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Protocol for a randomised controlled trial comparing aqueous with alcoholic chlorhexidine antisepsis for the prevention of superficial surgical site infection after minor surgery in general practice: the AVALANCHE trial

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ABSTRACT

Introduction: Surgical site infection (SSI) after minor skin excisions has a significant impact on patient morbidity and healthcare resources. Skin antisepsis prior to surgical incision is used to prevent SSI, and is performed routinely worldwide. However, in spite of the routine use of skin antisepsis, there is no consensus regarding which antiseptic agents are most effective. The AVALANCHE trial will compare Aqueous Versus Alcoholic Antisepsis with Chlorhexidine for Skin Excisions.

Methods and analysis: The study design is a prospective, randomised controlled trial (RCT) with the aim of investigating the impact of two different antiseptic preparations on the incidence of superficial SSI in patients undergoing minor skin excisions. The intervention of 0.5% chlorhexidine gluconate (CHG) in 70% alcohol will be compared with that of 0.5% CHG in aqueous solution. The trial will be conducted in four Australian general practices over a 9-month period, with 920 participants to be recruited. Consecutive patients presenting for minor skin excisions will be eligible to participate. Randomisation will be on the level of the patient. The primary outcome is superficial SSI in the first 30 days following the excision. Secondary outcomes will be adverse effects, including anaphylaxis, skin irritation, contact dermatitis and rash and patterns of antibiotic resistance.

Ethics and dissemination: The study has been approved by the James Cook University Human Research Ethics Committee (HREC). Findings will be disseminated in conference presentations and journals and through online electronic media.

Discussion: RCTs conducted in general practice differ from hospital-based projects in terms of feasibility, pragmatism and funding. The success of this trial will be cemented in the fact that the research question was established by a group of general practitioners who identified an interesting question which is relevant to their clinical practice and not answered by current evidence.

Trial registration number: ACTRN12615001045505; Pre-results.

Strengths and limitations of this study

- Practical clinical question relevant to clinical practice.
- Recruitment of clinicians and participants will be very feasible.
- Independent outcome assessor will assess photographs of all infections.
- Conduct of trial in general practice will provide clinically relevant results to end-user.
- Diagnosis of infection has an element of subjectivity.

BACKGROUND

It is a routine practice prior to surgery to carry out preoperative cleansing of the skin with antiseptic preparations at the site of surgical incisions (preoperative skin antisepsis).[1–3] The purpose of preoperative skin antisepsis is to reduce the incidence of surgical site infection (SSI) by removing microorganisms on the skin through a combination of mechanical removal and chemical killing.[1 3 4] The incidence of SSI arising from surgery in general practice is usually 1–3%, but has been recorded at rates as high as 10%.[5–8] The consequences of SSI include pain and discomfort for patients, increased healthcare-associated costs and temporarily reduced occupational and recreational productivity and functionality.[1 3 4 9] As a result, reducing the incidence of SSIs is in the interest of all stakeholders in healthcare.

The most commonly used preoperative skin antiseptic preparations are povidone iodine (PVI) and chlorhexidine gluconate (CHG). They are available in aqueous and alcoholic preparations and in different

concentrations.[1 3 4] PVI and CHG are effective against a wide range of Gram-positive and Gram-negative bacteria, viruses and fungi, though CHG has a more appreciable residual antiseptic activity on the skin after application.[1 2 4]

