Peritoneal Dialysis International, Vol. 29, pp. 303–309
Printed in Canada.

0896-8608/09 $3.00 + .00

THE HONEYPOT STUDY PROTOCOL: A RANDOMIZED CONTROLLED TRIAL OF EXIT-SITE APPLICATION OF MEDIHONEY ANTIBACTERIAL WOUND GEL FOR THE PREVENTION OF CATHETER-ASSOCIATED INFECTIONS IN PERITONEAL DIALYSIS PATIENTS

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♦ ***Objectives:*** **The primary objective of this study is to determine whether daily exit-site application of standardized antibacterial honey (Medihoney Antibacterial Wound Gel; Comvita, Te Puke, New Zealand) results in a reduced risk of catheter-associated infections in peritoneal dialysis (PD) patients compared with standard topical mupirocin prophylaxis of nasal staphylococcal carriers.**

♦ ***Design:*** **Multicenter, prospective, open label, randomized controlled trial.**

♦ ***Setting:*** **PD units throughout Australia and New Zealand.**

♦ ***Participants:*** **The study will include both incident and prevalent PD patients (adults and children) for whom informed consent can be provided. Patients will be excluded if they have had (1) a history of psychological illness or condition that interferes with their ability to understand or comply with the requirements of the study; (2) recent (within 1 month) exit-site infection, peritonitis, or tunnel infection; (3) known hypersensitivity to, or intolerance of, honey or mupirocin; (4) current or recent (within 4 weeks) treatment with an antibiotic administered by any route; or (5) nasal carriage of mupirocin-resistant *Staphylococcus aureus*.**

♦ ***Methods:*** **370 subjects will be randomized 1:1 to receive either daily topical exit-site application of Medihoney Antibacterial Wound Gel (all patients) or nasal application of mupirocin if staphylococcal nasal carriage is demonstrated. All patients in the control and intervention groups will perform their usual exit-site care according to local practice. The study will continue until 12 months after the last patient is recruited (anticipated recruitment time is 24 months).**

♦ ***Main Outcome Measures:*** **The primary outcome measure will be time to first episode of exit-site infection, tunnel infection, or peritonitis, whichever comes first. Secondary outcome measures will include time to first exit-site infection, time to first tunnel infection, time to first peritonitis, time to infection-associated catheter removal, catheter-associated infection rates, causative organisms, incidence of mupirocin-resistant microbial isolates, and other adverse reactions.**

♦ ***Conclusions:*** **This multicenter Australian and New Zealand study has been designed to provide evidence to help nephrologists and their PD patients determine the optimal strategy for preventing PD catheter-associated infections. Demonstration of a significant improvement in PD catheter-associated infections with topical Medihoney will provide clinicians with an important new prophylactic strategy with a low propensity for promoting antimicrobial resistance.**

Perit Dial Int **2009; 29:303–309** **www.PDIConnect.com**

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Received 21 May 2008; accepted 30 September 2008.

KEY WORDS: Exit-site infection; honey; Medihoney; mupirocin; peritonitis; randomized controlled trial; tunnel infection; bacterial infection; fungal infection.

Recurrent or severe exit-site infections (ESIs) and peritonitis are the Achilles' heel of peritoneal dialysis (PD) and represent the major causes of Tenckhoff catheter removal and PD technique failure. Up to one third of all PD peritonitis episodes result in hospitalization (1) and 5% – 10% of cases culminate in patient death (2). Exit-site infections are associated with a substantially increased risk of subsequent peritonitis (up to sixfold), and the simultaneous occurrence of ESI and peritonitis results in catheter removal in approximately 50% of cases (3). *Staphylococcus aureus* is the most common cause of

ESI (25% – 85% of cases) and accounts for up to 80% of infection-related catheter loss (4). Gram-negative organisms, especially *Pseudomonas aeruginosa*, also play a significant role in infection-related catheter loss (2,4).

