International Journal of Surgery Protocols 5 (2017) 18–21

Contents lists available at ScienceDirect

International Journal of Surgery Protocols

journal homepage: www.elsevier.com/locate/isjp

Impact of Surgihoney Reactive Oxygen on surgical site infection (SSI) after complex abdominal wall reconstruction (AWR) of grade 3 and 4 ventral Hernias: A single arm pilot study

Sam Parker, Tin Pavlovic *, Reeya Patel, Peter Wilson, Jonathan McCullough, Alastair Windsor

University College London Hospital, UK

ARTICLE INFO

Article history:
Received 3 July 2017
Accepted 16 July 2017
Available online 22 July 2017

ABSTRACT

Introduction: Following Abdominal Wall Reconstruction (AWR) wound infections occur in over one third of patients and rates can be even higher in entero-cutaneous fistula repair. A novel antimicrobial gel has been engineered by microbiologists called Surgihoney Reactive Oxygen (SHRO). SHRO gel will be applied to a group of patients. We aim to conduct a pilot case series with the hope to show a reduction in local wound complications after SHRO application.

Methods and analysis: A single arm pilot study of AWR patients will be carried out on patients with grade 3 and 4 (VHWG grade) ventral hernias. Patients' pre-operative wounds will be graded according to the CDC classification scale. Post operatively the wounds will be classified according to the Wilson surgical site infection classification. Intervention: SHRO will be applied after abdominal fascial closure and before skin closure through a standardised method. Our results from the series will be compared to our retrospective standard wound care results. Data will be collected from 01.03.2017 to 01.11.2017. Primary outcome: Surgical site infection within 30 days of surgery, assessed by clinicians at 5, 15 and 30 days and by patient's self-report for the intervening period. Secondary outcomes include other SSOs (haematoma, seroma, wound dehiscence, skin necrosis), duration of stay in hospital, reported side effects from local treatment and other systemic postoperative complications. We will aim for a cohort of 40 patients.

Conclusions: This study will provide an assessment of methods and feasibility of recruiting and following up patients who are treated with SHRO. On the basis of this pilot trial, a full trial may be proposed in the future which will provide additional, robust evidence on the clinical and cost effectiveness of SHRO in wound management following AWR. This may act as a model for the management of wounds in complex patients undergoing AWR.

1. Introduction

1.1. Background/Rationale

A wound infection or surgical site infection (SSI) occurs in up to 40% of open abdominal operations [1]. It can increase the length of time a patient stays in hospital, increase patient dissatisfaction and litigation, and it may impair oncological outcomes. The main additional costs are related to re-operation, extra nursing care, and drug treatment costs [2].

Reactive Oxygen Species (ROS) are a novel antimicrobial therapy, highly active against Gram positive and Gram negative bacteria, and active in preventing and suppressing biofilm [3,4]. The current licensed product for wound care is incorporated in a pharmaceutical honey preparation, Surgihoney, but ROS technology is being developed in a wide variety of delivery mechanisms for a range of clinical indications. It has been assessed in the management of chronic soft tissue lesions [5] and in the prevention of surgical site infection [6].

A surgical site infection (SSI) can double length of hospital stay, reduce quality of life and markedly increase healthcare costs. Following abdominal wall reconstruction wound infections occur in over one third of patients. Many patients undergoing AWR have a clean-contaminated, contaminated or dirty wound either from a violation of the GI tract during the operation or due to a pre-existing entero-cutanous fistula for which the patient is having their reconstruction. Surgihoney Reactive Oxygen offers a new antimicrobial option that could augment post-operative wound management and reduce local complication rates.

* Corresponding author at: 2 Pump House Close, London SE16 7HS, UK.
E-mail address: tin.pavlovic@ucdconnect.ie (T. Pavlovic).

http://dx.doi.org/10.1016/j.isjp.2017.07.001
2468-3574/

1.2. Objectives

We aim to conduct a single arm study to assess whether SHRO can reduce the rate of wound infections in our AWR patients. We will also consider the safety of the therapy and accurately record any local and systemic adverse effects. We will use the results of the study to inform a future, multicentre RCT to evaluate SHRO in the AWR setting.

1.3. Trial design

A prospective case series analysing the feasibility of using Surgihoney Reactive Oxygen on high risk abdominal wall reconstruction patients.

