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Increased Peritoneal Dialysis Exit Site Infections Using Topical Antiseptic Polyhexamethylene Biguanide Compared to Mupirocin: Results of a Safety Interim Analysis of an Open-Label Prospective Randomized Study

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Prophylactic mupirocin for peritoneal catheter exit sites reduces exit site infection (ESI) risk but engenders antibiotic resistance. We present early interim safety analysis of an open-label randomized study comparing polyhexamethylene biguanide (PHMB) and mupirocin. A total of 106 patients randomized to 53 in each group were followed up for a mean of 12.68 months per patient. On safety analysis, the PHMB group had a significantly greater ESI rate than the mupirocin group (odds ratio [OR], 0.26; 95% confidence interval [CI], 0.09 to 0.80), leading to discontinuation of the trial.

Peritoneal dialysis (PD) catheter exit site infections (ESI) can lead to peritonitis, morbidity, and mortality. Prophylaxis against ESI with the topical antibiotic mupirocin is recommended (1, 2, 3). Resistance to mupirocin is emerging, prompting a search for antiseptics, such as polyhexamethylene biguanide (PHMB), which will not confer resistance (4, 5, 6). Topical PHMB has an *in vitro* antibacterial activity comparable to that of mupirocin, is well tolerated, and is licensed as a wound care medical device in Europe (7, 8, 9, 10). PHMB has a published record of safety in wound care; however, there is no published data on its use in prophylaxis of PD catheter ESI in humans.

We designed a randomized clinical trial to compare ESI rates with PHMD and mupirocin. In order to detect a 50% reduction of Gram-negative ESI, we expected to recruit 200 patients. However, an intermediate safety analysis at 50% recruitment was required by the Ethics Committee and the Safety Monitoring Committee. The results of the interim safety analysis and its implication for the randomized trial are presented here.

MATERIALS AND METHODS

In this interim safety analysis, we wished to determine that patients using PHMB would not have inferior ESI rates compared to those of patients randomized to mupirocin.

Study group randomization and mupirocin/PHMB application. Patients who were receiving PD without active ESI or peritonitis or within 30 days of an episode gave consent to participate in the study and were randomized to daily application of either PHMB or mupirocin. Approximately 10 mg PHMB (Prontosan wound gel) was applied directly or with a cotton bud, or a "pea-size" amount of mupirocin ointment was applied using a cotton bud. All other catheter care protocols were identical for the 2 groups.

Definition and diagnosis of ESI and peritonitis. ESIs were defined by diagnostic criteria in keeping with current ISPD and United Kingdom Renal Association guidelines (11). ESIs were diagnosed clinically from peritoneal catheter exit site purulent discharge associated with pericatheter swelling, redness, or tenderness. Swabs were obtained, but identifying a causative organism was not required for diagnosis. Infection rates were calculated as the number of infections divided by the total time at risk and expressed as episodes per 100 patient-months at risk. Peritonitis, defined by ISPD guidelines, was diagnosed by cloudy effluent with >100/μl white cells, with >50% of these polymorphonuclear cells from a 4- to 6-h dwell (12). If polymorphonuclear cells were <50%, clinical judgment was used to determine the diagnosis.

Sample size calculation. Sample size calculation was based on ESI rates of 0.12 per dialysis-year (audit data). We set a noninferiority limit of 20% for interim safety analysis (i.e., a 20% difference between the treatments would not be clinically significant). With a significance level (alpha) of 5% and power of 90%, 80 patients followed for 1 year was required. Assuming a dropout rate of 20%, an interim analysis was conducted 1 year after 100 patients were recruited.

SAEs. Patients were followed up every 1 to 3 months in outpatient clinics. Serious adverse events (SAEs) were defined and documented in accordance with ICH guidelines for good clinical practice.

