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

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Abstract

Background. Peritonitis and exit-site infections (ESI) are major causes of technique failure and morbidity in peritoneal dialysis (PD) patients. Topical mupirocin on the exit-site has been shown to reduce such complications and prolong life in PD. Since the year 2000, such an approach has been adopted for our new incident PD population. We now report the results of this new protocol. We also studied the effect of comorbidity on peritonitis occurrence.

Methods. A total of 740 incident PD patients were studied. Patients were divided into two groups based on year of entry into PD (Group 1 from January 1998–December 1999 without topical mupirocin and Group 2 from January 2000–March 2004 with topical mupirocin). Variables studied included gender, age, diabetic status, ischaemic heart disease, peripheral vascular disease, cerebrovascular disease and serum albumin.

Results. Topical mupirocin at the exit-site has led to a significant reduction in peritonitis rate (0.443 vs 0.339 episodes/patient-year; P<0.0005) and ESI (0.168 vs 0.156 episodes/patient-year; P<0.005) attributed primarily to the significant reduction in Staphylococcus aureus infections. There was an unexpected finding of lower Pseudomonas aeruginosa peritonitis in the mupirocin group (P<0.005). Stepwise multiple logistic regression analysis revealed that only mupirocin application and serum albumin were significant predictors of peritonitis.

Conclusions. Our study, although limited by its retrospective nature, demonstrated that topical mupirocin was associated with a significant reduction in ESI and peritonitis with unexpected findings of lower Pseudomonas peritonitis. Serum albumin prior to 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 incident PD patients.

Keywords: albumins; CAPD; exit-site infection; mupirocin; peritonitis; Staphylococcus aureus

Introduction

Peritoneal dialysis (PD) is an alternative modality that relies on the peritoneal membrane to effect dialysis via the processes of diffusion and osmosis. Access to the peritoneum is via a catheter that traverses from the skin exterior through a subcutaneous tunnel into the peritoneal cavity, hence this ‘entry/exit’ site is a potential site for bacteria entry leading to peritonitis. Peritonitis and exit-site infections (ESI) in continuous ambulatory peritoneal dialysis (CAPD) are leading causes for PD catheter removal and exit from the program, and occasionally may be fatal [1]. Staphylococcus aureus (SA) has been recognized as the most common causative agent for exit-site infection [2], resulting in peritonitis. Chronic application of mupirocin at the catheter exit site has been shown prospectively to reduce SA infection and peritonitis [3–5].

We adopted the application of mupirocin (Bactroban; SmithKline Beecham Pharmaceuticals, Philadelphia, PA) at the catheter exit-site in the year 2000. We have retrospectively reviewed the impact of this therapy in reducing exit-site infection and peritonitis rates in our centre from 1998 onwards.

Subjects and methods

We retrospectively studied 740 incident CAPD patients in a single centre from 1998 onwards for a period of 2 years. They were divided into two groups, namely incident CAPD patients from January 1998 to December 1999 (Group 1, without topical mupirocin) and from January 2000 to March 2004 (Group 2, with topical mupirocin).
Impact of topical mupirocin on peritoneal dialysis infection rates

All patients were assessed and counselled by the dialysis coordinator on the suitability of treatment before 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 surgery. After implantation of the catheter, a break-in period of a minimum of 2 weeks was required before CAPD training was carried out. During this period, the exit-site was visually inspected on days 5 and 10 post-insertion. The catheter was immobilized with tape when not used. Patients and care giver(s) were then started on 1 week of CAPD training by a PD nurse.

A double-bag (Ultrabag) system was used for all incident PD patients. Prior to the year 2000, standard exit-site care included daily iodine-based dressings on the exit-site. Patients were taught to clean their exit-sites using single 10% Povidone-Iodine Swabsticks (Professional Disposables, Inc., Ontario) before wiping with sterile gauze. Patients were instructed to do so before each CAPD exchange. Regular exit-site mupirocin was used in all incident patients from the year 2000 onwards as part of their usual routine exit-site care routine. Mupirocin, in the form of 2% ointment, was applied 3–5 times each week after cleaning the area around it with iodine from single-use sterile packs. Patients were not screened for SA carrier status.

Exit-site infection and peritonitis were diagnosed according to the ISPD definition i.e. the presence of erythema/discharge around the Tenckhoff Catheter with/without tenderness for the former and positive abdominal symptoms (fever, abdominal pain and a cloudy dialysate) with either positive peritoneal fluid culture or peritoneal fluid cell count of >100 cell/mm³ for the latter.

