SPECIAL ARTICLE

ANZJSurg.com

A systematic review of dermal fillers for age-related lines and wrinkles

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Key words
dermal fillers, permanent, semi-permanent, face, ageing.

Abbreviations
CaHA, Calcium Hydroxylapatite; FFAS, Facial Fold Assessment Scale; GAIS, Global Aesthetic Improvement Score; HA, Hyaluronic Acid; NLF, Nasolabial Folds; PAAG, Polyacrylamide Gel; PMMA, Polymethylmethacrylate; RCT, Randomised Controlled Trial; WSRS, Wrinkle Severity Rating Scale.

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Accepted for publication 7 December 2009.

doi: 10.1111/j.1445-2197.2010.05351.x

Abstract

Background: Dermal fillers are gaining popularity for rapid aesthetic improvement. Long-term efficacy and safety have not been well documented. The aim of this systematic review was to assess the safety and efficacy of injectable dermal fillers compared with other facial augmentation techniques for the management of age-related lines and wrinkles.

Methods: Studies including patients receiving injectable semi-permanent or permanent dermal fillers for age-related lines and wrinkles were included in this review. Efficacy outcomes (including changes in skin thickness and patient satisfaction) and safety outcomes (including mortality, lumps and infections) were examined.

Results: Three randomized control trials and six case series were included. Permanent and semi-permanent dermal fillers improved subjective ratings of appearance and resulted in higher patient satisfaction than temporary fillers. Long-term efficacy appeared good in the few studies that reported it. Short-term safety appeared favourable. Lumps were reported in all but one study but received little follow-up. Long-term safety data were limited.

Conclusions: The treatment of age-related lines and wrinkles with permanent and semi-permanent dermal fillers is more efficacious compared with temporary fillers in those studies that compared them. Case series evidence suggests that these fillers achieve their objective, which is to decrease the visible effects of age-related changes. These fillers appear at least as safe as temporary fillers in the short term in those studies that compared them. Long-term safety could not be determined.

Introduction

Dermal fillers have become a popular means of addressing contour defects resulting from ageing, photo-damage, disease, trauma and scarification.[1] The reabsorption of biodegradable fillers (most within a year of injection) has resulted in the emergence of permanent and semi-permanent products to give patients longer lasting effects. The aim of this systematic review was to assess the safety and efficacy of semi-permanent and permanent dermal fillers, compared with other facial augmentation techniques, for the management of lines and rhytids on the ageing face. For the purposes of this review, semi-permanent fillers have been defined as fillers lasting between 1 and 2 years, and permanent fillers as those lasting longer than 2 years.

Methods

This systematic review is limited to the literature relating to age-related facial changes. The comprehensive report by the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S), which includes evidence relating to the use of dermal fillers for HIV-associated lipoatrophy patients can be found at http://www.surgeons.org/asernip-s/. Dermal fillers for Human immunodeficiency virus (HIV)-associated lipoatrophy are the subject of a separate publication.

Literature search strategies

Human patients receiving either injectable semi-permanent or permanent dermal fillers in the face to reduce the visible effects of fat

loss associated with ageing were included for review. Systematic reviews, randomized controlled trials (RCTs), pseudo-RCTs, non-randomized comparative studies and case series (with pre- and post-test outcomes) with a total sample size of at least 40 patients were included. Studies reporting on patients with facial reconstruction, injury, scarring, disease or a history of previous facial filling within 3 months of the study were excluded.

Studies were identified by searching PubMed, EMBASE, CINAHL, Current Contents and the Cochrane Library, from the inception of the databases to July 2008. The York (UK) Centre for Reviews and Dissemination databases, Clinicaltrials.gov, National Research Register, Meta-Register and the Australian Clinical Trials Registry were also searched during this period. Searches were conducted without language restriction.

The search terms were as follows:

(1) (Artecoll OR Artefill OR Arteplast), Bioplastique, (DermaLive OR DermaDeep), (New Fill OR Newfill OR Sculptra), (Radiesse OR Radiance FN), Reviderm, Matridex, (Hylan dex OR Hylandex OR Hyla dex OR Hyladex OR ReDexis), (Silikon OR Silskin OR VitreSil OR PMS 350 OR Adatosil), (Aquamid OR Formacryl OR Interfall OR Royamid OR Bioformacryl OR Argiform OR Kosmogel OR Beautical OR Phigel), Eutrophill, (Bio Alcamid OR Bio Alkamid OR Bioalcamid), Bioinblue, Isalogen, Amazingel, (Permacol OR Fibroquel), (Metacrill OR Bioplasty OR Aphrodite Gold), (Outline OR Evolution).

(2) Polyalkylimide, (calcium hydroxylapatite OR CaHA), (sephadex OR Dextran OR DEAE), (hydroxyethylmethacrylate OR HEMA), (poly-L-lactic acid OR polylactic acid OR PLA), (polyvinyl alcohol OR PVA), (porcine dermal collagen), (liquid silicon* OR injectable silicon* OR silicon* OR polydimethylsiloxane OR LIS), (polyacrylamide OR PAAG), (polymethylmethacrylate OR PMMA).

