was 65.16 days longer than the standard care group plus mupirocin which had an mean length of CDL installation of 49 days. A history of infection during CDL installation can include urinary tract infections, pneumonia, pedic ulcers, upper respiratory tract infections, CDL infections. In the standard care group there were 5 patients (26%), while in the standard care group plus mupirocin there were 8 patients (42%) who experienced an infection period during CDL insertion, this of course was followed by the use of antibiotics to overcome the infection. The results

of the analysis of differences between the two groups, only the data of CDL installation duration had significant differences between the two groups (p = 0.005).The condition of the difference in the duration of the CDL installation can affect the calculation and analysis of differences in biofilm growth between the two groups in this study.

The subjets were examined for biofilm growth to determine biofilm growth on CDL. There were 8 subjects (42%) in the standard care group and 3 subjects (16%) in the standard care group plus mupirocin had positive biofilm growth results. There was significant differences in the growth of biofilm between the two groups (p value = 0.036). The analysis results obtained a difference in the risk of biofilm formation on CDL by 26% (Table 3).

DISCUSSION AND CONCLUSION

Our results showed that the use of topical 2% mupirocin cream as an additional standard CDL exit site treatment during a hemodialysis session can reduce the growth of biofilms on CDL of routine HD patients. Mupirocin is an antibiotic that is bacteriostatic especially against Gram-positive bacteria and has good effectiveness in dealing with primary and secondary skin infections.(21)

CKD patients always experienced neutrophil dysfunction as a result of many complicated problems which placed the patients to high risk for infection. Patients with end-state renal disease are likely to experience infectious complications mainly urinary tract infection, pneumonia, and sepsis. Infection is a common event in patients with regular hemodialysis.(23) The most common type of infecting humans to cause serious illness to death is Staphylococcus aureus.(24) The potential for infection by Staphylococcus aureus is quite high because 50-60% of these bacteria form a deep colony human body and causes serious problems.(25) This study was in line with previous study that revealed there were 8 out of 22 patients (23.5%) who experienced catheter-related infections caused by *Staphylococcus aureus which* is a Gram-positive bacterium.(11) This bacterial infection causes factor aggravating skin lesion.(26)

There was a significant difference in biofilm growth between the standard care group plus mupirocin and the standard care group. The analysis found that the use of topical 2% mupirocin cream as CDL insertion treatment can reduce the risk of biofilm growth by 26%. There has not been any similar research to this study before. But as an analogy, we describe the data from previous studies that showed the effectiveness of mupirocin in reducing the risk of CRBSI. Based on the germ map from the previous study, it was found that there was a decrease in the colonization of *Staphylococcus aureus* bacteria on the skin around the CDL insertion.(17) In the group smeared with mupirocin there was no S. aureus colonization 96.4% (95% CI, 91.5-100), while the control group without mupirocin was 62% (95% CI, 47.9-76.1). The proportion of skin infections around the catheter insertion due to *S. aureus* in the mupirocin group was lower than in the control group without mupirocin.

Confounding factors in the form of the length of the CDL were unable to be controlled and obtained significant differences in the two groups, so that it could affect the results of biofilm growth. The immediate side effects were itching, pain, redness / rash due to the application of 2% mupirocin cream at the exit site in the standard care group plus mupirocin during the study. We can see the trend of the spread of biofilm density which increases with the length of CDL installed. Other studies, also mentioned that the longer the CDL was installed, the more biofilms formed.

Our study has several limitations. This study was conducted in routine hemodialysis patients regardless of the length of the installation of heterogeneous CDL so that it can affect the results. This research was only conducted at Dr. Soetomo and only in certain relatively short periods of 3 months. This is certainly not likely to reflect the general population of patients undergoing routine hemodialysis.

Our study concludes that there are differences in biofilm growth in the standard care group plus mupirocin compared to the standard care group. Topping 2% mupirocin cream at CDL exit site as a treatment for hemodialysis sessions can reduce the growth of biofilms.

