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Plastic and Aesthetic Research

Systematic Review

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Management of vascular complications following calcium hydroxylapatite filler injections: a systemic review of cases and experimental studies

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Abstract

Aim: Dermal fillers are increasingly popular procedures. Inadvertent intraarterial injection of fillers, particularly with calcium hydroxylapatite (CaHA), can result in devastating consequences. A systemic review was performed to summarize management strategies to treat CaHA-associated vascular complications.

Methods: The methodology of this review was derived from The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). In addition, this paper presents a previously unreported case of a CaHA-associated vascular complication.

Results: There were 32 articles describing 42 cases, plus our case included in this review. There were 15 cases of vision complications, 23 cases of non-vision complications, and 5 experimental studies. The most common injection sites reported were nasal region for vision complications (45%) and nasolabial folds for non-vision complications (40%). Of the 38 human cases, the most prevalent treatment choice was steroids (24 cases, 63%). Complete or near complete improvement was reported in 83% of non-vision complications and 40% of vision complications. There was no noticeable homogeneity in the management strategies and outcomes of the patients. Of the 5 experimental studies, no clear consensus on treatments was found.

Conclusion: Vascular complications of CaHA are seemingly uncommon, but it is widely suspected that this is due to underreporting. While best management is prevention, preparation for a potential complication is equally important. Derived from CaHA literature, hyaluronic acid filler complication protocols, findings of this review, and personal experiences, this report proposes management strategies for CaHA-associated vascular complications. We hope these strategies provide a much-needed framework for injectors to refer to and utilize as needed.

Keywords: Filler-associated intravascular complications, filler-associated blindness, vascular occlusion management, calcium hydroxylapatite, Radiesse

INTRODUCTION

Minimally invasive cosmetic procedures, such as filler injections, have quickly become popular for facial rejuvenation due to their many advantages over cosmetic surgeries. Filler injections are widely available, relatively affordable, have minimal downtime and provide immediate yet subtle improvements in natural appearance[1]. They work by restoring volume in the natural contours of the face or body, thus portraying a more youthful appearance[2].

There are different types of soft tissue fillers categorized into three groups: autologous, biologic, and synthetic[1,2]. The use of synthetic fillers has quickly surpassed the other types due to their long-lasting effects without donor morbidity[2]. Of these, hyaluronic acid (HA) is the most widely used filler, with effects lasting 3-12 months depending on molecular size, cross-linking, and injection location[3]. In contrast, calcium hydroxylapatite (CaHA; Radiesse®, Merz North America, INC., Raleigh, NC) is a filler composed of 30% synthetic CaHA microspheres suspended in a sodium carboxymethyl cellulose carrier gel and lasts an average of 12-18 months[4-6]. This filler is typically long-lasting because fibroblasts appear as the gel is absorbed, and the patient's own collagen is stimulated to grow, thus rebuilding the structural scaffolding of the subdermal layer of skin[4]. Over time, the CaHA microspheres degrade to their calcium and phosphate subparts and are metabolized by the body's normal processes[4].

CaHA filler is currently approved by the United States Food and Drug Administration (FDA) for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds (NLF), for the correction of HIV-associated lipoatrophy, and for hand augmentation to correct volume loss in the dorsum of the hands[4,5,7]. It is also commonly used off-label for wrinkle correction and volume replacement secondary to bone and fat loss in other facial and non-facial areas, such as improving nasal contours, vocal fold augmentation and treatment of stress urinary incontinence[7].

Like all procedures, fillers are susceptible to adverse effects. The most common adverse effects are mild and temporary, such as ecchymosis, edema, erythema, pain, pruritis, contour irregularities, and dissatisfaction[5]. With its increase in popularity, more serious and permanent complications such as vascular trauma and its subsequent effects have become more prevalently documented and dreaded by filler injectors[1,8,9]. Theoretically, HA fillers can be reversed by hyaluronidase, but CaHA fillers do not yet have any equivalent substance for enzymatic degradation[2]. There are three proposed mechanisms of vascular trauma following filler injections: intravascular embolism, extravascular compression, and vascular spasm, of which severe pain, skin blanching followed by dusky, purple discoloration, and cooled skin temperature are common signs and symptoms[8].

There are a few reports summarizing case studies of vascular complications following the injection of CaHA fillers; however, they are either dated or incomplete. This review presents our case report of a patient who

suffered a vascular complication following CaHA injection as well as a systemic review of all currently reported vascular complications and their associated management secondary to CaHA injections and all experimental studies proposing a management strategy for CaHA-associated complications.

Case report

A 28-year-old female received a CaHA filler injection in bilateral NLFs at an unknown medical spa (medi-spa). Within a few days, she reported severe pain and worsening bruising of her right NLF near the injection site. The medi-spa recommend her to an urgent care center for treatment. At the urgent care center, the patient was thought to have herpes simplex or zoster infection and was discharged with oral antibiotics and antivirals. After a few days of worsening skin changes, the patient presented to urgent care again and was transferred to a burn unit for wound care of the developing skin necrosis. Four weeks after the initial injection, the patient sought a second opinion from our office and was diagnosed with a right angular artery occlusion following inadvertent arterial CaHA injection [Figure 1]. Given her late presentation to our office, she was treated with emollient topicals and pulsed dye and non-ablative fractional laser treatments to address the developing scar. A follow-up on the patient six months later showed moderate improvements in skin texture and scarring. Consent was obtained from the patient for the publication of this report.

METHODS

A review of published literature was performed to gather information on the management of vascular complications following inadvertent injection of CaHA filler. The methodology and structuring of this review were derived from The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[10].

Eligibility criteria

Studies were grouped into two categories: case reports with human subjects and scientific intervention studies with animal subjects. Inclusion and exclusion criteria were as follows:

Inclusion criteria:

1. With human subjects - Original articles and posters published up to October 2021, discussing the management of vascular complications following the use of CaHA fillers

2. With animal or cadaveric subjects - Original studies published up to October 2021, evaluating management options for complications following the use of CaHA fillers

3. Articles available in English language

Exclusion criteria:

1. With human subjects - Articles where the discussed complications were not vascular-related

2. Articles where injections of non-CaHA fillers or unknown products were given

3. Articles that did not discuss their management strategy

4. Educational articles with no associated case reports

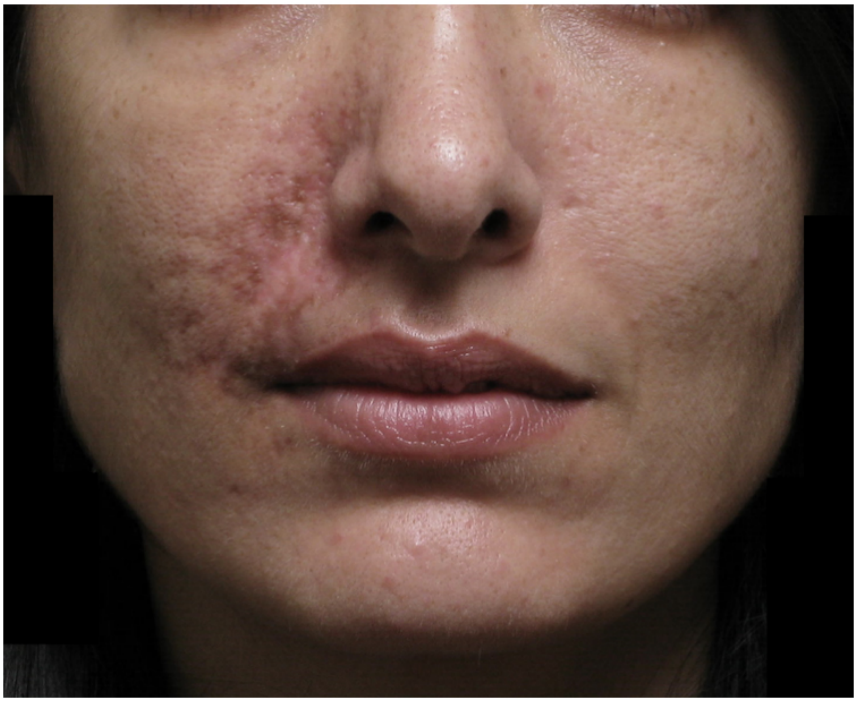

Figure 1. Textual changes and scarring in a 28-year-old female who presented four weeks after initial inadvertent calcium hydroxylapatite injection. The patient was diagnosed with right angular artery occlusion.

