

Hyaluronidase for Treating Complications Related to HA Fillers: A National Plastic Surgeon Survey

L'hyaluronidase Pour Traiter Les Complications Liées Aux Agents de Comblement à Base d'AH : un Sondage National Auprès Des Plasticiens

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Abstract

Background: Hyaluronic acid (HA) fillers have become a popular modality to address changes in the ageing face. There are many described indications of hyaluronidases in aesthetic medicine which include their use in the management of HA-associated complications. To better understand the current practice patterns, we surveyed Canadian plastic surgeons on their use of hyaluronidases. **Methods:** With the approval of the Canadian Society of Plastic Surgeons, an electronic survey was emailed to members. A total of 350 surveys were distributed and 98 surveys were completed for a response rate of 28%. **Results:** Approximately half (48%) of the survey respondents used HA fillers in their practice. Skin testing for hypersensitivity reactions was performed by less than 10% of hyaluronidase users. Nearly all respondents used hyaluronidase for filler over-correction (95.5%) and asymmetry (86.4%). Over half of the respondents have used hyaluronidase for inflammatory or infectious nodules and the Tyndall effect. Other reported applications included restoration of vascular compromise, and one respondent reported using hyaluronidase for assisting with haematoma resolution. When compared with the most recent guidelines, there was a wide range of doses used for common side effects and complications. Twenty-four percent of the respondents reported that their hyaluronidase formulation was prepared by a compounding pharmacy, and 20% of respondents who inject HA fillers did not stock hyaluronidase. **Conclusion:** There are many indications for hyaluronidase in aesthetic plastic surgery. Plastic surgeons should stock hyaluronidase and develop a specific plan in anticipation of adverse events. Although hyaluronidase is commonly used by plastic surgeons for over-correction and asymmetry, the dosages used in aesthetic practice is rather diverse and heterogeneous. When possible, plastic surgeons should perform allergy testing before hyaluronidase use.

Résumé

Historique : Les agents de comblement à base d'acide hyaluronique (AH) sont devenus populaires pour modifier la face vieillissante. De nombreuses indications sont décrites pour utiliser les hyaluronidases en médecine esthétique, y compris pour la prise en charge des complications liées à l'AH. Pour mieux comprendre les modes de pratique actuels, les chercheurs ont sondé les

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plasticiens canadiens pour connaître leur utilisation d'hyaluronidases. **Méthodologie :** Avec l'approbation de la Société canadienne des chirurgiens plasticiens, les membres ont reçu un sondage électronique par courriel. Au total, 350 sondages ont été distribués, et 98 ont été remplis, pour un taux de réponse de 28 %. **Résultats :** Environ la moitié des répondants au sondage (48 %) utilisent les agents de comblement à base d'AH dans leur pratique. Moins de 10 % d'entre eux effectuaient des tests d'hypersensibilité cutanée. Presque tous les répondants se servaient de l'hyaluronidase pour corriger les surcorrections (95,5 %) et l'asymétrie (86,4 %). Plus de la moitié utilisent l'hyaluronidase pour les nodules inflammatoires ou infectieux et l'effet Tyndall. La restauration d'une atteinte vasculaire était une autre application, et un répondant a déclaré y recourir pour contribuer à la résolution des hématomes. Par rapport aux directives les plus récentes, les doses utilisées étaient très variables pour les effets secondaires et les complications. Ainsi, 24 % des répondants ont déclaré qu'ils obtenaient leur formulation d'hyaluronidase par des préparations magistrales, et 20 % des répondants qui injectent les agents de comblement à base d'AH n'en conservaient pas en stock. **Conclusion :** Il y a de nombreuses indications pour utiliser l'hyaluronidase en chirurgie plastique. Les plasticiens devraient conserver des provisions d'hyaluronidase et se doter d'un plan détaillé en cas d'événements indésirables. L'hyaluronidase est souvent utilisée par les plasticiens pour corriger les surcorrections et l'asymétrie, mais les dosages utilisés en esthétique sont plutôt diversifiés et hétérogènes. Dans la mesure du possible, les plasticiens devraient effectuer des tests d'allergie avant d'utiliser l'hyaluronidase.

