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Systematic review

Use of biomaterials in the reconstruction of posterior lamellar eyelid defects: a systematic review and meta-analysis

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Abstract

Eyelid defects can occur secondary to tumours, trauma, burns, and congenital factors. Among the most challenging aspects of eyelid reconstruction is the rebuilding of a tarsal substitute due to its delicate and multi-layered tissue composition. Attempts to use biomaterials for posterior lamellar reconstruction are intended to provide an alternative to traditional autograft reconstructions. In this review, we aimed to assess the types of biomaterials used for the reconstruction of the posterior lamella associated with eyelid defects and the associated clinical outcomes. A literature search was conducted on Pubmed, Prospero, Dynamed, DARE, EMBASE, and COCHRANE databases. A total of 15 articles fulfilled the inclusion criteria, and 129 patients with 142 eyelids reconstructed, using artificial grafts, were included in the review. Acellular dermis allograft (AlloDerm®, LifeCell) ($n = 49$) was the most common artificial graft used. A meta-analysis was performed, which demonstrated a pooled success rate of artificial grafts of 99% (95% CI 96–100, $p = 0.05$; $I^2 = 40\%$, total complications seen 39% (95% CI 96–100, $p = 0.05$; $I^2 = 40\%$) and re-operation rates of 5.6% ($n = 8$). The biomaterials used demonstrated an overall success rate of 99%, which is similar if not greater than that reported with the use of traditional autograft reconstruction techniques, with similar complications and fewer re-operations than autografts. This suggests that clinicians should consider the clinical use of artificial grafts for posterior lamellar reconstruction.

Keywords: Eyelid reconstruction; Posterior Lamellar; Biomaterials; Allografts

Introduction

Eyelid defects can occur secondary to tumours, trauma, burns, and congenital factors.[1] Eyelid reconstruction remains among the most challenging areas of reconstruction,[1] with eyelid defects having a significant impact on the quality of life of patients.[2]

To optimise patient outcomes, essential understanding of eyelid anatomy is required. The eyelids are essentially bilamellar structures, which consist of the anterior and posterior lamellae. The anterior lamella is composed of skin and orbicularis muscles.[1] The posterior lamella comprises the tarsal plate and palpebral conjunctiva.[3] The primary support of the eyelids is the medial and lateral canthal tendons, which attach to the tarsi and provide anterior-posterior stability.[1]

The goals of eyelid reconstruction typically involve restoring eyelid structure and function and achieving an acceptable aesthetic appearance.[1] An ideal method for eyelid reconstruction should provide the following crucial charac-

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teristics: good contact without irritation of the bulbar conjunctiva, supportability, applicability to various types of defects, easy performance, and minimal damage to the donor site. Reconstruction should be tailored to the defect size, thickness, and location.[1,4]

Amongst the most challenging aspects of eyelid reconstruction is the reconstruction of a tarsal substitute due to its delicate and multi-layered tissue composition. Posterior lamellar defects are often reconstructed with tissues of similar strength to the native tarsus.[1] When defects are greater than 50% of the eyelid, free autograft or tissue flaps are often used.[1] Attempts to use biomaterials for posterior lamellar reconstruction provide an alternative to autograft reconstructions.[5] However, previous reports have raised issues with graft contraction, resorption, and inflammatory responses and therefore widespread clinical use is yet to be adopted. Many innovations in terms of technique, materials, and tissues have been proposed for the reconstruction of the posterior lamella.[5]

In this review, we aimed to assess the types of biomaterials used for the reconstruction of the posterior lamella associated with eyelid defects, the success rates of artificial grafts used in posterior lamellar reconstruction and total complications.

Methodology

Literature search

A literature search was conducted in December 2022 by two independent reviewers on Pubmed, Dynamed, DARE, EMBASE, Cochrane, and British Medical Journal (BMJ) electronic databases for articles published between 2000 and 2022. The following search parameters were used to retrieve the relevant articles: “posterior lamellar”, “eyelid defects”, “eyelid reconstruction”, “periorbital defects” “periorbital reconstruction”, “artificial grafts”, “prosthetic grafts”, “biomaterials” and “dermal substitute”. A grey literature search was conducted looking at conference abstracts for the British Association of Plastic, Reconstructive and Aesthetic Surgeons and the British Association of Oral and Maxillofacial Surgeons.

Only original research studies published between 1980 and 2022 were considered. The following study types were reviewed: randomised control trials, prospective cohort studies, retrospective cohort studies, case studies, and case series. Two independent reviewers screened titles and abstracts for eligibility and inclusion. The same reviewers then screened relevant full papers before inclusion. The systematic review has been registered on PROSPERO and is pending approval for registration. PROSPERO application ID: 421044.

Inclusion

For this article, all studies to focus on the reconstruction of eyelid defects using prosthetic/artificial grafts were included. Trials reconstructing either the upper or lower eyelids were all included.

Exclusion

For this paper, studies that focused exclusively on the reconstruction of defects other than eyelids were excluded. Studies describing reconstruction of the eyelid for their retraction or post-cosmetic surgery were also excluded. Studies not using artificial grafts for reconstruction were excluded. In-vitro and animal trials were excluded from our analysis.

Data extraction

The data were extracted on to a standardised data extraction template relating to: population, intervention, comparison, and outcome (PICO). The population studied included patients with eyelid defects requiring reconstruction. The intervention used was artificial grafts, primarily AlloDerm® (LifeCell). The comparator was other forms of artificial grafts. The success rate of intervention was the primary outcome and the secondary outcome included total complications. The definition of success varied across the studies, so this was defined as patients undergoing eyelid reconstruction with satisfactory cosmetic/functional outcomes and not requiring further reconstructive surgery. Repeat operations were only noted if they were related to eyelid reconstruction.

