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Hyaluronic acid is superior to autologous fat for treatment of temporal hollowing after lateral orbital wall decompression: A prospective interventional trial☆

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Summary *Purpose:* To compare injections of hyaluronic acid (HA) and autologous fat (AF) for the treatment of unsightly temporal hollowing after lateral orbital wall decompression in thyroid eye disease.
Methods: In this nonblinded prospective comparative interventional study, patients received injections of HA in the right temple and AF in the left temple. Additional injections were given when needed at follow-up after 6, 12, 18, and 24 months. Follow-up included an interview; clinical examination with an evaluation of symmetry, contour, and skin surface; and ultrasound measurements. From photographs, the temporal hollowing was graded 1–3. The main endpoints were grading of temporal hollowing and temporal soft tissue thickness.
Results: Seventeen patients were treated bilaterally and 12 unilaterally (five received HA and seven AF). Injection(s) of HA and AF administered at each site were a median (range) of 1 (1–4) and 2 (1–5), respectively. The total combined volume of HA injected per site was 0.9 (0.2–2.0) ml and that of AF was 3.1 (0.5–9.6) ml. At the final examination, a statistically significant difference in mean (SD) grading scores of temporal hollowing due to HA (1.18 (0.26))

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compared to those of AF (1.85 (0.44)) was observed ($p < 0.001$). Six months after administering an injection of HA, the temporal soft tissue thickness was 2.35 (0.24) cm compared to 2.19 (0.28) cm obtained with an injection of AF ($p < 0.001$). By using a linear mixed-effect model and adjusting for baseline values, age, sex, and refill, the difference in favor of HA persisted at all later follow-ups. Increased fibrosis of the subcutaneous tissue developed at 5/24 sites that received AF.

Conclusion: Injection of HA is superior to that of AF for treating temporal hollowing after lateral orbital wall decompression.

Introduction

Lateral orbital wall decompression is used for the treatment of thyroid eye disease with moderate proptosis and normal visual acuity. A skin incision is made in the lateral lid crease, and the temporalis muscle is detached from the lateral orbital wall before creating a bony window.[1] Although serious adverse effects are rarely seen after this procedure, minor side effects are relatively common. In a recent study, we observed various extents of temporal hollowing in 59% of the patients after lateral orbital wall decompression.[2] Several factors may contribute to the hollowing, including removal of the underlying bone, injury to the temporalis muscle, scarring, and atrophy of the subcutaneous fat.[3-5]

Temporal hollowing can be esthetically unacceptable to the patients and thus represents an indication for treatment. Conventional dermis-fat-grafts to correct temporal hollowing have the disadvantage of scars at both the donor and recipient sites.[6] A comprehensive stepwise reconstructive procedure including sheet implants, fat transfer, and hyaluronic acid (HA) injections has been tried in a small group of patients by Siah and coworkers,[7] whereas autologous fat (AF) injections have been used after decompressive craniectomy by Choi and colleagues despite concerns about survival of the grafted fat in the scar tissue.[8]

In esthetic surgical practice, temporal hollowing associated with upper facial thinning is perceived as a sign of aging. Several procedures have been used to treat age-related temporal hollowing. These techniques include surgical alloplasty, AF transfer, and HA injections.[9-13] Although volume restoration of the temporal region is becoming increasingly common, no studies have compared the effect of the different treatment options for temporal hollowing.

In the present study, we have prospectively compared the effect of AF and HA injections in patients with temporal hollowing after lateral orbital wall decompression in patients with thyroid eye disease.

Materials and methods

Study design and patients

This is a prospective comparative interventional study.

We identified temporal hollowing in 38 patients who underwent lateral orbital wall decompression at the Department of Ophthalmology, Haukeland University Hospital, between 1999 and 2013.[2] All patients were invited to participate in the present study. Among them, one individual was deceased, two declined to participate because of inconvenient long distance travel, and six patients did not want treatment. Finally, 29 patients were included.

All participants signed an informed letter of consent. The study was approved by the Regional Committee for Medical and Health Research Ethics, Western Norway (IRB# 00001872, ref. 2015/1175). It was registered at ClinicalTrails.gov with ID number NCT02693808. The study adhered to the tenets of the Declaration of Helsinki.

Reconstructive procedure

Injections of HA were given in the right temporal region and those of AF in the left temporal region. Individuals with bilateral hollowing received different treatments on each side. Unilateral hollowing received one of the treatment options, according to which side the defect was located. The intervention was not blinded to either the investigator or the patients.

