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Efficacy of Fibrin Glue in Skin Grafts for Skin Cancer (FiGSS): Open Randomised Clinical Trial

Ekta Paw, BSc, MBBS, BDS, MPH[1] · Rhys Jaa-Kwee, MBBS[1] · Mark Zonta, MBBS, FRACS[2] · Venkat Vangaveti, PhD[1] · Clare Heal, MBChB, FRACGP, MPH&TM, SM, PhD[1]

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Abstract

Background This study aimed to conduct the first randomized clinical trial on the use of fibrin glue in split-skin grafts for skin cancer. Fibrin glue is an accepted technique for affixing split-skin grafts. Evidence suggests that fibrin glue has greater effectiveness than sutures or staples, particularly in populations with more comorbidities.

Methods This randomized controlled clinical trial was conducted at a regional center in Queensland, Australia across the only two major hospitals in the area. The primary outcome assessed was graft take 1 month postoperatively. Pain with dressing changes and incidence of seroma, hematoma, and infection as well as operative time were assessed as secondary outcomes. Patients were recruited and randomized to either fibrin glue or staples and sutures for graft affixation. They were subsequently followed up at 1 week and 1 month for outcome assessment.

Results The study recruited 100 patients, and 83 patients with 133 grafts were analyzed for outcomes. Fibrin glue increased graft take by 17.13% when the study controlled for other variables. However, this was not statistically significant ($p = 0.058$; confidence interval [CI] −0.63 to 34.89). There was a statistically significant reduction in the odds of seroma (odds ratio [OR] 0.08; CI 0.01–0.50; $p < 0.01$) and infection (OR 0.04; CI 0.00–0.33; $p < 0.01$) at 1 week.

Conclusions Fibrin glue may be of benefit for patients at higher risk for graft failure and is likely to benefit patients at increased risk of seroma and infection.

Trial registration ANZCTR: ACTRN12618000484246.

Keywords Fibrin · Skin graft · Skin cancer · Randomised controlled trial · Split-skin graft

Fibrin glue has been used in many contexts intraoperatively. It was initially identified as a hemostatic agent that mimics the final events in the clotting cascade.[1–5] When first developed, fibrin glue was prepared from patient plasma before use, but currently, commercial preparations with bovine protein are available with higher concentrations of fibrin.[6,7]

Fibrin glue has been investigated as an adhesive in various surgical disciplines.[8–10] In split-skin-grafting, there is a suggestion that fibrin glue may improve graft take and other postoperative outcomes by adhering to the entire surface of the graft.[11–14] Traditional fixation methods typically secure grafts at the margins with or without individual sutures in the central graft. This tends to leave areas of incomplete contact between the graft and wound bed. Comparatively, fibrin glue provides uniform adhesion, which improves the imbibition of nutrients from the graft bed before vascularization.[13,15] This reduces the potential space for seroma formation and bacterial infection.[13,15]

Findings have shown that increased fibrin in wounds decreases the likelihood of graft failure and can induce angiogenesis.[16] Therefore, fibrin glue may benefit split-skin-graft healing via several mechanisms. Very few reports describe adverse events after fibrin glue. Two reports of potential hypersensitivity and two reports of emphysema relating to incorrect application have been identified in the literature.[17–19] Given its use across numerous surgical specialties, fibrin glue is likely both a safe and effective method to affix split-skin grafts.

Australia has high rates of skin cancer, with the state of Queensland as the skin cancer capital of the world.[20,21] Wide

✉ Ekta Paw, BSc, MBBS, BDS, MPH
ekta.paw@my.jcu.edu.au

[1] College of Medicine and Dentistry, James Cook University, Douglas, Townsville, QLD, Australia

[2] Department of Surgery, Townsville University Hospital, Douglas, QLD, Australia

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oncologic resection of skin cancers requires reconstruction, of which split skin grafting is a commonly used technique.[22]

The current literature about skin grafts and fibrin glue focuses on its use in patients with burns, which is typically a younger population.[23,24] Skin cancers are more common in the older adults, who have a higher incidence of comorbidities, which can affect wound healing.[20,25] Fibrin glue has been investigated in other high-risk grafts, such as infected sites, mobile skin areas, and difficult-to-graft areas, with good results.[11,26–29] Therefore, this technique may be of increased benefit for patients undergoing reconstruction with skin grafts after skin cancer resection. There is a paucity of prospective clinical trials examining the use of fibrin glue in skin grafts for skin cancer patients.[13,14] To date, no clinical trials have examined the use of fibrin glue in skin grafts for this population.[14]

In addition to improving healing, fibrin glue may reduce operative time and pain in dressing changes for patients with split-skin grafts.[30] Reduction in operative time may result from not needing to apply individual sutures or staples to a graft. Patients who require multiple dressing changes typically find it both inconvenient and painful, and an improvement in healing may reduce the number and duration of dressing changes.[31] Therefore the use of fibrin glue has the potential for skin grafts to become quicker and less painful for patients.

