



# Fibrin tissue sealant and minor skin grafts in burn surgery: A systematic review and meta-analysis

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## KEYWORDS

Fibrin glue;  
Tissue sealant;  
Skin grafts;  
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Meta-analysis

**Summary Background:** The indications for use of fibrin glue in skin grafting burn patients remains understudied. The purpose of this study is to review the efficacy of fibrin tissue sealant in skin graft adherence, establish guidelines for use of fibrin tissue sealant, and review the cost effectiveness of fibrin glue.

**Methods:** Publications with the following criteria were included: comparative human studies, autologous skin grafts, and autologous or commercial fibrin sealant. Outcomes assessed included evidence of engraftment, wound closure, rates of hematoma/seroma, graft loss and infection. Meta-analysis obtained pooled odds ratios for outcomes of interest. Cost analysis was performed using data available in the literature.

**Results:** 7 studies and 751 interventions (fibrin) and controls (staples) were included in the final analysis. 67.6% grafts with fibrin were 100% adherent by one week, vs. 55.5% (OR 1.45,  $p=0.086$ ). Complete wound closure by one month was 80.2% with fibrin, vs. 73.3% (OR 1.34,  $p=0.187$ ). Hematoma/seroma occurred 38.2% with fibrin, vs. 64.7% (OR 0.487,  $p=0.122$ ). Graft loss was higher in the control group, 21% vs. 12.6% (OR 0.891,  $p=0.604$ ). Average cost of fibrin glue was \$50 per ml, and averaged costs of stapler and staple remover was \$30 USD (\$10-50).

**Conclusion:** Fibrin glue is as effective as staples for adhering skin grafts, and trends towards lower rates of hematoma/seroma. In topographically complex regions, fibrin glue may be a better choice for adherence of skin grafts.

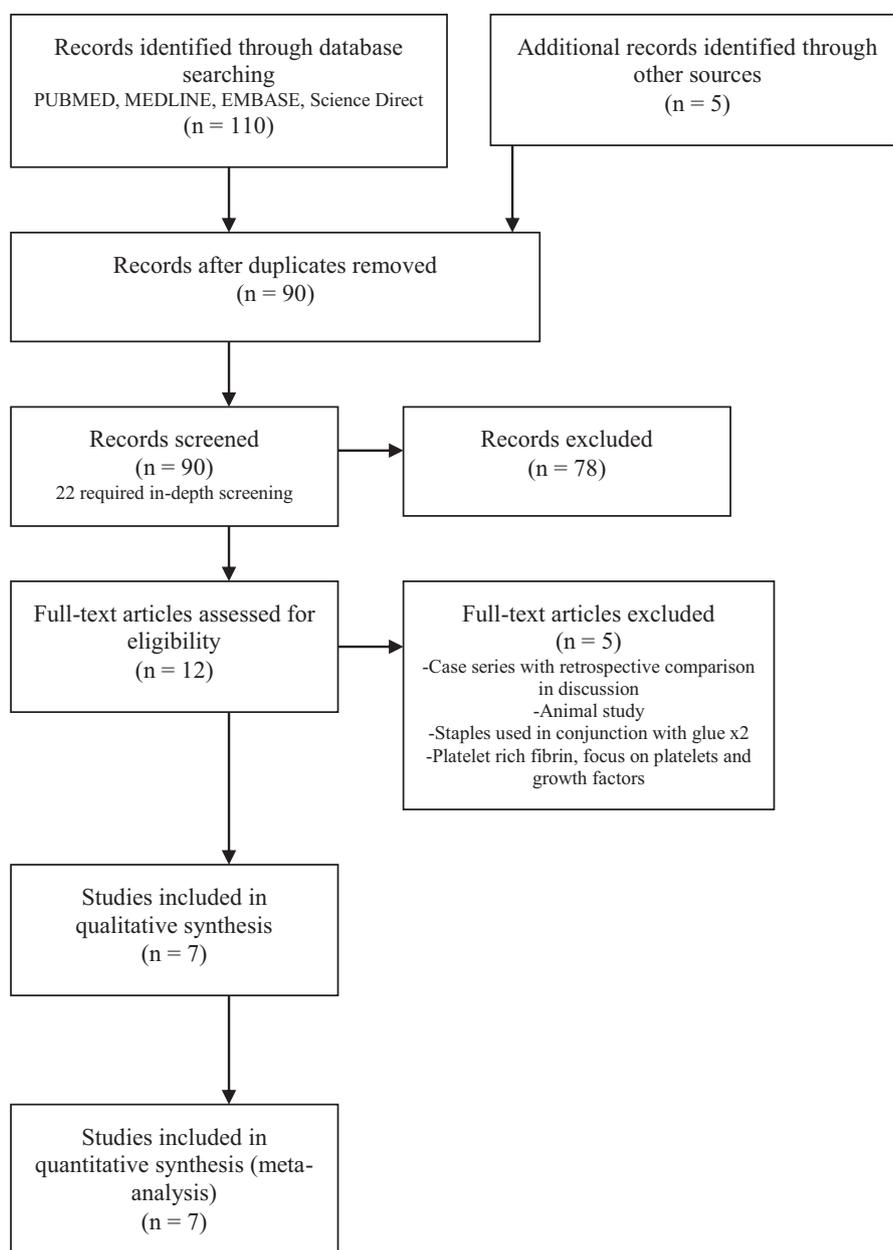
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## Introduction

Immobility of skin grafts is necessary for revascularization. Fibrin tissue sealant is a product of combined thrombin and fibrinogen, producing stable cross-linked fibrin clot.

