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Evaluation of Adverse Effect Reports of Hyaluronic Acid Based Medical Device Applications in the Last Ten Years (from 2013 to 2023)

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Abstract

Objective: Hyaluronic acid (HA) is a naturally occurring polymer, present in different tissues of human cells which is a crucial component of the extracellular matrix. Its exceptional properties—including biocompatibility, non-immunogenicity, biodegradability, rheological flexibility, high hydrophilicity, ease of chemical modification, and viscoelasticity—enable a wide range of therapeutic applications. However, HA injections/ applications can lead to both early and delayed complications, ranging in severity from mild to serious. Additionally, the risk profile may evolve as therapeutic approaches and technologies continue to advance.

Materials and Methods: In this study, a systematic literature search was achieved on PubMed on January 5, 2023 and only case reports conducted in humans in last ten years (from 2013 to 2023) were considered. Literature reviews, clinical trials, technical notes, recommendations, and instructional course were excluded. Reviewed case studies that did not match the determined criteria were removed.

Results: 109 case studies representing 154 patients with severe complications were examined. The year of publication, total number of patients, age and gender of patients, adverse effects/ symptoms, and the reason of adverse effects of each case was listed. The case studies were classified according to the reason of adverse effects after HA application as intravascular injection and vascular obstruction, hypersensitive/ allergic affect, delayed inflammatory reaction (DIR), virus infection, bacterial infections, and others. Reactions to HA were reported as frequent redness, swelling, bruising, nodules, erythema, edema, tenderness, blindness, pain, and rarely death.

Conclusion: To conclude, adverse effects after HA application were found to be of high incidence in the population due to its widespread use. Even though adverse reactions are declared, these findings do not increase safety concerns related to the use of HA compared to the beneficial effects of it. The majority of negative situations may be avoided with improved application procedures.

Keywords: Adverse effect, hyaluronic acid, medical device, toxic effect

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INTRODUCTION

Hyaluronic acid (HA), also known as hyaluranate or hyaluronan as a hyaluronan family member, is a linear high molecular mass polysaccharide that belongs to the glycosaminoglycans (GAGs) (1, 2). It is a crucial constituent of the extracellular matrix. The total HA amount in human is approximately15 g for an adult person at 70 kg body weight, and it is distributed in diverse tissues including synovial fluid, umbilical cord, kidney, blood vessels, vitreous body of eye, skin, cartilage, lung, brain, serum, heart valves, and muscle (2-6). The size and concentration distribution of HA varies with age, tissue type, and the severity of disease (7). The molecule mechanically holds water as the chain lengthens and coils into spherical form, allowing the passage of small molecules while excluding or retarding larger ones (8). Adjacent chains may communicate with each other to create a connection. The network-forming, viscoelastic and charge properties of living tissues are crucial for biochemical/ metabolic properties (9). The molecule has diverse biological functions because of these properties.

The crucial biological properties of HA result from its spatial and chemical structure, elasticity, high molecular mass, high viscosity, hydrophilic characters, and highly negative charge. The molecule has diverse biological functions because of these properties. Biological functions of HA can be listed as retention of water in the matrix, hydration of tissue, lubrication, water homeostasis, transportation, adhesion, proliferation and differentiation, neutrophil adhesion, cellular interaction/ division/ migration, fetal wound healing, bone resorption, development/ aggregation/ adhesion of red blood cell leading to formation of bone (8, 10). The average molecular mass of HA has an impact on its physico-chemical properties (7). The increase of the molecular concentration/weight enhances stability, viscosity and viscoelasticity (8).

HA can be derived from skin, synovial fluid, umbilical cord, and rooster comb of animals. It can also be isolated from ***bacteria*** through direct isolation or a biotechnological process named as fermentation (8). Most of commercially available HA is derived from bacterial fermentation for a few key reasons—mostly revolving around safety, scalability, sustainability, and purity. For example, animal-derived HA carries risks of allergic reactions and disease transmission (e.g., prions or viruses). It also raises ethical concerns regarding animal use. However, bacterial fermentation avoids these issues entirely. It uses non-pathogenic strains like *Streptococcus zooepidemicus, Streptococcus equi* or genetically engineered *Escherichia coli* to produce HA in a lab setting. Fermentation methods allow for more controlled environments, which means fewer impurities and easier standardization of molecular weight. For instance, bacterial sourced HA should be free of pyrogens (8). Bacterial fermentation is renewable, non-animal-based, and scalable, industrial fermentation tanks can be optimized for consistent, large-scale production, making it cost-effective and eco-friendly (8).

According to recent studies, HA is almost fully metabolized and reabsorbed within six months, without causing any type of fibrosis or implant waste on the applied area (11). Due to its unique properties, it became a great biomaterial for drug administration, medical, food and cosmetic applications (12-14). It has been used in different medical application including ophthalmology, rheumatology, orthopedics, dentistry, and dermatology (12). The increasing clinical usage of HA has stimulated the interest of industry leading to the development of many derivatives with enhanced residence time in the joint cavity. HA fillers can be applied safely and effectively with a needle or cannula if performed correctly. HA fillers are the well- known and preferable products for nonsurgical rejuvenation of face and discreet tissue augmentation. These activities have presented encouraging results, paving the way for future biological uses of HA-derivatives.