(3) 1 OR 2

(4) 3 AND (facial fill* OR facial volume OR cosmetic OR aesthetic OR facial contouring OR facial implant* OR permanent fill* OR dermal fill* OR soft tissue augmentation OR skin fill* OR soft tissue fill* OR dermal implant*).

Pearling was then undertaken to locate any articles that may have been missed by the electronic database searches.

Data extraction and analysis

Data from all included studies were extracted by one researcher and checked by a second using standardized data extraction tables. Each included study was critically appraised for its study quality and assigned a level of evidence according to the hierarchy of evidence developed by the National Health and Medical Research Council of Australia. Study quality was assessed according to the methods given in Section 6 of the Cochrane Reviewers' Handbook[2] on a number of parameters such as the quality of the study methodology reporting, methods of randomization and allocation concealment (for RCTs), blinding, sample sizes, and the ability of the study to measure 'true effect'.

Results

A total of nine studies were included in this review (Table 1).[3–11] There was great variation in the number of injections or treatments given to patients within the studies that reported this data (Table 2).

Efficacy

Changes in skin thickness

One retrospective case series study reported skin thickness measurements before and after dermal filler treatment. Fulton *et al.*[3] reported

Table 1 Dermal fillers for age-related changes – summary of included studies

Study	Study type	Level of E	*N*	Intervention	Follow-up (y)
Cohen *et al.*[4] (USA)	RCT	II	128	Permanent (PMMA)	4–5
			123	Temporary (collagen)	0.5
Moers-Carpi *et al.*[5] (Germany)	RCT	II	70†	Semi-permanent (CaHA)	1.3
			33‡	Temporary (HA 1)	1.3
			33	Temporary (HA 2)	1.3
			69§	Temporary (HA 3)	1.3
Smith *et al.*[6] (USA)	RCT	II	117	Semi-permanent (CaHA) (one side of face)	0.5
			117	Temporary (collagen) (other side of face)	0.5
Cohen *et al.*[10] (USA)¶	Case series	IV	145††	Permanent (PMMA)	5
Fulton *et al.*[3] (USA)	Case series	IV	608	Permanent (liquid silicone)	3
Jacovello *et al.*[11] (Argentina)	Case series	IV	40	Semi-permanent (CaHA)	1.5
Mladick[7] (USA)	Case series	IV	40	Permanent (silicone particles)	1
Reda-Lari[8] (Kuwait)	Case series	IV	1306	Permanent (PAAG)	0.3–6
Sklar & White[9] (USA)	Case series	IV	64	Semi-permanent (CaHA)	0.5

†Five subjects lost to follow-up at 4 months after initial treatment. Any losses at 8 and 12 months not described. ‡Two subjects lost to follow-up at 4 months after initial treatment. Any losses at 8 and 12 months not described. §Four subjects lost to follow-up at 4 months after initial treatment. Any losses at 8 and 12 months not described. ¶Same study patients as Cohen *et al.*[4] Original PMMA patients followed up. Patients initially in the Collagen group who crossed over to PMMA at 6 months also followed up. Original PMMA study patients $n = 100$; crossover patients $n = 45$. Authors grouped patients together, resulting in duplication of some results. ††One hundred forty-five subjects were followed up from original study.[4] This group included initial PMMA patients and patients that crossed over to PMMA after collagen treatment. One hundred forty-two patients included for efficacy, and 145 for safety. CaHA, calcium hydroxylapitite; HA, hyaluronic acid; Level of E, level of evidence; PAAG, polyacrylamide gel; PMMA, polymethylmethacrylate; RCT, randomized controlled trial. Artecoll (PMMA), Artes Medical Inc, USA.[4,10] Bioplastique (Silicone particles), Bioplasty, USA.[7] Cosmoplast (Collagen), Allergan, USA.[6] Juvederm 24 (HA 1), Allergan, & Juvederm 24 HV (HA 2), manufacturer not reported & Perlane (HA 3), Medicis.[5] Radiance and Radiance FN (CaHA): BioForm Medical Inc, USA.[5,6,9,11] Silikon (liquid silicone), Acon Labs, USA.[3] Zyderm II/Zyplast (Collagen), Inamed Corporation, USA.[4] PAAG (product name not specified)[8].

Table 2 Dermal fillers for age-related changes – number of injections or treatments

Cohen *et al.*[4]	*N*	Intervention	Number of treatments (mean)†					
Level II			Glabella	NLF	Upper lip	Mouth corners		
	128	PMMA	2.0	2.3	1.7	2.1		
	123	Collagen	2.0	2.0	1.8	2.2		
		P-value	0.97	0.32	0.71	0.61		
Cohen *et al.*[10]	*N*	Intervention	Number of treatments					
Level IV	100	PMMA	As for Cohen *et al.*[4]					
	45	PMMA cross over patients	NR					
Fulton *et al.*[3]	*N*	Intervention	Percentage of patients treated in number of lip augmentation sessions‡					
Level IV			2		3	>3		
	608	Liquid silicone	73%		51%	31%		
Sklar & White[9]	*N*	Intervention	Percentage of patients treated in two sessions for each facial area§					
Level IV			NLF ($n = 52$)	Tear trough ($n = 15$)	Lips ($n = 15$)	Mouth ($n = 11$)	Above upper lip ($n = 9$)	Cheek¶ ($n = 5$)	Chin ($n = 2$)
	64	CaHA	37%	40%	27%	17%	0%	60%	50%
Moers-Carpi *et al.*[5]	*N*	Intervention	Number of treatments††					
Level II	70	CaHA	2					
	33	HA 1	2					
	33	HA 2	2					
	69	HA 3	2					
Smith *et al.*[6] Level II	*N*	Intervention	Number of injection sessions‡‡					
			Baseline injection only *N* (%)		Two injection sessions *N* (%)	Three injection sessions *N* (%)		
	117	CaHA one side of face	61 (52.1)		51 (43.6)	5 (4.3)		
	117	Collagen other side of face	38 (32.5)		70 (59.8)	9 (7.7)		
		P-value	0.017		NR	NR		

