Fillers in Dermatology: Complications and Management

Weeranut Phothong, M.D.
Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

ABSTRACT

Filler augmentations are frequently performed in current dermatological practices. They serve as volume restoration and contour modification, and soft tissue fillers often give appreciable results with a wide range of product uses. However, the non-liquid products could be regarded as one type of temporary implantation and several adverse reactions have constantly been reported. Possible complications range from mild and spontaneously resolving events to vascular and ocular complications resulting in irreversible morbidities. This review article has emphasized on the comprehension of both immediate and delayed complications, as well as the practical knowledge of prevention and management.

Keywords: Soft tissue filler; dermatology; complication

Siriraj Med J 2016;68:313-318
E-journal: https://www.tci-thaijo.org/index.php/sirirajmedj

INTRODUCTION

As personal image plays an important role in social perception nowadays, cosmetic dermatology has gained a rapid popularity. Soft tissue filler injection can not only modify facial structures to be more appreciable, but can also restore the juvenile appearance of the person. In 2015, over 2.4 million soft tissue filler procedures were performed in United States which was a 6.3% increase from 2014. Among those, 80% were Hyarulonic acid (HA)-based injections.[1] Although regarded as a minimally invasive procedure, the augmentation with fillers put both injectors and patients at a considerable risk due to its non-liquid status. The occurrence of central retinal artery occlusion with ipsilateral cerebral infarction was reported following HA filler augmentation at glabella and cheeks.[2] In addition, filler materials were designated to comprise of several physical properties in order to "exist and fill" over a period of time. These temporary implantations were reported to cause various reactions.[3-6] It is crucial to acquire the knowledge of the possible complications, the rapid recognition and the appropriate management before performing filler injection.

Filler classification and indication

Soft tissue augmentation ranges from autologous fat transplantation to synthetic fillers. The latter have been distributed in a rapidly growing market. However, not all available fillers are approved by US Food and Drug Administration (FDA) and each approval is directed to a specific indication. Among FDA approved soft tissue fillers, a simple categorization could be made as temporary fillers and permanent fillers.[7] Suspended polymethylmethacrylate (PMMA) beads are the only permanent dermal filler approved by FDA. Overtime, the concerns has been raised toward

Correspondence to: Weeranut Phothong
E-mail: weeranut@gmail.com
Received 16 June 2016
Revised 18 August 2016
Accepted 25 August 2016

late-onset adverse events including granulomatous formation. As a result, PMMA has gained less popularity among injectables. Temporary fillers are more diversified. The earliest bovine and human collagen fillers have already been withdrawn from the market at the end of 2010 by the producing companies. Poly-L-lactic acid (PLLA) fillers are well-known for FDA-approval indication of lipodystrophy in patients with human immunodeficiency virus (HIV). Due to their physical properties and longevity, PLLA was also approved for nasolabial fold augmentation in non-HIV patients. Likewise, calcium hydroxylapatite (CaHA) fillers were approved with similar indications for mid and lower face. Although approved almost concurrently with PMMA and PLLA, hyarulonic acid (HA) fillers are by far the most preferred products for the injectors and patients. HA fillers are constantly developed and new arrival products are regularly released from various companies. Regarding the difference of HA concentration, gel hardness, percentage and type of cross-link particles, as well as the type of the gel, HA augmentation uses have been extended from FDA-approved indications (augmentation of nasolabial folds, cheeks and lips) to off-label uses by worldwide injectors.

Complication of filler injection

Unlike botulinum toxin which is a powder-based product to be prepared as liquid solution, dermal fillers are formulated in non-liquid status, gel-like particles. Minor and major adverse events have been reported globally together with several attempts to forecast, minimize and alleviate complications through a number of publications.

Early complication

The immediate complications are those which occur within 14 days after the procedure. Unfortunately, injections are performed in outpatient settings and most of the clinical signs of immediate complications are subtle during the early hours. The up-to-date comprehensive knowledge, especially of vascular-related complication, is encouraged for all injectors.

Vascular-related complication

Mild and transient vascular related complications can be regularly found in injection practices as the face is rich in vascular supply. A number of dietary supplements were known to exert an anticoagulant effect including gingko biloba, vitamin E and fish oil.[8] Patients who are currently on these supplements are at a greater risk of bruising.

