

ORIGINAL ARTICLE

Fibrotic reaction to hyaluronic acid fillers in the face

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Abstract

Background: Hyaluronic acids (HAs) can have very different actions not only depending on injector and host factors but also depending on their molecular weight. Whereas short chain HA has immunological activity long chain HA influences fibroblasts and may stimulate them to produce collagen. Although this is generally thought to be a positive feature it may be disadvantageous in certain localizations.

Patients and Methods: We have encountered 23 patients who developed fibrous tissue next to the nasolabial folds accentuating them and becoming very obvious while smiling. Hyaluronidase injection did not reduce this mass.

Results: Intralesional triamcinolone acetonide injection led to rapid improvement.

Discussion: Fibrotic tissue reaction not responding to hyaluronidase may be the result of HA injection and can effectively be treated with intralesional steroid injection

KEYWORDS

body dysmorphic disorder, dermal filler, fibroblasts, hyaluronic acid, nasolabial fold

1 | INTRODUCTION

Filler injections belong to the most frequently performed cosmetic interventions. They are very effective, demonstrating an immediately visible result and when performed by experienced injectors have a very good safety record. The nasolabial folds were actually the first FDA-approved indication for the collagen filler Zyderm®. This type of collagen fillers is no longer used even though no case of bovine spongiform encephalopathy was described in association with bovine collagen because hyaluronic acids (HAs) are easier to handle, much safer, good quality preparations are virtually without risk for allergic and granulomatous reactions, they are malleable and still the only fillers for which an antidote exists, hyaluronidase. Millions of cosmetic HA injections are performed yearly and almost all are well tolerated. The nasolabial fold injections are still extremely popular. The only feared complications are various types of vascular occlusion such as blindness, stroke, aphasia, and skin necrosis; however, vascular occlusion is not substance specific and can be observed with all different fillers.¹⁻⁵

Since 2006, we have seen a peculiar reaction after HA filler injection to correct the nasolabial fold in 23 female patients. These women felt that something did not fit in the face although the nasolabial fold was markedly improved. However, they could not exactly define what was wrong and described it as an “odd reaction.” One said it reminded her of a joker smile with a “sausage” (bulge) appearing at the lateral margin of the nasolabial fold. All attempts at treating it with hyaluronidase were unsuccessful. Curiously, when trying to inject directly into the bulge a rubber-like structure was felt quite different from normal cutaneous fat. We describe this hitherto unreported finding and try to give an explanation for its development.

2 | CASE REPORTS

Since 2006, 23 patients who had been injected for their nasolabial folds elsewhere consulted us as they felt that the face had become “heavier.” These women all said that they were principally satisfied and had good results with flattening and in part almost complete

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disappearance of the folds but that something unexplainable did not really fit. All patients were female and between 38 and 65 years old. They all had normal weight. No relevant internal diseases were reported.

Mrs X, 38 years old, came to the office for an aesthetic consultation. The last 8 years she had undergone several cosmetic treatments with HA fillers, including lip correction, cheek enhancement, jaw line and, of course, nasolabial folds. She belongs to the kind of patients who are somehow “addicted” to cosmetic treatments and due to the brain wash from the social media are absolutely convinced that this is the right way to look like. She was satisfied with the flattening of the nasolabial fold, but something in the total appearance of the face did not really fit. The lower part of the face was “heavier” and upon smiling the lower two thirds of the nasolabial folds pushed the cheeks up causing a weird hemispherical appearance of the cheek distorting the normal lip shape and elevating the commissure giving the patient a “joker smile” appearance (Figure 1A). Palpation revealed a sausage shaped bulge lying immediately under the dermis parallel to the lower two thirds of the nasolabial fold. She could feel this bulge, which was only to find in the nasolabial fold area and nowhere else where HA had been injected. Two courses of injecting the bulge with hyaluronidase (120 units in 2 mL normal saline) (Hylase Dessau®) did not affect the bulge although this product has been proven to be very effective in over 300 cases the last 20 years solving unwanted HA from lips, jawline, cheeks, and lower eyelids plus tear trough up to now. Thereafter, it was decided to try a steroid injection with 6 mg triamcinolone acetone (TA) crystal suspension, which made the bulge almost disappear giving the patient a normal appearance when she came for control after 6 weeks (Figure 1B). The fact that both medications (hyaluronidase and TA crystal suspension) are target specific allows us to assume that the bulge consisted of excess collagen deposition due to secondary fibrotic reaction and not from injected HA.

Visual inspection first did not reveal obvious abnormalities. However, upon smiling, the lower two thirds of the folds pushed the cheeks up causing a weird hemispherical appearance of the cheek and somehow distorted the normal lip shape with decreasing or disappearance of the lateral one fifth of the vermilion of the upper

lip while the commissure was slightly elevated (Figure 1A). This was called by one patient the “joker smile.” Palpation displayed another consistency reminding of hard rubber. Sliding palpation from the lateral cheek toward the philtrum revealed a sausage-shaped bulge in the superficial cutaneous fat just lateral of the fold extending over the lower two thirds of the fold. As this was not the consistency of HA an injection of TA crystal suspension was proposed to the patients. However, eight patients wanted first another trial with hyaluronidase, which remained unsuccessful. At the end, all patients got TA into the fibrotic tissue, approximately 4–6 mg per side. Seven patients had to be reinjected a second time, one three times. After approximately 4–6 weeks, reexamination of the patients revealed an almost complete disappearance of the bulge. The lips showed no distortion during smiling (Figures 1–3). None of the patients consulted us again for a recurrence.

