

PB-PG-0808-15115 – NIHR Research for Patient Benefit Programme – Final report

Project title: A pilot randomised controlled single-blind trial of a collagen implant for the prevention of sternal wound infection in cardiac surgery.

Authors:

Mr Adrian Marchbank - Derriford Hospital

Mr Vassilios Avlonitis - Plymouth Hospitals NHS Trust

Mr William Dalrymple-Hay - Plymouth Hospitals NHS Trust

Mr Kenneth Hosie - Plymouth Hospitals NHS Trust

Dr Peter Jenks - Plymouth Hospitals NHS Trust

Mrs Hilary Sanders - University of Plymouth

Dr Colin Pritchard - Royal Cornwall Hospitals NHS Trusts

Plain language summary

Infection of the chest wound after heart surgery is a complication which may affect up to 1 in 5 patients. Severe infections can result in serious, sometimes life-threatening illness, requiring prolonged hospital stay and expensive treatment. There is some evidence that placing an antibiotic-containing, absorbable sponge called GentaFleece into the chest wound at the end of surgery may reduce the risk of wound infection. We aim to conduct a large scale clinical trial to evaluate the clinical effectiveness of GentaFleece and to find out whether the costs associated with using the GentaFleece ultimately reduce the overall costs of treating chest wound infections. To plan such a trial, we conducted this 'pilot' trial, to test various procedures and use the information collected to help inform the design of the future trial.

Patients recruited to the pilot trial were randomly allocated to one of two groups: one group received GentaFleece and the other did not (patients were not aware of which group they were allocated to). Following heart surgery, patients' chest wounds were examined for signs of infection by research staff who did not know which group the patient was in. Patients (and GPs in some cases) were contacted 8 weeks after surgery to see if any chest wound problems had arisen.

Of the 394 patients considered for participation, 65 were ineligible, and a further 60 did not want to take part. Having successfully recruited and collected information from 200 patients as intended, we have been able to test systems for identifying and recruiting patients, and for collecting the necessary data. We have identified which systems were effective and which need to be improved, and we can estimate the level of resource needed to run a large trial.

We also examined different methods used to define wound infections. The ASEPSIS and CDC scoring systems are commonly used to assess surgical wounds but there is uncertainty about which is best for use in clinical trials. We used both methods and a small number of other definitions to calculate the rates of wound infection, and this will help us estimate how many patients we will need to recruit in the main trial.

This pilot study has shown that the planned trial is feasible and acceptable to patients and surgeons. The data collected suggests that GentaFleece may have the potential to reduce the number of infections after heart surgery, and that we should proceed with a large definitive trial.

Keywords

Cardiac Surgery, Wound Infection, Sternal Wound Infection, Infection Control, Collagen, Antibiotic, Gentamicin, Prevention, Pilot

Summary of research findings

Background

In the UK there are around 35,000 cardiac operations through median sternotomy each year. Sternal wound infection (SWI) is an uncommon but serious complication, with reported incidence rates between 0.5% and 20%. It is estimated that in the UK each year 1500-2000 patients will suffer a SWI after cardiac surgery, of whom 500-600 patients will require re-operations for deep sternal infection and over 40 will die. SWI requires further treatment with antibiotics and vacuum dressings, prolonged hospital stays and re-operations, incurring significant additional cost. Every extra bed-day costs a minimum of £280, which increases to over £1000 for an intensive care unit bed. Recent estimates of the additional hospital costs for the surgical episode are as low as US\$6,500 and as high as €22,900. Despite routine use of pre-operative antibiotic prophylaxis and improvements in preoperative preparation, intraoperative management and sternal closure techniques, SWIs remain a serious problem after cardiac surgery. As a consequence, some surgeons use antibiotic-containing collagen implants placed into the chest wound at the end of surgery, albeit based on conflictory evidence.

