A revision and summary of injectable fillers

Tin Hau Sky Wong, MBBS, MRCSEd, MScPD, MScAPS

Medaes Medical Centre, Hong Kong, Medaes Medical Clinic, Hong Kong

**Background:** Injectable fillers are common and useful tools in aesthetic medicine for reconditioning, restoring, or recontouring the quality and structure of the corresponding skin and body parts. Various choices with different properties are available, each unique and with its own advantages and disadvantages, which result in diverse indications and applications. Moreover, improper use of fillers also leads to complications and drawbacks. Awareness of the risks and management of the adverse effects are important and brief ideas of those injectables are essential.

**Objective:** This article provides a brief revision and summary of the common injectable fillers in terms of properties, functions, complications, and management.

**Methods:** Peer-reviewed articles published from 1984 to 2017 were identified from PubMed and Google Scholar, and qualitatively reviewed with respect to concurrent common injectable materials.

**Results and conclusion:** Knowledge of different injectables are important for proper application in different indications and safety of use. This article gives a brief revision.

**Keywords:** aesthetics; biofilm; dermal filler; hyaluronate sodium; injectables; intradermal injections

**Introduction**

An injectable filler by definition is a biocompatible material that is commonly injected in the cutaneous, subcutaneous, and periosteal layers for re-volumization of the respective areas to achieve the reconditioning, restoration, or recontouring of the quality and structure of the corresponding skin and body part. Injectable fillers are regarded as medical devices. They were first used in lipodystrophy to improve body appearance and avoid social stigmatization [1]. Patients were highly satisfied [2]; therefore, it is further widely adopted in the aesthetic field at fast paces. The properties of an ideal soft tissue filler are biocompatibility, nonallergenic, integrative to soft tissues, easy to administer, good plasticity and elasticity, adequate G-prime value, long-lasting, low-cost, and non-migratory. However, none of the fillers have all these properties, so a combination of fillers in a coherent approach with good knowledge of the fillers is of utmost importance to achieve an optimal effect.

**Materials and method**

Peer-reviewed articles published from 1984 to 2017 were identified from PubMed and Google Scholar, and qualitatively reviewed with respect to concurrent common injectable materials.

**Results and discussion**

**Filler choices and properties**

Numerous soft tissue fillers are available worldwide, among
| Variable                                 | HA                      | CaHA                    | PLA                      | PCL                      | CMC                      | Autologus fat injection |
|-----------------------------------------|-------------------------|-------------------------|-------------------------|--------------------------|--------------------------|-------------------------|
| Property                                | Organic, linear polysaccharide, a family of GAGs, naturally found in human skin | Inorganic, naturally found in human teeth and bone | Organic, polymer form of lactic acid | Organic, aliphatic polyester | Organic, non-cross-linked cellulose derivative | Organic, own tissue |
| Biodegradable                           | Yes                     | Yes                     | Yes                     | Yes                      | Yes                      | Yes                     |
| Manufacturing and processing             | Bacterial bioengineering | Inorganic bioceramic synthesis | Can be derived from starch | Ring opening polymerization | Etherification cellulose | Liposuction, filtering, centrifugation, and ASC enhancement |
| Metabolism                              | Hydrolysis              | Biodegraded to calcium and phosphate and then removed through phagocytosis | Biodegraded to carbon dioxide and water | Biodegraded to carbon dioxide and water | Biodegraded to carbon dioxide and water | As normal fat |
| Longevity                               | Variable, depending on the molecular size and cross-linking, from weeks to 2 years | 12–18 months, variable for the induced collagen | Up to 3 years, variable for the induced collagen | From 1 to 4 years, depending on the length of the polymer | No clinical data for injectables | 20%–90% survival rate of up to 3–6 years |
| Preferred level of injection            | From the intradermal to the subcutaneous layer and the periosteum | Mostly preferable from the subcutaneous layer to the periosteum | Mostly preferable from the subcutaneous layer to the periosteum | Mostly preferable from the subcutaneous layer to the periosteum | From the subcutaneous layer to the periosteum, together with the primary filler | Subcutaneous and deep fasciae |
| Hypersensitivity and allergic reaction  | Allergic reaction rate of approximately 1%–3%. Occurs as multiple erythema, cystic nodules, granulomatous reaction, etc. [3,4] | No epidemiological data | No epidemiological data | No epidemiological data | Granuloma reaction reported [9], but scientific research showed no effect on the systemic functions of the immune system [10] | No epidemiological data, but anaphylaxis was reported [11] |

