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Systematic review of fibrin glue in burn wound reconstruction

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Background: In the reconstruction of burns using split-skin grafts (SSGs), fibrin glue (FG) can be used to improve graft take and reduce haematoma formation, although the efficacy and cost-effectiveness is unknown. This systematic review evaluated outcomes of FG compared with conventional SSG attachment techniques. Outcomes of interest included SSG take, haematoma formation, patient satisfaction and cost-effectiveness.

Methods: This PROSPERO-registered review was performed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and PRISMA statement. Embase, PubMed, Cochrane and ClinicalTrial.gov databases were searched systematically. Observational and experimental studies comparing FG with other methods of SSG attachment in burn wounds were included. Risk of bias was assessed using the Cochrane risk-of-bias and Risk of Bias In Non-Randomized Studies – of Intervention tools. The quality of

the evidence was assessed using the GRADE tool.

Results: Two RCTs and four observational studies were included. Graft take at day 5 was not significantly different between groups (3 studies, 184 individuals). FG significantly reduced the risk of postoperative haematoma in two studies and reduced patient-reported pain in two studies, with suggested cost savings in four studies. All studies were at risk of methodological bias and the quality of the evidence was universally very low.

Conclusion: As the evidence is sparse, the quality very low and the risk of bias significant both within and across studies, it is not possible to make any recommendations regarding the use of FG in burn wounds. Better research is needed.

+A: Introduction

Burn injuries are common, and continue to pose a complex and expensive challenge for healthcare providers globally[1–3]. The surgical management of burns aims to facilitate timely wound healing, ideally within 2 weeks, in order to maximize function of the affected area and minimize pathological scarring[4]. Once the burned skin has been debrided (using a blade, hydrosurgery[5,6] or enzymatic debridement[7]) there may be insufficient healthy dermis remaining to achieve spontaneous wound healing within an appropriate timescale. In this situation, an autologous split-skin graft (SSG) may be used to reconstruct the wound bed. The SSG is harvested from an area of unburned skin, the thickness can be selected, and it is then either left as a sheet or meshed before being inset to the burn wound bed. Attaching the skin graft to the wound bed facilitates graft take, with particular emphasis on minimizing shear forces[8]. Skin grafts that do not adhere will undergo necrosis, necessitating either revision or healing by secondary intention, with additional morbidity and cost. In burns involving a large proportion of the body, measured by the percentage total body surface area (TBSA), it may

be challenging to find sufficient non-burned skin to harvest, emphasizing the goal of achieving a successful skin graft at the first attempt.

Conventionally, skin grafts are secured with either sutures, staples, tissue glue, dressings (tie-on, tie-over or negative pressure) or using a combination of these techniques. Fibrin glue (FG) or sealants were first introduced as haemostatic agents in 1909 and later in skin grafts during the Second World War[9]. They contain two key substances: fibrinogen and thrombin; these can be either autologous or synthetic[10]. The solution can be modified with additives such as growth factors, other blood products (for example platelets) or medications (such as antibiotics)[11]. Since approval by the Food and Drug Administration (FDA) in 1998[12], there have been significant advances in their application; there are now four FDA-approved fibrin sealants available for topical use[13]. FG has been used across surgical specialties, with several delivery systems available[13,14].

FG has been described widely for skin grafting, most extensively for SSG attachment following burn surgery[15–21]. Studies suggest a number of benefits, including improved graft take, reduced haematoma formation[18], improved donor-site haemostasis[22] and improved functional outcomes[23]. However, FGs are expensive and there is no clear evidence of their superiority over other techniques for securing SSGs. The aim of this review was to evaluate systematically the literature that compares FG with conventional methods of skin graft attachment in patients with burn wounds.

+A: Methods

This systematic review was performed in accordance with PRISMA guidelines[24] and the Cochrane Handbook for Systematic Reviews of Interventions[25]. The protocol was developed prospectively, peer-reviewed and registered in the PROSPERO database. (CRD42017082677)[26].

+B: Search strategy

The Cochrane Library, EMBASE, PubMed, ClinicalTrials.gov and PROSPERO databases were searched from inception until January 2018 (*Appendix S1*, supporting information). Only human studies were considered. Authors of trials registered in ClinicalTrials.gov were contacted if data had not been published. Titles and abstracts were screened independently by two authors. Full texts of potentially relevant articles were retrieved for consideration of inclusion. Reference lists of the included papers and previous reviews were screened for additional papers. Disagreements were resolved by a third author.

