Hyaluronic acid filler longevity, migration, diagnosis and implications in clinical practice

As the popularity of hyaluronic acid (HA) dermal filler treatments continues to grow, although still rare, injectors will increasingly likely see cases of dermal filler migration, alongside clinical histories of HA fillers having been placed some time ago, in excess of manufacturers' published product longevity periods.

The authors presented a case with demonstrated filler migration from the marionette area to the cheeks, confirmed with ultrasound and histopathological examinations. The presenting clinical feature was swelling to the left marionette and cheek areas, coincidental with a flare-up of the patient's systemic autoimmune disorder, psoriatic arthritis. A diagnosis of delayed-onset granulomatous inflammatory reaction following HA dermal filler was reached, and there was successful resolution of symptoms following treatment with hyaluronidase (Bell and Kelso, 2021).

This review seeks to examine HA filler longevity and migration, diagnosis and implications in clinical practice.

In its pure state, the HA molecule is present in nearly all species, including bacteria and mammals, and is considered immunologically inert (Ledon et al, 2013; De Boulle and Heydenrych, 2015). The half-life of the pure HA molecule is 24–48 hours (Choi et al, 2021). HA dermal filler products are linear, unbranched, high molecular weight glycosaminoglycan complex sugars that naturally bind water and provide volume (Bentkover, 2009; DeLorenzi, 2013). Cross-linkage of the strands, usually using 1,4-butanediol diglycidyl ether (BDDE), is used to form a viscous gel that resists degradation (Lowe et al, 2005; Choi et al, 2021).

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A HA filler will undergo a typical cycle of injection, tissue integration, function (volumisation and projection), degradation and elimination from the body (De Boulle et al, 2013). From an injector perspective, the filler products' safety, predictability and stability after implantation are essential.

Tissue integration

Immediately after injection, the cohesiveness and viscosity of the product will determine the product's behaviour within the tissue, affecting whether it will flow and distribute more widely or remain at the injection site (Gavard Molliard et al, 2018; La Gatta et al, 2019).

Tissue integration varies according to product rheology (Tran et al, 2014). The better the ability to flow without fragmenting (low viscosity, high cohesivity), the better the tissue integration and the more natural the aesthetic outcome (La Gatta et al, 2019). Tissue integration may significantly influence the clinical outcomes of treatment (Urdiales-Gálvez et al, 2020).

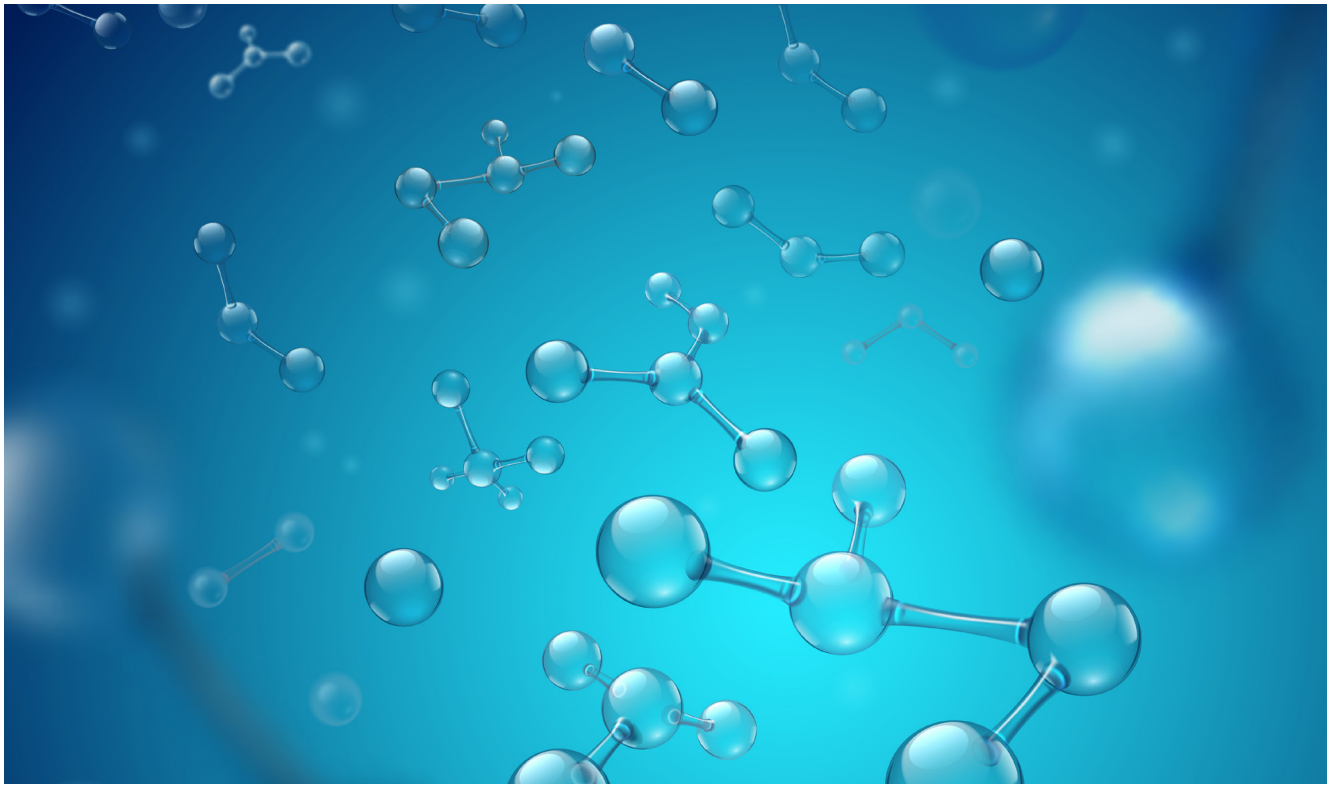
Features considered to indicate good tissue integration are even distribution of product across the tissue; homogenous appearance across the treated area; and sufficient entanglement of filler and tissue fibres (Choi et al, 2021). During one study, ultrasound analysis of Juvederm Voluma showed full integration of the product by day 30 (Urdiales-Gálvez et al, 2020).