Keywords

cosmetic surgery, hyaluronic acid, hyaluronoglucosaminidase

Introduction

Over time, human skin undergoes extrinsic and intrinsic ageing.^{1,2} Influenced by environmental exposures, genetics and hormonal changes, facial skin produces less collagen, elastin, and subcutaneous fat leaving patients with decreased facial volume.^{2,3} Since first appearing on the market 40 year ago, dermal fillers have become a cherished component of facial rejuvenation therapy.⁴ Dermal fillers may be composed of biological or synthetic materials and may be temporary, semipermanent, or permanent.⁵ The use of hyaluronic acid (HA)-based dermal fillers have become the treatment of choice due to their versatility, decreased immunogenicity, and availability of the reversal agent, hyaluronidase.⁶ In 2018, the American Society for Aesthetic Plastic Surgery reported that a total of 810 240 HA-based filler procedures were completed, demonstrating a 58% increase in HA filler use since 2014.⁷ Second to only botulinum toxin, HA is the next most common non-surgical aesthetic procedure.⁷

Over the years, Health Canada has received reports of adverse events secondary to HA filler injection including nodules, abscesses, infection, skin discoloration or hyperpigmentation, lip necrosis, difficulty breathing, and partial loss of vision.⁸ Hyaluronidases have demonstrated great utility when complications arise with HA filler use. Hyaluronidases are enzymes that depolymerize and subsequently degrade HA.⁹

In the United States, the Food and Drug Administration has approved hyaluronidase for extravasation injuries, and as an adjuvant to increase the absorption of coadministered subcutaneous or intramuscular medications.¹⁰⁻¹³ Hyaluronidases are not marketed in Canada but are available to clinicians for serious or life-threatening conditions through Health Canada's Special Access Program.¹⁴ In the plastic surgery and dermatological literature, there are many well-described uses and indications for hyaluronidases including, but not limited to vascular occlusion, blindness, Tyndall effect (a blue hue in the sub-ocular region), nodules, and unacceptable cosmetic outcome.^{10,13}

Despite the literature being rich of expert opinion and case series,^{10,13,15-17} there is limited high-level evidence on hyaluronidases best practice. In recognition of the variations in clinical practice, the authors collected data to describe trends of hyaluronidase use through the survey of approximately 350 members of the Canadian Society of Plastic Surgeons (CSPS). The survey included 12 questions focused on hyaluronidase practice patterns in the management of HA filler complications.

Methods

Permission was granted by the CSPS in October of 2018 to distribute the survey to 350 members who had a valid email address. Surgeons were given 2 weeks to complete and submit the survey to the investigators. The survey was developed and designed to collect information regarding the frequency, dosages, and reported uses of hyaluronidase in aesthetic surgery.

The short-12 question survey was to be completed by plastic surgeons without chart review and no personal identifying information was collected. Google Forms (Google) was used to distribute and record survey responses. A total of 350 surveys were distributed, and 98 surveys were completed for a response rate of 28%. In order to maximize survey response rates and completion, comprehensive demographic data were not collected, rather respondents were only asked to describe their length and type of practice. Early and late career plastic surgeons were defined as those with less than, or greater than 15 years of clinical practice, respectively. Data collected from incomplete surveys were included in the analysis. Categorical variables were summarized using counts and percentages. Continuous variables were summarized using medians and interquartile range (IQR). A χ^2 test of independence was performed to examine the relationship between categorical variables. Odds ratio was used to measure the association between the surgeon experience and use of hyaluronidase. Statistical

Table 1. Demographic distribution of survey respondents.

Length of practice	Number of respondents (n)	%	Used hyaluronidase at least once (n)	Frequency of hyaluronidase use (n) ^a			
				Weekly	Few times a month	Every few months	Less than once a year
Less than 5 years	19	19.4	6	0	0	2	0
5-9 years	18	18.4	10	0	0	1	1
10-15 years	15	15.3	10	1	3	2	2
>15	46	46.9	21	0	0	5	6

^aThe number of providers who use hyaluronidase and frequency of hyaluronidase use are inequivalent due to nonresponse.

analyses were performed using STATA, version 16 (Stata-Corp). *P* < .05 was used as the threshold for statistical significance for correlation and trends.

