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CLINICAL STUDY

Effect of Once-a-Week vs Thrice-a-Week Application of Mupirocin on Methicillin and Mupirocin Resistance in Peritoneal Dialysis Patients: Three Years of Experience

Caner Cavdar, Funda Saglam, Aykut Sifil, and Ali Celik
Department of Medicine, Division of Nephrology, Dokuz Eylul University School of Medicine, Izmir, Turkey

Tugba Atay
Department of Medicine, Division of Clinical Microbiology, Dokuz Eylul University School of Medicine, Izmir, Turkey

Ozkan Gungor
Department of Medicine, Division of Internal Medicine, Dokuz Eylul University School of Medicine, Izmir, Turkey

Ayse Ozder
Department of Medicine, Division of Nephrology, Dokuz Eylul University School of Medicine, Izmir, Turkey

Zeynep Gulay
Department of Medicine, Division of Clinical Microbiology, Dokuz Eylul University School of Medicine, Izmir, Turkey

Taner Camsari
Department of Medicine, Division of Nephrology, Dokuz Eylul University School of Medicine, Izmir, Turkey

Introduction. The application of mupirocin to the exit-site in peritoneal dialysis (PD) patients decreases peritonitis and exit-site infection (ESI) considerably. However, long-term application of mupirocin may result in the development of methicillin- and mupirocin-resistant strains. In this study, we aimed to investigate the effect of once-a-week vs. thrice-a-week application of mupirocin on mupirocin and methicillin resistance in PD patients. *Patients and methods*. Thirty-six patients were divided into two groups based on frequency of weekly mupirocin application at the catheter exit-site. In group 1, patients were randomly assigned to apply mupirocin once a week (n = 18), while patients in group 2 applied mupirocin three times a week (n = 18). We obtained cultures from the nares, inguinal area, axillae, and the exit site. The microorganisms reproduced, and the resistance to mupirocin and methicillin were recorded. Three years of follow-up of these patients were also recorded. *Results*. During the three-year follow-up period, seven episodes (0.26 episodes/patient-years) of ESI and 13 episodes (0.36 episodes/patient-years) of peritonitis were determined in group 1, and one episode of ESI (0.11 episodes/patient-years) and six episodes (0.24 episodes/patient-years) of peritonitis were determined in group 2. The rate of peritonitis and ESI were, respectively, 56% and 92% lower in group 2 when compared to group I ($p = 0.041$ and $p = 0.038$, respectively). Throughout three years, a total of 1852 samples were analyzed. In group 1, *S. aureus* reproduction rate and mupirocin resistance were 2.11% and 0.2%, respectively. In group 2, *S. aureus* reproduction rate was 0.93%, and no mupirocin resistance was observed. Methicillin-resistant *S. aureus* was not observed in both groups. Coagulase-negative staphylococcus (CNS) reproduction rate was 70.56% (mupirocin resistance: 59.87% and methicillin resistance: 33.7%) and 72.56% (mupirocin resistance: 64.7% and methicillin resistance: 33.3%) in groups 1 and 2, respectively. No peritonitis and ESI secondary to *S. aureus* and fungal agents were observed in both groups. *Conclusion*. The thrice-a-week application of mupirocin seems to be more efficient when compared to once-a-week application of mupirocin. Long-term application of mupirocin may cause the development of mupirocin- and methicillin-resistant strains, especially in CNS, which results in a difficulty for struggling against infections.

Address correspondence to Caner Cavdar, MD, Dokuz Eylul University School of Medicine, Department of Medicine, Division of Nephrology, 35340 Izmir, Turkey; Tel.: +90 232 4123763; Fax: +90 232 2790929; E-mail: caner.cavdar@deu.edu.tr

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INTRODUCTION

Infections, inadequate dialysis, and technical failure are still the leading causes of morbidity in peritoneal dialysis (PD) patients.[1,2] However, the infection rates have decreased considerably during the last decade by the efficient control of exit-site infections (ESI).