Longevity of hyaluronic acid dermal filler

When HA dermal filler is injected, inflammation occurs (Bentkover, 2009; Alijotas-Reig et al, 2013; Kim et al, 2017). Usually, phagocytosis follows and leads to resorption of biodegradable HA fillers, and it is the rate of this phagocytosis that appears to be the most important factor in determining the filler's resistance to degradation (Bentkover, 2009; Alijotas-Reig et al, 2013; Snozzi and van Loghem, 2018).

It is widely accepted that HA filler longevity is variable. Reasons include the characteristics of the filler used; area treated; depth of filler penetration; and patient biological response (Falcone and Berg, 2009; da Costa et al, 2017).

Cross-linking, particle size and HA concentration are of key importance in increasing HA filler longevity in tissues,



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which affects cohesiveness, hardness and swelling ratio and contributes to the resistance of the product to degradation by host hyaluronidase and free radicals, as well as impacting tissue integration and water uptake (Bentkover, 2009; Park et al, 2014; Urdiales-Gálvez et al, 2020; Choi et al, 2021). The cross-linking agent used in most HA fillers is BDDE, and, following the cross-linking and purification processes, levels of unreacted BDDE are reduced to trace levels of <2ppm, which the US Food and Drug Administration (FDA) has deemed a safe level (De Boulle et al, 2013).

During phagocytosis, cleavage of glycosidic bonds leads to depolymerisation and degradation of HA; this primarily involves two mechanisms: enzymatic degradation and free radical oxidative degradation. Long HA chains are degraded to smaller units, which are then either catabolised in situ or in the lymph nodes before elimination from the body through the liver and kidneys. The trace amounts of unreacted BDDE present are hydrolysed, yielding water and CO_2 (De Boulle et al, 2013).

In 2003, Lemperle et al conducted a study in which they implanted various filler substances into a forearm and histologically assessed excised specimens. They confirmed resorption of Restylane and resolution of histological response to it by 9 months post-implantation (Lemperle et al, 2003). However, it is coming to light that HA filler may be present in tissue for considerably longer than expected.

Indeed, it is well researched and accepted that late-onset complications associated with HA fillers can occur several years after their placement (Lowe et al, 2005; Pavicic and Funt, 2013).