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**Figure 1** PRISMA search and retrieval results.

\*PRISMA: Preferred reporting items for systematic reviews and meta-analyses.

This product has been used to adhere skin grafts in plastic surgery and burn surgery, and several fibrin sealants are commercially available. Current literature describes use of fibrin tissue sealant for hemostasis of skin graft donor sites, graft adherence, as well as for antibacterial purposes.<sup>1-4</sup> Fibrin tissue sealant has been promoted for its use in cardiothoracic surgery and general surgery as a hemostatic agent, and off-label use has been widely documented.<sup>5</sup> There are three main commercial sealants used for skin graft adherence on the US market: Tisseel and Artiss (Baxter International, Inc., Deerfield, Illinois, USA), and Evicel (Ethicon, Inc., Somerville, New Jersey, USA).<sup>5,6</sup>

Does fibrin glue represent a viable solution for skin graft fixation to allow for healing in comparison to standard use

of staples? Furthermore, does it provide other benefits to skin graft adherence and wound healing, such as decreased rates of seroma? The question of why to use fibrin glue is relevant when it is among several choices for skin graft adherence. Methods for adherence include staples, suture, traditional bolsters, and negative pressure wound therapy (NPWT). NPWT does not introduce an additional barrier between the graft and wound bed, and is commonly used for skin graft adherence. Introducing a foreign body between the graft and wound bed adds additional variables in the course of healing of skin grafts.

The current indications to use fibrin sealant in skin graft adherence in burn surgery remain understudied, and no large-scale comparative studies or meta-analysis have been

performed to date. The purpose of this study is to answer the following clinical question: when compared to recipient sites treated without fibrin sealant, do skin graft recipient sites treated solely with fibrin sealant have improved graft adherence, faster wound healing, lower complications, and lower overall treatment costs? We hypothesize that fibrin sealant will improve graft adherence, wound healing, lower complications and lower treatment costs when compared to non-fibrin sealant management of recipient sites. Our specific aims are to: (1) identify a cohort of patients undergoing skin graft recipient site treatment with and without fibrin sealant, (2) evaluate graft adherence, wound healing time, and complications rates for each group, and (3) compare the cost of total treatment between the two groups.

## Materials and methods

### Reporting methodology

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used as a review protocol and to guide the literature search (Figure 1).<sup>7</sup> As part of the protocol, the Methodological Index for Non-Randomized Studies (MINORS) criteria were applied to establish methodological quality of the papers chosen for full review and for ultimate selection (Table 1).<sup>8</sup>

### Literature search

The authors independently performed the literature search to identify comparative studies evaluating fibrin tissue sealant used as autologous skin graft adhesive. PubMed, MEDLINE, Embase and ScienceDirect databases were searched through July 2017 with the following key words: “Fibrin Tissue Adhesive” and “skin transplantation”, as well as derivatives. The MeSH terms and entry terms related to the key words were also used in this comprehensive literature search. To broaden return of results, “burn” was not used to refine results. Titles and abstracts of potential articles for inclusion were independently examined. Full-text articles were retrieved and examined when their title and abstract did not provide enough information for a definite decision.

### Inclusion and exclusion criteria

Inclusion criteria were the following: the design was a comparative study published in the English-language literature; the study subjects were primarily adult patients who underwent autologous skin graft due to burn injury or other injury requiring skin graft; the skin graft was secured with tissue glue and standard of care served as the control; and the study reported outcomes including skin graft take, hematoma, infection, or adverse reactions to the tissue glue. Exclusion criteria were the following: non-English language literature, sample sizes < 5, case series, artificial or cadaveric dermis in lieu of autograft, fibrin in conjunction with staples or sutures, fibrin application solely to donor site, fibrin tissue sealant used as a carrier for novel additives or cellular components, and animal-only models.

## Methodological quality assessment

MINORS guidelines were used to assess the methodological quality of the included studies. Papers scoring > 16 were considered methodologically rigorous. Papers scoring < 16 were considered in the meta-analysis only after in-depth review of reported data.

### Primary/Secondary predictor variable and outcomes

The primary predictor variable was the presence or absence of fibrin sealant. Secondary predictor variables were factors potentially associated with burn injury. These factors included gender (male vs. female), age (year) at time of surgery, burn type, percent total body surface area (TBSA%), and time to surgery, where included and applicable. Outcomes measured included: engraftment, hematoma/seroma, wound closure, and graft loss. Outcomes evaluated/reviewed but not included in statistical analysis due to inadequate primary data included pain, time to discharge, and cost-analysis. Cost data was extrapolated using contemporary data published in the literature.

### Data extraction and statistical analysis

The research team extracted data for: study details (design, first author, year of publication), demographics and patient descriptive statistics, number of patients in each study group, details of skin graft harvest and adherence, and outcome measures.

All data analysis was performed using RStudio statistical software Version 1.0.136 (RStudio: Integrated Development for R. RStudio, Inc., Boston, MA) and the metafor package.<sup>9</sup> Associations between graft type and selected outcomes of interest were assessed by computing odds ratios (ORs) and the corresponding 95% confidence interval (CI) for fibrin skin grafts vs. control skin grafts. Mantel-Haenszel fixed effects model analysis was performed (significance level of  $p < 0.10$ ), since the inclusion criteria and a full analysis of the studies selected allowed the assumption that all studies in the meta-analysis shared a common true effect size. Fixed effects models were used to analyze the following outcomes: engraftment, wound closure, graft loss, infection, and pruritus. Heterogeneity among the included studies was assessed using the Cochrane Q statistical test and  $I^2$  statistic, with significant heterogeneity defined as  $p < 0.1$  or  $I^2 > 50\%$ , respectively.<sup>10</sup> Dersimonian-Laird random-effects model analysis was performed when significant heterogeneity was identified, namely in hematoma/seroma data. Multivariate logistic regression was performed to examine associations between predictor variables and outcomes of interest, and ORs were calculated (significance level of  $p < 0.05$ ). Significance tests for differences in proportions were also calculated (significance level of  $p < 0.05$ ).