†During the 4 weeks after initial treatment, up to two additional treatments were permitted. ‡One month after initial treatment, there was a follow-up visit where reinjection could occur. Desired augmentation was gradually achieved with a series of treatments at monthly intervals. §The number of patients receiving less or more than two treatments was not reported. ¶Includes zygoma and buccal regions. ††Patients received an initial treatment and a touch-up treatment 4 months later. Only NLF treated. ‡‡After initial treatment patients were allowed up to two touch-up treatments at 2-week intervals. CaHA, calcium hydroxylapitite; HA, hyaluronic acid; NLF, nasolabial folds; NR, not reported; PMMA, polymethylmethacrylate.

changes in lip thickness measurements for 25/608 (4%) patients who received liquid silicone for lip augmentation. The quadrants of both upper lips were measured using a micrometer 30 days after each session. At baseline, the average lip thickness was 4.1 mm. After one, two and three sessions, the average lip thickness increased to 5.6, 7.8 and 9.2 mm respectively. No statistical analyses were reported.

Subjective ratings of appearance

Permanent and semi-permanent fillers were demonstrated to be better than temporary fillers in the three studies that compared them (Table 3). Cohen *et al*.[4] reported no differences in Facial Fold Assessment Scale (FFAS) ratings between the collagen and polymethylmethacrylate (PMMA) groups at 1 month, after which PMMA demonstrated to be significantly better ($P < 0.001$ at 3 and 6 months for both masked and unmasked ratings). From baseline, there were significant improvements in FFAS ratings at 12 months ($P \leq 0.047$ for masked ratings; $P < 0.001$ for unmasked ratings), and at 4–5 years ($P < 0.001$ for masked ratings of patients who had not undergone subsequent surgical procedures). Moers–Carpi *et al*.[5] reported that significantly more patients in the calcium hydroxylapatite (CaHA) group were considered improved or better (a Global Aesthetic Improvement Scale (GAIS) rating ≤3) than patients in the hyaluronic acid (HA) groups at eight, 12 and 16 months after initial treatment ($P \leq 0.03$ for all, except HA2 at 16 months where there was no difference). Smith *et al*.[6] reported that significantly more nasolabial folds injected with CaHA were improved from baseline than nasolabial folds injected with collagen ($P < 0.0001$ at 3 and 6 months after treatment; no statistical analyses reported for GAIS outcomes).

Patient satisfaction

Patient satisfaction after permanent and semi-permanent dermal filler treatment was high (Table 4). The three studies that compared permanent and semi-permanent fillers with temporary fillers demonstrated that patients were more satisfied with longer lasting fillers.[4,5,6]

Over-correction

Over-correction refers to the injection of too much product into an area, and can result in visibility of the substance under the skin, or lumpiness at the site. Over-correction was reported to have occurred in three studies.[7–9] Mladick[7] described that over-correction occurred four times (7% of injections) after silicone particle injections in three of 40 (8%) patients. Two (5%) patients had over-correction bulges in the infraoral depression areas after silicone particles were injected into each side. One patient had a nasoglabellar bulge after silicone particles were injected under frown lines. These bulges were corrected by needle aspiration. Reda-Lari[8] reported that two patients of 1306 (0.2%) were psychologically dissatisfied with the result of polyacrylamide gel (PAAG) treatment as they believed they had been over-corrected. The product was removed. Sklar & White[9] reported puffiness of the lower eyelids after injection with CaHA in one of 64 (2%) patients. The authors stated that they were unsure whether this was because of over-correction or lymphoedema. In addition, filler was placed too superficially in one (2%) patient, resulting in a pink-white plaque showing in the tear trough area.

Filler displacement

One study noted that displacement of PAAG occurred in 43/1306 (3%) patients.[8] The product was displaced to the perioral area in 18/43 (42%) cases and to the buccal area in 25/43 (58%) cases. Treatment consisted of local corticosteroid injections, or removal of the product.

Safety

There was great variation in the level of adverse event reporting between the studies, and only the main adverse events are described.

Mortality

Cohen *et al*.[4] reported one death in the collagen group. Although the authors did not consider the death to be treatment related, details were lacking. Cohen *et al*.[10] reported one case of death because of cardiac failure. The authors believed it was unrelated to treatment.

Allergic reactions

One of 1306 patients (0.1%) developed a local allergic reaction 8 h after PAAG treatment.[8] Oral antihistamine therapy was unsuccessful, and intravenous corticosteroid injections were given.