Results

Demographics

The respondents represented a large proportion of plastic surgeons in Canada, with 98 responses, the survey captured approximately 20% of CSPS members.¹⁸ Just under half (46.9%) of the respondents had been practicing for over 15 years. Complete demographic data are shown in Table 1. Almost half of survey respondents used HA fillers in their practice (48%). Of those who did not, nearly 2 of 3 were not interested in performing the procedure, while over 30% of respondents were not in a private practice setting. Lack of time and training were also cited reasons. The length of time in practice was not significantly associated with HA filler use (*P* = .198).

Frequency of Hyaluronidase Use

Fifty-two percent of surgeons who stated they inject HA fillers have never used hyaluronidase to treat complications or refine effects from HA filler use. Surgeons who are in practice for greater than 15 years were 4.3 times the odds to have ever used hyaluronidase (95% confidence interval (CI) = 1.1-17.6; *P* = .019). Overall, the frequency of hyaluronidase use was variable, as 39.1% of respondents used hyaluronidases less than once a year and 60.9% of surgeons used hyaluronidases once every several months. Notably, one respondent reported using hyaluronidases at least once every week.

Plastic surgeons most frequently used hyaluronidases in both their own private practice patients and referred complications (63.5%). A small proportion reported using hyaluronidases in only their own patients (22.7%) or solely in referred cases (13.6%).

The amount of hyaluronidase surgeons had in stock varied widely. The median number of units of hyaluronidase plastic surgeons had in stock was 1500 units (IQR: 100-10 000 units). Notably, 21.1% of plastic surgeons who used HA fillers stated their practice did not stock any hyaluronidase. Respondents commonly reported using a formulation prepared by a compounding pharmacy (23.5%).

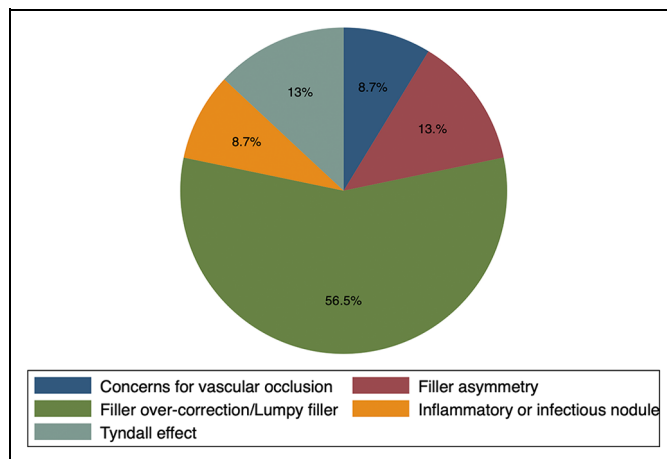


Figure 1. Plastic surgeon reported primary indication for hyaluronidase use.

Indication for Hyaluronidase Use

Over half of the respondents suggested they mostly commonly used hyaluronidases for lumps and HA filler overcorrection (56.5%). Approximately 26% of respondents stated they primarily used hyaluronidase for asymmetry or Tyndall effect. Nine percent of plastic surgeons reported their primary use of hyaluronidase was for vascular occlusion concerns, another 9% primarily used hyaluronidases for inflammatory and infectious nodules (Figure 1).

Every plastic surgeon who has used hyaluronidase reported using it for filler over-correction. A substantial majority (>59%) of plastic surgeons had experience using hyaluronidase for asymmetry, inflammatory or infectious nodules, and Tyndall effect. Approximately 40% of the respondents have used hyaluronidase for vascular occlusion concerns. Notably, one respondent had reported using hyaluronidase for hematoma resolution. Plastic surgeons almost unanimously (91.3%) reported they did not routinely perform skin testing before using hyaluronidase.

Dosages of Hyaluronidase

Although the amount of hyaluronidase used is dependent on the estimated volume of asymmetry and filler product, 55% of providers reported using a range within 5 to 30 units for

Tyndall effect following tear trough correction. Surgeons reported using a range of 5 to 500 units of hyaluronidase to fix tear trough asymmetry resulting from filler treatment. For treatment of a solitary 5-mm lip nodule, 28% of respondents suggested they would consider using at least 100 units to eliminate the nodule.

In response to vascular occlusion, surgeons stated that they would use 30 to 5000 units of hyaluronidase to restore vascularity. When treating suspected vessel occlusion, none of the respondents used ultrasound, Doppler, or other imaging device for assistance. Lastly, allergy skin testing for hyaluronidase was performed by 9% of plastic surgeons who have experiences using the enzyme.

