

## **PB-PG-0711-25081 – NIHR Research for Patient Benefit Programme – Final report**

**Project title:** A prospective, randomised controlled trial to determine the safety and efficacy of steroid impregnated tape compared to standard therapy with silver nitrate in the treatment of over-granulating peritoneal dialysis catheter exit sites.

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### **Plain language summary**

Kidney failure is a chronic illness requiring treatment with haemodialysis (HD), peritoneal dialysis (PD) or transplantation to preserve life. PD is the preferred option for many because it is a home-based therapy which preserves patient's independence and is associated with superior quality of life compared to HD. PD involves instilling dialysis fluid into the abdominal cavity via a catheter. Occasionally, where the catheter exits the skin, a reaction can occur resulting in lumpy red tissue known as overgranulation tissue. This tissue can be unsightly, bleed, become painful and if infected, can lead to serious complications including dialysis failure, sepsis and death. There is no agreement on treatment for overgranulation of the PD exit site, but traditionally PD staff have removed the tissue through the application of silver nitrate solution to chemically burn the tissue away. This treatment can be associated with complications including burns to surrounding skin and discolouration. It is also inconvenient requiring multiple hospital visits over several weeks. Steroid impregnated occlusive tape (Haelan, Typharm Ltd) is licensed for use in over-granulating wounds and can be self-applied at home but may increase the risk of infection. The aim of this project was to compare the treatment of over-granulating PD exit sites with standard therapy using silver nitrate or steroid impregnated tape, in terms of safety and effectiveness. 8 PD Units took part and a total of 32 patients were recruited, from an initial target of 80. 16 patients were allocated treatment with silver nitrate and 16 patients treated with steroid tape. Recruitment rates were lower than anticipated and a data monitoring committee reviewed the response rate scores from 2 independent observers who assessed photographic sequences taken at study visits. In terms of a complete response rate at 14 days, the data was unable to demonstrate whether either treatment was significantly more effective than the other. This assessment also showed no likelihood of the study showing a significant difference between

treatments if current recruitment and response rates continued to end. Therefore, the study was halted. Due to the fact that we did not recruit to target, we were unable to demonstrate statistically that either treatment was better than the other. However, valuable learning was gained through the conduct of this randomised controlled trial within the PD environment.

**Keywords:** Peritoneal Dialysis, Exit site care, Over-granulation, Randomised Controlled Trial, Steroid impregnated tape, Cautery with silver nitrate

## **Summary of research findings**

### **Background:**

According to the UK Renal Registry, in 2014, Peritoneal dialysis (PD) was the modality of renal replacement therapy used by 20% of individuals with end stage renal disease (ESRD). PD requires the placement of a silicone rubber catheter to obtain access to the peritoneal cavity. The commonest form of PD catheter has a coiled end which sits in the peritoneal cavity and two Dacron cuffs which anchor the catheter into the abdominal wall; the catheter exiting the body through a subcutaneous tunnel. Catheter exit sites are susceptible to complications including trauma, infection, allergy and over-granulation. Maintaining catheter function is important to allow uninterrupted dialysis and is associated with improved outcomes. It is therefore important to have proven strategies to manage catheter complications including over-granulation. Granulation tissue consists of a highly vascular matrix of fibroblasts and is an important part of normal wound healing. Over-granulation consists of excessive and disorganised granulation tissue, which stands proud of the rest of the skin. The phenomenon of over-granulation is commonly seen at exit sites of medical devices such as PD catheters, tracheostomy tubes and supra-pubic catheters and may be related to repeated skin trauma from the device. It poses a problem as it prevents epithelial cells from migrating across the wound surface leaving a moist and delicate surface over the exit site. The incidence and prevalence of over-granulation of PD exit sites is not reported in the literature but local experience suggests it may affect up to 10% of the PD population per year. Over-granulating exit sites can be uncomfortable for patients, harbour infection or bleed. Associated infection may then be difficult to treat and lead to removal of the catheter and interruption of the therapy, severe complications could include sepsis and death.

Current treatment for over-granulating exit sites includes cautery with silver nitrate, topical steroid ointments or a variety of proprietary dressings. No literature exists comparing treatments for over-granulating PD exit sites but cautery with silver nitrate has been recommended by Gokhal and others and is the most widely used treatment. Steroid ointments may be effective but there are concerns that this might increase exit site infection rates.

