

AlloDerm implants for prevention of Frey syndrome after parotidectomy: A systematic review and meta-analysis

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Abstract. Although Frey syndrome is not life-threatening, it is identified as the most serious and widely recognized sequela of parotidectomy and has significant potential negative social and psychological implications. Several studies have investigated whether AlloDerm® implants prevent Frey syndrome effectively and safely, however, the conclusions are inconsistent. We aimed to evaluate the precise effectiveness of AlloDerm implants for preventing Frey syndrome after parotidectomy, using a systematic review and meta-analysis. We searched randomized and quasi-randomized controlled trials in which AlloDerm implants were compared to blank controls for preventing Frey syndrome after parotidectomy, from the PubMed, Embase, the Cochrane Library and the ISI Web of Knowledge databases, without any language restriction. Two reviewers independently searched, identified, extracted data and assessed methodological quality. Relative risks with 95% confidence intervals were calculated and pooled. Five articles involving 409 patients met the inclusion criteria. Meta-analyses showed a significant 85% relative risk reduction in objective incidence (RR=0.15, 95% CI 0.08-0.30; P<0.00001) and 68% in subjective incidence (RR=0.32, 95% CI 0.19-0.57; P<0.00001) of Frey syndrome with AlloDerm implants; there was a significant 91% relative risk reduction in salivary fistula (RR=0.09, 95% CI 0.01-0.66; P=0.02); there was no statistical significance for the incidence of facial nerve paralysis (RR=0.96, 95% CI 0.84-1.09; P=0.51); there was no statistical significance for the incidence of seroma/sialocele (RR=1.36, 95% CI 0.66-2.80; P=0.40); there was a trend for a small effect in improving facial contour. Adverse events related to AlloDerm implants were not found. There is evidence that

AlloDerm reduces the incidence of Frey syndrome effectively and safely, and also has the potential to improve facial contour and decrease salivary fistula. However, it is unclear whether AlloDerm implants improve facial contour and decrease other complications. Thus, further controlled evaluative studies incorporating more precise measures are required.

Introduction

Neoplasms of the salivary glands constitute 3-10% of all tumors of the head and neck (1), and are located in the parotid gland in 34-86% of cases (2,3). Among parotid tumors, benign tumors are more common than malignant ones (4,5). Parotidectomy is commonly used in the treatment of gland tumors; it is the first choice to treat gland tumors (5-7). However, complications, such as Frey syndrome (8), transient or permanent facial nerve paresis (9), cosmetic disfigurement (10), pain and discomfort, and subsequent xerostomia, can reduce the quality of life of patients after parotidectomy (11). Among these complications, Frey syndrome has the highest incidence, from 11 to 95% (12-14).

Frey syndrome was first described by Łucja (Lucie) Frey in 1923 (15,16). Andre Thomas in 1927 and later Ford and Woodhall in 1938 postulated the theory of aberrant regeneration of the sectioned parasympathetic fibers that regrow to innervate the vessels and sweat glands of the skin overlying the parotid to explain the symptoms (15,17). Although Frey syndrome is not life-threatening, the surveys show that Frey syndrome and concave facial deformity are identified as the most serious self-perceived sequelae with significant potential negative social and psychological implications, which result in discomfort worsening with time (7,11,12,18,19). Thus, the goals of parotidectomy are to remove the primary tumor, prevent severe functional loss, avoid cosmetic defects, and particularly to prevent Frey syndrome.

The therapeutic and preventive methods for Frey syndrome can be subdivided into surgical and non-surgical modalities. Non-surgical techniques used to prevent Frey syndrome include drugs; the most common is a local injection of botulinum toxin. Yet, this has many side effects, including mild and temporary muscle weakness and pain at the injection site,

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easy recrudescence, and the procedure also frequently affects the quantity and quality of salivary flow (20,21).

The major surgical techniques include implantation of a 'barrier', including autogenous vascularized tissue [such as the sternocleidomastoid muscle flap (22), temporoparietal fascia rotational flap (23) and the superficial muscular aponeurotic system (24)], non-vascularized tissue [such as fascia lata (25) and dermis fat grafts (26)], and synthetic biomaterials [such as expanded polytef (27)]. However, these surgical management options are limited by at least one of the following factors: i) the need for a second operation (with its associated potential morbidity), ii) the need for an additional donor site, iii) prolonged period of time under general anesthesia, iv) insufficient amount of tissue to cover the wound surface completely, v) inability to reduce the incidence of Frey syndrome (28), and vi) the higher incidence of wound infection, rejection reaction or other postoperative complications (29).

