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A PROSPECTIVE STUDY OF THE EFFICACY OF LOCAL APPLICATION OF GENTAMICIN VERSUS MUPIROCIN IN THE PREVENTION OF PERITONEAL DIALYSIS CATHETER-RELATED INFECTIONS

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♦♦ ***Background:*** **Peritoneal dialysis (PD)-related infections are the major cause of technique failure. Exit-site infections (ESI) can be prevented by local application of antibiotics. Mupirocin (M) is the most extensively studied drug for this application. Long-term use can result in the development of resistance. Gentamicin (G) is an attractive alternative, with both gram-positive and gram-negative activities. We studied the comparative efficacy of G cream versus M ointment in the prevention of PD-related infections in a Chinese cohort.**

♦♦ ***Methods:*** **This was a prospective study of adult PD patients of the Princess Margaret Hospital, Hong Kong. Patients were excluded if they had active infection, recent ESI or peritonitis, history of allergy to either drug, or were unable to apply the drug or give consent. Patients were taught to apply the drug daily to the exit site after routine exit-site care. Records were tracked prospectively during hospital admissions and clinic follow-ups.**

♦♦ ***Results:*** **95 patients were recruited; 14 discontinued the study. The ESI rates were 0.38 and 0.20 episodes/patient-year for the G group and the M group respectively ($p = 0.36$). Gram-positive ESI rates were 0.18 and 0 episodes/patient-year for the G group and the M group respectively. Gram-negative ESI rates were 0.20 episodes/patient-year for both groups ($p = 0.62$). The overall peritonitis rates were similar in the two groups ($p = 0.91$).**

♦♦ ***Discussion:*** **In addition to good perioperative care and strict exit-site care, local antibiotic application can prevent ESI. Mupirocin has been extensively studied and shown to be effective. Similar if not superior effects of G cream have been demonstrated. In this study, neither antibiotic gave significantly better results in the prevention of either ESI or peritonitis.**

♦♦ ***Conclusions:*** **Both gentamicin and mupirocin were effective as prophylaxis for ESI. Longer study is required to determine the long-term efficacy and the potential beneficial effect on the prevention of peritonitis.**

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KEY WORDS: Exit-site infection; peritonitis; prophylaxis; gentamicin; mupirocin.

In the landmark paper by Bernardini *et al.* (1), infection was referred to as the Achilles' heel of peritoneal dialysis (PD). In the CANUSA study, peritonitis accounted for 15% – 35% of hospital admissions, was the major cause (40% – 45%) of transfer to hemodialysis, and was associated with 7% – 10% of deaths (2). The importance of preventing PD-related infections was emphasized in the latest ISPD guidelines (3). Exit-site infection (ESI) can be prevented by the daily application of mupirocin ointment (4–8). Our group has demonstrated the effectiveness of local mupirocin application in the prevention of both ESI and peritonitis (4). Questions, however, have been raised about the emergence of both gram-negative infections and mupirocin resistance. Bernardini's was the first group to show the efficacy of gentamicin cream in the prevention of ESI (1). Therefore, we hypothesized that gentamicin cream is as good as mupirocin ointment in the prevention of PD catheter-related infections and set out to perform a comparative study in a cohort of Chinese PD patients.

METHODS

This study was carried out in the Dialysis Unit of the Princess Margaret Hospital of the Hong Kong SAR. From June to November 2005, all adult PD patients attending the outpatient clinic were screened for exclusion criteria. The exclusion criteria were (1) active infection, (2) ESI or peritonitis within the previous 4 weeks, (3) allergy to either gentamicin or mupirocin, (4) inability to apply the drug, and (5) inability to give consent. Suitable candidates

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were interviewed by the attending nephrologists, with full explanation of the study protocol given. Participating patients were taught to apply the drug sparingly around the exit site after their routine daily cleaning procedure. Signs and symptoms of ESI and peritonitis were reinforced and patients were instructed to report to the unit once infection occurred. The patients were assigned to either drug on a one-to-one alternate basis. A designated pharmacist interviewed the patients and reinforced the application technique, with special emphasis on compliance and side effects. Episodes of infection and adverse events were tracked during hospital admissions and clinic visits. Moreover, the pharmacist followed the progress of the patients every 4 – 8 weeks.

Infection rate was expressed as episodes per patient-year. The respective rates were compared using the Poisson regression model. A p value of <0.05 was considered statistically significant.

RESULTS

Ninety-five patients were recruited; 81 patients completed the study and 14 patients discontinued the study for the following reasons: reluctance (2/14), local irritation (2/14), itchiness (4/14), rash (3/14), transplantation (1/14), and unknown (2/14). The demographic data are summarized in Table 1.

Total duration of the study was 475.6 patient-months for the gentamicin group and 538.7 patient-months for the mupirocin group. Fifteen episodes of ESI occurred in 12 patients in the gentamicin group. The overall rate was 0.38 episodes/patient-year, 7 of them being gram positive and 8 gram negative. In the mupirocin group, 9 episodes of ESI were recorded in 7 patients. The overall rate was 0.20 episodes/patient-year. All were gram-negative. Six patients in the gentamicin group developed 13 peritonitis episodes, whereas 12 peritonitis episodes were reported in 10 patients in the mupirocin group. The p value could not be calculated for gram-positive ESI since no episode was recorded for the mupirocin group. No statistically significant results were found. The results are summarized in Tables 2 and 3.