+B: Study selection

Included study types were randomized or quasi-randomized trials, observational studies, systematic reviews and meta-analyses. Case reports were excluded. There was no restriction on patient age. Studies were included if they directly compared FG with conventional methods of SSG attachment in burn wounds. Studies using within-participant randomization or variations were included. Studies were included if they reported one or more of the following outcomes: skin graft take, skin graft loss, postoperative infection, postoperative pain, return to the operating theatre, patient satisfaction, postoperative haematoma, postoperative wound breakdown and scar outcome.

+B: Data extraction

Data were extracted on to a predefined electronic data extraction form by one author, and checked separately by another author. The published data from included studies were scrutinized for reporting of outcomes. If relevant data were not available for extraction, the corresponding author was contacted by e-mail with a specific data request. If there was no reply, a reminder e-mail was sent after a week. If again no response was received, a further e-mail was sent. If there was still no response, the study was excluded and the authors notified.

+B: Outcomes

The primary outcome was skin graft take. Secondary outcomes included overall wound closure, graft loss, haematoma formation, pain, patient satisfaction, blood loss, cost-effectiveness, return to theatre and post-operative infection.

+B: Risk-of-bias assessment

The risk of bias for RCTs was assessed using the Cochrane risk-of-bias tool. The risk of bias for non-randomized studies was evaluated using the Risk Of Bias In Non-Randomized Studies – of Intervention (ROBINS-I) tool[27]. The risk-of-bias judgements were summarized across studies for each of the domains listed. When considering treatment effects, bias assessment was done at an outcome level. A descriptive assessment of risk affecting the cumulative evidence was conducted using GRADE tool[28] to establish the quality of evidence and the strength of recommendations.

+B: Data analysis

A descriptive analysis was performed for all outcomes to allow narrative evaluation of difference in outcomes. Data were insufficient for any pooled analysis or an assessment of publication bias.

+A: Results

+B: Study selection

In total, 168 articles were identified. Ultimately, six full-text articles[15,18–21,29] were included. Articles were excluded based on the population (FG used for skin grafting in non-burned patients or used exclusively on donor sites), the intervention (keratinocyte application rather than FG) and lack of comparison groups (Fig. 1).

+B: Study characteristics

Two RCTs[18,19] and four cohort studies (3 retrospective[20,21,29] and 1 prospective[15]) were included (Table 1). The sample size ranged from 18 to 250 individuals. Three studies[15,18,19] used within-subject controls, two[20,21] used historical controls and one[29] a prospective control cohort. The control groups had SSGs secured with staples[15,18,19] or a mixture of staples, sutures and dressings[20,21,29]. Medical co-morbidities were not reported in four studies studies[18,19,21,29]. One study[15] documented no co-morbidities, and another[20] reported smoking and diabetes only, with no significant difference between groups. Half of the included studies received funding from Baxter Healthcare. Two studies[30,31] were not in the English language and full texts could not be retrieved for translation, resulting in their exclusion.

+B: Study results

Overall, graft take and graft loss were similar in the FG and control groups (Table 2). No adverse events attributed to FG were reported in any study.

+C: Graft take

Graft take was assessed most commonly on day 5[15,18,19]. Boccara and colleagues[15] reported that all grafts took without lysis or necrosis. Ihara and co-workers[21] found no difference in graft take between groups, although no supporting statistics were given. The rate of graft take reported by Foster et al.[18] was 62.3 per cent for FG and 55.1 per cent for control (P = 0.089). The rate of graft take documented by Gibran and colleagues[19] was 62 and 46 per cent for FG and control respectively (P = 0.070).

+C: Wound closure

Overall wound healing was described by proportions healed on day 14[18,19] and at 1 month[20]; time to complete healing was reported in two studies[15,29]. One study[21] did not report this outcome. There was no difference in complete wound healing on day 14 between groups (48.8 versus 42.6 per cent for FG versus control; P = 0.230)[18] or the decrease in wound size (18.3 versus 14.7 per cent respectively; P = 0.773)[19]. Gibran and co-workers[19] reported 100

per cent graft survival in both groups on day 14 (P = 0.352). Although mentioned in the methods, Butts et al.[20] did not report rates of complete wound closure. Boccara and colleagues[15] reported complete wound closure after a mean of 17 days, but with no comparison between the six patients with treatment and control burn sites. McGill and co-workers[29] reported no significant difference between groups in would healing time after adjustment for graft size (mean (s.d) 5(4) versus 18(64) days per 100 cm^2; P = 0.77). ~~significantly improved time to wound healing with FG compared with control (mean(s.d.) 26(16) versus 20(12) days; P = 0.009). However, when wound healing time was adjusted for graft size there was no significant difference between groups (5(4) versus 18(64) days per 100 cm^2; P = 0.77).~~ One study[18] reported odds ratios for complete wound closure on day 28 after treatment for the FG group according to the surgical site, rather than comparing with staples.