HA is biocompatible, biodegradable and also non-immunogenic which made it a useful material for many different applications (4). In literature, biocompatibility tests of HA cover various sets of test methods including reproductive and developmental toxicity studies, repeated dose oral toxicity test, mutagenicity tests, acute/ chronic/ subacute toxicity tests, antigenicity tests and micronucleus assays. However, the toxic effect of HA application is observed. Injecting larger volumes of hyaluronic acid may increase the risk of foreign-body reactions. Moreover, breakdown products of HA products could induce hypersensitivity, and also variations in H_2O-binding capacity. These products could lead to localized responses including pain and swelling. Native form of HA has a very long polymer (high-molecular-weight hyaluronic acid - HMWHA) which is present in the majority of tissues as a primary component of the extracellular matrix (6) and the molecule may be cut down into smaller components, referred as low-molecular-weight hyaluronic acid (LMWHA) in some conditions (6, 13). While HMWHA has an effect on cancer resistance ***via*** inhibiting cellular motility, LMWHA shows a tumor progression effect by cell movement (13). LMWHA promotes angiogenetic activity (a potent stimulator of blood vessel growth) and can present pro-inflammatory activity or promote tumor progression (6, 8, 13).

There have been few instances of adverse hypersensitivity responses including the emergence of hematoma, asymmetry, over-correction, under-correction, and tissue necrosis caused by HA injection experience (15).

This study aims to evaluate published adverse effects/ reactions of HA based medical devices applications in the last ten years (from 2013 to 2023).

MATERIALS AND METHODS

Data collection and search strategy

A systematic case study search was carried out on PubMed up to January 5, 2023. The search was limited to case reports/ studies conducted in humans in the last ten years (from 2013 to 2023) and studies were selected based on inclusion *criteria*. The following key words were used: ("hyaluronic acid" and "adverse effect"), ("hyaluronic acid" and "adverse reactions"), ("hyaluronic acid" and "toxic effect"), ("hyaluronic acid" and "toxicity"), ("sodium hyaluronate" and "adverse effect"), ("sodium hyaluronate" and "toxic effect"), ("sodium hyaluronate" and "toxicity") and last ten years (from 2013 to 2023) limit was chosen for the years of publication.

Only studies in English were considered. Literature reviews, clinical trials, technical notes, recommendations, and instructional course were excluded.

During the research phase, case studies that were strictly relevant to the issue were discovered initially in each of the journals, with studies on animal models and in vitro studies being discarded following the main selection. The full text of the remaining accessible articles *via* Yeditepe University Information Center Electronic Resources Library were retrieved and reviewed to determine if they met the inclusion *criteria*. Each case study was reviewed for its year of publication, total number of patients, age and gender of patients, adverse effects/ symptoms, and reason of adverse effects.

Results and Discussion

In total, 588 case studies presenting the forementioned key words were identified through the initial search on PubMed database for the last ten years (from 2013 to 2023). Following de-duplication, the title and abstracts of the case studies were examined. Reviewed studies that did not match the determined inclusion ***criteria*** were not included. The full text of the remaining accessible case studies ***via*** Yeditepe University Information Center Electronic Resources Library were retrieved and reviewed to specify whether they met the inclusion ***criteria***. Finally, 109 case studies representing 154 patients with severe complications were included. Then, the case studies were categorized according to reason of adverse effects.

Fifty-one case studies representing 69 patients were found to be related to intravascular injection and vascular obstruction caused by HA soft tissue fillers (Table 1). Dermal vascular obstruction due to accidentally intravascular injection of filler was found to be rare but caused serious adverse effects. Dermal ischemia can contain skin necrosis, livedo reticularis, erythromelalgia, ulceration, or dermal infarct (16). The severity of the consequences related with the nature and amount of the filler (17). The nature of HA fillers vary in terms of viscosity (high density), particle size and crosslinking density (16). For example, increasing density and/or particle size may cause fillers to more easily block blood vessels and become more difficult to disperse after injection. Cross-linking makes fillers more durable, but they are more difficult to dissolve with hyaluronidase, the enzyme used to reverse filler complications (16). Therefore, a high-viscosity, large-particle filler used inappropriately (wrong depth or wrong area) increases the chance of serious vascular events. The injected amount is also critical as higher volume increases pressure within tissues, making it easier for the filler to enter into a blood vessel if the needle or cannula is improperly placed, which obstructs blood flow, and a larger embolus means a higher risk of ischemia and necrosis (16-18). HA products may cause erythema, swelling, bruising, pain, blindness and pruritus because of deterioration of the vascular and dermal structures (Table 1).