Granuloma and lump formation

Granuloma and lump formation are tabulated in Table 5. The rate of lumps was less than 10% for all studies reporting this outcome. Granulomas were reported in three studies.[3,4,10] If treated, the most common therapy for granulomas and lumps was steroid injection and/or excision.

Abscess formation and infections

Cohen *et al*.[4] reported one infection and three instances of abscess formation in the collagen group. Two (2%) patients underwent removal and/or drainage of abscesses. One (1%) patient suffered recurring herpes labialis following PMMA treatment. Cohen *et al*.[4] also reported one event of flu-like symptoms in both study groups; however, the event in the collagen group was not considered to be treatment related. Reda-Lari[8] stated that infections occurred in three of 1306 (0.2%) patients. The first patient developed a severe infection in both cheeks following 1.5 mL PAAG into each cheek. The patient was given antibiotics and underwent surgical removal of the gel. Culture of the removed material revealed no bacteria. All complications were resolved at 18 months follow-up. The second patient developed an infection 1 year after treatment (at the same time, the patient was receiving hormone therapy for ovulation and had recently had an influenza-like illness). The infection resolved after incision and drainage under anaesthesia. The infection recurred 6 months later. The gel was removed under anaesthesia at the patient's request. The third patient developed several episodes of minor infections in the malar area that resolved after oral antibiotics. This patient later developed contour deformities which were corrected by a fat graft procedure 2 months after the removal of the product.

Discussion

For the purposes of this review, semi-permanent fillers were defined as fillers lasting between 1 and 2 years, and permanent fillers were defined as lasting longer than 2 years. Permanence of fillers refers to a lack of degradation of the *in vivo* material over time rather than to a permanent cosmetic result. Permanent aesthetic results are seldom

Table 3 Dermal fillers for age-related changes – subjective ratings of appearance

Cohen *et al.*[4]	*N*	Intervention	1 month	3 months	6 months	12 months†
Level II				Overall observer ratings (masked FFAS), mean ± SD		
	128	PMMA	*n* = 109	*n* = 102	*n* = 107	*n* = 108
			0.53 ± 0.59	0.53 ± 0.61	0.50 ± 0.67	0.55 ± 0.71
	123	Collagen	*n* = 108	*n* = 107	*n* = 110	NA
			0.59 ± 0.55	0.02 ± 0.48	0.16 ± 0.57	NA
		P-value	0.422	<0.001	<0.001	NR‡
				Overall investigator ratings (unmasked FFAS), mean ± SD		
	128	PMMA	*n* = 111	*n* = 106	*n* = 112	*n* = 109
			1.50 ± 0.68	1.50 ± 0.83	1.51 ± 0.95	1.68 ± 0.94
	123	Collagen	*n* = 111	*n* = 108	*n* = 115	NA
			1.47 ± 0.79	0.59 ± 0.73	0.17 ± 0.74	NA
		P-value	0.593	<0.001	<0.001	<0.001
	N	Intervention		Points improved from baseline at 4–5 years follow-up (FFAS)		
				Unmasked investigator ratings (*n* = 69)§		Masked observer ratings (*n* = 43)¶
	128	PMMA		1.67		1.22
		P-value		<0.001		<0.001
Cohen *et al.*[10]	*N*	Intervention		Points improved from baseline at 5 years follow-up (for both groups) (FFAS)		
Level IV				Unmasked investigator ratings (*n* = 122)††		Masked observer ratings (*n* = 113)††
	145‡‡	PMMA		1.7		1.0
		P-value		<0.001		<0.001
Moers–Carpi *et al.*[5]	*N*	Intervention		Total improved compared with CaHA (masked GAIS)§§ (%)		
Level II			8 months after initial treatment (*n* = 195)¶¶ (%)	12 months after initial treatment (*n* = 198)¶¶ (%)		16 months after initial treatment (*n* = 194)¶¶ (%)
	70	CaHA	96	88		62
		P-value	NA	NA		NA
	33	HA 1	2	5		0
		P-value	<0.001	<0.001		<0.001
	33	HA 2	71	53		50
		P-value	<0.001	<0.001		NS
	69	HA 3	72	64		48
		P-value	<0.001	<0.001		0.03
Smith *et al.*[6]	*N*	Intervention		Number of patients with improvement from baseline (masked FFAS)		
Level II				3 months after end of treatment, *n* (%)		6 months after end of treatment, *n* (%)
	117†††	CaHA one side of face		102 (87)		96 (82)
	117†††	Collagen other side of face		32 (27)		32 (27)
		P-value		<0.0001		<0.0001
	N	Intervention		Number of patients with improvement from baseline (masked GAIS)		
			Very much improved	Much improved	Improved	No change	Worse
				3 months after end of treatment, *n* (%)			
	117†††	CaHA one side of face	23 (20)	47 (40)	42 (36)	5 (4)	0 (0)
	117†††	Collagen other side of face	1 (1)	6 (5)	22 (19)	68 (59)	21 (18)
		P-value	NR	NR	NR	NR	NR
				6 months after end of treatment, *n* (%)			
	117†††	CaHA one side of face	17 (14)	35 (30)	41 (35)	24 (20)	0 (0)
	117†††	Collagen other side of face	1 (1)	5 (4)	21 (18)	69 (59)	21 (18)
		P-value	NR	NR	NR	NR	NR