## Results

Over the study period, seven studies were identified with 538 subjects (751 skin grafts).<sup>11-17</sup> Average MINORS score was

**Table 1** Characteristics of intervention, outcomes, and demographic data.

Author, Year	Study type	Fibrin tissue glue		Standard of care		Demographic data	Key results	MINORS score
		<i>n</i>	Details of intervention	<i>n</i>	Details			
Boccaro et al., 2017	Prospective single center clinical study with a subset of case control	28	Population: Patients with burns on dorsum of hands.  Sealant: Artiss Sealant ®.  Graft: Split thickness skin grafts with microperforations. Dressing: paraffin case and splint	6	Staples	<ul style="list-style-type: none"> <li>• 2013-2015 data collection</li> <li>• 34 graft sites: 22 men, 6 women</li> <li>• Mean age: 45</li> <li>• None with DM, smoking</li> <li>• 18 burns due to fire, 8 due to hot oil, 2 due to wax</li> <li>• Mean TBSA 10% (1-40%)</li> <li>• Mean time to surgery was 8.7 days</li> <li>• Follow-up for 18 months</li> <li>• Fibrin cases from 2011-2012, staple cases from 2007-2008</li> <li>• Mean age 41/38</li> <li>• 68% male in intervention, 71% male in control</li> <li>• Demographic data equivocal except for the staple group had more burns to the face and feet</li> <li>• TBSA &lt; 10% for both groups (mean 3.5% and 3.6%)</li> </ul>	<ul style="list-style-type: none"> <li>• Dressing opened on POD3, then daily dressing changes up to POD7-10.</li> <li>• Quality of graft take at POD3, POD5</li> <li>• VAS of three patients with Fibrin + Control on hands: 1.66 (0-4) for fibrin hand vs. 4.33 (3-6) for stapled hand. Mann-Whitney U test <math>P=0.0035</math>.</li> <li>• Complications: 12 small serosanguinous collections drained at bedside.</li> <li>• POD5: case and control all took without lysis or necrosis</li> <li>• Average healing: 17.3 (11-33 range) days. No difference in flexion/function of hands 18 months post-operatively between fibrin and staple groups.</li> </ul>	13/24
Butts et al., 2015	Retrospective single center case control	202	Population: Burn patients.  Sealant: Artiss Sealant ®.  Graft: autologous, further details not specified. Dressing: not specified.	48	Staples	<ul style="list-style-type: none"> <li>• Graft loss: <math>n=3</math>, staples 4%, fibrin &lt; 1% (<math>P=0.03</math>)</li> <li>• Post-operative days to discharge: 4.2 days with fibrin, 5.0 for staples (<math>P &lt; 0.001</math>)</li> <li>• Decrease of 1.8 days savings \$746 per patient</li> </ul>	17/24	

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Table 1 (continued)

Author, Year	Study type	Fibrin tissue glue		Standard of care		Demographic data	Key results	MINORS score
		n	Details of intervention	n	Details			
Dahlstrom et al., 1990	Prospective randomized trial	8	Population: chronic leg ulcer patients.  Sealant: Autologous fibrin adhesive application, mean fibrin content 20-29 mg/ml. Graft: Meshed split thickness skin graft. Dressing: paraffin gauze.	8	No adhesive - adherent method not specified	<ul style="list-style-type: none"> <li>• 7 patients, eight grafts</li> <li>• Randomly allocated to receive fibrin adhesive in either medial or lateral aspect of ulcer.</li> <li>• No demographic data provided</li> </ul>	<ul style="list-style-type: none"> <li>• Intraoperatively, strength of adhesion tested with dynamometer: fibrin grafts breaking strength after 3.5 min was 12-26 g, while &lt; 5 in unsealed.</li> <li>• Immobilization of grafted site. Dressing opened POD7.</li> <li>• 90-100% graft take in sealed and unsealed areas</li> <li>• Biopsies taken from POD7 and POD21: splitting between graft and recipient bed in 50% of unsealed. No difference between grafts at POD21.</li> </ul>	12/24
Foster et al., 2008	Phase 3, multicenter, prospective, randomized, evaluator blind clinical study	138	Population: burn patients.  Sealant: Artiss ®.  Graft: Split thickness sheet grafts.  Dressing: not specified.	138	Staples	<ul style="list-style-type: none"> <li>• Digits and genitalia excluded</li> <li>• Excluded DM, electrical or chemical burns, infected sites</li> <li>• 137 grafted areas; intention to treat: 127</li> <li>• Mean age 29</li> <li>• 127 ITT: 66.1% male</li> </ul>	<ul style="list-style-type: none"> <li>• Evaluated POD0 and onward</li> <li>• Wound closure POD14: 48.8% fibrin sites, 42.6% control, <math>P=0.2299</math></li> <li>• Wound closure POD28: wound closure 70.3% in fibrin group, 65.8% in staple group by planimetry, and 43.3% vs. 37% in blinded photographic review. Wounds located on neck/torso more likely to close compared to extremities by day 28 for fibrin <math>P=0.0016</math>. Rate of extremity closure equal between groups, 37.3% and 35.1%</li> <li>• Hematoma/Seroma POD1: occurred 29.7% in fibrin vs. 62.3% control (<math>P &lt; 0.0001</math>)</li> <li>• Engraftment POD5: 100% in 62.3% fibrin, 55.1% in staple (<math>P=0.0890</math>)</li> </ul>	24/24