Injectable fillers are used in many different anatomic locations; however, some areas show increased risk of complications. Due to their rich terminal blood supply, the glabella, the nose, forehead, and periorbital region are particularly prone to visual complications. The injection technique and slow injections of small volume of HA filler may cause vascular damage during removal of the needle or cannula (17, 18). Therefore, the needles must be used with caution in highly risky areas to avoid vascular complications. Moreover, the technique of the operator is an important issue for the safety of the patient. Performing of hyaluronidase injection is the most effective and immediate way for the treatment of HA associated cases (16).

In theory, non-animal stabilized HA does not have any risk of allergic reactions due to its unique characteristic of biocompatibility. However, Table 2 represents case studies where hypersensitive/ allergic effect of HA for 18 case studies and 27 patients in last ten years (from 2013 to 2023) were observed. Bacterial derivative HA is most popularly used as facial filler because of its very low incidence of hypersensitivity/allergic activity.

Depending on the time of onset, hypersensitive activity may be classed as acute/ early or delayed/ late. Type I hypersensitive activity occur within minutes or hours after HA application as a result of an immunoglobulin-mediated immunological response (67). The most typically reported adverse effects with HA usage as dermal face

Table 1. Information of case studies with vascular injection and obstruction after hyaluronic acid application..

References	Age/ Gender	Application Side	Adverse Effects	Reason
Kim et al., 2015 (19)	34/F	Eyelid	Upper eyelid retraction, blunt pain, swelling, and heaviness of the affected eye	Intravascular injection
Kim & Alhusayen, 2015 (20)	64/M	Knee	Painful skin eruption over the right knee	Intravascular injection, vascular obstruction
Choi et al., 2016 (21)	29/F	Lower eyelids	Nodules	Inadequate injection (depth)
Li et al., 2016 (22)	25/F	Nose (non-surgical rhinoplasty)	Right eye blindness, limb weakness	Intravascular injection, vascular obstruction
Hu et al., 2016 (18)	41/F	Forehead	Blindness, edema, skin discoloration	Intravascular injection, vascular obstruction
Kang et al., 2016 (23)	46/F	Glabella, forehead, and nose	Redness, swelling, numerous pustules, and dark regional necrosis	Intravascular injection, vascular obstruction
Andre & Haneke, 2016 (24)	46/F	Nasolabial folds	Sensitivity and redness of right nasolabial crease and nose, Nicolau syndrome	Intravascular injection, vascular obstruction
	35/F	Nasolabial folds	Pain and redness	
	32/F	Nasolabial folds	Pain and redness	
	40/F	Nose tip	Livedoid pattern	
	30/F	Lips	Pain, livedoid pattern	
	42/F	Nasolabial folds	Pain, swelling, redness, livedoid pattern	
Bertl et al., 2017 (25)	28/F	Dental tissue (intra oral)	Swelling on lip, pain	Inflammatory reaction, intravascular injection
	30/F	Dental tissue (intra oral)	Swelling, pain, discoloration (livedo reticularis)	
Yang et al., 2017 (26)	27/F	Bilateral temple augmentation	Swelling and burning pain, alopecia	Intravascular injection, vascular obstruction
Maruyama, 2017 (27)	57/F	Glabella, eyebrow	Erythema, purple discoloration, and severe pain	Vascular obstruction
Salval et al., 2017 (28)	22/F	Nose tip, forehead	Pain, swelling, discoloration, and edema	Infection, intravascular injection, vascular obstruction
Bae et al., 2018 (29)	29/F	Nasal tip	Painful erythematous swelling, ain and dizziness, and her vision became blurred	Intravascular injection, vascular obstruction

Table 1. (Continued)

References	Age/ Gender	Application Side	Adverse Effects	Reason
Wang et al., 2018 (30)	24/F	Mentum	Soreness and swelling, the anterior region of chin became pale	Intravascular injection, vascular obstruction
	42/F	Chin	Pain, headache and discomfort, swelling	
Hao et al., 2018 (31)	20/F	Right forehead	Blindness, erythema, cherry-red spots	Emboli, pressure, thrombosis
Thanasarnaksorn et al., 2018 (32)	36/F	Nose (non-surgical rhinoplasty)	Nausea and pain in the left eye, vision loss, phthalmoplegia, ptosis, dizzines	Intravascular injection, vascular obstruction
	36/F	Nose (non-surgical rhinoplasty)	Pain and vision loss	
	26/F	Nose (non-surgical rhinoplasty)	Blindness	
	23/M	Nose (non-surgical rhinoplasty)	Blindness, pain, headache, nausea, and vomiting	
	61/F	Forehead	Severe headache, skin blanching and blurred vision	
	31/F	Temporal area	Blurred vision	
Vidič & Bartenjev, 2018 (33)	50/F	Glabellar region, upper lip, nasal root	Erythematous, livedoid rash, swollen of eyelids	Infection, blood vessel damage on the application site
Jeong et al., 2018 (34)	37/F	Nose (non-surgical rhinoplasty)	Purpuric discoloration, swelling, and pain	Intravascular injection, vascular obstruction
Loh et al., 2018 (35)	50/F	Face	Painful skin eruption on the left knee, erythematous reticulate, livedo reticularis	Intravascular injection, vascular obstruction
Wibowo et al., 2019 (36)	40/F	Nasal dorsum	Upper eyelid ptosis, blindness, deep pain, skin color change	Intravascular injection, vascular obstruction
Park et al., 2019 (37)	58/F	Face	Alopecia on the ipsilateral scalp	Intravascular injection, vascular obstruction
Yao et al., 2019 (38)	21/F	Forehead	Blindness, severe pain in eye, headache	Vascular obstruction
Shoughy, 2019 (39)	36/F	Glabeller region	Blindness, weakness of the left arm, dark pigmented lesions over the eyelid	Intravascular injection, vascular obstruction
Ansari et al., 2019 (40)	20/F	Glabellar region	Blindness, iolaceous pigmentation	Vascular obstruction
Lima et al., 2019 (41)	42/F	Cheeks, nasolabial folds and the chin	Yellowish spot, small lump	Intravascular injection, vascular obstruction