Risk of bias and quality assessment

Each study was reviewed individually for risk of bias associated with the selection, comparability and outcome reporting using the Newcastle Ottawa Tool for cohort studies. The results from the Newcastle Ottawa Tool were translated into the Agency for Healthcare Research and Quality (AHRQ) scores.[6,7]

Publication bias was assessed using R (version 4.2.2), package meta version 6.0-0 to create funnel plots, which assessed bias for the outcomes of posterior lamellar success rates and complications, respectively.

Statistical analysis

Pooled analysis estimates and 95% confidence intervals were calculated for the outcomes of successful reconstruction rates and total complications in all studies utilising either AlloDerm® or non- AlloDerm® grafts, with the application of both random and fixed models. Statistical analysis was performed using R (version 4.2.2), package meta version 6.0-0. Heterogeneity was assessed using R (version 4.2.2), package meta version 6.0-0 to determine the I^2 statistic (in percentage) and Cochran’s Q value.

Results

The number of studies screened, assessed for eligibility, and included in the review, with reasons for exclusion are pre-

sented in the PRISMA flow diagram. (Fig. 1) Using the key search terms described earlier yielded a total of 552 results across Pubmed, Dynamed, DARE, Cochrane, and grey literature searches. Articles were initially reviewed by two independent reviewers and included/excluded based on the title and abstract. Next, the full text was reviewed for 32 articles. Reasons for the exclusion of full texts included studies focusing on the reconstruction of eyelid retraction or other facial defects aside from the eyelid, and those not available in English. A total of 15 articles fulfilled the inclusion criteria. The study characteristics can be seen in Table 1.[8–21]

A total of 129 patients were included in this review with 142 eyelids reconstructed and an age range from 8 to 90.5 years. Fifty-two patients were female and 58 were male with the remaining patients not having their gender reported. The aetiology of the eyelid defects included excision of malignancy (n = 87), trauma-related (n = 10), burns (n = 23) and trachoma (n = 11). The size of defects varied across the studies, and these can be seen in Table 1. Seven of the studies were conducted in low- and middle-income countries (LMIC).

Method of reconstruction

Upper eyelid defects were seen in 90 cases and lower eyelid defects in 38 cases. In 15 cases the location of the eyelid defect was not mentioned. For upper eyelid reconstruction, the posterior lamella was reconstructed using acellular dermis allograft (AlloDerm®) (n = 40), silicone plate (n = 30), xenogeneic bovine acellular matrix (n = 15) and Integra (Integra LifeSciences) (n = 4). Five studies reported on the thickness of the graft used and this varied from 0.2 to 1.78 mm.

For lower eyelid defects (n = 25) the posterior lamella was reconstructed using AlloDerm® (n = 9), polyethylene porous implant (n = 1), Integra (n = 1), xenogeneic bovine acellular matric (n = 13) and Permacol™ (Medtronic) (n = 1).

Results

Follow up of patients ranged from 0 to 60 months. Successful reconstruction ranged from 0% to 100% as seen in Table 1. 37 (26.1%) complications were seen within the