Aims and objectives

The overall intention of this study was to provide the necessary information for the planning of a definitive trial investigating the clinical- and cost-effectiveness of a gentamicin-impregnated collagen implant to reduce sternal wound infections after cardiac surgery. The main aim was to conduct a pilot randomised controlled trial with the following specific objectives:

- test procedures for recruitment and randomisation
- estimate the rate of recruitment of patients
- assess procedures for, and success of, blinding of patients and outcome assessors
- test procedures for wound assessment using CDC and ASEPSIS scoring and the timing of those assessments
- test the timing and mechanisms for capturing wound infections as previously defined early and late after cardiac surgery
- test procedures of follow-up after discharge, specifically to understand how pro-active follow-up needs to be to capture data effectively and efficiently
- test general data collection procedures
- confirm the level of resource required to ensure successful delivery of a full trial
- assess how ASEPSIS (both the overall score and its component parts) is related to other clinical outcomes such as clinically defined infection and length of stay

- identify how ASEPSIS may optimally be used to define the primary outcome measure for the full trial

Methods

Setting: The South West Cardiothoracic Centre (SWCC) in Plymouth, where approximately 1350 cardiac operations are performed each year.

Ethics and research governance: Final REC and NHS R&D approvals were granted in November 2010.

Study Design: Single-centre, randomised, controlled, patient and assessor blind pilot study. Two hundred cardiac surgery patients were randomised (1:1) to receive treatment as usual (TAU) or GentaFleece into the sternal wound prior to closure of the sternum. During the hospital stay, sternal wounds were assessed using the ASEPSIS scoring system and the CDC wound criteria, by assessors blinded to the participants' allocated group. Participants were then followed up, post-discharge, 8 weeks post-surgery.

Study outcomes: In addition to the study objectives described above, the following endpoints were assessed:

- ASEPSIS score
- Wound infection rate by CDC 1992 criteria
- Length of hospital stay
- Mortality
- EQ-5D questionnaire
- Incremental cost effectiveness ratio

Primary care records: In advance of recruitment starting, 50 study numbers were randomly selected, using computer generated numbers, for follow-up of primary care records. The information obtained from the primary care practice was reviewed for consistency with the participant's account.

Recruitment and randomisation: 394 sets of patients' hospital notes were reviewed by the research nurse team. Of these, 370 patients were provided with a Participant Information Sheet and 208 were subsequently recruited. Factors affecting recruitment and reasons for non-inclusion were recorded. 8 consented participants were withdrawn prior to surgery (for clinical and other reasons). As per target, 200 participants underwent surgery and were randomised to GentaFleece or Treatment As Usual (TAU) by the opening of a sealed envelope just prior to closure of the sternal wound.

Trial Management and oversight: Data was centrally monitored and double entered by Peninsula Clinical Trials Unit (PenCTU). In addition to informal visits, PenCTU personnel made six site monitoring visits and one audit visit to support the Research Nurse team and maximise data quality. The Trial Management Group met at least monthly throughout the study to review progress. The Trial Steering Committee has convened three times as planned, once before the start and six-monthly thereafter.

Safety reporting: 82 Serious Adverse Events (SAEs) were reported, none related to the study intervention (the majority being common clinical scenarios which develop after cardiac

surgery). All were reported to the study Sponsor in accordance with protocol and Standard Operating Procedures.

Key findings

Appendix 1 shows the recruitment and retention of participants. 200 hundred participants had their surgery and were randomised to GentaFleece (n=98) or TAU (n=102). Wound checks were made as planned on Days 2 and 4 post-surgery for 98% (195/200) of participants. One participant died shortly after surgery, one participant only had wound checks on Day 2, and three participants had wound checks either one day early or late. One participant died 22 days after surgery. At 8 weeks post-surgery, 97% (95/98) of the GentaFleece group and 98% (100/102) of the TAU group were followed-up.

There was good balance between the two groups in terms of demographics and key risk factors. All participants received prophylactic antibiotics. 21 participants had at least one reoperation (8 in the GentaFleece group and 13 in TAU group), 83% were re-sternotomy for bleeding. The proportions with post-operative complications and the average duration of post-operative ventilation and stays in ICU and hospital were similar across the two groups. However, the average length of time spent in secondary care was longer in the TAU group compared to the GentaFleece group (median (IQR) total length of stay in secondary care: GentaFleece: 9 (6-17); TAU: 13.5 (6-32)). The proportions of participants readmitted to hospital were similar in the two groups.

Little evidence of sternal wound infection (SWI) was detected at Day 2 or Day 4; only one patient was diagnosed with superficial infection at Day 2 (TAU group). At 8 weeks post-surgery, 18% of the GentaFleece group and 23% of the TAU group reported some problem with wound healing. By the end of the follow-up period, the median (IQR) ASEPIS scores in the two groups were: GentaFleece: 2.5 (0-7.5); TAU: 5 (0-12.5). Using previously published cut-offs, in the GentaFleece group 1% were classified as having a minor wound infection and 1% as a moderate wound infection, compared to 10% and 2% respectively in the TAU group.