TABLE 1 Demographics of patients

Parameter	Mean value (SEM) for group receiving:	
	Mupirocin	Prontosan
No. enrolled	53	53
Follow-up (mo/patient)	13.1	12.2
Age (yr)	58.0 (1.9)	59.9 (1.7)
Dialysis vintage (mo)	23.5 (3.6)	26.3 (4.5)
Diabetes mellitus (%)	26	47
CAPD (%)[a]	42	47
Biocompatible solution (%)	23	25

[a] Proportion of patients receiving continuous ambulatory PD versus automated PD.

RESULTS

A total of 106 prevalent PD patients were randomized for application of either mupirocin ($n = 53$) or PHMB ($n = 53$). The 2 groups were well matched apart from a higher percentage of diabetics in the PHMB group (47% versus 26%; $P < 0.05$). The mean

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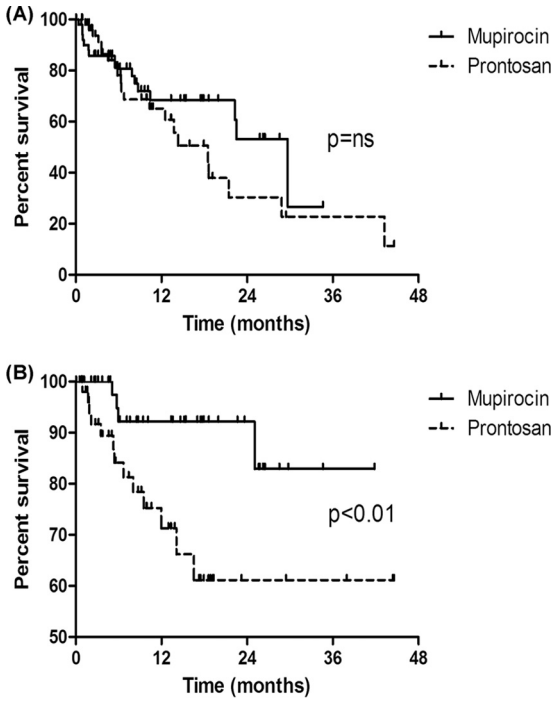

FIG 1 Infection-free patient survival. (A) Peritonitis; (B) exit site infection. ns, not significant.

(± standard error of the mean [SEM]) follow-up was 12.68 ± 1.03 months (mupirocin, 697 patient-months; PHMB, 647 patient-months) (Table 1).

Infection rates. Patients randomized to PHMB had a significantly greater ESI rate than those randomized to mupirocin (2.17 episodes versus 0.57 episode of ESI/100 patient-months at risk; $P < 0.02$). Similar differences in ESI rates were seen after stratification for diabetes (nondiabetic, PHMB versus mupirocin, 2.0 versus 0.58; diabetic, PHMB versus mupirocin, 2.3 versus 0.57). ESI-free survival was significantly shorter in the PHMB group (odds ratio [OR], 0.26; 95% confidence interval [CI], 0.09 to 0.80) (Fig. 1). Peritonitis rates were not significantly different between the 2 groups (3.7 versus 3.3 episodes of peritonitis per 100 patient-months at risk) (Table 2).

Bacterial isolates. The organisms that caused the infections are listed in Table 2. Most striking, all episodes of exit site infections caused by *Pseudomonas* ($n = 6$) and *Staphylococcus aureus* ($n = 4$) occurred in the PHMB group ($P < 0.001$ by chi-square test). The difference in infection rates from these organisms was marked in the nondiabetic patients; there were 4 infections from *Staphylococcus aureus* or *Pseudomonas* in the nondiabetics on Prontosan (336 months at risk), compared with no such infections in the nondiabetics on mupirocin (519 months at risk) ($P = 0.02$ by Fisher's exact test).

Adverse events. PHMB was well tolerated, with only 2 reports of transient skin erythema local to PHMB application. There were 35 SAEs in the mupirocin group and 45 SAEs in the PHMB group, but none were attributable to PHMB application. Of note were significantly more cardiovascular events in the PHMB group (13 versus 5), in keeping with a higher proportion of diabetics in the PHMB group (Table 3).