A 'barrier' that is able to demonstrate efficacy with regard to preventing Frey syndrome, while at the same time eliminating the disadvantages mentioned above would be preferred and is now being considered. AlloDerm®, in addition to serving as a nerve barrier, may serve as an effective soft tissue augmentation device in the head and neck region (30,31). Since it undergoes fibrous tissue ingrowth, has extensive sources, convenient manufacturing, efficient industrialization and virtually no side effects, it is considered as an ideal barrier in the field of oral health to date (32).

The first published study on the utilization of AlloDerm in humans was conducted by MacKinnon in 1997 (33), and it has been widely used in this field and reported in many research articles (34-41). It is a new type of biological material, yet its long-term side effects are unknown. Therefore, we performed this systematic review and meta-analysis in order to evaluate the effectiveness and safety of AlloDerm to prevent Frey syndrome after parotidectomy.

Materials and methods

Selection of studies. A comprehensive systematic search was conducted by two independent reviewers (X.T.Z. and M.Z.L.) in PubMed (1966 to May 2011), Embase (1974 to May 2011), the Cochrane Library (issue 4, 2011) and the ISI Web of Knowledge databases (1994 to May 2011) for relevant citations. In addition, we searched the reference lists of all known primary and review articles. All identified articles were screened for cross-references; no language restrictions were imposed.

The search terms were combined with ('Frey syndrome' OR 'Frey's syndrome' OR 'gustatory sweating' OR 'auriculo-temporal syndrome') AND ('AlloDerm' OR 'acellular tissue patch' OR 'acellular dermal matrix' OR 'acellular dermal' OR 'acellular dermis' OR 'Permacol' OR 'porcine dermal matrix' OR 'allograft dermis' OR 'allograft dermal matrix'), then duplicated results were removed. The remaining citations were displayed and examined.

Inclusion and exclusion criteria. Eligibility was determined by two independent reviewers (X.J.T. and W.H.), with consensus from the third reviewer (W.D.L.), on the basis of information found in the article's title, abstract or full text.

Studies were included in the review if they met the following criteria: randomized controlled trials (RCTs) and quasi-RCTs of all the articles, the study patients included adults (≥ 18 years) who were diagnosed with parotid tumors and had received a partial or total parotidectomy with facial nerve preservation, AlloDerm was applied as the experimental group and a placebo (blank) as the control group. Studies that included patients with previous surgical procedures in the parotid area or with previous radiotherapy were excluded. Review articles, commentaries, guidelines and letters were also excluded.

Data extraction. The data were extracted by two reviewers (X.J.W and Y.M.N.) independently. In case of discrepancies, a third reviewer (W.D.L.) was consulted and, after agreement, a consensus was reached. Data were extracted on publication data (the first author's last name, year of publication and country of population studied), sample size, patient characteristics (mean age and sex ratio), study design, follow-up period, outcome measures and method of measurement. Authors were contacted by e-mail for additional information if data was unavailable.

The primary outcome measure was the incidence of Frey syndrome (objective or subjective). Secondary outcomes included facial contour, adverse events (wound infection and rejection), other postoperative complications (seroma or sialocele, salivary fistula and facial nerve paralysis) that were noted when they were reported in the studies.

Quality assessment. We assessed the study quality using the Cochrane Handbook's evaluation tool for assessing the risk of bias (42) and the Jadad scoring system (43). It was also conducted by two independent reviewers (X.T.Z. and M.Z.L.) and an agreement was reached after consulting a third reviewer (Y.G.).

The Cochrane Handbook's evaluation tool included: Sequence generation – Was the allocation sequence adequately generated? Allocation concealment – Was allocation adequately concealed? Blinding – Was knowledge of the allocated intervention adequately blinded during the study? Blinding of participants and personnel? Blinding of outcome assessors? Incomplete outcome data – Were incomplete outcome data adequately addressed? Selective outcome reporting – Were reports of the study free of suggestion of selective outcome reporting? Other sources of bias – Was the study apparently free of other problems that could put it at a high risk of bias?

The Jadad scoring system included: Was the study described as randomized? Was the method used to generate the sequence of randomization described and appropriate? Was the study described as double-blind? Was the method of double-blinding described and appropriate? Was there a description of withdrawals and dropouts?

This is a five-point scale, with low-quality studies having a score of ≤ 2 and high-quality studies a score of at least 3.