Information sources and search strategy

The following computerized bibliographic databases: PubMed, Medline, SCOPUS, and EMBASE were searched for reports published up to October 2021 using keywords and Medical Subject Headings (MeSH) search terms relevant to this review. The keywords used in the primary search strategy were: (vascular OR arterial OR venous) AND (occlusion OR insult OR injury OR obstruction OR trauma) AND ("Calcium hydroxylapatite" OR CaHA OR Radiesse OR "Calcium hydroxylapatite filler"). An additional search of the first results page from Google Scholar and Google search engine was executed using the phrases "vascular occlusion 'calcium hydroxylapatite'". A complete summary of the full search strategy for all databases and online sources is outlined in [Table 1]. Additional eligible literature not identified in the primary search was searched via a backward, chronological search of the bibliographies of all relevant articles identified in the primary search. All results were limited to those published in English language only.

Study selection, data items, extraction, synthesis, and analysis methods

The resulting records from the primary search were first reviewed by one author (Lindgren AL) for the removal of duplicates. Then, titles and abstracts from the search results were screened for relevance, of which 70 full-text documents were obtained. One author (Lindgren AL) read each relevant full-text article and, using the defined eligibility criteria, included 32 articles and excluded 38 articles. Then, Lindgren AL extracted the relevant data from each eligible article and summarized the data in tables. The articles with human subjects were broadly categorized into ocular and non-ocular vascular complications. The data fields for both categories included: author name(s), year of article publication, country of case(s), number of cases, type of filler used, anatomical area of injection, symptoms, and signs of reported vascular complication, management of complication, and case outcome. For articles with animal or cadaveric subjects, the data fields included: author name(s), year of article publication, study objective, substance being tested, study methods, study results, and conclusions. Any missing information was indicated in the tables as "Not Reported (NR)". Then, two authors (Lindgren AL and Welsh KM) individually evaluated the extracted data

Table 1. This table details the full electronic search strategies utilized for all the computerized databases in this review, all conducted on 20 October 2021

PubMed Advanced Search Builder	
Search string	**Results**
1 Vascular*[tiab] OR arterial*[tiab] OR venous[tiab] AND occlusion*[tiab] OR insult[tiab] OR injury[tiab] OR obstruction[tiab] OR trauma*[tiab]	1,201,546
2 "Calcium hydroxylapatite"[tiab] OR CaHA[tiab] OR radiesse[tiab] OR "Calcium hydroxylapatite filler"[tiab]	539
3 1 AND 2	27
4 Limit 3 to (English language)	27
Medline Advanced Search Builder	
1 TX (vascular* OR arterial* OR venous*) AND TX (occlusion* OR insult OR injury OR obstruction OR trauma*) AND TX ("Calcium hydroxylapatite" OR CaHA OR radiesse OR "Calcium hydroxylapatite filler")	49
2 Limit 1 to (English language)	49
SCOPUS Advanced Document Search Builder	
1 TITLE-ABS-KEY (vascular* OR arterial* OR venous*) AND TITLE-ABS-KEY (occlusion* OR insult OR injury OR obstruction OR trauma*) AND TITLE-ABS-KEY ("Calcium hydroxylapatite" OR caha OR radiesse OR "Calcium hydroxylapatite filler")	19
2 Limit 1 to (English language)	19
EMBASE Quick Search Builder	
1 (Vascular OR arterial OR venous) AND (occlusion OR insult OR injury OR obstruction OR trauma) AND ("calcium hydroxylapatite" OR caha OR radiesse OR "calcium hydroxylapatite filler")	21
2 Limit 1 to (English language)	21
Google Scholar (first page results only)	
1 Vascular occlusion "calcium hydroxylapatite filler"	10
Google Search Engine (first page results only)	
1 Vascular occlusion "calcium hydroxylapatite"	20

The * is a wildcard tool. When used, it indicates to the search engine that similar spellings of the word that precedes * can be included in the search results.

to determine final inclusion in this review. Any differences or disagreements were resolved through discussion and consensus between the authors. The selected articles were then qualitatively and quantitatively analyzed by both authors. Derived from PRISMA guidelines, the process of screening, selection, and inclusion of articles and reasons for exclusion were displayed in Figure 2[10]. Due to the small number of cases and evident heterogeneity of the variety of management strategies to address vascular complications following CaHA injection, the findings were presented using tables and narrative summaries.

RESULTS

A total of 42 cases of vascular complications following CaHA injections were extracted from the 32 eligible articles identified in this literature search. Including our patient, this review analyzed 43 total complication cases. The cases were divided into three categories and their characteristics were extracted and summarized in their respective tables. There were 15 cases with vision-related complications [Table 2], 23 cases with non-vision-related complications [Table 3], and 5 cadaveric/animal experimental cases [Table 4].

Of the 15 cases with vision complications, there were 20 injection locations reported, with the two most common sites being the nasal region (9 cases, 45%) and glabellar region (6 cases, 30%). The summary of all sites is depicted in Figure 3. Administration of steroid(s) was the most common management strategy reported in 12 of these cases (80%), followed by anti-coagulating agent(s) (8 cases, 53%), hyperbaric oxygen therapy (HBOT; 7 cases, 47%), and antibiotic medication(s) (6 cases, 40%). Other reported treatments included anti-glaucoma agents, oral vasodilating agents, topical nitroglycerin (NTG), ocular massage, aspiration, and various wound care strategies. Of note, two of the 15 cases reported observation as the only

Table 2. Summary of data extracted from search results reporting vision-related vascular complication(s) in human subjects following calcium hydroxylapatite injection

Author(s), year	Country	# of cases	Injection location	Signs & symptoms	Management	Outcome
Sung *et al*., 2010[11]	Korea	1	Nasal dorsum	Minutes/Hours: OD: ophthalmoplegia, ptosis, exotropia, chemosis, corneal edema, hyphema, hypopyon, pain & vision loss to hand movements OS: not affected Skin: necrosis and reticulated erythematous pattern on glabella, nasal bridge, and right eyelid	Minutes/Hours: -Aspiration, NS rinses, & wound care Hours/Days: -PO steroid -Ophthalmic antibiotic & steroid -IV antibiotic	Skin (minimal scarring) and OD vision improvement to 20/20 with pinhole reported at 3-month follow-up
Czyz & Allen, 2011[12]	USA	1	Glabella	Minutes: Pain with injection 1st day: Pain & edema at injection areas OD: vision loss to 20/30, pain with adduction, conjunctival vessel blanching OS: not affected 3rd day: OD: keratitis, lower lid erythema with ulceration vision improved to 20/20	1st day: -PO anti-coagulant (ASA) -Topical NTG paste & petrolatum 3rd day: -Ophthalmic antibiotic	Skin and OD vision improvement reported at 3-month follow-up
Kim & Choi, 2013[13]	Korea	1	Nose	OU: vision loss to NLP, ptosis, ophthalmoplegia, blepharoptosis, conjunctival injection Skin: central necrosis with reticulated erythematous pattern on nasal bridge & frontal area	Observation (patient presented late)	No vision improvement reported
Chang *et al*., 2014[14]	Taiwan	1	Nose	Minutes/Hours: OU: blurred vision OD: lower visual field defect OS: pain, vision loss to finger counting at 20 cm, Marcus Gunn pupil, full visual field defect, conjunctival injection	Hours: -PO anti-coagulant (ASA) & glaucoma agent (acetazolamide) -Ophthalmic antibiotic, steroid, & glaucoma agent (brimonidine) -NS rinses -HBOT (6 sessions)	No OS vision improvement reported at 8-month follow-up
Hsiao & Huang, 2014[15]	Taiwan	1	Glabella	Hours: OD: not affected OS: vision loss to hand motion at 15 cm, dilated pupil, RAPD	Hours/Days: -PO anti-coagulant (ASA), glaucoma agent (unspecified), & steroid -Ophthalmic glaucoma agent -Isovolemic hemodilution -Ocular massage -Carbogen inhalation therapy -HBOT (6 sessions)	OS vision improvement to 20/200 at 3-month follow-up
Chou *et al*., 2015[16]	Taiwan	1	Nasal tip & nasal dorsum	Minutes/Hours: Nausea, vomiting, headache OD: not affected OS: pain, vision loss to hand motion at 30 cm, exotropia, ophthalmoplegia, sluggish pupillary light. reflex, RAPD, Skin: necrosis over nasal dorsum, glabella, & left forehead	Hours/Days: -IV vasodilator (alprostadil) & anticoagulant (dextran) -HBOT (10 sessions)	OS vision improvement to 20/200 at 1-month follow-up
Hsieh *et al*., 2015[17]	Taiwan	2	Glabella	Minutes/Hours:	Minutes/Hours:	No OS vision improvement