The objective of this study was to examine the effectiveness of fibrin glue as an adhesive for split-skin grafts after skin cancer excision, which is of importance for any surgeon performing split-skin grafts for this population.

Methods

Ethical approval for this study was granted by the Townsville Hospital Human Research Ethics Committee (approval HREC/17/QTHS/196). Representatives of the public and patients were present on the Ethics Committee reviewing the design and research. The full protocol for this trial has been published.[32] The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618000484246).

This study was conducted as a prospective randomized controlled superiority trial. The intervention group had fibrin glue applied to the graft bed intraoperatively as a thin even layer before graft-positioning. Dressings were applied with a standardized dressing protocol as pictorially represented in Fig. 1.[32]

The intervention used in this study was fibrin glue commercially available as two syringes containing human plasma-derived coagulation factors. The fibrin glue has had Australian Therapeutic Goods Administration approval since 2010.[33] The treatment control group had grafts secured peripherally with sutures or staples and was recruited in parallel with the treatment group. The trial was conducted within the outpatient and surgical department of two sites (one public and one private hospital) in Townsville, Queensland, Australia.

All patients presenting to surgical clinics who required split-skin grafts were considered potential participants. The eligibility criteria specified patients who underwent surgery at one of the trial centers, had any histologic type of skin cancer, and were at least 18 years of age. Patients were

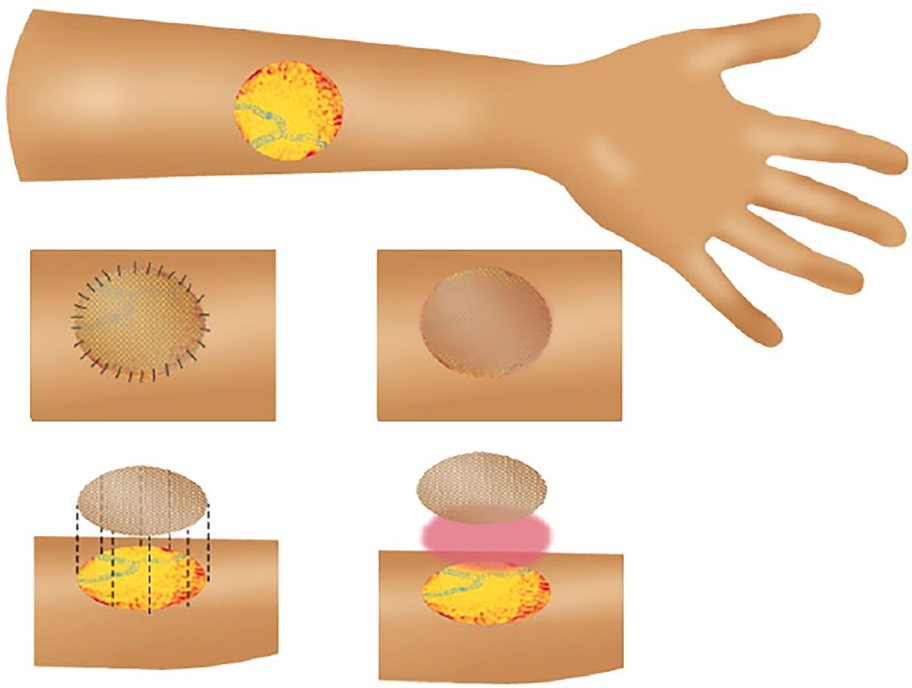

Fig. 1 Affixation of skin graft with sutures (*left*)) and fibrin glue (*right*)

excluded if they had an adverse reaction to fibrin glue in the past, had a hypersensitivity to the product, had skin grafts on digits or genitalia, or were pregnant.

