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Original Article

Comparison of the effect of antibiotic-lock and ethanol-lock methods on infection rate in children with hemodialysis catheter

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Abstract: Background: Hemodialysis catheter-related infection has a high incidence and complications. Antibiotic-lock or ethanol-lock can be used to prevent such infections. The aim of this study was to compare the effectiveness of antibiotic-lock and ethanol-lock methods in children undergoing hemodialysis and to evaluate the optimality of these methods. Methods: In this cohort clinical study, 25 children with chronic renal failure with hemodialysis catheter referring to Imam-Hossein Hospital in Isfahan, Iran, in 2016-2017 were studied. During two 6-month course, their catheter was locked first with antibiotics for 6 months, and then with ethanol for 6 months. Side effects, paraclinical findings and infectious species were also studied and data were analyzed. Results: In the first 6 months, 44% of the subjects and in the second 6 months, 12% of the subjects had catheter infections. The rate of infection, redness and catheter site sensitivity at the second 6-month course was significantly lower compared to the first 6-month course ($P<0.05$). Conclusion: Both Antibiotic-lock and ethanol-lock are useful and practical methods for controlling infection. However, according to the results of this study, the ethanol-lock method seems to be more effective than antibiotic-lock in controlling the infection in children with hemodialysis catheter.

Keywords: Hemodialysis, catheter, children, antibiotic lock, ethanol lock

Introduction

When for any reason, kidney damage is so high that GFR reaches below 15 ml/min (stage 5 of chronic kidney disease or CKD), the last stage is called ESRD, which is an indication for dialysis treatment [1, 2]. There are several techniques for dialysis; however, two major types of it, i.e., peritoneal dialysis and hemodialysis, are currently being mostly used [3]. In order to perform peritoneal dialysis, access to the peritoneum space should be provided and hemodialysis needs access to blood vessels to exchange and control the substances. The hemodialysis catheter is used for this purpose, and there are various types of hemodialysis catheter that can be used to transfer blood from the body to the device and vice versa [4]. A double lumen catheter is most commonly used in hemodialysis patients [5]. Dialysis catheter-related infection may be caused by several bacteria. The most common pathogens causing dialysis catheter-related infection are Staphylococcus aureus and Staphylococcus epidermidis, and prevalence of antibiotic resistance is significantly high among them [6-9]. Despite the provision of various guidelines for catheter use and the necessary care to maintain its safety and sterility, the rate of catheter infection has increased in the last decades [8, 10, 11]. Biofilm formation in the inner layer of the catheters, central venous infections, and septicemia are among important factors that have been associated with increased mortality and morbidity according to previous studies [12-14]. To prevent infection, antibiotics can be used as combination of one or more antibiotic with specific dosage with an anticoagulant within the catheter lumen; vancomycin and gentamicin has a wide use [15]. Results of various studies have shown that the success rate of this method is modest, and more studies are needed to more clearly exam-

ine the role of new types of antibiotics in preventing infection [16].

Ethanol lock is another method and related research indicates its role in eliminating biofilms and reducing catheter infection rate [17]. Various studies have shown that ethanol lock is more effective compared to antibiotic lock, and side effects associated with ethanol lock are tolerable. Also, the toxicity of this method is low and it can be considered as a safe and inexpensive technique [18-22]. Several solutions have been suggested to prevent catheter infection, many of which have been significantly effective; however, a method that completely prevents the infection is not suggested so far. Also no unique dose or specific types of antibiotics have been conclusively reported in various studies. There are limited studies to compare the effect of antibiotic lock and ethanol lock in children. The aim of this study was to further evaluate these techniques by comparing the effectiveness of the antibiotic lock with ethanol lock techniques in children undergoing hemodialysis, and to evaluate which of these methods is more effective in practice.

