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Alcoholic Chlorhexidine or Alcoholic Iodine Skin Antisepsis (ACAISA): protocol for cluster randomised controlled trial of surgical skin preparation for the prevention of superficial wound complications in prosthetic hip and knee replacement surgery

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ABSTRACT

Introduction: Wound complications following arthroplasty are associated with significant impact on the patient and healthcare system. Skin cleansing prior to surgical incision is a simple and effective method to prevent wound complications however, the question of which agent is superior for surgical skin antisepsis is unresolved.

Methods and analysis: This cluster randomised controlled trial aims to compare the incidence of superficial wound complications in patients undergoing elective prosthetic hip or knee replacement surgery receiving surgical skin antisepsis with either: 0.5% chlorhexidine gluconate (CHG) in 70% alcohol or 10% povidone in 70% alcohol. The trial will be conducted at an Australian tertiary, university affiliated hospital over a 3-year period involving 750 participants. Participants will be drawn from the surgical waiting list. Consent for this study will be 'opt-out' consent. On a given day, all eligible participants will have skin preparation either with 0.5% chlorhexidine in 70% alcohol or 10% povidone iodine in 70% alcohol. The primary outcome is superficial wound complications (comprised of superficial incisional surgical site infections (SSI) and/or prolonged wound ooze) in the first 30 days following prosthetic joint replacement surgery. Secondary outcomes will include the incidence of wound complications according to the joint replaced, assessment of the causative agents of SSI and cost-effectiveness analysis. The primary analysis is an intention-to-treat analysis including all participants who undergo randomisation and will be performed at the individual level taking into account the clustering effect.

Ethics and dissemination: The study design and protocol was reviewed and approved by the St Vincent's Hospital Human Research Ethics Committee (HREC-A 016/14 10/3/2014). Study findings will be disseminated in the printed media, and learned forums. A written lay summary will be available to study participants on request.

Trial registration number: The trial has been registered with the Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN12614000177651.

BACKGROUND

Following prosthetic joint replacement surgery, superficial wound complications (SWC), comprised of superficial surgical site infections (SSI) and prolonged wound ooze, have been consistently linked to prosthetic joint infections; increasing the risk of these infections by 55–60%.[1–3] In Australia the conservative estimate of annual direct healthcare costs of treating SWC following prosthetic joint replacement surgery is $34 million.[4–6] SSI, such as superficial incisional SSI and organ/space SSI (such as prosthetic joint infections) may occur in up to 15% of patients undergoing surgery and are associated with significant patient suffering including the need for prolonged hospitalisation, further surgical procedures, prolonged antibiotic use and negative impact on quality of life.[5 7 8] There is also a significant ecological impact of these infections with the generation of increasingly resistant microorganisms as a consequence of antibiotic therapy.[9–11] The economic burden of SSI is also substantial; SSI increase the direct

healthcare costs by more than 300%.[6] Prevention of SWC may substantially decrease morbidity and mortality, improve patient outcomes and reduce the economic burden to the healthcare system.[6]

Human skin is colonised with millions of bacteria and is the major source of infecting pathogens, including *Staphylococcus* spp.[7 8 12] The number of contaminating microorganisms required to produce infection is low, particularly in the setting of implantation of prosthetic material (such as a prosthetic joint surgery).[13 14] Surgical skin antisepsis is a simple and effective strategy to decontaminate patient's skin prior to surgical incision.[15 16] The three main agents commonly used for surgical skin antisepsis are chlorhexidine gluconate (CHG), iodophors or alcohol.[15] Alcohol is frequently combined with CHG or iodophors to optimise the activity of the surgical skin antisepsis.[8 17] These agents are inexpensive and are well tolerated; adverse reactions, predominantly mild skin reactions, are rare and occur in <1% of patients.[16] Current international guidelines, including National Institute for Health and Care Excellence (NICE) and Centers for Disease Control and Prevention (CDC), recommend use of either iodophors or CHG as surgical skin antisepsis.[7 8 18 19]