ESI is predominantly attributable to *S. aureus* and coagulase-negative staphylococcus (CNS). The presence of nasal and/or exit-site carriage is related to infections in PD patients. The eradication of the carrier-state is therefore helpful in achieving effective control of ESI and peritonitis.[3] Prophylactic antibiotics (mupirocin, neomycin sulfate, rifampin, trimethoprim-sulfamethoxazole, and ciprofloxacin) have been administered to eradicate *S. aureus* colonization and prevent catheter-related infections.[4,5]

In recent studies, it has been shown that decreases in infection rates have been achieved by the application of mupirocin at the exit site.[6] Currently, the most popular regimen for mupirocin is to apply it at the exit site once a day, 3–5 times a week. A major problem that may appear during long-term repetitive mupirocin application is the poor compliance of the patient, as well as the development of mupirocin resistance (MuR) and methicillin resistance (MeR).[7] The emergence of antibiotic-resistant microorganisms is a great concern in PD-related infections. On the other hand, the data regarding less frequent application of mupirocin at the exit site is limited.

In this study, we aimed to assess the effects of once-a-week or thrice-a-week application of mupirocin on MuR and MeR in *S. aureus* and also CNS in PD patients. We naturally expect a lower rate of mupirocin resistance with thrice-a-week application of mupirocin. On the other hand, the once-a-week application of mupirocin to the exit site is a consideration that we have never seen in the literature. However, we planned the implementation of this application if a higher rate of resistance does not develop with once-a-week mupirocin, if only for the easy application by the patients; therefore, we compared once-a-week application with more common, thrice-a-week application. In addition, we also include resistance patterns in the study.

PATIENTS AND METHODS

Mupirocin in the form of 2% ointment (Bactroban®, GlaxoSmithKline, Istanbul, Turkey) was prescribed to be applied once a week in 36 PD patients (21 males, 15 females; mean age 55.1 + 1.4 years) who previously did not use mupirocin at their exit site. In this study, prevalent PD patients were included. The demographical findings of patients are presented in Table 1.

Table 1
Demographic characteristics

	Group 1 (once weekly mupirocin)	Group 2 (thrice weekly mupirocin)	*p*
Age	57.4 ± 7.3	57.6 ± 9.6	NS
Sex (M/F)	10/7	9/7	NS
Diabetes	1	3	NS
Etiology of ESRD	Diabetes: 1 HT: 5 Chronic PN: 4 Other: 7	Diabetes: 3 HT: 4 Other: 9	
Dialysis duration	34.6 ± 25.3	43.3 ± 28.7	NS
Hb (g/dl)	11.8 ± 1.39	10.7 ± 0.8	NS
Albumin (g/dl)	3.8 ± 0.2	3.7 ± 0.3	NS
Kt/V	1.9 ± 0.3	1.8 ± 0.2	NS
Creatinine clearance (1/week)	56.2 ± 5.2	54 ± 10	NS

Data are presented as mean±SD.

Abbrevations: ESRD = end stage renal failure, HT = hypertension, PN = pyelonephritis, Hb = hemoglobin, NS = non-significant, $p > 0.05$.

Two years later, the patients were randomly assigned to one of two groups. Randomization lists were computer-generated using a random-number generator. In group 1, 18 patients (10 males, 8 females; mean age 55.3 ± 1.8 years) continued to apply mupirocin once a week. In group 2, 18 patients (11 males, 7 females; mean age 55 ± 2.3 years) began to apply mupirocin at their exit site three times per week. Also, swabs were collected from the nares, inguinal area, axillae, and exit site after two years (see Figure 1). Patients were evaluated for evidence of ESI or peritonitis during each monthly outpatient clinic

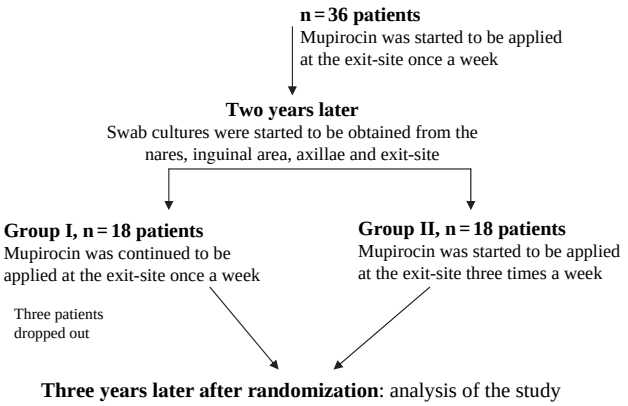


Figure 1. Enrollment flow.

visit, and swabs were taken at each visit. ESI was defined as pericatheter cutaneous erythema, soreness, symptomatic swelling, and purulent drainage at the catheter exit site.[8] Peritonitis was defined by the criteria of ISPD guidelines.[9] Also, routine exit-site care is detailed as below.