Patients using anticoagulants terminated such treatment (acetylsalicylic acid for at least 10 days and warfarin for at least 4 days) before the procedure. In all cases, preoperative sedation with diazepam 5 mg p.o. was used.

After chlorhexidine disinfection, AF was harvested from the subcutaneous tissue in the periumbilical region using a Black & Black Surgical Standard 60 cc Toomey cannula with a 3×150 mm needle. The fat was prepared according to the method by Coleman.[14] To ensure viable adipocytes, the fat tissue was processed by passive filtration through nonwoven compresses without centrifugation.[15] Fat injection in the temporal region was carried out under local anesthesia using lidocaine 1% with epinephrine 0.005%. Before injection, the temporal vessels were located by palpation.[16] The vasoconstriction produced by epinephrine and the use of a blunt 14 G cannula minimized the risk for intravasal injection.

The fat was injected as a bolus into the subcutaneous tissue above the temporalis muscle, and the defect was slightly overfilled. Extensive overfilling at the injection site was restricted by subcutaneous scarring, and high subcutaneous pressure was avoided due to the risk of an unfavorable environment for the fat transplant. While injecting fat, blunt dissection of the scar tissue with the cannula was performed if necessary. In two patients, where the scar tissue persisted despite multiple injections, rigotomy was performed with a sharp needle.

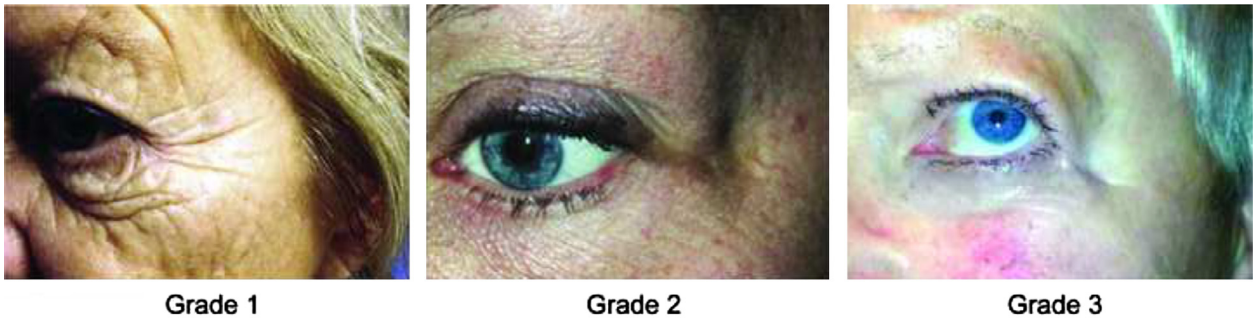

Figure 1 Grading of temporal hollowing. 1: No temporal hollowing, 2: Noticeable hollowing, and 3: Disfiguring temporal hollowing (more than 2 square centimeters or hollowing in combination with noticeable scarring). Reprinted with permission from John Wiley and Sons.[1]

The long-lasting HA used in this study was Juvederm Voluma® with Lidocaine (Allergan, Pringy, France). It was administered by multiple injections at the level deep to the temporalis muscle. Care was taken not to overfill, with an aim to only level the hollowing. To reduce any prominent humps, the filler was carefully massaged after injection.

Patient examination and follow-up

Patients were seen before and at 6, 12, 18, and 24 months after the first treatment. Each visit included an interview, clinical examination (evaluation of symmetry, contour, and skin surface of the temporal area), photographs, and ultrasound measurement. Questions asked during the interview included how the patients experienced the procedure, especially any feeling of pain and any side effects, and whether they were satisfied with the cosmetic outcome or not. Degree of pain was not graded. Patients were offered repeated injections if they were dissatisfied with the outcome, and clinical examination revealed insufficient effect.

Photographs taken by a medical photographer were used for grading of temporal hollowing. The pictures were taken when a camera was positioned straight in front of the patient's face and at a 45-degree angle to the sagittal plane.

In all patients, the temporal hollowing was categorized according to the grading scale illustrated in Figure 1. Photographs obtained before treatment and at every follow-up were graded by three experienced investigators (two oculoplastic surgeons (ER and HOU) and one plastic surgeon (SAJ)). When the investigator found the temporal hollowing to be between two grading scores, the mean of the two numbers was used. An average grading score was calculated from the scores of the three investigators.

Ultrasound examination was performed using the Edge Ultrasound System with an HFL50x transducer (SonoSite, Seattle, USA). The soft tissue thickness from the skin surface to the periosteum was measured in centimeters (Figure 2) and was calculated from an average of three different measurements. All examinations were performed by the same investigator (HOU).