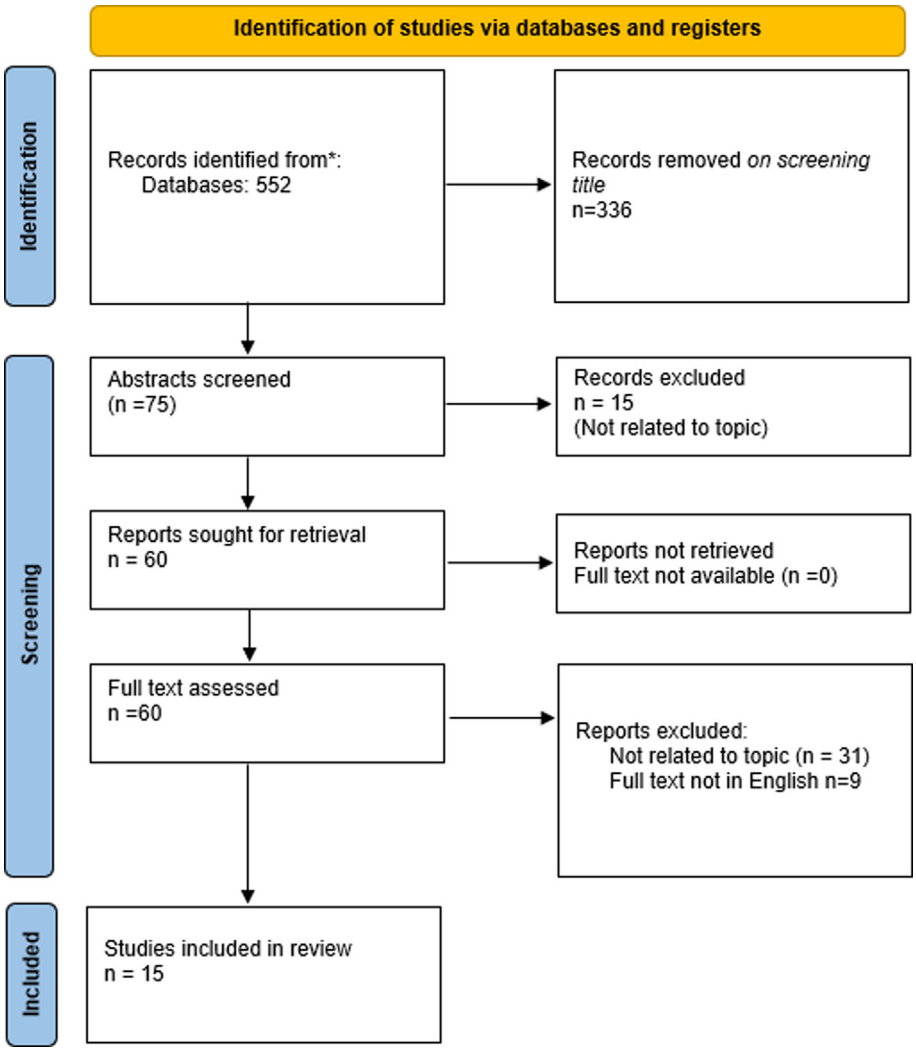


Fig. 1. PRISMA Search.

Table 1
Study characteristics.

First author, year, and reference	Country Published	Number of Patients	Age range (mean/median)	Gender ratio (female: male)	Location of the defect (number of cases)	Posterior lamellar reconstruction	Thickness of graft (mm)	Size of defect	Breakdown of aetiology	Success rates (%)	Complications	Repeat surgery required (n)
Jiaqi, 2006[8]	China	13	12–51 (mean 34)	N/A	Upper: N/A Lower: N/A	Upper: AlloDerm® graft Lower: Nil	Not reported	Not reported	Thermal burns (n = 5), Chemical burns (n = 8)	100	Eyelid incisura (n = 1), ptosis (n = 1)	2
Naimi, 2007[9]	USA	5	52–86 (median 80)	4:1	Upper: 5 Lower: 1	Upper: AlloDerm® graft Lower: AlloDerm® graft	Not reported	50–100%	Sebaceous cell carcinoma (n = 2), melanoma (n-2), SCC (n = 1)	100	Residual keratopathy (n = 2), corneal abrasion (n = 1)	Nil
Pushpoth, 2008[10]	UK	3	41–72	1:2	Upper: 2 Lower: 1	Upper: AlloDerm® graft Lower: AlloDerm® graft	0.78–1.78	66.7%	BCC (n = 2), trauma (n = 1)	100	Nil	Nil
Hayek, 2009[11]	USA	5	52–86 (mean 80)	4:1	Upper: 5 Lower: 1	Upper: AlloDerm® graft Lower: AlloDerm® graft	0.2	66.7%-100%	Sebaceous gland carcinoma (n = 2), melanoma (n = 2), SCC (n = 1)	100	Recurrence (n = 1), residual exposure keratopathy (n = 2) adjuvant radiotherapy (n = 1) , corneal abrasion (n = 1)	Nil
Gu, 2009[12]	China	14	8–68	7:9	Upper: 14 Lower: 0	Upper: AlloDerm® graft Lower: Nil	0.3–0.6	Not reported	Thermal injuries (n = 5), trachomas causing severe cicatricial entropion/ shrinkage of post lamellar area (n = 11	85.7	Recurrence of upper eyelid entropion (n = 2), corneal ulcer (n = 1)	2
Sahin, 2012[13]	Turkey	1	33	0:1	Upper: 1 Lower: 1	Upper: Nil Lower: Polyetheylene porous implant	Not reported	100%	Mine explosion	100	Nil	Nil
Gu, 2012[14]	China	8	22–52	1:7	Upper: 8 Lower: 0	Upper: AlloDerm® graft Lower: Nil	0.5	20–28 mm × 5–8 mm	Trauma (n = 3), Burns (n = 5)	100	Eyelid margin notching (n = 1), mild ptosis (n = 1)	Nil

Thinda, 2012[15]	USA	1	35	1:0	Upper: 1 Lower: 0	Upper: Integra Lower: N/A	Not reported	8 × 5 cm	RTC upper eyelid defect (n = 1)	0	Residual defect requiring two further clavicular autografts, one lagophthalmos requiring surgery and autograft	3
Peter, 2013[16]	UK	1	79	1:0	Upper: 0 Lower: 1	Upper: N/A Lower: Permacol	Not reported	80%	Basal cell carcinoma (n = 1)	0	Dehiscence causing graft exposure (n = 1)	1
Chen, 2018[17]	USA	3	Mean 46	1:3	Upper: 3 Lower: 1	Upper: N/A Lower: N/A	Not reported	Not reported	Trauma (n = 4), road traffic crash (n = 3)	100	Mild medial cicatricial lid retraction, asymptomatic (n = 1)	Nil
Mandal, 2021[18]	India	30	40–86 (mean 71.5)	14:16	Upper: 30 Lower: 0	Upper: Culter beard silicon plate Lower: Nil	Not reported	60–100% (87.3%)	Sebaceous gland cancer 76.7%, SCC 10%, BCC 6.7 %, porocarcinoma and melanocytic melanoma 3.3%	100	Upper lid entropions (n = 2), transient lagopthalmos (n = 2), Extrusion of silicone plate (n = 2), infection (n = 1)	Nil
Eah, 2021[19]	Korea	6	Not reported	Not reported	Upper: 6 Lower: 0	Upper: AlloDerm® graft Lower: N/A	Not reported	70–100%	Sebaceous gland cancer (n = 6)	100	Nil	Nil
Custer, 2021[20]	USA	12	42.3–90.5 (mean 65.4)	5:7	Upper: 0 Lower: 12	Upper: N/A Lower: Dermal matrix porcine graft	Not reported	6–16 mm (11.7 mm)	Post-Mohs surgery	100	Trichiasis (n = 2), misdirected eyelashes (n = 1), prolonged erythema from conjuctival overgrowth of lid margin required marginal cauterisation	Nil
Ma, 2022[21]	China	6	52–77 (mean 58)	1:5	Upper: 0 Lower: 6	Upper: N/A Lower: AlloDerm® graft	Not reported	Not reported	Malignancy	100	Nil	Nil
Huang, 2022[22]	China	21	55–65 (mean 68.48)	14:7	Upper: 15 Lower: 13	Xenogeneic bovine acellular dermal matrix	0.7	50–100%	Eyelid adenocarcinoma (n = 8), BCC (n = 8), eyelid SCC (n = 3), eyelid malignant melanoma (n = 1), squamous cell papilloma (n = 1)	100	Lid entropion and large palpebral fissure with eye irritation (n = 2), mild margin irregularities (n = 21), Transient lagopthalmos, which resolved six months postoperatively (n = 3)	Nil