HA, hyaluronic acid; CaHA, calcium hydroxylapatite; PLA, poly lactic acid; PCL, polycaprolactone; CMC, carboxymethylcellulose; GAG, glycosaminoglycan; ASC, adipose-derived stem cell; PLLA, poly-L-lactic acid.
which the most commonly used are as follows (Table 1) [3-12].

**Hyaluronic acid**

Hyaluronic acid (HA) is a temporary filler under the family of glycosaminoglycans (GAGs), which is found abundantly in the skin as an extracellular matrix of various molecular sizes. It is negatively charged and binds to water molecules. It provides numerous biological functions such as structural support, nutrient diffusion, cell migration, and proliferation. It is metabolized by hydrolysis facilitated by hyaluronidase. Pharmaceutical manufacturing of HA uses biochemical engineering by the fermentation of bacteria such as *Bacillus subtilis* and *Streptococcus equi* [13]. Small molecular-size and non-cross-linked HA provide hydration and rejuvenation functions, while large molecular-size and cross-linked HA provide more structural support and last longer to exert re-volumization and recontouring functions.

**Calcium hydroxylapatite**

Calcium hydroxylapatite (CaHA) is a non-pyrogenic biocompatible inorganic bioceramic synthesized through chemical deposition, biomimetic deposition, the sol-gel route (wet-chemical precipitation), or electrodeposition [14]. It is usually available in a semi-solid state in the form of 25- to 45-µm-diameter microspheres in a suspension of a gel carrier with carboxymethylcellulose (CMC). It is biodegradable in the same metabolic pathway as that of the human bone and is removed by phagocytosis. Apart from being a filler and biostimulator, CaHA provides support and a scaffold lattice that guides fibroblast ingrowth for neocollagenesis and promotes surrounding soft tissue formation. It can provide different functional properties, G-primes, and viscosities by varying the degree of hyperdilution. Therefore, it can be used in different areas and indications ranging from filler effects (i.e., tissue augmentation and re-volumization) to biostimulator effects (i.e., collagen induction and rejuvenation) [15,16]. The longevity of CaHA is generally 12–18 months [17], but hyperdilution may shorten its shelf life and may require a greater number of injections. It is approved by the FDA for moderate to severe wrinkles and folds (nasolabial and other facial wrinkles). The FDA has approved CaHA for the treatment of facial folds and wrinkles and for soft tissue augmentation and facial rejuvenation. CaHA provides support and a scaffold lattice that guides fibroblast ingrowth for neocollagenesis and promotes surrounding soft tissue formation. It can provide different functional properties, G-primes, and viscosities by varying the degree of hyperdilution. Therefore, it can be used in different areas and indications ranging from filler effects (i.e., tissue augmentation and re-volumization) to biostimulator effects (i.e., collagen induction and rejuvenation) [15,16].

**Poly lactic acid**

Poly lactic acid (PLA) is a polymer of lactic acid from the alpha-hydroxy acid family, which can be derived from starch and is commercially prepared in L-enantiomer (poly-L-lactic acid [PLLA]) or racemic form. It is biocompatible, biodegradable, and fully metabolized to carbon dioxide and water. The PLA microparticles (40–63 µm in size in some pharmaceutical preparations) initiate neocollagenesis as a result of the activation of fibroblasts [18]. It is reconstituted in sterile water with lignocaine and then injected in the skin and soft tissue. Reconstitution at least 24 hours (optimal 72 hours) before use is recommended [19], although the protocol differs in different preparations. Post-injection massage is controversial, but studies showed that the incidence of nodule formation as a complication was reduced when the rule of 5 (post-injection for 5 days, 5 times a day, 5 minutes each time) was followed [20]. The shelf life of PLA ranges from 25 months [21] to 3 years [22]. PLA has been approved by the FDA for restoration and correction of the signs of facial fat loss, nasolabial folds, and other facial wrinkles.

