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Hyaluronidase in Dermatology: Uses Beyond Hyaluronic Acid Fillers

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ABSTRACT

Hyaluronidase is mostly widely recognized for its off-label use in correction of complications of hyaluronic acid fillers. However, its utility in other aspects of dermatology is less widely acknowledged. We describe the varied uses of hyaluronidase in dermatology and the underlying evidence base for its dermatological indications. This includes its uses in enhancing drug delivery (for local anesthesia, keloid and hypertrophic scars, and for Kaposi's sarcoma), in the treatment of disorders associated with mucin deposition (myxedema, scleroderma, scleredema, and cutis verticis gyrata) and its potential uses in surgery (as a pre-operative adjuvant in dermatofibrosarcoma protuberans, for periorbital edema, and for hematomas). In select circumstances, hyaluronidase might be more efficacious than more established treatments with fewer adverse effects. We propose hyaluronidase as the latest addition to our global dermatological armamentarium and implore dermatologists to consider its use to enhance their practice.

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BACKGROUND

Hyaluronidase is an enzyme used in ophthalmic surgery and dermatology. Its use is well-established and is the standard approach in dissolving Hyaluronic acid (HA) fillers (off-label) both in overcorrection and vascular emergencies.[1] More recently, its uses in dermatology have expanded to include medical and surgical applications.[2,3]

HA, produced by fibroblasts, is a key component of the extracellular matrix (ECM).[2] Hyaluronidase hydrolyzes HA, reducing ECM viscosity, facilitating dispersal of injected substances and increasing bioavailability leading to its use in aiding the diffusion of local anesthetic injections.[2,4]

Hyaluronidase is used in dermatological conditions in which excessive or abnormal ECM is implicated, such as mucin deposition disorders (resulting in increased glycosaminoglycans) and scars, and where dissolution of physiological HA may be advantageous. We present the wide usage of hyaluronidase in dermatology beyond its cosmetic uses.

Hyaluronidase as an Enzyme

Hyaluronidase is a soluble enzyme, available endogenously in six variants (HYAL1,2,3,4, PH-20, and HYALP1)[5] and exogenously as bovine (Hylase® Dessau, Riemser Pharma GmbH, Greifswald, Germany), ovine (Vitrase®, Bausch & Lomb, Rochester, NY, USA), or human recombinant (Hylenex® Halozyme Therapeutics, San Diego, CA, USA) preparations. Its dosing is expressed in international units (IU) and the dose per preparation depends on the manufacture brand. Its main mechanism of action is degradation of HA through hydrolysis with resultant ECM alteration. Hyaluronidase is licensed by the FDA for increasing absorption and dispersion of other injected drugs, for hypodermoclysis, and as an adjunct in subcutaneous urography.[6] In the European Union, hyaluronidase is licensed for adjunctive subcutaneous drug administration, for increasing LA coverage area, for promoting contrast medium reabsorption in urology, and for promoting reabsorption of subcutaneous hematomas.[2,7-8] Across the world, its most recognized use off-label is for dissolving injected HA or filler-related vascular complications.[8]

Most side-effects are minor and transient and consist of post-injection pruritus, bruising, and swelling.[9] The risk of anaphylaxis is reportedly increased in those with wasp allergies.[8] Two case reports of shock[1] with co-administration of chemotherapy[10] and one report of anaphylaxis[11] have been observed.[8]

Allergy to bee or wasp stings might be associated with an increased risk of allergic reaction to hyaluronidase due to cross-reactivity.[1] A pre-treatment patch test or skin-prick testing might be considered for ovine and bovine preparations as these formulations contain an antigen that can be allergenic.[12] The risk of allergic reactions increases with higher doses.[8]

TABLE 1.