Exit-Site Care

In our center, exit-site care is performed in accordance with international guidelines. We placed a Tenckhoff catheter using a closed-blinded trochar procedure. Incision region and exit site are kept sterile during the first week. The region is not opened if possible. If a dressing is needed, a sterile technique is used (Betadine is not applied to exit site), and the wound site is closed with sterile gauze pads. During the period after wound healing, a dressing with Betadine for six months is recommended. It is requested that Betadine not come in contact especially with the sinus and the epithelial region. After the six months, standard care with physiological serum three times per week is recommended. The patients are also recommended to apply mupirocin one or three times per week after the above-mentioned standard care of exit site is completed for the study.

Microbiological Analyses

The swabs were inoculated on blood agar plates and incubated for 18–24 hours at 37°C. The plates were then evaluated for the growth of gram-positive cocci, and tube coagulase test was applied to catalase-positive colonies to discriminate *S. aureus* and CNS. Methicillin and mupirocin susceptibility were tested by disc diffusion according to the interpretative criteria of the National Committee for Clinical Laboratory Standards.[10] The colonies were studied for mupirocin and methicillin resistance on Mueller Hinton agar with disk diffusion method. An inhibition zone larger than 18 mm in CNS and larger than 13 mm in *S. aureus* was considered as oxacillin-sensitive, and an inhibition zone larger than 14 mm was considered as mupirocin-sensitive in both CNS and *S. aureus*.

Statistics

We investigated the effects of once-a-week or thrice-a-week prophylactic application of mupirocin on the MuR and MeR in *S. aureus* and CNS, as well as on the overall rate of ESI and peritonitis.

Statistical analyses were performed using EPI INFO 2000 and SPSS 12.0 (Statistical Package for the Social Sciences Inc., Chicago, Illinois, USA) for Windows. Comparisons between groups were performed by X^2 and Fisher exact tests for categorical data, and Mann-Whitney *U*-test for continuous data. $p < 0.05$ ($X^2 > 3.84$) was considered significant.

RESULTS

Thirty-six patients were enrolled to the study. Three patients dropped out during the three-year period; one patient was switched to hemodialysis because of inadequate dialysis and two were transferred to another dialysis center. Therefore, the results of seventeen patients in group 1 (10 males, 7 females; mean age 58 + 7.99 years) and sixteen patients in group 2 (9 males, 7 females; mean age 54 + 8 years) who had completed the study were evaluated at the end. A total of 1852 samples were analyzed during the three-year period.

S. aureus and CNS Growth Profile

Among 992 samples collected in group 1, CNS rate was 70.56% and *S. aureus* rate was 2.11%. In group 2, 860 samples were obtained, and CNS isolation rate was determined as 72.56% while *S. aureus* isolation rate was determined as 0.93% (see Tables 2 and 3). *S. aureus* rate was statistically higher in group 1 ($p = 0.04$).

It was observed that nasal *S. aureus* carriage rate was higher in group 1 when compared to group 2; however, it was not statistically significant (1.6% vs. 0.5%, respectively; $p = 0.646$).

Mupirocin Resistance (MuR)

The MuR for *S. aureus* was 0.20% in group 1, while no MuR was assessed in group 2. The MuR for CNS was statistically higher in group 2 when compared to group 1 (64.7% vs. 59.87%, respectively; $p = 0.021$).

Methicillin Resistance (MeR)

There was no MeR for *S. aureus* either in group 1 or in group 2. The MeR for CNS was 33.7% in group 1 and 33.3% in group 2.

Table 2
The results of a three-year period of microbiological analysis with antibiotic resistance patterns

