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Comparison of topical mupirocin and gentamicin in the prevention of peritoneal dialysis-related infections: A systematic review and meta-analysis

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ABSTRACT

Background: Topical antibiotics have been shown to reduce exit-site infection and peritonitis. The aim of this study was to compare infection rates between mupirocin and gentamicin.
Methods: Multiple comprehensive databases were searched systematically to include relevant randomized controlled trials and observational studies. Pooled risk ratios (RRs) and 95% confidence intervals were calculated for the incidences of exit-site infection and peritonitis.
Results: Seven studies (mupirocin group n = 458, gentamicin group n = 448) were analyzed for exit-site infection. The risk of gram-positive exit-site infection was similar between the groups. Gram-negative exit-site infection rate was higher in the mupirocin group (RR = 2.125, $P = 0.037$). Six studies were assessed the peritonitis risk. There was no difference in the gram-positive and -negative peritonitis rate.
Conclusions: Topical use of gentamicin is associated with fewer exit-site infections caused by gram-negative organisms. Gentamicin has comparable efficacy to mupirocin for peritonitis and gram-positive exit-site infection.

1. Introduction

Infectious complications (exit-site infections, tunnel infections, and peritonitis) represent a major cause of technique failure among patients on peritoneal dialysis. Furthermore, infection-related hospitalizations are associated with readmissions and significant mortality.[1] Some risk factors for infectious complications are not modifiable such as old age and diabetes mellitus.[2] Nonetheless, there are modifiable factors, including obesity smoking, and patient training.[3] According to the latest International Society for Peritoneal Dialysis (ISPD) guidelines, it is recommended to use topical exit-site or nasal antibiotics to reduce exit-site infection and peritonitis.[4,5] The topical use is probably preferable because the nasal application requires repeated nasal swabs and repeated courses of intranasal treatment, which are more expensive and difficult to implement.

Mupirocin, a polyketide antibiotic produced by *Pseudomonas fluorescens*, has an excellent activity against gram-positive organisms but has little or no effect on *Pseudomonas* or other gram-negative bacteria. Mupirocin prophylaxis (at the exit site or intranasally) has been shown to effectively prevent exit-site and peritonitis in patients undergoing peritoneal dialysis.[6,7] Thus, topical mupirocin application has become the standard of care in most centers. However, accompanying with decreasing *S. aureus* infections associated with mupirocin prophylaxis, the proportion of infections secondary to gram-negative bacteria has been increasing.[8] In 2005, Bernardini and colleagues reported the results of a randomized controlled study comparing topical mupirocin and gentamicin.[9] They found that the use of gentamicin was associated with a lower catheter infection rate and a decrease in the peritonitis

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rate. Nonetheless, the superiority of gentamicin over mupirocin in preventing infectious complications was not demonstrated in the subsequent studies.[10,11] Therefore, although topical antibiotic prophylaxis is recommended for patients on peritoneal dialysis, the optimal topical antibiotic regimen at the exit site remains unknown.

Given the controversies arising from conflicting studies on the superiority of topical antibiotic regimen, we performed a systematic review and meta-analysis to compare the effect of topical gentamicin with that of mupirocin on infection rates in patients on peritoneal dialysis.

2. Materials and methods

This meta-analysis was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12,13]

2.1. Data sources and search strategy

Two authors (CCT and SPC) independently performed a comprehensive electronic search of the published literature indexed in the MEDLINE/Pubmed, Cochrane Library, Embase, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) from the earliest records to June 2016. Keywords used for the searches were 'mupirocin' and 'peritoneal dialysis'. Reference lists of retrieved articles and previous reviews were hand searched for additional relevant studies.

2.2. Eligibility criteria

Articles were considered eligible for inclusion if the following criteria were met: (i) randomized controlled trials, non-randomized interventional studies, and observational studies; (ii) comparison of topical mupirocin and gentamicin ointment in patients on peritoneal dialysis; and (iii) reporting the incidence of peritoneal dialysis-related infections, particularly exit-site infection and peritonitis. Conference abstracts were included, but reviews, case reports, and studies performed on animals or conducted *in vitro* were excluded. No language restrictions were applied.

2.3. Data extraction

A predesigned data collection form was used to extract the following information: last name of the first author, year of publication, study design, country of origin, year of study, sample size, participant characteristics, event counts and incidences of peritoneal dialysis-related infections, and microbiological profile. Disagreements were resolved through discussion and consensus.

2.4. Assessment of quality

The methodological quality of eligible randomized trials was evaluated with the Cochrane Collaboration's tool for assessing risk of bias.[14] The methodological quality of non-randomized and observational studies was evaluated with the checklist proposed by Wells and colleagues.[15] Four domains were assessed with this checklist: study design features, risk of residual confounding, risk of selective outcome or analysis reporting, and directness of the evidence to the research question.

2.5. Statistical analysis

The reported number of events or estimate was used for the comparison between the mupirocin and gentamicin group. Effect size computed for the analyses was risk ratio (RR) with 95% confidence interval (CI). Considering the likelihood of between-study heterogeneity, random-effects models were used throughout. We excluded studies from meta-analysis and only presented the result with narrative description when there were no sufficient data for quantitative analysis. The significance level for the overall estimates of effect was set at $P < 0.05$.

The heterogeneity of effect size estimates across studies was quantified using the I^2 statistic. In general, I^2 values of 50%–74% and over 75% represent moderate and high heterogeneity, respectively.[16] The presence of publication bias was assessed by funnel plots and the Egger linear regression method.[17] All analyses were performed using STATA statistical software package version 14.0 (Stata Corp., College Station, TX, USA).

3. Results

The initial search yielded 299 articles, and 237 articles were excluded by reviewing only title and abstracts (Fig. 1). A total of 62 articles underwent full-length review. Nine studies were included in qualitative analysis.

3.1. Characteristics of included studies

Table 1 describes the detailed characteristics of the included studies. There were two randomized trials (including one conference abstract),[9,18] two prospective non-randomized studies,[10,19] and five retrospective studies.[11,20–23] Five studies specifically indicated that only adults patients were included.[9–11,19,22] Nonetheless, the average age of participants of all studies was in the fifties. Exclusion criteria were defined in three studies, including allergy to the study cream and active or recent infections.[9,10,19]

Two studies were not included in the quantitative meta-analysis. One retrospective study was an audit of 12 UK centers, and exact event numbers were not reported.[21] The other was a longitudinal study and comparison with heterogeneous historical controls.[23]

3.2. Quality assessment

A randomized study published as a conference abstract was excluded from quality assessment.[18] The other randomized, double-blind trial had a low risk of bias for all key domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias).[9] Further quality assessment of two prospective non-randomized studies[10,19] and three retrospective studies[11,20,22] showed that none of these studies had a high risk of bias.

3.3. Exit-site infection

Seven studies were considered for the analysis of exit-site infection. There were 458 patients in the mupirocin group and 448 patients in the gentamicin group.

As shown in Fig. 2A and B, there was no difference between the two groups in overall (RR = 1.064, 95% CI 0.606 to 1.868, P = 0.829) and gram-positive (RR = 0.915, 95% CI 0.451 to 1.856, P = 0.806) exit-site infection rates. However, heterogeneity was substantial (I^2 = 76.0% and 59.7%, respectively). The mupirocin group tended to have fewer *Staphylococcus aureus* exit-site infections (RR = 0.553, 95% CI 0.297 to 1.029, P = 0.062, I^2 = 0.0%), but the difference did not reach statistical significance (Fig. 2C).

As shown in Fig. 2D, gram-negative exit-site infection rate was significantly lower in the gentamicin group (RR = 2.125, 95% CI

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