

Fibrin Glue in Skin grafts for Skin cancer (FiGSS): Open randomised clinical trial



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I. Summary, significance and innovation

Skin cancer is incredibly common in North Queensland. Many people require large sections of skin removed to treat their cancer, and subsequent skin grafts to close their wounds. Instead of affixing these grafts with sutures or staples, a novel technique is to use fibrin glue, which is derived from clotting factors. By adhering to the entire surface of the graft, it is thought that Fibrin glue may improve graft take. It may have an important effect in patients for whom graft take is quite low, such as those with vascular disease, smokers, or the elderly.

II. Introduction

Fibrin glue was initially used for haemostatic purposes (to stop bleeding intraoperatively), because when it is introduced to a wound with Thrombin, Factor XIII and Calcium it mimics the final events in the clotting cascade, turning fibrinogen into fibrin [1-3]. Originally spun from plasma intraoperatively, commercial preparations are now available which produce high concentrations of fibrin and can be used as an adhesive [4, 5]. Fibrin glue has been investigated for use in skin grafts relating to burns and shown no inferiority to staples/sutures in terms of wound closure [6]. Specifically, fibrin glue adheres the entire surface of the graft (figure 1) to the site and significantly reduces the formation of haematoma or seroma immediately post-op which commonly results in graft failure [7]. Studies have also shown less of a requirement for dressings to ensure close adherence of the graft, better haemostasis and less contraction of scar tissue for various uses of skin grafts [8-10]. Skin graft survival is dependent on vascularisation of the graft which usually begins after a 2-3 day period. During this initial period poor adherence or hematoma/seroma formation can disrupt further vascularisation and lead to graft failure. Formation of a hematoma/seroma is the most common cause for graft failure but issues with the graft recipient site such as poor vascularity, infection and inflammation can lead to graft failure [7]. Grafts over mobile sites (such as joints) can break down due to shearing forces. Also after the graft heals, the site can contract leading to aesthetic defects or functional defects where range of motion is reduced [4].

In Australia, and particularly Far North Queensland, skin cancers are a common phenomenon and many patients have cancers which are sizeable enough to require grafting after resection for adequate wound closure [11]. Many of these patients are elderly and may have diseases which impair wound healing. 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 [12-16]. 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 [17]. If it can be shown to be beneficial in skin cancer patients (particularly the elderly and vasculopathic) and significantly decrease operative time and required operative follow up (i.e. for suture/staple removal) it may become a viable alternative to sutures. This could potentially change the management of skin grafts to become quicker, easier, less painful for patients and require less follow up.