The more severe vascular-related complications involve the major vascular structures of the face. Vascular supplies of the face are from both internal and external carotid systems. Filler material can cause either extravascular occlusion (compression) or intravascular occlusion. In vivo animal model study, the authors replicated intravascular and extravascular occlusion by HA gel and found the more extensive non-perfusion area in intravascular model.[9] In a clinical setting, the earliest sign could be carefully observed as a result of diminished blood flow to the target organ. If the affected vascular portions are responsible for surface supply, an injector should be able to detect the sudden blanching, followed by greenish or reticulated purplish hue of the skin. Pain should also be the useful surrogate indicator. However; with the increased use of anaesthesia-admixed fillers and nerve block procedures, pain recognition nowadays is not totally reliable. Without treatment, patients will develop skin necrosis characterized by crust, scab or pustules in the following days.

One of the characteristic features of facial vasculatures is the abundance of anastomosis of external and internal carotid systems and this is one of the risks to the most dreadful vascular-related complication. Vascular compromise involving ophthalmic artery, either from direct occlusion or embolic events through anastomosis, were reported to result in permanent morbidities of vision and brain function. Two large reported series of ophthalmic complications following filler injections correspondingly indicated that the autologous fat injection was found as the most frequent material injected, followed by HA. Glabella area was the most frequent area of injection.[10,11] Other treated areas included nasolabial fold, nasal dorsum, temple, forehead and scalp.

Most of the cases noted the significant visual impairment as an initial symptom. Other findings included ocular pain, opthalmoplegia and ptosis. Long-term sequelae demonstrated the persistence of decreased visual acuity in more than 70% of the follow-up cases.[11] A case of ptosis with third nerve palsy without significant visual acuity impairment was reported after multiple sites of CaHA injection.[12]

Non-vascular related complication

Most of the non-vascular related complications which occur within the first two weeks are a result of poor injection technique. When placed too superficially, some products can cause unwanted nodular textures or bluish hue of skin due to Tyndall effect. Poor technique of skin preparation placed patients at risk of infections. For immediate non-infectious events, a few studies described acute hypersensitivity reaction to fillers. Leonhardt et al., reported the case of angioedema of upper lip where HA gel was injected.[13] Cohen et al., described the anaphylactic reaction occurring ten minutes after vocal cord augmentation by CaHA.[14] Both cases were immediately treated and resolved without significant morbidity. This emphasized the importance of necessary emergency medications regardless of the scale and location of the practices.

Delayed complication

Delayed complications can arise later than two weeks, following soft tissue filler injection. In some cases, the manifestation could be detected several years after the procedure. History taking is important in such cases.

Infectious complication

Due to the specific and distinctive treatment, the first step when one encounters a delayed complication of soft tissue filler is to differentiate the possible infectious cause. The findings include pain, swelling, redness, nodules and indurated deep masses at the injection sites. Slow-growing organisms such as mycobacterium was reported as a pathogen in a patient who underwent PLLA augmentation.[15] *Mycobacterium mucogenicum* was successfully identified by tissue biopsy and polymerase chain reaction. However, the major concern of infectious complications of soft tissue fillers has recently shifted toward the emergence of biofilm-forming organisms. Biofilms were previously described as important pathogens in orthodontic and orthopedic prosthesis for more than a decade.[16,17] With the property of special polymeric matrix, organisms that produce biofilms can irreversibly adhere to the surface of prosthesis and protect themselves from phagocytosis. Moreover, this exclusive environment facilitated biofilm-forming pathogens to be less detectable by investigation and more resistant to antibiotics when compared with planktonic pathogens.[18] Christensen et al., reported the investigation in a series of patients with PLLA adverse reactions and a control group (those without adverse reactions). Interestingly, none in a control group demonstrated detectable bacterial pathogens from either cytology or histology specimens. In 98 percent of patients with adverse reactions, causative bacteria were identified by one of the following methods; gram stain, culture, 16S gene sequencing, or fluorescencein situ hybridization (FISH). The most common pathogens are Propionibacterium spp., Staphylococcus spp. and streptococcus spp.[19] Another study emphasized the role of FISH in detecting biofilm-forming pathogens when the routine bacterial culture yielded negative result[20]. These findings emphasized how important biofilms are in delayed adverse reaction from fillers, and how difficult it is to detect them. Other sources of infections include the adjacent and occult infections such as periodontal infection.[21]

