Development of Antimicrobial Gendine Coated Central Catheters: In Vivo Biocompatibility and In Vitro Efficacy

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ABSTRACT

- Background: Antimicrobial Peripheral inserted central catheters (PICCs) might reduce the incidence of CLABSI. We tested biocompatibility of a novel gendine (combination of chlorhexidine-GV and gentamicin-GV) PICCs in a rabbit intravascular model and tested antimicrobial efficacy in comparison with commercially available minocycline/terrifin (M/R), and CHX PICCs in an in vitro biofilm colonization model.
- Methods: Gendine and uncoated control PICCs were inserted in the jugular veins of rabbits for 4 days. Histopathological analysis was performed at the end of the four day period and circulating levels of CHX and GV in blood were measured at different time points using liquid chromatography/mass spectrometry. Antimicrobial efficacy of the PICCs was tested following simulated intravascular indwells of 24 hours and 1 week against clinical isolates of methicillin-resistant Staphylococcus aureus, Vancomycin-resistant enterococcus, Pseudomonas aeruginosa, E. coli, Acinetobacter baumanii, Enterobacter cloaceae, Candida albicans, and Candida glabrata.
- Results: Rabbits implanted with gendine PICCs exhibited reduced levels of thrombosis and inflammation compared to rabbits with uncoated controls. No GV was detected in blood samples over the entire study period and trace concentrations of CHX were detected.
- Conclusions: Gendine-PICCs were highly effective in preventing biofilm formation of multidrug-resistant pathogenic bacteria and fungi. Gendine-PICCs were biocompatible in an intravascular setting. Further, the pharmacokinetic testing established that acute systemic exposures of CHX and GV from the gendine catheters were well within safe levels.

INTRODUCTION

Indwelling central lines such as peripherally inserted central catheters (PICCs) have become essential vascular devices and the use of PICCs has recently been increasing. Antimicrobial PICCs might reduce the incidence of catheter-related bloodstream infections (CRBSIs) that extend hospitalization, increase cost and mortality. The rate of PICC-associated CRBSIs occur annually in patients outside ICUs and at least 400,000 episodes of CLABSI occur annually in patients outside ICUs and at least 400,000 episodes of CLABSI occur every year among cancer patients alone with annual cost estimates ranging from $296 million to $3.2 billion.

In order to meet this need, we developed a novel gendine (combination of Genticol Violet and Chlorhexidine) antimicrobial efficacy and durability against highly pathogenic, resistant pathogens from our hospital in a well established biofilm colonization model and compared it to commercially available M/R and CHX PICCs. We also tested the gendine catheter in vivo for acute biocompatibility in a rabbit intravascular model utilizing histopathological examination and pharmacokinetics of circulating antiseptic levels in blood by liquid chromatography/mass spectrometry.

MATERIALS & METHODS

- Sequential coating of catheter with gendine
  Gendine PICCs were produced by applying a proprietary sequential treatment process to polyurethane PICCs. This incorporated gendine into the catheter walls as well as the luminal and external surfaces. Gendine consisted of a mixture of gentian violet and chlorhexidine. Commercially-available polyurethane PICCs which were uncoated (non-antimicrobial), M/R treated (Spectrum, Cook Medical, Bloomington, IN), and CHX treated (Chlorogard, Arrow International Inc., Reading, PA) were included in the study as controls and comparisons. Uncoated and gendine coated PICCs were gamma sterilized at the MD Anderson Cancer Center Radiation facility and the M/R and CHX PICCs were packaged sterile.
- Durability of gendine catheters by biofilm colonization
  To test the durability of inhibition of biofilm formation, uncoated control, M/R, CHX and gendine PICC segments were challenged against clinical isolates of methicillin-resistant S. aureus, Pseudomonas aeruginosa, E. coli, and Acinetobacter baumanii. Segments of PICC were placed in different concentrations of bacteria for 24h, 72h, and 96h, and each segment was removed and challenged in a broth tube to quantify the number of bacteria remaining as a positive, gram-negative bacterium. The results were analyzed using the Mann-Whitney U-test.
- In Vivo Biocompatibility testing
  The study was performed at the MD Anderson Cancer Center animal research facility. Female New Zealand White rabbits (weight 2.5-3.5 kg) were used after 1 week acclimation. After general anesthesia with 5% isoflurane (inhalation) and 2% isoflurane (intravenous), animals were divided into two groups. Group A contained three rabbits that had gendine-PICCs inserted in the jugular veins and Group B had two rabbits with uncoated control PICCs. Before insertion of catheters, blood samples were collected at 0, 24, 72, and 96h (post-mortem) of insertion of catheters and were analyzed by liquid chromatography/mass spectrometry for levels of chlorhexidine and gentian violet.

RESULTS

- Table 1: Chlorhexidine (CHX) and gentian violet (GV) concentrations in plasma (ng/ml) as assessed by liquid chromatography/mass spectrometry

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>CHX</th>
<th>GV</th>
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<tbody>
<tr>
<td>0</td>
<td>0.12</td>
<td>0.2</td>
</tr>
<tr>
<td>24</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>72</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>96</td>
<td>0.00</td>
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CONCLUSIONS

1. Gendine treated PICCs were very effective in preventing biofilm formation of a range of highly pathogenic gram-positive, gram-negative bacteria and fungi, and were significantly superior to commercially available M/R and CHX PICCs.
2. The pharmacokinetic testing established that acute systemic exposures of chlorhexidine and gentian violet from the gendine catheters were either negligible, in the case of gentian violet, or well within safe levels, in the case of chlorhexidine.
3. Gendine catheters were found to be biocompatible with a good safety profile in an intravascular setting, and exhibited in vitro severe implant responses than those to non-antimicrobial catheters as assessed by histopathologic analysis in rabbits.
4. In future, larger animal studies would enable comparisons of statistical significance.