Table 2
Newcastle-Ottawa scores and Agency for Healthcare Research and Quality (AHRQ) classification.

First author, year, and reference	Selection score	Comparability score	Outcome score	AHRQ rating
Jiaqi, 2006[8]	2	0	1	Poor
Naimi, 2007[9]	3	0	2	Poor
Pushpoth, 2008[10]	2	0	2	Poor
Hayek, 2009[11]	2	0	1	Poor
Gu, 2009[12]	1	0	2	Poor
Sahin, 2012[13]	1	0	2	Poor
Gu, 2012[14]	1	0	1	Poor
Thinda, 2012[15]	1	0	2	Poor
Peter, 2013[16]	1	0	2	Poor
Chen, 2018[17]	1	0	2	Poor
Mandal, 2021[18]	1	0	2	Poor
Eah, 2021[19]	1	0	2	Poor
Custer, 2021[20]	0	0	2	Poor
Ma, 2022[21]	1	0	2	Poor
Huang, 2022[22]	1	0	2	Poor

cohort with mild margin irregularities (n = 21), entropion (n = 6), keratopathy (n = 4) and lagophthalmos (n = 6) being the most common. A total of eight (5.6%) repeat procedures were performed on six (4.7%) patients. Five procedures (3.5%) had failed (AlloDerm® (n = 3), Integra (n = 1) and Peramacol™ (n = 1)). Three of the failed procedures were conducted in LMIC and two within high-income countries.

Risk of bias

Of the studies included in this paper, all were of poor quality (n = 15) according to the AHRQ standards. All studies had evidence of comparability bias and eleven studies had evidence of selection bias. Three studies had evidence of outcome bias (Table 2).

Funnel plot analysis showcased the possibility of publication bias for both outcomes of posterior lamellar success and complication rates. The funnel plots for both outcomes displayed slight asymmetry, which was more visible in the funnel plot displaying complication rates (Figs. 2 and 3)

Meta-analysis

Success rates

Overall, the pooled analysis of success rates in all studies was 99% (95% CI 96–100, $p = 0.05$; $I^2 = 40\%$; Fig. 4). When comparing studies that used AlloDerm® to studies using all other grafts for posterior lamellar reconstruction, the pooled success rate for the AlloDerm® grafting group was 99% (95% CI 93–100, $I^2 = 0\%$; Fig. 5), whilst the pooled success