DISCUSSION

Our interim analysis demonstrated a significantly higher ESI rate and shorter ESI-free survival in the PHMB group, leading to discontinuation of the trial. The mupirocin group ESI and peritonitis rates were comparable to published infection rates from other centers (13). The theoretical promise of reduced antibacterial resistance using the antiseptic PHMB was overshadowed by objective clinical events (ESIs). The increased ESI rate should be interpreted with caution in view of the discrepancy in diabetes prevalence between study groups. However, the differences in ESI rates were almost identical after stratification for diabetes, and

TABLE 2 ESI and peritonitis absolute numbers over study period and rates

Condition	Parameter	Value for group receiving: Mupirocin (53 Patients)	PHMB (53 patients)	*P* value
ESI	No. of isolates over study period			
	Gram positive	0	5	
	Staphylococcus aureus	0	4	
	Gram negative	1	6	
	Pseudomonas	0	6	
	Fungal	0	0	
	Sterile	3	3	
	Total no. of ESIs	4	24	<0.001
	ESI rate[a]	0.57	2.17	
Peritonitis	No. of episodes over study period			
	Gram positive	11	17	
	Staphylococcus aureus	0	1	
	Gram negative	8	4	
	Pseudomonas	1	0	
	Fungal	1	0	
	Sterile	3	3	
	Total no. of peritonitis episodes	24	25	NS
	Peritonitis rate[a]	3.3	3.7	

[a] Expressed as the number of episodes per 100 patient-months at risk. *P* values were calculated using the chi-square test (with Yates correction).

TABLE 3 Serious adverse event reports

Event[a]	No. in group receiving: Mupirocin (53 patients)	Prontosan (53 patients)
Infection (nonperitonitis)	2	3
Soft tissue	1	3
Postvaccination pyrexia	1	
Cardiovascular	5	13
Angina/ACS/CVA		4
Hypotension/dehydration	3	5
Cardiac failure	1	2
Arrhythmia/palpitations	1	1
Fluid overload		1
Rheumatological	1	6
Arthralgia/arthritis	1	3
Gout		1
Bursitis		1
Sciatica		1
ENT	0	2
Vertigo		1
Epistaxis		1
Gastroenterological	11	4
Gastroenteritis/vomiting	8	1
Hernia	2	
Constipation	1	2
Diverticulosis		1
Surgical	4	7
Renal transplant	3	3
Breast lump excision		1
Parathyroidectomy		1
CABG/valve	1	1
Bowel		1
Dialysis related	7	6
Transfer to HD		1
Access (nonsurgical)	3	3
Access-related operation	4	2
Metabolic	2	1
Hypoglycemia	1	
Calciphylaxis		1
HONK	1	
Fall	1	
Death	2	1
Total no. of SAEs	35	43

[a] ACS, acute coronary syndrome; CVA, cardiovascular accident; ENT, ear, nose, and throat; CABG, coronary artery bypass graft; HD, hemodialysis; HONK, hyperosmolar nonketotic coma.

more worryingly, those in the PHMB group suffered more infections from *Staphylococcus aureus* and *Pseudomonas*. The latter may be a surprise, but mupirocin inhibits *Pseudomonas* flagellum formation and motility (14, 15). Interestingly *Pseudomonas aeruginosa* peritonitis rates fell in a large PD unit when mupirocin was introduced as standard care (16).

The value of robust interim safety analysis of new therapeutic agents in clinical trials is underscored by these findings. While confounding factors of group matching are appreciated, the extent of the ESI rate increase with PHMB gave enough concern for the Safety Monitoring Committee to discontinue this randomized open-label clinical trial early. Further research is required to determine if other antiseptics or formulations can be as efficacious as mupirocin for PD catheter exit site care without inducing antibiotic resistance.

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