Eventos adversos do ácido hialurônico injetável

Adverse events in injectable hyaluronic acid

RESUMO

Nos últimos anos, o uso de preenchedores para tratamento de rítides e aumento do volume facial cresceu consideravelmente. Há atualmente diferentes tipos de preenchedores, divididos em temporários, semipermanentes (permanência de no mínimo 18 meses no tecido) e permanentes, também classificados conforme a composição do material (colágeno, ácido hialurônico, ácido polilático, polimetilmetacrilato, hidroxiapatita); o ácido hialurônico pode ser sintético ou de origem animal. Dos diversos produtos, o ácido hialurônico (preenchedor reabsorvível, temporário) tem sido um dos mais utilizados. Ainda não há disponível no mercado substância ideal, pura e livre de efeitos colaterais.

O objetivo do trabalho é auxiliar o reconhecimento dos efeitos colaterais com uso de preenchedor à base de ácido hialurônico. Isso permite diagnóstico e tratamento precoces, diminuindo a morbidade e sequelas dos pacientes.

Palavras-chave: ácido hialurônico; erupção por droga; administração cutânea.

ABSTRACT

The use of fillers for treatment of rhytids and facial volume enlargement has grown considerably in recent years. The various filler types used currently can be classified into temporary, semi-permanent (permanence of at least 18 months in the tissue) and permanent. Fillers can also be classified according to their composition (collagen, hyaluronic acid, polylactic acid, polymethylmethacrylate, hydroxyapatite). Moreover, the hyaluronic acid may be of synthetic or animal origin. Hyaluronic acid (temporary resorbable filler) has been one of the most frequently used substances. There is no ideal, pure and commercially available substance that is free of side effects. This study evaluates the side effects of using hyaluronic acid-based fillers in order to enable early diagnosis and treatment, and reduce morbidity and sequelae among patients.

Keywords: *hyaluronic acid; drug eruptions; administration, cutaneous.*

Continuing Medical Education

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INTRODUÇÃO

Cutaneous fillers are used to treat rhytids, correct atrophic scars and minor skin defects, and to improve facial contours. Ideally, the substances contained in those products should produce good cosmetic results, belong lasting, stable and safe, and cause no (or minimal) complications. Of the current commercially marketed fillers, hyaluronic acid (HA) best meets these criteria, however it presents some side effects that should be studied and identified by the physician carrying out the procedure.

HA is present in the extracellular matrix of connective tissues, synovial fluid, aqueous and vitreous humors. In the skin, it forms the elastoviscous fluid matrix that envelops collagen and

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elastic fibers and intercellular structures. Its concentration in the skin decreases with age, resulting in decreased local hydration and a general loss of volume, leading to rhytids formation.

Injectable HA is composed of polysaccharides and glycosaminoglycans, and is non-permanent, with an average duration of six months.[1,2] The products available on the market – which may or may not be combined with an anesthetic (lidocaine) in the vial –can also be classified as either biphasic or monophasic.[2]

Injectable HA's molecules have a simple structure, high molecular weight, and high attraction to water (hydrophilic). Stabilization of HA through the crosslinking technique aims to increase its duration. Molecules that crosslink to HA produce more stable macromolecules (which are water insoluble and present less reabsorption) but are equally biocompatible (their affinity to water remains unchanged and they form a three-dimensional network in the dermis). [3] Given that the higher the crosslinking level, the lower the substance's hydrophilic property (and thus its effectiveness), the optimum level must be calculated.[4] The most commonly used substances in this technique are divinyl sulfone and butanediol-diglycidyl-ether; the addition of those products to HA is thought to be correlated to allergic reactions in some patients.[5]

After being injected into the skin, HA is metabolized into carbon dioxide and water and then eliminated through the liver.[6]

The sources of industrialized HA can be divided into two categories. Animal-derived HA originates from the dermis of cocks' combs, and is purified and chemically linked with divinyl sulfone.[3] Synthetic HA is formulated from the bacterial fermentation of *Streptococcus spp*[1,6] (HA chains are chemically stabilized by cross-linking epoxides). [3]

Synthetic HA is marketed as a thick, non-particulate, colorless gel in syringes with needles and can be stored at room temperature. It does not require skin testing prior to use.

HA is approved for rhytids and furrow corrections, however it is used for various purposes. It is routinely used to correct nasolabial folds, increase the volume of the lips, dark circles' infraocular grooves, and to rejuvenate the periauricular region.[6] Its use in the glabella is rarely recommended due to the higher incidence of necrosis in that region, which is linked to local compression or intra-arterial injection into the supratrochlear artery and its branches.[7] The area with the second greatest risk of necrosis is the nasal wing (occlusion of the angular artery and limited collateral circulation to irrigate the ischemic region).[8] Other indications, such as acne scar correction, facial volumizing to correct the loss of fat pads due to aging or post-traumatic loss of subcutaneous tissue, and increase in the volume of the back of the hand for rejuvenation, are also mentioned in the literature.