				Headache, general weakness OD: not affected OS: vision loss to NLP, ophthalmoplegia, ptosis, pain Days: OS: hypotony Skin: multiple reticulated, erythematous-to-violaceous ulcerative skin lesions over glabella, perinasal, & periorbital areas	-PO anti-coagulant (ASA) & glaucoma agent (acetazolamide) -Ophthalmic glaucoma agent (timolol) -Hydration Days: -Ophthalmic steroid	reported at 3-week follow-up
			Nasal bridge	Minutes/Hours: OD: not affected OS: vision loss to 20/60, pain, lower visual field defect 5th day: OS: vision loss to 20/50, hypotony	Hours/Days: -PO anti-coagulant, glaucoma agent (unspecified), & steroid -Ophthalmic glaucoma agent & steroid -HBOT	Worsened OS vision to 20/200 at 2-month follow-up
Cohen *et al.*, 2016[18]	Israel	1	Nasal bridge	Minutes: OD: pain, blurred vision OS: not affected Hours: OD: vision 20/20, ptosis, exotropia, ophthalmoplegia Skin: bruising on nasal bridge & forehead, periorbital hematoma	Minutes: -Aspiration, warm compresses, ocular massage Days: -PO anti-coagulants (ASA, enoxaparin), antibiotic, steroid -Ophthalmic antibiotic -Topical antibiotic	Worsened OD vision to 20/60 at 18-month follow-up
Glass *et al.*, 2017[19]	USA	1	Temples, cheeks, forehead, chin	Minutes: Nausea, vomiting, pain Skin: hematoma at right temple Hours/Days: OD: vision loss to 20/25, ptosis, diplopia, ophthalmoplegia OS: not affected	Days: -PO steroid	Improvement of skin and ocular symptoms reported at 2-month follow-up
Marumo *et al.*, 2018[20]	Japan	1	Glabella	Minutes/Hours: Nausea, impaired consciousness OD: not affected OS: vision loss to 20/200, diplopia, ophthalmoplegia, conjunctival injection, dilated pupil Skin: purpura from glabella to left forehead Days: OS: vision loss to hand motion, hypopyon, hyphema Skin: necrosis from glabella to left forehead	Days: -PO steroid -Ophthalmic steroid -Topical ointment & wound care	Skin and OS vision improvement to 20/25 at 2-month follow-up
Sung*et al.*, 2018[21]	Taiwan	1	Nasal bridge	Hours: Headache, vomiting OD: not affected OS: vision loss to 20/63, diplopia, pain, ophthalmoplegia, exotropia Skin: bruising along nose to glabella & forehead	Days: -PO steroid & antibiotic -HBOT	Skin and OS vision improvement to 20/20 at 2-month follow-up
Vu *et al.*, 2018[22]	USA	1	Glabella & nasal dorsum	Minutes/Hours: Nausea, vomiting, headache OD: vision loss to NLP, conjunctival injection & chemosis, afferent pupillary defect OS: not affected Skin: discoloration of right forehead, glabella, & nasal dorsum	Days: -Hyaluronidase injections, ocular massage -PO anti-coagulant (ASA) & steroid -Topical NTG paste -HBOT	Skin and OD vision improvement to light perception at 3-month follow-up

Oh *et al.*, 2019[23]	USA	1	Glabella & eyelid areas	OD: vision loss to NLP, RAPD, nonreactive pupil OS: not affected	Observation (patient presented late)	No OD vision improvement reported at 9-month follow-up
Liu *et al.*, 2020[2]	Taiwan	1	Nasal dorsum	Minutes: Nausea, vomiting OD: vision loss to 20/50 OS: vision loss to 20/63, ophthalmoplegia, severe pain Skin: ecchymosis over nasal dorsum	Days: -IV steroid, vasodilator (alprostadil), & antibiotic -Ophthalmic antibiotic & glaucoma agent (timolol) -Topical antibiotic -HBOT	OU vision improvement to 20/20 at 4-day follow-up Skin & ophthalmoplegia improvement reported at 2-month follow-up

CaHA: Calcium hydroxylapatite; OD: oculus dexter (right eye); OS: oculus sinister (left eye); OU: oculus uterque (both eyes); NS: normal saline; PO: per oral; IV: intravenous; ASA: aspirin; NTG: nitroglycerin; NLP: no light perception; HBOT: Hyperbaric Oxygen Therapy; RAPD: relative afferent pupillary defect.

management and these cases had no improvement in their respective complications[13,23].

Of the 23 cases with non-vision-related complications, the 25 reported injection locations were depicted in Figure 4, with the most common sites being NLF (10 cases, 40%), nasal region (4 cases, 16%), and cheek (4 cases, 16%). The most common management approaches were administration of steroid(s) in 12 cases (52%), antibiotic medication(s) in 11 cases (48%), topical NTG in 10 cases (43%), and anti-coagulant agent(s) in 8 cases (35%). Other reported management strategies included vasodilating agent(s), hyaluronidase injection, oral antivirals, HBOT, sodium thiosulfate injection(s), warm compresses, massage, and assorted wound care and laser treatments.

Addressing all 38 of the case reports, there was no noticeable homogeneity in the timeline of management strategies with care ranging from minutes to months after injection administration depending on patient presentation. Outcomes were reported in 33 of the 38 cases (87%), of which the final follow-up times ranged from 5 days to 18 months with an estimated average of 3.5 months. It is also interesting to note that 15 of the 18 non-vision-associated cases that reported outcomes (83%) described complete improvement of signs and symptoms at follow-up, while only 6 of the 15 vision-related cases (40%) reported complete or near-complete resolution of visual defects.

This review also identified 5 experimental studies with cadaveric or animal subjects that investigated the efficacy of treatments in dissolving CaHA. One study tested topical NTG ointment, and the other four studies tested sodium thiosulfate (STS). The STS study by Robinson[39] additionally investigated the effects of topical sodium metabisulfite (SMB) in combination and in isolation from intralesional STS. Topical SMB was not found to be helpful in CaHA-associated complications. Results were varied in the four STS studies. One found complete dissolution of CaHA with STS[39], one found partial reduction[38], and the remaining two found no evidence indicating STS could dissolve CaHA[40,41]. Of note, the two studies that found no evidence supporting STS were the most recently published in 2020 and 2021, respectively[40,41].