Table 1. (Continued)

References	Age/ Gender	Application Side	Adverse Effects	Reason
Hu et al., 2019 (42)	22/F	Eyebrow	Orbital pain on the right side, blurry vision, perineuritis (OPN)	Obstruct blood flow
Khalil et al., 2020 (43)	54/F	Eyebrow and glabellar crease	Edema, xerophthalmia, and dryness	Wrong application
Cassiano et al., 2020 (44)	57/F	Rejuvenation of the frontal region	Pain, erythema, and edema in the frontal region	Intravascular injection, vascular obstruction
Downie et al., 2020 (45)	54/F	Temples and periorbital region	Severe frontal headache and nausea, dizziness, binocular diplopia, and vomiting, blindness	Intravascular injection, vascular obstruction
	37/F	Nasal bridge and periorbital region	Binocular diplopia, blindness	
Desmottes et al., 2020 (46)	63/M	Knee	Painful livedoid patch	Excessive pressure and vascular compression
Kim et al., 2020 (47)	23/F	Nasal dorsum	Dizziness, headache, horizontal diplopia, oculodynia, blurred vision, and lateral deviation	Vascular occlusion
Hirsch et al., 2020 (48)	19/F	Upper lip	Instant burning pain	Vascular occlusion
Akoglu et al., 2020 (49)	37/F	Cheekbone	Pain, stinging sensation on eye,	Vascular obstruction
Uz et al., 2020 (50)	46/F	Buttocks	Agitation, altered mental status, and drowsiness	Intravascular injection, vascular obstruction
Yang et al., 2020 (51)	40/F	Nose	Periocular pain and blindness, nausea, vomiting, and headache, and lost consciousness	Intravascular injection, vascular obstruction
Zeltzer et al., 2020 (52)	21/F	Upper lip	Pain, ischemia	Intravascular injection, vascular obstruction
Yang et al., 2020 (53)	33/F	Vagina	Dyspnea, cough, dizziness, fatigue, and cyanosis of the lips, vaginal infection, pulmonary vascular embolism, death	Intravascular injection, vascular obstruction
Toussi et al., 2020 (54)	72/F	Right ankle (long-standing osteoarthritis)	Worsening, burning, painful rash on right foot	Tissue necrosis and arterial injury
Berríos-Hernández et al., 2020 (55)	72/F	Knee	Pain, extensive, livedoid, erythematous lesion	Intravascular injection, vascular obstruction, incorrect injection
Sud et al., 2021 (56)	37/F	Lip and chin	Lip pain, swelling, and rash	Intravascular injection, vascular obstruction

Table 1. (Continued)

References	Age/ Gender	Application Side	Adverse Effects	Reason
Aaron et al., 2021 (57)	66/F	Knee	Cutaneous necrosis of right ankle and foot	Intravascular injection, vascular obstruction
Chen et al., 2021 (58)	22/F	Nasal dorsum	Diplopia and orbital pain, erythematous, pupil dilation, exotropia, visual field defect, and limitation of extraocular movements	Intravascular injection, vascular obstruction
Master et al., 2021 (59)	30/F	Tear trough	Lumpiness and significant malar edema	Inadvertent placement
	64/F	Tear trough	Longstanding puffiness under the left eye	
	58/F	Cheeks and tear toughs	-	
Tao et al., 2021 (60)	22/F	Left temporal and forehead	Headache, vertigo, nausea, and blindness of left eye, hemiplegia, sensory disturbance, and petechiae	Intravascular injection, vascular obstruction
Moore et al., 2021 (61)	59/F	Glabella and nasal dorsum	Right eye blindness, dizziness, nausea, and a right frontal headache, stroke	Intravascular injection, vascular obstruction
Sasongko et al., 2022 (62)	55/F	Face	Blindness	Vascular obstruction
Danks et al., 2022 (63)	38/F	Nose (non-surgical rhinoplasty)	Blindness	Intravascular injection, vascular obstruction
Yang et al., 2022 (64)	18/F	Chin augmentation.	Numbness and intense pain, dysphonia, limited mouth opening, and paleness	Intravascular injection, vascular obstruction
Davidova et al., 2022 (65)	43/F	Glabella	Blindness, swelling, no light perception on left eye, pupillary defect, cherry-red spots	Intravascular injection, vascular obstruction
Nguyen et al., 2022 (66)	27/F	Nasal augmentation	Nasal pain, headache, and blindness	Intravascular injection, vascular obstruction

filler are hypersensitive/ allergic action and inflammation at the application area (5, 16, 68). Injection area inflammations include redness, swelling/ nodules, erythema, edema and tenderness (17, 69, 70). Same symptoms were also determined in this case study research project.

