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Effect of Local Polyhexanide Application in Preventing Exit-Site Infection and Peritonitis: A Randomized Controlled Trial

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Abstract: Topical antibiotic and antiseptic agents have been documented to reduce exit-site infection (ESI) and peritonitis in PD. The aim of this randomized controlled study was to evaluate the efficacy of polyhexanide in the prevention of ESI and peritonitis. Patients were excluded if they had active infection, > 18 years of age, ESI and peritonitis within the previous 4 weeks, received PD for less than 3-months and history of allergy to either drug. All patients were followed up until catheter removal, death, switch to dialysis, transplantation or the end of the study. ESI, tunnel infection, peritonitis, catheter removal and microorganism cause of catheter-related infection were recorded prospectively during clinic follow-up. A total of 88 patients (41 povidone-iodine group; 47 polyhexanide group) were enrolled with a total follow-up duration of 480 and 555 patient-months for povidone-iodine and alternating group, respectively. There were no significant differences in the age, sex, BMI, time of PD, rate of DM, and *S. aureus* carriage state. A total of 8 ESI and 25 peritonitis episodes were detected during the study. ESI and peritonitis rates tended to be lower in polyhexanide group compared with the povidone-iodine group (0.06 episodes/patient-year vs. 0.12 episodes/patient-year; 0.26 episodes/patient-year vs. 0.32 episodes/patient-year, respectively), but were not significant statistically. Moreover, catheter removal was similar in both groups (0.04 / patient-year vs. 0.05 / patient-year). Polyhexanide is efficient and safe for the prevention of ESI and peritonitis and it may be used as an alternative procedure for the care of healthy exit sites. **Key Words:** Exit-site infection, Peritoneal dialysis, Peritonitis, Polyhexanide.

Peritonitis and exit-site infection (ESI) are frequent complications of peritoneal dialysis (PD). These complications may lead to not only the removal of the PD catheter and switching of the renal replacement therapy to hemodialysis but also occasionally to fatalities. Therefore, prevention of all catheter-related infections, especially ESI, is essential for successful long-term PD (1,2). To date, several antiseptic agents have been used in the clinical setting for this purpose (1–5). However, the data are insufficient to show if one agent is superior to the others.

Polyhexanide is a modern antiseptic with low toxicity, and its antimicrobial spectrum includes Gram-positive and -negative bacteria, plaque-forming and biofilm-building bacteria, intracellular bacteria such as chlamydiae and mycoplasma, and fungi including *Candida* and *Aspergillus* spp. (6). It has also been approved for its effect on mycobacteria (7). This enhanced antimicrobial spectrum encouraged us to hypothesize that polyhexanide might reduce the risk of developing PD-associated infections more than conventional applications. In this randomized controlled trial, we aimed to evaluate the efficacy of polyhexanide compared to povidone–iodine in the prevention of ESI and peritonitis.

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PATIENTS AND METHODS

This randomized controlled trial was reviewed and approved by the Ethics Committee of Ankara Training and Research Hospital (Registration no:

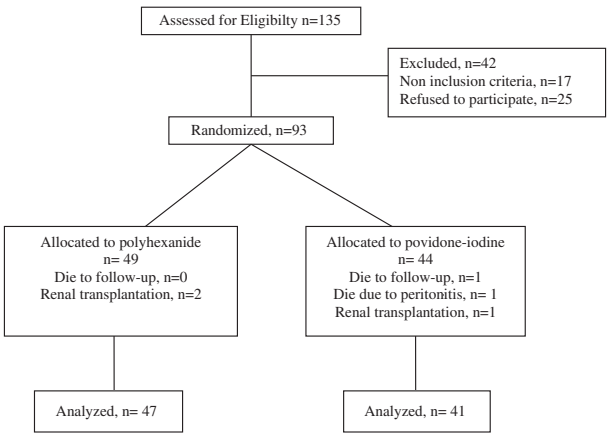

FIG. 1. Allocation of patients evaluated for study eligibility.

0402–3356), and informed consent was obtained from all participants. A detailed medical history was taken and a physical examination for the participants was performed. Patients >18 years of age with active ESI and peritonitis within the previous 4 weeks, those who received PD for less than 3 months, and those who were allergic to polyhexanide or povidone–iodine were excluded.