+C: Graft loss

Three studies considered graft loss[18–20]. Butts et al.[20] reported significantly lower graft loss rates in the FG group (<1 per cent versus 4 per cent; P = 0.03). Foster and co-workers[18] noted partial or complete graft loss as the most common adverse event in both treatment and control groups (25.4 and 23.2 per cent respectively), but without statistical comparison. Gibran and co-workers[19] reported 48 episodes of graft loss over the study (18 in FG-treated sites; 22 in staple sites; 8 in non-test sites), but again without statistical comparison.

+C: Haematoma formation

Haematoma formation was assessed in three studies[15,18,19]. This was most commonly evaluated on day 1. Foster and colleagues[18] reported a significant reduction in the rate of haematoma in FG-treated sites compared with control (29.7 versus 62.3 per cent; P < 0.001). Gibran et al.[19] reported a significantly lower median percentage grafted area with haematoma (0.0 versus 2.1 per cent; P = 0.014). Boccara and co-workers[15] commented that seroma or

serosanguinous collection was more common with FG but provided no supporting statistics. Butts et al.[20] stated that they measured haematoma rates in their methods, but did not report these results.

+C: Pain

Pain was reported by two studies[15,18]. Using a visual analogue scale (VAS), Boccara et al.[15] reported that pain scores were lower with FG than staples (mean 1.66 (range 0–4) versus 4.33 (range 3–6); $P = 0.004$) in the six patients in whom comparison was possible. Foster and co-workers[18] reported significantly higher mean pain scores after staple removal compared with before removal (6 versus 3; $P < 0.001$), indicating that staples were more painful. However, they offered no pain score data for the FG test sites. Overall, patients reported less anxiety about pain with FG compared with staples.

+C: Patient satisfaction

Patient satisfaction was reported by one study[18] using within-subject controls. A significant preference for FG over staples was noted on days 5, 14 and 28, and at 12 months ($P < 0.001$), although the raw data were not available.

+C: Blood loss

Two[21,29] studies focused on blood loss and the use of blood products, rather than graft take or healing. Ihara and colleagues[21] reported a blood transfusion requirement of 1226 ml in the FG group compared with 2038 ml in the control group. Their observations regarding improved haemostasis with FG were subjective. McGill et al.[29] reported no statistically significant difference in estimated blood loss or decrease in haemoglobin level between the FG and non-FG groups. In subgroup analyses, they demonstrated a significant reduction in estimated blood loss for subjects aged at least 16 years (0.5 versus 0.8 ml per cm^2 graft size; $P = 0.03$), and a significant reduction after adjustment for graft size in one of the two centres. They also

reported significantly less requirement for red blood cells (P = 0.02) and 5 per cent albumin (P = 0.001) in the FG groups, although these data were complete for only one centre.

+C: Cost effectiveness

Cost savings were addressed in in four studies[15,18,20,29]. McGill and colleagues[29] suggested that FG resulted in cost savings of up to US $1500 (€1313, exchange rate 27 October 2018) per patient as a result of lower transfusion requirements. Boccara et al.[15] suggested cost savings through reduced analgesia and medical and paramedical staff input, but provided no objective data to support this statement. Foster and co-workers[18] made similar comments, but again without objective data. The only study to assess cost objectively was that of Butts and colleagues[20], who reported a mean decrease in duration of hospital stay of 1.8 days in the FG group and suggested a saving of US $746 (€652) per patient; however, this was not statistically significant. Duration of stay was discussed further in two studies[15,29]. Boccara et al.[15] commented that all patients treated with FG were discharged on the third postoperative day, whereas patients treated without FG were usually discharged on the fifth day; however, no statistics were reported so no inferences can be made. The second study[29] reported a significant reduction in duration of stay with use of FG compared with that in control patients, but not when adjusted for graft size (3(4) versus 5(7) days; P = 0.26).

There was insufficient information to report on return to the operating theatre or postoperative infection. Formal direct comparison by meta-analysis was not possible owing to issues of unit of analysis and variable outcome reporting. Three studies reported graft take at 5 days; one[19] was a within-participant intervention study with the unit of analysis being the site, whereas the other two studies[15,18] randomized individual patients to interventions with the unit of analysis being the patient. Only two studies[18,19] reported long-term graft take and haematoma formation.