DISCUSSION

Complication prevalence

Inadvertent intraarterial injection of filler material is an uncommon but severe complication. Vascular complications specifically following CaHA injections seem to be even more rare, with only 43 cases identified in our comprehensive search compared to hundreds of reported vascular complication cases following other filler types[1,42]. The true prevalence of CaHA-associated complications is unknown, in part, due to the widely accepted theory that complications are underreported in the literature[42,43]. Antidotally,

Table 3. Summary of data extracted from search results reporting non-vision-related vascular complication(s) in human subjects following calcium hydroxylapatite injection

Author(s), year	Country	# of cases	Injection location	Signs & symptoms	Management	Outcome
Georgescu *et al.*, 2009[24]	USA	2	Glabella	Hours: Bruising & pain in injection area 2nd day: Skin necrosis along right supratrochlear artery 3rd day: Eschar formation	Days: -PO steroids -Topical NTG paste Months: -Microdermabrasion	Some improvement (residual hyperemia) reported at 4-month follow-up
			NLF	Hours: Pain, edema, ecchymosis, & necrosis along right angular artery	Hours: -PO antibiotic & steroid Months: -Topical steroid -Microdermabrasion	Full improvement reported at 4-month follow-up
Winslow, 2009[25]	USA	1	Nose	Minutes: Blanching Days: Ischemic purpura, edema, mild epidermolysis of nose	Days: -Topical NTG paste	Full improvement reported at 2-week follow-up
Dayan *et al.*, 2011[26]	USA	3	NLF & infraorbital region	Minutes: Blanching over left cheek, left NLF, & left upper lip Days: Upper lip tenderness, edema & erythema of left lower face; reticulated vascular congestion of upper lip & left buccal mucosa	Days: -Hyaluronidase injection -PO anti-coagulant (ASA) & steroid -Topical NTG paste & oxygen infusion cream	Full improvement reported at 5-day follow-up
			NLF	Days: Soreness, edema, erythema, thick serous drainage of right NLF, erythematous & congested reticular pattern of overlying skin Weeks: Increased area of erythema & induration	Days/Weeks: -Betadine, warm compresses -Hyaluronidase injections -PO anti-coagulant (ASA) & antibiotic -Topical NTG paste, oxygen infusion cream & antibiotic	Full improvement reported at 4-week follow-up
			NLF	1st day: Edema, erythema, & bruising of right NLF 1st week: Worsening edema & erythema, skin breakdown & ulceration 4th week: Large patch of reticulated skin, mild edema, atrophic skin	1st week: -IV antibiotic -PO antibiotic & antiviral -Topical steroid 4th week: -Hyaluronidase injection -PO anti-coagulant (ASA) & antibiotic -Topical NTG paste & oxygen infusion cream	Full improvement reported at 8-week follow-up
Beer *et al.*, 2012[27]		2	NLF	Minutes: Blanching & pain along right angular artery Days: Superficial erosions & small yellowish papules	Days: -PO anti-coagulant (ASA), steroid, antibiotic, & antiviral Months: -Pulsed dye & fractionated erbium laser sessions	Full improvement reported at 4-month follow-up
			NLF	Minutes: Blanching along right angular artery	Minutes/Hours: -Hyaluronidase injections, massage -Incision and drainage -Topical NTG paste Days: -PO anti-coagulant (ASA), vasodilator (sildenafil) & steroid -Topical antibiotic -HBOT (10 sessions)	Some improvement (residual bruising) reported at 2-week follow-up
Darling *et al.*, 2014[28]	USA	1	Cheek	Days: Eroded plaque on right cheek	Days/Weeks: -PO anti-coagulant (ASA), vasodilator (pentoxifylline)	Full improvement reported at 11-week follow-up

					antibiotic, & antiviral -Topical NTG paste & petrolatum -Red light therapy -HBOT (14 sessions) Months: -Pulsed dye & fractionated erbium-doped laser sessions	
Tracy *et al.*, 2014[29]	USA	1	NLF	Hours: Swelling & skin changes of left NLF Days: Frank tissue necrosis, diffuse inflammation, & fibrinous exudate of left NLF	Days/Weeks: -PO steroid, antibiotic & antiviral -Wound care & debridement Months: -Pulsed dye laser sessions	Full improvement reported at 4-month follow-up
Schuster, 2015[30]	Germany	2	Nasal radix & columella	2nd week: Painless red nasal tip	2nd week: -PO antibiotic -Topical steroid	Full improvement reported at 4-week follow-up
			Nasal dorsum	1st day: Local infection at injection area & punctate skin lesions 3rd day: Worsening infection	1st day: -Topical disinfection & antibiotic	NR (Lost to follow-up after 3rd day)
Dominguez *et al.*, 2017[31]	USA	1	NLF	Minutes/Hours: 30 seconds of blurred vision (then, OU vision 20/20), epiphora, blanching of left cheek & upper lip, fine touch & pinprick sensation of left cheek diminished	Hours/Days: -PO anti-coagulant (ASA), vasodilator (sildenafil), & steroid -Subcutaneous anti-coagulant (enoxaparin) -Topical NTG paste -HBOT	Full improvement reported at follow-up (unknown date)
Rocha & Hirano, 2019[32]	Brazil	1	Temples	Minutes: Intense pain & vivid red telangiectatic discoloration Days: Ecchymosis	Minutes: -Hyaluronidase injections, compresses Hours/Days: -PO anti-coagulant (ASA), vasodilator (sildenafil) & steroid	Full improvement reported at follow-up (unknown date)
Uittenbogaard *et al.*, 2019[33]	Nether-lands	1	Unreported facial location	Days: Burning pain, numbness, & white discoloration in injected area	Days: -Hyaluronidase injections, warm compresses -PO vasodilators (sildenafil, nifedipine) & steroid -HBOT (10 sessions)	Full improvement reported at 6-month follow-up
Schelke *et al.*, 2020[34]	Nether-lands	4	Cheek	Skin changes (reticulated blueish pattern with/without pustules & wounds) & doppler-ultrasound images (hypervascular turbulent artery with/without detectable filler blockage) along transverse facial artery	4th hour: -STS injections (250 mg/mL- 0.2 mL/cm^2) x2	NR
			Cheek	Skin changes (reticulated blueish pattern with/without pustules & wounds) & doppler-ultrasound images (hypervascular turbulent artery with/without detectable filler blockage) along transverse facial artery	1st day: -STS injections (250 mg/mL- 0.2 mL/cm^2) x2	NR
			Tongue	Skin changes (reticulated blueish pattern with/without pustules & wounds) & doppler-ultrasound images (hypervascular turbulent artery with/without detectable filler blockage) along submental artery	1st day: -STS injections (250 mg/mL- 0.2 mL/cm^2) x2	NR
			Chin	Skin changes (reticulated blueish	1st day:	NR

				pattern with/without pustules & wounds) & doppler-ultrasound images (hypervascular turbulent artery with/without detectable filler blockage) along infralabial artery	-STS injection (250 mg/mL- 0.2 mL/cm^2) x1	
van Loghem *et al.*, 2020[35]	USA	2	NLF	Minutes/Hours: Erythema & reticulated skin changes of left nasal ala and NLF Days: Vascular necrosis & ischemia	Hours/Days: -Massage & warm compresses -PO vasodilator (sildenafil), antibiotic & antiviral -Topical NTG paste & petrolatum	Full improvement reported at 2-month follow-up
			Nasal bridge & columella	Minutes: Slight blanching of upper lip Hours: Reticulate livedo & cyanosis 1st day: Edema, blue discoloration & decreased sensation 3rd day: Increased edema & burning sensation of upper lip, nose tip numbness	Hours/Days: -Hyaluronidase injections -PO vasodilator (sildenafil) -IV vasodilator (pentoxifylline) -Intramuscular steroid -Topical wound jelly (*Solcoseryl*®) -HBOT (1 session)	Full improvement reported at 2-week follow-up
Williams & Burgess, 2021[36]	USA	1	Cheek & infraorbital region	1st day: Bruising & dull aching pain in right cheek 1st week: Pain, crusted erythematous plaque on right cheek, reticulated non-blanching erythema of right infraorbital region; injected right sclera (OU vision normal)	1st week: -NS rinses -Topical NTG paste -Red light therapy (8 sessions)	Full improvement reported at 6-month follow-up
Our Case	USA	1	NLF	Hours/Days: Severe pain, bruising 1st month: Textural skin changes and scarring	Days: -PO antibiotic & antiviral -Wound care 1st month: -Pulsed dye and non-ablative fractional laser	Some improvement reported at 6-month follow-up

CaHA: Calcium hydroxylapatite; PO: per oral; NTG: nitroglycerin; NLF: nasolabial folds; ASA: aspirin; IV: intravenous; HBOT: Hyperbaric Oxygen Therapy; NR: not reported; OU: oculus uterque (both eyes); STS: sodium thiosulfate; NS: normal saline.

this is thought to be due to a reluctance to report stemming from embarrassment or evidence of poor technique[42]. Unlike the reversal action of hyaluronidase on HA-fillers, CaHA fillers do not have an antidote and severe complications are possibly more likely to occur following inadvertent injections. Therefore, another possible theory is that CaHA complications often require a greater immediate focus on the patient's wellbeing and reporting seems inconsequential at the time. Regardless of the reason, it is important to report complications so wary injectors can stay informed.