2. Method

2.1. Study setting

Colorectal Department, University College London Hospital, 235 Euston Road, London, NW1 2BU.

2.2. Eligibility

2.2.1. Inclusion criteria checked during the screening assessment

1. Patients undergoing Abdominal Wall Reconstruction will be included with or without a stoma.
2. Patients with ventral hernias of Ventral Hernia Working Group (VHWG) grades 3 and 4 will be included.
3. Age $\geq$ 18 years.
4. All patients will be fully informed of the trial and the Surgihoney Reactive Oxygen product before their operation. Written and signed consent will be obtained before any study-related procedure is conducted.
5. All types of reconstruction for ventral hernia repair and enterocutaneous fistula will be included.
6. Parastomal hernia repair with or without stoma re-siting or closure of stoma.

2.2.2. Exclusion criteria checked during the screening assessment

1. Redo surgery.
2. Emergency ventral hernia repair/surgery.
3. AWR for abdominal wall sarcoma or invasive intra-abdominal carcinoma.
4. Negative pressure dressing applied to wound site.
5. Inability to close the skin.

2.3. Intervention

ROS in the form of Surgihoney (SH) will be prophylactically applied to the wound after fascial closure and before skin closure as a single dose. A 20 g SH tube will be applied to the subcutaneous layer. Initially, it will be dispensed into a sterile dish and then either a 'sponge brush' or a 'swab on a stick' will be used to spread it evenly across the wound. Wound closure will be standardised, using a three-layer technique. The abdominal cavity will be closed using 0 PDS. Scarpa's fascia will be closed with 2/0 Vicryl, the skin will be closed with surgical clips. The wound will then be dressed with a mepore non-absorbent dressing. The primary surgeon may use drains should they wish. The surgical clips will be removed on day 10 after the operation.

2.3.1. Control

Our wound infection rates will be compared to our past wound infection rates of our AWR patients of grade 3 and 4 ventral hernias.

2.4. Outcomes

2.4.1. Primary outcome

Incidence of surgical site infection in our cohort.

Primary Endpoint measure: assessors' scored the grade of the wound at 5 days, 15 days and 30 days (full wound epithelialisation) according to a standardised tool [7]. The Additional treatment, the presence of Serous discharge, Erythema, Purulent exudate, and Separation of the deep tissues, the Isolation of bacteria, and the duration of inpatient Stay (ASEPSIS) score was chosen as this is a simple reliable tool that has been shown to have excellent inter-rater agreement between surgeons with 96% agreement [8].

The ASEPSIS criteria: The score is calculated by assigning a score based on Table 1. A score greater than 20 defines a SSI. Scores are grouped into 4 categories (satisfactory (0–10), disturbance of healing (11–20), minor SSI (21–30), moderate SSI (31–40), severe SSI (>40)) [8].

Table 1
The ASEPSIS Criteria.

Wound characteristic	Proportion of wound affected (%)				
	<20	20–39	40–59	60–79	>80
Serous Exudate	1 pts	2pts	3 pts	4 pts	5 pts
Erythema	1 pts	2 pts	3 pts	4 pts	5 pts
Purulent Exudate	2 pts	4 pts	6 pts	8 pts	10 pts
Separation of deep tissues	2 pts	4 pts	6 pts	8 pts	10 pts
Additional points for					
Antibiotics	10 pts				
Incision and Drainage	5 pts				
Debridement of the Wound	10 pts				
Isolation of Bacteria	10 pts				
Inpatient Stay > 14 days	5 pts				
Need for Home Health	5 pts				
Total points	Category of Infection				
0–10	Satisfactory Healing				
11–20	Disturbance of Healing				
21–30	Minor Wound Infection				
31–40	Moderate Wound Infection				
>40	Severe Wound Infection				

**Pts = points.

2.4.2. Secondary outcomes

- Length of Stay.
- Antibiotic usage/duration of usage.
- Duration of wound treatment.
- Presence of any wound event (seroma, haematoma, wound dehiscence (superficial or deep), skin necrosis. (Total SSOs in our cohort).
- Overall morbidity - significant events (e.g. re-hospitalisation, hospital acquired pneumonia, pulmonary embolism, reoperation), adverse events.
- Number of patients entering trial, Response rates, Withdrawal rates, Number followed up.
- Device problems and treatment compliance.