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TABLES

Table.1 Demographic and laboratory characteristics of research subjects

Characteristics	Total N=38	Group		*p**
		Standard group mupirocin (19)	care plus Standard care Group (19)	
Sex				
Men	12 (37%)	8 (42%)	4 (21%)	0.168
Women	26 (63%)	11 (58%)	15 (79%)	
Age				
Median (min-max)	51.3 (20-73)	51.3 (35-73)	51.2 (20-73)	0.617
Nutrition (BMI)				
Underweight	8 (21.1%)	4 (21%)	4 (21%)	0.410
Normal	21 (55.3%)	9 (47%)	2 (63%)	
Overweight	7 (18.4%)	4 (21%)	3 (16%)	
Obesity	2 (5.2%)	2 (11%)	0	

Cause of ERSD				
Hipertension	14 (37%)	8 (42%)	6 (31%)	
DM	17 (45%)	9 (47%)	8 (42%)	
Cervix Ca	4 (10%)	2 (11%)	2 (11%)	0.446
Autoimmune	1 (3%)	0	1 (5%)	
Kidney stone	2 (5%)	0	2 (11%)	
Glucose (mg/dl)				
Median	113	107	118	0.40
(min-max)	(74-329)	(76-249)	(74-329)	
Hemoglobine (g/dl)				
Median	8.4	8.2	8.7	0.568
(min-max)	(2.3-11.5)	(5.3-11.5)	(2.3-10.7)	
Albumine (g/dl)				
Mean	3.09 ± 0.47	3.1 ± 0.48	3.09± 0.47	0.938
BUN (mg/dl)				
Mean	75.5± 41.3	88.1±49.53	63±26.63	0.06
Site of insertion				
Subclavia	33 (87%)	17 (89%)	16 (84%)	
Jugular	1 (3%)	0	1 (5%)	0.709
Femoralis	4 (10%)	2 (11%)	2 (11%)	

Characteristics	Total (n=38)	Research subjects		*p**
		Standard care group plus mupirocin (19)	Standard care group (19)	
Duration of instalation				
Mean	7.1±18.2	49±12.56	65.16 ± 19.67	0.005*
Infection				
Yes	13 (37%)	8 (42%)	5 (26%)	0.311
No	25 (63%)	11 (58%)	14 (74%)	
Antibiotics using				
Yes	13 (37%)	8 (42%)	5 (26%)	0.311
No	25 (63%)	11 (58%)	11 (74%)	

Table 3. Biofilm growth in research subjects

Indicator	Total research subjects (n=38)		p	rd *(risk different*)
	Standard care group plus mupirocin (n=19)	Standard care group (n=19)		
Biofilm				
Positive	3 (16%)	(42%)	0,036	26%
Negative	16 (84%)	11 (58%)		

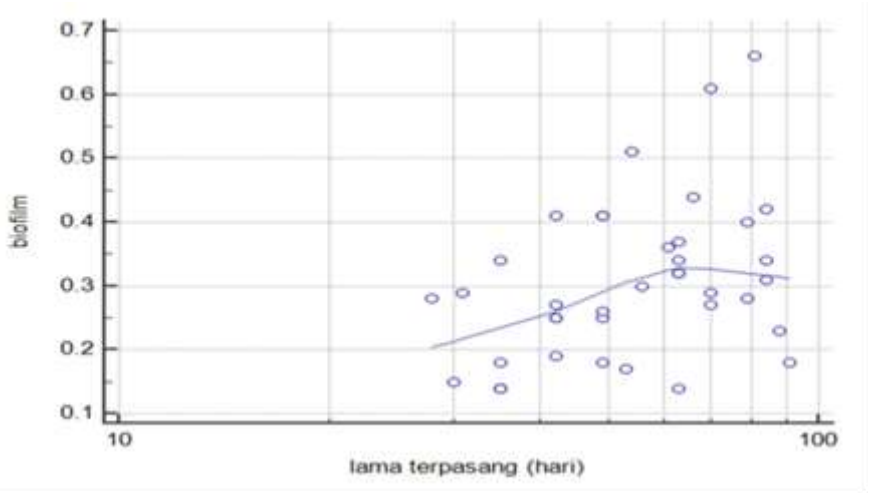

Figure 1. The corellation graphic between the lenght of time attached CDL with biofilm density