

BMJ Open Protocol for an open randomised controlled trial investigating Fibrin Glue in Skin grafts for Skin cancer (FiGSS)

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ABSTRACT

Introduction Skin cancer is a common disease in the tropics, and oncological resection typically requires reconstruction with skin grafts. Fibrin glue, initially established as a haemostatic agent, has been studied extensively as an adhesive for skin grafts in burns. This study aims to investigate the use of fibrin as an adhesive for split skin grafts in skin cancers.

Methods and analysis The study design is a prospective randomised controlled trial with the aim of investigating the impact of two different methods of split skin graft fixation. The intervention of fibrin glue will be compared with the control of staples or sutures. The trial will be conducted at two sites, a public hospital and a private hospital in Townsville, Australia, over a 24-month period with 334 participants to be recruited. Consecutive patients presenting for skin excisions and grafting will be eligible to participate in this study. Randomisation will be on the level of the patient. The primary outcome is graft take based on wound healing at 1 month. Secondary outcomes will be pain on dressing changes and operative time.

Ethics and dissemination The study has been approved by The Townsville University Hospital Human Research Ethics Committee. Findings will be disseminated in conference presentations and journals and through online electronic media.

Trial registration number ACTRN12618000484246.

INTRODUCTION

The first described use of intraoperative fibrin was in 1909 when German surgeons used it as a haemostatic agent.^{1 2} When fibrin is introduced to a wound alongside thrombin, factor XIII and calcium it mimics the final events in the clotting cascade, cleaving fibrinogen to fibrin.^{3–5} Fibrin was originally derived from patient plasma intraoperatively, but now commercial preparations of fibrin glue are now available with high concentrations of fibrin which can be used as an adhesive.^{6 7} Fibrin glue has been investigated for adhesive use in skin grafts for burns and has shown no inferiority to peripheral fixation (staples/sutures) in terms of wound closure.^{8–11} Specifically, fibrin glue

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Practical question, clinically relevant to surgical management of skin cancer.
- ⇒ Blinded independent outcome assessor will assess photographs of all wounds.
- ⇒ Outcomes include clinical measurements, patient-reported measures and hospital system measures.
- ⇒ Surgeons and patients cannot be blinded.
- ⇒ Assessment of graft take has an element of subjectivity.

adheres the entire graft surface to the wound bed ([figure 1](#)) and significantly reduces the formation of haematoma or seroma immediately postoperatively.¹⁰ Studies have also shown that the use of fibrin glue results in decreased dressing requirements to ensure close adherence of the graft; better haemostasis; and less contraction of scar tissue.^{8–10} Skin graft survival is dependent on vascularisation of the graft which usually begins after 2 or 3 days. During this initial period poor adherence or haematoma or seroma formation can reduce graft imbibition of oxygen and nutrients from the graft bed and disrupt further vascularisation.^{10 12} Formation of a haematoma or seroma is the most common cause for graft failure.^{10 12} Issues with the graft recipient site such as poor vascularity, infection, inflammation or shearing forces over mobile skin areas can also lead to graft failure.¹⁰ After wound closure, the graft site can also contract, leading to aesthetic defects or functional defects due to reduced range of motion.⁶

In Australia, and particularly Far North Queensland, skin cancers are incredibly common and many patients have skin cancers which are sizeable enough to require grafting after resection for adequate wound closure.¹³ This is particularly true of patients with melanoma where the surgical margins range from 1 cm upwards.¹⁴ This margin results in an