The minor inflammatory responses are considered as normal, caused by resident macrophage infiltration and fibroblast activation. These immunologic activities lead to collagen synthesis which attaches the HA filler to the tissue. These symptoms usually resolve within a few days, and biodegradable HA dermal fillers are reabsorbed (70).

Table 3 presents the case studies with delayed inflammatory reaction (DIR) after HA injection. 21 case studies and 31 patients meeting the inclusion *criteria* were determined in the literature for the last ten years (from 2013 to 2023). DIR (Type IV reactions) can be seen from one month to years after injection of HA (70). Various mechanisms can be involved during DIRs including systemic infections, trauma, injection technique (for example: intramuscular implantation), circulating anti-HA antibodies, volume of filler, repeated application, vaccines, and immunogenic reactions to the cross-linking agents produced during product degradation (87, 88). Delayed type IV hypersensitivity reactions are mostly triggered

Table 2. Information of case studies with hypersensitivity/ allergy reaction after hyaluronic acid application.

References	Age/ Gender	Application Side	Adverse Effects	Reason
Colbert et al., 2013 (71)	65/F	Nasiolabial folds	Perioral augmentation, granulomatous inflammation	Properties of the filler, the volume injected and previous infection or trauma, hypersensitivity reaction
Hatcher & Goldman, 2014 (72)	46/F	Nasolabial fold	Swelling and redness, erythema	Inflammatory reaction
Kim et al., 2015 (73)	41/F	Nasolabial folds	Erythematous plaque	Allergic reaction
Bertl et al., 2017 (25)	28/F	Dental tissue (intra oral)	Swelling on lip, pain	Inflammatory reaction, intravascular injection
	30/F	Dental tissue (intra oral)	Swelling on lip, pain, discoloration (livedo reticularis)	
Dominguez et al., 2017 (74)	57/F	Vocal fold	Dysphonia, odynophagia, and dyspne	Hypersensitivity reaction
	28/M	Vocal fold	Odynophagia and rough voice quality, erythematous, edematous	
	51/F	Vocal fold	Odynophagia, ipsilateral otalgia, and dyspnea	
	65/F	Vocal fold	Dysphonia, edema, decreased amplitude, and wave	
	57/F	Vocal fold	Severe pain, edematous and erythematous	
	66/M	Vocal fold	Dyspnea, rough voice quality, and odynophagia	
	58/F	Vocal fold	Rough voice and odynophagia, dyspnea	
Kocak et al., 2017 (75)	77/M	Knee	Pain, swelling	Inflammatory reaction
Mitsuyama et al., 2017 (76)	78/F	Eye (dry eye treatment)	Bilateral periocular pruritic erythema and oedema, allergic contact dermatitis	Immune mediated adverse effects
Paolino et al., 2017 (77)	41/F	Lip	Pigmented lesion of the lower lip (melanosis)	Immune mediated adverse effects
Traboulsi et al., 2017 (78)	23/F	Laryngeal (laryngoscopy using the trans nasal route)	Globus sensation, dysphagia, and shortness of breath	Allergic and hypersensitivity
Alcântara et al., 2017 (79)	54/F	Dental gel application	Asymptomatic firm nodularities in the lower and upper lips, granulomatous reaction	Foreign body reactions
Gandy et al., 2017	55/F	Perioral area	Swelling and redness, erythematous, granulomatous plaque, nodules	Immune mediated adverse effects

Table 2. (Continued)

References	Age/ Gender	Application Side	Adverse Effects	Reason
Wu et al., 2018 (81)	39/F	Full face	Facial nodules, redness, and swelling	Hypersensitivity reaction, allergy
Sarigul Guduk, 2021 (82)	41/F	Tear trough	Eyelid swelling	Allergic reaction
	40/F	Midface and lower eyelids	Eyelid swelling	
	43/F	Midface and tear trough, periorbital area	Eyelid swelling	
Schattner & Haj-Yahya, 2018 (83)	100/F	Inner-lower-lip and gums to treat gingival sores	Swelling of the tongue and inability to swallow, angioneurotic edema	Allergic reaction
Decates et al. 2020 (68)	32/F	Tear trough	Swelling of the left cheek, edema	Hypersensitivity
Chen et al., 2020 (84)	21/F	Lip, nose tip, chin, and the right nasal root	Redness and pain, swelling, periorbital edema, and conjunctival congestion, adache and fever, with gradual hyper myotonia.	The ingredients of the filler essence, hypersensitivity, and inflammatory reaction by infection
Wege et al., 2021 (85)	27/F	Lips	Lumps on upper lip, swelling	Immune mediated adverse effects
Hayat et al., 2022 (86)	41/F	Cheek	A mass on left eye	Inflammatory reaction

by $CD4^+$ cells and T lymphocytes (67). It may manifest as inflammatory nodules, induration, erythema, swelling and edema (15, 67, 87, 89).