There is a paucity of well-controlled studies examining the impact of surgical skin antisepsis on SWC.[8] In particular there are no randomised controlled trials comparing CHG/alcohol and iodophor/alcohol combination and the question of which agent is superior is unresolved.[15] Current recommendations for surgical skin antisepsis are drawn from studies including a seminal, large, multicentre randomised clinical trial by Darouiche *et al*[16] comparing skin preparation with 2% CHG plus 70% isopropyl alcohol to 10% povidone iodine in clean-contaminated surgery. This study demonstrated a reduction in SSI with the use of CHG plus alcohol compared to povidone iodine. However, this study did not include a comparator arm with povidone iodine combined with alcohol therefore it is difficult to attribute the observed difference to chlorhexidine or alcohol (or both in combination).[16] Authors from a Cochrane Review concluded "there was insufficient evidence from randomised trials to support or refute the use of one antiseptic over another" and called for further research.[7] Similar conclusions have been drawn in other systematic reviews and meta-analyses.[15 20] In addition, no data exists on the cost effectiveness of preoperative skin antisepsis.[7]

Prosthetic joint surgery is an important setting to study the efficacy of surgical skin antisepsis. It represents high volume, high-cost surgery in which SWC can have a devastating effect. In 2012, 90 000 Australian patients underwent prosthetic joint surgery, representing an increase of 40% over the previous 10 years and this is expected to double again by 2020.[21 22] Our pilot data have shown that SWC occurred in 9% of patients undergoing prosthetic hip and knee replacement surgery and 30% required re-admission to acute care hospital for management of the wound complication. Furthermore there was a 92% increased risk of subsequent prosthetic joint infection in patients with SWC. In multivariate analysis of risk factors for SWC, we showed that surgical skin antisepsis with 0.5% CHG in 70% alcohol was associated with a 60% increased risk of SWC compared with 10% povidone iodine (1% available iodine) in 70% alcohol. The association was particularly marked in the prosthetic hip replacement cohort with an 80% increased risk of SWC.[23] The aim of this cluster randomised controlled trial is to compare the incidence of SWC in all patients undergoing elective prosthetic hip or knee replacement surgery receiving surgical skin antisepsis with either 0.5% CHG in 70% alcohol or 10% povidone iodine (with 1% available iodine) in 70% alcohol.

METHODS AND ANALYSIS

Study centre

St Vincent's Hospital Melbourne (SVHM) is a Victorian State Centre for joint replacement surgery and a leading academic orthopaedic department with a major focus on prosthetic joint surgery. The SVHM Department of Orthopaedics pursues a major research interest in predictors of outcomes after prosthetic joint surgery and maintains a comprehensive database of all lower limb primary arthroplasties performed since 1998. Extensive follow-up data to 12 years are also captured; the SVHM arthroplasty registry has a minimum of 12 months of follow-up data for 98% of patients undergoing prosthetic hip and knee replacement surgery. SVHM Orthopaedic Department is currently staffed by 15 orthopaedic surgeons performing over 700 elective prosthetic hip and knee replacements per year. All hospital postoperative care is performed according to the SVHM Hip or Knee Replacement Clinical Pathway.[24]

Study design

We propose a cluster randomised controlled trial comparing 0.5% CHG in 70% alcohol with 10% povidone iodine (with 1% available iodine) in 70% alcohol for surgical skin preparation in the prevention of SWCs in hip and knee prosthetic joint replacement surgery. The study will be conducted at SVHM over a 3-year period. As a prospective randomised controlled trial, the study strategy will be constructed and presented in accordance with the recommendations of the CONSORT statement.[25]

Intervention

Study arm (A): surgical skin antisepsis with 0.5% CHG in 70% alcohol.

Study arm (B): surgical skin antisepsis with 10% povidone iodine (1% available iodine) in 70% alcohol.

Recruitment of study participants

Participant consent for this study is 'opt-out consent'. The study population will be drawn from patients on the

waiting list for elective hip and knee replacement surgery at SVHM. Following procedural consent of the patient by the treating orthopaedic surgeon for the planned surgery (hip or knee joint replacement), the patient is placed on the Surgical Waiting List. Once a participant is placed on the waiting list, they will be sent the Patient Information Statement for Opt-Out Consent, which will detail the problem of SWC and the nature of the study. In addition the Patient Information Statement for Opt-Out Consent will explain the process to 'opt-out' of the study. The Project Research Officer will review the Patient Administration System demographic page to identify any participants with a primary language other than English. If such participant is identified, they will be sent the Patient Information Statement for Opt-Out Consent translated to their primary language by a certified translation service, in addition to the English version. The participants will be given a number of options to contact the Project Research Officer to opt-out, including phone, email and mailing address. In addition, patients may request to opt-out of the study at the time of presentation to the pre-admission clinic or on the day of surgery.

After the Patient Information Statement for Opt-Out Consent is sent to the participant, the Project Research Officer will review the medical record and any potential participant with a documented allergy to either study agent; will be excluded from the study.