3 | DISCUSSION

Nasolabial folds are extremely common, often very deep and embarrassing. They are already often observed in young persons, particularly after weight loss. Many women request aesthetic improvement with HA fillers. In the 40 years since fillers have been on the market, nasolabial folds were the most frequent indication. The techniques of treating nasolabial folds with HA have changed over the last 25 years, from intradermal multi-puncture to linear and fan-like threading to deep injections right on the periosteum with the tower technique. The latter technique is possible with HA fillers as they are malleable and gentle massage can spread the filler to yield the wanted result. The safety of the HA filler products has been continuously improved so that allergic, granulomatous, and infectious reactions have become rare. There is a big demand for filler injections and quite a number of patients are now treated by non-medical personnel, which is not legal in many countries. This is mainly done to save money; however, those persons then may get low-quality cheap HA and the procedure may not be performed according to good medical practice. Further, the lay injectors often neglect full asepsis and may inject through makeup. They usually do



FIGURE 1 (A) Before (left) and (B) 6 weeks after triamcinolone injection (right).

FIGURE 2 (A) A 50-year-old patient before (left) and (B) 10 weeks after triamcinolone injection (right).

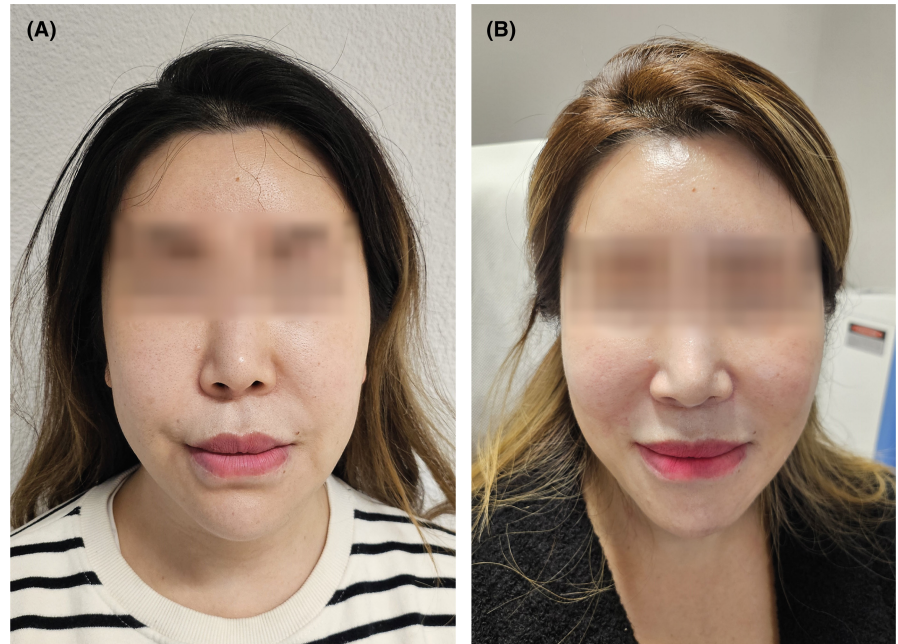


FIGURE 3 (A) A 43-year-old patient before (left) and (B) 6 weeks after triamcinolone injection (right).



not understand the biomechanics of facial movements and do not inject into the proper site and level of cutaneous fat. As it first looks satisfying when the fold is flat the patients are content and do not associate late unwanted effects with this injection technique.

HAs are said to be extremely well tolerated and not being species specific. This is true for the carbohydrate moiety; however, for biosynthesis each organism needs to add a species-specific protein. This has been split off before using HA for cosmetic injections but early HA preparations had, and low-quality still have, some protein potentially causing adverse reactions such as granulomas and abscesses. It has long been known that the biologic properties of HA depend on the size of the molecule. Commercially available HA fillers have distinct properties depending on HA concentration, length of the molecules, rheology, degree of cross-linking, and cohesivity properties. Many different formulations are marketed with slight variations in these features. What is rarely mentioned in publications

on the cosmetic use of HA is the intrinsic action of HA on host cellular systems.