Discussion

Over the years, the use of non-surgical facial rejuvenation has risen exponentially, and HA dermal fillers are among one of the most sought-after procedures. Undoubtedly, its increased use is associated with an increase in complications, and there is a tendency for plastic surgeons to be referred these complications for definitive management.

This study provides a description of hyaluronidase practice patterns among Canadian plastic surgeons. Almost half of the respondents used HA fillers in their practice and just under half of those practitioners have experience using hyaluronidases to treat complications or unacceptable cosmetic outcomes. Surgeons with longer years in practice were just as likely to use HA fillers, but surgeon experience was associated with having experience with hyaluronidase. Most surgeons used hyaluronidase a few times a year, only one individual reported using the enzyme on a weekly basis. The most common indication was over-correction, followed by asymmetry, nodules, Tyndall effect, and concerns for vascular occlusion. The results of this survey suggest the use of hyaluronidase among plastic surgeons is quite heterogenous across the country. The wide range of hyaluronidase doses used is likely a reflection of the lack of consensus in the literature. Various studies report a range of using 5 to 30 units of hyaluronidase to break down 0.1 mL of HA filler (at a concentration of 20 mg/mL).^{9,13,19}

There lacks consensus in the literature regarding the dosing of hyaluronidase for filler-related complications and the offered recommended doses are widely divergent. In June of 2018, a set of guidelines was published by the Aesthetic Complications Expert group¹⁰ to address this void. According to this guideline, a range of 450 to 1500 units are advocated for the treatment of vascular occlusion. Providers infiltrate the entire area of affected skin including the course of the vessel by serial puncture ideally within 4 hours of filler injection and repeating this treatment up to 4 times.⁹ There was considerable overlap among the doses used in our sample and those that were recommended for the treatment of vascular occlusion. Knowledge translation efforts of the recently published guidelines may shrink the wide range of doses used to treat vascular occlusion.

In terms of allergy testing, respondents almost unanimously did not engage in allergy skin testing despite the nonurgent use

of hyaluronidase in most cases. Incidence rates of local allergic reactions range from 0.05% to 0.69%, and urticaria and angioedema have reported incidence rates of less than 0.1%.^{12,13} Albeit rare, plastic surgeons should test for allergies and develop a specific prevention plan, to anticipate harmful allergic reactions and have treatments ready. Skin testing involves injecting 20 units of hyaluronidase subcutaneously in the forearm and observing the results after 30 minutes.⁹ Although this survey did not explore why surgeons forego skin testing, the historically low incidence rates of an allergic reaction to hyaluronidase may be a contributing factor.¹² Lastly, this survey found that approximately 20% of surgeon injectors did not stock hyaluronidase in their office. The authors feel hyaluronidase is an essential tool for the aesthetic plastic surgeon to have stocked in the event of common complications such as elimination of nodules and correcting poor cosmetic results, or more serious adverse events such as vascular occlusion.

Strengths of this study include the high response rate of 28% across a national sample of plastic surgeons. This study documents current practice patterns which can help understand changes in practice over time. It is the first survey to highlight surgeons' experiences using hyaluronidase across the country and it involved a non-random sample of CSPS members. This study has important limitations. First, no concrete conclusions regarding efficacy of techniques or doses can be made. No outcome or complication data were collected, and therefore, the efficacy of certain techniques can only be speculated. Moreover, this study used years of practice as surrogate for experience using hyaluronidase which may not always be the case. As the survey was distributed electronically, respondents who are not technologically savvy, may have been less likely to participate in the survey. Lastly, as the sample was non-random, there may be a disproportionate representation from some geographical areas in the country.

Conclusion

This survey describes the practice patterns among Canadian plastic surgeons using hyaluronidase to treat HA filler-related complications. Hyaluronidase use in aesthetic practice is rather diverse and heterogeneous.

Authors' Note

Oluwatobi R. Olaiya and Diana Forbes contributed equally to this work and are co-first authors. This study was conducted according to the principles of the Declaration of Helsinki (64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2). Informed consent was obtained from all participants.