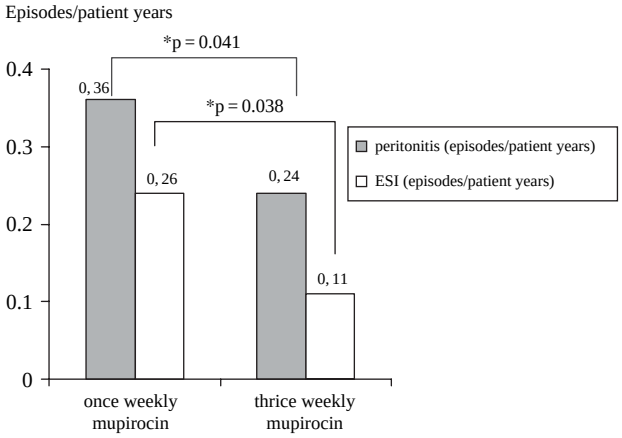
	Group I (once weekly mupirocin), n = 992		Group II (thrice weekly mupirocin), n = 860			
	n	%	n	%	X^2	*p*
CNS	700	70.56	625	72.6	0.91	0.341
MuR	594	59.87	557	64.7	5.26	**0.021**
MeR	335	33.7	287	33.3	0.50	0.480
S. aureus	21	2.11	8	0.93	4.21	**0.04**
MuR	2.0	0.20	0.0	0.0		
MeR	0.0	0.0	0.0	0.0		
Diphteroid	94	9.47	98	11.3	1.83	0.176
Gram negative	12	1.2	15	1.74	0.92	0.338
Others*	8	0.85	4	0.46		
No growth*	157	15.82	113	13.1		

*The percentages of isolates were calculated for each isolate group of total number of samplings.
Abbreviations: ESI = exit site infection, MuR = mupirocin resistance, MeR = methicillin resistance, CNS = coagulase-negative staphylococcus.

Table 3
Distribution of bacteria grown in swab cultures according to the site of culture

	Nasal	Inguinal	Axillary	Exit site
Micro-organism	n (%)	n (%)	n (%)	n (%)
Group I (once weekly mupirocin), n = 992				
CNS	186 (18)	217 (21)	214 (21)	84 (8)
S. aureus	16 (1.6)	2 (0.2)	3 (0.3)	—
Diphtheroid	36 (3.6)	11 (1.3)	11 (1.3)	38 (3.7)
Others	9 (0.9)	4 (0.4)	9 (0.9)	2 (0.2)
No growth	1 (0.1)	14 (1.4)	11 (1.3)	125 (12)
Group II (thrice weekly mupirocin), n = 860				
CNS	153 (17)	186 (21)	199 (22)	87 (10)
S. aureus	5 (0.5)	3 (0.3)	—	—
Diphtheroid	42 (5)	10 (1.2)	8 (0.9)	33 (4)
Others	9 (1)	5 (0.5)	1 (0.1)	4 (0.4)
No growth	6 (0.6)	11 (1.3)	7 (0.8)	91 (10)

The percentages of isolates were calculated for each isolate group of total number of samplings.



* As compared to once-a-week application of mupirocin.
ESI = exit-site infection

Figure 2. Peritonitis and exit-site infection ratio in once-a-week and thrice-a-week application of mupirocin.

ESI and Peritonitis

During the three-year study period, we observed seven episodes of ESI (0.26 episodes/patient-years) and 13 episodes of peritonitis (0.36 episodes/patient-years) in group 1, and 1 episode of ESI (0.11 episodes/patient-years) and 6 episodes of peritonitis (0.24 episodes/patient-years) in group 2. The rates of peritonitis and ESI were 56% ($p = 0.041$) and 92% ($p = 0.038$) lower in group 2 when compared to group 1 (see Figure 2 and Table 4). There was no Tenckhoff catheter removal as a result of infection in any of the groups. The duration of PD is important for the development of an infection. Therefore, the groups were also compared with each other for the duration of PD, and no statistically significant difference was determined.

Table 4
The results of a three-year period of peritonitis and exit site infection

	Peritonitis	ESI
Group I (once weekly mupirocin)		
CNS	5	3
S. aureus	0	0
Diphtheroid	1	0
Gram negative	4	0
Others	1	1
No growth	2	3
Total	13	7
Group II (thrice weekly mupirocin)		
CNS	4	1
S. aureus	0	0
Diphtheroid	0	0
Gram negative	1	0
Others	0	0
No growth	1	0
Total	6	1

Abbreviation: ESI = Exit site infection.
CNS = Coagulase-negative staphylococcus

DISCUSSION

Mupirocin has been used extensively to prevent *S. aureus* infections in patients undergoing peritoneal dialysis. Three-to-five times/week application of mupirocin at the exit site is recommended in the literature, while there are few studies regarding less frequent application of mupirocin. In the present study, thrice-a-week application of mupirocin at the exit site decreased the rates of peritonitis and ESI in PD patients. On the other hand, the finding that no ESI and peritonitis attributable to *S. aureus* was seen in the once-weekly mupirocin application group is interesting. A major problem that may appear during long-term mupirocin application is the development of antibiotic resistance. There are scant data regarding the effect of maintenance of mupirocin treatment on the MuR and MeR CNS prevalence, especially in PD patients. Another important result of the present study is that the prevalence of MuR CNS was significantly higher in the group with thrice-a-week application of mupirocin. Thus, the other important feature of our study is the evaluation of MuR and MeR in both S. *aureus* and CNS.