Complications

Side effects were divided into two categories: Early complications were defined as occurring at operation or within 2 weeks after the treatment and late postoperative complications appeared 2 weeks or more after treatment.

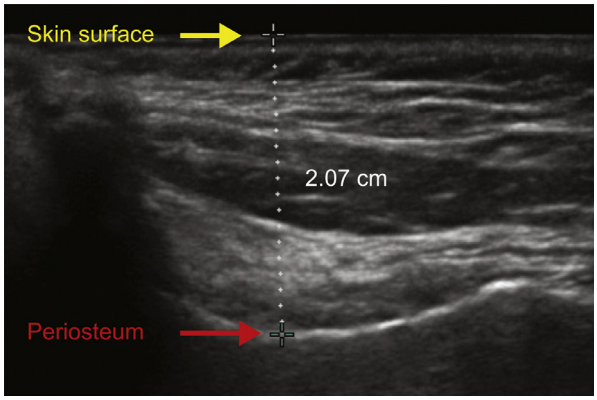

Figure 2 Soft tissue thickness from the skin surface (yellow arrow) to periosteum (red arrow) marked on the ultrasound image before injection.

The following early possible complications were registered: bruising, allergic reaction, infection, inflammation, pain/tenderness, skin surface irregularities, local skin necrosis, and thrombosis and embolism (local and systemic) and at the donor site umbilical secretion and abdominal pain. Late postoperative complications included disfiguring skin surface, subcutaneous scarring, swelling, and alteration in sensation and at the donor site pain and abdominal dump.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS Version 21.0; IBM Corporation, Armonk, NY, USA) and Stata SE version 14.0 (Stata Statistical Software, College Station, TX, USA). A sample size of 30 patients was estimated by a power calculation, using a 0.05 significance level, power of 80%, and an expected difference in treatment effect (soft tissue thickness) of 15%. Continuous data were represented as mean (SD) and median (range) when appropriate. The significance level was set at $p < 0.05$. A chi-square test was used to examine differences in patient's satisfaction.

Table 1 Characteristics of patients.

	Study subjects* ($n = 29$)	
Women, n (%)	27	(93)
Age, yrs (range)	62	(33-77)
Time from decompression to inclusion, months (range)	119	(31-198)
Smokers, n (%)	11	(38)
BMI, kg/m^2 (range)	25.8	(20-39)
Diabetes, n (%)	3	(10)

* Categorical data are given as number (percent) and continuous data as median (range).

Inter-observer reliability for ordinal categorical variables and test-retest reliability for continuous variables were assessed by interclass correlation coefficient (ICC) (95% CI) using an absolute agreement definition in a two-way mixed-effects model, where people effects are random and measured effects are fixed. Average-measure and single-measure ICC were used for inter-observer reliability and test-retest reliability, respectively. An ICC < 0.50 is considered as poor reliability, 0.50-0.75 as good, and ≥ 0.75 as excellent.[17]

To estimate differences in outcomes between treatment with HA and AF, a linear mixed-effects model for repeated measures was used.[18] Our model defined treatment, visit time, and treatment-by-time interaction as fixed effects. We included the baseline outcome value, age, and sex as covariates to control for potential imbalance preintervention. Refill (of either AF or HA) was included as a time-varying covariate. To account for the intraindividual correlation between repeated measures within patients and treatment sides, the patient and a patient-by-treatment interaction were specified as random effects. Furthermore, to account for other variation not captured by the variance-covariance structure formed by random effects, a method for obtaining cluster-robust standard errors of model parameters was applied.[19] To obtain 95% confidence intervals (CI) and P values for difference in mean values between the comparison groups at different time points, we performed a post-hoc test for pairwise comparison accounting for multiple testing (Sidak correction). To obtain P for trend in mean values within treatment groups, the effect of time was included as a linear term using the z-test. To test whether the predicted means changed differently with time across treatment groups, we used the likelihood ratio test by comparing the log-likelihood between models with and without the treatment-by-time interaction.

Results

Patient characteristics

A total of 29 patients were included. Patient characteristics are presented in Table 1. Median (range) age at first injection was 62 (33-77) years. Median time from decompression surgery to inclusion was 119 (31-198) months.