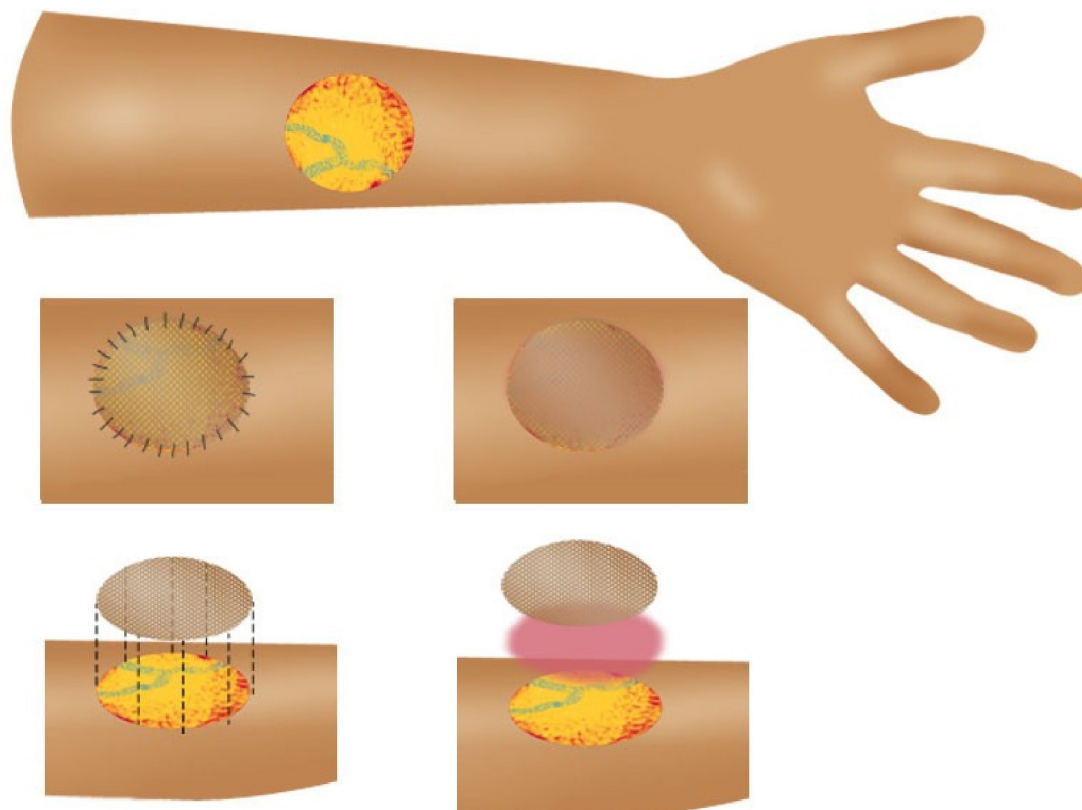


Figure 1 A graphic to demonstrate the differences in skin graft fixation between sutures and staples (left) and fibrin glue (right).

area of skin loss usually at least 3 cm across which cannot be primarily closed, particularly in extremities due to taught skin. Many of these patients are elderly and may have diseases which impair wound healing. One of the most common sites for skin cancer is the lower leg, which is particularly prone to poor healing in the presence of vascular risk factors.¹⁵ Previous studies have not addressed the use of fibrin glue in skin cancer resections nor in elderly patients and patients with vascular risk factors. Fibrin glue has been investigated for use in other difficult to graft situations such as infected sites, mobile skin areas and difficult to graft areas with good results.^{8 16–19} These are all areas which can contribute to skin graft failure. It is possible that fibrin glue can increase graft take in patients who have vascular issues as it has been shown that increased fibrin decreases likelihood of graft failure and can induce angiogenesis.²⁰ If fibrin glue can be shown to be beneficial in patients with skin cancer (particularly elderly and patients with vasculopathy) and significantly decrease operative time and follow-up it may be a viable alternative to sutures. This could potentially change the management of skin grafts to become quicker, easier and less painful for patients with less follow-up required.

There have been no clinical trials looking at the use of fibrin glue for skin grafts in skin cancer to date.¹¹ There have been few trials of reasonable size looking at the use of fibrin glue in skin grafts for burns.^{10 11} These trials have shown apparent benefits in using fibrin glue, and it may be an effective way to improve graft take. Currently the

accepted standard of care would be use of any of these techniques, however, the use of glue is less common.