The dermatologist should evaluate each patient individually prior to the procedure, conduct a thorough interview (assessing allergy and medication history), assess risks and benefits, and discuss the patient's expectations. If possible, always request patients to sign a consent term and take pictures before and after the HA application. Absolute contraindications for cutaneous filling are pregnancy, breastfeeding, autoimmune diseases, and immunodeficiency.5 When possible, discontinue anticoagulant and non-steroidal anti-inflammatory medications 7-10 days before the procedure to avoid increased bleeding.[5]

This article reviews the side effects of HA-based cutaneous fillers published on PubMed from January 2001 to July 2011. There are few reports in the literature, probably due to the fact that HA adverse effects are not usually published and have a frequency of less than 2% in the literature.

SIDE EFFECTS

Complications arising from the use of HA-based fillers may result from inexperience, improper technique, or be inherent to the product itself. Side effects can be classified as either early or late.

EARLY SIDE EFFECTS

Erythema and Edema

These side effects are generally immediate and can be observed in most cases. They occur due to local inflammation (response to tissue injury) and the product's hydrophilic property. Multiple injections, thick material, and incorrect application technique can also exacerbate these side effects.9 Ice must be applied for 5-10 minutes and the head must be kept elevated. Regression takes place within hours or at most after one or two days.[1] Edema can be avoided or minimized with the use of anesthetics with epinephrine, cold compress, and a smaller number of punctures in the skin.[5]

ECCHYMOSIS/HEMATOMA

These effects occur due to the perforation of small vessels at the site of application or to the compression and secondary rupture of vessels. Immediate local compression should be applied. There is a greater risk of high-volume bleeding if deep vessels are ruptured. The application should be performed under good lighting in order to improve visibility and avoid the perforation of vessels. It is important to note that fillers combined with lidocaine cause vasodilation and may increase the risk of local bleeding.[5] Improvement generally occurs in 5-10 days. There is no impact on the outcome. In cases of profuse bleeding, vessel cauterization may be necessary.[5,9]

NECROSIS

Necrosis is a rare complication caused by local compression (overcorrection or intense inflammation) or accidental intra-arterial injection (with vascular embolization). Published cases describe necrosis in the angular artery (nasolabial region) and supratrochlear artery (glabella) areas.[8,10] In a retrospective study with 28 patients with side effects, the glabella region presented an increased risk of tissue necrosis due to arterial occlusion.8 Patients reported pain immediately after the procedure, and the skin became pale a few hours later (due to ischemia), later acquiring a bluish-gray hue. There was ulceration and local necrosis within 2-3 days. There is no consensus on the optimal

treatment in such cases, however it is important to keep the area clean and to apply warm compresses and local massage to dissolve the embolus, and 2% nitroglycerin ointment.[8] Hyaluronidase injections, as early as possible –within the first 24 hours after the procedure –are also administered to reduce the damage caused by the necrosis.[7] In case of embolization, full heparinization of the patient can be carried out.10 One case of renal embolization was described.[8] Venous occlusions generally occur later on and develop more slowly, with less local pain and a bluish hue in the skin.[8]

INFECTION

Infection was reported in only two articles and was probably caused by product contamination or inadequate patient asepsis.[11] It can be of bacterial or viral origin. There is a case report on the reactivation of herpes simplex, however herpes prophylaxis is not usually carried out in this procedure. There is one reported case of infection by Mycobacterium chelonae after the application of HA, however it was impossible to determine whether the product or the application site was contaminated.[12,13]

There is one case report of an extensive abscess in the face that developed in the application path of the filler one month after the procedure. The secretion culture evidenced Enterococcus faecalis.[11,14] Treatment was carried out by draining the abscess and administering intravenous antibiotic therapy. The authors believe that the contamination occurred due to poor skin asepsis.