Therefore, the primary goal of chronic exit-site care is to prevent ESIs and, ultimately, peritonitis and catheter removal. However, the optimal means of providing this care has not been subjected to rigorous study. Previous trials have largely focused on either cleansing agent or dressings and have not clearly demonstrated superiority of any regimen (5,6). Topical application of mupirocin ointment to either the nares or the exit site is commonly employed to try to reduce the incidence of PD catheter-associated infections (6) but there has been only one randomized controlled trial of topical mupirocin versus no prophylaxis (7), which found that regular use of nasal mupirocin (twice daily for 5 consecutive days each month) in continuous ambulatory PD patients that were nasal carriers significantly reduced (by 68%) the rate of staphylococcal ESIs. Consequently, the Caring for Australasians with Renal Insufficiency (CARI) guidelines recommended intranasal mupirocin prophylaxis in PD patients with nasal staphylococcal carriage to "reduce the risk of *S. aureus* catheter exit-site/tunnel infections and peritonitis" (8). However, the appearance of mupirocin-resistant microbial isolates has been a significant concern (9–12) and treatment failures associated with mupirocin prophylaxis have been reported (11).

Recently, a double-blind randomized controlled trial in 133 patients of daily exit-site application of gentamicin cream versus mupirocin ointment demonstrated that gentamicin was associated with a risk reduction of 57% for ESIs and 35% for peritonitis (13). However, topical gentamicin application has generated clinical concerns about promotion of antimicrobial resistance given that gentamicin is a cornerstone of treatment for gram-negative PD peritonitis. The International Society for Peritoneal Dialysis (ISPD) guidelines recommend topical antibiotic prophylaxis with either exit-site or nasal mupirocin (in either all patients or restricted to nasal *S. aureus* carriers) or daily exit-site gentamicin. However, an alternative strategy that effectively prevents catheter-associated infections but minimizes antimicrobial resistance selection and toxicity is an unmet and urgent need.

Honey is a very promising agent in this respect as it has been shown to exert an antimicrobial action against a broad spectrum of fungi and bacteria, including antibiotic-resistant bacteria such as methicillin-resistant *S. aureus*, multidrug-resistant gram-negative organisms, and vancomycin-resistant enterococci (14,15). (In comparison, mupirocin is mainly active against gram-positive organisms and gentamicin is mainly active against gram-negative organisms.) The reasons for this antibacterial activity include relatively low water activity (0.56 – 0.59), low pH (3.2 – 4.5), the production of hydrogen peroxide on dilution (due to the presence of the enzyme glucose oxidase), and phytochemical components, including flavonoids and phenolic acids (15). There have been a number of reports of honey being used successfully as a dressing for wounds, including burns, ulcers, infected surgical wounds, necrotizing soft tissue infections, meningococcal wounds, and abdominal wound dehiscence (16–19). A meta-analysis of seven randomized controlled trials involving the use of honey as a wound dressing showed it to be superior to antiseptics and/or systemic antibiotics for wound healing, maintenance of sterility, and eradication of infection (20). Despite a considerable accumulated experience of honey use in wound infections, antimicrobial resistance has not yet been reported, thereby making it very attractive as a potential means of antimicrobial prophylaxis (21). A recent randomized controlled trial in hemodialysis patients at an Australian center has demonstrated that three-times weekly application of standardized antibacterial honey (Medihoney Antibacterial Wound Gel; Comvita, Te Puke, New Zealand) to hemodialysis catheter exit sites was safe, cheap, and effective and resulted in a rate of catheter-associated infection comparable to that obtained with topical mupirocin prophylaxis (22). It was concluded that the effectiveness of honey against antibiotic-resistant micro-organisms and its low likelihood of selecting for further resistant strains suggested that this agent may represent a satisfactory alternative means of chemoprophylaxis in patients with central venous catheters. Moreover, it was further suggested that the results of this study might have been potentially generalizable to other patients with prosthetic devices, such as PD catheters. To date there have been no trials of topical exit-site application of Medihoney in PD patients. Given the demonstrated cheapness, safety, efficacy, and low propensity of Medihoney to promote resistant microbial strains in hemodialysis patients with catheters, a trial in PD patients is warranted.