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Table 1 (continued)

Author, Year	Study type	Fibrin tissue glue		Standard of care		Demographic data	Key results	MINORS score
		n	Details of intervention	n	Details			
Gibran et al., 2007	Phase ½, multicenter, prospective, randomized	40	Population: Burn patients.  Sealant: Artiss®.  Graft: Sheet grafts.  Dressing: not specified.	40	Staples	<ul style="list-style-type: none"> <li>• Mean TBSA of all burn sites 11.8% (2-40%)</li> <li>• Average TBSA test sites 1.5%</li> <li>• Demographic data equivocal</li> <li>• Digits, genitalia, face excluded</li> <li>• Patients served as own control</li> <li>• Excluded pregnancy, clotting disorder, immune deficiency, steroid use within 30d, insulin-dependent DM</li> <li>• Majority of patients were male, white adults</li> <li>• Mean age 30.5 (SD 14.19)</li> <li>• 72.5% male</li> <li>• Mean burn size of total test area: 3.2% (1.26%, range 2-8%) for both groups</li> <li>• Mean total TBSA for all burns: 15.6% (9.62%)</li> <li>• Intention to treat: 40 enrolled, 38 through POD21, 31 through 3 months</li> <li>• Demographic data equivocal</li> </ul>	<ul style="list-style-type: none"> <li>• Scar maturation: no significant difference at 3, 6, 9, 12 months</li> <li>• Less anxiety regarding pain with fibrin population vs. staple population on POD14 (<math>P &lt; 0.0001</math>)</li> <li>• Equal rates of graft loss due to secondary effect (infection, mechanical shearing)</li> <li>• Evaluated POD0 and onward</li> <li>• Hematoma/seroma formation POD1: 2.1% area hematoma median in staple group vs. 0% (<math>P = 0.0138</math>)</li> <li>• Area of questionable viability POD5: 0.5% medial in staples vs. 0% (<math>P = 0.0182</math>)</li> <li>• Surgical closure POD5: 61.5% grafts in fibrin vs. 46.2% in staples (<math>P = 0.0735</math>)</li> <li>• Survival POD14: 100% both groups</li> <li>• POD28: completely closed wounds in 79.5% of intervention vs. 59%, <math>P = 0.0215</math></li> <li>• Pain: 29.7% of staple patients required sedation/additional pain meds for staple removal</li> <li>• 4 patients required regrafting: two in test and two in control</li> <li>• Adverse events equal between intervention groups</li> </ul>	22/24

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Table 1 (continued)

Author, Year	Study type	Fibrin tissue glue		Standard of care		Demographic data	Key results	MINORS score
		n	Details of intervention	n	Details			
Han et al., 2016	Prospective single center, comparative study	25	Population: Upper and lower extremity defects  Sealant: fast-clotting fibrin glue (Sealant 400 IU/mL). Graft: not specified.  Dressing: moderate compressive dressing with mesh gauze and bandage	30	Sutures or staples used to adhere skin graft	<ul style="list-style-type: none"> <li>Upper and lower extremity defects from pedestrian/bike accidents and contact burns</li> <li>Median area of skin graft 35.5 cm<sup>2</sup> in fibrin group, and 39.85 cm<sup>2</sup> in control</li> <li>Demographic data not provided</li> </ul>	<ul style="list-style-type: none"> <li>Dressing taken down POD5</li> <li>Hematoma/seroma POD5: fibrin 7.84%, control 9.55%</li> <li>Graft dislocation POD5: fibrin 1.29%, control 1.45%</li> <li>POD30 necrosis and take: 1.86% and 98.14% in fibrin, 4.65% and 95.65% in control</li> <li>Fibrin sealant &lt; P0.05 for all except graft dislocation</li> <li>Clots formed before graft application</li> </ul>	11/24
Vibe et al., 1983	Prospective, single center comparative study	20	Population: reconstructive wounds, primarily melanoma.  Sealant: Tisseel ®.  Graft: Meshed and sheet grafts. Dressing: Not specified.	20	Cat gut secured	<ul style="list-style-type: none"> <li>Majority due to malignant melanoma. Recipient sites not clarified.</li> <li>Average age 45 (17-72)</li> <li>13 females, 7 males</li> <li>Meshed grafts for "difficult" sites and non-meshed for others</li> <li>Total recipient area - control: 959 cm<sup>2</sup>, 1607 cm<sup>2</sup></li> <li>Demographic statistics not provided</li> </ul>	<ul style="list-style-type: none"> <li>Evaluated POD10</li> <li>Total graft take: 83% control, 92% Tisseel; <i>P</i> &lt; 0.01</li> <li>"Strained recipient sites" - 44% control, 88% take in fibrin <i>P</i> &lt; 0.01</li> <li>Hepatitis antigens: negative 6 months later.</li> </ul>	15/24