Small-molecule HA has an immunostimulatory action of which large HA molecules are virtually devoid. In contrast, large-molecule HA has almost no effect on the immune system but acts on fibroblasts, which have receptors for large HA. Also cross-linked HA stimulates collagen production under the mechanical effect of stretching the fibroblasts.⁶⁻¹¹ The localization of the fibrotic bulge along the lower two thirds is exactly where the tissue is stretched during speaking, smiling, laughing, and chewing giving strong evidence that this reaction may be due to the fibroblast stimulatory action of long chain HA.^{10,11}

Probably the most important advantage of HA fillers is that there is a natural enzyme, hyaluronidase, which is able to dissolve HA in a relatively short time and thus to revert many of the unwanted effects. Mild complications such as the Tyndall effect, noninflamed

nodules, and allergic or hypersensitivity reactions may be treated with low or moderate hyaluronidase doses. If inflammatory nodules are treated with hyaluronidase is worth being considered. The enzyme may also be tried for granulomas not responding to intral-lesional steroids. Serious complications like vascular occlusion and blindness have to be immediately treated with high doses of hyaluronidase. Whether the retrobulbar or supraorbital injection technique is used for blindness remains controversial. Ultrasound guidance can increase the efficacy of the above interventions. The effect of hyaluronidase injections is so fast and reliable that if a swelling does not respond the nature of the filler or of the mass to be treated has to be questioned.^{12,13} This prompted us to consider another cause for the peculiar rubber-like bulge in our patients. Thus, we hypothesize that this reaction might be due to the fibroblast stimulating action of long-chain HA as used in cosmetic fillers.¹³

4 | CONCLUSION

Injections of HA for nasolabial folds should preferentially be performed in the non-moving upper part of the folds.

5 | LIMITATION STATEMENT

This is a real-world retrospective observation with no control group.

ACKNOWLEDGMENTS

The authors thank the patients for their cooperation.

FUNDING INFORMATION

The authors did not receive any funding for their work.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Anonymous de-identified data are available on reasonable request.

ETHICS STATEMENT

This is a retrospective observational study and no experiments were performed on human or animal beings. All patients gave their verbal permission for publication.

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REFERENCES

1. Kroumpouzou G, Treacy P. Hyaluronidase for dermal filler complications: review of applications and dosage recommendations. *JMIR Dermatol*. 2024;7:e50403. doi:10.2196/50403
2. Wang R, Li Y, Li Z, Yao H, Zhai Z. Hyaluronic acid filler-induced vascular occlusion – three case reports and overview of prevention and treatment. *J Cosmet Dermatol*. 2024;23(4):1217-1223. doi:10.1111/jocd.16147
3. Soares DJ, Hynes SD, Yi CH, Shah-Desai S, Irving SC. Cosmetic filler-induced vascular occlusion: a rising threat presenting to emergency departments. *Ann Emerg Med*. 2024;83(1):59-67. doi:10.1016/j.annemergmed.2023.07.006
4. Zhao F, Chen Y, He D, You X, Xu Y. Disastrous cerebral and ocular vascular complications after cosmetic facial filler injections: a retrospective case series study. *Sci RepSci Rep*. 2024;14(1):3495. doi:10.1038/s41598-024-54202-w
5. Tan YJ, Sugianto N, Li Y. Multifocal strokes and vision loss from PDLLA filler injections. *J Stroke Cerebrovasc Dis*. 2024;33(3):107556. doi:10.1016/j.jstrokecerebrovasdis.2024.107556
6. Laurent TC, Laurent UB, Fraser JRE. The structure and function of hyaluronan: an overview. *Immunol Cell Biol*. 1996;74:a1-a7. doi:10.1038/icb.1996.32
7. Meran S, Thomas D, Stephens P, et al. Involvement of hyaluronan in regulation of fibroblast phenotype. *J Biol Chem*. 2007;282(35):25687-25697. doi:10.1074/jbc.M700773200
8. Wang F, Garza LA, Kang S, et al. In vivo stimulation of de novo collagen production caused by cross-linked hyaluronic acid dermal filler injections in photodamaged human skin. *Arch Dermatol*. 2007;143(2):155-163. doi:10.1001/archderm.143.2.155
9. Turlier V, Delalleau A, Casas C, et al. Association between collagen production and mechanical stretching in dermal extracellular matrix: in vivo effect of cross-linked hyaluronic acid filler. A randomised, placebo-controlled study. *J Dermatol Sci*. 2013;69(3):187-194. doi:10.1016/j.jdermsci.2012.12.006
10. Landau M, Fagien S. Science of hyaluronic acid beyond filling: fibroblasts and their response to the extracellular matrix. *Plast Reconstr Surg*. 2015;136(5):188S-195S. doi:10.1097/PRS.0000000000001823
11. Gómez-Aristizábal A, Kim KP, Viswanathan S. A systematic study of the effect of different molecular weights of hyaluronic acid on mesenchymal stromal cell-mediated immunomodulation. *PLoS One*. 2016;11(1):e0147868. doi:10.1371/journal.pone.0147868
12. Borzabadi-Farahani A, Mosahebi A, Zargaran D. A scoping review of hyaluronidase use in managing the complications of aesthetic interventions. *Aesthetic Plast Surg*. 2024;48(6):1193-1209. doi:10.1007/s00266-022-03207-9
13. Gold M. Use of hyaluronic acid fillers for the treatment of the aging face. *Clin Interv Aging*. 2007;2:369-376.

How to cite this article: Peros I, Haneke E. Fibrotic reaction to hyaluronic acid fillers in the face. *J Cosmet Dermatol*. 2024;00:1-4. doi:10.1111/jocd.16419