**Polycaprolactone**

Polycaprolactone (PCL) is an organic aliphatic polyester belonging to the poly-α-hydroxy acid group. It is hydrolytically degradable into carbon dioxide and water [23] and is bioresorbable. Investigations have also shown that it is non-cytotoxic, non-pyrogenic, and biocompatible. Its biostimulator effect induces collagen formation, which results in a filling effect. Similar to CaHA, it also provides a scaffold for tissue infiltration, which facilitates soft tissue building. It is prepared in a suspension of CMC for adequate texture and immediate effect after injection. PCLs are delivered as microspheres of 25- to 50-µm in size in some pharmaceutical preparations. The longevity of PCL depends on the extensiveness of the polymer chain, from 1 to 4 years. Before injection, PCL can be mixed with lignocaine for the comfort of the patient during injection. Its parental PCL medical devices (e.g., suture materials) are FDA approved, but not the current injectable PCL itself, although some studies, including randomized controlled trials, demonstrated its efficacy and safety [24].

**Carboxymethylcellulose**

CMC is a non-cross-linked cellulose derivative that forms a bioabsorbable gel with water, which provides an immediate filler effect and structural support to tissues. It is not usually administered alone but as a suspension and texture modifier mixed with other filler materials, commonly CaHA and PCL. It allows these primary materials enough time to exert their biostimulatory effect to produce collagen, which fills up the site of interest before the CMC degrades and is resorbed. The rate of resorption of CMC depends on the molecular size [25], but no clinical data have been reported in the literature.
Autologous fat

Autologous fat has been used as a filler since a century ago. Despite being perfectly compatible, adipocyte survival rate, which directly affects the outcome and longevity, is the chief concern. The uptake rate can be anywhere from 20% to 90% [26]. Therefore, patient selection, harvesting technique, processing, and transfer injection are particularly important. For underweight patients, the outcome may include a poor quality and low amount of fat; therefore, a nourishing diet may be required before the procedure is performed. During harvesting, low heat and trauma at favorable quality sites are required to ensure that good-quality adipocytes are collected without damaging them. Adipose-derived stem cells have been shown to have improved uptake and can be prepared using special techniques by isolating the stromal vascular fraction, which provides better neovascularization for fat survival [27].

Filler safety and complications

Fillers are regarded as medical devices in Hong Kong. No compulsory regulation or legislation has been established for mandating product registration. However, choosing a registered product guarantees better quality and safety profiles. Since the structure of the skin, body compartments, and vital structures, including the nerves and vessels, are complicated, only well-trained aesthetic doctors are allowed to perform the procedure. Complications range from mild (e.g., bruising and bleeding) to severe (e.g., vascular insultation, nerve injection, and infection) [28]. Even a small amount of filler, as little as 0.085 ml, can induce disastrous arterial embolism consequence [29]. Moreover, incorrect reconstitution, uneven product distribution in the suspension, and improper injection techniques all contribute to undesirable outcomes, nodule formation, and other complications. Therefore, comprehensive training in both theory and skills is important. Among all the fillers, only HA has a counteracting dissolution agent, hyaluronidase. The others are non-dissolvable and must wait for natural biodegradation or surgical correction once the unpleasant filling effect is established. Early intralesional administration of normal saline or corticosteroids can be useful [12], but injection site unevenness or even atrophy may result.