Surprisingly, despite the routine use of preoperative skin antisepsis, there is no definitive scientific consensus regarding which antiseptic preparation is most effective in preventing SSI.[1 4 9] There are even less definitive data available for antisepsis prior to clean surgery, which the Centre for Disease Control (CDC) defines as 'an uninfected operation in which no inflammation is encountered and the respiratory, alimentary, genital or uninfected urinary tract is not entered' (CDC, 2011).[10] Prior studies of wound infection after minor surgery in general practice in the Mackay region have shown an SSI rate of ~9.5%—an incidence that is much higher than expected based on published results of similar cohorts in other regions of Australia and the world.[11–14] The reason for this high infection rate is unclear, but may be related to the hot, humid environment or to patient behaviour in our rural setting. On the one hand, this infection rate is suboptimal, as the CDC suggests that an acceptable rate of SSI after clean minor surgery is <5%.[15] However, in settings where there is a low risk of infection after clean surgery, studies of over 5000 procedures may be required to detect a clinically relevant difference in infection from an intervention with statistical confidence, making such trials unfeasible.[16] Conversely, because of the high rate of infection in our patient cohort and the high minor surgery workload in rural general practice,[17] a study of skin antisepsis for the prevention of SSI in our setting is highly feasible.

In general, the evidence base guiding appropriate selection of antiseptic agents is poor. A landmark study found 2% CHG in 70% isopropyl alcohol to be superior to an aqueous solution of 10% PVI; however, as alcohol is known to have significant antimicrobial properties, this was likely to be an active treatment component in this study.[18] Most recent meta-analyses, including a Cochrane review, concur that it is difficult to make conclusive statements about whether there are differences in the efficacy of CHG and PVI[1 2 9] and the latest guideline on surgical skin antisepsis released by the Queensland Department of Health agrees with this position.[4] The Queensland Department of Health does, however, endorse the use of alcoholic solutions in preference to aqueous preparations,[4] and two recent meta-analyses have asserted that there is some evidence to suggest that alcoholic solutions may be more effective than aqueous solutions.[1 2] Nonetheless, they agree that the marked heterogeneity in type and application of antiseptic preparations between available studies hinders direct comparisons between them.[1 2] This, combined with the overall low statistical power of almost all available studies, makes it difficult to draw firm conclusions about the proposed superiority of alcoholic solutions.[1 9]

Previous research in the Mackay region[6 7 19 20] and recent interviews (personal communication) have revealed that the majority of Mackay general practitioners (GPs) use CHG in preference to PVI, one of the reasons behind this being perceptions of 'messiness' and skin staining. Therefore, for practical reasons, our team has chosen to examine the difference between alcoholic and aqueous CHG, rather than comparing the relative efficacy of CHG and PVI.

The aim of our study is to determine whether there is a difference in the incidence of SSI after minor skin excisions in general practice (clean surgery) when alcoholic CHG is used for preoperative skin antisepsis in comparison with aqueous CHG.

We hope this research will provide more authoritative direction about skin antisepsis to clinicians carrying out a clean surgery. If our research demonstrates a difference in efficacy between alcoholic and aqueous CHG, its dissemination may lead a change in behaviour which may serve to reduce overall incidence of SSI after minor skin excisions in general practice in Australia.

METHODS AND ANALYSIS

Study centre

This study will be conducted in four private general practices in Mackay, Queensland (latitude 21E8S). Mackay is a rural centre with around 100 local GPs servicing a population of 112 798.[21] The study team have previously carried out a number of successful randomised controlled trials (RCTs) on minor skin excisions within the Mackay region.[6 8 19 20]

Study design

This is a prospective RCT comparing the intervention of 0.5% CHG in 70% alcohol with that of 0.5% aqueous CHG surgical skin preparation for the prevention of SSI following 'minor skin excisions'—benign or malignant skin lesions excised under local anaesthetic—conducted in general practice. Data will be collected over a 9-month period. The study will be conducted in accordance with the CONSORT statement.

Intervention

The intervention of surgical skin antisepsis with 0.5% CHG in 70% alcohol will be compared with that of the control group of 0.5% CHG aqueous solution. The 0.5% concentration of CHG aligns with guidelines released by the Queensland Centre for Healthcare Related Infection Surveillance and Prevention.[22] The 70% alcoholic concentration of CHG is standard for alcoholic preoperative skin preparations.[2] The antiseptic solutions will be purchased from an independent supplier with research funding.