Statistical analysis. Data were processed in accordance with the Cochrane Handbook (42). Intervention effects were expressed with relative risks (RRs) and associated 95% confidence intervals (CIs) for dichotomous data and mean differences (MDs) and 95% CIs for continuous data, respec-

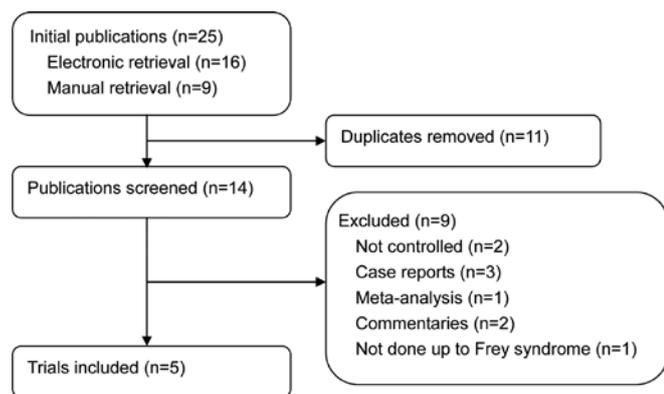


Figure 1. Summary of the study selection process.

tively. Heterogeneity among studies was informally assessed by visual inspection of forest plots, and formally estimated using the Chi-square test and I^2 test (both $P > 0.05$ and $I^2 < 50\%$ indicated there was no evidence of heterogeneity between the pooled studies) (44). The fixed-effects model was first used for meta-analyses; if there was heterogeneity, the random-effects model was used. Publication bias was tested from separate funnel plots (when the number of included studies was ≥ 9). Symmetry of and outlying results on, the funnel plots implied lack of bias, whereas asymmetry would imply that the results were subject to reporting or publication bias (45). All statistical analyses were performed using Review Manager (version 5.0.2; The Cochrane Collaboration). Description analysis was performed when the quantitative data could not be pooled. The data were entered into Review Manager by X.T.Z., and M.N.Y. checked data entry.

Results

Characteristics and quality of the included studies. A database search yielded 25 publications, of which both of the reviewers considered 14 to be potentially eligible. We excluded 9 of the articles during the second phase of the inclusion process, 2 were not controlled (39,41), 3 were case reports (33,40,46) and 1 was a meta-analysis (47). One was not done up to Frey syndrome (48) and 2 were commentaries (49,50). The remaining 5 articles were included in the meta-analysis (34-38). A summary of the study selection process is presented in Fig. 1. There were 3 studies published in English (34,36,37) and 2 in Chinese (35,38). A total of 409 participants were included. The sample size ranged from 20 to 168, and the follow-up period ranged from 5 to 39 months. All of the studies had similar eligibility criteria (Table I).

There was good agreement between the reviewers in regards to the validity assessments. All studies were clinical controlled trials, and the methodological quality of the included trials ranged from poor to excellent (Table I). Fig. 2 shows the risk of bias summary; the majority had adequate patient follow-up, and the main study biases may be caused by sample size, randomization, the procedure for concealing the treatment allocation and blinding (as it is not feasible to blind staff in these studies, blinding of investigators is feasible). For example, only 1 study (35) mentioned randomization and blinding, but did not describe how the random allocation sequence was generated.

Table I. Characteristics and Jadad scores of the included studies.

Author/(Ref.)	Year and country	Group	No.	Mean age (years)	Gender (M:F)	Interventions	Study period (years)	Follow-up (months)	Measurement	Outcomes	Jadad scores
Govindaraj <i>et al</i> (34)	2001 USA	E	32	51.7	12:20	AlloDerm	1997-1999	≥ 6	Subjective	Frey syndrome	1
		C	32	49.8	14:18	Blank			Objective	Facial contour Complications	
Sinha <i>et al</i> (36)	2003 USA	E	10	≥ 18	Not reported	AlloDerm	Not reported	≥ 12	Subjective	Frey syndrome	1
		C	10			Blank			Objective	Complications	
Yu <i>et al</i> (38)	2007 China	E	30	45	Not reported	AlloDerm	2005-2006	5-14	Objective	Frey syndrome	1
		C	27	43		Blank			Objective	Complications	
Ye <i>et al</i> (37)	2008 China	E	64	42	Not reported	AlloDerm	2004-2005	11-27	Subjective	Frey syndrome	1
		C	104			Blank			Objective	Facial contour Complications	
Li <i>et al</i> (35)	2006 China	E	50	40	20:30	AlloDerm	2001-2004	10-39	Subjective	Frey syndrome	3
		C	50		21:29	Blank			Subjective	Complications	