Biofilm formation is one of the most important (though rare) but underdiagnosed conditions associated with the use of filler injections. It is sometimes misdiagnosed as hypersensitive reactions or missed because of subtle presentation and negative culture results [30]. It has an extensive extracellular matrix that is devoid of the immune attack of the body and antibiotic functions. It forms a self-sustaining “ecosystem” that can last for an extremely long period. It can mimic hypersensitive reactions, which occur in 0.02% of the total cases [31]. Management of such conditions includes a high index of suspicion and administration of hyaluronidase for hydrolysis of HA [32] and long-term high-dose broad-spectrum antibiotics. Surgical removal or excision away from the filler may be required if the above-mentioned strategies fail. As prevention is always better than cure, meticulous aseptic techniques are required. Complications occur more commonly with longer use of fillers and will resolve after removal of the filler.

Conclusion

Fillers are useful devices for reconditioning, restoring, and recontouring of the skin and body parts. They not only improve one’s appearance but also prevent psychological problems by improving self-confidence or avoiding stigmatization. A wide range of filler selection is available in the market, with different properties, and adequate indication and combination of fillers provide the best outcome. Training for knowledge and techniques is required to prevent both trivial and disastrous morbidity and perhaps mortality.

Conflicts of interest

The author has nothing to disclose.