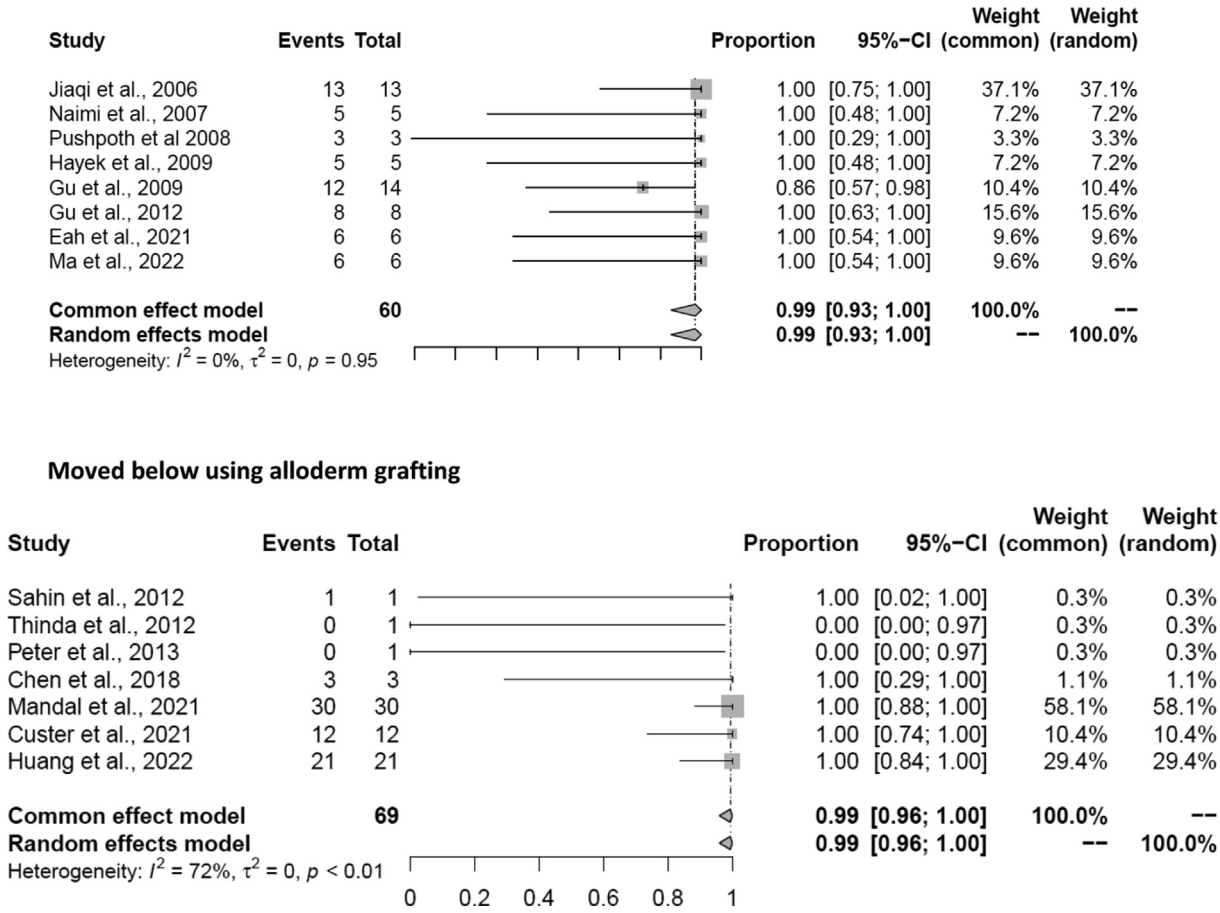
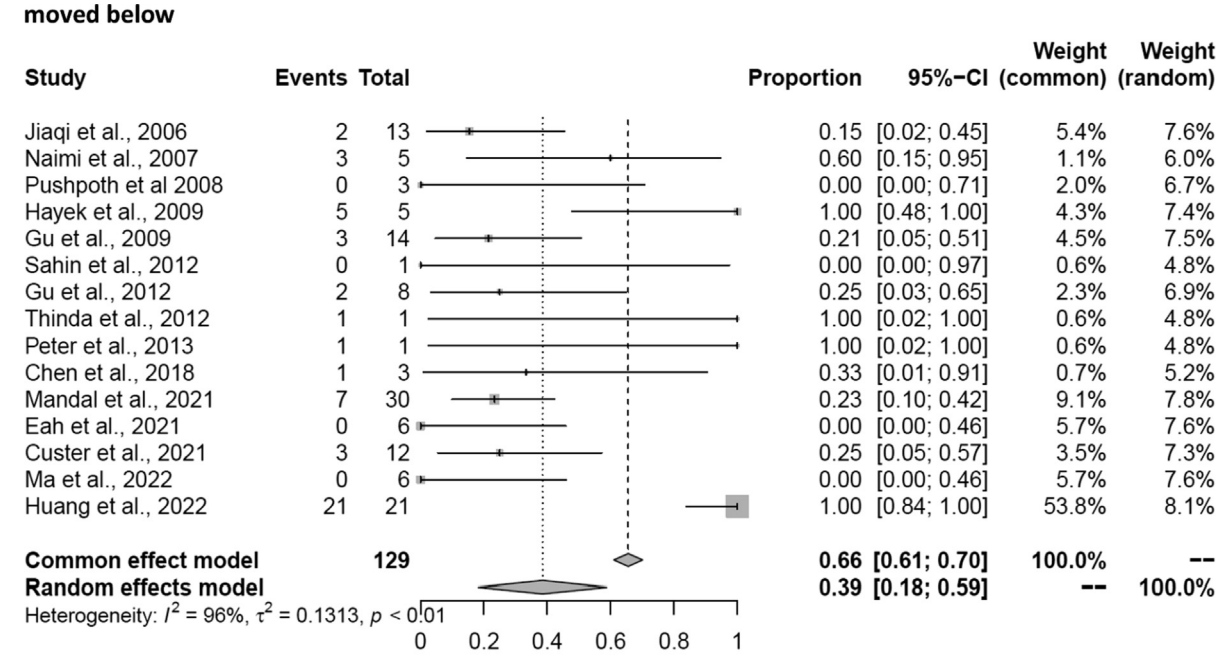


Fig. 2. Funnel plot of pooled success rates for posterior lamellar reconstruction.