Statistical analysis was done using SPSS Inc. (version 10.1.3 for Windows; Chicago, IL, USA) to identify the different predictors in the cohorts that could independently affect the occurrence of peritonitis. Data are expressed as means with SD or medians with range. Continuous variables were compared with the Student’s t-test. Time to first exit-site infection or peritonitis was analysed using Kaplan-Meier survival analysis and log-rank test. A P value of <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 was no difference in term of co-morbidities, serum albumin before initiation of PD and age of starting PD between the two groups. We have a high proportion of patients who either had diabetes or ischaemic heart disease on entry to the PD program. A large number of our patients also had serum albumin <30 g/l pre-initiation of PD.

Independent sample’s t-tests were used to compare infection rates between the two groups. The rate of infection is expressed in terms of episodes per patient year. Application of mupirocin at the exit-site was associated with a significant reduction in peritonitis rate (0.443 vs 0.339 episodes/patient-year; P < 0.0005) and ESI (0.168 vs 0.156 episodes/patient-year; P < 0.005). This was mainly attributed to the reduction in SA peritonitis (P < 0.0005) and SA ESI (P < 0.005). The incidence of other Gram-positive infections i.e. Methicillin-resistant Staphylococcus aureus (MRSA) peritonitis (P < 0.04), Streptococcus peritonitis (P < 0.04) and MRSA exit-site infections (P < 0.005) also decreased. These results are summarized in Figures 1 and 2. An unexpected finding was that there was a lower Gram-negative peritonitis rate despite the fact that mupirocin has no impact on the overall incidence of Gram-negative exit-site infection in

<table>
<thead>
<tr>
<th>Type of Organisms</th>
<th>Incidence (Episode per patient-year)</th>
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</thead>
<tbody>
<tr>
<td>Total* SA* MRSA* Strep. Sp Gram Negative*</td>
<td></td>
</tr>
<tr>
<td>No Mupirocin</td>
<td>With Mupirocin</td>
</tr>
<tr>
<td><img src="image1" alt="Impact of mupirocin on exit site infections" /></td>
<td></td>
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<tr>
<td><img src="image2" alt="Impact of mupirocin on peritonitis" /></td>
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Table 1. Demographic data of the 740 PD patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>1998–1999 (&lt;without mupirocin&gt;)</th>
<th>&gt; 2000 (&lt;with mupirocin&gt;)</th>
</tr>
</thead>
<tbody>
<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 onset of PD</td>
<td>57.4 ± 12.6</td>
<td>57.8 ± 12.0</td>
</tr>
</tbody>
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CAPD, continuous ambulatory peritoneal dialysis; CVA, cerebral vascular accident; DM, diabetes mellitus; IHD, ischeamic heart disease; PVD, peripheral vascular disease; PD, peritoneal dialysis.

Fig. 1. Impact of mupirocin on PD exit-site infections. SA, Staphylococcus aureus; MRSA, methicillin-resistant Staphylococcus aureus; Strep. Sp, Streptococcus species.

Fig. 2. Impact of mupirocin on PD peritonitis. SA, Staphylococcus aureus; MRSA, methicillin-resistant Staphylococcus aureus; Strep. Sp, Streptococcus species.
our centre. As shown in Figure 3, although mupirocin has no effect on *Pseudomonas aeruginosa* (PA) exit-site infection, it has significantly reduced the incidence of PA peritonitis ($P < 0.005$).

Only mupirocin application (RR, 0.31; 95% CI, 0.23–0.44; $P < 0.0005$) and serum albumin pre-initiation of dialysis (RR, 0.97; 95% CI, 0.95–0.99; $P = 0.015$) emerged as significant predictors of peritonitis using a stepwise logistic regression that included other variables such as race, age at onset of PD, diabetic status, and a previous history of cerebrovascular disease, ischaemic heart disease, hypertension and peripheral vascular disease.

The time to first exit site infections and peritonitis were further analysed by using Kaplan–Meier. As seen in Figures 4 and 5, the mupirocin group had a significantly longer time before first infections occurred.

**Discussion**

Peritonitis rate varies across regions and amongst different centres. Much of this variance in the early years was related to the different connectology systems. Since the early 1980s the experience in United Kingdom was an episode every 9 patient-months (1.33 per patient-year). The European experience on the other hand was an episode once every 12–13 patient-months (0.92–1.0 per patient-year).