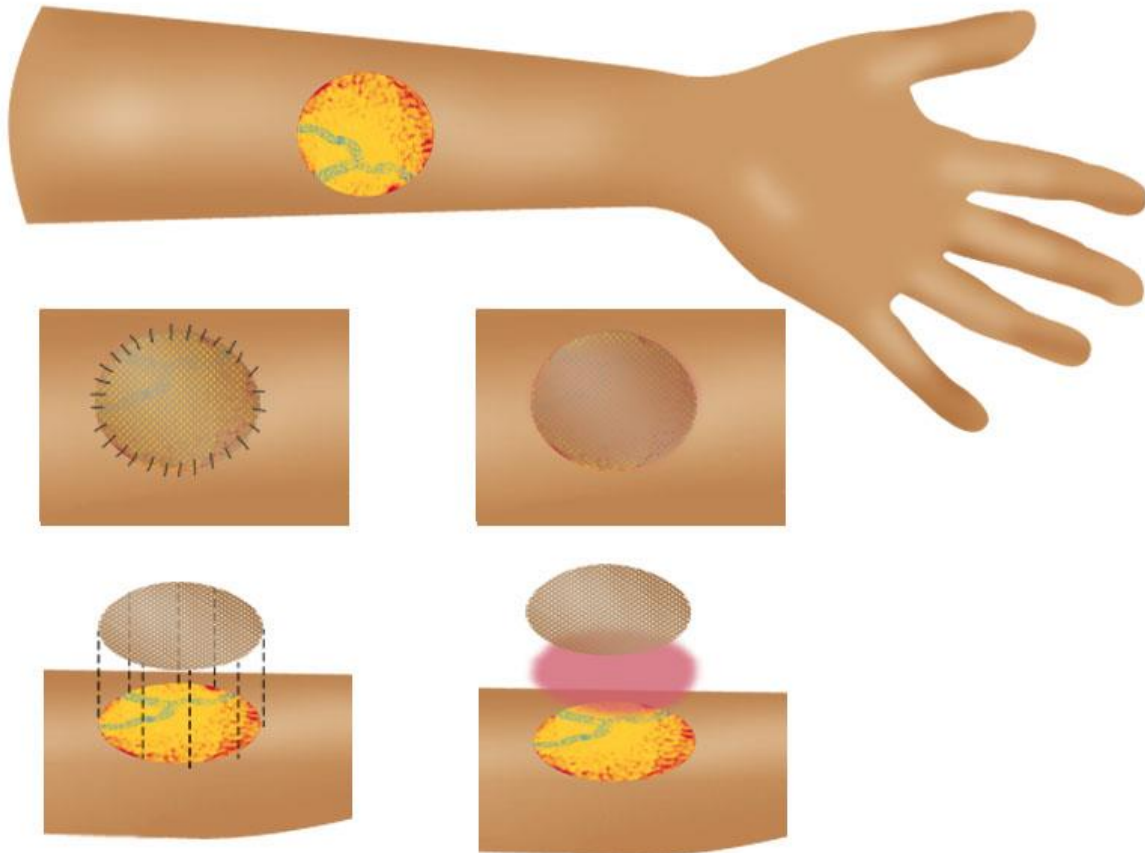


Figure 1: Depicted on the left are sutures or staples which affix the graft only at the edges, whereas on the right the fibrin glue is applied to the entire graft surface.

III. Study rationale

There have been no clinical trials looking at the use of fibrin glue for skin grafts in skin cancer to date. There have been few trials of reasonable size looking at the use of fibrin glue in skin grafts for burns. 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. This research seeks to provide a better evidence base to justify its use in clinical practice.

IV. Study Objective / Aim

The objective of this study is to compare the use of fibrin glue with sutures or staples for affixing skin grafts.

A. Primary research questions

a) Will use of fibrin glue increase graft take?

B. Secondary research questions

- a) Will use of fibrin glue increase graft take in patients with vascular disease?
- b) Will use of fibrin glue decrease pain in patients with skin grafts?
- c) Will use of fibrin glue decrease operative time?

V. Patients and Methods

A. Study design

Randomized controlled clinical trial (RCT) using two unmatched groups. One group will have grafts secured with sutures or staples and one group will have grafts secured with fibrin glue (figure 2). These methods apply in both public and private hospital settings.

B. Study outline / logistics

1. Screening and inclusion of patients

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. At surgical clinics patients who are undergoing skin grafts for skin cancer will be asked by their assessing clinician if they could be assessed for suitability by the inclusion criteria. If the patient declines then no further action is required. If the patient accepts, clinicians will check that they fit the inclusion criteria and give the patient an information sheet on the study, along with a consent form.

2. Data collection

If patients consent to inclusion in the study they will complete a questionnaire prior to booking for surgery to assess their medical conditions and risk/presence of vascular disease. After their surgery, usual follow up will occur with collection of information relating to graft take, post-operative healing and any complications.

C. Study population

1. Sample size calculations

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 [18]. It would likely take approximately one to two 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 [6]. In this paper at day 28 approximately 68% of 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.

2. 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:

- a) Will be undergoing surgery at one of the trial centres
- b) Have any histological type of skin cancer
- c) Age \geq 18 years

3. Exclusion criteria

The exclusion criteria for this study are:

- a) Adverse reaction to the product
- b) Hypersensitivity to bovine protein
- c) Skin grafts on digits or genitalia
- d) Pregnancy
- e) Not cognitively intact to consent to participation
- f) Known immunodeficiency (HIV, Leukemia, etc), or haemolytic anaemia
- g) Chronic malnourishment