The primary outcome measured was graft take 1 month after surgery as a percentage of each graft. This was assessed by the treating clinician and by an independent assessor via photographs. The secondary outcomes measured were operative time and pain at dressing changes (reported using Wong-Baker pain faces from 1 to 10 as integers), presence of infection, presence of hematoma, presence of seroma at 1 week and 4 weeks, and graft take at 1 week. Adverse effects were assessed intraoperatively at the time of fibrin glue administration and during follow-up appointments at 1 week and 1 month.

Sample size calculation was performed with a two-tailed analysis assuming a power of 0.80, an alpha of 0.05, and a clinically significant difference for the primary outcome of 15%.[32] A sample size of approximately 300 was determined. Positive and negative stopping rules were in place for interim analyses.[32]

Randomization was performed at the patient level by the primary investigator with randomized blocks of two or four. Patient allocation was provided by sequential, opaque, sealed, tamper-proof envelopes by clinicians who could not access the full randomization sequence. Post-randomization blinding of clinicians and patients was impossible, so an independent outcome assessment was introduced.

Statistical Analysis

Statistical analysis was completed in STATA 16.[34] Demographic data were analyzed, and differences between treatment and intervention groups were analyzed using Fisher's exact test for non-parametric data, chi-square for parametric data, and Mann-Whitney *U* for continuous non-parametric data. Multivariable regression analysis was used for outcome variables to control for differences between the treatment and intervention groups. Models were determined using forward selection and tests for covariance with variance inflation factor testing to determine collinear variables. Continuous outcome variables used linear regression with data transformations as appropriate. Binary or ordinal logistic regression was used for ordinal and binary variables such as pain (scored 1–10) and seroma. Goodness of fit and normality of residuals was checked for each model. Less than 10 % of data was missing for the primary outcome of interest and all secondary outcomes except pain at 1 month, for which 20 % of data was missing. Therefore imputation of missing values was not used. All secondary outcomes were pre-specified in the trial protocol.[32]

Results

Enrolment for the trial was open from June 2018 to November 2022, with final data collection in December 2022. During this time, 191 patients were assessed for eligibility, and 100 were randomized as specified in Fig. 2. Ultimately, 37 patients in the intervention arm and 46 patients in control arm were assessed for primary outcome. All patients analyzed received the intervention as per the randomization, so separate intention-to-treat and per protocol analyses were not required. Some of these patients had multiple grafts, and data were recorded for each graft site.

For the primary outcome measure, 133 grafts (70 in the intervention group and 63 in the control group) were analyzed. As per previous research with multiple wound sites in one patient, adjustment for clustering was not used because it was previously noted to have negligible effects on overall results.[35] Analyzing per patient would have introduced aggregation issues. In discussion with the trial steering committee, recruitment was ceased early because of inability to achieve sufficient numbers. The COVID-19 pandemic led to significant restrictions on surgical services globally and in Queensland, and participant interest was lower than anticipated, potentially due increased hesitancy about participation in clinical research.

Intervention delivery was ensured by the operating surgeon and delivered as intended. One minor adverse event of slight graft-shearing immediately after surgery due to a patient accidentally removing dressings was reported. This was determined not to be related to the intervention.

Demographic Data

Demographic data are summarized in Table 1, demonstrating no significant differences between the groups. Grafts all were ovoid in shape, so graft area was estimated by using documented width and length, and the area of an ellipse was calculated in cm^2. Similarly, pack years were calculated using collected data on number of cigarettes smoked per day and years of smoking. Examples of other skin pathology include malignant eccrine tumor or atypical fibroxanthoma.

Outcomes Analysis

Inter-rater reliability was assessed between clinically assessed graft takes by assessors who were not blinded and the independent outcome assessor who was blinded. Cohen's kappa was 0.27 for week 4 graft take and 0.20 for week 1 graft take. Therefore, independent outcome assessments