MATERIALS AND METHODS

Ethics approval was obtained from the local Institutional Ethics Committee in all participating centers prior to study initiation and patient enrolment. The study will be performed in accordance with the 2000 Edinburgh, Scotland, Revision of the Declaration of Helsinki, the National Health and Medical Research Committee (NHMRC) Statement on Human Experimentation, Joint

NHMRC/AVCC Statement and Guidelines on Research Practice, applicable ICH guidelines and the Therapeutic Goods Administration (TGA) Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (23).

PATIENT POPULATION

The study population includes adults and children with end-stage renal disease who are receiving PD and for whom informed consent can be provided. The study will include both incident and prevalent PD patients (defined according to whether they initially participated in the study either less than or greater than 3 months after PD commencement respectively). Potential trial participants that are using nasal mupirocin will be asked to stop using it for a month, have a nasal swab taken and tested as per protocol, and stratified as a nasal staphylococcal carrier or non-carrier on the basis of the results of this swab.

Patients will be selected from PD units throughout Australia and New Zealand. The multicenter nature of the study together with the broad inclusion criteria used will greatly enhance the generalizability of the trial. Exclusion criteria include

1. History of psychological illness or condition that interferes with ability to understand or comply with the requirements of the study;
2. Recent (within 1 month) ESI, peritonitis, or tunnel infection;
3. Known hypersensitivity to, or intolerance of, honey or mupirocin;
4. Current or recent (within 4 weeks) treatment with an antibiotic administered by any route; and
5. Nasal carriage of mupirocin-resistant *S. aureus*.

STUDY DESIGN

The study will follow a prospective, open label, randomized controlled trial design. Patients will be randomized in equal proportions to one of two treatment groups (Figure 1). To ensure adequate concealment of allocation, the randomization will be performed using a Web-based system provided through the Australasian Kidney Trials Network. Patients will be randomized in permuted blocks with stratification for center, incident/prevalent patient status, and nasal carriage of *S. aureus* (see below).

EXPERIMENTAL INTERVENTION

Patients in the experimental intervention arm will receive daily exit-site application of gamma irradiated,