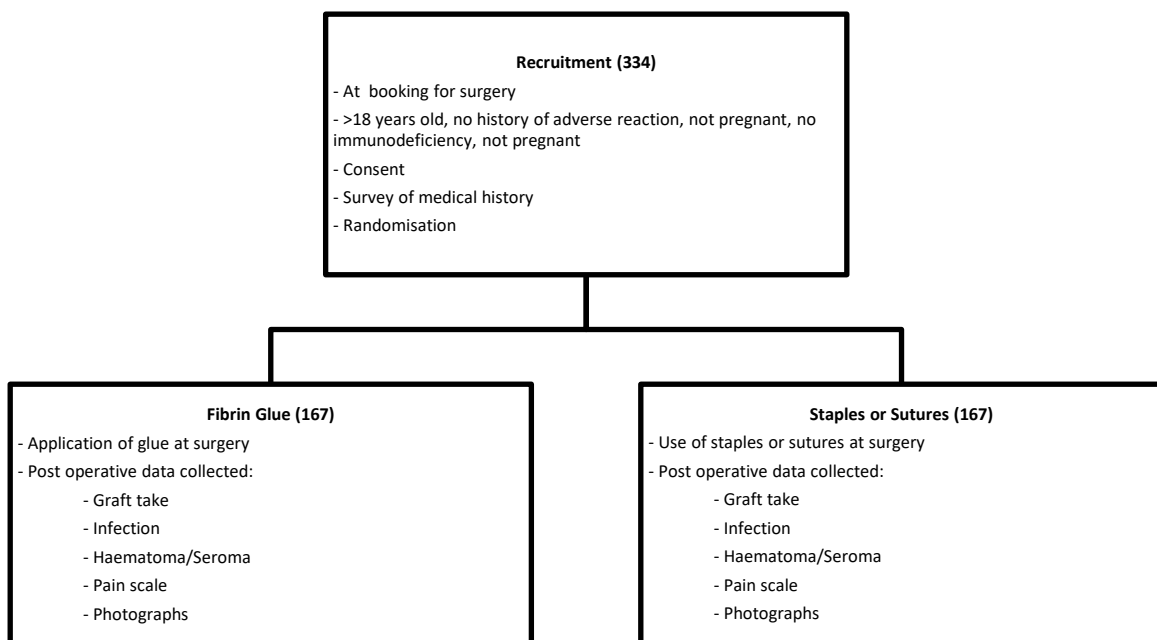


Figure 2: Flowchart of trial process.

4. Summary of Patient Characteristics

We expect patients to be within the 18-99+ age group, with a slight predilection towards older male patients according to studies showing that the most common forms of skin cancer (non melanoma) are more common in the elderly and slightly more common in males [19]. The Australian Cancer Council notes that two in three Australians will be diagnosed with skin cancer by the age of 70 [20].

D. Study product

1. Study product

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 together start the coagulation process and form a clot. It has had TGA approval since 2010.

2. Randomisation procedure

A sequence of 350 random numbers will be created. The outcome is transferred to a hardcopy with two columns. The left column indicates sequential order (1-350) and the right column contains the random number. The random numbers will be allocated in blocks to ensure equal numbers in each arm of the trial, and the block size will be randomised. The random numbers will be transformed to the letter F (for fibrin glue) or S (for staples/sutures) and thus creating a third column on the hardcopy. This hardcopy is labelled "randomisation code – version A". A copy of this code will be kept in the event of an adverse event.

350 opaque envelopes are sequentially numbered 1-350. They will be filled with an allocation of fibrin glue or staples/sutures according to the sequence of random numbers and then sealed.

3. Blinding procedure

Due to the nature of the product this will not be a blinded study as it is impossible to blind surgeons to the product they are using, and also it is obvious to patients as to whether they have had sutures/staples or glue.

E. Data collection

1. 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 to assess vascular risk factors.

2. Operative Data

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

3. Post-operative Data

At one week follow up, patients will be asked to rate their post procedure and dressing change pain on a pain scale. Incidence of post-operative haematoma and seroma will be noted.

At one month follow up, blinded assessors will assess graft take or rejection and photos will be taken for independent validation. Surgical site infections will be noted at any time post operatively.

F. Safety Management

1. Clinical Safety Assessments

There will be a steering committee who will regularly monitor differences in outcome between the two groups and monitor any adverse effects. The trial may be stopped if there is a significant difference in outcome or if there are any adverse effects.

2. Adverse events

An adverse event would be an outcome not expected in the usual peri-operative or post-operative course of the patient which are 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 as a result of 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 589 papers. Out of all of these papers, only four cases of hypersensitivity were noted, with two cases of anaphylaxis [21]. Three cases noted adverse events as a result of incorrect application of glue (air embolus, subcutaneous emphysema and incidental adhesion to surrounding structures) [22-24]. Patients with a hypersensitivity to bovine protein will be excluded from the trial as a precaution. Also 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 IDMC and HREC. A logbook of adverse effects would also be kept, including those which are not related to fibrin glue.