2.5. Sample size

The aim is to reduce our 30-day wound infection rates from 30% to 10%. If we compare our SHRO case series to a retrospective sample of patients, at a 95% confidence interval, we need a sample size of 40 to make a 20% reduction in wound infection rates significant.

2.6. Participant timeline

The schedule of enrolment, interventions and assessments is presented in Table 2.

2.7. Participant recruitment

All patients with grade 3 and 4 ventral hernia scheduled to have complex Abdominal Wall Reconstruction will be invited to participate in the study. The patients will receive the patient information sheet and the informed consent form on the day of admission. Sufficient time will be given to read the details of these documents and informed consent will be obtained by the Study Researchers before any study procedures begin. For Doctors and Nurses taking part in the trial, relevant information including possible risks will be explained in detail by the Researchers.

3. Data collection, management, and analysis

3.1. Data collection methods

3.1.1. Wound assessment

The ASEPSIS assessment will be used at 5 days, 15–17 days and 30–35 days after surgery. The patient may have been discharged by the time of wound assessment. Therefore, adhoc clinic appointments will be made as the patients are tracked by the researchers. Wound assessment will be performed consistently by two researchers with a third researcher making sure both wound assessors adhere to the ASEPSIS criteria. For our retrospective cohort we plan to obtain ASEPSIS scores via our microbiology ASEPSIS hospital surveillance scheme and from telephoning the patient and from reading the patient's discharge summary. If the patient reports a wound infection or if the discharge summary reports an infection, we will assign an ASEPSIS score of 20 which implies a wound infection.

3.1.2. Secondary outcomes

All secondary outcomes, complications, local and systemic complications, adverse effects and therapy deficiencies will also be recorded at the first assessment (Day 5) and at the second assessment (Day 15) and at the final assessment (Day 30). This data will also be added to our excel spreadsheet proforma.

3.1.3. Open interviews

Descriptive open interviews with the patients about the effect of the therapy will be carried out at the second assessment point (Day 30). If they have a wound complication they will be asked about their symptoms from this.

3.2. Data management

Designated members of the research team will be responsible for data entry at each step of the patient pathway. All persons entering or amending patient data will be listed in the delegation log.

All researchers will be responsible for the accuracy of the documentation and must ensure that all entries can be verified by the source data. An explanation will be given for all missing data.

3.3. Statistical methods

3.3.1. Analysis populations

Safety population – includes all enrolled patients.

Intention-to-treat population – contains all patients who have received surgery, and entered our pilot study. If they are lost to follow up they are included in the analysis.

Per-protocol population – is a subset of the intention-to-treat-population that excludes patients with major protocol deviations (i.e., patients who do not receive a surgical wound dressing, (as per normal care pathway), lost to follow up).

3.3.2. Analysis of the primary endpoint measure

Primary Endpoint measure: Two researchers, TP and RP will act as assessors' with supervision from SP, JM and AW. They will grade the wound at 5 days, 15–17 days and 30–35 days (full wound epithelialisation) according to a standardised tool [7].

After the pilot trial, we will analyze a retrospective cohort of 40 patients who have grade 3 and 4 ventral hernia repairs. This will be

Table 2
Study Pathway for the Surgihoney Pilot in AWR.

Procedure	Screening/Enrolment/Assessment	Day 1–2 (Admission	Surgery	Post- Operative Assessments		
				Post-Op Day 5	Post-Op Day 15–18	Post-Op Day 30
Informed Consent	X	X				
Medical History	X	X				
Inclusion/Exclusion	X	X				
Surgery Details		X	X			
Wound Assessment			X	X	X	X
Complications				X	X	X
Record AE/SAE		X	X	X	X	X
Record Therapy Deficiencies		X		X	X	
End of Pilot Review						X

**AE/SAE = Adverse Events/Serious Adverse Events.

compared with our previous wound infection rates. An ASEPSIS score will not be achieved for our retrospective cohort. We will only obtain data that will either tell us whether there has been or hasn't been a surgical site infection in the past. An ASEPSIS score of >20 will be considered as a wound infection for our prospective cohort. This categorical data for surgical site infections will allow for binomial tests for group comparison (Odds ratios and Risk Ratios). This part of the project is not part of our primary pilot, which is purely an evaluation of Surgihoney amongst a single cohort of patients. The comparison with the retrospective cohort will occur at a later stage.