Thodis et al. studied the efficacy of local mupirocin ointment in PD patients. They confirmed that a local application of mupirocin at the exit site decreases not only the rate of ESI due to *S. aureus* but also the rates of peritonitis and catheter removal due to *S. aureus*. However, no difference in the incidence of infections was observed among patients applying mupirocin daily when compared to patients who applied mupirocin three times a week.[11]

The most significant problem to be faced during its long-term application is the development of MuR. Mupirocin was first used in 1980, and the first resistant strains were reported in 1987. In many recent studies, mupirocin-resistant *S. aureus* strains are reported in PD patients.[12] Annigeri et al. conducted a study including 146 PD patients who applied mupirocin at their exit site. At the end of a four-year follow-up period, mupirocin-resistant *S. aureus* was determined as 3% of the total study population—15% of total *S. aureus* isolates—while no methicillin resistance was observed.[13] On the other hand, a high rate of mupirocin-resistant *S. aureus* (14.5% of *S. aureus* isolates) in the study of Perez-Fontan et al.[14] was present in a significant proportion of their dialysis patients. Lobbedez et al.[15] reported that MuR and MeR *S. aureus* rates were respectively 2.7% and 1.4% of total isolates in patients receiving mupirocin daily or three times a week.[15] In our study, MuR *S. aureus* rate was 0.20% of the total isolates in group 1, while no mupirocin resistance was determined in group 2. These rates are lower when compared to other studies, and we believe that this difference is a consequence of genetic and environmental factors along with patient compliance. No MeR *S. aureus* was observed in either group. Hence, multi-drug-resistant strains are not in question in our patient group at this time.

CNS has an important role in the development of ESI and peritonitis. In a study performed by Kesli et al., the growth rate of CNS and methicillin resistance in the cultures of various samples were found to be 62% and 66%, respectively.[16] In a report by Refsalh et al., the rate of CNS and methicillin resistance in the general population was 51.9% and 31%, respectively.[17] In a study by De Mattos et al.,[18] the incidence of MeR CNS in PD patients was reported as 38%. The number of studies on MeR CNS in PD patients is limited. In the present study, CNS was investigated in terms of mupirocin resistance and methicillin resistance; in this regard, these are the first data in the literature. CNS was determined as 70.56% (MuR: 59.87%, MeR: 33.7%) and 72.56% (MuR: 64.7%, MeR: 33.3%) in groups 1 and 2, respectively. These findings should stimulate additional comprehensive studies to search for antibiotic resistance in CNS. Although the mupirocin-related methicillin resistance (33%) is acceptable, the rate of mupirocin resistance in CNS is higher than expected. This might be a consequence of the geographic conditions of the study population and the genetic properties of the CNS. This heightens the need for more extensive studies from different centers and countries. Studies investigating the effect of hypertonic saline, topical gentamicin, or the combination with mupirocin on the antibiotic resistance pattern should be a consideration. These should importantly

include the resistance pattern of either *S. aureus* or CNS. To avoid antibiotic resistance, the patients should be warned to be aware about the regular application, when thrice-a-week and more frequent application is performed. Although the rates of ESI and peritonitis were acceptable in group 1, nasal carriage was higher when compared with group 2. Nasal carriage might have a causal effect on this result; however, the absence of *S. aureus* growth in cultures from exit site of both groups reduces the likelihood of this hypothesis.

CONCLUSION

From a clinical point a view, we can say that the rate of mupirocin resistance among the isolated *S. aureus* strains is low in both groups (i.e., once-a-week versus thrice-a-week application of mupirocin) after at least three years on PD. When applications with long intervals are performed, the eradication of CNS may or may not be completed, and the more resistant surviving microorganisms confront us in the next application.

Thus, we recommend that mupirocin be applied at least thrice weekly to the exit site, and should be the prophylaxis of choice for PD programs. Further studies should investigate the results of antibiotic resistance in CNS as well as *S. aureus*.

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