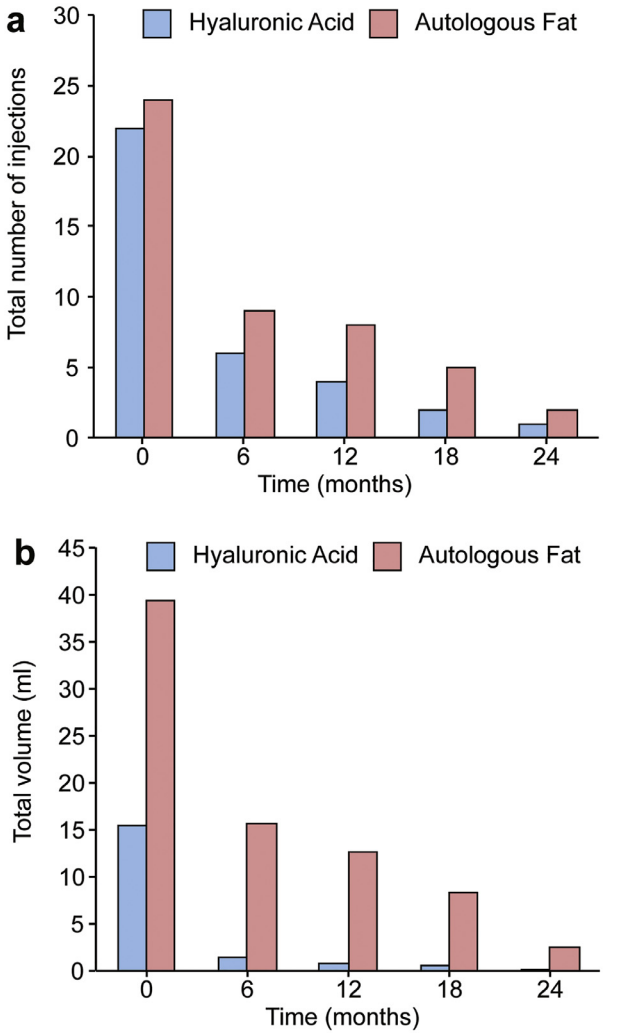

Figure 3 Total number of injections (**a**) and total volume (**b**) of hyaluronic acid and autologous fat at each time point.

Injections

Seventeen patients were treated bilaterally. Twelve patients received unilateral injections, five injections of HA and seven injections of AF. A total of 35 injections of HA and 48 injections of AF were given during the study period. The number of injections and the total volume injected of both HA and AF decreased at each follow-up. More number of injections and a higher total volume of AF than HA were recorded at all time points (Figure 3).

Each site treated with HA received a median (range) of 1 (1-4) injection(s) during the 2-year study period. The median total combined volume of HA in each site during the same period was 0.9 (0.2-2.0) ml. The median volume per injection of HA was 0.7 (0.2-2.0) ml. A defect treated with AF received a median of 2 (1-5) injections and a median total combined volume of 3.1 (0.5-9.6) ml of fat. The median volume per injection of AF was 1.4 (0.5-4.5) ml.

For 12/22 sites receiving HA and for 9/24 treated with AF, one single injection provided a sufficient effect lasting for 2 years (Table 2). Figure 4 shows a patient treated with a single HA injection in the right temporal region and two