Uses of Hyaluronidase in Dermatology

Study Authors	Intervention	Outcomes	Side-effects
Clark LE, Mellette JR[4]	Hyaluronidase added (7.2 IU/mL) to LA in 72 patients over a one year	Hyaluronidase decreased loss of surface contour	Mild post-operative bruising
Lewis-Smith P[17]	In eight patients, 1500IU of hyaluronidase was diluted in 10mL of 1% lidocaine and injected into a patient, whilst another part of the same patient's arm was injected with 1% lidocaine monotherapy	Hyaluronidase plus anesthesia treated part experienced immediate effects of the anesthesia and area of anesthesia was increased	Minor injection pain
Ahmed S, Ahmed OA[20]	A mixture of 0.5% Marcaine with 1:200 000 epinephrine and 1% lidocaine with 1:200000 epinephrine mixed with 1500U of hyaluronidase was used	Larger areas were covered by the same amount of anesthetic	None reported
Wohlrab J, Finke R, Franke WG, et al[16]	44 patients were injected subcutaneously with either bovine testicular hyaluronidase (0.5mL or 75IU) or 0.5mL placebo (0.9% sodium chloride). All patients were injected with 0.5mL of 0.5% aqueous lidocaine hydrochloride	The addition of hyaluronidase to lidocaine increased the anesthesia's efficacy and increased area lidocaine acted on.	None reported
Aggarwal A, Ravikumar BC, Vinay KN, et al[23]	Group A treated with intralesional TAC (40mg/mL injected at a depth of 3–7mm), group B treated with intralesional TAC with hyaluronidase (1500IU/ml), group C, intralesional verapamil hydrochloride (2.5mg/mL), group D intralesional radiofrequency (at low to medium power), and group E intralesional radiofrequency with TAC (40mg/mL). Groups A, B, and C treated every three weeks for eight treatments, while groups D and E were treated every six weeks for 4 treatment sessions (n=100)	Resolution of scar was most effective in the TAC (75% clearance), TAC and hyaluronidase group (68.75%) and the intralesional radiofrequency with TAC groups (75%), all with comparable outcomes (P<0.01).	Atrophy, reported in 18.75% of the combination TAC and hyaluronidase group compared with 31.25% of patients treated with TAC alone P<0.001)
Goyal NN, Gold MH[24]	A 1mL combination of 5-fluorouracil (250mg/5mL), TAC (40mg/mL), and hyaluronidase (1500U) was injected into 20 patients suffering from keloids or hypertrophic scars	Flattening of scars and resolution of pain and pruritus were reported effects of the treatment. Patients required an average of three treatments to produce the desired results	Pain, superficial ulceration, and scabbing in three patients which resolved by itself
Eisert L, Nast A[25]	Treatment of recalcitrant keloids using a combination of intralesional cryosurgery, triamcinolone (160mg/4mL), 5-fluorouracil (150mg/3mL), and hyaluronidase (100mg/mL)	Treatment of recalcitrant keloids using a combination of intralesional cryosurgery, triamcinolone (160mg/4mL), 5-fluorouracil (150mg/3mL), and hyaluronidase (100mg/mL)	One of the two patients developed hypopigmentation
Hoesly PM, Tolaymat LM, Sluzevich JC[31]	Intralesional hyaluronidase (150U/mL) weekly for 18 weeks was used on the left foot of two patients suffering from pretibial myxedema with clobetasol cream	The left foot had partial plaque resolution after 24 weeks. Another patient had marked flattening of their plaque and a decrease in pain. The untreated feet showed no improvement	Mild injection pain
Menzinger S, Kaya G[33]	Repeated injections of hyaluronidase (120U) were given for a patient with scalp myxedema	The thickness of the scalp was reduced from 1.97mm to 1.15mm assessed with ultrasound after 138 days of treatment	None reported
Smith K, Menon P, Rolfe A[47]	Intralesional hyaluronidase was injected into five DFSPs three times/week with a dose from 300–350 turbidity-reducing units Mohs micrographic surgery was carried out 2–10 days after the last injection	The margins required for the non-hyaluronidase pre-treated patients were 1.5–2.5cm as a maximum margin. The injections treated with hyaluronidase pre-operatively required margin of 0.5–1.5cm	None reported
Menon P, Smith KJ, Crittenden J[49]	DFSP was treated with four weeks of intralesional hyaluronidase injections (three times/week for four weeks; 450 turbidity reducing units) followed by Mohs micrographic surgery four days later	Decreased margin width for excision and a smaller than expected post-operative wound. At 24 months there was no relapse	None reported
Kiyohara T, Tanimura H[44]	Injections of hyaluronidase solution (80U and 1% lidocaine) were given over a 12-week period, with a total of 18 injections given.	Reduced dermal thickening and reduced thickness in the subcutaneous tissue observed. At 2 years follow–up, this was maintained	None reported
Welborn M, Dallo C, Altmeyer M[46]	Patient CVG treated with 150U of hyaluronidase injections every six weeks for a six treatments	After three treatments, furrows were less noticeable and there was some hair regrowth	None reported
Hilton S, Schrumpf H, Buhren BA[53]	20 patients with eyelid edema were treated with 0.2-0.5mL of hyaluronidase (20IU-75IU)	This regimen resulted in rapid reduction of eyelid edema after one injection	Decrease tear trough augmentation
Han JH, Kim J, Yoon KC[54]	2 patients treated with hyaluronidase 1500IU/2ml following post-traumatic hematoma and fibrosis (three-four injections)	The hematoma and fibrosis rapidly resolved	None reported