3. Exclusion and withdrawal from treatment

The following patient categories are to be excluded and withdrawn:

- Patients with any known previous adverse reaction to the fibrin glue
- Any other adverse events which would be evaluated case by case

As any adverse events would occur during theatre or the time in recovery they would be managed at the time of occurrence, with patients advised to present to the emergency department if they were to have any delayed symptoms at home. Adverse effects will be analysed by intention to treat.

4. Discontinuation of the study

The study is to be discontinued in any of the following cases:

- The number and nature of adverse events compromises patient safety to the extent that it is justified to discontinue the trial
- If the use of fibrin glue significantly improves graft take and is clearly advantageous over sutures or staples. To influence clinical decision making this would need to have very strong evidence, therefore the positive stopping rule will only apply in the case of a very low p-value for the primary research question:
25% recruited ($p < 0.0000001$)

50% recruited ($p < 0.000001$)

75% recruited ($p < 0.000001$).

- If patients with fibrin glue show a worse rate of graft take, the negative stopping rule is $p < 0.05$.

A decision to discontinue the study can only be made by the steering committee with at least 50% of members participating. The chair of the steering committee (see below) can decide to temporarily pause the study in case it is difficult to arrange a meeting with the full steering committee. If this decision is made, all participants and the ethics committee must be contacted.

G. Statistical analysis

1. Graft Take

Graft take will be compared based on review at 1 month post operatively, including photographic data and reported wound healing and graft take. Groups will be compared using a two proportion z-test. A sub group 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 SPSS 22. 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.

Data will be stored on a secure excel spread-sheet available only to investigators and stored for 10 years following the completion of the study.

VI. Ethical requirements

A. Declaration of Helsinki

This study will be in accordance with the Declaration of Helsinki recommendations guiding research involving human subjects.

B. Ethical approval

Ethical approval will be sought from the appropriate ethics committees and they will be kept informed of any serious adverse events or amendments to the protocol. Informed consent

All patients will be asked for to sign a written consent form.

C. Research involving Aboriginal and Torres Strait Islander people

This project does not specifically target Aboriginal and Torres Strait Islander people, although they may be incidentally recruited into the study. All participants will be given information about the project to obtain informed consent prior to participation.

D. Patient data protection

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.

VII. Management and Monitoring

A. Trial Management Group

The trial management group consists of one General Surgical Principal House Officer (Ekta Paw), one General Surgeon (Mark Zonta), one senior research officer (Venkat Vangaveti) and two professors in general practice (Ronny Gunnarsson and Clare Heal). All members of the team have different areas of expertise, and the majority have experience in randomised controlled trials. This combination of research expertise, specific experience in surgical research and experience in surgical practice is an ideal combination to determine the efficacy of fibrin glue.

This group will deal with all of the practicalities involved with the study, including ethics, funding and planning.

B. Independent data-monitoring committee (IDM)

This study is not funded or supported by any drug company and is more about evaluation of a treatment which is already used in clinical practice. Given this and the size of the trial it was considered to be adequate to have one independent person for IDM who will be Dr Daniel Lindsay. Data will be assessed at 25%, 50% and 75% of data collection by a person who is free of apparent significant conflicts of interest.

C. Trial Steering Committee

The steering committee will determine if the study needs to be discontinued early or has issues with scientific quality. The committee will consist of the primary investigator as chair and supervisors as per the beginning of this document and be advised by the IDMC.

The committee will meet initially to approve the study protocol, and subsequently at 25%, 50% and 75% of data collection. Ideally decisions will be voted unanimously but in the event where there is no majority, the chairs vote will count for two votes. In the case of any adverse events, these will be reported to the IDMC ethics committee and the recommendations discussed and implemented by the steering committee.

VIII. Miscellaneous

A. Liability / Insurance

Townsville Hospital and Queensland Health has insurance for clinical trials run by the Hospital.

B. Reporting and communication of results

The outcome will be presented at scientific conferences, as well as in a peer reviewed scientific publication.

C. Clinical trials databases

Once ethics approval is obtained the study will be registered in the following databases:

- Australian New Zealand Clinical Trials Registry (ANZCTR)
- ClinicalTrials.gov
- Researchweb.org/is/jcu

IX. Study time frame

The study will commence as soon as ethics approval is given. Data collection will begin as soon as possible until 334 patients are recruited:

	2017			2018			2019	
	April - May	June - Oct.	Nov.- Dec.	Jan.- April	May- June	July- Dec.		
Planning & ethics approval								
Practical preparations								
Data collection								
Analysis & writing								
Submission (and author responses to reviewers comments)								

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