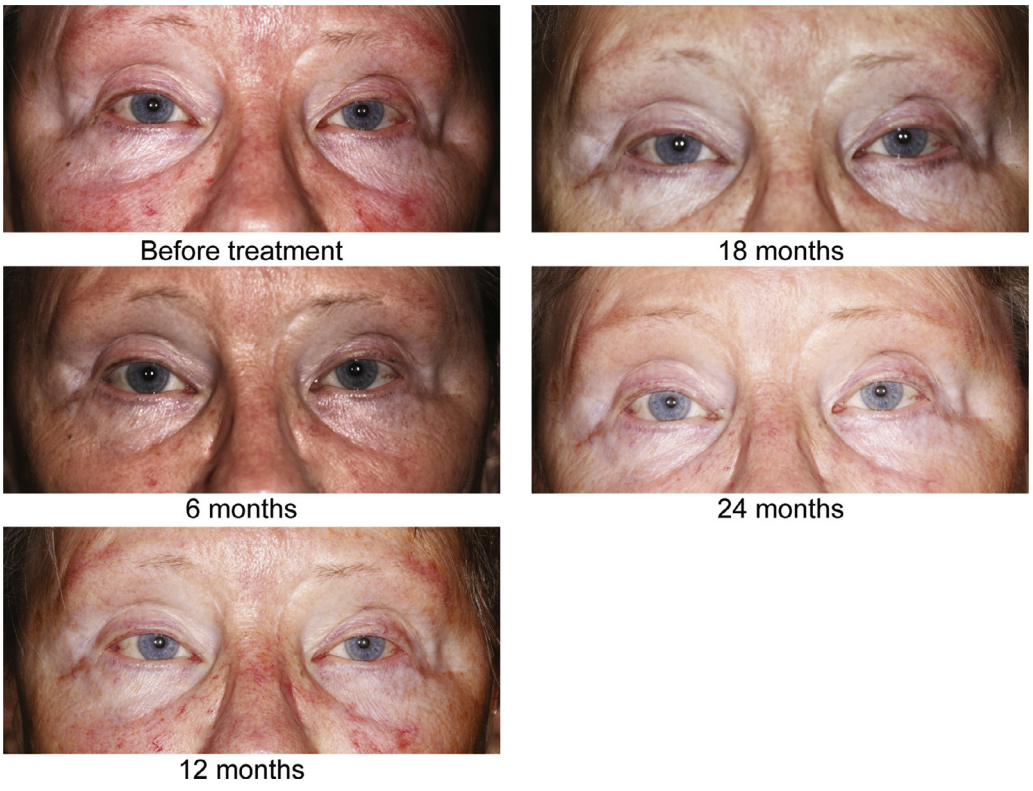

Figure 4 Photographs of a patient given one injection of hyaluronic acid in the right and two injections of autologous fat in the left temporal region (reinjection with autologous fat after 6 months). Photos are taken before treatment (upper left) and then at follow-ups, as indicated.

Table 2 Total number of injections (1–5) according to the number of hyaluronic acid (HA) or autologous fat (AF) injection sites.

Number of injections*	Number of injection sites	
	HA	AF
1	12	9
2	8	9
3	1	4
4	1	1
5	0	1
Total	22	24

* Total number of injections required during 2 years of follow-up.

treatments with AF in the left. At final examination, a normalized appearance in the right temple was observed, but the hollowing on the left side persisted.

Outcome

The degree of inter-observer reliability obtained for 219 grading scores of temporal hollowing performed by three different investigators in terms of ICC was estimated to be 0.78 (95% CI 0.52–0.88, $p < 0.05$) (excellent). Before start of the treatment, a statistically significant difference ($p = 0.001$) in mean (SD) grading score of temporal hollowing between the sites allocated to the two different treatment modalities was observed (Figure 5). After administering injections of HA, the mean grading score decreased from 2.33 (0.35) before treatment to 1.18 (0.26) at final follow-up. During the same follow-up period, the mean grading score for sites injected with AF decreased from 2.56 (0.29) to 1.84 (0.44). By using a linear mixed-effect model, adjusting for baseline values, age, sex, and refill, the mean differences in grading score between HA and AF were statistically significant at all visits after initial treatment (Table 3).

The test–retest reliability of the 287 ultrasound measurements of soft tissue thickness at the injection sites as estimated by ICC was 0.89 (95% CI 0.86–0.91, $p < 0.05$) (excellent). Pre intervention, equal soft tissue thickness was observed for the sites allocated to the two different treatment modalities. Mean (SD) soft tissue thickness was 2.35 (0.24) cm 6 months after HA injections and 2.19 (0.28) cm after AF injections (Figure 6). The mean soft tissue thickness increased for both types of treatments. We observed that temples injected with HA had a significant thicker soft tissue component at all follow-ups throughout the study period using a mixed-effect model (Table 3).

Side effects

We did not observe any allergic reactions to local anesthetics or the HA. No patients had to be treated for local or systemic infection after the procedures. We observed no signs of skin necrosis, thrombosis, or embolism after treatment.

Table 3 Grading score of temporal hollowing and soft tissue thickness at injection sites after treatment with HA and AF.

	HA ($n=22$)		AF ($n=24$)		HA vs. AF Mean difference (95% CI)*	P value†	P value for interaction‡
	No.	Mean (SD)	No.	Mean (SD)			
Grading score (1-3)							0.08
Baseline	22	2.33 (0.35)	24	2.56 (0.29)			
6 months	22	1.61 (0.37)	24	2.15 (0.47)	−0.41 (−0.70, −0.12)	0.002	
12 months	22	1.36 (0.32)	24	2.02 (0.47)	−0.53 (−0.80, −0.25)	<0.001	
18 months	22	1.22 (0.26)	24	1.94 (0.43)	−0.59 (−0.85, −0.32)	<0.001	
24 months	22	1.18 (0.26)	24	1.85 (0.44)	−0.54 (−0.82, −0.26)	<0.001	
P for trend§		<0.001		<0.001			
Soft tissue thickness (cm)							0.74
Baseline	22	2.07 (0.31)	24	2.08 (0.39)			
6 months	22	2.35 (0.24)	24	2.19 (0.28)	0.17 (0.07, 0.27)	<0.001	
12 months	22	2.37 (0.20)	24	2.24 (0.22)	0.15 (0.06, 0.25)	<0.001	
18 months	22	2.53 (0.24)	24	2.34 (0.27)	0.21 (0.09, 0.33)	<0.001	
24 months	22	2.66 (0.29)	24	2.52 (0.34)	0.16 (0.03, 0.28)	0.005	
P for trend§		<0.001		<0.001			