E, experimental group; C, control group. Subjective symptom use questionnaires, while objective use MIST.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias): Subjective outcome	Blinding (performance bias and detection bias): Objective outcome	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Govindaraj 2001	+	?	?	?	+	+	?
Li 2006	+	?	?	+	+	+	+
Sinha 2003	?	?	?	?	+	+	+
Ye 2008	?	?	?	?	+	+	-
Yu 2007	+	?	-	?	+	+	+

Figure 2. Summary risk of bias assessment.

Frey syndrome. We extracted data for the incidence of Frey syndrome from the included 5 studies. Four studies reported data of the objective incidence (34,36-38), for which outcomes were consistent across studies (heterogeneity $P=0.49$, $I^2=0\%$), so the fixed effects model was used. The result showed that there was a significant trend toward lower incidence in the AlloDerm group (Fig. 3; $RR=0.15$, 95% CI 0.08-0.30; $P<0.00001$).

Four studies reported data involving subjective incidence (34-37); there was significant heterogeneity ($P=0.01$, $I^2=71\%$), therefore, the random effects model was used. The result also showed that there was a significant trend toward lower incidence in the AlloDerm group ($RR=0.16$, 95% CI 0.09-0.28; $P<0.00001$). We explored possible causes of heterogeneity, taking into account the imbalance of patients between the two groups in one trial (37). When we excluded this trial from the analysis, the heterogeneity disappeared (Fig. 4; $P=0.83$, $I^2=0\%$), and the trend toward the AlloDerm group weakened (Fig. 4; $RR=0.32$, 95% CI 0.19-0.57; $P<0.00001$).

Facial contour. Two trials reported the perception of cosmetic appearance and facial symmetry (36,37). They found that using AlloDerm to fill in the parotid bed resulted in better cosmesis and restoration of good soft tissue contour at the surgical site (symmetrical, with fine scars), while the scars

of the control patients were noticeable, locally depressed and with wrinkled skin.

Adverse events. Adverse events in the original studies consisted of wound infection and rejection. Four studies reported data on wound infection (34-37); there was no significant trend toward increased incidence in the AlloDerm group (Fig. 5; $RR=3.00$, 95% CI 0.14-65.90; $P=0.49$). The reason for the adverse event was streptococcus species, not the AlloDerm (36).

Four studies reported data for rejection (34-37), but all of them reported that there were no cases of implant extrusion that occurred in the AlloDerm group.

Other postoperative complications. Other postoperative complications in the original studies consisted of seroma/sialocele, saliva fistula and facial nerve paralysis. Fig. 6 summarizes the results.

Three studies reported data regarding seroma/sialocele (34-36), for which outcomes were consistent across studies ($P=0.46$, $I^2=0\%$). There was no significant trend toward an increase in incidence in the AlloDerm group ($RR=1.36$, 95% CI 0.66-2.80; $P=0.40$).

Two studies reported data regarding salivary fistula (36,37), the result revealed that the incidence was lower in the AlloDerm group and the difference had statistical significance ($RR=0.09$, 95% CI 0.01-0.66; $P=0.02$).

Three studies reported data concerning facial nerve paralysis (34-36); there was no significant trend toward a lower incidence in the AlloDerm group ($RR=0.96$, 95% CI 0.84-1.09; $P=0.51$).

Discussion

Principal findings. Our systematic review identified 5 studies that addressed the relative impact of AlloDerm and a blank control. We found that the use of AlloDerm was associated with significant reductions in Frey syndrome (both subjective and objective symptoms) after parotidectomy.

The period of onset of Frey syndrome is more than 3-6 months after surgery: 3 years (51), 8 and a half years (52) and, at present, the longest is 14 years (53) as reported in research articles. The follow-up period ranged from 5 to 39 months in the included studies, so we believe that the preliminary results are reliable.

The present meta-analysis confirms that, despite various confounding factors, AlloDerm does decrease the occurrence of Frey syndrome after parotidectomy by 85% (objective) and 68% (subjective). We also found a possible trend that AlloDerm may decrease the incidences of salivary fistula and facial nerve paralysis, and improve facial contour. Although AlloDerm has several potential adverse effects, they are minimal compared to Frey syndrome and other complications, and these effects are able to be prevented or solved easily.