Type IV hypersensitivity after HA application due to virus infection (like *influenza*, COVID-19 and *Herpes simplex*) seems to be the most common cause for delayed hypersensitivity reaction in recent years. Table 4 presents the delayed hypersensitivity case reports related to viral infection in the last ten years. Some cases reported that a hypersensitivity reaction was seen more than 24 hours after a vaccination for COVID-19 (108-111). Currently, it remains unclear whether there is a specific progression to delayed hypersensitivity reactions following COVID-19 vaccination, how long adverse effects are most likely to occur after hyaluronic acid (HA) injection, and what the optimal waiting period is for HA treatment after receiving the COVID-19 vaccine. Treatment with HA changed from weeks to months before vaccination, and while the responses resolved within a few days, others remain refractory, with phases of worsening, improvement, and recurrence months following vaccination according to case studies presented in Table 4.

Table 5 represents the case studies related to bacterial infections after HA application in poor conditions. Infection risk may be increased with filler injection as a result of skin barrier damage. Therefore, the use of aseptic techniques is very crucial during the application. In recent years, the fact that dermal fillers purchased from the electronic trade web sites has increased the rate of the self-injection of the formulations under unsuitable environmental conditions, and this has caused an increase in infections (117-119). Cellulitis, abscess formation, nodules or granulomatous inflammation are the most common complications after skin disruption during HA filler injection (33, 117, 120). In this research, similar symptoms were summarized in Table 5.

In this study, the reasons of adverse reactions after HA application were categorized as intravascular injection and vascular obstruction, hypersensitivity/ allergic effect, DIR, viral and bacterial infections. The rest of the

Table 3. Information of cases with delayed inflammatory reaction (DIR) after hyaluronic acid injection.

References	Age/ Gender	Application Side	Adverse Effects	Reason
D'Acunto et al., 2013 (90)	49/F	Eyelid	Anthelasma palpebrarum on right lower eyelid	Delayed inflammatory reaction (DIR)
	67/F	Eyelid	Xanthelasma, ellow-colouredplaque	
Novoa et al., 2013 (91)	54/F	Interciliary sulci and nasolabial folds	Erythematous-violaceous nodules on face, brownish papules on shoulder, elbowa, knees	DIR
Rongioletti et al., 2015 (92)	59/F	Glabella, cheeks, nasolabial and perioral areas	Firm, nodular swellings	DIR
	53/F	Face	Multiple- painful- nonulcerated, hard nodules, deep granulomatous giant cell reaction	
	72/F	Lip	Nodular swelling, tender, non-painful,	
Goodman, 2015 (93)	49/F	Prejowl sulci, marionette regions, and nasolabial grooves	Swelling	DIR
Bitterman-Deutsch et al., 2015 (94)	29-56/F (5 patients)	Glabella area, lips, and the back of the hands (for 2 patients) Nasolabial folds Matriderm / matridur to nasolabial folds and zygomas Glabella and eyes	Asymmetrical edema of the face	Delayed side effects
Iverson & Patel, 2017 (95)	72/F	Tear trough	Bilateral lower eyelid "fluid filled" bags, late-onset edema	Delayed side effects
Hibler et al., 2019 (96)	50/F	Face	Facial swelling	DIR
Boger et al., 2019 (97)	68/F	Midface	Swelling around eyes, oedema	Delayed migration
Capodiferro et al., 2019 (98)	50/F	Lip	Nodular lesion	DIR
Parulan et al., 2019 (99)	49/F	Lateral zygomatic regions	Swelling on eye area	DIR
Choi et al., 2019 (100)	69/F	Forehead	Erythematous nodules on the forehead and scalp	Delayed side effects
Pathmanathan & Dzienis, 2019 (101)	52/M	Cheeks	Nodules and oedema	Cetuximab-related dermal filler reaction, DIR

Table 3. (Continued)