+B: Risk of bias within studies

All studies were considered at risk of methodological bias (Fig. S1 and Table S1, supporting information). The risk of bias is given at the outcome level for each study, except that of Boccara et al.[15].

+B: Risk of bias across studies

There was a significant risk of bias across the studies regarding the use of control groups. Of the six included studies, only two were RCTs[18,19]. Both used within-subject controls and neither the subject nor assessor was blinded to outcome measurement, except in the study by Foster and colleagues[18] where assessors were blinded to complete wound closure on day 28. Neither study gave details of patient recruitment or randomization sequence generation, and there was poor reporting of intention-to-treat (ITT) analysis and information regarding missing data. Foster et al.[18] excluded participants with no primary outcome data, those lost to follow-up and those without photographs on day 28 from their ITT analysis. This information was reported within FDA product development information[15], but not in the published study. However, further details regarding differences between treatment groups were not given, introducing the risk of bias.

Of the four cohort studies, one[15] used within-subject controls, but for only six patients. For these patients it was not reported whether the two burn sites were comparable or how they were chosen. The remaining three studies used retrospective controls. Ihara et al.[21] did not clearly define their control group, nor was it comparable in terms of percentage TBSA and there was no assessment of differences in patient or burn characteristics between groups. Butts and colleagues[20] presented a comparison of patient and burn characteristics between cases and controls. However, the controls were from 2007–2008 and the cases from 2011–2012, which may have led to a systematic difference between groups in patient management. McGill and co-workers[29] used mixed methods; they identified patients for FG prospectively (they were recruited for a different study concerning the manufacture of FG to

prevent viral contamination), whereas controls were identified retrospectively and comprised patients who declined participation in the parent study. Insufficient information was provided regarding the management of control patients, who were recruited across two institutions, which increased the risk of bias.

The composition of FG is a further potential source of bias across studies. Although this should not introduce a systematic error, there may be an error over time. Recent studies use a more consistent and refined FG. Ihara and colleagues[21] in 1984 and McGill et al.[29] in 1997 described a process of FG synthesis from fibrinogen solution and thrombin solution immediately before intraoperative application. Ihara and colleagues[21] used a thrombin concentration of 4.2 units/ml. The method of application was not described, although the solutions were mixed before application. In contrast, McGill and co-workers[29] used a thrombin concentration of 250–350 units/ml and applied it via a Y-connector spray. Gibran and colleagues in 2007[19] and Foster et al. in 2008[18] reported clinical trials for the development of the same product (ARTISS; Baxter Healthcare, Sydney, New South Wales, Australia). Both used 4 units/ml thrombin with the sealant, although the FG was heat- and solvent-treated in the study by Foster et al.[18], but not in that by Gibran et al.[19]. Both components were administered by spray. Butts and colleagues[20] and Boccara et al.[15] used ARTISS in 2015 and 2017 respectively.

+B: Quality of evidence and strength of recommendations

The overall quality of the research concerning FG was very low and so it is not possible to make recommendations regarding its use (Table S2, supporting information).

+A: Discussion

FG is used widely across surgical subspecialties. There have been many recent advances in its synthesis and application. However, despite over half a century of use in burns, there is little evidence to support the use of FG in this patient group.

The search identified only 18 full-text articles for review. Nine of these provided no comparison group and were therefore excluded; only six studies qualified for inclusion. Both RCTs[18,19] were funded by Baxter Healthcare which produces ARTISS, and both were at high risk of bias. Both excluded hands and genital burns, chemical burns and diabetics, which limits extrapolation of the results to all burn surgery. However, these exclusion criteria are reasonable to facilitate a comparative study. Furthermore, blinding of participants and investigators for the majority of outcomes was not possible, although Foster and colleagues[18] did use blinded investigators for the primary endpoint analysis on day 28 using photographs, finding that FG was at least as effective as staples. Regarding the non-randomized studies, levels of bias were critical in two, serious in one and high in one. Taken together, the overall level of evidence for the use of FG in burn surgery is poor.