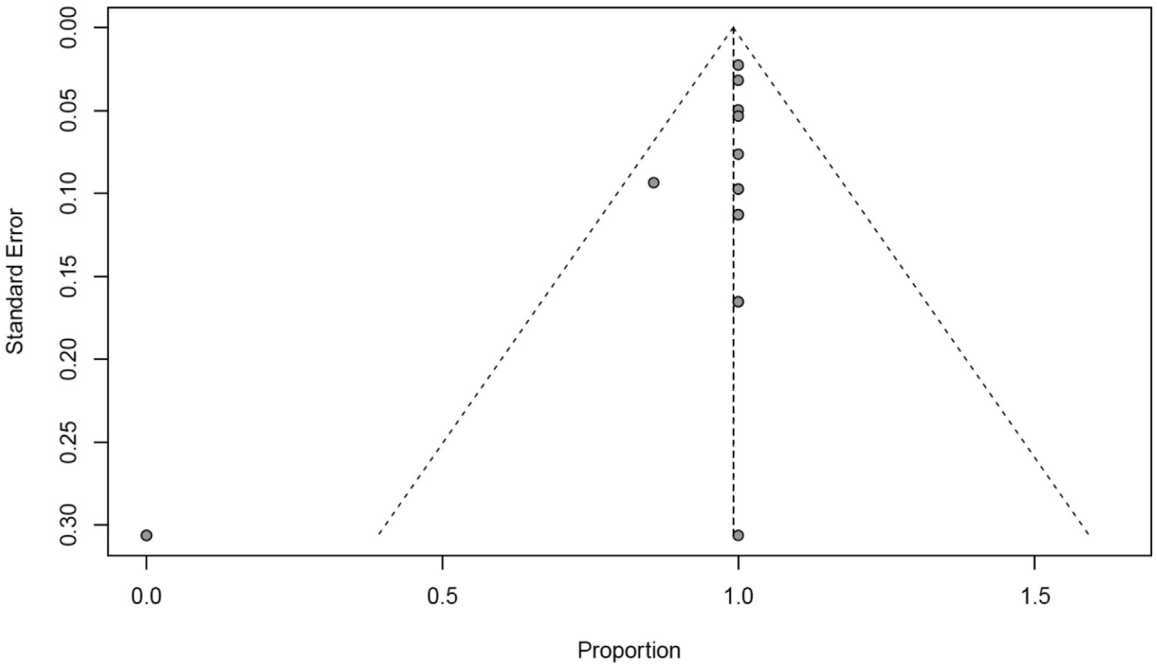


Fig 2. *(continued)*

rate for non- AlloDerm® studies was 99% (95% CI 96–100, I^2 = 72%; Fig. 6). There was no statistically significant difference between reconstructions using either AlloDerm® or any other artificial graft (p > 0.05).

Complications

Overall, the pooled analysis of complications in all studies was 39% (95% CI 96–100, p = 0.05; I^2 = 40%; Fig. 5). The pooled complication rate after posterior lamellar reconstruction in the AlloDerm® studies was 27% (95% CI 2–52, p < 0.01; I^2 = 89%), compared to 54% (95% CI 22–86, p < 0.01; I^2 = 95%) in the non- AlloDerm® studies (Fig 7).

Discussion

Eyelid reconstruction can present a challenging surgical problem due to the significance of the eyelids as a key feature of the face, contributing to both essential function and aes-

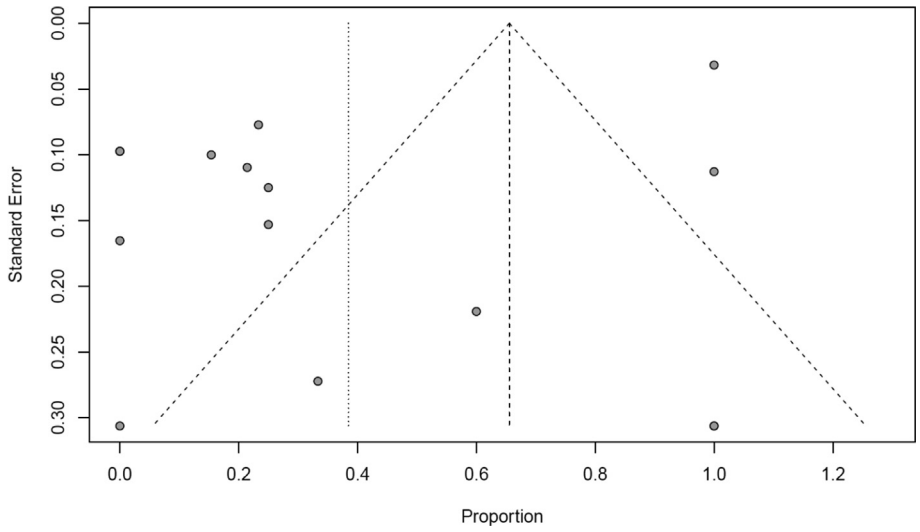


Fig. 3. Funnel plot of pooled success rates for posterior lamellar reconstruction.

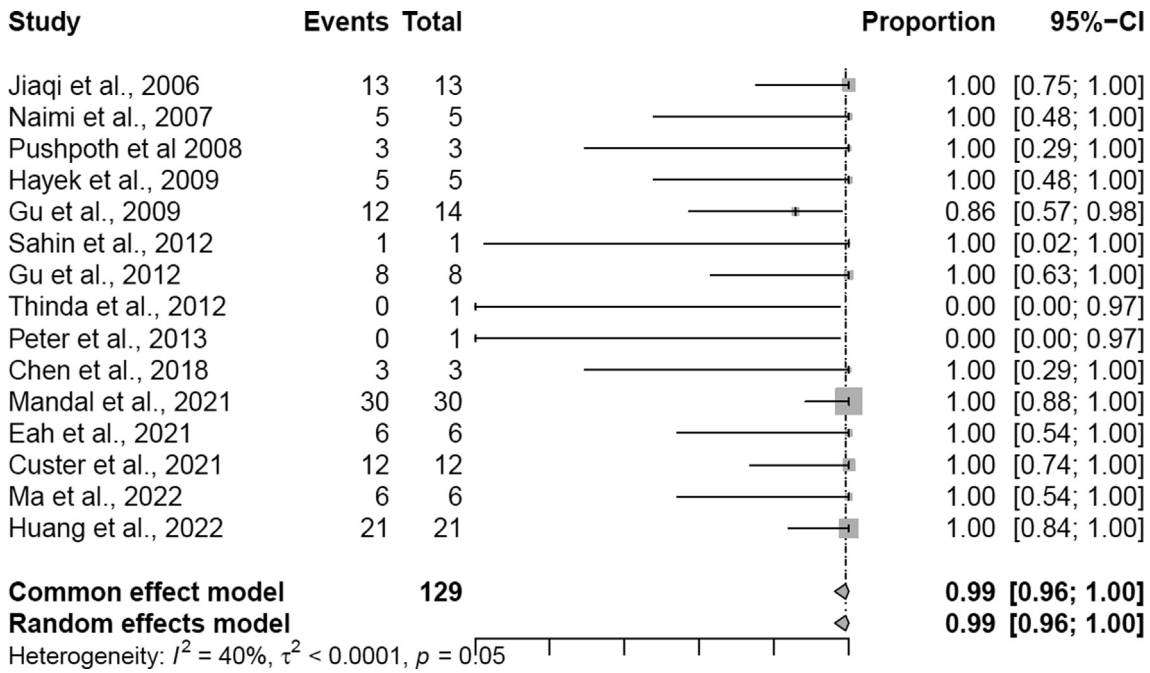


Fig. 4. Forest plot of pooled meta-analysis of success rates for posterior lamellar reconstruction.