References	Age/ Gender	Application Side	Adverse Effects	Reason
Caldas Pozuelo et al., 2020 (102)	74/F	Lips	Nodules in both lips and perioral region	Delayed side effects
Horriat et al., 2020 (103)	48/F	Glabella, nasolabial folds, and marionette line	Facial edema, erythema, itchiness, and mild fever	DIR
Tonin et al., 2020 (104)	70/F	Upper arm skin	Multiple subcutaneous nodules on both arms	Delayed side effects
Alawami & Tannous, 2021 (105)	47/F	Different sites of face	Episodic abdominal pain, facial and lip swelling	Delayed type IV hypersensitivity
Sarigul Guduk, 2021 (82)	43/F	Temples and lips	Fever, swelling and bruising in the lips, headache, and malaise	DIR, Viral infection
Sullivan & Hawkes, 2021 (106)	71/M	Knee	Pain and swelling, erythema, inflammatory reactions associated with chills, erythematous- pruritic- scaly papules and plaques	DIR
	65/F	Knee	Erythematous macules and papules	
Grillo, 2022 (107)	45/F	Lip, full face	Edema,	DIR
Alli et al., 2022 (89)	66/F	Midface and peri-oral areas	Firm- slightly warm peri-oral swellings,	DIR
Dua & Bhardwaj, 2022 (67)	61/F	Cheeks and sunken eyes	Nodules in the subalar area on both cheeks	DIR
	44/F	Tear trough	Non-tender nodules	
	36/F	Lip, cheek	Edema and tender nodules	

case studies were presented as “other” in Table 6. Factors affecting adverse reactions after HA injection may also include the amount and specifications of product, and previous infection or trauma (71). On the other hand, although the results of cosmetic face injections are typically positive and problems are rare, some patients have experienced extreme anxiety or depression as a result of the application. These individuals have serious emotional issues, which reduce satisfaction with cosmetic operations and may result in lawsuits and disagreements. These cases are not uncommon in the clinic. In this study, only one case related to an emotional disorder was identified (122).

Another reason of adverse reaction that was reported in the literature is the presence of other filler components such as crosslinkers (like 1,4-butanediol diglycidyl ether (BDDE) which has the most popular use in the market, polyethyleneglycol diglycidyl ether (PEGDE), divinylsulfone (DVS)) or the physiologic buffer solution (PBS) within the HA products (84, 123). When these filler components were considered, safety data sheets for BDDE includes that exposure at concentrations exceeding 2 ppm may result in skin irritation or allergic sensitization. Consequently, the residual BDDE content in commercially approved HA-based fillers is expected to be either non-detectable or maintained well below this toxicity threshold, typically <2 ppm, to ensure biocompatibility and patient safety. PEGDE exhibits chemical properties and reactivity due to the presence of epoxide groups which is also seen in BDDE structure. These groups enable both compounds to form covalent cross-links with hydroxyl groups on HA chains, enhancing the mechanical stability and longevity of the resulting hydrogels (124). Especially, the purchased products via e-trade platforms usually have a low amount of HA (non-animal

Table 4. Information of case studies with viral infection after hyaluronic acid application.

References	Age/ Gender	Application Side	Adverse Effects	Reason
Wang et al., 2020 (112)	24/F	Nose (non-surgical rhinoplasty)	Crusted papules, erythema, pain and swelling	Exposure to viral infection (Herpes simplex)
Munavalli et al., 2022 (110)	50/F	Cheels, lips, tear toughs over	Lips burning, swelling of face, edema, erythema, and tenderness	Exposure to COVID-19 spike protein (DIR)
	51/F	Nasolabial folds, tear troughs, malar, and mid cheeks and upper/ lower lips, earlobes,	Injection site pain and irritation, edema, erythema, and tenderness	
	36/F	Bilateral tear troughs and upper and lower lip	Bilateral infraorbital perioral edema, infraorbital swelling and perioral angioedema	
	43/F	Tear trough	A mild tenderness underneath the right eye, swelling under the left eye	
Michon, 2021 (109)	39/F	Tear trough	Tender, erythematous, swelling, swollen, tender to touch	Exposure to COVID-19 spike protein (DIR)
	61/F	Chin and jawline, palpebromalar groove, tear trough	Facial swelling	
Savva et al., 2021 (113)	38/F	Lip	Small erythematous nodules on both the upper and lower lip, mild pain, mild tenderness	Exposure to COVID-19 spike protein (DIR)
Rowland-Warmann, 2021 (87)	22/F	Nose (non-surgical rhinoplasty)	Erythema, edema, induration, mild associated tenderness, and a tight feeling	Exposure to COVID-19 spike protein (DIR)
Beamish et al., 2022 (108)	23/F	Malar eminences, lips, jaw and chin	Painful asymmetric swelling over maxilla, lips and lower jaw	Exposure to COVID-19 spike protein (DIR)
Calvisi, 2022 (114)	60/F	Lip	Swelling in the upper lip	Exposure to COVID-19 spike protein (DIR)
	45/F	Lip	Angioedema in the upper lip	
	40/F	Nasolabial fold	Erythema and edema	
Liu & Ledinh, 2022 (115)	58/F	Facial rejuvenation, abiomental folds	Nodule in right perioral area	Exposure to COVID-19 spike protein (DIR)
Bulatova et al., 2022 (116)	58/F	Nasolabial area	Chills, myalgia, dysphagia, sore throat, dry cough, fatigue, and intermittent fever, Painful subacute thyroiditis	Immune mediated adverse effects, influenza vaccine

Table 4. (Continued)

References	Age/ Gender	Application Side	Adverse Effects	Reason
Ortigosa et al., 2022 (111)	35/F	Lips, nasojugal furrow, malar, and chin regions	Delayed swelling, induration, and edema in lips and chin	Exposure to COVID-19 spike protein (DIR)
	47/F	Around eye	Edema in the lower eyelids	
	34/F	Superior and inferior lips	Pain and mild edema in the lips	
	56/F	Lip and chin	Induration and edema in the mandible and chin	
	43/F	Nasolabial folds and lips	Edema, erythema, increase in the temperature of lips, fever, sensation of fatigue, and purpuric lesions of the extremities.	