Strengths and limitations. Our study is more precise than previous ones (47). Previously published meta-analyses have focused on the preventive effect of surgical techniques, and carried out a search only in PubMed for English-language studies. They included many surgical techniques (AlloDerm was one of them), yet no subgroup analysis was performed,

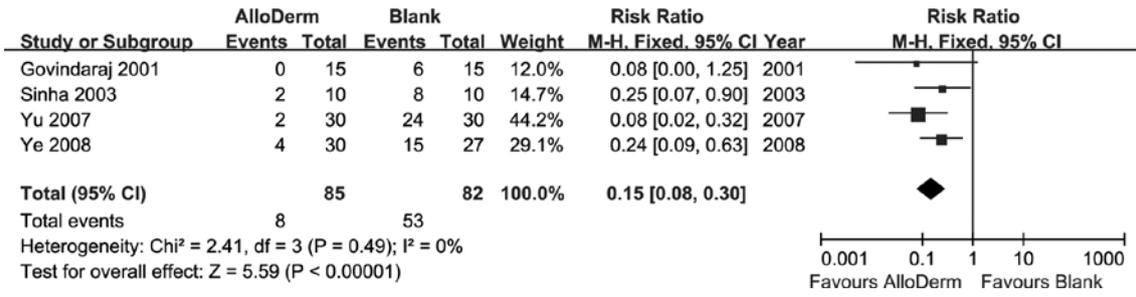


Figure 3. Effect of AlloDerm on the objective incidence of Frey syndrome.

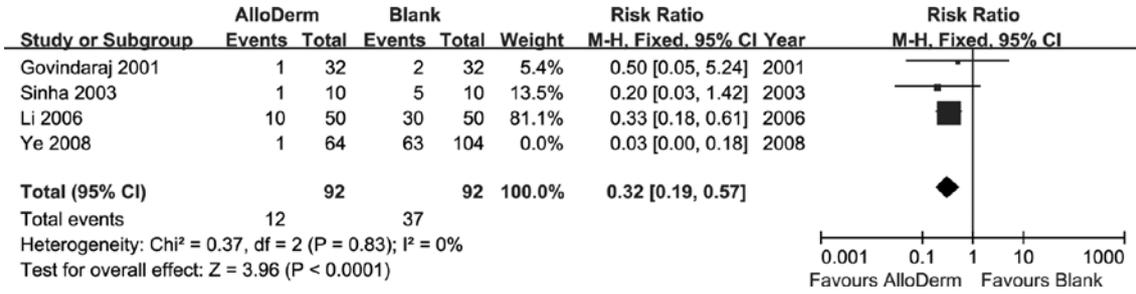


Figure 4. Effect of AlloDerm on the subjective incidence of Frey syndrome.

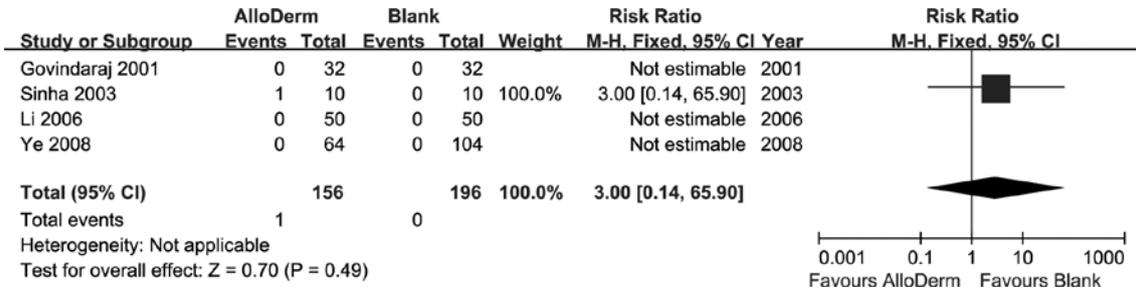


Figure 5. Effect of AlloDerm on the incidence of infection.