Methodology

In this cohort clinical study, 25 out of 35 children with chronic renal failure with hemodialysis catheter referring to Imam-Hossein Hospital in Isfahan, Iran, in 2016-2017 were studied considering the inclusion and exclusion criteria. The inclusion criteria for participation in the study included patients with less than 18 years of age who had chronic renal failure and had a silicon dialysis catheter (negative blood sample culture). Patients with a local infection source other than hemodialysis catheter, allergy and reaction to ethanol, kidney transplants, and also those who did not do 6 or 12 months follow up or their parents did not sign written and informed consent form for participation in the study were excluded. It should be noted that this study was approved by the Ethics Committee of the University of Medical Sciences with the code 396038. The procedure of the study is as follow. Two 6-month periods were considered and patients were examined for infection. Patients' catheter was locked with antibiotics for first 6 months, and then with ethanol for the next 6 months. So, the total evaluation and data collection took 12 months. At the beginning of both 6-month periods, blood sample cultivation (at least 10 ml) was obtained by intravenous catheter. The culture medium used in this study was a two-phase medium and the patient would have been included in the study in case of negative blood culture. At first, according to the instructions of catheter-infection control services, the hands are washed with 10 ml 0.9% normal saline as push-stop-push. At the first 6-month period, an antibiotic lock with 10 mg of clindamycin with 5000 to 15,000 heparin units (proportional to the catheter size between 1.2 and 4 ml) was injected into catheter lumen. In the second 6-month period, ethanol lock with a ratio of 1 ml of 70% ethanol with 500 heparin units was injected in proportion to the size of the catheter in each lumen. It should be noted that patients were dialyzed 3 times a week. In the first six months after each dialysis, antibiotics and heparin were locked; and in the second six months, only in one out of three dialyses, ethanol and heparin were locked and in the other two dialyses only heparin was locked. Although alcohol was not effective on the catheter, with precaution, we carried out an ethanol lock treatment for patients in 1 out of 3 dialyses in a week to prevent any possible damage to the catheter and thereby replacing the catheter. After the end of the time of antibiotic lock or ethanol lock and restarting dialysis, catheter was discharged by a syringe to observe the blood return, and then the dialysis was carried out. If any hemodynamic instability or fever occurred before the next dialysis or during dialysis, blood cultivation was carried out, and if necessary, based on the advice of the pediatric nephrologists, an experimental antibiotic regimen (including vancomycin) was administered immediately. Subsequently, based on the results of the culture and antibiogram, a change in antibiotic was made in case of observing no improvement. Any side effects including lethargy, headache, dizziness, nausea, and alcohol taste in mouth expressed by the patient were recorded by dialysis physician. During this study, hemoglobin, Ferritin, CRP (C-reactive protein test) and white blood cells (WBC), as well as infectious species (gram-positive, gram-negative and fungi) were studied at the two time periods.

Statistical analysis

The mean and standard deviation are used to describe quantitative data and frequency index and frequency percent are used to describe the

Table 1. Demographic information of patients

Number of cases		25
Sex	Male	(56%) 14
	Female	(44%) 11
Age (yrs) (average ± standard deviation)		4.38±10.88
Information of patients		Frequency index or average
Weight (Kg) (average ± standard deviation)		18.47±35.16
Duration of disease (yrs) (average ± standard deviation)		0.68±1.24
Kidney disease	Dysplastic kidneys	(8%) 2
	Focal segmental glomerulosclerosis	(24%) 6
	Systemic lupus erythematosus	(8%) 2
	Diabetic nephropathy	(24%) 6
	Congenital nephritic syndrome	(4%) 1
	Obstructive uropathy	(4%) 1
	IgA nephropathy	(4%) 1
	Rapidly progressing glomerulosclerosis	(8%) 2
	Undeterminate	(16%) 4

qualitative data. For analysis, Chi-square test was used. The data were analyzed by SPSS22 considering the significance level of 0.05. The tests used to compare the two time periods in term of infections were Independent t-test, Mann-Whitney and Chi-square.