†Artecoll treatment was offered to everyone in the collagen group at the 6-month follow-up. Of the 116 collagen subjects who completed the 6-month follow-up evaluation, 106 (91%) were treated with Artecoll; hence, no 12-month follow-up data available for collagen group. Single group tests performed to determine whether Artecoll could be detected 12 months after treatment. ‡Significant improvement in FFAS ratings for each of the four facial areas and the overall average ($P = 0.047$ to $P < 0.001$). *P*-values for individual areas not given. ¶Twenty-six patients had surgical procedures between the PMMA treatment and the 4–5-year follow-up. §Forty-three patients had no other surgical procedures between the PMMA treatment and the 4–5-year follow-up. ††An unspecified number of patients had undergone 44 subsequent cosmetic procedures since initial PMMA treatment. In patients who had not any subsequent cosmetic procedures, there was significant improvement in blinded observer ratings from baseline to 5 years ($P < 0.001$). There was no difference in change in blinded observer efficacy ratings between those patients who had undergone subsequent cosmetic procedures to those who had not at 5 years relative to 6 months. Of the other cosmetic procedures performed, it was reported that 16/44 (36%) had probably impacted results, and 28/44 (64%) had possibly impacted results. When grouped into subgroups of whether these procedures had or had not impacted the results, the groups did not significantly differ from each other. ‡‡One hundred forty-five subjects were followed up from original study.[4] This group included initial PMMA patients (*n* = 82) and patients that crossed over to PMMA after collagen treatment (*n* = 60). Three patients excluded because follow-up period was shorter than 4.5 years. ¶¶It was reported that patients for whom there was no difference between the products were excluded from the GAIS analysis. It was unclear whether or where this occurred. Moers-Carpi *et al.*[5] also calculated mean WSRS scores and WSRS scores from baseline. It was reported that the results from these ratings over time showed no statistical significance for any product (specific data not reported in the study). §§Details of losses to follow-up (if any) not reported. †††It was stated that 115 and 113 patients were available at the 3 and 6-month follow-ups respectively, but 117 patients used in results. CaHA, calcium hydroxylapitite; FFAS, Facial Fold Assessment Scale (0, no wrinkles to 5, very deep wrinkle); GAIS, Global Aesthetic Improvement Scale (1, very much improved to 5, worse); HA, hyaluronic acid; NA, not applicable; NR, not reported; PMMA, polymethylmethacrylate; SD, standard deviation.

Table 4 Dermal fillers for age-related changes – patient satisfaction

Cohen *et al.*[4]	*N*	Intervention	Masked subject satisfaction rating (1, satisfied to 5, dissatisfied) mean ± SE					
Level II			Glabella		Nasolabial folds	Upper lip	Mouth corners	
			1 month					
	128	PMMA	2.2 ± 0.1		2.2 ± 0.1	2.0 ± 0.1	2.0 ± 0.1	
	123	Collagen	2.0 ± 0.1		2.0 ± 0.1	2.0 ± 0.1	2.2 ± 0.1	
		P-value	NS		NS	NS	NS	
			3 months					
	128	PMMA	2.3 ± 0.2		2.2 ± 0.1	2.0 ± 0.2	2.3 ± 0.2	
	123	Collagen	2.7 ± 0.3		2.8 ± 0.2	3.1 ± 0.3	2.1 ± 0.2	
		P-value	0.038		<0.001	<0.001	<0.001	
			6 months					
	128	PMMA	2.2 ± 0.2		2.0 ± 0.1	2.0 ± 0.2	2.3 ± 0.2	
	123	Collagen	3.5 ± 0.3		3.6 ± 0.2	3.9 ± 0.3	3.9 ± 0.3	
		P-value	<0.001		<0.001	<0.001	<0.001	
			12 months†					
	128	PMMA	2.2 ± 0.2		2.0 ± 0.2	2.3 ± 0.2	2.2 ± 0.2	
	123	Collagen	NR		NR	NR	NR	
		P-value	NA		NA	NA	NA	
Moers–Carpi *et al.*[5]	*N*	Intervention	8 months after initial treatment (*n* = 195)‡		12 months after initial treatment (*n* = 198)‡		16 months after initial treatment (*n* = 194)‡	
Level II			Beneficial, % yes					
	70	CaHA	100		100		95	
	33	HA 1	53		19		10	
		P-value*	<0.001		<0.001		<0.001	
	33	HA 2	90		78		74	
		P-value*	0.031		<0.001		0.004	
	69	HA 3	97		85		82	
		P-value*	NS		0.001		0.026	
			Feel more attractive, % yes					
	70	CaHA	86		86		82	
	33	HA 1	50		19		10	
		P-value*	<0.001		<0.001		<0.001	
	33	HA 2	77		63		55	
		P-value*	NS		0.01		0.013	
	69	HA 3	86		75		75	
		P-value*	NS		NS		NS	
			Better emotional well-being, % yes					
	70	CaHA	86		83		77	
	33	HA 1	50		16		10	
		P-value*	<0.001		<0.001		<0.001	
	33	HA 2	61		53		48	
		P-value*	0.008		0.003		0.01	
	69	HA 3	77		66		64	
		P-value*	NS		0.029		NS	
			More confidence, % yes					
	70	CaHA	79		80		77	
	33	HA 1	47		19		10	
		P-value*	0.002		<0.001		<0.001	
	33	HA 2	61		50		35	
		P-value*	NS		0.004		<0.001	
	69	HA 3	73		66		64	
		P-value*	NS		NS		NS	
Smith *et al.*[6]	*N*	Intervention	Nasolabial fold preferred at 6-month follow-up, *n* (%)					
Level II	117	CaHA	113 (96.5)					
	117	Collagen	4 (3.5)					
		P-value	NR					
Jacovello *et al.*[11]	*N*	Intervention	18-month patient satisfaction (description of survey not given), *n* (%)					
Level IV	40	CaHA	Glabella (*n* = 12)	NLF (*n* = 24)	Lips (*n* = 10)	Nose (*n* = 5)	Infraoral (*n* = 4)	
		Very good	9 (75)	20 (83.3)	8 (80)	5 (100)	4 (100)	
		Good	2 (16.6)	2 (8.3)	2 (20)	0 (0)	0 (0)	
		Acceptable	1 (8.3)	2 (8.3)	0 (0)	0 (0)	0 (0)	
Mladick[7]	*N*	Intervention	Patient satisfaction (1, poor – 5, excellent), mean score					
Level IV			Cheek (*n* = 8)	Chin (*n* = 7)	Lips (*n* = 18)	NLF (*n* = 6)	Glab (*n* = 4)	Mouth (*n* = 6)	Nose (*n* = 3)	Misc (*n* = 3)
	40	Silicone particles	4.2	4.7	4.5	3.7	4.4	3.8	5.0	4.3
Reda-Lari[8]	*N*	Intervention	Number of patients satisfied immediately after treatment, *n* (%)					
Level IV	1306	PAAG	1241 (95.0)§					