The objective of this study is to examine the effectiveness of fibrin glue in reconstruction of oncological skin resection. If our research demonstrates increased effectiveness of glue it may lead to a change in behaviour which may reduce the incidence of graft failure in this patient population.

METHODS AND ANALYSIS

Study centre

This study will be conducted in Townsville, Queensland (Latitude 19.2590° S). Townsville is a regional centre with a population of approximately 200 000²¹ with only two hospitals. One hospital is government funded with the other privately funded, and patients will be recruited from both sites. Members of the study team have conducted multiple randomised controlled trials (RCTs) on skin excisions in the North Queensland region.^{22–24}

Study design

This is a prospective RCT. The intervention group will have grafts secured with fibrin glue applied across the entire graft bed (figure 1). The normal treatment control group will have grafts secured peripherally only with sutures or staples. These methods apply in both public and private hospital settings. Data will be collected over a 24-month period. The study will be reported in accordance with the

Consolidated Standards of Reporting Trials statement. Clinical Trial Protocol V.5 dated 22 October 2019 and WHO Trial Registration Data Set provided in [table 1](#). We used the Standard Protocol Items: Recommendations for Interventional Trials checklist when writing our report.²⁵

Intervention

The fibrin glue being used in this study is already in clinical use under the brand name ARTISS. It consists of two syringes, each containing human plasma derived coagulation factors which when mixed, initiate coagulation and form a clot. It has had Australian Therapeutic Goods Administration approval since 2010. This study specifically examines the effect of intraoperative application of a thin layer of fibrin glue across the entire graft bed immediately prior to the skin graft placement. This is diagrammatically represented in [figure 1](#).

Recruitment of study participants

Patients will be recruited in the process of booking for surgery. Potential patients will be identified in two places: at surgical clinics and during the booking process for surgery. Clinicians will discuss study participation with patients who are undergoing skin grafts for skin cancer. If the patient declines, then no further action is required. If the patient accepts, clinicians will check that they fit the inclusion criteria and provide an information sheet and consent form (online supplemental appendix 1). Informed consent will be discussed by the recruiting clinician.

Randomisation

Randomisation will be performed at the level of the patient with an allocation ratio of 1:1. A computer generated random number table will create random numbers in blocks of two or four and block size will be randomised. The patient allocation will be provided in sequential, opaque, sealed, tamperproof envelopes. Patients and clinicians will only be aware of the treatment allocation after the patient has been recruited into the trial. Blinding of the patient and the treating clinician to the intervention will not be possible, however, an independent outcome assessor will be blinded to treatment allocation.

Inclusion criteria

All patients presenting to surgical clinics requiring skin grafting will be potential participants. They will be assessed to see if they meet the following inclusion criteria:

1. Will be undergoing surgery at one of the trial centres.
2. Have any histological type of skin cancer.
3. Age ≥ 18 years.

Exclusion criteria

The exclusion criteria for this study are:

1. Adverse reaction to the product.
2. Hypersensitivity to bovine protein.
3. Skin grafts on digits or genitalia.
4. Pregnancy.
5. Not cognitively intact to consent to participation.

