The impact of topical mupirocin on peritoneal dialysis infection in Singapore General Hospital

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Abstract

Background. Peritonitis and exit-site infections (ESI) are major causes of morbidity in peritoneal dialysis (PD) patients. The application of topical mupirocin to exit sites reduces such complications, and prolongs life in PD. Since the year 2000, this topical treatment has been used in our hospital on new PD patients. We analysed the results of this protocol, and studied the effects of comorbidities on the incidence of peritonitis.

Methods. We studied 740 incident PD patients, who were divided into two groups based on year of entry into PD (Group 1 from January 1998 to December 1999 inclusive, topical mupirocin not used, and Group 2 from January 2000 to March 2004 inclusive, topical mupirocin used). The variables we studied included gender, age, diabetic status, ischaemic heart disease, peripheral vascular disease, cerebrovascular disease and serum albumin.

Results. The application of topical mupirocin at the exit site led to a significant reduction in the rate of peritonitis (0.443 vs 0.339 episodes per patient-year; \( P < 0.0005 \)) and in ESI (0.168 vs 0.156 episodes per patient-year; \( P < 0.005 \)), results attributed primarily by the significant (\( P < 0.005 \)) reduction in \textit{Staphylococcus aureus} infection. There was also an unexpected lowering of \textit{Pseudomonas aeruginosa} peritonitis in the mupirocin group (\( P < 0.005 \)). Stepwise multiple logistic regression analysis revealed that only the application of mupirocin and serum albumin levels were significant predictors of peritonitis.

Conclusions. Our study, although retrospective, has demonstrated that the topical use of mupirocin was associated with a significant reduction in ESI and peritonitis and, unexpectedly, with findings of fewer incidences of \textit{Pseudomonas} peritonitis. Serum albumin level before the initiation of PD was a strong predictor of subsequent peritonitis. Mupirocin, with its low toxicity, ease of application and demonstrable beneficial effect in reducing ESI and peritonitis is now used on all of our incident PD patients.

Keywords: albumins; CAPD; exit-site infection; mupirocin; peritonitis; \textit{Staphylococcus aureus}

Introduction

Peritonitis and exit-site infections (ESI) in patients on continuous ambulatory peritoneal dialysis (CAPD) are the leading reasons for peritoneal dialysis (PD) catheter removal and patient exit from the program, which occasionally may lead to fatalities [1]. \textit{Staphylococcus aureus} (SA) has been recognized as the most common causative organism of ESI [2], with or without peritonitis. The long-term, regular application of mupirocin at the catheter exit site has prospectively been shown to reduce SA infection and peritonitis [3–5].

In the year 2000, we adopted the practice of applying mupirocin (Bactroban; SmithKline Beecham Pharmaceuticals, Philadelphia, PA) at the catheter exit site. We have now retrospectively reviewed the impact of this therapy on reducing the ESI and peritonitis rates between 1998 and 2004 in our centre, Singapore General Hospital.

Subjects and methods

We retrospectively studied 740 incident patients started on CAPD in a single centre, from 1998 onwards for a period of 2 years. They were divided into two groups: incident CAPD patients from January 1998 to December 1999 inclusive (Group 1, in whom topical mupirocin was not used) and incident patients from January 2000 to March 2004 inclusive (Group 2, in whom topical mupirocin was used).

Each patient was assessed and counselled by the dialysis coordinator to determine the suitability of the treatment before the elective insertion of a coiled, double-cuff Tenckhoff catheter (Accurate Surgical Instruments Corporation,
Toronto, Ontario, Canada). Antibiotic prophylaxis with intravenous cephazolin was given prior to the surgery. After the insertion of the catheter, a break-in period of at least 2 weeks was required before the patient received CAPD training. During that period, the exit site was visually inspected on days 5 and 10 after catheter placement. The catheter was immobilized with tape when not in use. Patients and their caregiver(s), if any, were then trained for 1 week on the use of CAPD by a PD nurse.

The double-bag (Ultragbag) system was used for all PD patients. Prior to the year 2000, standard exit site care included the daily application of iodine-based dressings on the exit site. Patients were taught to clean exit sites before each CAPD exchange with single-use 10% Povidone-Iodine Swabsticks (Professional Disposables, Inc., Ontario, Canada) before wiping off with sterile gauze. Mupirocin was used regularly on exit sites in all incident patients from 2000 onwards, as part of their routine of exit site care. Mupirocin in the form of a 2% ointment was applied three to five times per week, after cleaning the area around the site with iodine (single-use swab sterile packs). Patients were not screened for their SA carrier status.