In 2010 the PD unit at University Hospitals Birmingham NHS Trust (UHBFT) undertook a pilot study of a steroid (Fludrocortide) impregnated tape (Haelan tape, Typharm Ltd) in the

treatment of over-granulating exit sites. This prospective, uncontrolled and non-randomised study suggested that the tape was safe, effective and superior to the previous standard therapy of silver nitrate. 15 patients were recruited over 6 months from a prevalent PD population of 153 patients. Steroid impregnated occlusive tape is licensed for use in over-granulating wounds, however, no prospective trials of any treatment in this condition have been conducted. Silver nitrate is known to be associated with side effects that include skin irritation, ulceration and bleeding and steroid treatment may be associated with increased risk of infection. Therefore, a randomised controlled trial (RCT) comparing the treatments was proposed.

## Aims and Objectives

To conduct a RCT to determine the safety and efficacy of steroid impregnated tape compared to standard therapy with silver nitrate in the treatment of over-granulating peritoneal dialysis catheter exit sites.

Methods: A multi-centre, prospective, RCT of Haelan tape versus silver nitrate therapy. Participants who met study inclusion/exclusion criteria requirements and who had an over-granulating exit site judged to require treatment according to protocol and who provided valid informed consent, were randomised to either study arm using an internet-based randomisation service. Block randomisation was used to ensure even distribution of allocation across the 8 active UK sites. Upon recruitment, assigned treatment was administered according to standard operating procedures for 2 weeks followed by an additional 2 weeks if clinically indicated. If after 14 days the over-granulation was worse than at day 0, then a medical decision to continue treatment could be taken. A further 2 weeks of the designated treatment could then be administered although this could be discontinued at any point if a satisfactory clinical response was observed. Patients requiring further treatment after 28 days could have treatment according to original randomisation at the discretion of the local investigator. The protocol did not allow for crossover of treatment. Cautery with silver nitrate was undertaken by nursing staff either at the PD unit or a home visit, up to twice weekly. Patients were taught to self-apply the haelan tape on a daily basis. Study visits were undertaken at Day 0, 7, 14, 21, 28 and day 56 (with +/- 24-hour time allowance). At each study visit the following data was collected: a patient questionnaire recording pain, discomfort, and convenience; assessment of the exit site by PD staff using a standardised exit site assessment tool. A swab for microscopy, culture and sensitivity was taken and adverse events recorded. At each visit a sequence of standardised photographs were taken according to study specific guidelines using equipment provided by the co-ordinating centre (camera, colour calibration card, distance bar and scale labels). Patients, PD and research staff and local investigators were unblinded to treatment allocation.

The primary outcome measure was complete response rate at 14 days. Secondary outcomes included overall (partial or complete) response rate and recurrence of over-granulation within the 56-day study period. Additional secondary outcomes included the

exit site infection rate, patient reported pain, discomfort and satisfaction scores and exit site assessment by PD staff using a standardised exit site assessment tool.

Assessment of over-granulation is necessarily subjective and made by visual inspection of the exit site. Assessment was made by the local therapy administrator by direct inspection of the exit site to determine the treatment schedule. However, assessment for the trial endpoint was undertaken by two, independent observers, blinded to the treatment received, following review of the sequential photographs. Each independent observer scored the exit sites according to a standardised response rate developed specifically for the study.

Data, including photographs, were recorded electronically onto a study specific database based within an NHS server that was accessible via the N3 network by all sites. Thus, allowing remote monitoring of all study data.

In order to detect a 30% difference in complete response rates between treatments the sample size of 80 participants was set (40 patients in each treatment arm). This was to be achieved by recruiting across 8 PD Units. However, recruitment rates were much lower than anticipated, and a total of 32 participants were recruited. All sites reported lower rates of overgranulation than were anticipated by the QE pilot study. 16 patients were allocated to each arm, 30 patients received treatment with 2 withdrawals prior to treatment commencement but post randomisation, before the decision to halt the study was made by the Trial Steering Group, upon recommendation by the Data Monitoring Committee and study statistician. Various initiatives were taken to combat the reduced rate of recruitment, from the introduction of reasonable travel expenses for patients, closure of non-recruiting sites, addition of new sites, use of poster aides advertising the study and the request for a no-cost extension to increase the total period of recruitment.