Table 1 WHO trial registration data set

Primary registry and trial identifying number	Australian New Zealand Clinical Trials Registry ACTRN12618000484246
Date of registration in primary registry	04 April 2018
Secondary identifying numbers	Nil
Source(s) of monetary or material support	Townsville University Hospital grant
Primary sponsor	Townsville University Hospital grant
Secondary sponsor(s)	Nil
Contact for public queries	EP, MBBS, MPH (ekta.paw@my.jcu.edu.au)
Contact for scientific queries	EP, MBBS, MPH (ekta.paw@my.jcu.edu.au)
Public title	Determining the efficacy of Fibrin Glue in Skin grafts for Skin cancer (FIGSS): open randomised clinical trial
Scientific title	Determining the efficacy of Fibrin Glue in Skin grafts for Skin cancer (FIGSS): open randomised clinical trial
Countries of recruitment	Australia
Health condition(s) or problem(s) studied	Skin cancer, skin graft failure.
Intervention(s)	Active comparator: topical fibrin glue. Placebo comparator: suture or staple fixation.
Key inclusion and exclusion criteria	Ages eligible for study: ≥ 18 years. Sexes eligible for study: both. Accepts healthy volunteers: no. Inclusion criteria: 1. Will be undergoing surgery at one of the trial centres. 2. Have any histological type of skin cancer. Exclusion criteria: 1. Adverse reaction to the product (fibrin glue). 2. Hypersensitivity to bovine protein. 3. Skin grafts on digits or genitalia. 4. Pregnancy. 5. Not cognitively intact to consent to participation. 6. Known immunodeficiency (HIV, leukaemia, etc), or haemolytic anaemia. 7. Skin conditions or medications affecting skin thickness and quality (eg, prolonged corticosteroid use, autoimmune conditions of skin). 8. Chronic malnourishment.
Study type	Interventional Allocation: randomised intervention model. Masking: open with blinded outcome assessors. Primary purpose: treatment. Phase IV
Date of first enrolment	April 2018
Target sample size	334
Recruitment status	Recruiting
Primary outcome(s)	Graft take based on wound healing at 1 month.

Continued

Table 1 Continued

Primary registry and trial identifying number	Australian New Zealand Clinical Trials Registry ACTRN12618000484246
Key secondary outcomes	Pain on dressing changes and operative time.

6. Known immunodeficiency (HIV, leukaemia, etc), or haemolytic anaemia.
7. Skin conditions or medications affecting skin thickness and quality (eg, prolonged corticosteroid use, autoimmune conditions of skin).
8. Chronic malnourishment.

Surgical and wound protocol

The surgical and wound management protocol is to standardise management across the study arms. This is modelled on similar protocols and in consultation with participating clinicians.^{10 26} Intraoperative application of fibrin glue includes standardised technique and timing. Dressings have been standardised at all wound sites to include a paraffin-based gauze dressing directly on the wound site, followed by foam dressing and an adhesive, non-woven fabric. Patients received standard postoperative and wound care instructions, and all had two follow-up appointments at the specialist clinic at 1 week and 1 month.

Outcome measures

The primary outcome of graft take will be measured based on review at 1 month postoperatively, including photographic data and clinical reports of wound healing and graft take. Graft healing at 1 week will also be examined as a secondary outcome measure. Additional secondary outcomes will include reported pain post dressing change scores and operative time. Subgroup analysis of patients who have vascular risk factors (including smoking, hypertension, diabetes, hypercholesterolaemia) or vascular disease (myocardial infarction, stroke or other vascular disease) will be performed.

Outcome assessors at the time of clinical assessment include surgical medical practitioners or nursing staff with specific wound management skills. Although outcome assessors are not advised of allocations, due to the nature of sutures or staples being present in the wound at some points of assessment, allocation may be evident to the initial outcome assessors. To mitigate this bias, independent blinded outcome assessors will be shown photographs to estimate graft take. Both assessments will be compared in the analysis.

Secondary outcome measures include pain on dressing changes, operative time and adverse events.

Definitions

Graft take is defined as wound healing over grafted areas within the period of weeks after the skin graft procedure, rather than healing via secondary intention and granulation tissue in a prolonged period. This will be assessed

both clinically and photographically to reduce inter observer variability.

Pain on dressing change is a patient-reported outcome where patients will indicate pain on a 10-point scale with the assistance of the Wong-Baker pain FACES chart. Operative time is defined as the time from first incision of the lesion until final dressing placement over the wound.

Data collection

Patient characteristics

When patients are recruited to the study, they will fill out a simple questionnaire with their gender, age and a targeted medical history.

Operative data

Operative time will be recorded for all procedures, as well as graft site and size.

Postoperative data

At 1-week follow-up, blinded assessors will assess graft take or rejection and photos will be taken for independent validation. Patients will be asked to rate their post procedure and dressing change pain on a pain scale.

At 1-month follow-up, blinded assessors will assess graft take or rejection and photos will be taken for independent validation.