HA, hyaluronic acid; AF, autologous fat; SD, standard deviation; CI, confidence interval.
* Predicted mean difference was obtained using a linear mixed-effect model, adjusted for baseline outcome value, age, sex, and refill.
† P for difference was obtained using the post-hoc test for pairwise comparisons.
‡ P for interaction was obtained using the likelihood ratio test.
§ P for trend within treatment groups was obtained by incorporating visit time (from 6 to 24 months) as a continuous model term.

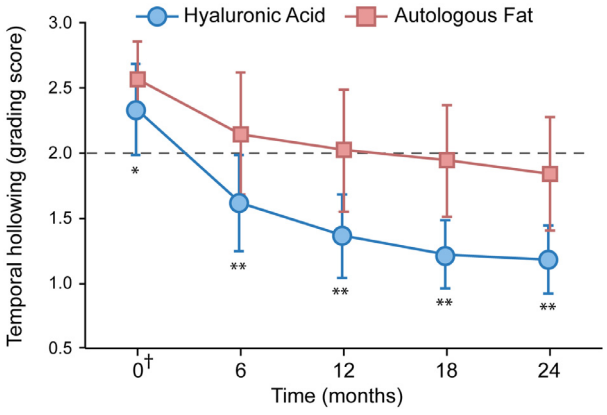

Figure 5 Changes in temporal hollowing assessed as grading scores following injections with either hyaluronic acid or autologous fat. Data are given as mean +/− SD. The dashed line equals temporal hollowing grade 2.
P values were obtained using a linear mixed-effects model as described in the methods, but instead of adjusting for the baseline value of the outcome by including it as an independent variable (as in Table 3), this value was included as a repeated observation of the dependent outcome variable.
*, $p=0.001$; **$p<0.001$.
†Measures at time 0 indicate pre intervention.

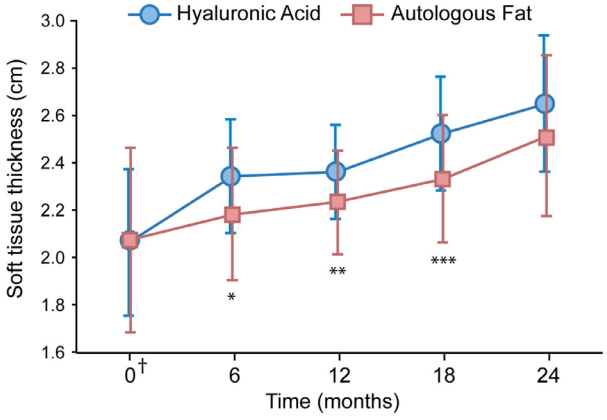

Figure 6 Changes in soft tissue thickness at injection sites measured by ultrasound following treatment with either hyaluronic acid or autologous fat. Data are given as mean +/− SD.
P values were obtained using a linear mixed-effects model as described in the methods, but instead of adjusting for the baseline value of the outcome by including it as an independent variable (as in Table 3), this value was included as a repeated observation of the dependent outcome variable.
*, $p=0.04$; **, $p=0.02$; ***, $p=0.003$.
†Measures at time 0 indicate preintervention soft tissue thickness.

Hyaluronidase for dissolution of the HA was not warranted in any of the patients.

For both types of treatment, the most frequent complication during the first two weeks was bruising (Table 4). After 5/35 HA injections, a temporary irregularity of the skin surface was seen during the first weeks.

Four of 24 patients treated with AF were considered to be in need of a reinjection and refused further treatment because of undesirable pain during the harvesting or injection procedure.