Enhancing Local Drug Delivery

Adjunct in local anesthesia

The first report of the synergistic effects of hyaluronidase with local anesthetic was reported in 1951 with procaine.[13] Subsequently, several studies have demonstrated its surgical advantages in ophthalmologic and dermatologic surgery (Table 1).[2,4,14] HA hydrolysis with hyaluronidase increases connective tissue permeability, decreasing HA's viscosity and enabling greater dispersion of injected solutions.[15] Example mixtures reported have included doses between 3–75IU.[8] Diluent volume depends on the treated area and a range of 1–10ml has been reported.[1]

In all reported studies, addition of hyaluronidase led to faster onset of anesthetic effect and a greater anesthetized surface area due to increased dispersion of injected solutions.[4,14,16-20] Additionally, there was decreased surface contour irregularities, which could particularly assist in anatomically sensitive areas prone to distortion, such as the lips and eyelids, which require precise alignment during surgery.[4] A notable limitation of concomitant hyaluronidase use was the shorter duration of anesthesia though this did not seem to impact adversely on most procedures.

Distal nerve blocks

Using hyaluronidase and lidocaine could allow for distal nerve blocks, when regional nerve blocks have not dispersed to a large enough area.

A mixture of 0.5% Marcaine was used with 1:200,000 epinephrine and 1% lidocaine mixed with 1500IU of hyaluronidase (Hyalase®,CP pharmaceuticals), allowing for larger areas to be covered by the same amount of anesthetic, with one injection.[20] Adding hyaluronidase might reduce pain associated with injections by decreasing tissue tension.[20]

Keloid and hypertrophic scars

Keloid scars are characterized by excessive collagen and ECM production with dysregulated expression of hyaluronidase mRNA compared to normal skin.[21] HA has a fundamental part in wound-healing and ECM genesis and its disrupted expression in keloid disease is thought to be related to dysregulated hyaluronidase expression.[22]

A randomized controlled trial[23] (n=100) in keloid and hypertrophic scars involved multiple treatment arms. Addition of hyaluronidase (1500IU/ml) to intralesional injection of triamcinolone (TAC) (40mg/ml) in a recombinant mixture appeared to have a lower side-effect profile (atrophy, depigmentation, telangiectasia, injection pain, ulceration, and infection) than intralesional TAC monotherapy, although had a marginally lower resolution rate of keloid scars at 21 weeks follow-up (69% resolution with combination versus 75% with TAC monotherapy).[23] The main side-effects reported were atrophy, reported in 18.75% of the combination group compared with 31.25% of patients treated with TAC alone (P<0.001).[23]

In a separate study,[24] a 1mL combination of 5-fluorouracil (5-FU) (250mg/5mL), TAC (40mg/mL), and hyaluronidase (1500U) recombinant mixture was injected into 20 patients with keloids or hypertrophic scars. Flattening of scars and resolution of pain and pruritus were reported effects of the treatment. Patients required an average of three treatments to produce flattening of keloids and symptom resolution.[24] Triple therapy enabled the reduction in number of injections with a reduced side-effect profile compared to TAC monotherapy.[24]

Hyaluronidase has been shown to support the penetration of 5-FU and TAC.[25] Two patients had a reduction of their scar size of 80% following treatment with a combination of intralesional cryosurgery, TAC (160mg/4mL), 5-fluorouracil (5-FU) (150mg/3mL), and hyaluronidase (100mg/mL).[25]

Taken together, the addition of hyaluronidase to TAC and 5-FU appears to enhance efficacy of treatment of intralesional therapy with reduced side-effects.