TABLE 1
Demographic Data

	Gentamicin	Mupirocin	*p* Value
Patients (*n*)	43	38	
Age (years)	57.6	61.2	0.019
Sex (M:F)	1.69:1.00	4.40:1.00	0.267
Diabetes mellitus	41.9%	28.9%	0.116
Helper	20.9% (9/43)	26.3% (10/38)	0.073
Davies score[a]			
None	34.9%	50.0%	0.112
Intermediate	60.5%	34.2%	0.172
Severe	4.7%	15.8%	0.316

[a] Davies score: none = no comorbidity; intermediate = presence of 1 or 2 significant conditions; severe = 3 or more comorbid conditions (*i.e.*, diabetes mellitus, congestive heart failure, cancer, peripheral vascular disease, cerebrovascular accident).

TABLE 2
Exit-Site Infection

	Gentamicin (*n*)	Gentamicin Rate[a]	Mupirocin (*n*)	Mupirocin Rate[a]	*p* Value
Total	15	0.38	9	0.20	0.36
Gram positive	7	0.18	0	0	NA
SA	2	0.05	0	0	
MRSA	3	0.08	0	0	
CoNS	0	0	0	0	
Streptococcus spp	0	0	0	0	
Diphtheroids	1	0.03	0	0	
Corynebacterium sp	1	0.03	0	0	
Gram negative	8	0.20	9	0.20	0.62
PA	7	0.18	6	0.13	
Mixed	1	0.03	3	0.07	

SA = *Staphylococcus aureus*; MRSA = methicillin-resistant SA; CoNS = coagulase-negative staphylococcus; PA = *Pseudomonas aeruginosa*, NA = not available.
[a] Rate expressed as episodes/patient-year.

TABLE 3
Peritonitis

	Gentamicin (*n*)	Gentamicin Rate[a]	Mupirocin (*n*)	Mupirocin Rate[a]	*p* Value
Total	13	0.33	12	0.27	0.91
Gram positive	6	0.15	8	0.18	0.45
Streptococcus spp	5	0.13	2	0.04	
SA	0	0	1	0.02	
MRSA	1	0.03	0	0	
CoNS	0	0	4	0.09	
Mixed	0	0	1	0.03	
Gram negative	7	0.18	4	0.09	0.49
PA	2	0.05	1	0.02	
Campylobacter sp	1	0.03	0	0	
Plesiomonas sp	1	0.03	0	0	
Escherichia coli	2	0.06	2	0.04	
Klebsiella sp	1	0.03	1	0.02	

SA = *Staphylococcus aureus*; MRSA = methicillin-resistant SA; CoNS = coagulase-negative staphylococcus; PA = *Pseudomonas aeruginosa*.
[a] Rates expressed as episodes/patient-year.

Five patients in the mupirocin group died. The causes of death were peritonitis (2/5), acute pancreatitis (1/5), peripheral vascular disease (1/5), and unknown (1/5). One patient underwent removal of the PD catheter secondary to refractory Klebsiella peritonitis. Three patients in the gentamicin group died. Two patients had prehospital cardiac arrest and 1 patient died of recurrent transitional carcinoma of the urinary tract. Three catheters were removed: two due to peritonitis and one after persistent ESI.

DISCUSSION

Prevention is better than cure. The PD community has tried very hard to prevent catheter-related infections; however, there is no uniform policy. In recent years, the effectiveness of local application of mupirocin at the exit site has been observed in different parts of the world (4–8). Very low rates of ESI, especially gram-positive ESI, have been demonstrated. Long-term use of mupirocin, however, is not without its problems. First, emergence of resistance after several years of routine use of mupirocin has been reported (9,10). The clinical impact of mupirocin resistance is yet to be demonstrated. Second, mupirocin is not active against most gram-negative organisms. This is reflected by the very low incidences of gram-positive infection in most studies. After eradication of gram-positive infection, other organisms, gram-negative organisms in particular, may take the lead. Last but not least, the high cost of routine mupirocin application is another major consideration. Gentamicin, on the other hand, possesses activities against both gram-positive and gram-negative organisms and the cost of gentamicin cream is much lower than that of mupirocin ointment.

Bernardini's was the first group to compare gentamicin cream versus mupirocin ointment in the prevention of ESI (1). Their study showed the superior effect of gentamicin against gram-negative organisms while at the same time maintaining gram-positive coverage. In our study, similar infection rates were observed: concerning ESI, the group on gentamicin cream had infection rates similar to mupirocin ointment. One important observation was the virtual absence of gram-positive ESI in the mupirocin group. This, once again, underscored the exquisite activity of mupirocin toward gram-positive organisms. On the other hand, peritonitis rates were similar in the two groups. In contrast to the study by Bernardini *et al.* (1), gram-negative peritonitis occurred at the same rate in both groups. In fact, 1 patient in the gentamicin group developed 6 separate peritonitis episodes with different etiologic agents. If this patient were excluded from analysis, the peritonitis rate of the gentamicin group would be much lower. The reason for lower peritonitis rates in the Bernardini study was not known. There may be a chance that gentamicin is more effective at eradicating probable causative organisms and maintaining a relatively "sterile" exit site. Migration of organisms is thus prohibited. An alternative explanation is that subclinical infections are prevented since protocol culture of the exit site is not performed. Finally, systemic absorption of gentamicin is unlikely to produce significant effects since only a small amount is applied to the intact skin.

There are limitations to the present study. The numbers are small and the follow-up period is not long enough. In addition, no power calculations were performed prior to the commencement of the study. As a result, the study might be underpowered. One further drawback is the lack of a conventional randomization method, which may have introduced bias in group selection.

In conclusion, gentamicin cream was not superior to mupirocin ointment in the prevention of ESI. In this study, peritonitis occurred at the same rates in both groups. At this moment, both drugs can be recommended for prophylaxis of PD-related infection. Future studies should be extended to investigate long-term efficacy and consideration should be given to protocol bacterial screening of exit sites. With respect to long-term mupirocin resistance, once-weekly application of mupirocin may reduce the development of resistance on one hand and maintain the effectiveness on the other (11).

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