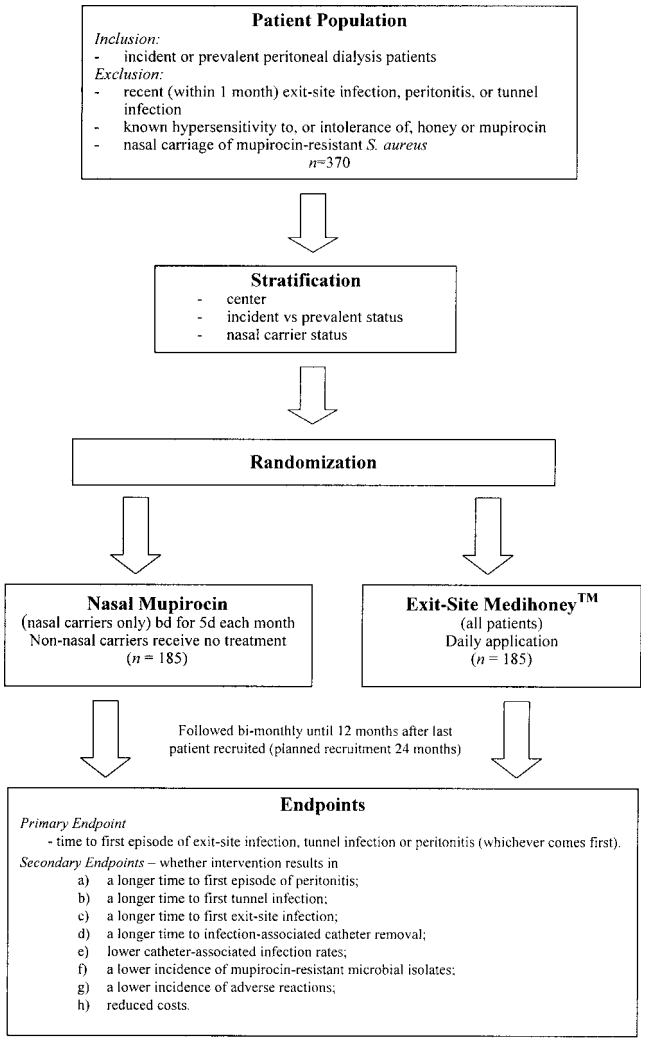

Figure 1 — Schema for the HONEYPOT Trial. Medihoney Antibacterial Wound Gel manufactured by Comvita, Te Puke, New Zealand.

commercially available, pooled antibacterial honeys, including *Leptospermum* sp honey (Medihoney, approximately 10 mg). This will be applied each day following exit-site cleaning and drying for the duration of the study. Patients will not undergo nasal swabs after baseline, be treated for staphylococcal colonization during the course of the study, or receive either exit-site or nasal mupirocin.

CONTROL INTERVENTION

Based upon the recommendations of the CARI Guidelines (8), 2% mupirocin (GlaxoSmithKline, Melbourne, Australia) will be self-administered twice daily to both anterior nares for 5 consecutive days each month for the duration of the trial for subjects randomized to the control intervention who are identified as staphylococcal carriers at any time during the study. Patients that do

not have nasal staphylococcal carriage at any time throughout the study will not receive nasal mupirocin. Ascertainment of carriage of *S. aureus* will involve nasal swabs at trial commencement and every 6 months thereafter: premoistened swabs will be collected, inoculated in enrichment broth for 24 hours then solid media, and isolates identified as *S. aureus* and tested for mupirocin susceptibility using standard techniques (24). Patients will not be permitted to receive topical honey.

CONCURRENT TREATMENTS

All patients in the control and intervention groups will perform usual exit-site care as per local protocol. Catheters will be anchored with tape and a small gauze dressing to prevent exit-site trauma. Patients in the trial are not permitted to receive prophylactic antibiotics (gentamicin cream, oral cephalexin, oral rifampicin, topical bacitracin, *etc.*) except as temporary cover in the case of line contamination or prior to dental procedures or colonoscopy. In addition, following the CARI Guideline is recommended: "Antibiotic prophylaxis with a first generation cephalosporin should be used at peritoneal dialysis catheter insertion to reduce the incidence of peritonitis" (25). The use of antibiotics for treatment of acute infections according to local protocols is also permissible. Exit-site application of mupirocin is prohibited in all patients.

BLINDING

Blinding of investigators and patients is not possible because of the completely different characteristics of Medihoney and mupirocin ointment. Outcome assessment will be based on well-defined internationally accepted objective criteria, and microbiology staff in local laboratories will not be informed of the treatment allocation group of patients.

OUTCOME MEASURES

The primary outcome measure will be time to first episode of ESI, tunnel infection, or peritonitis, whichever comes first.

Secondary outcome measures include

1. Time to first episode of peritonitis;
2. Time to first tunnel infection;
3. Time to first ESI;
4. Time to infection-associated catheter removal;
5. Catheter-associated infection rates, including subgroup analyses according to causative organisms;
6. Occurrence of mupirocin-resistant microbial isolates;
7. Incidence of adverse reactions; and
8. Costs.

CLINICAL ASSESSMENT OF OUTCOME

Catheter-related infections will be defined according to standard guidelines (6,26–28).

Exit-site infection will be defined as purulent discharge or two of three of erythema >13 mm, induration, and tenderness. Exit-site swabs will be obtained using sterile premoistened swabs in all suspected cases of ESI (erythema, tenderness, induration, or discharge) and sent for microscopy and culture at the local microbiology laboratory.