**Table 2(a)** Data: number of grafts with 100% engraftment, POD5-7.

Study	Fibrin sealant <i>n</i> grafts*	Control <i>n</i> grafts	Engraftment: fibrin sealant <i>n</i> grafts	Engraftment: control <i>n</i> grafts
Boccaro et al.	28	6	28	6
Butts et al.	202	48	Endpoint not included	
Dahlstrom et al.	8	8	6	6
Foster et al.	138	138	86	76
Gibran et al.	39	39	24	18
Han et al.	25	30	Endpoint not included**	
Vibe et al.	20	20	Endpoint not included	
Sum: Outcome/Included studies			144/213	106/191
%			67.6%	55.5%

\* *n* assumed to be initial population unless otherwise specified by source data

\*\* Han et al.: "graft dislocation" at POD5: 1.29% for fibrin group, 1.45% for staple group,  $p > 0.05$

**Table 2(b)** Data: number of grafts with 100% engraftment, POD5-7 - training affiliation.

Affiliation	Fibrin sealant <i>n</i> grafts	Control <i>n</i> grafts	Engraftment: fibrin <i>n</i> grafts	Engraftment: control <i>n</i> grafts
Plastic surgery affiliation*	36	14	34	12
% Total			94.4%	85.7%
General Surgery affiliation**	177	177	110	94
% Total			62.2%	53.1%

\* Boccaro et al., Butts et al. (excluded), Dahlstrom et al., Han et al. (excluded), Vibe et al. (excluded).

\*\* Foster et al., Gibran et al.

16. All subjects were included based on data provided in the studies. 461 (61.4%) sites were skin grafted and adhered with fibrin, and 290 (38.6%) sites were skin grafted and adhered with staples or sutures. 314 (58.4%) patients were male subjects, 151 (28.1%) were female subjects, and 73 (13.6%) had no gender provided. The sample's mean age was 38 years based on available data. Average duration of clinical follow-up ranged from 10 days to 18 months between studies. Graft size varied amongst studies, but was relatively consistent between study and control groups within the studies. Han et al. graft size ranged from 35.5 cm<sup>2</sup> to 39.85 cm<sup>2</sup>. Butts et al. reported mean graft size of 291-312 cm<sup>2</sup>. Vibe et al. reported a wide variety in graft area, from 87 cm<sup>2</sup> to 1607 cm<sup>2</sup>. Dahlstrom et al. did not comment on wound size but did report area tested, 1 cm<sup>2</sup>. Gibran et al., Foster et al., and Boccaro et al. did not report graft size, but reported burn site as an average of 3.2%, 11%, and 10% TBSA.

100% engraftment at post-operative days 5-7 (POD5-7) was similar between studies ( $p = 0.086$ ), as was 100% wound closure by 30 days (POD30,  $p = 0.187$ ). Hematoma/seroma incidence was lower in the fibrin group vs. control (38.2% vs. 64.7%), and had significance dependent on the model used ( $p < 0.0001$  vs.  $p = 0.122$ ). Total graft loss trended lower in the fibrin group, but was not significant (12.6% vs. 21.0%,  $p = 0.604$ ). Local site infection and pruritus were not significantly different between groups ( $p = 0.672$  and 0.889). Stapler and staple removers cost around \$30 (\$10-50), and fibrin glue cost \$50/ml or \$100 for application over 100 cm<sup>2</sup>.

The search and retrieval process is summarized in [Figure 1](#). Demographic data and study review, including review of endpoints, study type, quality and MINORS score are in [Table 1](#).

### Engraftment at 5-7 days

Due to the nature of the data, the endpoint was set at the total number of grafts with 100% graft take by POD5-7. 67.6% of the fibrin-adhered grafts met this endpoint, vs. 55.5% of those secured with staples ([Table 2\(a\)](#)). Fibrin skin glue suggested a higher rate of engraftment but did not reach significance (OR 1.45,  $p = 0.0857$ , [Table 6](#)). Logistic regression for fibrin produced an odds ratio of 1.09 ( $p = 0.0588$ , [Table 7](#)).

When separated into general surgery and plastic surgery affiliations, general surgeons performed the majority of procedures ([Tables 2\(b\)](#) and [7](#)). Among plastic surgery trained burn surgeons, 100% engraftment for fibrin glue vs. staples was not significant ( $p = 0.6591$ , no table). This was the same for subset analysis within general surgery ( $p = 0.1067$ , no table).

### Wound closure <30 days

Amongst the studies, blinded and unblinded reviewers, as well as planimetry determined wound closure. Due to the data available, the metric used was 100% wound closure by post-operative day 30 ([Table 3](#)). Some data sets had to be extrapolated to fit this metric: any study reporting 100% wound closure by day 30 was included as "wound closure by post-operative day 30". The range reported was from POD10 to POD30. In some cases, a percentage was applied to determine number of grafts with 100% closure; if the number of total grafts included in the subject was not specified for that metric, the original sample size reported in the study was used. Eighty percent (80.2%) of skin grafts adhered with

**Table 3** Data: number of grafts with 100% wound closure by POD30.

Study	Fibrin sealant <i>n</i> grafts*	Control <i>n</i> grafts	Wound closure: fibrin sealant <i>n</i> grafts	Wound closure: control <i>n</i> grafts
Boccaro et al.	28	6	28	6
Butts et al.	202	48	Endpoint not included	
Dahlstrom et al.	8	8	8	8
Foster et al.	138	138	97	94.5
Gibran et al.	40	40	31.8	23.6
Han et al.	25	30	24.5	28.6
Vibe et al.	20	20	18.4	16.6
Sum: Outcome/Included studies			207.7/259	177.3/242
%			80.2%	73.3%

\* *n* assumed to be initial population unless otherwise specified by source data.