Mechanism of CaHA-associated vascular complications

Current consensus suggests that inadvertent injection of CaHA into arterial vessels can result in filler emboli formation and occlusion via retrograde flow against the blood pressure to a point or past the point of vessel branching[1,44]. Subsequent release of syringe pressure allows the patient's blood pressure to reestablish antegrade flow, which potentially can further push the emboli into smaller peripheral vessels[1]. The final resting place of the emboli determines the location and extent of ischemia that occurs. Many factors influencing the etiology and outcome of vascular complications have been suggested. The location selection of the injection is thought to be highly influential in complication outcomes as some facial areas are more vascular and considered at higher risk than other areas[1]. The size of the needles, syringes, and cannulas used for injection has been suggested to influence the risk of vascular trauma[44]. Finally, the

Table 4. Summary of data extracted from search results reporting treatment experiment(s) for vascular complications following calcium hydroxylapatite usage in human cadaver and/or animal subjects included in this review

Author(s), year	Objective	Methods	Results & conclusions
Hwang *et al*., 2016[37]	To evaluate vascular perfusion effects of NTG ointment following filler-associated vascular occlusion & ischemia in rabbit ears	All rabbit ear models were injected with four different soft-tissue fillers to create skin ischemia. After 20 min, models received one of the following: -Application of topical NTG ointment 2% -No treatment to serve as controls Vascular perfusion images using ICG imaging were obtained at baseline, immediately after, & 30 min after filler injection, & again at 30, 60, 90, & 120 min after application of NTG ointment	No statistically significant improvement in perfusion was noted after topical application of NTG with ICG imaging Topical NTG could possibly worsen ischemia as vasodilation could propagate product into smaller vessels. NTG paste also has systemic effects, which some patients may not tolerate
Kreymereman & Miller, 2018[38]	To study efficacy & concentration of intralesional STS for dissolving CaHA particles *in vivo* & to assess any histologic changes	Animal models received intralesional injections of CaHA (0.5 mL/site). Models then received one of the following: -0.25 mL of 25% STS solution injection at 1 h, 24 h, or 7 days after CaHA -0.50 mL of 25% STS solution injection at 1 h, 24 h, or 7 days after CaHA -No STS injection to serve as controls Samples were collected via 5-mm punch biopsy, then stained & examined by light microscopy. A semiquantitative 5-point scale was used to estimate the number of CaHA microspheres present	CaHA particles had the greatest reduction with the 0.5 mL STS doses 1 h after CaHA injection. Reduction was greater with the 0.5 mL STS dose compared to the 0.25 mL dose. Reduction of CaHA particles was less pronounced at 24 h & 7 days after CaHA injection No CaHA-related histologic changes were observed
Robinson, 2018[39]	To determine whether intralesional STS & topical SMB may help dissolve CaHA in porcine skin models	Cadaveric porcine skin models were injected with CaHA (0.4-0.8 mL). Models then received one of the following: -0.2 mL of intralesional STS (12.5 g/50 mL) -1-2 g of topical SMB (25% SMB in 120 mL gel) applied with occlusion -Both intralesional STS & topical SMB -No treatment to serve as controls Samples were collected via 4-mm punch biopsy 24 h after treatment & then stained & examined by light microscopy. A board-certified dermatopathologist estimated the amount of CaHA present in each sample	Intralesional STS alone or combined with topical SMB completely dissolved CaHA in porcine skin models. Topical SMB treatment partially reduced CaHA from tissue samples Intralesional STS alone was as effective as STS & SMB combination, indicating that intralesional STS could possibly be used to dissolve CaHA dermal filler
Danysz *et al*., 2020[40]	To verify previous findings suggesting the efficacy of intralesional STS in the reduction of CaHA volume & nodule formation	*In vitro* → Three systems (glass tubes, human skin equivalent, & human *ex vivo* skin) were each administered CaHA microspheres. Models in each system were then administered one of the following: -Aqua distilled water -Phosphate-buffered saline (PBS) -25% STS -0.1 M ethylenediamine tetraacetic acid (EDTA) solution to serve as controls *In vivo* → Live pig models were injected with 500 μL of CaHA. An hour later, models received one of the following: -1500 μL of STS -1500 μL of saline -No treatment to serve as controls *In vitro* samples were collected after 3 days & *in vivo* samples after 7 days. Samples were analyzed via 3D camera, histopathology, scanning electron microscopy, & computer tomography *in vivo* (CT) & micro-CT *ex vivo*	Results suggest no indication of CaHA degradation by STS, either *in vitro* or *in vivo* Histology, micro-CT *ex vivo*, & CT *in vivo* indicated a decrease in CaHA volumes after STS treatment, which authors attributed to dispersion effect Observed necrosis & hemorrhaging are further obstacles to the use of STS
Yankova *et al*., 2021[41]	To test whether CaHA fillers can be trans-arterially dissolved by STS	Cadaveric → Human cadaveric facial arteries were filled with 0.2 cc of CaHA & submerged in the following solutions:	CaHA was detected after 24 h, independent of the STS concentration. STS & hyaluronidase combined also did not

when evaluated in cadaveric & *in vitro* models	-10 cc STS (300 mg/cc) (pure) -5 cc STS (300 mg/cc) & 5 cc 0.9% saline (1:1 dilution) -3.3 cc STS (300 mg/cc) & 6.6 cc 0.9% saline (1:2 dilution) -5 cc STS (300 mg/cc) & 5 cc 300 IU (bovine) hyaluronidase (1:1 ratio) *In vitro* → 0.5cc CaHA injected directly into the four solutions listed above Samples were collected after 24 h. The cadaveric arteries were dissected and visually analyzed for CaHA product. *In vitro* samples were analyzed via gray-scale imaging	dissolve the CaHA product. Gray-scale analyses from the *in vitro* testing showed that higher STS concentrations resulted in increased disintegration of CaHA Results indicate STS has limited potential to dissolve intraarterial CaHA of cadaveric facial arteries, even though it appears effective when in direct contact with CaHA

NTG: Nitroglycerin; ICG: indocyanine green; STS: sodium thiosulfate; CaHA: calcium hydroxylapatite; SMB: sodium metabisulfite.

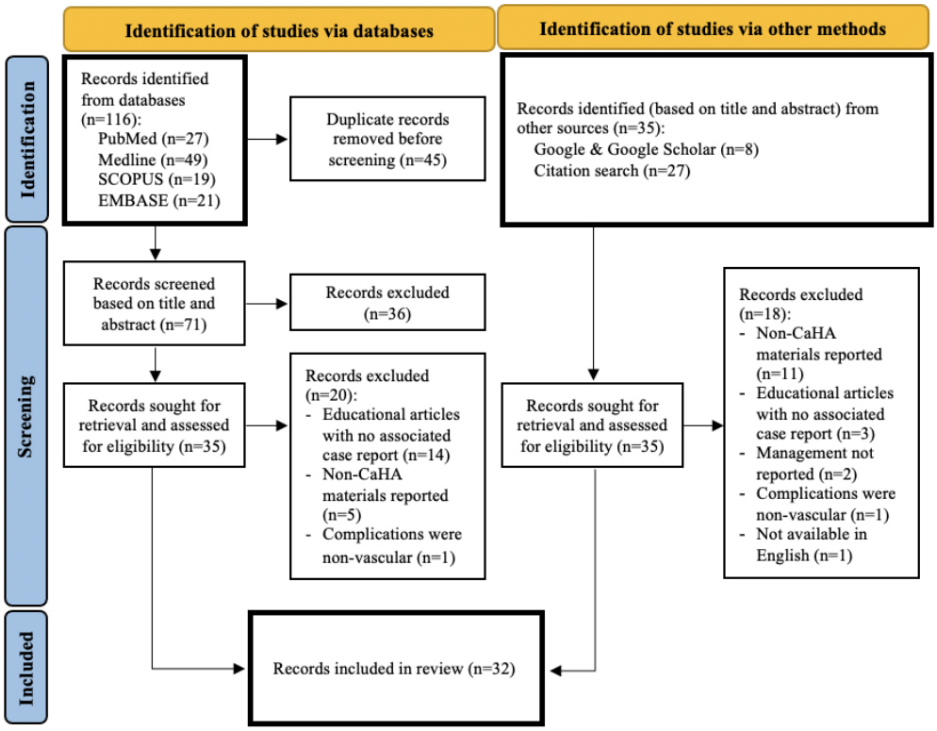

Figure 2. Flow diagram for study screening, selection, and inclusion process based on PRISMA guidelines.

volume, speed, and pressure of the injection are all thought to impact the retrograde flow of the filler and, therefore, the potential extent of vascular compromise[44].