Double-cuff Tenckhoff catheters were placed percutaneously by an experienced nephrologist in our PD unit, and all patients used the twin-bag system. A total of 135 patients were assessed, and 93 were randomized. Five patients discontinued treatment. The remaining 88 patients were randomized into either the polyhexanide group ($n = 47$) or the povidone–iodine group ($n = 41$) according to the exit-site care regime (Fig. 1). Dressing changes were applied thrice per week with either polyhexanide in the form of a 0.1% spray or povidone–iodine. Patients were examined by the same physician and nurse every month. During the study period, infection-related complications, ESI, peritonitis, catheter removal, causative organisms and adverse reactions were monitored. Moreover, all patients were screened for their *Staphylococcus aureus* carriage status.

ESI, tunnel infection, and peritonitis were diagnosed according to International Society for Peritoneal Dialysis definitions (8,9). An exit-site infection is defined by the presence of purulent drainage with or without erythema, edema, and tenderness, and the swabs obtained from the exit-site area were sent to a microbiology laboratory for evaluation.

Peritonitis is defined as a cloudy fluid and/or abdominal pain associated with a white blood cell count ≥100/μL (with >50% neutrophils), and dialysate effluent was sent for microscopy and culture.

Tunnel infection is defined as erythema, induration, or tenderness over the subcutaneous pathway and radiographic evidence (on ultrasound scan) of a collection along the PD catheter tunnel.

TABLE 1. *Demographic data of study population*

	Povidone–iodine group	Polyhexanide group
Patients (*n*)	41	47
Age (years)	45.1 ± 14. 9	43.5 ± 14. 2
Gender (M/F)	20/21	22/25
BMI (kg/m^2)	26.1 ± 5. 4	24.4 ± 4. 9
Diabetes mellitus	13/41 (31.7%)	8/47 (17%)
Time on PD (months)	25.1 ± 21. 8	28.4 ± 25. 5
Study time (months)	11.7 ± 1. 2	11.8 ± 0. 7
S. aureus nasal carriers (*n*)	7/41 (17%)	8/47 (17%)
Causes of CKD		
Diabetic nephropathy	13	8
Hypertensive nephropathy	3	2
Glomerulonephritis	6	12
Amyloidosis	3	2
Other causes	7	10
Unknown	9	13
CRP (mg/L)	1.4 ± 2	1.2 ± 2. 1
Albumin (mg/dL)	3.6 ± 0. 46	3.7 ± 0. 51

BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein.

All analyses were performed using SPSS 15.0 (SPSS, Chicago, IL, USA). Results were presented as means (±standard deviation). For the analysis of parametric variables, the Student's *t*-test was used, and for nonparametric variables, the Mann–Whitney *U* test was used. For analysis of categorical parameters, the Chi-square test was used. Pearson's correlation tests were performed to assess the correlations between parameters. A P value < 0.05 was considered statistically significant. Infection rate was expressed as episodes per patient-year.

RESULTS

Of the 135 evaluated patients, 93 were randomized, and five patients discontinued the study because of death (2 of 5) and renal transplantation (3 of 5). Deaths occurred in the povidone–iodine group. The cause of one death was peritonitis, and another participant died of gastric carcinoma. Demographic data are shown in Table 1.

Total duration of the study was 555 patient-months for the polyhexanide group and 480 patient-months for the povidone-iodine group. Three episodes of ESI occurred in the polyhexanide group, and the overall rate was 0.06 episodes/patient-year. In the povidone–iodine group, five episodes of ESI were recorded during the study. The overall rate was 0.12 episodes/patient-year. Therefore, the ESI rate was

TABLE 2. *Breakdown of microorganisms causing peritonitis*

Microorganism	Povidone–iodine (n = 13)	Polyhexanide (n = 12)
Staphylococcus aureus	3	2
CoNS	3	4
Gram-negative organism	2	1
Streptococci	1	0
No growth	4	5

CoNS, coagulase-negative *Staphylococcus.*

TABLE 3. *Infection-related events during study and adverse effects*

Complication	Povidone–iodine (n/†rate)	Polyhexanide (n/†rate)	P value
Peritonitis	13/0.32	12/0.26	0.54
Exit-site infection	5/0.12	3/0.06	0.27
Catheter removal	2/0.04	2/0.05	0.86
Allergic dermatitis	0	2	

†Rate expressed as episodes/patient-year.

similar in both groups. Twelve peritonitis episodes in 12 patients occurred in the polyhexanide group, whereas 13 peritonitis episodes were reported in 10 patients in the povidone–iodine group. Although peritonitis rates tended to be lower in the polyhexanide group compared with povidone-iodine group (0.26 episodes/patient-year vs. 0.32 episodes/patient-year, $P = 0.54$), the difference was not significant statistically. The results are summarized in Tables 2 and 3.