Results

25 patients participated in this study, including 14 men and 11 women, with an average age of 10.88±4.38 years. The average duration of the disease in the patients was 1.24±0.68 years; their underlying kidney diseases included dysplastic kidneys (8%), focal golomerulosclerosis (24%), rapid progression (8%), lupus erythematosus (8%), renal nephropathy (24%), obstructive diseases (4%), IgA nephropathy (4%), etc. Other demographic information of patients is summarized in **Table 1**. Based on the comparison of the infection rate in the first and second six months (antibiotic lock and ethanol lock) in patients, catheter site infection was observed for 44% of the patients in the first six months and 12% of the patients in the second six months. Also, the rate of pus, redness, and catheter site sensitivity at the second six months was less than the first six months; so there was a significant difference between the two time periods in terms of the presence of infection, redness, and the sensitivity of the catheter site; however, there was not a significant difference between the two time periods in terms of symptoms such as pus drainage, catheter site stiffness, and the number of cases of fever and chills (P>0.05). In addition, the infectious strains were usually Staphylococcus epidermidis, Aureus and klebsiella pneumoniae; and there was no a significant difference between two time periods in term of the type of strain (P=0.56). In addition, hemodialysis catheters were replaced in 20% of cases in the first 6 months and 8% of the cases in the second 6 months; and there was no significant difference between the two time periods in term of the replacement of the catheter (P= 0.22). The other items are summarized in **Table 2**. It is noteworthy that no sediment in the use of ethanol 70% and heparin (500 units of heparin per 1cc of ethanol 70% once a week) was observed in patients.

Based on the paraclinical observations, there was no significant difference in term of hemoglobin, Ferritin, CRP and WBC between the two time periods (P>0.05) (**Table 3**).

Discussion

One of the most important problems associated with catheter insertion is the related infections. It has been estimated that annually 250,000 to 500,000 blood infections occur due to the insertion of central venous catheter [23]. High mortality, High hospital costs and longer hospitalization are among the related problems [24, 25]. Despite the existence of solutions to treat catheter-related infections, a

Table 2. Comparison of the infection rate in the first and second six months (antibiotic lock and ethanol lock)

Variant		First six months (antibiotic lock)	Second six months (ethanol lock)	*P*-value
Catheter site infection		(44%) 11	(12%) 3	0.01*
Number of cases of fever and chills (average ± standard deviation)		0.95±1.01	0.89±0.72	0.26**
Pus drainage from catheter site		(16%) 4	(4%) 1	0.15*
Catheter site redness		(40%) 10	(12%) 3	0.02*
Catheter site stiffness		(20%) 5	(8%) 2	0.22*
Sensitivity of the catheter site		(40%) 10	(8%) 2	0.008*
Type of microorganisem	Staphylococcus epidermidis	(28%) 7	(12%) 3	0.06*
	Staphylococcus aureus	(12%) 3	0	
	Klebsiella pneumonia	(4%) 1	0	
Replacement catheter		(20%) 5	(8%) 2	0.22*

*Chi Square test, **Mann Whitney.

Table 3. Paraclinical information of patients in the two time periods

Variant (average ± standard deviation)	First six months (antibiotic lock)	Second six months (ethanol lock)	*P*-value*
hemoglobin (g/dl)	11.28±0.95	11.39±0.88	0.66
CRP	5.32±2.87	4.74±2.29	0.10
ferritin (mg/dl)	358.08±58.14	370.68±54.72	0.82
WBC (10^6 cells/μL)	7618.60±1958.67	7128.76±1356.08	0.08

*Independent test, CRP: C-Reactive Protein Test, WBC: white blood count.

definitive approach to prevent these infections has not been suggested so far. Antibiotic lock and ethanol lock solutions have been suggested to prevent colonization of bacteria and biofilm formation. Qu *et al.* investigated the role of various optimal anti-microbial solutions in the Catheter Lock technique (central venous catheter); they reported the role of ethanol in eliminating biofilm of coagulase negative staphylococcus to be more effective than others [20]. To the best knowledge of authors, there is currently no study on the role of antibiotic lock and ethanol lock in controlling the catheter infection in children with renal failure undergoing dialysis and the current study is the only study on this regard; however, the role of each of these techniques is previously investigated separately and with the simultaneous treatment with systemic antibiotics [19, 26]. The results of some of those studies are controversial. In a study by Souweine *et al*. on patients admitted to ICU, it was reported that there was no statistically significant difference in term of the incidence of catheter-related infections between the ethanol-treated group and control group [27]. They used dialysis catheter in a short term and 0.9% saline solution was used as the lock in the control group. The average duration of dialysis in their study was 4 days. Despite the short duration of their study and the difference in the control group in term of the catheter lock solution, their results are consistent with ours. Cober *et al*. performed a study on the role of ethanol therapy in preventing central venous catheter infections in children with intestinal failure using a 70% ethanol solution for an average of 263 days [23]. In this study, the blood infection associated with the catheter after the introduction of ethanol lock was significantly reduced. Strains involved were Staphylococcus aureus and Staphylococcus epidermidis, which respectively had higher effect in incidence of infection; however, there was no statistically significant difference in term of the strains. In our study, although Staphylococcus epidermidis was more prevalent compared to Staphylococcus aureus in the cases of infection; however, there was no statistically significant difference in term of the strains. Therefore, the results of the above