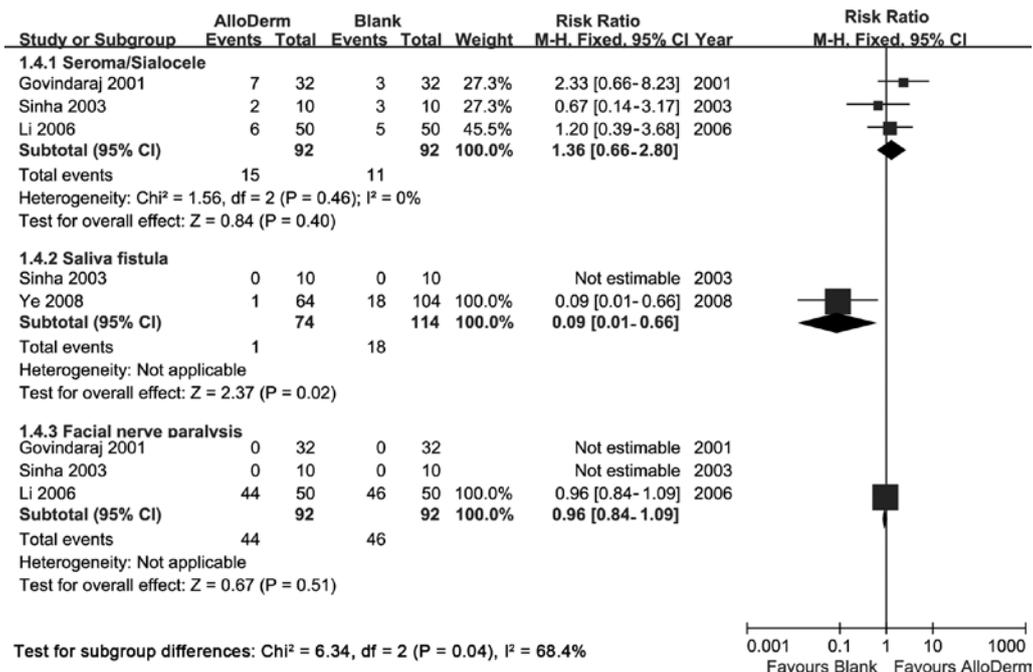


Figure 6. Effect of AlloDerm on other postoperative complications.

although heterogeneity was high. Therefore, the authors suggested that further studies were necessary to stratify differences among the various available techniques. Also, they did not take into account adverse events or other complications.

Our study also has limitations. Firstly, the number of studies contributing substantial data to the meta-analysis was small; therefore, we could not fully assess the effects of important clinical factors that may have influenced outcomes. Possible problems with concealment, lack of blinding and loss of follow-up could have introduced bias. The sample sizes were quite few, thus we could not adequately assess effects. Finally, potential limitations of any meta-analysis is the 'file-drawer' effect, in which studies with negative results may remain unpublished, thus biasing the literature toward positive findings.

Clinical and policy implications. Our results may have potential implications for clinical practice and health policy. Frey syndrome is a widely recognized sequela of parotidectomy; there exist many strategies for both its prevention and treatment. Before the development of AlloDerm, previous strategies were able to effectively prevent Frey syndrome (47), but had various disadvantages (20,21,28,29). Our results, although based on only 5 randomized controlled trials, indicate that it is plausible that AlloDerm delivers a clinically significant reduction in preventing Frey syndrome, without adverse effects. It may also reduce salivary fistula and facial nerve paralysis, and improve facial contour.

Shuman and Bradford (54) supported the fact that surgeons are obligated to inform patients regarding the significance of Frey syndrome prior to surgery. Yet, to date the process of informed consent and pre-operative decision-making has posed a potential ethical quandary. Many studies have also come to the conclusion that Frey syndrome interferes with the quality of life of patients (7,11,12,18,19). Therefore, surgeons and policy makers need to address the clinical importance and value of the heightened focus in relation to the goals of treatment, so that AlloDerm may meet their and their patients' expectations.

Implications for research. The methods in trials were limited by the inability to blind clinical staff to the method of operation, yet the blinding of investigators to evaluate and collect outcome data is feasible. Unfortunately, only 1 study performed blinding of investigators (35). Therefore it is possible that the decisions and actions of the clinicians could have been influenced, resulting in biased estimates of treatment effect.

We also found that AlloDerm may reduce salivary fistula and facial nerve paralysis, and improve facial contour. As a result, future studies should follow the CONSORT 2010 statement (55) to design and report, in order to provide high-quality evidence.

In conclusion, evidence from the included studies suggests that use of AlloDerm results in decreased total incidence of Frey syndrome. Evidence also suggests that AlloDerm improves facial contour, may reduce salivary fistula and facial nerve paralysis, without adverse events. Yet limited data from the included studies is currently available to confirm this. Our study also shows that it is unclear whether the use of AlloDerm permits any conclusions about the incidence of other periop-

erative complications. Further studies are required to establish the optimal design and optimal outcome indicators.

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