Preventative management

The best management is, of course, prevention. Injectors should have a thorough knowledge of facial and non-facial vascular anatomy, its common variants, and the safest tissue planes for injection. It is highly suggested that injectors regularly attend training courses to learn and practice the safest and most up-to-date injection techniques, in addition to monitoring literature for updates on techniques and management. One example is the growing appreciation for handheld Doppler Ultrasound analysis devices to map the facial vasculature prior to filler injections[45,46]. It is important to note that while the use of technology like this has the potential to supplement anatomical knowledge and training, it should never replace this education.

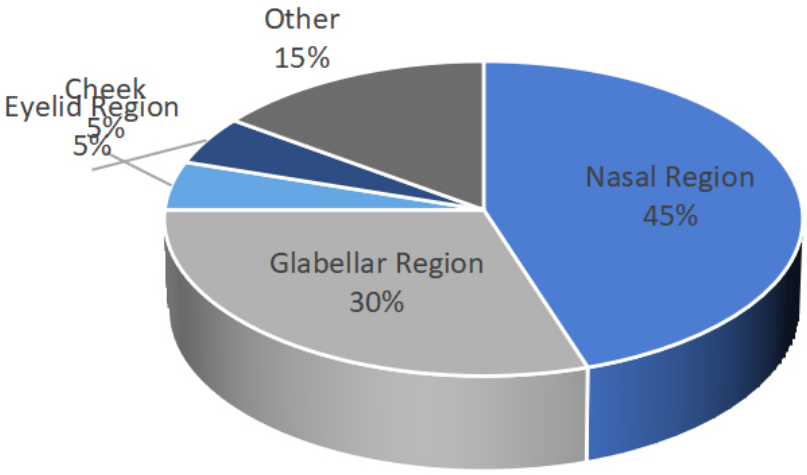

Figure 3. Reported injection locations of calcium hydroxylapatite (percentage; %) extracted from cases of vision-related vascular complications.

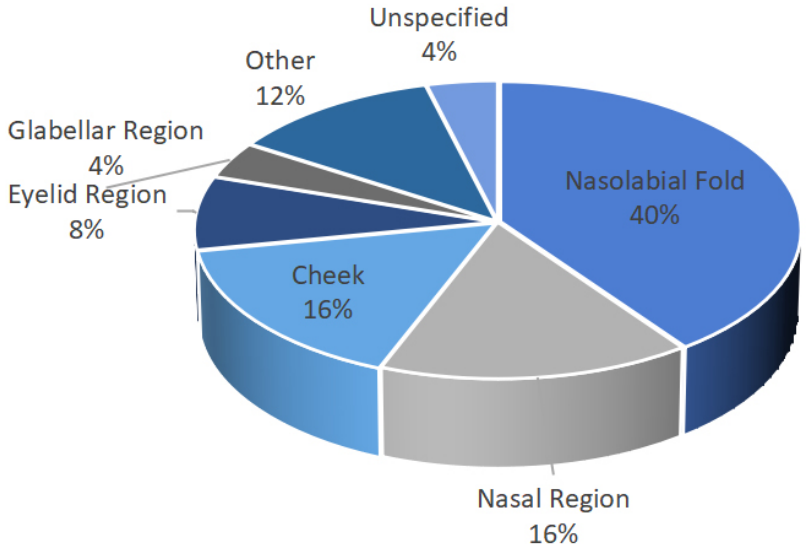

Figure 4. Reported injection locations of calcium hydroxylapatite (percentage; %) extracted from cases of non-vision-related vascular complications.

As evidenced by the cases in this review, all areas of the face have the potential for inadvertent intraarterial injection, but injectors should be particularly wary of high-risk areas when selecting filler placement. Among all 45 reported injection sites reported in the 38 cases, complications were mostly attributed to the nasal region (15 sites, 33%), NLF (10 sites, 22%) and glabellar region (7 sites, 16%). The nasal and glabellar regions are known high-risk areas, but it was surprising to see nasolabial fold in the top three as it is generally considered a safe injection location. Given the FDA approval for CaHA in NLFs, it is likely that there has been a much larger absolute number of injections to NLF compared to other facial areas, and the proportion of NLF-associated complications seems more significant than it really is in this study. Of note, 8 of the 10 NLF-associated cases reported full resolution, one case reported residual bruising at a 2-week follow-up, and one case resulted in visible scarring. CaHA injection in the nasal and glabellar regions is considered high-risk due to the complex vascularity in these facial areas. The angular artery of the nasolabial fold area branches into the dorsal and lateral nasal arteries which supply the nasal region, and the

supratrochlear artery which supplies the glabella. These branches connect to the ophthalmic artery which in turn branches into the central retinal artery, a terminal vessel critical in supplying the retina. This high-risk label for these areas was supported by this review. Fourteen out of the 15 case reports (93%) affecting vision involved the glabella, nasal region, or both. Of those 14 cases, 5 patients (36%) had resolution of vision to 20/25 or better, one patient had worsened vision to 20/60, and 8 patients (57%) were reported to be legally blind or worse.

Best injection practices continue before the needle even pricks the skin. The utility of blunt, flexible cannulas versus sharp needles is thought to minimize intraarterial perforation[47]. Additionally, the size selection of the cannula influences outcomes. Studies found that the force needed to penetrate vessels was greater for most cannulas compared with correspondingly sized needles and significantly decreased with smaller diameter cannulas compared to large diameters[48,49]. In practice, this means that cannulas are considered safer than needles until they are about 27-gauge and smaller, at which point, the cannula is close to the sharpness of a needle[48,49]. It is also thought that the application of a local vasoconstrictor and/or tumescent injection with saline before filler injection can help reduce the risk of arterial puncture and vascular trauma[44,50].

When the needle is finally ready to pierce the skin, it is a common practice and is even encouraged to aspirate before the filler is injected into the skin. While this is widely accepted, it is important to be wary that aspiration is extremely variable in its sensitivity, depending on the gauge and length of tools used, thickness of the filler, and length of time allowed for observation of the aspirate. Therefore, a negative aspirate is no guarantee of safety[51,52]. Injection placement, particularly with cannulas, should not parallel arteries and should not be attempted if met with increased resistance or patient pain. Special caution should also be taken in pre-traumatized areas of skin from past surgery or injury where landmarks and vascular anatomy may be disturbed[44].

Once filler injection begins, it is advised to inject slowly and in small increments[8,42,44]. Smaller injection volumes of filler are thought to be less obstructive and allow blood to bypass via collateral vessels[42]. Injections should also be slow and with minimal pressure exerted to avoid retrograde propulsion of filler emboli into an artery[42,44]. Injectors should actively observe for signs of arterial occlusion, including blanching, mottling, severe bruising, extraordinary pain, evidence of peripheral reperfusion, and/or fluctuations in vision[8,44]. Delayed vision changes and/or pain with or without severe bruising can also be signs of delayed embolization and associated vascular occlusion[8].

Review of post-complication management therapies

Anti-inflammatory agents

Steroids

Steroid medications were a mainstay of vascular complication management. In this review, 24 of the 38 case reports (63%) administered steroids orally, intravenously, topically, and/or ophthalmologically. This class of medication is thought to reduce edema and inflammation in the affected tissues and thus prevent potential worsening of vascular compromise[35,53]. Blood glucose levels should be carefully monitored in diabetic patients; notably, there is no evidence that steroids will positively affect the ischemic outcome[35]. However, if tissue edema is present, there is a strong consensus for a 7-day oral steroid taper with an initial dose of 50-60 mg[31,35].