Catheter removal was similar in both groups (0.04/patient-year vs. 0.05/patient-year, $P = 0.86$) (Table 3). Both of the catheters were removed because of refractory peritonitis and tunnel infection, which were caused, respectively, by methicillin-resistant *S. hominis* and methicillin-sensitive *S. aureus*, in the polyhexanide group. In the other group, two catheters were removed because of culture-negative nonresponsive peritonitis. Moreover, transient skin erythema developed in only two patients with polyhexanide application, but there was no difference between the groups.

DISCUSSION

In this randomized controlled trial, we present the similar effects of polyhexanide and povidone–iodine in preventing ESI and peritonitis. These results show that polyhexanide may be feasible as a different exit-site care protocol because it is easy method for all PD patients. Moreover, the rate of side effects did not differ between both groups.

Polyhexanide has increasingly been used for the prevention of catheter-related infections. It affects frequently seen pathogens responsible for ESI and peritonitis, such as Staphylococcus and Pseudomonas species with a broad antimicrobial spectrum (6,7). In the literature, two studies have reported its efficacy in the prevention of infections. Only one study in adults has been published by Núñez-Moral et al. concerning the efficacy of topical polyhexanide for exit-site care instead of traditional treatment. They reported that ESI and peritonitis rates are lower in the polyhexanide group (10). The other study showed a significantly higher ESI rate in polyhexanide patients when compared to the mupirocin group. However, peritonitis rates were similar in both groups (11). According to the present study, patients using polyhexanide had a lower rate of both ESI and peritonitis, but there was no statistically significant association. Moreover, neither side effect nor withdrawal was seen with topical polyhexanide and povidone–iodine treatments in the aforementioned trials (10,11). Both methods were well tolerated in the present study as well, and neither were withdrawn because of any side effects. It appears that using polyhexanide in ESI and peritonitis prevention has no additional side effects.

Despite being a cheap and easy method, exit-site care is an effective step for the prevention of serious catheter-related infections in modern PD treatment. Several antiseptics and antibiotic creams/ointments have been used for the reduction of peritonitis and ESI (1–5,12). Currently, topical mupirocin or gentamicin application are recommended by the International Society for Peritoneal Dialysis for exit-site care in PD patients (2,12,13). However, there is a concern that the widespread use of topical agents may lead to the development of bacterial resistance or the overgrowth of fungal organisms with altered local flora (2,12). We consider that polyhexanide with a broad antimicrobial spectrum may be an alternative agent when bacterial resistance is developed against a topical antibiotic or the combination with topical antibiotics may aid the prevention of bacterial resistance and fungal overgrowth in local flora. However, further prospective studies are needed.

All worldwide PD units have made an effort to reduce the number of PD catheter-related infections, although we have still have a long way to go regarding this, and we hope that this study may help reduce the average ESI and peritonitis rates. In light

of these results, we also consider that polyhexanide may have a similar efficacy in the prevention of infections related to hemodialysis catheters. Additional studies are needed to investigate the effect of this agent on hemodialysis catheter care.

There are some limitations to our study. First, the patient population in our study was relatively small, and the follow-up time was not long enough, so statistical power could not be achieved. Second, culture-negative peritonitis rates were high during the study. Finally, we excluded patients who had received PD for less than 3 months. Therefore, the incidences of ESI and peritonitis may have been underreported.

CONCLUSION

Polyhexanide is efficient and safe therapy for the prevention of exit-site infection and peritonitis, and it may be used as an alternative procedure for the care of healthy exit sites. However, further prospective studies with a large sample number are needed to confirm our findings about the use of polyhexanide for daily exit-site care.

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Conflict of Interest: None.

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