ESI and peritonitis were diagnosed according to their ISPD definitions: the presence of erythema/discharge around the Tenckhoff catheter with or without tenderness, for the former, and the presence of abdominal symptoms (fever, abdominal pain and cloudy dialysate), with either a positive peritoneal fluid culture or a peritoneal cell count >100 cells per cubic millimetre, for the latter.

**Statistical analysis**

Statistical analysis was done using the software of SPSS Inc. for Windows (version 10.1.3; Chicago, IL, USA) to identify the different predictors of the occurrence of peritonitis. Data are expressed as means with SD or medians with range. Continuous variables were compared with a t-test. Times to the first ESI or peritonitis were analysed using a Kaplan–Mier survival analysis and the log-rank test. A P < 0.05 was considered to be statistically significant. All reported P-values were two-tailed.

**Results**

The demographics of the 740 incident CAPD patients are presented in Table 1. There were no differences between the two groups in terms of comorbidities, serum albumin before the initiation of PD and age at the start of PD. A high proportion of our patients had diabetes or ischaemic heart disease, or both, at entry into the PD program; a large number of them also had serum albumins below 30 g/l before starting PD.

The independent-samples t-test was used to compare infection rates between the two groups. The rate of infection is expressed in episodes per patient-year. The application of mupirocin at the exit site was associated with a significant reduction in the rate of peritonitis (0.443 vs 0.339 episodes per patient-year; P < 0.0005) and ESI (0.168 vs 0.156 episodes per patient-year; P < 0.005). This was mainly attributed to the reduction of SA peritonitis (P < 0.0005) and SA ESI (P < 0.005). The incidence of other Gram-positive infections also decreased—methicillin-resistant SA peritonitis (P < 0.04), *Streptococcus* peritonitis (P < 0.04) and methicillin-resistant SA ESI (P < 0.005). These results are summarized in Figures 1 and 2. An unexpected finding was the lower rate of Gram-negative peritonitis, despite the fact that mupirocin has no impact on the overall incidence of Gram-negative ESI in our centre. As shown in Figure 3, although mupirocin has no effect on ESI with *Pseudomonas aeruginosa* (PA), it significantly reduced the incidence of PA peritonitis (P < 0.0005).

Emerging as the only significant predictors of peritonitis were the application of mupirocin (RR, 0.31; 95% CI, 0.23–0.44; P < 0.0005) and serum albumin before initiation of dialysis (RR, 0.97; 95% CI, 0.95–0.99; P = 0.015), after a stepwise logistic regression that included other variables—race, age at onset of PD, diabetic status, and a history of cerebrovascular disease, ischaemic heart disease, hypertension or peripheral vascular disease.

The times to first ESI and peritonitis were further analysed using the Kaplan–Meier method. As seen in Figures 4 and 5, the mupirocin group had a significantly longer time on PD before first infections occurred.

**Discussion**

In our study, the incidence of peritonitis in groups 1 and 2 were 0.443 and 0.339 per patient-year, respectively. The application of mupirocin at the exit site contributed significantly to the reduction in peritonitis.

Mupirocin (pseudomonic acid A) was isolated originally from *Pseudomonas fluorescens*. When administered intravenously, mupirocin is rapidly metabolized to an inactive monoacid, thus making it an unsuitable agent for systemic use. When applied topically, however, it is highly effective against SA, and has a minimal inhibitory concentration of ≤1 mg/l [6]. It works by selective inhibition of bacterial isoleucine-tRNA-synthetase, preventing the incorporation of isoleucine into the polypeptide chain.

<table>
<thead>
<tr>
<th>Variables</th>
<th>1998–1999</th>
<th>&gt;2000</th>
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<tbody>
<tr>
<td>n=249</td>
<td>n=491</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>116 (47%)</td>
<td>262 (53%)</td>
</tr>
<tr>
<td>CVA</td>
<td>57 (23%)</td>
<td>103 (21%)</td>
</tr>
<tr>
<td>DM</td>
<td>131 (53%)</td>
<td>255 (51%)</td>
</tr>
<tr>
<td>IHD</td>
<td>146 (59%)</td>
<td>300 (61%)</td>
</tr>
<tr>
<td>PVD</td>
<td>39 (16%)</td>
<td>83 (17%)</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>28.8 ± 6.5</td>
<td>28.9 ± 6.9</td>
</tr>
<tr>
<td>Age at start of PD</td>
<td>57.4 ± 12.6</td>
<td>57.8 ± 12.0</td>
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PD, peritoneal dialysis; CVA, cerebral vascular accident; DM, diabetes mellitus; IHD, ischaemic heart disease; PVD, peripheral vascular disease; PD, peritoneal dialysis.
Mupirocin is active against skin infections caused by Gram-positive organisms in the form of SA, *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; Strep. Sp, *Streptococcus* species and certain gram-negative infections [7].