In the case of vision loss and retinal edema, 1 g intravenous methylprednisolone is a refractory treatment option reported in the literature, but it is usually reserved for inflammatory artery occlusions and there is no

evidence of its positive effect on ischemic outcomes[53]. Notably, 11 of the 15 vision-related case reports (73%) administered steroids with outcomes ranging from full vision restoration to worsened vision. In cases of retinal ischemia, steroid administration is not recommended in ocular cases without the input of an ophthalmologist.

Sodium thiosulfate

STS has been found in some studies to effectively treat calciphylaxis via its anti-inflammatory, calcium-chelating, and vasodilatory properties[54]. It can be applied directly intradermally or intravenously into the skin lesions of hemodialysis-dependent patients within the last 30-60 min of hemodialysis. When SRS is administered via hemodialysis, common adverse effects include nausea, metabolic acidosis, volume overload, and hypocalcemia[54]. Given its calcium-based composition, it has been theorized that STS injections could potentially degrade CaHA into smaller subparts[39]. Four cases of vascular dermal ischemia following CaHA treated with only STS injections in the Netherlands were included in this study[34]. Unfortunately, individualized results were not reported by the authors, so the estimated efficacy of STS could not be determined from these cases[34]. Four experimental studies addressing the effects of STS on CaHA fillers were also included in this study[38-41]. Two of these studies were published in 2018 m and both concluded that STS was capable of partially or completely reducing CaHA volume in animal models. The other two studies published their data more recently in 2020 and 2021 and found that STS did not appear to dissolve any CaHA product in their various experimental models. In fact, one of these studies even concluded that observed necrosis and hemorrhaging are further potential obstacles to the use of STS[40]. Without further research into the efficacy and dosage of STS, it is not recommended to use the following intraarterial CaHA injection at this time.

Anti-coagulant/Thrombolytic agents

Acetylsalicylic acid (aspirin)

Aspirin assists in fibrinolysis by limiting platelet aggregation and clot formation[8,31,35]. An immediate dose of 650 mg is recommended, followed by a maintenance dose of 75 mg a day for 3-5 days[8,35]. Aspirin should be given with a prophylactic antacid such as esomeprazole 40 mg to prevent the most common side effect of gastritis and esophagitis associated with aspirin[8,31,35]. Its use is contraindicated with the concurrent use of enoxaparin[31]. At least one dose of aspirin was used in 14 of the 38 case reports (37%). Doses in many of these cases were not reported, and patient outcomes were different. Given its low cost, easy accessibility, and minor side effects, an initial dose of aspirin is recommended for immediate use following vascular occlusion. It is not recommended to use this as monotherapy. Dosage and time of administration should be carefully documented, particularly in cases with ocular symptoms where care will be emergently transferred to an ophthalmologist. A maintenance dose is recommended in cases of persistent dermal compromise.

Low molecular weight heparin

Low molecular weight heparin (LMWH), such as enoxaparin, has been suggested in previous filler occlusion protocols because it is thought to reduce further thrombus formation and minimize necrosis[29]. If aspirin therapy is not available or contraindicated, an initial dose of LMWH should be injected within four hours of the intra-vascular event[35]. If vascular occlusion persists, subsequent dosing of subcutaneous enoxaparin 30mg twice a day for 7-14 days is recommended[31]. Enoxaparin was used in two case reports: one ocular complication[18] and one dermal complication[31]. Interestingly, these two cases treated their patients with both aspirin and enoxaparin. Although this duo-therapy is considered contraindicated, the exact timing of medication administration was not reported and could explain the choice of co-treatment. There is not enough evidence to recommend LMWH as a standard treatment; therefore, its use should only be considered when aspirin is contraindicated[8].

Treatments that increase blood oxygen

Hyperbaric oxygen therapy

HBOT increases the partial pressure of oxygen delivery, and it is thought that this mechanism of action aids in increasing oxygen to ischemic tissue until reperfusion occurs. While exact pathogenesis and its efficacy are still being discussed, there is still literature that endorses that HBOT has an excellent track record in treating tissue and wounds with compromised blood supply[53,55]. The recommended dosing is 45-minute sessions at 3 atmospheres of pressure once or twice a day for up to two weeks[31]. Seven vision-associated cases and five non-vision-associated cases utilized HBOT as part of their various treatment "cocktails" with various outcomes. Further, there was no consistent reporting of the length, atmospheric strength, number, and timing between sessions. If available, HBOT has the potential to supplement other treatment modalities, but it is not recommended to be used in isolation.

Phosphodiesterase type 5 inhibitors

Phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil and tadalafil inhibit the PDE5 enzyme which increases cyclic guanosine monophosphate (cGMP) levels and causes vascular smooth muscle relaxation[56]. As with all vasodilatory agents, it is thought this could help dislodge emboli and increase oxygenation perfusion to ischemic tissues[35,53]. A dose of sildenafil 100 mg or tadalafil 20 mg for 7-14 days is recommended[31]. Common side effects of PDE5 inhibitors include headaches, flushing, hypotension, dizziness, and rhinitis[56]. An absolute contraindication to PDE5 inhibitor use is the concurrent use of nitrates or nitroglycerin[56]. Six cases, all non-ocular dermal complications, reported usage of sildenafil. Five of the cases reported outcomes of full improvement and the final case reported residual bruising at their two-week follow-up. Sildenafil was not used as monotherapy in any of these case reports, nor were the dosages reported. Therefore, its true influence on ischemic tissue can be established. Given its potential effectiveness, it is recommended to consider PDE5 inhibitors in cases of dermal ischemia. For ocular ischemic events, it is recommended to consult an ophthalmologist for guidance.

Prostaglandin E1 analogs

Prostaglandin E1 (PGE1) analogs such as alprostadil achieve vasodilation by increasing cAMP production which in turn reduces intracellular calcium levels[57]. PGE1 analogs are commonly used to treat erectile dysfunction and ductus arteriosus, but antidotally, they have been thought to be an effective adjunct treatment in cases of retinal artery embolism[42,57]. When injected intravenously, common side effects include flushing, apnea, fever, hypotension, and heart rate changes[57]. Given its potency, careful monitoring is recommended with systemic usage[42]. Alprostadil was reported in two case reports, both of which involved ocular complications[2,16]. Neither case utilized alprostadil as a monotherapy and reported varied outcomes. With the evidence currently available, PGE1 analogs are not recommended for vascular occlusion therapy.

Calcium channel blockers

Comparable to PGE1 analogs, Calcium channel blockers (CCB) such as nifedipine directly inhibits calcium channels in smooth muscle cells, which reduces intracellular calcium levels and causes vasodilation[58]. Common adverse effects include flushing, peripheral edema, dizziness, and headaches, and it is contraindicated in patients with a previous ST-elevation myocardial infarction[58]. The use of nifedipine was used in only one case report reported from the Netherlands[33]. Given the lack of supporting evidence, CCB are not generally recommended following CaHA-associated vascular occlusions.

Nitroglycerin

Nitroglycerin (NTG) is a medication that causes vascular smooth muscle relaxation by stimulating intracellular cyclic guanosine monophosphate (GMP). Sublingual NTG, in the form of isosorbide dinitrate,

has been used in cases of central retinal artery occlusion, while topical NTG paste has been studied for its effectiveness in reducing tissue ischemia[53]. Common side effects include headache, hypotension, tachycardia, dizziness, and flushing, and contraindications include severe anemia and the recent use of phosphodiesterase inhibitors[53]. Twelve of the 28 case reports (43%) reported using topical NTG paste. There were varied outcomes in 11 of the cases that used NTG paste paired with other treatment modalities, but one case used NTG paste as the only treatment of suspected impending tissue ischemia of the nose and resulted in complete resolution[25]. One of the animal studies evaluated topical NTG ointment and found no statistically significant improvement in perfusion following filler-induced ischemia[37]. In fact, they reported that the NTG tended to worsen perfusion and cause further circulatory compromise[37]. Despite the occasional positive outcome, the authors conclude that topical NTG has not yet been determined to be beneficial and therefore should not be utilized following CaHA-associated occlusions.

Of note, none of the case reports in this review utilized sublingual NTG in their management plans despite its potential effectiveness seen in central retinal artery occlusion from other thromboembolic events[59]. Given the poor vision prognosis of CaHA-induced central retinal artery occlusion, administering sublingual NTG should be considered when there are no contraindications.