Improvements in connectology using Y-set systems have demonstrated superior reduction in the occurrence of peritonitis rates since the early 1980s. The Y-set system uses flushing and filling at the port of connection with the transfer set. This technique alone significantly reduces the periluminally mediated forms of peritonitis found in the conventional straight-line spike systems. The Y-set was further modified to produce the double-bag system, which has a pre-connected drain bag and fresh dialysate bag, thereby reducing the number of connections–disconnections required. In one systemic review of 12 randomized controlled trials comparing the incidence of peritonitis of double-bag and Y-set against standard systems, significantly fewer patients (133/363 vs 158/263) experienced peritonitis using the disconnect systems (odds ratio 0.33; 95% CI, 0.24–0.46).

We have used the double-bag system since 1998. In our study, the incidence of peritonitis in Groups 1 and 2 were 0.443 and 0.339 per patient-year, respectively. There is a significant reduction in peritonitis rates in the mupirocin group despite using the same connectology systems. The application of mupirocin at the exit site has contributed significantly to the reduction in peritonitis.

Mupirocin (pseudomonic acid A) was isolated originally from *Pseudomonas fluorescens*. It works by selective inhibition of bacterial isoleucine-tRNA-synthetase, preventing the incorporation of isoleucine into the polypeptide chain. Mupirocin is rapidly metabolized to an inactive monoacid when administered intravenously, thus making it an unsuitable agent for systemic administration. However, when applied topically, it is highly effective against SA with minimal inhibitory concentration of $\leq 1\text{mg/l}$ [6]. Mupirocin is active against skin infections caused by...
gram-positive organisms in the form of \textit{Staphylococcus aureus}, \textit{Staphylococcus epidermidis}, Methicillin-resistant \textit{Staphylococcus aureus}, \textit{Streptococcus} species and certain gram-negative infections [7].

In our study, mupirocin has been found to be effective in reducing both Gram-positive and -negative peritonitis as well as Gram-positive exit-site infections. Our results differed to those from a study by Piraino et al. [8], who reported that mupirocin has no effect on Gram-negative infections. The reduction in Gram-negative, in particular 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. Recent antibiotic therapy has been shown to be a major risk factor for peritonitis due to \textit{Pseudomonas} species [9]. On the other hand, the lower hospitalization rate presumably led to less nosocomial transmission of PA infections that could otherwise cause PA peritonitis.

Mupirocin is known to eradicate \textit{Staphylococcus aureus} carriage leading to a reduction in both exit-site and peritonitis rates. Although mupirocin has been demonstrated to reduce exit-site infections when used in the intranasal route, its impact on reducing peritonitis rates from such applications is more variable [10]. This is because intermittent and recurrent carriage is common. Furthermore, most exit-site infections occurred among patients without previous undetectable colonization [11]. Possible explanations 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 that some strains of SA may cause infection whilst others are colonizing bacteria. We did not initiate an SA nasal screening program as it was not cost effective and was too labour intensive.

Recent prospective trials demonstrated a reduction in all causes of peritonitis and exit site infections with the application of mupirocin to the exit site [12,13]. 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 \textit{Staphylococcus aureus} [14]. However, resistant organisms isolated become more significant with prolonged usage [15] and mupirocin-resistant \textit{Staphylococcus aureus} has been reported after 4 years of continuous use [16]. Although we did not look specifically for mupirocin-resistant \textit{Staphylococcus aureus} (the methods to evaluate mupirocin resistance were not available in our hospital), the effectiveness of mupirocin in reducing \textit{Staphylococcus aureus} exit-site and peritonitis in our patients would suggest that its presence was highly unlikely.

Recently gentamicin cream has been shown to be an effective prophylactic agent against both Gram-positive and -negative PD infections [17]. However, there is the possibility of fungal infections with gentamicin creams. Nevertheless, the possibility exists that mupirocin resistance could be diminished or delayed with a protocol that alternates gentamicin 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, frequency of exit-site cleaning, dressing and inspection could have contributed to the overall reduction in infection rates in one way or another. However the fact that SA infections, rather than other Gram-positive or -negative infections was more significantly reduced made topical mupirocin an important intervention. This is further supported by multiple logistic regression analysis.

Our finding of an inverse relationship between increasing peritonitis rates and low serum albumin at the start of PD concurred with that by Wang et al. [18], who performed a retrospective study of 393 CAPD patients.

Hypoalbuminaemia is a strong predictor of patient mortality in both PD and haemodialysis patients [19]. Although non-specific in nature, it is a useful surrogate marker for malnutrition and the well being of an individual. Hence hypoalbuminaemia may be a reflection of a reduction in general immunity, malnutrition and cellular immune response, hence it can be associated with an increased risk of infection and mortality.

\textit{Conflict of interest statement. None declared.}

\textbf{References}


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