**Table 4** Data: presence of hematoma/seroma POD1 or later.

Study	Fibrin Sealant <i>n</i> grafts*	Control <i>n</i> grafts	Wound closure: fibrin sealant <i>n</i> grafts	Wound closure: control <i>n</i> grafts
Boccaro et al.	28	6	12**	0
Butts et al.	202	48	Endpoint not included	
Dahlstrom et al.	8	8	Endpoint not included	
Foster et al.	138	138	41	86
Gibran et al.	39	39	33***	49
Han et al.	25	30	1.96	2.87
Vibe et al.	20	20	Endpoint not included	
Sum: Outcome/Included studies			87.96/230	137.87/213
%			38.2%	64.7%

\* *n* assumed to be initial population unless otherwise specified by source data.

\*\* Boccaro et al. listed 12 hematoma/seroma for total *n* = 34, these were intentionally placed under fibrin sealant for the purpose of statistical analysis.

\*\*\* Gibran et al. separately listed hematoma and seroma, they are combined here for the purpose of analysis.

fibrin closed by POD30, compared to 73.3% of skin grafts adhered with staples. The odds ratio was 1.343 for fibrin glue ( $p = 0.187$ , Table 6).

## Hematoma/Seroma

Presence of hematoma/seroma was evaluated POD1 and later (Table 4). 38.2% of grafts adhered with fibrin were complicated by hematoma or seroma, vs. 64.7% of grafts adhered with staples. The fixed effects model calculated an odds ratio of 0.360 for development of hematoma/seroma with application of fibrin ( $p < 0.0001$ , CI 0.240-0.541, no table). However, significant heterogeneity was identified between studies reporting hematoma and seroma formation (Q statistic  $p$  value = 0.0665,  $I^2$  statistic = 58.2%), thus a random effects model was employed to analyze this outcome more appropriately. The random effects model calculated an odds ratio of 0.487 for fibrin glue ( $p = 0.122$ , Table 6).

## Complications

Graft loss was observed in 12.6% of grafts adhered with fibrin, and 21% of those adhered with staples (Table 5(a)). Odds ratio for graft loss was 0.891 ( $p = 0.604$ , Table 6). Infection was uncommon and relatively similar between groups, 2.0%

vs. 4.6% (Table 5(b)). Odds ratio for infection was 0.465 ( $p = 0.672$ , Table 6). Pruritus was a common complication in both groups (Table 5(c), Table 6).

## Discussion

The purpose of this study was to review efficacy of fibrin tissue sealant in adherence of skin grafts, establish indications for use of fibrin tissue sealant in securing skin grafts, and review the cost of fibrin glue vs. traditional interventions. We hypothesized that fibrin tissue sealant is as effective in skin graft adherence as staples or sutures, and this has been demonstrated by the results of the meta-analysis.

Engraftment over the entire cohort was lower than expected, and subset analysis was performed. Subset analysis by training affiliation revealed general surgery affiliated burn surgeons performed the majority of skin grafts. Affiliation did not impact engraftment for fibrin compared to staples. Overall engraftment was slightly higher for plastic surgery affiliated programs.

Graft size significantly impacted the applicability of the data, however it appears that based on the data, the grafts were overall smaller in nature. It is difficult to reflect on the impact of fibrin on the larger grafts, and thus limits the reach of this study.

**Table 5(a)** Data: complications - graft loss.

Study	Fibrin sealant <i>n</i> grafts*	Control <i>n</i> grafts	Graft loss: fibrin sealant <i>n</i> grafts	Graft loss: control <i>n</i> grafts
Boccara et al.	28	6	0	0
Butts et al.	202	48	1	2
Dahlstrom et al.	8	8	0	0
Foster et al.	138	138	35	32
Gibran et al.	40	40	18	22
Han et al.	25	30	0.456	1.4
Vibe et al.	20	20	1.6	3.4
Sum: Outcome/Included studies			56.06/461	60.8/290
%			12.6%	21.0%

\* *n* assumed to be initial population unless otherwise specified by source data.

**Table 5(b)** Data: complications - clinical infections/abscess<sup>#</sup>.

Study	Fibrin sealant <i>n</i> grafts*	Control <i>n</i> grafts	Infection: fibrin sealant <i>n</i> grafts	Infection: control <i>n</i> grafts
Boccara et al.	28	6	Endpoint not included	
Butts et al.	202	48	0	0
Dahlstrom et al.	8	8	6	7
Foster et al.	138	138	1	2
Gibran et al.	40	40	Endpoint not included	
Han et al.	25	30	Endpoint not included	
Vibe et al.	20	20	Endpoint not included	
Sum: Outcome/Included studies			7/348	9/192
%			2.0%	4.6%

<sup>#</sup> No Study included endpoint of systemic viral infections related to fibrin adhesive except for Vibe et al., who reported 0 incidence of hepatitis at 6 months.

\* *n* assumed to be initial population unless otherwise specified by source data.

**Table 5(c)** Data: complications - pruritus at test/control site.

Study	Fibrin sealant <i>n</i> grafts*	Control <i>n</i> grafts	Pruritus: fibrin sealant <i>n</i> grafts	Pruritus: control <i>n</i> grafts
Boccara et al.	28	6	Endpoint not included	
Butts et al.	202	48	Endpoint not included	
Dahlstrom et al.	8	8	Endpoint not included	
Foster et al.	138	138	Endpoint not included	
Gibran et al.	40	40	28	29
Han et al.	25	30	7	7
Vibe et al.	20	20	Endpoint not included	
Sum: Outcome/Included studies			35/65	36/70
%			53.8%	51.4%

\* *n* assumed to be initial population unless otherwise specified by source data.