NODULES

Usually observed in the short or medium term, nodules appear as whitish or normochromic papules, or nodules. Most often, they occur as a result of improper application technique (excessively superficial injection of HA).[5] The papules may acquire a slightly bluish hue due to the Tyndall effect. The condition can be treated with local massage, and oral corticosteroids are recommended in extreme cases. The material can be surgically removed in severe cases. Fortunately, most cases resolve spontaneously.[5]

LATE SIDE EFFECTS

GRANULOMAS

Granulomas occur in 0.01-1% of cases from 6-24 months after the filler application.[9] They emerge as painless palpable nodules in the path of the filler application.9,15 The formation of foreign body granulomas was verified through histopathological examination in all cases reported.9,15,16 Granulomas are believed to be caused by impurities in the process of bacterial fermentation during the production of HA rather than by hypersensitivity to the product.9,16 The treatment of nodules is controversial. Hyaluronidase (in concentrations ranging from 50U/mL10 150U/mL17) or intralesional corticosteroid (triamcinolone injection at 5mg/mL) can be applied.17 There was one report in which the surgical removal of a granuloma was necessary.16

ALLERGIC REACTIONS

Allergic reactions are reported in 0.1% of cases, and usually star t3-7 days after the application of the product – however reactions can appear up to 1-6 months later. Clinically, there is swelling, erythema, and hyperemia in the path of the application.13 The treatments described include oral or intralesional injections of corticosteroids.[9]

HYPERTROPHIC SCARS

Hypertrophic scars can develop at the puncture sites. The patient in the reported case had a history of keloids, and was treated with occlusive corticosteroids.[12]

CONCLUSION

Injectable HA has been one of the most performed procedures in recent years, and demand has been rising in dermatologic practices. HA is becoming increasingly safer, and complications from its use are currently related primarily to the application technique and inadequate asepsis of the skin.

The early identification of any complication, as well as swift and decisive treatment, is key to preventing long-term sequelae and improving the safety of the procedure. ●

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Questions for continuing medical education (CME)

1) About Hyaluronic Acid (HA),which of the following is incorrect to state:
a) it is present in the extracellular matrix of connective tissues, synovial fluid, aqueous, and vitreous humors
b) it forms the elastoviscous fluid matrix that surrounds collagen and elastic fibers, as well as intercellular structures
c) its concentration in the skin tends to decrease with age
d) it consists of polysaccharides and glycosaminoglycans
e) it is a permanent gel

2) About HA, it is correct to state that:
a) it has a low molecular weight
b) it is lipophilic
c) the crosslinking technique is aimed at reducing the duration of the filler
d) through crosslinking, molecules that interlink to HA produce macromolecules that have the same biocompatibility yet are less stable and provide less reabsorption
e) it can be derived from cocks' combs or synthetically produced (from the bacterial fermentation of *Streptococcus spp*)

3) All are indications for the use of HA, except for:
a) correction of rhytids
b) paralysis of muscles in the upper third of the face
c) increase in lip volume
d) correction of acne scars
e) correction of folds

4) All are contraindications to HA-based cutaneous filling, except for:
a) pregnancy
b) autoimmune disease
c) use of aminoglycoside
d) severe immunodeficiency
e) breastfeeding

5) Complications arising from the use of HA may derive from several factors, except for:
a) neurological disorders
b) lack of experience
c) incorrect technique
d) product used
e) lack of patient skin antisepsis

6) Which of the following is not a possible adverse reaction to HA filling:
a) erythema
b) edema
c) necrosis
d) melasma
e) hematoma

7) About adverse events linked to the use of HA, mark the incorrect option:
a) erythema is a rare complication that improves in a few hours or days
b) hematomas are caused by vessel perforation or rupture secondary to compression
c) treatment of bleeding can be carried out with local pressure and, if necessary, cauterization
d) ecchymosis tends to improve in 5-10 days
e) necrosis is a rare and serious complication

8) Regarding necrosis associated with the use of HA, which of the following is incorrect:
a) it is caused by local compression or accidental intra-arterial injection
b) the most common sites are the glabella and the nasal ala
c) the patient usually feels no pain and there is no change in the color of the skin
d) warm compresses, 2% nitroglycerin cream, and local hyaluronidase injections are treatment options for tissue necrosis
e) venous occlusions usually emerge later on

9) Mark the incorrect option regarding infections related to HA-based cutaneous filling:
a) they are probably caused by product contamination or lack of asepsis
b) they are very frequent
c) they can have bacterial or viral origin
d) routine herpes prophylaxis is not recommended
e) mycobacteriosis may occur

10) Mark the correct option:
a) nodules may occur primarily as a result of excessive superficial applications of HA in the skin
b) early papules always have the same color, and never improve
c) in late nodules, it is usually possible to observe the formation of foreign body granulomas in a histological examination
d) granulomas may require treatment with hyaluronidase and, in extreme cases, surgical removal
e) allergic reactions can be treated with oral or intralesional corticosteroids

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1c 2d 3c 4e 5b 6a 7a 8b 9c 10e

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