thetics.[1,23] The posterior lamella poses more of a challenge to the reconstructive surgeon due to its delicate and multi-layered composition.[1,5] The current review demonstrates a pooled success rate of 99% associated with the use of artificial grafts in the reconstruction of posterior lamellar defects with minimal re-operations (5.6%).

Reconstructive techniques

Previous work has reported on the use of local flaps and substitute grafts including palatal mucosa, auricular cartilage, chondro-mucosal, buccal-mucosal and tarso-conjunctival grafts to repair posterior lamellar defects; the success rates for autografts are reported as 70–100%.[5,22–27] Although complications were reported, the rates for re-operation varied from 0% to 30%[5,22–27] and there were added challenges posed by donor site morbidity. Issues encountered with such substitutes include difficulty with harvest, inadequate strength to support the eyelid, and difficult donor healing. Currently, no tissue can fully replicate the native tarsal tissue.

Biomaterials in posterior lamellar reconstruction

Biomaterials provide several advantages over autografts, such as: biocompatibility, plasticity, and rigidity, which make them suitable for allowing a scaffold for conjunctival

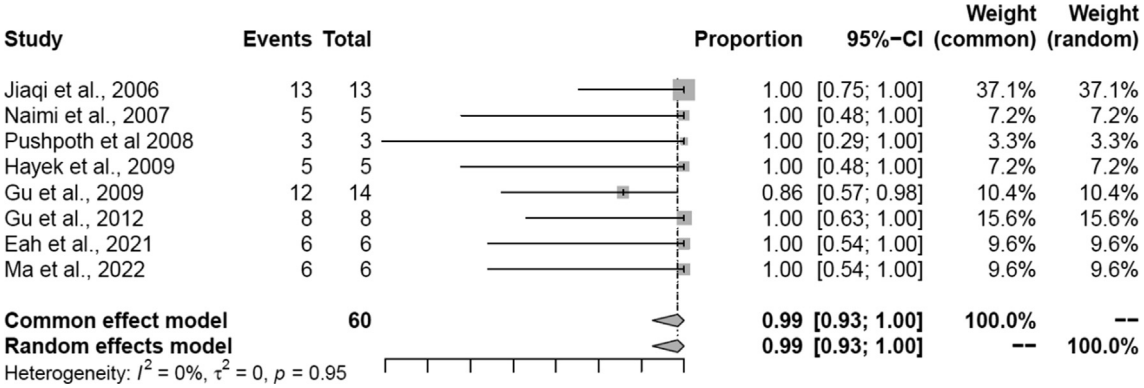


Fig. 5. Forest plot of pooled meta-analysis of success rates for posterior lamellar reconstruction using alloderm grafting.

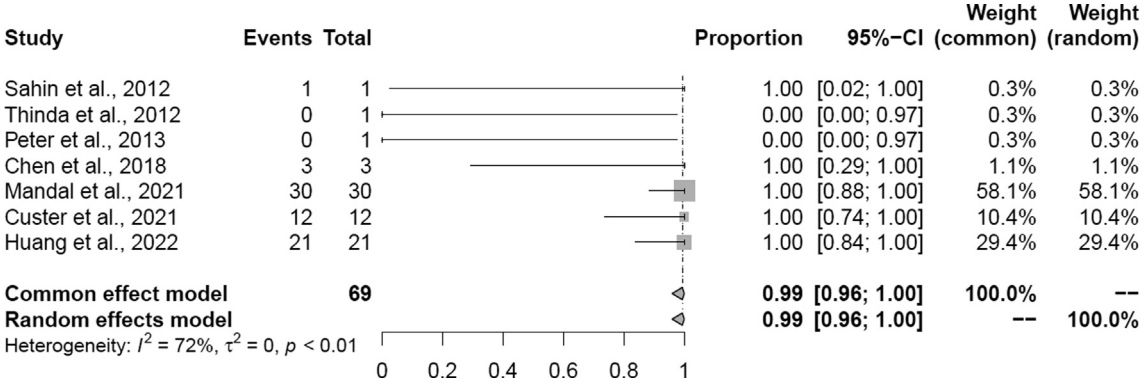


Fig. 6. Forest plot of pooled meta-analysis of success rates for posterior lamellar reconstruction using non-alloderm grafting.