HA filler presence has been demonstrated up to 12 years post-placement, well beyond manufacturers' claims of 6–24 months (Soparkar et al, 2004; De Pasquale et al, 2013; Chang et al, 2017; Skippen et al, 2019; Master, 2020). It is likely that viscosity, cohesivity and hydrophilicity of the filler, and whether it is implanted in the deep or superficial tissue, will impact the duration of action, in addition to a patient-variable biological and inflammatory response (Falcone and Berg, 2009). Additionally, it has been demonstrated that treatment with onabotulinum toxin A alongside HA filler treatment can almost double the longevity of the HA filler. Carruthers and Carruthers (2003) examined the duration of HA filler in the glabellar area and found that the median time duration of aesthetic effect was 18 weeks for the group who were treated with HA filler alone and 32 weeks for the group who were treated with HA filler and onabotulinumtoxin A. There is also a suggestion that the persistence of HA fillers is due to stimulation of new type 1 collagen formation by fibroblasts in response to skin being mechanically stretched (Wang et al, 2007).

It should be noted that, although there are multiple examples of confirmed persistence of HA fillers in the tissue, the cosmetic effects or patient perception of the cosmetic effect of treatment may wear off considerably sooner

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(Young et al, 2008). This potentially leads the patient to seek retreatment, compounding such product accumulation. During one study, Narins et al (2011) examined retreatment of nasolabial folds with HA filler 18 months after the initial treatment to obtain optimal results. Although there was some reduction of the treatment effect, they found that subjects had not reverted to baseline, and significantly less product was used to retreat to optimum once again. When reviewed 18 months later, these patients required less filler again to return to optimum, and a significant proportion (23%) had maintained their result and required no treatment. Similar results were found by Ogilvie et al (2020), who treated 119 patients with Juvederm Volux to the chin. Physical improvements lasted beyond 18 months. Patients were offered retreatment between 18–24 months, and the authors found that less product was required at retreatment, between one-tenth and two-thirds of the initial treatment volume (Ogilvie et al, 2020).

Although there is an awareness of characteristics described to increase HA half-life and prevent its degradation, there is a paucity of research and evidence to explain why some patients retain HA filler for longer than others.

Filler migration

Filler migration is a rare but recognised complication of filler treatment (Davy, 2020). It is diagnosed when filler material is confirmed at locations distant from the site injected. Although the incidence is higher when permanent and semi-permanent fillers are used due to the longstanding nature of these products, migration of HA fillers has also been reported (Jordan and Stoica, 2015; Chae et al, 2016; Chiang et al, 2016; Chang et al, 2017; Master, 2020). The most common sites of filler migrations described in the literature are the forehead, glabella, nose and eyelid (Kim et al, 2017). It should be noted that, clinically, the authors' experience is that migration appears to be most visibly noticeable in the upper lip. However, the authors surmise the lack of reporting in the literature may be due to these cases not being investigated due to a reliable history of lip fillers and clinical diagnosis of migration reached based on signs and symptoms, and subsequent treatment with hyaluronidase prior to any repeat aesthetic intervention.

Causes of migration in individual cases may be difficult to ascertain, but those that have been described are poor injection technique; high volumes of filler injected; gravity; antigravity; muscular activity; lymphatic spread; intravascular injection; and overzealous massage post-procedure. Consequently, advice to avoid migration includes using smaller filler volumes under lower injection pressure and avoiding extreme muscular activity for 24 hours (Jordan and Stoica, 2015; Kim et al, 2017).

Evidence of filler migration may not be observed unless a second complication, such as foreign body granuloma, is associated with it, such as the case the authors presented; therefore, the true incidence of migration is likely to be higher than recognised (Bell and Kelso, 2021). Furthermore, in the absence of signs and symptoms, migration may be of no consequence clinically and not require treatment intervention.

Granuloma formation can follow the failure of effective phagocytosis, with aggregates of activated macrophages, giant cells and a surrounding infiltrate of T lymphocytes that secrete cytokines responsible for ongoing macrophage activation (Alijotas-Reig et al, 2013). Additionally, foreign body granulomas function to prevent migration of the product, enclosing them in a capsule of monocytes and phagocytes (Pavicic and Funt, 2013).

Kopp et al (2014) reported three cases of HA filler migration following tear trough treatments. They suggested that there is a subset of patients who do not break down HA in a normal way when it is injected into the submucosal plane, potentially due to it being able to evade the host's typical inflammatory response to a foreign body and muscular contraction aiding product migration (Kopp et al, 2014). Migration through muscular contraction is a well-known phenomenon. This is supported by Kim et al (2014), who described the migration of filler following lip augmentation as being caused by the obicularis oris muscle essentially acting as a pump, making the material coalesce and form nodules. Some feel that 'dislocation of the filler' when migration occurs through this mechanism to be a more appropriate description (Jordan and Stoica, 2015).