Kaposi's sarcoma

Patients with Kaposi's sarcoma (KS)[26] were treated with intralesional vinblastine following prior treatment with 1% lidocaine with or without intralesional hyaluronidase every three weeks. Both vinblastine with and without intralesional hyaluronidase cleared the KS, although combination treatment with hyaluronidase proved more effective in treating tumor nodules. Relapse was reduced in patients treated with the hyaluronidase addition.[26]

Mucin Deposition Disorders

A major constituent of dermal mucin is glycosaminoglycans with HA being abundant.[27] Hyaluronidase has been used successfully in several cutaneous conditions characterized by increased mucin deposition such as pretibial myxedema, scalp myxedema, scleredema, scleroderma, and cutis verticis gyrata.[27]

Pretibial myxedema

Pretibial myxedema is a rare condition in which glycosaminoglycans accumulate in pretibial skin and is associated with Grave's disease and to a lesser degree Hashimoto's thyroiditis.[28] Normalization of thyroid levels rarely corrects this condition and treatment often proves challenging with topical and intralesional corticosteroids used in addition to systemic therapy.[28]

The rationale for hyaluronidase use in pretibial myxedema relates to hydrolysis of excessive HA and ECM reduction, with reported cases of its use in 1949 and 1950.[29-30]

More recently, intralesional hyaluronidase (150IU/mL) weekly for 18 weeks was used on the left foot of two pretibial myxedema patients.[31] One patient had substantial plaque regression, while a second patient treated with the same regimen had marked flattening of their plaque and a decrease in pain.[31]

Paver reported the successful treatment of pretibial myxedema and cutaneous myxoid cysts following treatment with hyaluronidase (1500IU) and TAC (1mg) combination (n=4).[32]

Localized myxedema (distinct from pretibial) can also occur in Grave's disease.[33] A case report[33] presented a patient with scalp myxedema treated with repeated hyaluronidase injections with a reduction in the scalp thickness confirmed by ultrasound.[33]

Scleroderma

Scleroderma is an autoimmune disorder that can result in sclerosis and cutaneous inflammation leading to impairment of function and quality of life.[34] Excessive fibrosis with increased collagen deposition is the hallmark with increased HA in the ECM.[34] The first report of hyaluronidase used in localized scleroderma (off-label) dates back to 1953.[35] Further uses in scleroderma were in microstomia and radiation-induced morphea all demonstrating a symptomatic improvement and a low side-effect profile.[36-39]

Abbas and colleagues[40] demonstrated the efficacy of hyaluronidase (four injections, 150IU) in improving sclerosis.[40] Their patient suffered from microstomia of the mouth resulting in tongue atrophy and decreased mouth-opening.[40] The patient's sclerotic bands resolved almost completely and the patient could open her mouth more widely.[40]

Scleredema

Scleredema is a rare disorder of connective tissue, characterized by mucin deposition with skin induration.[41] It has been reported to occur after streptococcal infection[42] and in diabetic patients (scleredema diabeticorum).[43-44] Dermal thickening is associated with an increase in glycosaminoglycans and can be recalcitrant and challenging to treat.[41]

Injections of hyaluronidase solution (80U,1% lidocaine) were given over 12-weeks to a diabetic scleredema patient (total of 18 injections) with no reported adverse effects.[44] Reduced dermal thickening and reduced thickness of subcutaneous tissue was observed upon T2-weighted magnetic resonance imaging. Other lesions progressively flattened and became softer and this was maintained at two years follow–up.[44] The authors did not comment upon control of diabetes during this time.[44]

Cutis verticis gyrata

Cutis verticis gyrata (CVG) is a cutaneous fibrotic scalp condition characterized clinically by scalp folds and furrows, which may be malodorous, pruritic, and cause a burning sensation.[45] A biopsy-confirmed case of CVG was successfully treated with 150IU of hyaluronidase injections every six-weeks for a total of six treatments,[46] with less noticeable furrows and some hair regrowth with no reported adverse effects. The authors postulate that hyaluronidase decreased HA in scalp areas with excessive dermal thickening, resulting in decreased skin elasticity and hence, improved cosmetic appearance.[46]