We found mupirocin to be effective in reducing both Gram-positive and -negative peritonitis as well as Gram-positive ESI. Our results are different from those of the study by Piraino *et al.* [8], which reported mupirocin had no effect on Gram-negative infections. The reduction we observed in Gram-negative, particularly PA, peritonitis was possibly due to the fact that our PD patients who used topical mupirocin prophylaxis have fewer hospitalizations because of the lower rate of PD infections. As a consequence, these patients were less likely to be treated with antibiotics.

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**Fig. 1.** Impact of mupirocin on peritoneal dialysis ESIs. SA, *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; Strep. Sp, *Streptococcus* species.

**Fig. 2.** Impact of mupirocin on peritoneal dialysis peritonitis. SA, *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; Strep. Sp, *Streptococcus* species.

**Fig. 3.** Impact of mupirocin on *Pseudomonas* ESIs and peritonitis.
Recently, antibiotics have been shown to be the major risk factor for peritonitis due to *Pseudomonas* species [9]. On the other hand, a lower hospitalization rate presumably led to less nosocomial transmission of PA, therefore a lesser probability of PA peritonitis.

Mupirocin is known to eradicate SA growth leading to reduction in the rates of both exit-site and peritoneal infections [10]. Although mupirocin has been demonstrated to reduce ESI when used via the intranasal route, the impact of such applications on reducing peritonitis rates is more variable [11]. This is because intermittent and recurrent carrier states are common. Furthermore, most ESI occurred among patients without any previously detectable colonization [12]. Possible explanations for these findings include the erratic shedding of SA to other parts of the body, unknown host factors predisposing some patients to infection whilst others remain only colonized, and the fact that some strains of SA may cause infection whilst others are colonizing bacteria. We did not initiate a program for nasal screening for SA, as it was too labour intensive and not cost effective.

Recent prospective trials demonstrated the reduction in all-cause peritonitis and ESI that followed the application of mupirocin to the exit site [13,14]. However, there is concern over the development of antibiotic resistance in long-term use. In early trials, short-term use of mupirocin did not lead to the development of resistant strains of SA [15]. However, isolated resistant organisms become more significant with prolonged use [16], and mupirocin-resistant SA has been reported after 4 years of continuous use of
mupirocin [17]. Although we did not look specifically for mupirocin-resistant SA (the methods to detect mupirocin resistance was not available in our hospital), the effectiveness of mupirocin in reducing SA ESI and peritonitis in our patients would suggest that the presence of such resistance was highly unlikely.

Recently, gentamycin cream has been shown to be an effective prophylactic agent against both Gram-positive and -negative PD infections [18]; however, there are warnings of the occurrence of fungal infections with gentamicin creams. It is possible that mupirocin resistance could be diminished or delayed with the use of a protocol that alternates gentamycin and mupirocin creams.

The major weakness of our study is that it used historical controls, hence the observed reduction in peritonitis infection could be due to factors other than mupirocin—factors such as change of PD staff, patient education, and frequency of exit site cleaning, dressing and inspection. However, the fact that SA infections, rather than other Gram-positive or -negative infections, were more significantly reduced showed topical mupirocin to be an important intervention. This is further supported by the results of our multiple logistic regression analysis.

Our finding of an inverse relationship between increasing peritonitis rates with low serum albumin at the start of PD concurs with the finding of Wang et al. [19], who performed a retrospective study of 393 CAPD patients.

Hypoalbuminaemia is a strong predictor of patient mortality in both PD and haemodialysis patients [20]. Although non-specific in nature, hypoalbuminaemia is a useful surrogate marker for malnutrition and well-being of an individual, and may reflect reduction in general immunity, malnutrition and cellular immune response—hence it can be associated with increased risks of infection and mortality.

Conflict of interest statement. None declared.

References