3.3.3. Analysis of secondary endpoint measures

Our secondary outcomes may be compared with a retrospective cohort after the original pilot. The data may be binomial or continuous and the appropriate statistical tests will be used for comparison according to data type and distribution.

Descriptive open interviews with patients about the effects of post-operative complications and the device itself will be reported as narrative.

4. Monitoring

4.1. Data monitoring

The trial will be performed in accordance with GCP guidelines and standard operating procedures of the University College London Hospital NHS Foundation Trust, to ensure patient's safety and integrity of the clinical data.

4.2. Adverse events

From the day the patient signs the informed consent until the end of the trial or until premature withdrawal of the patient, all adverse events and serious adverse events will be documented on our data spreadsheet and on a serious adverse event form, available in the investigator site file.

An adverse event (AE) is defined as any untoward medical occurrence in a study patient that does not necessarily have a causal relationship with the trial treatment. The following exceptions are predefined in the study protocol and will not be recorded as adverse events:

1. Occurrence of surgical site infection (the primary endpoint measure) is assessed as an endpoint measure only.
2. Any adverse event that is expected during the postoperative course of the underlying disease and that does not exceed grade I of the Dindo-Clavien classification of postoperative complications.

Assessment will be performed by the investigator or the designated sub-investigator.

A serious adverse event (SAE) will be defined as an event that

- Results in death.
- Is life-threatening.
- Requires or prolongs hospitalisation.
- Results in persistent or significant disability/incapacity.

4.3. Auditing

The investigators will make all study-related source data and records available to regulatory inspectors, after a reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the patients have been adequately protected, and that all data relevant for the assessment of safety and efficacy of the new intervention have been reported to the Sponsor.

Ethics approval

Product is fully licensed for surgical prophylaxis.

Funding Author contribution

All own account work, no funding. Mr. Jonathan McCullough and Mr. Alastair Windsor – Primary Surgeons. Prof. Peter Wilson-Supervising Microbiologist. Mr. Sam Parker - Study design, data collection, surgeon, writing. Dr. Tin Pavlovic - Data collection, data analysis, writing. Dr. Reeya Patel - Data collection, data analysis, writing.

Conflict of interest statement

Mr. Alastair Windsor declares conflicts of interests not directly related to the submitted work.

Guarantor Research registration UIN

Sam Parker, but all authors involved in integrity of trial. researchregistry2693.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.isjp.2017.07.001.

References

[1] Bluebelle Study Group, Feasibility work to inform the design of a randomized clinical trial of wound dressings in elective and unplanned abdominal surgery, Br. J. Surg. 103 (2016) 1738–1744.
[2] WMRC Study Group, Impact of wound edge protection devices on surgical site infection after laparotomy: Randomized controlled trial (ROSSINI Trial), BMJ 347 (2013) f4305.
[3] M. Dryden, G. Lockyer, K. Saeed, J. Cooke, Engineered honey: in vitro antimicrobial activity of a novel topical wound care treatment, J. Glob. Antimicrob. Resist. (2014), http://dx.doi.org/10.1016/j.jgar.2014.03.006.
[4] F.D. Halstead, M.A. Webber, M. Rauf, R. Burt, M. Dryden, B.A. Oppenheim, In vitro activity of an engineered honey, medical-grade honeys, and antimicrobial wound dressings against biofilm-producing clinical bacterial isolates, J. Wound Care 25 (2016) 93–102.
[5] M. Dryden, A. Dickinson, J. Brooks, L. Hudgell, K. Saeed, K. Cutting, A multi-centre clinical evaluation of reactive oxygen topical wound gel in 114 wounds, J. Wound Care 25 (2016) 140–146.
[6] M. Dryden, C. Goddard, A. Madadi, M. Heard, K. Saeed, J. Cooke, Bioengineered Surgihoney as an antimicrobial wound dressing to prevent Caesarean wound infection: a clinical and cost-effectiveness study, Br. J. Midwifery 22 (2014) 23–27.
[7] A.P.R. Wilson, T. Treasure, M.F. Sturridge, R.N. Gruneberg, A scoring method (asepsis) for postoperative wound infections for use in clinical trials of antibiotic prophylaxis, Lancet 1 (8476) (1986) 311–313.
[8] T.L. Hedrick, A.M. Harrigan, R.G. Sawyer, et al., Defining surgical site infection in colorectal surgery: an objective analysis using serial photographic documentation, Dis. Colon Rectum 58 (2015) 1070.