Surgical site infections and incidence of postoperative haematoma and seroma will be noted at any time postoperatively, as will any other relevant outcomes or management (eg, unexpected prolonged inpatient stay or use of hydrocortisone or silver nitrate to manage hypergranulation).

An adverse event would be an outcome not expected in the usual perioperative or postoperative course of the patient which is related to the use of fibrin glue. The analysis from the Therapeutic Goods Administration in 2010 determined that none of the adverse effects noted in the trial were due to the fibrin glue and there were no significant safety issues. A literature search of MEDLINE and Embase looking for papers with the terms 'tissue adhesive' and related terms with 'adverse effect' and related terms found a total of 589 papers. Out of all these papers, only four cases of hypersensitivity were noted, with two cases of anaphylaxis.²⁷ Three cases noted adverse events resulting from incorrect application of glue (air embolus, subcutaneous emphysema and incidental adhesion to surrounding structures).^{28–30} Patients with a hypersensitivity to bovine protein will be excluded from the trial as a precaution. Additionally, all surgeons administering the glue have experience and knowledge in the proper application. If any adverse events were to occur, then they would be discussed with the chair of the steering committee who would determine if an extra meeting of the committee would be required and notify the data safety monitoring committee and the human research and ethics committee. A logbook of adverse effects would also be kept, including those which are not related to fibrin glue.

For data safety management, patient data will be collected in a de-identified format, with a potential for re-identification for situations of adverse events. The re-identification code will be password protected, as will the data collected and will only be able to be accessed by the principal investigator and co-investigators.

Due to the size of the trial a trial management group consisting of both clinicians and researchers was established. One independent person was deemed to be sufficient as an independent data monitor who has no affiliation with the management group. The positive stopping rule for the trial management group for each interim analysis is 25% recruited ($p < 0.0000001$); 50% recruited ($p < 0.000001$); 75% recruited ($p < 0.00001$). If patients with fibrin glue show a worse rate of graft take, the negative stopping rule is $p < 0.05$.

Sample size calculation

A two-tailed analysis assuming a power of 0.80 and alpha of 0.05 gave 334 patients in total with 167 in each group.³¹ It would likely take approximately 1–2 years to recruit enough patients for this study. Sample size was determined by power testing with similar papers, one of which compared approximately 300 cases of split skin graft.¹⁰ In this paper, on day 28 approximately 68% of the participants had 100% take of skin graft in the group using sutures or staples rather than fibrin glue and a 10% difference was considered significant. An estimate of graft take in the general population patients would be drawn from was roughly estimated as 50% and a clinically significant difference was determined to be 15% for this study.

Data analysis

Graft take will be compared based on review at 1 week and 1 month postoperatively, including photographic data and reported wound healing and graft take. Groups will be compared using a two-proportion z-test. A subgroup analysis on the impact of vascular risk factors will be performed, as well as on haematoma and seroma formation, although the study is not powered for this analysis.

Data will be analysed using statistical software Stata/SE V.16.³² Demographic data will be presented as percentages. Continuous variables will be tested for normality and based on the outcome of the test, parametric or non-parametric analyses of the data will be undertaken. Z-test analysis to compare two proportions will be used for analysis of graft take. A p value of < 0.05 will be considered statistically significant. The data may also be used in aggregate to conduct a cost-effectiveness analysis.

Potential problems

Based on the number of patients seen in both hospitals presently for skin cancer excisions, we believe that recruitment of adequate numbers is feasible. However, if we fail to recruit enough patients, other North Queensland hospital sites may be approached and invited to participate.

Patients currently attend for wound redressing appointments initially at the hospital where their operation is performed. After these initial reviews if further dressings are required and the patient has a significant travel time then community dressings may be organised. Given that most patients already receive their wound care within the hospital they will have their postoperative outcomes assessed at these appointments.

Patient and public involvement

Patient and public representatives were present on the Ethics Committee reviewing the design and research. Results from this trial will be reported publicly.