*Compared with CaHA. †Artecoll treatment was offered to everyone in the collagen group at the 6-month follow-up. Of the 116 collagen subjects who completed the 6-month follow-up evaluation, 106 (91%) were treated with Artecoll, hence no 12-month follow-up data available for collagen group. ‡Details of losses to follow-up not reported. ¶Compared with CaHA. §It was reported that most of the remaining patients were dissatisfied because they felt the augmentation was insufficient. Two of 1306 (0.2%) patients were dissatisfied as they felt they had been over-corrected. CaHA, calcium hydroxylapatite; HA, hyaluronic acid; NA, not applicable; NLF, nasolabial folds; NR, not reported; NS, not significant; PAAG, polyacrylamide gel; PMMA, polymethylmethacrylate; SE, standard error.

Table 5 Dermal fillers for age-related changes – adverse event reporting: lumps

Study	Level of E	*N*	Intervention	*N* patients (%)	N events reported
Cohen *et al.*[4]	II	128	PMMA	NR	20†
		123	Collagen	NR	6 (one granuloma or enlargement of implant)
			P-value	NR	NR
Cohen *et al.*[10] (patient overlap with Cohen *et al.*[4])	IV	145‡	PMMA	13 (9.0) (two granuloma or enlargement of implant)§	NR
Smith *et al.*[6]	II	117	CaHA (one side)	1 (0.9)	NR
		117	Collagen (other side)	3 (2.6)	NR
			P-value	NS	NA
Fulton *et al.*[3]	IV	608	Liquid silicone	11 (1.8)¶ (all granulomas)	NR
Mladick[7]	IV	40	Silicone particles	1 (2.5)††	NR
Jacovello *et al.*[11]	IV	40	CaHA	1 (2.5)‡‡	NR
Reda-Lari[8]	IV	1306	PAAG	56 (4.3)	NR
Sklar & White[9]	IV	64	CaHA	3 (4.7)§§	NR

†One lump present because PMMA used contrary to protocol for lip augmentation. One lump reported to be a seborrheic keratosis (diagnosed after excision). Four to 5 years after initial treatment, five patients experienced six late adverse events in the PMMA group. One patient had two severe nodular minimally to non-inflammatory reactions in both nasolabial folds (treated with steroid injections). There were four other mild events in four patients; a lump in a marionette line was excised. ‡One hundred forty-five subjects were followed-up from original study.[4] §One case presented as an inflammatory, lumpy area in the lip and the melabial fold 6 months after the last PMMA injection. The area was treated with intralesional steroids followed by intraoral excision. The other case presented as a lumpy, inflamed nodule in each of the nasolabial folds approximately 5 years after treatment. The affected areas partially responded with intralesional steroid therapy. No histological examination was conducted in either patient. ¶Four cases not treated; five given intralesional steroids; two lumps excised (pathology demonstrated granuloma formation). ††A palpable nodule under lower lip mucosa, which was excised. ‡‡Excised. §§Lumps occurred in 20% of lip patients. The nodules developed 2–4 weeks after treatment. All patients given intralesional corticosteroids. CaHA, calcium hydroxylapatite; Level of E, level of evidence; NA, not applicable; NR, not reported; PAAG, polyacrylamide gel; PMMA, polymethylmethacrylate.

possible because of continued tissue volume loss and other factors associated with ageing. Less than half of the included studies had follow-up periods longer than 1 year, and of these, only four had follow-up periods longer than 2 years (two studies reported the same cohort of patients,[4,10] while the two other studies were retrospective case series that did not measure long term efficacy[3,8]).