Table 5. Information of case studies with bacterial infection after hyaluronic acid application.

References	Age/ Gender	Application Side	Adverse Effects	Reason
Park & Seo, 2013 (120)	62/F	Glabella, forehead	Inflamed nodule on the glabellar, swelling	Bacterial Infection
Salval et al., 2017 (28)	22/F	Nose tip, forehead	Pain in the glabella and forehead region, swelling, reticulated nasal skin discoloration and edema	Infection, intravascular injection, vascular obstruction
Vidič M & Bartenjev, 2019 (33)	50/F	Glabellar region, upper lip, nasal root	Erythematous, livedoid rash, swollen of eyelids	Infection, Blood vessel damage on the application site
Chen et al., 2020 (84)	21/F	Lip, tip of the nose, chin, and the right nasal root	Redness and pain, swelling, periorbital edema and conjunctival congestion, adache and fever, with gradual hypermyotonia	The ingredients of the filler essence, Hypersensitivity and inflammatory reaction by infection
Matsuki et al., 2021 (121)	73/F	Left shoulder and knee	Dead, bullae, and erythema	Infection (streptococcal toxic shock syndrome - STSS)
Allepot et al., 2021 (117)	45/F	Breast	Bilateral breast infection, fewer, nodules	Not sterile product, infection
Khor et al., 2021 (119)	31/M	Penile girth	Pain and swelling of the penile shaft	Bacterial Infection

Table 6. Information of case studies with other complications after hyaluronic acid application.

Authors	Age/ Gender	Application Side	Adverse Effects	Reason
Colbert et al., 2013 (71)	65/F	Nasolabial folds	Perioral augmentation, granulomatous inflammation	Filler properties, injected volume, previous infections, trauma, hypersensitivity
Vasquez el al., 2019 (126)2B	61/F	Tear trough and nasojugal groove	Infraorbital edema	Particulate, hydrophilic nature of the selected filler
Wang et al., 2020 (122)	32/F	Forehead and glabella	Panic, headache and insomnia, tension headache, tachycardia, breath shortness, sleep disorders	Emotional disorder syndrome
Chen et al., 2020 (84)	21/F	Lip, chin, tip of the nose, and the right nasal root	Redness and pain, swelling, periorbital edema and conjunctival congestion, headache and fever, with gradual hypermyotonia.	The ingredients of the filler essence, hypersensitivity and inflammatory reaction by infection
Simões Pires, et al., 2021 (127)	38/F	Over eyelid	Edema and erythema, a yellowish plaque, Development of xanthelasma	Unknown
Liu et al., 2021 (128)	43/F	Tear trough	Thin, soft, and yellow papules, development of xanthelasma	Unknown
Kato & Inoue, 2022 (123)	63/F	Rejuvenation of entire face	Severe pain, minimal lacrimation, abdominal colic and nausea, facial redness and swelling, urticaria all over body, abdominal colic	Other filler components (e.g., crosslinker or Phosphate Buffer Saline" (PBS) within the filler products)

based), herbal extracts (poorly identified or non-standardized), and additional ingredients (such as preservatives, stabilizers, colorants or fragrances) which are produced in poor safety conditions (125).

CONCLUSION

HA/ sodium hyaluronate is a very well-known and widely used commercial product due to its unique properties of biocompatibility, non-immunogenicity, biodegradability, rheological behavior, high hydrophilicity, ease of chemical modification and viscoelasticity. These unique properties have rendered it as a great biomaterial for drug administration, medical, food and cosmetic applications. Moreover, HA fillers become one of the most common temporary fillers on market due to their low immunogenicity and ability to be enzymatically destroyed by hyaluronidase.

HA including products are now widely accepted as a material of choice for the relatively less invasive medical applications. However, HA injection/ application can cause acute and/or delayed adverse effects ranging from mild to severe degree, and the profile of risk may change as the therapeutic landscape advances.

Adverse effects after HA application are prevalent in the population because HA containing products are used so often. Even though adverse reactions are reported after HA application, these data do not increase safety concerns regarding the use of HA compared to the beneficial effects of it. The majority of negative situations are avoided with adequate preparation and approach. Therefore, to decrease its adverse reactions, the physician who applies the HA should have enough experience to decide, to select and to apply HA. HA containing product application should be carried out in a registered health care facilities having all the necessary equipment to combat any adverse reactions during the application.

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