Non-infectious complication

Permanent fillers are at the higher risk of non-infectious delayed complication due to their physical properties and longevity. Manifestations included migration, non-inflammatory nodules, low-grade inflammation and abscess formation.[22] Large volume and non-medical grade products in the hands of inexperienced injectors resulted in chronic complications resistant to treatments.[5] Non-permanent filler augmentation can also cause various delayed adverse reactions.[23] Unwanted HA reactions include sterile abscess, foreign-body granuloma and fibroma.[24] A case of histological-

proven encapsulated formation of HA was reported following the injection of non-animal stabilized hyarulonic acid (NASHA)[4]. Patients with PLLA reactions presented with either inflammatory or cystic nodules which often required excision treatment. A report of delayed neuropathic pain following temple augmentation with PLLA was reported.[25] Although designated to be deep and large volume restoration, CaHA was sometimes used for lip augmentation and reported to cause whitish or yellowish nodules. The definitive treatment is surgical excision since its calcium composition and fibrosis formation were resistant to medical therapy.[24] Histological investigation is useful for filler identification when actual information of substance could not be obtained from the history. Some of fillers displayed specific microscopic findings among foreign body granulomatous reactions that guided a pathologist to the diagnosis.[26] The pathogenesis of these reactions has not yet fully elucidated. Delayed type hypersensitivity, activation of adaptive immune system by some medications and the role of plasmacytoid dendritic cells have been described in foreign body reactions.[27,3]

Management

Pre-procedural management

One of the most crucial steps in any medical procedure is the patient selection. Since soft tissue filler augmentation is neither an urgent nor a mandatory procedure, identifying patients who are at high risk to develop complications and providing them with appropriate counselling is the essential element for skilful injectors. A patient who has undergone previous surgery are at the greater risk of vascular complications, compared with the virgin case, because of the possible distorted structures and neovascularization. To minimize the risk of infection, make-up should be totally removed. Area of procedure should be clear from inflammatory or infectious skin lesions and then cleaned with 4% chlorhexidine gluconate.[28] The location and plane of filler placement should be carefully planned based on the physical properties of fillers, anatomy of vital structures and anticipated volume/contour effect. Important details include underlying disease, medication and supplement usage, previous herpes infection and drug allergy which should be obtained prior to the procedure.

Intra-procedural management

Sterile technique is exclusively encouraged throughout the procedure. Other than wearing sterile gloves, the good skill of injection can minimize the risk of infection as well. The selected technique and sharp/blunt cannula should facilitate the least number of punctures. The appropriate plane of filler placement should prevent Tyndall appearance. The precise and less pressured injection with non-forceful massage would lessen the risk of filler migration.[29] Anaesthesia, both premixed with filler products and administration by injector, can masquerade the initial manifestations of the possible vascular accidents. Good injectors have to be able to concentrate on the procedure and be alert for signs and symptoms of vascular complications at the same time.

Post-procedural management

With the fact that soft tissue filler augmentation is an out-patient implantation operation, post-operative observation is necessary. Re-examination of the patient again 30-45 minutes after the injection allows injectors to detect immediate complications especially pain, change of skin colour and ophthalmic symptoms. If the vascular-related complication is suspected, the injector should promptly determine the extension of involvement of vasculatures and prepare for the use of hyarulonidase in the case of HA injection. Although type I hypersensitivity is rare, skin test is recommended before hyarulonidase administration due to its animal origin. Three units of hyarulonidase should be intradermally injected with 5-10 minutes observation of wheal and flare.[30] There are several preparations, but one of the most prevalent uses is to dilute 150 units of hyarulonidase in 1 ml of saline.[31] The injection should be performed adequately at the territory of suspected vascular compromise. Other beneficial steps include warm compression, nitroglycerine paste, oral administration of aspirin and re-evaluation every 5-10 minutes until the signs of ischemia disappears. In the case of suspected ocular compli-

cation, ocular massage and emergency contact to ophthalmologist at referral centre is crucial since retinal ischemia could be irreversible after a few hours.[32] For patients who present with delayed onset nodules, it is necessary to identify possible infectious cause prior to immunosuppressive drug administration. With the growing importance of biofilms, special laboratory investigation other than conventional gram stain and culture is needed to direct to appropriate and specific treatment.[28]

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to Associate Professor Rungsima Wanitphakdeedecha for the immense knowledge and valuable discussion.

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