Direct comparisons of improvements between products were difficult owing to the variations in treatment protocols and outcome measurements. Only one study determined skin thickness measurements, but this was for less than 5% of the study population.[3] The remaining studies used wrinkle scales to determine changes in aesthetic appearance after treatment (FFAS, GAIS and Wrinkle Severity Rating Scale (WSRS)). The results of these subjective ratings suggest that temporary fillers can provide better or comparable aesthetic results in the short term (within the first month), but that permanent or semi-permanent fillers provide significantly better aesthetic results in the longer term. This is consistent with the mode of action of these fillers, such as local foreign body response and collagen production, which occur over the course of months after injection, and with the degradation of temporary fillers. Cohen *et al*.[4,10] reported a continued and significant aesthetic improvement from baseline 4–5 years after treatment, demonstrating that PMMA has a long lasting effect in this group of patients. Further studies are required before the long term aesthetic effects of other fillers are known.

Long-term follow-up of individual dermal fillers is likely to be complicated by patients undergoing further cosmetic interventions in an effort to maintain aesthetically pleasing results. The studies included in this review were selected on the basis that patients had not undergone treatment with permanent or semi-permanent dermal fillers within 3 months prior to commencement of the study, but five of the nine studies did not report whether patients had received previous filling or not. [3,7–9,11] More than a third of patients in Cohen *et al*.,[4] and an unspecified number of patients in Cohen *et al*.[10] had undergone further cosmetic procedures before their respective follow-ups. Any reported adverse events in studies that did not report previous filling could potentially be attributed to previous procedures, or from a combination of procedures. These additional cosmetic procedures effectively reduced the number of patients available for follow-up, and diminished the ability to create long-term safety and efficacy profiles for individual fillers.

In general, many adverse events were transient and mild in nature; the majority of events were associated with the injection process, such as oedema, ecchymosis and erythema (results not shown). Many of the studies suffered from attrition bias as losses to follow-up were poorly reported, resulting in data for adverse events only representing the patients who returned to clinic. Lumps were reported in all but one of the studies,[5] with the rate of lumps generally being less than 5%. There is limited knowledge regarding the exact mechanism of lump formation. Nodules and some other bumps are not inflammatory, and are generally technique dependent.[12,13] These lumps can result from excess product being injected into an area (over-correction), or injecting too superficially.[14] Many lumps are not bothersome to patients, and are therefore not biopsied.

Cohen *et al*.[4,10] reported lumps in patients 2–5 years after initial injection, but it was difficult to determine the precise number of patients affected as there was patient overlap. These late adverse events, however, suggest that long-term complications may be associated with this, or potentially any other filler, and that reported complication rates in patients may increase over time. Liquid injectable silicone is a notable example where this has occurred, with the debate over the safety of liquid silicone spanning over half a century.[15,16] A review of complications after liquid silicone injections found that the average time to first complication was 8–10 years, with a range of 6 months to 36 years.[16] Since first being used in the 1960s, information regarding liquid silicone treatments has been difficult to locate, resulting in difficulties identifying the exact causes of these complications. It is believed that many of the complications arising from liquid silicone injections, such as granulomas[17–19] may have

been because of high volumes of impure, low-viscosity silicones, poor injection technique and/or concomitant disease.[16]

Granulomas were reported in three studies,[3,4,10] with the highest incidence being reported in patients who had received liquid silicone injections in the lips (2%).[3] The lack of reporting of losses to follow-up within many studies may have biased these results. Granulomas are a result of a hyper-inflammatory reaction and can occur in areas distant from the injected area. The reasons for these granulomas are unclear, but may be related to the viscosity of the product.[3] It has been predicted that increasing numbers of foreign body-type granulomatous reactions will be seen in the oral facial regions of mainly middle-aged women because of the injection of one or more cosmetic fillers.[20]

Of the four studies that reported injecting dermal fillers into the lips, all reported nodules or granulomas at a rate of between 2% and 5%.[3,7,9,11] The occurrence of lumps in the lips was seen by some authors to be the reason for not injecting into this area.[4,9] Although steroid injections and excision were the preferred treatment options for lumps, they were left untreated in many cases, leaving their exact nature largely unknown.

