A revision and summary of injectable fillers

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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

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Table 1. Comparisons of the different aspects of the commonly used fillers

Variable	HA	CaHA	PLA	PCL	CMC	Autologous 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 A study showed almost no foreign body reaction, maybe some mild inflammation but resolving quickly [5–7]	No epidemiological data No hypersensitivity reported for injected PLA, but allergic reaction cases were reported for orthopedic PLLA screw [8] and granuloma formation [12]	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]	Autologous transfer principally does not have allergic reaction

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- μ m-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 folds), facial augmentation, and hand rejuvenation.

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, biodegrad-

able, and fully metabolized to carbon dioxide and water. The PLA microparticles (40–63 μ m 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- μ m 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 func-

tions. 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 prevents 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.

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