Peritonitis will be classified as cloudy effluent with at least 100 white cells/μL, of which at least 50% are polymorphonuclear leukocytes. In all cases of suspected peritonitis (abdominal pain, cloudy bags, fever, *etc.*), dialysate effluent will be collected, inoculated in blood culture bottles, and sent for microscopy and culture at the local microbiology laboratory.

Tunnel infection will be defined as two of three of induration, tenderness, and radiographic evidence of a collection along the PD catheter tunnel (on ultrasound scan or computed tomography scan). If able to be collected, purulent material obtained from collections will be sent for microscopy and culture at the local microbiology laboratory.

Infection rates will be calculated as the number of infections divided by the total time at risk, and expressed as episodes per patient-year at risk. An infection *relapse* will be defined as recurrence of the same type of infection due to an identical organism with 1 month of completion of treatment for an infection episode. The date of any infectious event will be taken as the date of diagnosis on clinical grounds. In all cases of PD catheter-associated infection, the causative micro-organism will be recorded for the purposes of subanalysis. Staphylococcal isolates will be routinely screened for mupirocin resistance using disc diffusion according to the guidelines of the Clinical and Laboratory Standards Institute (29) using 5-μg disks. Isolates with a zone diameter of <14 mm around 5-μg disks will be classified *resistant* (30).

When a patient reaches a trial outcome event and acute treatment for the event has been completed, ideally they will continue on the study treatment unless the patient wishes to cease study treatment or the clinician feels that ceasing study treatment is in the patient's best interest. If the infectious outcome is caused by mupirocin-resistant *S. aureus*, the patient may be withdrawn

from study treatment. All instances where PD catheters are removed because of infection (exit site, peritonitis, and/or tunnel) will be recorded as secondary outcome events.

The number and proportion of subjects that report treatment-emergent adverse events will be summarized for each treatment group. Treatment emergent events include events that start on or after day 0 of the study (*i.e.*, the first day of study treatment administration) and were not present at baseline, or were present at baseline but increased in severity after the start of the study. Medical Dictionary for Regulatory Activities terminology will be used to classify all adverse events with respect to System Organ Class, high level group term, and preferred term.

Details of study treatment usage and infection-associated treatments and hospitalizations will be recorded to permit assessment of direct treatment costs.

Compliance with treatment will be assessed by tube collection, inspection, and counting.

SAMPLE SIZE CALCULATIONS

Prospective power calculations indicate that the study will have adequate statistical power (80% probability) to detect a clinically significant increase in infection-free survival from 18 months to 30 months (hazard ratio 0.6) if 150 patients are recruited in each group, assuming alpha = 0.05, a recruitment period of 24 months, a follow-up period of 12 months, and an attrition rate of 2% per month (approximately 20% per annum, calculated using compounding). In addition, the sample size has been adjusted for possible noncompliance of the Medihoney group, allowing for 10% of this group to have changed to standard practice treatment by the end of the study. This means the study size needs to be increased by a factor of 1.23, from 150 to 185 per group (370 total). The infection-free survival figure of 18 months for controls is based on the current peritonitis-free survival in Australia. The actual infection-free period is likely to be worse in controls in the study because the end point will also incorporate exit-site and tunnel infections. Moreover, New Zealand patients have a shorter median peritonitis-free survival period (16.5 months); however, the more conservative figure has been used for power calculations.

STATISTICAL ANALYSES

Infection-free survival curves, survival probabilities, and estimated median survival times for the time to first occurrence of the primary composite outcome (ESI, peritonitis, or tunnel infection) will be generated according to the Kaplan–Meier method. Data will be censored at the time of study completion, permanent transfer to hemodialysis (if unrelated to infection), renal transplantation, spontaneous recovery of dialysis-independent renal function, or loss to follow-up. Differences in the survival curves between the two groups will be evaluated using the log rank test.