References

1. Gooderham M, Solish N. Use of hyaluronic acid for soft tissue augmentation of HIV-associated facial lipodystrophy. Dermatol Surg 2005;31:104-8.
2. Sturm LP, Cooter RD, Mutimer KL, Graham JC, Maddern GJ. A systematic review of permanent and semipermanent dermal fillers for HIV-associated facial lipoatrophy. AIDS Patient Care STDS 2009;23:699-714.
3. Skrzypek E, Górnicka B, Skrzypek DM, Krzysztof MR. Granuloma as a complication of polycaprolactone-based dermal filler injection: ultrasound and histopathology studies. J Cosmet Laser Ther 2019;21:65-8.
4. McLoughlin CE, Smith MJ, Auttachoaot W, Bowlin GL, White KL Jr. Evaluation of innate, humoral and cell-mediated immunity in mice following in vivo implantation of electrospun polycaprolactone. Biomed Mater 2012;7:035015.
5. Dumond P, Franck P, Morisset M, Sainte Laudy J, Kanny G,
Moneret-Vautrin DA. Pre-lethal anaphylaxis to carboxymethylcellulose confirmed by identification of specific IgE—review of the literature. Eur Ann Allergy Clin Immunol 2009;41:171-6.
6. Goisis M. Injections in aesthetic medicine: atlas of full-face and full-body treatment. Milan: Springer; 2014.
7. Khan TT, Colon-Acevedo B, Metru P, DeLorenzi C, Woodward JA. An anatomical analysis of the supratrochlear artery: considerations in facial filler injections and preventing vision loss. Aesthet Surg J 2017;37:203-8.
8. Narins RS. Minimizing adverse events associated with poly-L-lactic acid injection. Dermatol Surg 2008;34 Suppl 1:S100-4.
9. Dayan SH, Arkins JP, Brindise R. Soft tissue fillers and biofilms. Facial Plast Surg 2011;27:23-8.
10. Friedman PM, Mafong EA, Kauvar AN, Geronomes RG. Safety data of injectable nonanimal stabilized hyaluronic acid gel for soft tissue augmentation. Dermatol Surg 2002;28:491-4.
11. Pecharki D, Petersen FC, Aa Scheie A. Role of hyaluronidase in streptococcus intermedius biofilm. Microbiology 2008;154:932-8.
12. Requena L, Requena C, Christensen L, Zimmermann US, Kutzner H, Cerroni L. Adverse reactions to injectable soft tissue fillers. J Am Acad Dermatol 2011;64:1-34; quiz 35-6.
13. Chong BF, Blank LM, Mclaughlin R, Nielsen LK. Microbial hyaluronic acid production. Appl Microbiol Biotechnol 2005;66:341-51.
14. Ferraz MP, Monteiro FJ, Manuel CM. Hydroxyapatite nanoparticles: a review of preparation methodologies. J Appl Biomater Biomech 2004;2:74-80.
15. Hevia O. A retrospective review of calcium hydroxyapatite for correction of volume loss in the infraorbital region. Dermatol Surg 2009;35:1487-94.
16. de Albuquerque GC. Fillers and collagen stimulator for body rejuvenation and cellulitis. In: Issa M, Tamura B, editors. Botulinum toxins, fillers and related substances. Clinical approaches and procedures in cosmetic dermatology. Cham: Springer; 2017. p. 1-7.
17. Tzikas TL. Evaluation of the radiance FN soft tissue filler for facial soft tissue augmentation. Arch Facial Plast Surg 2004;6:234-9.
18. Simamora P, Chern W. Poly-L-lactic acid: an overview. J Drugs Dermatol 2006;5:436-40.
19. Narins RS. Minimizing adverse events associated with poly-L-lactic acid injection. Dermatol Surg 2008;34 Suppl 1:S100-4.
20. Palm MD, Woodhall KE, Butterwick KJ, Goldman MP. Cosmetic use of poly-l-lactic acid: a retrospective study of 130 patients. Dermatol Surg 2010;36:161-70.
21. Narins RS, Baumann L, Brandt FS, Fagien S, Glazer S, Lowe NJ, et al. A randomized study of the efficacy and safety of injectable poly-L-lactic acid versus human-based collagen implant in the treatment of nasolabial fold wrinkles. J Am Acad Dermatol 2010;62:448-62.
22. Salles AG, Lotierzo PH, Gimenez R, Camargo CP, Ferreira MC. Evaluation of the poly-L-lactic acid implant for treatment of the nasolabial fold: 3-year follow-up evaluation. Aesthetic Plast Surg 2008;32:753-6.
23. Heimowska A, Morawska M, Bocho-Janiszewska A. Biodegradation of poly(ε-caprolactone) in natural water environments. Pol J Chem Technol 2017;19:120-6.
24. Moers-Carpi MM, Sherwood S. Polycaprolactone for the correction of nasolabial folds: a 24-month, prospective, randomized, controlled clinical trial. Dermatol Surg 2013;39(3 Pt 1):457-63.
25. Siritientong T, Aramwit P. Characteristics of carboxymethyl cellulose/sericin hydrogels and the influence of molecular weight of carboxymethyl cellulose. Macromol Res 2015;23:861-6.
26. Toyserkani NM, Quaade ML, Sørensen JA. Cell-assisted lipotransfer: a systematic review of its efficacy. Aesthetic Plast Surg 2016;40:309-18.
27. Yoshimura K, Sato K, Aoi N, Kurita M, Hirohi T, Harii K. Cell-assisted lipotransfer for cosmetic breast augmentation: supportive use of adipose-derived stem/stromal cells. Aesthetic Plast Surg 2008;32:48-55.
28. Matarasso SL, Herwick R. Hypersensitivity reaction to non-animal stabilized hyaluronic acid. J Am Acad Dermatol 2006;55:128-31.
29. Lupton JR, Alster TS. Cutaneous hypersensitivity reaction to injectable hyaluronic acid gel. Dermatol Surg 2000;26:135-7.
30. Froeb HP, Rothstein SS, Gumaer KI, Sherer AD, Slighter RG. Histologic observation of soft tissue responses to implanted, multifaceted particles and discs of hydroxylapatite. J Oral Maxillofac Surg 1984;42:143-9.
31. Misiek DJ, Kent JN, Carr RF. Soft tissue responses to hydroxyapatite particles of different shapes. J Oral Maxillofac Surg 1984;42:150-60.
32. Mastrokalos DS, Paessler HH. Allergic reaction to biodegradable interference poly-L-lactic acid screws after anterior cruciate ligament reconstruction with bone-patellar tendon-bone graft. Arthroscopy 2008;24:732-3.