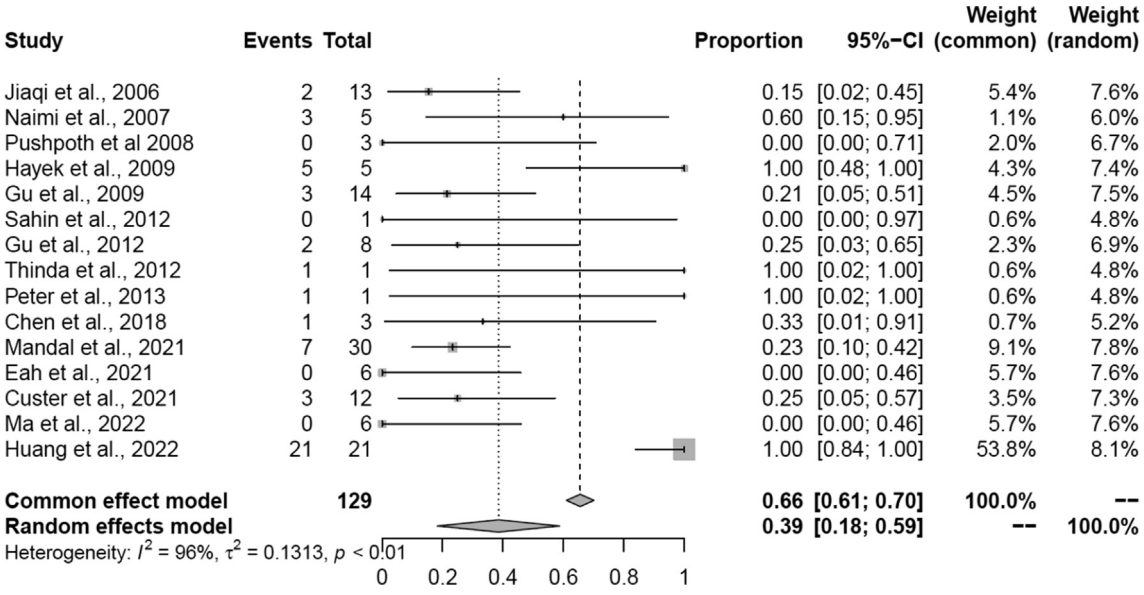


Fig. 7. Forest plot of pooled meta-analysis of complication rates for posterior lamellar reconstruction.

tissue growth. Despite a pooled 39% complication rate being seen within this review, these were often mild complications that were managed conservatively and did not require further surgery, and higher complication rates (20–100%) have been reported with autografts.[22,23,26,27]

Concerns arise with regards to the resorption and shrinkage of the artificial graft, which have been reported in some animal models, and would likely correlate to higher re-operation rates.[5] Although within our review only 5.6% of patients required re-operations and only 1.8% of patients

required re-operation related to graft shrinkage. Therefore, graft shrinkage despite being a possibility does not significantly impact the functional outcomes.[5]

In the studies reviewed, the biomaterials used demonstrated an overall success rate of 99%, which is similar, if not greater, than that reported with the use of autograft reconstruction techniques with fewer complications and re-operation than autografts. There was no difference in success rates based on the type of reconstruction used. However, AlloDerm® was noted to have lower complication rates. The use of biomaterials also removes the issue of donor site morbidity which is an added benefit.[5] With artificial grafts being adopted in other reconstructive surgeries including the use of Integra for the reconstruction of skin defects secondary to burns and cancer defects with success rates over 90%.[28] Therefore, such substitutes are readily available and approved for use in clinical practice and therefore adopting their use in posterior lamellar reconstruction can occur more promptly.

Some limitations, which may present when reconstructing may be the economical constraints, but with posterior lamellar reconstruction the amount of artificial graft is small, with no second-stage surgeries and minimal re-operation rates possibly offsetting the initial graft cost.[5]

Biomechanical properties of autografts and allografts

The biomechanical properties of the tarsus are essential to consider whilst planning for the reconstruction of the posterior lamella.[1,5] Reconstruction requires use of a substitute that is rigid enough to allow for stabilisation of the eyelid margin and mobile enough to avoid the restriction of blinking.[1,5] The tarsus consists of collagen, which provides elasticity and aggrecan, which promotes stiffness.[29] Commonly used autografts in posterior lamellar reconstruction have not previously undergone biomechanical studies to assess their properties compared to the tarsus.[29] Despite auricular cartilage having a similar composition to the tarsal plate it does, however, contain significantly more elastin, which has considerably lower tensile modulus than collagen and greater extensibility.[29,30] Meanwhile, similar biomechanical studies have yet to be done with the use of artificial grafts.

The future of eyelid reconstruction

Future work should provide a biomechanical analysis of traditional autografts in comparison to artificial allografts and the native tarsus to determine the optimum method for reconstruction of the posterior lamella. Despite the biomaterials mentioned within this review demonstrating high success rates, they are still unable to fully replicate or replace the function of the native tissue of the tarsus.[31] No studies that we know of have reported on the biomechanical properties of the artificial graft being used and comparison with the native tarsus. Future work is required to derive an artificial tarsus that resembles the function and consistency of the native tarsus. Modern tissue engineering may provide the stepping-stone to devise such a material as this would allow greater flexibility with design and structure. Prior work had derived a chitosan scaffold that demonstrated similar biomechanical properties to the native tarsus.[31,32] These studies are still in the pre-clinical phases and therefore adopting their use in the reconstruction of human eyelids is far off. However, artificial grafts that are clinically available have demonstrated good functional/aesthetic outcomes with minimal complication and re-operation rates and appear to be the next transition point in the reconstruction of the posterior lamellar.

Limitations

All studies included within this review often focused on different aims with no universal definition of graft failure, which has made an objective comparison difficult. The quality of the papers included in this review and the significant heterogeneity between them was a major limitation. Certain parameters, such as graft thickness, were not reported in all papers making the comparison equivocal and possible confounders difficult to account for. Specific parameters, such as defect size, were not reported consistently within the literature and various definitions were used across the studies, which made comparison difficult.

Ethics statement/confirmation of patient permission

Not required.

Conflict of interest

We have no conflicts of interest.

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