Recruitment of study participants

Consecutive patients over the age of 18 with capacity to give informed consent, who present to participating GP

practices for minor skin excisions, will be invited to participate. The practice nurses will be responsible for recruitment. Many provisions have been developed to assure informed consent. First, all eligible participants will be provided with a participant information sheet before giving written informed consent. In addition, practice nurses, rather than practice GPs, will recruit patients. This is intended to minimise the risk of perceived coercion, as nurses are somewhat less responsible for direct decisions regarding patient care than the patient's GP. Furthermore, all nurses involved in the trial will receive formal training regarding appropriate consenting procedures.

Randomisation

In this prospective RCT, randomisation will be performed at the level of the patient with an allocation ratio of 1:1. The random sequence will be generated from a computer-generated random number table. Allocation concealment will be attained using sealed, numbered, tamperproof opaque envelopes such that neither the patient, nor the clinicians involved in their care, will be aware of their allocation until after they have consented to be a part of the trial, thereby minimising selection and confounding bias. 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, although there are differences in the alcoholic skin preparation which are identifiable to the patient. Blinding of the operating doctors to the assigned skin antiseptic is not feasible given the differing smell of the two solutions. The practice nurse or doctor assessing outcomes will be blinded to the treatment allocation, as will the practice nurse collecting data and the investigator team.

Inclusion criteria

- All patients over the age of 18 undergoing minor skin procedures at the participating practices during the study period who:
  - have the capacity to give informed consent;
  - are able to return for removal of sutures.
- Patients who are not presenting for:
  - excision of sebaceous cyst;
  - suturing of lacerations;
  - excisions not requiring sutures, such as shave biopsies;
  - punch biopsies;
  - excisions on body sites where epinephrine is contraindicated.

Exclusion criteria

- Allergy to alcohol or chlorhexidine;
- Evidence of infection at or adjacent to the operative site;
- Current use of antibiotics;
- Clinical indication for antibiotic treatment following excision (besides SSI);
- Periocular excisions;
- Patients with a primary language other than English for which certified translation services for that language are not available.

Surgical and wound protocol

A surgical and wound management protocol will standardise the management across the study arms. The protocol is modelled on previous protocols used in similar trials, as well as in international guidelines,[6 8 10 19 20] and was developed in consultation with participating doctors and nurses. As per this protocol, skin antisepsis will be applied in a consistent manner for the study arms—drapes, gloves, sutures, local anaesthetic and dressings will be the same across all sites and postoperative wound care processes will be identical, with all patients receiving a standard set of verbal and written postoperative wound care instructions.

Outcome measures

Primary outcome measure

The primary outcome measure is the incidence of postoperative SSI occurring within 30 days of the procedure (defined below). Patients' wounds will be assessed for evidence of SSI when they present for the removal of sutures; at any other time, if they present for wound review due to signs and/or symptoms of SSI, or opportunistically if they represent for any other reason. Wound assessment will be carried out by doctors or nurses at each general practice and the presence or absence of SSI recorded. There will be standardised in-house training regarding the definition of infection.

All infections will be photographed and assessed for infection by a second blinded independent outcome assessor to improve validity and reliability.

If patients are deemed to have an SSI, they will be treated with antibiotics as clinically indicated, and as per standard practice, all wounds with a purulent discharge will be swabbed.

Secondary outcome measure

Secondary outcome measures will be:

1. Adverse reactions to the preoperative skin antiseptic agent, manifesting as any one of
   A. Anaphylaxis,
   B. skin irritation or contact dermatitis,
   C. rash.
2. Microbiology of infected wounds with a purulent discharge, and any patterns of antibiotic resistance.