ETHICS AND DISSEMINATION

Ethical considerations

We do not expect the intervention in this study to place participants at any significant risk of harm, as current evidence demonstrates at least equivalent outcomes for the fibrin glue intervention.¹¹ Protocol amendments will be communicated to all relevant parties electronically.

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. Electronic copies of any forms will be kept on encrypted hard drives and patients will be de-identified in all data collection.

This project has been reviewed and approved by the Townsville University Hospital Human Research Ethics Committee (HREC). HREC Reference number: HREC/17/QTHS/196.

Dissemination

Once adequate data collection has been attained, dissemination of findings will occur via conference presentations and scientific journals. The researchers will also aim to present their findings at clinical meetings in the North Queensland area where there is a potential impact on surgical practice patterns.

DISCUSSION

The purpose of this trial is the evaluation of a new surgical technology in an alternative patient population to previous research in this area. North Queensland has the highest rate of skin cancer in the world and an ageing population which is susceptible to chronic disease and poor healing. In a systematic review of the literature, only two studies (with a total number of 54) out of 15 RCTs (with a cumulative number of 594) included patients with skin cancer at all.¹¹ This is clearly an area where further work is required, and it is particularly relevant to the population in regional North Queensland. In epidemiological research tracking back several decades, Queensland, and in particular North Queensland where Townsville is situated, has been noted as the region with

the highest incidence of skin cancer in the world.^{33–36} The most recent of these studies notes a strong predilection towards elderly men and echoes the finding that these high rates of skin cancer likely relate to phenotypic predisposition (low Fitzpatrick skin type) and environmental exposures (ultraviolet radiation).³⁶ Age predisposes to increased vascular disease or diabetes which impairs wound healing.^{37,38} As well as increased incidence of skin cancer, wound healing may be affected by the tropical climate in Townsville where mean maximum daily temperature ranges from 25.2°C to 31.6°C and mean relative humidity between 50% and 70% throughout the year.³⁹ These weather patterns have been theorised to increase risk of infection due to humidity causing damp dressings which are an ideal environment for bacterial ingress and the authors' clinical experience supports this.⁴⁰ This is a unique population in a unique setting of a humid tropical climate which likely contributes to higher infection rates and graft failure.

Therefore, this is a phase four clinical trial with a focus on pragmatic outcomes and to achieve this has a simple design. A pragmatic trial design is most appropriate to evaluate the broad applicability of this intervention. Controlling all patient factors would also limit the ability of this trial to answer the question of whether fibrin glue is superior in patients who do not have optimal wound healing. There are a few potential issues with the trial design, a major one being blinding of the surgeons using the fibrin glue, which is an issue evident in the use of any new interoperative surgical technology. Similarly, there is an issue with the blinding of patients once they can see their wound during dressing changes. Therefore, we have implemented the use of blinded outcome assessors via photographs taken after removal of suture or staple affixation. There is also a possibility of a difference between the two comparators: staples and sutures. However, recent literature suggests equivalence between sutures and staples for all outcome measures except for postoperative pain, where we plan to analyse sutures and staples separately.⁴¹ We expect that this trial, like many, may have issues in recruitment but the patient pool is quite large and hopefully reasonable endpoints can be made. The use of sealed opaque envelopes and a specific order for allocation will also reduce allocation bias.

One issue which has been noted in other trials is the heterogeneity of chosen endpoints. Selection of specific endpoints for reporting in the literature is a potential issue, as is usage of different methods to measure endpoints. This may reflect differences in opinion as to which outcomes are important to measure but makes pooled data comparisons difficult. For this study we have chosen several outcomes which reflect several areas including clinical measures; patient-reported measures; and hospital system measures. We hope that this adequately captures the many levels of decision-making involved in choosing to use new surgical technology.

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Contributors EP conceived of the study idea and developed the protocol and study design. WV, CH and MZ contributed to the development of the study design and protocol with WV also assisting with sample size calculation and statistics. All authors contributed to the drafting of the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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