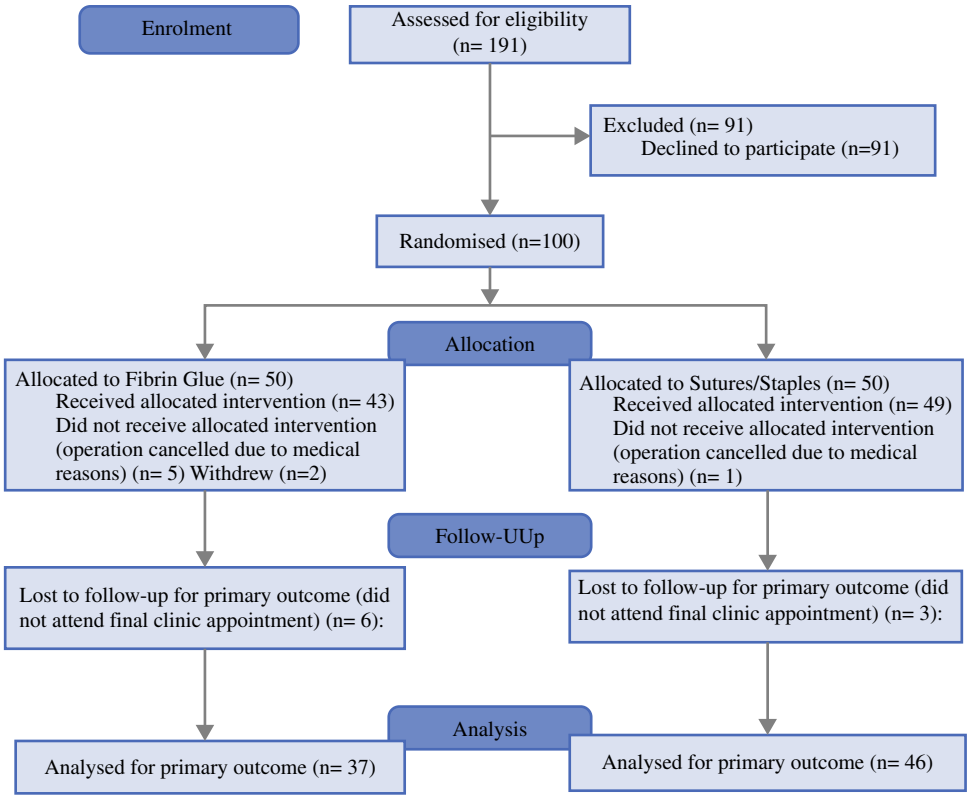

Fig. 2 CONSORT 2025 flow diagram

were used for the outcome analysis. Table 2 outlines direct comparisons between intervention groups without control for other confounders, which may have affected outcome. Table 3 outlines the results of multivariable regression analysis for the primary outcome of graft take at 4 weeks. All planned secondary outcome measures were analyzed except for hematoma and seroma at 1 month because there were fewer than five events limiting the ability to perform logistic regression. Fisher's exact test was performed to determine whether there were any differences in additional treatment (oral antibiotics, drainage of seroma, or admission for intravenous antibiotics) between the two groups, and there were no significant differences at 1 week ($p = 0.61$) or 1 month ($p = 0.21$). Table 3 notes the results of multivariable analysis for secondary outcome measures and any variables with a statistically significant impact on the outcome of interest.

The intervention of fibrin glue was found to increase graft take by 17.13 % when the analysis controlled for other variables. However this result was not statistically significant (CI − 0.63 to 34.89; $p = 0.058$). At 1 week, the fibrin glue group did see a statistically significant reduction in the odds of seroma (OR 0.08; CI 0.01–0.50; $p < 0.01$) and infection (OR 0.04; CI 0.00–0.33; $p < 0.01$). Multivariable analysis for secondary outcomes is summarized in Table 4. Type 2 diabetes; smoking; presence of vascular disease, and graft size all were significant confounders of measured outcomes.

Discussion

The primary endpoint of graft take at 1 month did not reach a statistically significant threshold, but the data do suggest that after control for other comorbidities affecting graft take, there may be a clinically significant difference in graft take for patients in this population. Other studies examining fibrin glue have focused on burn populations, which generally are younger and have fewer comorbidities, and whereas fibrin glue has been noted as non-inferior, there may be a role for patients in this study population, for which the risk of graft failure is higher.[30,36–39] The secondary outcome measures showed a reduction in the odds of seroma and infection at 1 week, which was statistically significant, and a clinically significant reduction in the odds. This again suggests a role for fibrin glue in patients at higher risk of seroma or infection, an idea supported by the current literature.[40] Graft take at 1 week appeared to be reduced by application of fibrin glue, but this was neither a statistically nor a clinically significant change in the coefficient.