Definitions

Surgical site infection

SSI will be determined in accordance with a modified version of the CDC definition for superficial SSI:

- Infection occurs within 30 days after the excision,
- Infection involves only skin or subcutaneous tissue of the incision;
- At least one of the following:

  - Purulent drainage with or without laboratory confirmation from the superficial incision,
  - At least one of the following signs or symptoms: pain or tenderness, localised swelling, redness or heat,
  - Diagnosis of superficial SSI by the GP;
- Stitch abscesses, characterised by minimal inflammation and discharge confined to the points of suture penetration, will not be included as SSIs.[6 8 10]

Data collection

Data will be primarily collected through the use of a written spreadsheet which will be completed by practice nurses. A member of the research team will visit practices on a fortnightly basis to audit the data collection.

Baseline data will be collected regarding patient demographics, including age, sex, occupation and smoking status, as well as comorbidities, such as diabetes mellitus or peripheral vascular disease, and current relevant medications, such as anticoagulants and immunosuppressants. Data will also be recorded regarding the excision itself, such as the incision length, the suture size and the type of excision performed (ie, simple, flap, two-layer procedure). A body site map will be used to record excision site and the histology of the lesion will also be recorded. Each item of data has been chosen based on data extracted from other trials on risk factors for SSI.[5–8]

Sample size calculation

Our sample size was calculated on the basis of three previous studies of SSI in the Mackay region.[6 19 20] These studies used mostly aqueous chlorhexidine as surgical antisepsis. Pooled analyses showed a weighted mean SSI rate of 9.35%, which has been rounded up to 10% as our predicted baseline infection rate.[6 19 20] We decided that an absolute reduction in the SSI rate of 5% (to 5%) would be clinically significant. To reach this conclusion with statistical confidence, a power in excess of 80% and a significance level of 0.05, a total of 435 patients would be required in the intervention group and 435 patients in the control group, thus 870 in total.

Our previous similar trials[6 8 19 20] have had a drop-out rate of <5%, so we will enrol an additional 50 patients to counter potential attrition, providing a final sample size of 920.[6 8 19 20]

Data analysis

The primary analysis is an intention-to-treat analysis including all participants who undergo randomisation. The analysis will be performed taking the individual person as the unit of analysis. All reported p values will be two-tailed and for each analysis, $p<0.05$ will be considered statistically significant. The main analysis will follow the intention-to-treat principle. Baseline data across control and intervention groups will first be assessed for marked differences. The incidence of SSI (the primary dependent variable) in each of the two groups of the trial will then be compared using Pearson's χ^2 test. Multivariable logistic regression analysis will be applied in case differences exist between intervention and control groups at baseline and the analysis requires adjustment for confounders. We will also carry out sensitivity testing for lost to follow-up patients and per-protocol analysis for non-compliers to assess for the possible effects of systematic biases on results.

Potential problems

On the basis of our previous studies, we feel that the recruitment of adequate patient numbers is feasible; however, if we fail to recruit patients, we will invite additional general practices to participate.

In our previous studies, we have found that assessing for infection at the time of removal of sutures facilitates a high rate of follow-up. Any patients not followed up will be analysed on an intention-to-treat basis.

We have not planned to perform an interim analysis as we feel that variation in antisepsis is a minor intervention, and the outcome of SSI is usually a minor medical issue which is treated with a course of antibiotics. An interim analysis would further increase the required sample size reducing the feasibility of our trial.

DISSEMINATION

This project is due for completion 1 year after the start of data collection. The translation of important findings to clinical practice will be facilitated through dissemination in conference presentations and journals as well as electronic media. The researchers will also aim to publish their findings on a range of Australian FOAM (Free Open Access Meducation) websites to reach the next generation of technology-savvy health professionals. A written lay summary of the results will also be displayed at the participating general practices for the information of study participants.

ETHICAL CONSIDERATIONS

We do not expect the intervention in this study to place participants at any significant risk of harm, as we hypothesise a lower incidence of SSI in the intervention group due to the use of alcoholic CHG. In any case, SSI is a minor condition which can be easily treated without significant long-term sequelae. To assure privacy and confidentiality, all data spreadsheets and consent forms will be kept in a locked cupboard throughout the trial, then transferred to a locked safe at the conclusion of the trial, where they will be kept for 15 years. Patients will be deidentified in all data collection.