Declaration of Conflicting Interests

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References

- Zhang S, Duan E. Fighting against Skin Aging. *Cell Transplant.* 2018;27(5):729-738. doi:10.1177/0963689717725755
- Farage MA, Miller KW, Elsner P, Maibach HI. Intrinsic and extrinsic factors in skin ageing: a review. *Int J Cosmet Sci.* 2008;30(2):87-95. doi:10.1111/j.1468-2494.2007.00415.x
- Papakonstantinou E, Roth M, Karakiulakis G. Hyaluronic acid: a key molecule in skin aging. *Dermatoendocrinol.* 2012;4(3):253-258. doi:10.4161/derm.21923
- Kontis TC, Rivkin A. The history of injectable facial fillers. *Facial Plast Surg.* 2009;25(2):67-72. doi:10.1055/s-0029-1220645
- Liu MH, Beynet DP, Gharavi NM. Overview of deep dermal fillers. *Facial Plast Surg.* 2019;35(3):224-229. doi:10.1055/s-0039-1688843
- Park TH, Seo SW, Kim JK, Chang CH. Clinical experience with hyaluronic acid-filler complications. *J Plast Reconstr Aesthet Surg.* 2011;64(7):892-896. doi:10.1016/j.bjps.2011.01.008
- American Society for Aesthetic Plastic Surgery. *Cosmetic (Aesthetic) Surgery National Statistics.* American Society for Aesthetic Plastic Surgery; 2018. Accessed May 27, 2021. https://www.surgery.org/sites/default/files/ASAPS-Stats2018_0.pdf
- Health Canada. *Adverse Incidents with Injectable Hyaluronic Acid Dermal Fillers;* 2010. Accessed May 27, 2021. https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/medeff/bulletin/carn-bcei_v20n3-eng.pdf
- King M, Convery C, Davies E. This month's guideline: the use of hyaluronidase in aesthetic practice (v2.4). *J Clin Aesthet Dermatol.* 2018;11(6):E61-E68. Accessed May 27, 2021. <http://www.ncbi.nlm.nih.gov/pubmed/29942426>
- Bailey SH, Fagien S, Rohrich RJ. Changing role of hyaluronidase in plastic surgery. *Plast Reconstr Surg.* 2014;133(2):127e-132e. doi:10.1097/PRS.0b013e3182a4c282
- Dunn AL, Heavner JE, Racz G, Day M. Hyaluronidase: a review of approved formulations, indications and off-label use in chronic pain management. *Expert Opin Biol Ther.* 2010;10(1):127-131. doi:10.1517/14712590903490382
- Yocum RC, Kennard D, Heiner LS. Assessment and implication of the allergic sensitivity to a single dose of recombinant human hyaluronidase injection: a double-blind, placebo-controlled clinical trial. *J Infus Nurs.* 2007;30(5):293-299. doi:10.1097/01.NAN.0000292572.70387.17
- Cavallini M, Gazzola R, Metalla M, Vaienti L. The role of hyaluronidase in the treatment of complications from hyaluronic acid dermal fillers. *Aesthetic Surg J.* 2013;33(8):1167-1174. doi:10.1177/1090820X13511970
- Centre hospitalier universitaire Sainte-Justine. Hyaluronidase < Hyalase(md), Wydase(md). Accessed May 27, 2021. <https://www.chusj.org/fr/soins-services/P/Pharmacie/Outils/Guide-Pratique/Medicaments/H/Hyaluronidase>
- Narins RS, Coleman WP, Glogau RG. Recommendations and treatment options for nodules and other filler complications. *Dermatol Surg.* 2009;35(suppl 2):1667-1671. doi:10.1111/j.1524-4725.2009.01335.x
- Menon H, Thomas M, D'silva J. Low dose of hyaluronidase to treat over correction by HA filler-a case report. *J Plast Reconstr Aesthet Surg.* 2010;63(4):e416-e417. doi:10.1016/j.bjps.2010.01.005
- Hirsch RJ, Cohen JL, Carruthers JDA. Successful management of an unusual presentation of impending necrosis following a hyaluronic acid injection embolus and a proposed algorithm for management with hyaluronidase. *Dermatol Surg.* 2007;33(3):357-360. doi:10.1111/j.1524-4725.2007.33073.x
- About CSPS | Canadian Society of Plastic Surgeons. Accessed May 27, 2021. <http://plasticsurgery.ca/about/>
- Woodward J, Khan T, Martin J. Facial filler complications. *Facial Plast Surg Clin North Am.* 2015;23(4):447-458. doi:10.1016/j.fsc.2015.07.006