It was noted there were no significant demographic differences between the two intervention groups. The increased age of the study population compared with other studies on split-skin grafts is reflective of the population treated in regional Australia and the focus on skin cancer rather

Table 1 Baseline data analysis

Demographic	Fibrin glue Intervention group ($n = 37$) n (%)	Sutures/staples Intervention group ($n = 46$) n (%)	p Value[a]
Age (years)	72.96 ± 11.56	74.56 ± 10.54	0.61
Sex	75	0.64	0.28
Male	25	0.36	
Female			
Comorbidities	60	76	0.13
Hypertension	2	0	0.49
Type 1 diabetes	25	16	0.32
Type 2 diabetes	38	52	0.16
Hypercholesterolemia	15	32	0.06
Ischaemic heart disease	4	6	1.00
Cerebrovascular disease	8	18	0.23
Peripheral vascular disease			
Smoking status	40	52	0.38
Non-smoker	12	14	0.29
Current smoker	48	34	
Ex-smoker	21.60 ± 16.66	32.04 ± 27.88	
Pack years			
Graft characteristic	Fibrin glue Intervention group ($n = 70$) n (%)	Sutures/staples Intervention group ($n = 63$) n (%)	p value[a]
Graft area (cm^2)	16.5 ± 12.8	19.8 ± 16.4	0.30
Histopathology	51	50	0.17
SCC	31	24	
BCC	12	24	
Melanoma	5	1	
Other			
Graft site	7	22	0.08
Upper limb	68	59	
Lower limb	23	19	
Head	2	0	
Torso			

SCC, squamous cell carcinoma; BCC, basal cell carcinoma

[a]Mann-Whitney U for continuous variables; Fisher's exact test for categorical outcomes. Shapiro-Wilk and visual q-q plots used to test for normality

than burns (a commonly studied population in the split-skin grafting literature).[20,24,41,42] The significant proportions of patients who had comorbidities also reflected the increased age of this study population. These comorbidities can significantly alter the postoperative course and must be accounted for in any wound-healing analysis.[43–45]

The results also indicate some other factors that significantly altered skin-grafting outcomes. The presence of hypertension appeared to increase graft take at 4 weeks, although this was when the analysis controlled for other vascular diseases, thus indicating patients for whom the sequelae of hypertension were not present. Therefore, this likely indicates an erroneous association. Grafts of the head had significantly increased take at 1 week, likely due to the increased collateral vasculature of the head and neck.[46] Type 2 diabetes mellitus was shown to significantly decrease graft take at 1 week, significantly increase pain with dressing changes, and significantly increase the risk of infection. This is consistent with the current published literature on the microvascular complications of diabetes and their effects on wound-healing.[47] Smoking also appeared to increase pain significantly with dressing changes at week 4.

Several statistically significant effects on operative time were observed. However, the interpretation of the coefficient was that an increase in each independent variable corresponded to less than a 2-min difference in operative time. Therefore, it is unlikely that any of these would be of any clinical significance.

Table 2 All outcomes direct comparisons between intervention groups

Outcome (unit, *n*)	Fibrin glue (*n*)	Sutures/staples (*n*)	*p* Value[a]
Week 4 graft take (average %, 128)	75.10 ± 31.34 (67)	67.01 ± 33.52 (61)	0.03
Week 1 graft take (average %, 130)	82.94 ± 23.28 (68)	88.10 ± 11.24 (62)	0.63
Week 4 pain (average reported pain, 1–10, 109)	0.63 ± 1.53 (52)	1.70 ± 2.71 (57)	0.07
Week 1 pain (average reported pain 1–10, 116)	2.78 ± 2.77 (54)	3.24 ± 2.61 (62)	0.27
Week 4 hematoma (%, 131)	0 % (0)	0 % (0)	
Week 1 hematoma (%, 130)	0 % (0)	6 % (4)	0.07
Week 4 seroma (%, 131)	3 % (1)	2 % (2)	0.55
Week 1 seroma (%, 131)	10 % (6)	15 % (10)	0.27
Week 4 infection (%, 131)	10 % (6)	11 % (8)	0.45
Week 1 infection (%, 131)	17 % (11)	16 % (11)	0.51
Operative time (min, 129)	26.74 ± 19.18 (63)	28.79 ± 16.13 (66)	0.09

[a]Mann-Whitney *U* for continuous variables; Fisher's exact test for categorical outcomes

Table 3 Multivariable regression analysis of primary outcome (percentage graft take at 4 weeks)