Additionally, overzealous massage post-procedure has been suggested to cause the filler to be redistributed into the fresh needle tracts (Funt, 2011). Jordan and Stoica (2015) presented a case of migration of HA filler from the nasolabial fold, treated 4 years previously, to the obicularis oculi muscle, where the patient recalls vigorous post-procedure

massage, to a significant level of discomfort (Jordan and Stoica, 2015).

The authors considered whether the degree of tissue integration might affect the likelihood of the filler migrating. It is known that the degree of tissue integration varies (Urdiales-Gálvez et al, 2020). It is worth asking whether a poorly integrated filler would be more likely to migrate, and, if so, whether it would migrate within a specific time period. It would also be worth asking if products that are more resilient to fragmentation during muscular action are less likely to migrate. Further research is necessary to possess a deeper understanding of migration.

Clinical diagnosis and implications for the practitioner

Diagnosis of retained and/or migrated HA filler may be made through clinical history, as well as biopsy or magnetic resonance imaging (MRI) scanning or ultrasound scanning. Last year, 2021, saw an upward trend in practitioners using ultrasound devices in clinical practice, which raises the question of whether there is a role for ultrasound in the clinical management of filler retention and migration.

Of the non-invasive techniques, MRI scanning holds the advantage of full-depth imaging and the ability to interpret results in a temporal manner of choice, with the ability to refer scans for a second opinion, if desired, without rescanning the patient. However, ultrasound scanning has the advantage of easy access, as more practitioners invest in hand-held devices, and it is particularly useful for recent injections and clinically apparent focal nodules, both of which are beyond the resolution of MRI, but it has the limitation of the depth of scan and requires real-time interpretation of results (Master, 2020). Rocha et al (2020) performed ultrasound-guided injections of HA for two patients and, 180 days later, confirmed migration of this filler posteriorly in one of the patients (Rocha et al, 2020). It should be asked whether increased clinical use of ultrasound will increase the reported diagnosis of retained and/or migrated filler.

Following diagnosis, treatment options include observation only, dissolution of the HA filler with hyaluronidase or surgery (Skippen et al, 2019). Indeed, many cases rapidly improve with hyaluronidase treatment (Iverson and Patel, 2017; Bell and Kelso, 2021). Further research into the area of retained HA filler resistance to hyaluronidase treatment is suggested by the authors.

It is unlikely that the true incidence of retained or migrated HA filler will be known, as a symptomatic complication may never occur, and patients are not routinely investigated unless they present with a secondary complication, such as a nodule or delayed reaction (Jordan and Stoica, 2015; Bell and Kelso, 2021). If retention or migration are suspected, the patient may not be willing to undergo an invasive procedure such as biopsy or an additional cost of scanning and may opt to electively treat with hyaluronidase, viewing it as a straightforward and cost-effective option.

Furthermore, due the authors' experience and the suggestion of potential accumulation of dermal filler in patients who regularly receive HA filler treatments that could resist degradation over the years, the question remains whether this is more significant in patients who are at increased risk of sensitivity to HA filler, for example, autoimmune patients.

Warning the patient and ensuring their understanding of potential complications forms part of the process of obtaining valid, informed consent (Department of Health, 2009). If the patient presents with a mass or nodule distant to the injection site months or years after placement of dermal fillers, it may not be immediately obvious to include filler migration in a differential diagnosis (Jordan and Stoica, 2015). Warning of this potential complication before treatment will increase patients' awareness in the event of a delayed cutaneous presentation of unknown aetiology. In this situation, the patient may be more likely to present to their general medical practitioner rather than their aesthetic practitioner and may not recall or regard relevant their aesthetic treatment history without being prompted. This could potentially subject the patient to unnecessary investigations and highlights the need to include any aesthetic treatment history during medical consultation (Jordan and Stoica, 2015). Such an example was presented by Kaczorowski et al (2020), who reported a case of misdiagnosis, where a patient underwent radical surgery to excise a lesion that mimicked a buccal tumour, only to have a diagnosis of migration of hyaluronic acid concomitant with a granulomatous inflammatory response following histopathological examination. The patient received HA filler to the lip and nasolabial areas 2 years previously (Kaczorowski et al, 2020). This case demonstrates the importance of recognising potential HA retention and migration as failure to do so can lead to devastating outcomes for the patient who initially sought treatment for rejuvenation reasons, as the popularity of HA fillers is ever-growing and, consequently, complications become more common.

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