The results suggest that there is insufficient evidence to support the use of FG in terms of improved skin graft take or wound closure. No meaningful difference was demonstrated for these outcomes in any study, although one[20] suggested that FG may reduce graft loss, reporting a significantly lower graft loss rate in the FG group. However, it is not clear if the statistical analysis was conducted on the raw data or the percentage value and, given the low numbers involved, provides only weak evidence. Furthermore, the heterogeneity of terms used to describe the clinical assessment of grafts, particularly on day 5, makes interpretation of outcomes challenging. Terms used included engraftment[18], surgical closure (defined as graft vascularization and formation of a contiguous layer of viable epithelium covering the entire wound)[19], percentage area of questionable viability[19], graft take[15] and graft fixation[21]. Although these terms give an assessment of skin graft success at the time of review, and therefore facilitate comparison between treatment groups, they are probably not synonymous across studies. Clear and practical definitions are required for

future studies that will facilitate comparison, and clear outcomes need to be stated, such as graft adherence or graft take.

FG appeared to reduce postoperative haematoma formation[15,17,19]. Both RCTs demonstrated a significant reduction in haematoma formation 24 h after surgery. The third study[15] described lower rates of seroma or serosanguinous collection, but no statistics were provided to qualify their claim. The authors attributed this observation to FG obstructing fenestrations made in the SSGs rather than a direct effect.

The two studies[21,29] that focused primarily on blood loss did not measure haematoma formation. Ihara and colleagues[21] reported reduced blood loss, with a lower requirement for blood products in the FG group; however, they did not control for differences in percentage TBSA (47.5 and 56 per cent in FG and control groups respectively), which may have confounded the outcome. McGill et al.[29] found no significant difference in blood loss overall when adjusted for graft size, although it was significantly reduced in one of their centres. In a subgroup analysis, patients aged over 16 years showed significantly less blood loss; however, the data were generated from estimates made by the surgical and anaesthetic teams based on the amount of blood collected on swabs and in the suction catheters. Furthermore, these data were collected retrospectively from charts.

Data regarding red blood cell transfusion volume was available from only one centre, and the median volume administered to the treatment and control groups was 0 ml[29]. Of note, articles assessing blood loss were from 1984[21] and 1997[29] so it is reasonable to suggest that operative techniques may have evolved, with more widespread use of subcutaneous infiltration of adrenaline solutions, improvements in excisional surgery techniques and the advent of hydrosurgical debridement. A further point for consideration in relation to graft take and haemostasis is the thickness of FG; this was reported in the methods of only two papers[18,19] during the development of ARTISS, which had a recommended dose of 2–4 ml

per 100 cm^2. No articles reported the dose used or thickness applied. A thicker layer of FG might provide better haemostasis and adherence, but it could also impede revascularization or increase haematoma rates owing to obstruction of fenestrations.

FG may be beneficial for reducing pain[15,18] and duration of hospital stay[15,20,29], with subsequent improvements in patient satisfaction[18] and costs. It is logical that there will be less pain if staples are not removed; this was supported by two studies[15,18]. The costs of FG will necessarily increase overall costs, but savings may be made from reductions in inpatient stay[29]. A detailed economic analysis of the use of FG in burn wound reconstruction should be incorporated into future RCTs.

The role of FG in elective surgery was assessed recently in a systematic review and meta-analysis[14]. This excluded all studies included in the present review as burn injuries did not meet the inclusion criteria. Meta-analysis of 32 included RCTs demonstrated no difference in the risk of seroma with FG (odds ratio 0.84, 95 per cent c.i. 0.68 to 1.04; P = 0.13; n = 3472; I^2 = 12.7 per cent), but a significant benefit regarding haematoma formation from 24 studies (OR 0.62, 0.44 to 0.86; P = 0.01; n = 2403; I^2 = 0 per cent). This is in keeping with the present findings.

In the plastic surgery literature, FG has been used for haemostasis at skin grafting donor sites in two RCTs[32,33], one of which reported a small beneficial effect and the other no effect. In the burns literature, several groups have reported improved wound healing[16,34–36], graft adherence[16,34–38], reduced blood loss[39] and improved haemostasis[16,34,37] with FG. Additional advantages may include the use of FG for skin graft attachment in areas that are hard to graft such as the face, eyelids and ears, and areas of high mobility[35,37], use in diabetics and smokers[38], and improved functional outcomes with FG use[40]. Unfortunately, the majority of these studies were of poor quality and at high risk of bias. They were excluded from this

review as they provided no comparison groups or were conducted in mixed patient groups (such as skin grafting for trauma and chronic wounds), not specifically burn surgery.