Based on all the available evidence, and using the CDC criteria extended to 8 weeks, SWI rates of 15% and 22% in the GentaFleece and TAU groups were observed. In the GentaFleece group, the superficial SWI rate was 12% and the deep or organ SWI rate was 3%, with corresponding rates in the TAU group of 15% and 7%.

Primary care follow-up

49 participants were randomly selected for primary care follow-up (25 in the GentaFleece group, 24 in the TAU group) and contact was made with 48 participants' GPs. Of these 48 participants, 9 self-reported problems with wound healing at 8 week follow-up. According to GP records, 45 of these 48 participants had contacted their GP, 7 about their sternal wound. In 6 of these cases, the GP diagnosed SWI and prescribed antibiotics. All 7 of these participants also self-reported problems with wound healing and the 6 who were prescribed antibiotics by their GP for sternal wound infection had self-reported being prescribed antibiotics.

Success of blinding

90% of participants (178/198) stated they did not know to which group they had been allocated. Of the 18 who thought they had been allocated to GentaFleece, 11 had been allocated to TAU. Assessors reported they did not know the allocated group for 99.5% (197/198) of participants. In four cases an assessor did become aware of the participant's allocation due to the treatment being noted in the patient's notes. Another member of the research team, still blinded, completed the remaining assessments.

Economic evaluation

This pilot trial emulated the economic evaluation planned for the future definitive trial with the main aims of testing the plans for collecting resource use data and exploring the properties of the ASEPSIS as an economic outcome. Results confirm that the main cost drivers were associated with the initial in-patient stay (90% of average cost/patient). Similar to findings from other studies, the average additional cost associated with a sternal wound infection within trial was £2439. The ASEPSIS score will not be used as an economic outcome in the full trial. Complete EQ5-D data were collected from 198 (98%) participants at 5 days and 189 (94.5%) at 8 weeks.

Expected impact

As this was a pilot trial, there will be no immediate impact on routine patient care. However, the pilot has shown it is feasible to identify, recruit and follow-up patients undergoing cardiac surgery to a randomised controlled trial, and determine SWI rates, including those which develop after discharge. The pilot will help refine the design and protocol for a definitive study.

Conclusions

The experiences from and results of this pilot study suggest a definitive UK trial of GentaFleece is both feasible and warranted, to end the current clinical and cost-effectiveness uncertainty.

Patient and public involvement

Prior to initial funding application, we conducted a small survey asking 18 cardiac surgery patients whether they were concerned about infections, and whether they would be prepared to be involved in research projects in attempts to reduce the incidence of infections. While only 44% of them were worried about an infection, all of them stated that they would be interested in participating in such a trial, reaffirming the relevance of our research question to patients.

We recruited a patient advisor to give advice on the grant application Lay Summary and other documentation for public consumption. We were aware this was crucial to provide a lay perspective to our otherwise clinical and academic assumptions about patient behaviour, thus helping to construct a feasible study design.

We recruited a second lay member to the Trial Steering Committee. They had input into trial design, participant recruitment processes and overall trial progress. They will continue to advise the team on dissemination of results and has expressed initial willingness to be involved in planning the definitive trial.

The patient representative input has been valuable. To further develop our PPI we have made links with the Local PPI Manager and South West PPI Forum, and plan to attend local PPI events in future in order to ensure we remain aware of the latest guidance. We have identified local and national training courses for lay members covering the research environment, research concepts (randomisation, controls, blinding, etc), ICH-GCP and how to review lay summaries. We envisage greater levels of PPI for our research projects in the future and will use local lay member groups to access a larger pool of patients. We anticipate including fees for patient representatives (in addition to reimbursement of travel and subsistence expenses) in future applications for funding.

For the definitive trial, we will invite more patient representatives to be involved in the development and conduct of the project, including pilot trial participants (some of whom have already expressed interest and all of whom will be invited to consider being patient representatives when they receive a lay summary of the pilot trial results), and representatives of relevant patient support organisations (we are currently in correspondence with the HeartSWell charity).

Ongoing patient and public involvement is seen as central to delivering the definitive trial.

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

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This project was carried out between August 2010 and February 2012. 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.