study are consistent with ours. A similar study by Jones *et al*. [28] was carried out. A 70% ethanol solution was used for the application of lock 3 times a week in their study. Staphylococcus pathogens were reported to be the most prevalent ones in their study; however, no detailed information was provided in term of the Staphylococcus species. The result of this study suggests the effectiveness of the ethanol lock therapy regimen three times a week in reducing the rate of central venous catheter infections. The lack of use of antibiotic lock in their study to compare it with ethanol lock may indicate the differences in the results of ethanol lock efficiency between their and our studies. In addition, the average duration of Ethanol Lock treatment in this study is also longer than our study. On the other hand, their study was performed on patients undergoing parenteral therapy and there was no dialysis. So, their methodology was different from the present study. Studies on the effect of antibiotic lock on reducing the rate of catheter-related infections have mostly reported the benefits and effectiveness of this technique; however, one of the most important issues in this regard is antibiotic resistance which has been raised in various studies. Landry *et al.* used gentamicin-heparin lock in their study and stated that resistance to gentamicin increased over a period of 6 months [29]. They suggested that the use of a non-antibiotic catheter lock may result in decreased catheter-related infection. In the study of Venditto *et al*., increased enterobacteriacea resistance to gentamicin is noted; however, staphylococcus resistance was reported to be insignificant in this study [30]. Also, in other studies, the antibiotic resistance was low [31, 32]. The reason for these differences may be the difference in the dosage of antibiotics and the antibiotics combination with other solutions such as the use of a lock consisting of heparin, gentamicin and citrate. Thus, it seems that co-administration of ethanol, antibiotics and solutions with adjusted doses, despite the effect on reducing antibiotic resistance, more effectively prevents catheter-related infections. In our study, comparing the two time periods, the albumin and ferritin serum levels increased at the end, which was reported statistically significant. Hoen *et al*. in study found that adult patients with prolonged dialysis catheters and bacterial infection, three parameters were independently and significantly considered as risk factors for infection, namely, the background of previous bacterial infection, the type of catheter, and the level of increased ferritin serum (higher or lower than 500 μg/L) [33]. Despite the higher level of ferritin serum in their study compared to the values measured in our study, this finding may indicate that host defective disorder in hemodialysis, which may occur during prolonged dialysis, is associated with bacterial infection. A study by Nassar *et al.* also showed that high levels of ferritin were associated with catheter-associated bacteremia. Also, low levels of albumin contributed to the development of catheter-associated bacteremia [34]. In our study, the infection rate was significantly lower in ethanol lock than antibiotic lock. Also, there was no significant difference in term of ferritin level in the two time periods. Further studies are needed to compare paraclinical parameters and their changes after the introduction of catheter-related infections prevention techniques, so that more precise results can be obtained.

Conclusion

The use of antimicrobial lock is necessary to prevent biofilm formation and the occurrence of catheter related infections. Antibiotic lock technique has been proven useful for this purpose. Ethanol lock has also been considered as an alternative with acceptable results. According to the results of our study, both methods were effective; however, the ethanol lock method outperformed the antibiotic lock method in terms of controlling infection, complications, microbial resistance, and lower costs (due to the lower cost of ethanol than antibiotics). The low sample size of the present study, as well as the limited number of studies that compare these techniques simultaneously on children undergoing hemodialysis through catheter, it is recommended that more extensive studies be conducted with a larger sample size in several centers.

Disclosure of conflict of interest

None.

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