The rate of hematoma/seroma was lower in the fibrin group, and may have reached significance in both models if not for the heterogeneity of the meta-analysis data. It has been postulated that the adhesive might limit diffusion of fluid collections under grafts, and some surgeons in these studies practiced microperforations of the grafts to encourage drainage of collections trapped by adhesive. Data did not allow for subset analysis of hematoma/seroma between meshed and unmeshed grafts. Not meshing the grafts may have significantly impacted the results. As another common method of fixation, NPWT may also provide a reliable method to decrease rates of seroma. Seroma rates for NPWT

are suggested to be lower than no dressing, however numbers vary from 66% reduction to 5% increase. Graft failure for NPWT is suggested to be equal to standard of care.<sup>18</sup> Furthermore, in the burn population Waltzman et al. suggest that the ability of NPWT to conform to contour and cover large surface areas makes it a reasonable choice for skin graft bolsters.<sup>19</sup> This is also a benefit of employing fibrin glue.

Fibrin sealants have also been employed for wound healing, and may improve graft viability. Whether related to lower rates of hematoma/seroma or other factors, graft loss occurred less frequently in the fibrin adhesive group

**Table 6** Results of random and fixed study effects models for selected outcomes of interest.

Outcome	Model type	Odds ratio estimate <sup>b</sup>	Lower CI limit	Upper CI limit	P-value
Graft loss	Fixed effects	0.8909	0.5760	1.3780	0.6037
Infection	Fixed effects	0.4646	0.0783	2.7565	0.6720
Pruritus	Fixed effects	1.0205	0.4789	2.1749	0.8890
Hematoma + Seroma <sup>c</sup>	Random effects*	0.4865	0.1952	1.2124	0.1220
Wound closure	Fixed effects	1.3430	0.8670	2.0802	0.1866
Engraftment	Fixed effects	1.4499	0.9492	2.2148	0.0857

a Observations were rounded to whole numbers.

<sup>b</sup> Odds ratios represent odds of fibrin over control.

<sup>c</sup> Significant heterogeneity was identified between studies reporting hematoma and seroma formation, therefore a random effects model was employed.

\* Fixed effects results: OR 0.3601, CI 0.2396-0.5412,  $p < 0.0001$ .

**Table 7** Results of logistic regression output examining odds of engraftment by graft type and surgeon specialty.

Variable	Odds ratio estimate	P-value
Graft type = fibrin	1.094261	0.0588
Specialty = plastic and reconstructive surgeon	1.382525	<0.001

compared to the control (although did not reach significance). Overall graft loss was high in several of the studies, however due to lack of information on surgical preparation further analysis was limited.

The proteins in the fibrin glue degrade within two weeks of application, and the thin layer of fibrin sealant potentially mimics the exudation of fibrin during the healing process.<sup>14,20</sup> The sealant matrix may optimally allow for spread of cytokines, nutrients and inosulation with subsequent angiogenesis.<sup>3,15</sup> In burn patients, smoking and hyperglycemia have demonstrated significant impact on skin graft survival and wound healing. Perez-Guisado et al. used fibrin glue to augment staples for graft adherence in these difficult populations. Compared to staples alone, fibrin adhesive restored skin graft adherence and healing in these patients to "near normal."<sup>21</sup> The concentration of thrombin directly impacts time of polymerization and time to position the graft, and ranges from 4IU/ml to 400-500 IU/ml traditionally used for hemostasis.<sup>22,23</sup> Rapid polymerization has not shown to impede a well-placed graft or graft viability,<sup>16</sup> and this study included both rapid polymerizing and slower polymerizing fibrin glue. Thicker applications are also known to impair graft viability and lead to necrosis of the grafts.<sup>24</sup> The introduction of a foreign matter between graft and wound bed did not prove to impact graft take or infection in this study.

Several studies suggested the true value of fibrin adhesive was in areas of high mobility/complex topography. Vibe et al.'s paper demonstrates almost double the improvement in graft take in "strained recipient areas," although the term was not further extrapolated on.<sup>17</sup> Boccarda et al. and Han et al. demonstrated excellent graft take when grafting upper extremities and the dorsum of hands, which are traditionally considered areas of difficulty.<sup>11,16</sup> Especially in the

pediatric population (Foster et al. and Gibran et al. included patients as young as 6 years old in their studies), improved early adhesion in areas of mobility/difficult grafting areas would improve care and patient quality of life.<sup>14,15</sup>

Pain control may be improved with the use of fibrin adhesive. Several studies documented superior pain management for patients with fibrin adhesive versus staples.<sup>11,14,15</sup> This includes baseline pain with movement, dressing changes, anxiety about pain, as well as having to undergo staple removal. Foster et al. also noted that providers preferred fibrin adhesive to staples ( $p < 0.0001$ ). Dependent on the burn size and state of the patient, not requiring staple removal relieves not only the patient but also the system from costs of sedation, additional pain medication, and costs associated with provider time.