Local swelling at the injection site was reported in 3/22 after HA injection (Table 4), but this regressed after 12 months. When interviewed, two patients experienced pain in the umbilical region after harvesting fat: in one

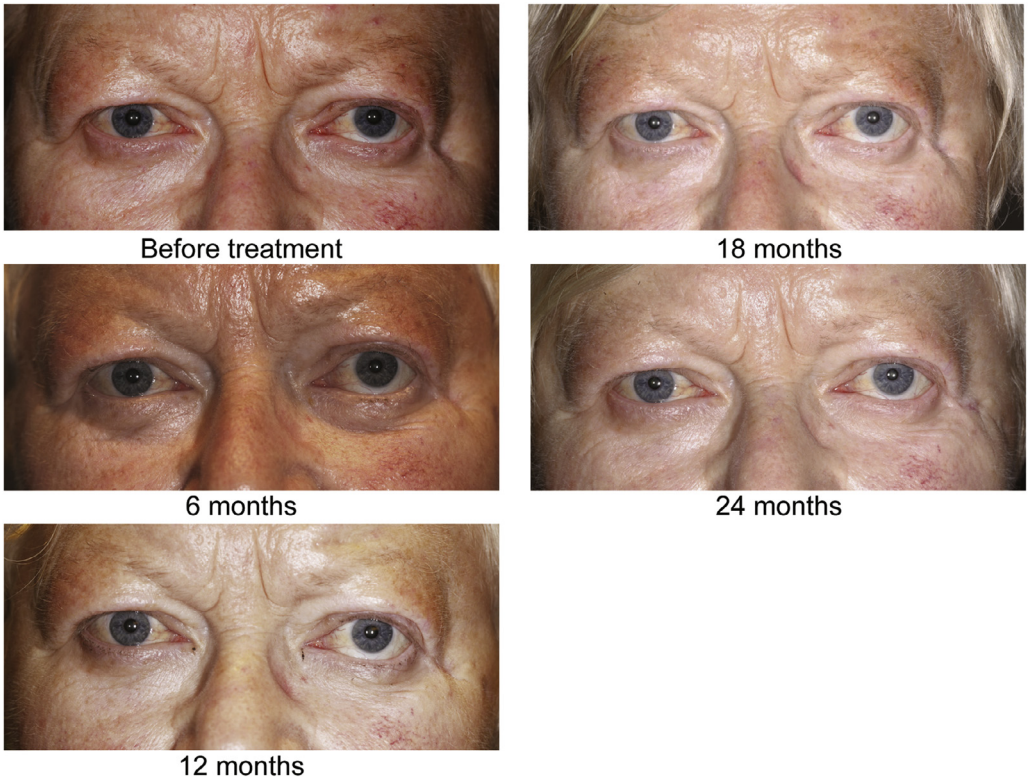

Figure 7 Photographs of a patient injected with autologous fat in the left temporal region. Photos are taken before treatment (upper left) and then at follow-ups, as indicated. She received additional injections at each follow-up. At 18 months, rigotomy was performed.

Table 4 Number of injection sites with early complications and late complications.

	HA		AF	
	No.	%	No.	%
Early complications				
Bruising	8	23	14	29
Irregular surface	5	14	1	2
Pain	2	6	4	8
Swelling	2	6	2	4
Total	35		48	
Late complications				
Disfiguring surface	2	9	1	4
Subcutaneous scarring	0	0	5	21
Swelling	3	14	0	0
Abdominal dump	0	0	1	4
Abdominal pain	0	0	2	8
Total	22		24	

HA, hyaluronic acid; AF, autologous fat.

individual, the pain lasted for 4 weeks, but in the other, it lasted for 1 year.

We did not observe any fibrosis of the subcutaneous tissue after treatment with HA but at 5/24 sites receiving AF, subcutaneous fibrosis developed. In these cases, it was difficult to reinject the fat, and blunt resolution of the fibrotic tissue with a cannula had to be performed in all five individuals. In two of the five patients, rigotomy was necessary after 18 months to restore normal temporal configuration. Figure 7 illustrates a patient who received four repetitive treatments of AF, where the last treatment included subcutaneous rigotomy.

Patient satisfaction

At final examination, 20/22 patients treated with HA and 19/24 patients administered with AF injection reported to be satisfied with the appearance of the injection site. The difference was not statistically significant ($p = 0.268$) but indicated an advantage due to treatment with HA injections.

Discussion

This prospective study was designed to evaluate and compare two treatment alternatives for patients with temporal hollowing after lateral orbital wall decompression. The study design is unique in the way that in the majority of the cases (17 in total), the effect of the injection could be compared in each participant. This reduces the effect of additional covariates such as age, smoking, diabetes, and allergy. A linear mixed-effects model was used to control for differences in reinjection rate and baseline value of temporal hollowing when comparing the two treatments. We observed that treatment with HA injections required lower total volumes and less frequent injections than treatment with AF injections during a follow-up period of 2 years. The cosmetic results achieved using HA injections were more

satisfactory than using AF injections as evaluated from clinical examination, photographs, and patient interviews.