Comparisons between the honey and mupirocin (control) groups will be performed using Student's t-test or the Mann–Whitney U test, depending on data distribution. Differences in proportions will be evaluated by chi-square or Fisher's exact tests, as appropriate. Multivariate Cox proportional hazards model analysis will be used to adjust for any differences in baseline characteristics between the Medihoney and mupirocin groups as a sensitivity analysis. Time to first occurrence of individual events (ESI, peritonitis, tunnel infection, or infection-associated PD catheter removal) will be evaluated by Kaplan–Meier survival analysis. Differences in infection rates between the two groups will be analyzed by Poisson regression.

Because of power considerations and the previously demonstrated safety and efficacy of Medihoney Antibacterial Wound Gel in preventing catheter-associated infections in hemodialysis patients, no interim analyses are planned. All data will be analyzed on an intention-to-treat basis using the software packages SPSS release 12.0 (SPSS Inc., North Sydney, Australia) and Stata/SE 9.2 (College Station, TX, USA). *p* Values less than 0.05 will be considered significant.

DISCUSSION

This multicenter Australian and New Zealand study has been designed to provide evidence to help nephrologists and their PD patients better determine whether, when compared with standard topical mupirocin prophylaxis of nasal staphylococcal carriers, daily exit-site application of standardized antibacterial honey (Medihoney Antibacterial Wound Gel) results in a reduction in PD catheter-associated infections.

One of the significant barriers to establishing this trial has been the extreme diversity of practices of different renal units around the two countries with respect to exit-site care and infection prophylaxis strategies. A number of units were only prepared to participate if they were permitted to follow local center protocols for exit-site care and dressings. This could be accommodated by stratifying for center such that both randomization groups were approximately equally represented within each center. Although there was some divergence of

practice with respect to prophylaxis strategy, the majority of units favored targeted nasal mupirocin eradication of staphylococcal carriage as the control intervention on the basis that this practice was (1) supported by randomized controlled trial evidence (in contrast to exit-site mupirocin application); (2) recommended as the standard of care by the CARI Guidelines; and (3) likely to be associated with a lower propensity to promote mupirocin resistance than daily application of mupirocin to all patients in the control group.

The inclusion criteria have been kept as broad as possible and the exclusion criteria as restricted as possible to maximize the generalizability of the trial results. Moreover, the trial sample size has been carefully and prospectively calculated using conservative estimates of trial infection rates and generous estimates of trial drop-in and dropout rates to minimize the risk of a type 2 statistical error. Patient compliance will be closely monitored.

The accurate determination of nasal carriage of *S. aureus* has also been identified as a crucial issue in this trial in view of the fact that patients in the control group will be treated with nasal mupirocin only if staphylococcal nasal carriage is detected. This has been optimized by the use of broth enrichment procedures by microbiology laboratories, in addition to direct plating.

Standardization of the diagnosis of peritonitis, ESIs, and tunnel infections will be facilitated by regular investigator meetings and distribution of educational materials, including instructional videos. A key early issue that has been identified is the need to provide education to clinical staff to allow them to distinguish between exit-site honey and purulent discharge. This difficulty is most easily overcome by avoiding excessive local application of Medihoney.

It is hoped that results will be available in 2011. Demonstration of a significant improvement in PD catheter-associated infections with topical Medihoney will provide clinicians with an important new prophylactic strategy with a low propensity for promoting antimicrobial resistance.

ACKNOWLEDGMENTS/DISCLOSURE

The study is funded by grants from Baxter Healthcare (Extramural Grant Program), Queensland Government (Smart State Health Grant), and Gambro. The study is registered with the NHMRC (Australian Clinical Trials Registry Number 12607000537459). D. Johnson is a consultant for Baxter Healthcare Pty Ltd and has previously received research funds from this company. He has also received speakers' honoraria and research grants from Fresenius Medical Care.

The authors gratefully acknowledge the contributions of all members of the HONEYPOT Trial Study Group, dialysis nursing staff, trial coordinators, research staff, and patients. The invaluable assistance provided by Ms. Alicia Smith, Ms. Melissa Gardiner, and Ms. Peta-Anne Paul–Brent from the Australasian Kidney Trials Network is very much appreciated.

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