Variable	Coefficient (change to % graft take)	*p* value	Confidence interval
Fibrin glue (intervention)	17.13	0.058	–0.63 to 34.89
Hypertension	16.42	0.03	1.40 to 31.45
Graft site	1 (Comparator)	0.14	– 44.94 to 6.23
Upper limb	– 19.35	0.88	– 27.37 to 31.97
Lower limb	2.30	0.61	– 45.00 to 76.34
Head	15.67		
Torso			
Cardiovascular disease	– 38.98	0.09	– 84.50 to 6.53
Smoking (pack years)	0.035	0.86	– 0.37 to 0.44
Type 2 diabetes mellitus	4.51	0.59	– 12.34 to 21.36
Ischemic heart disease	22.26	0.06	– 0.45 to 44.98

Study Limitations

This trial was limited by inability to recruit participants due to a decrease in ability to assess and treat surgical patients during the COVID-19 pandemic, an effect observed internationally.[48] Lack of interest in participation also may have been affected by the spread of misinformation, reducing trust in medical institutions generally.[49] Inability to reach the planned sample size for the population impacted the statistical significance of the primary outcome. It also was difficult to infer the effect of patients lost to follow-up evaluation on the outcomes. Due to the open nature of the trial, the primary outcome was assessed by independent assessment of photographs, but there may have been slight inaccuracy in assessing photographs versus clinically assessing the wound in person.

Conclusions

Fibrin glue may offer some advantages over sutures and staples for split-skin-graft affixation in patients at higher risk of seroma and infection at their graft site. This includes older and more comorbid patients. There may be an additional benefit for patients who may not be able to travel long distances for suture removal. There may be an increase in overall graft take, but this study did not find the effect to be statistically significant. This is relevant to patients undergoing skin-grafting for skin cancer resection, or potentially any patients who are older and have more comorbidities, increasing the risk of graft failure.

Future Directions

Clinical trials on the use of fibrin glue in skin-grafting still are sparse, particularly on the technique of reconstruction for skin cancer. More published data would be useful to pool for meta-analysis or a trial with increased power.

Table 4 Multivariable regression analysis of secondary outcomes

Outcome variables (*n*)	Coefficient/OR	*p* Value	Confidence interval
Week 1 graft take (130)	Coeff	0.61	−7.56 to 4.44
Fibrin glue (intervention)	−1.56	< 0.01	−0.75 to −0.15
Age (cm^2)	−0.45	0.01	2.90 to 24.08
Graft site–head	13.49	< 0.01	−25.98 to −10.90
Type 2 diabetes mellitus	−18.44		
Week 4 pain (109)	OR	0.09	0.14–1.17
Fibrin glue (intervention)	0.41	< 0.01	3.27–95.74
Smoker	17.68	0.04	1.07–21.87
Cerebrovascular disease	4.84	0.05	1.00–8.06
Type 2 diabetes mellitus	2.84		
Week 1 pain (116)	OR	0.11	0.24–1.15
Fibrin glue (intervention)	0.53	0.01	1.30–9.63
Type 2 diabetes mellitus	3.54	0.05	0.12–0.98
Peripheral vascular disease	0.34		
Week 1 seroma (130)	OR	**< 0.01**	**0.01–0.50**
Fibrin glue (intervention)	**0.08**	0.02	0.02–0.72
Hypertension	0.11		
Week 4 infection (131)	OR	0.99	0.17–6.07
Fibrin glue (intervention)	1.01	<0.01	0.75–0.96
Area (cm^2)	0.85		
Week 1 infection (131)	OR	**< 0.01**	**0.00–0.33**
Fibrin glue (intervention)	**0.04**	< 0.01	0.00–0.26
Sex–female	0.03	< 0.01	2.85–117.03
Type 2 diabetes mellitus	18.27		
Operative time (129)	Coeff	0.27	0.66–1.13
Fibrin glue (intervention)	0.86	0.05	1.00–1.02
Area (cm^2)	1.01	< 0.01	1.42–2.27
Type 2 diabetes mellitus	1.80	< 0.01	0.98–1.00
Smoking (pack years)	0.99	0.03	1.05–2.85
Cerebrovascular disease	1.73	0.04	1.02–2.07
Peripheral vascular disease	1.46		

Bold values indicate statistically significant change due to intervention.

OR odds ratio

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Data Availability De-identified participant data that underlie the results will be made available via James Cook University data repository.

Disclosure There are no conflicts of interest.

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