Randomisation

In the opt-out approach, willingness to participate is presumed unless the participant communicates a choice not to participate in the research by the day of surgery. In this cluster randomised controlled trial, the unit of randomisation is the day of surgery. On a given day, all eligible participants will have skin preparation either with (A) 0.5% chlorhexidine in 70% alcohol or (B) 10% povidone iodine (1% available iodine) in 70% alcohol. Each cluster will be randomly assigned in a ratio of 1:1. Randomisation will be performed by a computer-generated random assignment sequence by a statistician and opaque, numbered, tamperproof envelopes containing assignment will be prepared in advance. In addition, the research team involved in the assessment or treatment of patients will have no role in the assignment process. The patients will be blinded to treatment allocation. We recognise that blinding of the operating surgeons to the assigned preventative strategy is not feasible given the different appearance of the CHG and povidone iodine; however, the operating surgeons will be blinded to the allocation until the day of surgery. In addition, the Project Research Officer will be blinded and data will be analysed on an intention-to-treat basis.

Inclusion criteria

All patients undergoing prosthetic hip or knee total joint replacement surgery at SVHM.

Exclusion criteria

- Patients <18 years of age.
- Patients with a documented allergy to chlorhexidine, alcohol or iodophors.
- Patients with a primary language other than English for which certified translation services for that specific language are not available.
- Patients undergoing arthroplasty surgery for traumatic fractured neck of femur.
- Patients undergoing insertion of a tumour endoprosthesis for bone and soft tissue tumours.

Treatment protocol

Surgical skin antisepsis will be applied in a consistent manner for both study arms (A and B) and will be consistent with international guidelines.[7 8 18 19] In addition the surgical skin antisepsis product will be single use and iodophor-impregnated incise drapes will not be used throughout the course of the study.[8 17]

Outcome measures

Patients will be followed for 30 days postprosthetic joint replacement surgery.

Primary outcome measure

The primary outcome measure is the incidence of postoperative SWC (defined below).[23]

Secondary outcome measures

The secondary outcome measures of the study will include:

- The incidence of SWC according to the joint replaced (knee or hip)
- The incidence of SSI and clinically significant wound ooze
- Assessment of the causative microorganisms of SSI
- The incidence of prosthetic joint infection (defined below)
- Undesirable adverse consequences from surgical skin antisepsis including toxicity and allergies
- Economic analysis including cost-effectiveness of surgical skin antisepsis

Definitions

Superficial wound complication

Defined if the participant develops a superficial SSI *and/or* clinically significant wound ooze within 30 days of the indexed prosthetic joint replacement surgery.

Superficial SSI (modified from the CDC definition of SSI)

- Infection occurs within 30 days after prosthetic joint surgery.
- Involves only skin or subcutaneous tissue of the incision.
- It meets at least one of the following:
  - Purulent drainage from the superficial incision with or without laboratory confirmation, from the superficial incision.

- Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
- At least one of the following signs or symptoms of infection: pain or tenderness, localised swelling, redness or heat *and* superficial incisions deliberately opened by surgeon, *unless* incision is culture negative.
- Diagnosis of a superficial incisional SSI by the surgeon or attending physician.[8 26]

Clinically significant wound ooze

- Occurs within 30 days after prosthetic joint surgery.
- It meets at least one of the following:
  - There is documented drainage from the surgical incision that required intervention, such as superficial surgical debridement.
  - The documented drainage leads to deviation from normal care as per the SVHM arthroplasty clinical pathway, such as delayed discharge from hospital or readmission.[2 3 24 27 28]

Prosthetic joint infection (organ/space SSI)—modified from the Musculoskeletal Infection Society definition for periprosthetic joint infection

- Occurs within 365 days from prosthetic hip or knee replacement surgery.
- It meets at least one of the following criteria:
  - Presence of a sinus tract in direct communication with the prosthetic joint;
  - ≥1 indistinguishable microorganism/s cultured from ≥2 aseptically obtained tissue or fluid samples (including intra-operative tissue cultures or joint aspirate) taken from the affected prosthetic joint.
- Four of the following six criteria exist:
  - Elevated serum C reactive protein concentration >5 mg/mL;
  - Elevated synovial leucocyte count (>1.7×10^3/μL);
  - Elevated synovial neutrophil (polymorphonuclear leucocytes; PMN) percentage (>65% PMN);
  - Presence of purulence in the affected joint as documented in the operative notes;
  - Isolation of a microorganism in one culture of periprosthetic tissue or fluid;
  - Histological evidence of acute inflammation as per the pathology report.[8 26 29–32]