To our knowledge, there is no consensus on the systematic classification of the degree of postoperative temporal hollowing. A validated photo-numeric grading scale has previously been developed for the evaluation of temporal hollowing in esthetic treatment.[20] These criteria were not suitable for the grading of postoperative temporal hollowing in our patients because the initial defect was more localized. We, therefore, used a grading scale from 1–3 (normal-moderate-disfiguring) based on photographs. In our opinion, it is important to use the same angle between the camera and the face of the patient and the same illumination to obtain reproducible results. When assessing for temporal hollowing using this scale, we found a difference between the two treatment options in favor of HA.

Temporal hollowing following lateral orbital wall decompression is a localized defect corresponding to the absent bone piece. Less volume of AF is needed for the treatment of this confined area than to correct the more generalized tissue atrophy in age-related temporal hollowing. Shue and coworkers reported a usual amount of AF per injection in esthetic treatment of temporal hollowing to be 5.9 (2–10) ml compared to 1.4 (0.5–4.5) ml in our patients.[21]

A higher total injection volume of AF than that of HA was required to achieve the same soft tissue volume. Ultrasound measurements showed that although the soft tissue thickness increased with time for both HA and AF injections, it appeared earlier after HA injections and the soft tissue was thicker at all follow-ups than that with AF injection. These observations may be related to the properties of the fillers. After fat has been filtered, some liquid remains in the fat suspension. This liquid is resorbed after injection and the volume of the injected suspension decreases in the first days after treatment. On the contrary, HA expanded slightly in the first 24 hours after injection because of its water-binding ability.[22]

We observed that in 15/24 sites injected with AF, additional injections were required. This could be due to the reabsorption of liquid, but it is suggested that only some of the injected fat adapts in the subcutaneous tissue.[23] The survival of the grafted fat is known to depend on the recipient tissue.[24] Transferred AF seems to adapt best in adequately vascularized recipient tissue.[25] In contrast to most patients treated with esthetic procedures, our patients have undergone surgery in the temporal region. A postoperative scar is generally considered a poor candidate for fat grafting because of fibrosis and scarcity of capillaries.[26]

At 5/24 of the AF injection sites, extensive fibrosis was observed. This could result from the primary decompression surgery or be a side effect of the fat grafting. As we only observed fibrosis after AF injections, it is likely that it occurred because of the treatment. We found patients with fibrosis more difficult to treat, as they needed repeated and more extensive treatment.

The duration and reinjection rate of HA are dependent on the HA polymer.[27] In the area of the eye brows, the effect of Restylane® may persist for 2 years.[28] In the present study, Juvederm Voluma® was found to be a stable option for restoring volume in the temporal region. We observed that 12/22 of the temples needed only a single injection of Juvederm Voluma® during the 2 years of follow-up. This finding could be due to the high viscosity of the HA filler and relative immobility of the skin and subcutaneous tissue in the treatment area.

We did not observe any change in vision in any of the patients. Loss of vision after intravascular injections in the lids and periocular region has been reported.[29,30] The most common complication reported in the literature is transient bruising.[10] In line with this, our patients reported temporary bruising after 8/35 and 14/48 of the injections with HA and AF, respectively. Temporary contour irregularities were seen at sites injected with HA. After 5/35 of HA injections, a transient bumpiness in the skin surface was reported. This can be overcome by injecting the HA at the level deep to the temporalis muscle so that the overlying fat, muscle, and skin might conceal the irregularity. Prolonged swelling was observed in 3 patients after injection with HA, which could be caused by an inflammatory reaction against HA.

The main limitations of the present study are the relatively small number of individuals included and the lack of randomization. The patients could have been randomized to receive HA or AF on either side, thereby allowing the study to be blinded for the investigators that did not perform the injections. Further, randomization could have reduced the impact of the different status of temporal hollowing of the two sides at the outset. We attempted to adjust for this by analyzing the data with a mixed-effects model. Another limitation is that the last examination after initial treatment for temporal hollowing was 2 years. A longer observation time could have revealed additional aspects of the two treatment options.

Conclusion

Both injections of synthetic long-lasting HA and AF are safe and effective alternatives for treating temporal hollowing after lateral orbital wall decompression. However, treatment with HA on average requires fewer injections, is less time consuming and painful, as it does not involve harvesting of fat from the abdomen and there is no increase in the risk of developing subcutaneous fibrosis. Furthermore, the cosmetic result is more satisfactory than that achieved using AF. Our study suggests that injection with long-lasting HA is a better option than AF for treating postoperative temporal hollowing.

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Conflict of interest

None of the authors has any commercial associations or financial disclosures that might pose or create a conflict of interest with information presented in this article.

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