The safety of FG is an important consideration. None of the included studies reported adverse outcomes attributed to FG. There have been concerns regarding viral transmission with the use of synthetic FG, which is overcome by use of autologous FG; however, the general consensus is that FG is risk-free[32]. A significant safety concern was raised regarding air embolism with FG spray delivery systems. However, the European Medical Agency concluded that the benefits outweighed the risks[14,41]. Furthermore, this complication was predominantly seen in intra-abdominal or vascular surgery and is unlikely to arise in skin grafting.

This study had a number of limitations. At an outcome level, it was limited by the level of bias demonstrated across the included studies and reflected by the very low GRADE score (Table S2, supporting information). No studies reported risk or odds ratios, and the definitions used for graft take, graft adherence and wound healing were inconsistent. A significant challenge, as in many surgical studies, is achieving adequate control groups, and blinding. The use of within-subject controls in the two RCTs offers significant advantages, but limits the size and type of burn injuries that can be included. Furthermore, given the type of interventions being assessed, blinding is a significant challenge until after staples have been removed. For the remaining studies, matching of cases and controls was weak throughout. On a study level, this review was limited by the risk of publication bias. Researchers are unlikely to report poor outcomes from the use of FG, particularly when funded by a pharmaceutical company.

The quality of evidence for the use of FG in skin grafting for burn injuries is very low and based on few studies with significant risks of methodological bias. No meaningful conclusions can be drawn, and no recommendations suggested. The inconsistency in outcome

reporting encountered here supports the need for agreement regarding the core outcomes, and how they should be measured and reported in future studies.

+A: Acknowledgements

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Supporting information
Additional supporting information can be found online in the Supporting Information section at the end of the article.

Typesetter: please refer to marked-up figure

Fig. 1 PRISMA diagram showing selection of articles for review

Table 1 Summary of study characteristics

Reference	Design	No. of participants	Cases versus controls	Exclusion criteria	Median age (years)	Median TBSA (%)	Comparison intervention	Funding
Ihara et al.[21]	Retrospective cohort	18	10 versus 8	No	Cases: 37.3* Controls: 38.3*	Cases: 47.5* Controls: 56*	Various	None declared
McGill et al.[29]	Retrospective cohort	95	31 versus 61	No	Cases: 23.6 Controls: 20.8	Cases: 10 Controls: 10.9	Various	Baxter Healthcare
Gibran et al.[19]	RCT	40	40 (within-subject control)	Yes	Overall: 30.5*	Total: 14 Test sites: 3	Staples	Baxter Healthcare
Foster et al.[18]	RCT	138	138 (within-subject control)	Yes	Overall: 29	Total: 11.8 Test sites: 1.5	Staples	Baxter Healthcare
Butts et al.[20]	Retrospective cohort	250	202 versus 48	No	Cases: 41 Controls: 37	Cases: 3 Control: 3	Various	None declared
Boccara et al.[15]	Prospective cohort	28	6 (within-subject control)	No	Overall: 45*	Overall: 10*	Staples	None declared

*Mean values. TBSA, total body surface area.

Table 2 Summary of results by outcome

Outcome	Unit of measurement	Fibrin glue	Conventional technique	*P*	Reference
Graft take (day 5)	% graft take	100	100	–	Boccara et al.[15]
	% of patients with 100% graft take	62.3	55.1	0.089	Foster et al.[18]
	% graft site closure	62	46	0.07	Gibran et al.[19]
Postoperative haematoma (day 1)	% of patients with haematoma	29.7	62.3	< 0.001	Foster et al.[18]
	Median % graft area	0.0	2.1	0.014	Gibran et al.[19]
Graft loss	% of patients with loss	< 1	4	0.03	Butts et al.[20]
	% of patients with loss	25.4	23.2	–	Foster et al.[18]
	No. of patients	18	22	–	Gibran et al.[19]
Postoperative pain	~~Mean pain score~~	~~3.3~~	~~6.2~~	~~< 0.001~~	~~Foster et al.[18]~~
	Mean VAS pain score	1.66	4.33	0.004	Boccara et al.[15]
Cost*	Suggested saving per patient (US $)	1500 (1313)	–	–	McGill et al.[29]
	Mean cost (US $)	4336 (3796)	5082 (4448)	–	Butts et al.[20]
Duration of hospital stay	Mean days	3	5	0.26	McGill et al.[29]
		3	–	–	Boccara et al.[15]
		4.2	6	< 0.001	Butts et al.[20]
Blood loss	Mean operative blood loss (ml)	352	411	0.4	McGill et al.[29]
		1226	2038	–	Ihara et al.[21]

*Values in parentheses are costs in euros (exchange rate 27 October 2018).