Data collection

The processes for identifying outcomes will be conducted by the Project Research Officer who will be blinded to the intervention allocation. The Project Research Officer will collect the baseline demographic data on all study participants including sex, age, comorbidities and operation details. Participant information will be stored in a reidentifable format for the purposes of conducting phone follow-up and medical record review follow-up. Information will be stored both electronically and in paper copy during and after the research study. In order to maintain complete confidentiality and security, all files will be password protected, on a computer within the Orthopaedic Department at SVHM, which is a locked facility, and all paper documents stored in a locked cabinet within the department. Only researchers listed within this study will have access to these files. Information will be stored for 15 years as required by law.

In keeping with the institutional Human Research Ethics Committee (HREC) approval, the study will be conducted in accordance with the ethical and research arrangements of SVHM and relevant legislation and regulations. In addition, any serious or unexpected adverse effects on participants or any unforeseen events that might affect continued ethical acceptability of the project will be immediately reported to the HREC. Further, in keeping with the conditions of approval stipulated by the HREC, an annual progress reports and a final report will be provided to the HREC.

Sample size

From the pilot data the proportion of patients with SWC was 27% in the 0.5% chlorhexidine/70% alcohol group versus 8% of patients in the 10% povidone iodine (1% available iodine)/70% alcohol group. On multivariate analysis there was an 80% reduction in the risk of SWC in the group receiving 10% povidone iodine (1% available iodine) in 70% alcohol surgical skin antisepsis (OR 0.20, 95%CIs 0.06 to 0.67).[23] The sample size estimation for this study is based on a minimally clinically significant difference of 9% (based on the upper limit of the 95% CI of the pilot study) and includes the following parameters: (1) α value=0.05, two-sided; (2) power=80%; (3) expected rates of the primary outcome (defined above) at 30 days post-prosthetic hip or knee replacement surgery of 27% for 0.5% CHG in 70% alcohol and 18% for 10% povidone iodine (1% available iodine) in 70% alcohol. The sample size required in each of the two (equally sized) groups is 359 patients for individual randomisation.[23] Previous published data suggests that the intracluster correlation coefficient is very small (median ICC <0.01) between infections in patients in the same surgical day, and therefore the design effect allowing for clustering is minimal.[33–35] Based on the SVHM arthroplasty registry 12-month loss to follow-up rate of 2%, we will aim to recruit 750 patients in total. At SVHM, over 700 prosthetic joint replacements are performed each year therefore recruitment will be completed within the first 2 years of the study.

Epidemiological analysis

Although the intervention is implemented at the day of surgery level (the cluster), the analysis will be performed at the individual level but will take into account the clustering effect. The primary analysis is an intention to treat analysis including all participants who underwent randomisation. The OR of SSI associated with the treatment arm compared with the control arm will be

estimated using the generalised estimation equations accounting for potential clustering in the unit of randomisation, adjusting a priori for the joint replaced, gender, age group and presence of rheumatoid arthritis; these are all factors known to impact on the risk of infection. All reported p values will be two-tailed and for each analysis $p<0.05$ will be considered statistically significant when using Huber–White robust SE.

Economic analysis

Costs will be compared between groups using a Poisson regression, which assumes that costs are log-normally distributed. We will apply health economic modelling to estimate the potential cost effectiveness of 0.5% CHG in 70% alcohol compared with 10% povidone iodine in 70% alcohol. A decision analysis will be used to compare the downstream consequences of surgical skin antisepsis.[36] Markov and life-tabling techniques will allow for the modelling of outcomes beyond 1 year and will include 5% discounting of estimated future costs and health gains.[37 38]

ETHICS AND DISSEMINATION

This project is due for completion 3 years after the start. We expect that soon after the completion of the project, important findings will be readily translated into practice through dissemination in the printed and electronic media, and at learned forums. A written lay summary of the results will be available to study participants on request.

Expected outcomes

This proposal provides new knowledge to the field of prevention of SWC in patients undergoing prosthetic joint-replacement surgery, addressing questions raised in the recent Cochrane review.[7] The research proposal involves a collaborative approach between orthopaedic surgeons, infectious diseases physicians, infection control clinicians and clinical epidemiologists. This research is embedded within the healthcare system facilitating the direct translation of research evidence into clinical practice.

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Ethics approval The study design and protocol were reviewed and approved by the St Vincent's Hospital Human Research Ethics Committee (HREC-A 016/14 10 March 2014).

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

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