DISCUSSION

Very few large RCTs are conducted in a primary care setting.[23 24] Difficulties have been reported in recruiting patients and clinicians,[25] and RCTs have been reported as being methodologically and practically difficult to

conduct in general practice.[11] However, it is important that clinical practice be informed by adequate primary care evidence. Otherwise GPs, the end-user of the research process, who attempt to practise evidence-based medicine, may have flawed tools and the guidelines they use may not be applicable to the patients they see.[26 27]

Funding for primary care research in Australia is very limited, particularly compared with UK and the Netherlands with only 2% of NHMRC grants awarded to primary care research between 2000 and 2008.[28] General practice-based research differs in many ways from hospital-based research in issues of funding, feasibility and pragmatism, and we have used our experience from conducting previous successful trials in general practice to inform the design and methods of the present study.[6 8 19 20] Our study will be conducted for total funding of $20 000, which is similar to the cost of our previous trials.

Skin excisions form a large proportion of the workload of Australian GPs[17] and this is even greater in Queensland, the state with the highest incidence of skin cancer in the world.[29] This effect is magnified in regional towns such as Mackay, where there are no permanent dermatologists or plastic surgeons. Using a research question that is relevant to our clinical situation increases the feasibility of recruitment of patients because of our high case load of patients presenting for skin excisions.

Our research question is practical and clinically relevant. Local clinicians do not use betadine antisepsis because of perceptions of 'messiness' and skin staining. Therefore, to be pragmatic, our team has chosen to examine the difference between alcoholic and aqueous CHG, rather than comparing the relative efficacy of CHG and PVI. We have also found that using a clinically relevant research question engages GPs and practice nurses, and facilitates practitioner recruitment, as well as increases the potential for translation into clinical practice.[30]

Our surgical and wound management protocol was developed in consultation with participating doctors and practice nurses, which again increases the ownership and practicality of the project. Occasionally, scientific rigour may be compromised at the expense of pragmatism. For instance, in contrast to hospital-based research, it is simply not practically or financially feasible to have an independent outcome assessor assessing each wound at each of the three geographically dispersed practices. To compensate for this, infections will be photographed and assessed for infection by a second independent and blinded outcome assessor, who will reassess every wound.

It is also not feasible to have an independent researcher to recruit patients. In our trial, practice nurses will be responsible for recruitment. Many provisions have been developed to assure informed consent. This is intended to minimise the risk of perceived coercion, as nurses are somewhat less responsible for direct decisions regarding patient care than the patient's GP. The practice nurses are also responsible for data collection and are paid on a fee per service basis that compensates them for their time. The study involves very little additional work for the participating GPs—they are not responsible for any data collection, and were only required to have knowledge of the process involved to answer any possible queries.

The trial will provide guidance to GPs regarding skin antisepsis, and will inform current clinical guidelines and healthcare worker education. Although our study is conducted in a tropical rural setting and we are aware that our baseline infection rate is comparably high,[6 7] we have no reason to believe that any relative risk reduction detected will not be generalisable to other settings. If we detect a measurable decrease in the incidence of SSI with alcoholic CHG, this may result in a change in clinical practice, with an increase in the use of alcoholic CHG, which could reduce SSI rates following clean surgery. As this is a pragmatic trial, the findings can potentially be immediately translated into clinical practice.

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Contributors CFH conceived the study idea and oversaw the development of the study design and protocol. DC led the development of the study protocol. AH, MD, JB and SS assisted with the development of the study design and protocol. PB assisted with the sample size calculation and statistics. All authors contributed to the drafting of the manuscript.

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Competing interests None declared.

Ethics approval This project has been reviewed and approved by the James Cook University Human Research Ethic Committee; HREC approval ID H6065.

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