Of the studies that measured patient satisfaction, all reported high levels of satisfaction after dermal filler treatment. The quick and relatively noninvasive nature of these treatments is likely to be a significant key to their popularity. For all fillers, aesthetic improvement (or the beginnings thereof) can be seen immediately after the first injection procedure (particularly for temporary fillers), giving patients instantly visible results without the need for lengthy recovery periods or hospitalization. Popularity may also be attributable, in part, to the normalization of cosmetic surgery.[21] As the number of people undergoing cosmetic procedures continues to grow, more are being performed outside of hospitals. In the US, nearly 11.7 million surgical and non-surgical cosmetic procedures were performed in 2007, with over half being performed in office-based facilities.[22]

In the literature, it is not uncommon to find studies concerning patients with dermal filler complications after treatment by unqualified practitioners, or cases where a patient is uncertain of the product that was injected.[23–25] These instances can result in complications being difficult or impossible to treat.[26] It was acknowledged by many authors of the included studies that experience, proper indication and skilful injection technique by the practitioner are important factors for the potential success of filler materials, particularly to help minimize skin irregularities, lumps and nodule formation.[7,9–11] The majority of the results in the included studies came from centres with experienced physicians. Despite this, however, over-correction occurred in three studies[7–9] and too superficial placement occurred in one study.[9] Although the occurrence of these events was low, rates could be much higher when practising physicians are untrained or unskilled in proper injection technique. To mitigate this, one study reported that the sponsor of a product offers a training programme for the injection of their material.[10]

In Australia, the cosmetic industry is largely self-regulated and there is little research on clinical standards and skills required to perform cosmetic procedures.[27] In addition to this, anyone with a medical degree can perform cosmetic surgery in Australia,[28] and the relationship between a potential consumer and service provider can be direct, without mediation or quality control by a referring doctor. Consumers undergoing cosmetic procedures could therefore be at risk in this unregulated field of medicine, especially if under the care of a poorly qualified clinician looking to make rapid profit from these relatively quick procedures. The development of national training standards or the enforcement of minimum training requirements could go some way to contributing to consumer safety in Australia and worldwide; responsible clinicians should have some surgical training or certification because complications arising from some injectables may require surgical intervention. In addition to this, the industry has an obligation to ensure that the fillers they manufacture are safe for their intended use, and that they perform as expected. It is therefore both appropriate and necessary for the industry (in conjunction with independent research bodies) to undertake studies to assist in quantifying the purported clinical benefits of dermal fillers.

Limitations of the evidence

This review, examining the efficacy and safety of semi-permanent and permanent injectable dermal fillers for ageing was limited by the quantity and quality of the available evidence. The review selected studies for inclusion based on the number of study participants, and may have benefited from the inclusion of all relevant RCTs and comparative studies. If this had been done, it could have increased the number of RCTs included in the review, and in turn may have increased the validity of the overall outcomes.

This systematic review included nine studies, of which only three were RCTs.[4–6] This resulted in a small number of studies with comparable interventions, and resulted in much of the study data originating from retrospective case series, which, by their nature, lack methodological rigour when compared with comparative studies. This review was further limited by the variability in units used to report outcomes, making comparisons between the studies difficult. In addition to this, some of the studies compared permanent and/or semi-permanent fillers with temporary interventions, such as collagen and hyaluronic acid which are known to have a temporary aesthetic effect (less than 1 year). This may have prevented valid efficacy comparisons between longer-lasting fillers in those studies that compared them.[4–6] The results using these temporary products appeared to reflect the expectation of diminution of aesthetic effect over time.

Some of the studies were limited by the lack of randomization and blinding. No studies reported conducting and meeting an *a priori* power calculation, and nearly half of the studies did not report what statistical analyses, if any, were used.[3,7–9,11] Some of the studies used unvalidated assessment tools. There are currently no consistent and validated tools to measure outcomes such as patient satisfaction and skin thickness for dermal filler interventions. Some studies measured these outcomes subjectively, which may have introduced bias in favour of a particular treatment if the patient or assessor was not blinded to treatment allocation.

The number of treatment sessions and volumes of dermal filler products injected varied greatly between studies (Table 2). The number of treatments was pre-determined in some studies and not in others. In addition to this, some studies allowed follow-up injections, while others did not. There was great gender disparity, with men accounting for less than 5% of the patients, which is likely to

reflect that women currently undergo more dermal filler procedures for age-related changes than men.

This review recognizes that semi-permanent and permanent dermal fillers are rapidly evolving and that many long-term follow-up studies are not yet available. Searches for this review were updated approximately 1 year after first being conducted and found an additional four studies. This resulted in two of the three RCTs included in the review being published within the last year. A search of ongoing and unpublished trials demonstrates that more studies are currently underway, suggesting that more efficacy and safety data on dermal filling products will continue to emerge.

Conclusion

The aim of this systematic review was to determine the safety and efficacy of permanent and semi-permanent dermal fillers for age-related lines and wrinkles. The small number of well-designed studies limited the ability to draw firm conclusions. The products included for review increased skin thickness as measured subjectively using wrinkle scale ratings of appearance, but long-term efficacy has not been well established. Patient satisfaction was high in all of the studies that reported it, reflecting the desire for people to feel better about their appearance. The results of the review indicate that semi-permanent and permanent fillers appear safe in the short term, but long-term clinical safety data are lacking. Although the most common adverse events were mild and appeared to be related to the act of injection, palpable lumps were present in many patients. Biopsy of these lumps rarely occurred, leaving their exact nature largely unknown. Although permanent products offer longevity, adverse events, should they occur, may be difficult to manage and of long duration. Long-term studies investigating the safety and efficacy of dermal filling products may be problematic because patients are likely to continue to undergo subsequent cosmetic interventions. More studies with long-term safety and efficacy data are required before definitive statements regarding dermal fillers can be made.

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