While difficult to quantify, fibrin glue may also assist in earlier discharge on appropriate patients. Butts et al. documented the mean number of days to discharge was shorter for fibrin adhesive compared to staples (4.2 days in fibrin control vs. 6 days for staples), however given that length of stay is not a parametric value, our study was unable to assess if the statistics were run using an appropriate non-parametric model.<sup>12</sup> Juang et al. found using fibrin as an adjunct to staples enabled their team to discharge patients in less than 24 h after a split thickness skin graft, when the area grafted was less than 10% TBSA.<sup>25</sup>

In terms of purchasing cost in the United States health system, skin staplers range from basic to expensive, costing \$5-\$45, while staple removers cost less than \$5,<sup>26</sup> leading to an average cost of \$30 (\$10-\$50) for materials. In government run health systems, costs may in fact be much lower. In the included studies, the median number of staples was 30 (range of 7-88, Foster et al.; 33.7 mean staples, Gibran et al.).<sup>14,15</sup> Skin staplers on average contain 35 staples.<sup>27</sup> This suggests the graft sizes in the included studies were small.

Tissue adhesive cost varies based on volume and type of applicator, however our study estimated a cost of \$50 per ml of commercially prepared fibrin tissue glue,<sup>5,28</sup> and generally 2 ml is used for 100 cm<sup>2</sup> of skin graft.<sup>22</sup> There are also inherent costs to running the operating room while the tissue glue and applicator are prepared. To return to the modalities discussed in the introduction, a Cochrane review found NPWT to cost on average \$96/day for commercial therapy.<sup>18</sup>

The cost of fibrin glue is greater than the cost of staples or sutures. Our study suggests there are other indications for the use of fibrin tissue sealant. These include: potential

reduction in incidence of hematoma/seroma, use in difficult to graft areas with complex topography, use in areas where patients cannot tolerate staples or in the pediatric population, and perhaps application in cases where the patient can be discharged home with a small graft treated solely with fibrin glue and basic wound care. NPWT also has supportive data regarding complex graft areas, but is beyond the scope of this study. In the United States health care system, for patients where there delays related to insurance approval for NPWT, fibrin may be a potential alternative. Furthermore, decreased sedative or narcotic medication required for painful dressing changes is warrants further evaluation. Other papers have shown the efficacy of fibrin as a topical dressing that accelerates hemostasis and improves donor site pain from skin graft harvest as well as a vehicle for platelet enriched plasma to speed epithelialization at donor sites.<sup>2,3,29-31</sup>

No instances of systemic viral infection or other safety concerns were noted in the papers reviewed, where those outcomes were reported. However, there are documented safety concerns for use of fibrin glue, including anaphylaxis due to bovine aprotinin in Tisseel, and hypersensitivity reactions have been documented as well (0.5 per 100,000 cases).<sup>6</sup> Frequent cases of viral transmission have not been demonstrated, despite numerous retrospective reviews and case series. B19 parvovirus has been noted in several rare cases.<sup>5,22,23</sup> Nonetheless, whenever the use of human or bovine product is employed in the care of patients, appreciation of the potential transmission of disease must be maintained.

To our knowledge, this is the first meta-analysis to look at fibrin tissue sealant and skin graft adherence in humans. This study was limited by several variables, including size of skin graft, however it may have impact on burn surgery: particularly small grafts on difficult contour areas where the patient might otherwise be healthy and capable of discharge home. Any mechanisms to improve adherence and shorten hospital stays are prudent to employ, and evaluation of fibrin glue is worthwhile.

Limitations of this study include the heterogeneity between papers and outcomes. Furthermore, bias is introduced due to Artiss industry sponsorship for two of the included studies (Baxter International, Inc., Deerfield, Illinois, USA).<sup>14,15</sup> However, despite inclusion of studies with industry sponsorship, the authors strove to present the data available as reliably as possible. Publication bias ultimately affects all meta-analyses, which rely on previously published data. Due to the heterogeneity of the data, some extrapolation was required for data points included in the meta-analysis. In order to include Gibran et al.'s data in the meta-analysis for hematoma/seroma, the separately listed hematoma and seroma data were averaged. Furthermore, the heterogeneity of the studies meant our study could not reliably establish size of the grafts adhered with fibrin, but only reflect on TBSA grafted. This limited the study to small to medium grafts based on data available, and impact of our results is temporized by this uncertainty. The high rates of hematoma/seroma may reflect limitations related to surgical technique and hemostasis that cannot be reliably explored in this study.

Strengths of the study include the methodological approach to the literature search and application of the MI-

NORS criteria. Furthermore, this study provides a much larger population to evaluate the subject of interest as a result of the meta-analysis. Only comparative studies were used for the meta-analysis. Rigorous statistical methodology was applied, taking into account the heterogeneity of meta-analysis data. Lastly, this paper uniquely presents criteria based on the studies reviewed, to guide use of fibrin in skin grafts.

## Conclusions

Fibrin tissue sealant is effective for adhering skin grafts but cannot be shown to be more effective than staples. According to this study, use of fibrin shows tendencies towards decreasing hematoma/seroma formation and graft loss, and integration and healing of the skin. This study also illustrates the possibility of fibrin glue to decrease pain at dressing changes in minor burns, especially when absorbable sutures or NPWT are not employed, and avoidance of secondary procedures for staple removal and sedation. Comparison of graft adherence and wound healing in comparison to NPWT is beyond the scope of this study, but with the exploration of the use of fibrin it opens up to future studies exploring benefits and costs of NPWT versus fibrin glue. Fibrin sealant fixation benefits children and those with burns located on the hand, resulting in less discomfort during therapy and dressing changes, which may merit its high cost in such situations.

## Conflict of interest statement

No authors have conflicts of interest to disclose. None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

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## IRB

This meta-analysis of published data did not require IRB approval.

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