## Results

32 participants were recruited, 16 participants in each arm. Data was made available for 30 participants: 2 patients withdrew before treatment commenced but post randomisation as their over-granulation had resolved. Statistical analysis of response rates were based on 'intention to treat', with primary outcome defined as complete response (CR) at 14 days. For analysis purposes, CR was considered achieved if at least one of the blinded assessors graded the response as complete and the other assessor graded at least a partial response (PR).

Following preliminary analysis 3/16 patients were assessed as demonstrating a CR at 14 days in the Haelan tape arm and 1/14 patients treated with silver nitrate. Applying a

Chi-squared test (0.8705, p-value .350807  $p < 0.05$ ) there was no observed significant difference in CR at 14 days between the two treatment arms. When rates of PR were analysed, there was no significant difference between the two groups at 14 days (chi square test). Furthermore, no significant differences in AE's or satisfaction rates were observed. Therefore, whilst unable to demonstrate a significant difference in the primary outcome measures between the two treatment arms, it has been possible to gather safety, compliance, and satisfaction data. Further analysis will compare exit site assessment made by unblinded clinical staff with the response rate scores from the blinded independent assessors. Additionally, valuable information has been gathered in terms of methodology and the experience of undertaking a nurse-led multi-centre interventional study within the PD clinical environment.

### **Patient and public involvement**

The Queen Elizabeth Hospital Kidney Patients Association has been consulted about the type of research that patients wish to see happening locally. They have stated they are keen to support in terms of both finance and experience, research projects that have relevance to the patient experience of their chronic disease

Peritoneal dialysis is a home based and self-administered modality of renal replacement therapy. Therefore, patients are intimately involved in managing their therapy, identifying and dealing with complications and liaising with medical and nursing staff. The problem of overgranulating PD exit sites was identified by patients as a concern and alternatives to standard therapy were sought since it required additional clinic attendance to be treated with silver nitrate. Patients were involved in designing the pilot project, particularly with regard to practical considerations of how to administer the trial treatment, which is self-administered by patients. This input in study design was reflected in the final study protocol and associated patient relevant documentation, which was reviewed by patients undergoing PD for ease of understanding and relevant content. This review of study documentation by PD patients continued throughout the study, when amendments were made.

Members of the STOP study team were invited to attend a national PD Research study day in Sheffield on 6 May 2016. The aim of this meeting was not only to reflect on PD Research in the UK but also to look at how PPI could influence PD research programmes. Several PPI representatives were speakers at this event, and members of the audience included local PPI representatives of R&D departments and local kidney groups as well as national representatives from kidney charities and research organisations. This representation proved invaluable when discussing ways in which to increase recruitment to the STOP study, and whilst most suggestions had already been implemented or considered by the STOP steering committee it was agreed that a patient poster for use in participating PD units would be designed. The initial draft of the poster was then sent to PPI representatives from the May meeting who were instrumental in refining the poster design.

The Sponsor Trust website carries a dedicated research section which lists all the research studies active within the Trust, including the STOP study. This disseminates details of the study including recruitment figures and targets to members of the public. The Sponsor Trust supports an annual Research Showcase during which researchers are offered the opportunity to share their research projects with members of the public attending the hospital. STOP team members have been present at the Showcase for the last 3 years.

A challenge faced is the continued clinic and hospital attendance burden faced by the PD population, this means that they do not always want to attend for additional events. Therefore, it is important that PPI be linked to current clinic visits and training.

### **Data sharing statement**

See link

[\[https://www.nihr.ac.uk/documents/nihr-position-on-the-sharing-of-research-data/12253\]](https://www.nihr.ac.uk/documents/nihr-position-on-the-sharing-of-research-data/12253) for the NIHR position of the sharing of research data. The NIHR strongly supports the sharing of data in the most appropriate way, to help deliver research that maximises benefits to patients and the wider public, the health and care system and which contributes to economic growth in the UK. All requests for data should be directed to the award holder and managed by the award holder.

### **Disclaimer**

This project is funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0711-25081). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

This project was carried out between December 2013 and March 2017. This final report has not been peer-reviewed. The report was examined by the Programme Director at the time of submission to assess completeness against the stated aims.