Surgical Uses

Neoadjuvant for dermatofibroscarcoma protuberans

Dermatofibrosarcoma protuberans (DFSP) is a cutaneous malignancy arising in the dermis that shows increased HA.[47] Adjunctive hyaluronidase prior to surgical excision of DFSP was used in two studies.[47-48] Intralesional hyaluronidase was injected at doses of 300–450 IU, followed by Mohs surgery 2–10 days later.[47] Greater polarizable collagen was seen further from the biopsy scar of hyaluronidase-treated tumors and these cells had decreased CD34 expression. Inflammatory reactions further from the biopsy site were greater in hyaluronidase pre-treated cells.[47] The transmembrane glycoprotein CD34 was used to confirm tumor-free margins, since CD34 is commonly used to identify residual DFSP.[49] The decreased CD34 and increased polarized collagen, not usually found in DFSPs, could support hyaluronidase's role in increasing cell differentiation in spindle cells.[47] Decreased margins following hyaluronidase treatment might be due to increased cellular differentiation, possibly accelerating apoptotic progression.[49]

Larger RCTs and long-term recurrence data are required to assess hyaluronidase's use in adjuvant DFSP treatment.[47] Hyaluronidase poses little risk, and could have significant surgical and cosmetic benefits in DFSP treatment.[47]

Periorbital edema

Chronic periorbital edema is a non-specific sign manifesting as swelling beneath the eyelid skin with possible immunological, dermatological, endocrinological, cardiological, and gastroenterological causes.[50]

Acquired lymphedema is a common post-surgical cancer treatment side-effect shown in several animal studies.[51-52] Animal studies revealed that post-operatively, mice had higher HA accumulation following lymph-node removal.[51] This lymphedema was reduced following hyaluronidase treatment in animal studies and immunohistochemical analysis demonstrated that hyaluronidase could augment lymphangiogenesis in lymphedematous limbs.[51] In a separate study, mice with post-surgical lymphedema were injected with human hyaluronidase sustained-release gel pre and post-surgery.[52] Statistically significant enzyme degradation of HA was found, highlighting that hyaluronidase activity can support dispersal of accumulated post-surgical edema.[52]

Hyaluronidase is commonly used to decrease overcorrection or periorbital edema secondary to HA filler placement, although one study reported the successful decrease in periorbital edema in patients with idiopathic edema, not necessarily treated with HA fillers.[53] The effects of hyaluronidase on the edema is therefore not necessarily linked to previous HA filler placement.[53] This can be particularly beneficial as an adjunct during and post periorbital surgery for tumor excision to decrease the common complication of periorbital edema.[53]

Hematoma

Hyaluronidase is licensed by the European Union for reabsorption of subcutaneous hematomas.[8] Swelling and hematoma post facial contusion are frequently reported post-traumatic sequelae and can leave patients with intolerable cosmetic results.[54] A case report presented a patient with a post-traumatic hematoma successfully treated with three injections of hyaluronidase 1500IU/2ml (given at weekly intervals).[54] All hematomas resolved with no adverse cosmetic effects. A different presentation with post-traumatic facial fibrosis in another patient was successfully treated with four hyaluronidase 1500IU/2ml injections, significantly improving fibrotic dimpling.[54] Hyaluronidase liquified the solidified hematoma allowing for absorption and hematoma dissolution, preventing fibrosis.[54] Hyaluronidase is thought to inhibit fibroblast proliferation, degrading HA and reducing fibrosis.[54] Hyaluronidase could plausibly be of therapeutic benefit in highly symptomatic or functionally impairing post-procedural hematomas in dermatology.

CONCLUSION

Hyaluronidase has demonstrated significant promise when used outside of its licensed use in numerous dermatological conditions spanning medical, surgical, and cosmetic disciplines. As an adjunct to anesthesia, it has demonstrated the ability to disperse the LA over a larger area in a faster timeframe. It may also reduce tissue distortion caused by LA administration, particularly of perioral and periocular skin, which is of particular utility in dermatologic surgery. Hyaluronidase may play a useful role in keloid and hypertrophic scarring, distributing established therapies more effectively while degrading the aberrant ECM. Its use in the pre-treatment of conditions such as DFSP and as combination therapy in KS may be of further interest to dermatologic surgeons. Conditions with excess mucin deposition and fibrosis such as scleroderma could allow for life-changing results in improving microstomia and fibrotic tissue.

Hyaluronidase appears to be a safe and cost-effective treatment, with few adverse effects. We would like to draw the attention of dermatologists to the increasing uses of hyaluronidase and to consider it in cases resistant to common conventional treatments.

DISCLOSURES

The authors have reported no relevant conflicts of interest.

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