Pentoxifylline

Pentoxifylline is a xanthine derivative that increases tissue perfusion by increasing red blood cell flexibility and reducing blood viscosity[53]. This medication treats peripheral vascular disease and has been previously thought to help reperfusion in central retinal artery occlusions. This medication is contraindicated if the patient is allergic to theophylline or caffeine and has many potential side effects. This medication was used in only two case reports in this review. Both cases had suspected impending skin necrosis and, after multi-modal treatments, had made a full recovery. More research is needed on pentoxifylline's efficacy on impending skin necrosis. For ocular complications, recent guidelines have stated that there is more evidence of potential harm than benefit and, therefore, support not using pentoxifylline in treatment management[60].

Carbogen inhalation

Increasing carbon dioxide levels in the patient's blood are usually achieved by having the patient re-breath from a paper bag. It is thought that the increased carbon dioxide levels will cause arterial vasodilation and, in the case of retinal occlusion, potentially dislodge the arterial blockage and help restore oxygenation[35,53]. Administration guidelines recommend conducting carbogen inhalation for ten minutes every hour during the day and every four hours during sleeping hours for up to three days post-occlusion[53]. This treatment modality was only utilized in one case report included in this review. The authors described a patient with vision loss to hand motion in their left eye following CaHA injection to the glabella[15]. Following a multi-modal treatment approach, they reported vision improvement to 20/200. With the currently available evidence, carbogen inhalation has the potential to supplement other treatment modalities, but it is not recommended to be used in isolation.

Tissue massage and/or warm compress

Tissue massage and warm compresses may help break up vascular blockage and increase vasodilation[35,42]. Six of the 38 cases (16%) reported using tissue massage and/or warm compresses. One case reported tissue massage[27]; four cases reported using warm compresses[18,26,32,33]; and one case reported using both massaging and compresses[35]. Literature also mentions that tapping over the injection area can possibly dislodge the intra-arterial emboli and help propagate the emboli, but this specific technique was not mentioned in any of the case reports of this review[8]. Given the subjective descriptions and unknown efficacy of these therapies, massaging and warm compresses should never be used as a monotherapy.

Treatments that reduce intraocular pressure

Ophthalmic glaucoma drops

Glaucoma eyedrops aim to lower intraocular pressure, increase perfusion pressure, and allow for any emboli to dislodge further downstream[44,53]. There are a few mechanisms of action that can achieve these results. Beta-adrenergic blockers and carbonic anhydrase inhibitors decrease aqueous humor production, while prostaglandin analogues and alpha-agonists work by increasing humor outflow[53]. Use of timolol 0.5% (beta-adrenergic antagonist) and brimonidine 1% (alpha-2 adrenergic agonist) are the most common medications described in the literature[61]. The use of glaucoma eye drops was described in 5 of the 15 ocular complication cases (33%), but once again, the details, such as the number of drops and duration of use, were not consistently described. Further, ophthalmic drops have a slow onset of action compared to systemic medications and therefore are unlikely to have a significant influence on the initial stages of recovery[53]. If available, in-office administration of an ophthalmic glaucoma agent is recommended until the patient can be transferred.

Acetazolamide

Acetazolamide is a carbonic anhydrase inhibitor that reduces aqueous production in the eye, which in turn reduces the intraocular pressure and increases retinal blood flow[53]. It is usually administered intravenously as a short-term therapy. Side effects include gastrointestinal upset, electrolyte imbalance, urticaria, tinnitus, and rarely, nervous system dysfunction and hematological dyscrasias[53]. Contraindications include hypokalemia, hyponatremia, sulfa allergy, and liver or renal disease[53]. When contraindicated or unavailable, intravenous mannitol can be considered an acceptable substitute. Two case reports, both with ocular complications, utilized acetazolamide in their treatment regimen[14,17]. The cases reported administrating acetazolamide within hours of the occlusive incident, but dosages were not given, and both cases reported no vision improvement at follow-up. Despite the two unfavorable outcomes in this review, a systemic dose of acetazolamide 500 mg is still generally recommended once the patient is transferred to the hospital or an ophthalmologist[61].

Ocular massage

With proper technique, ocular massage produces fluctuations in intraocular pressure which theoretically results in enough intraocular pressure reduction to allow emboli to dislodge and improve retinal artery perfusion[35,53,60]. The patient should be positioned in a supine position, looking down with their eyes closed and the technique involves rapidly applying enough digital pressure to indent the front of the eye by a few millimeters[35]. This action should be continued for at least 1-3 h or until the patient reaches an ophthalmologist[35]. The ocular massage was reported as a co-therapy in 3 of the 15 ocular complication cases (20%)[15,18,22]. Unfortunately, its influence on the complication outcomes cannot be elicited due to its use as a co-therapy and the lack of technical details described in these reports. Additionally, no study has confirmed the positive effects of ocular massage, despite over a hundred years of documented use[60]. For these reasons, ocular massage can be considered but should not be used as monotherapy following ocular vascular occlusions.

Anti-microbial agents

Antibiotics

At least one type of antibiotic was used in 17 of the 38 case reports (45%). Antibiotics were administered orally, intravenously, topically, and/or ocularly, depending on the presenting complication. Most cases described using antibiotics as a prophylactic treatment when skin breakdown, ulceration, and/or necrosis were present. As antibiotics do not directly influence the healing of ischemic tissues and superinfection is very unlikely, their use is not recommended when the clinical picture of ischemic tissue suggests a favorable

course[35]. In cases of severe skin compromise and necrosis, there is a higher risk of opportunistic infection, and therefore, prophylactic systemic antibiotics such as ciprofloxacin or clarithromycin are recommended[8,35]. Unless there is significant ocular surface damage, there is no evidence supporting the use of ophthalmic antibiotic drops in cases of ocular ischemia. If uncertain, the discretion of its use should be left to an ophthalmologist.

Antivirals

Antiviral medication was used in 6 of the 38 case reports (16%), all of which only described dermal complications. All six cases used antivirals as a prophylactic treatment. Literature concurs that prophylactic acyclovir is an appropriate choice in at-risk patients with impending or known necrosis[8,31]. A dose of 800 mg per day until the skin is epithelized is considered appropriate. Patients are considered at-risk if they are immunocompromised, have a history of herpetic infections, and/or necrosis is spread in a perioral distribution[8].

Wound and scar care

Open wound care

Thirteen of the case reports (34%) reported administering various open wound care treatments to their patients. Described wound care treatments included emollient topicals and/or antiseptics, but a few case reports simply reported "wound care". Six of the 38 cases (16%) utilized normal saline rinses or washes in their treatment regimen. Two of these six cases used some other type of wound care described prior, while the other four cases did not. With any open wound, it is strongly recommended to keep the area moist with occlusive dressings with debridement as needed.

Interestingly, eight cases (21%) administered hyaluronidase flushes despite no evidence that hyaluronidase can break down or dissolve CaHA fillers. It is thought that hyaluronidase has been used in non-hyaluronic filler incidents for its edema-reducing and anti-inflammatory properties[35]. For ischemic events involving skin tissue, a dose of 600 units of hyaluronidase per 0.1 mL CaHA is recommended right after the event and every two hours up to four cycles if no improvement is seen[35]. For ocular ischemic events, there is no known evidence or consensus that hyaluronidase would aid in ischemia reversal; therefore, its usage is not recommended without the consultation of an ophthalmologist.

Closed wound care

Even if early reperfusion is achieved, significant skin compromise may still occur. Patients may develop a prominent reticular or livedo pattern and may progress to develop necrosis. If the tissue is not compromised, early use of pulsed dye laser and/or red (640 nm) light emitting diode (LED) therapy can be used to decrease inflammation and promote wound healing[35]. One of the authors (Welsh KM) has found that utilizing these treatments as soon as two days after arterial occlusions of hyaluronidase fillers has resulted in timely and satisfactory resolution and may be applicable to CaHA-associated complications[35].

Despite proper wound care, the healing process of skin often results in scar formation which can be a traumatic burden to the patient[35]. At this stage, treatments such as microdermabrasion, pulsed dye laser, non-ablative fractioned laser resurfacing, and fractionated laser resurfacing can be used monthly to improve texture and scarring[35]. Seven of the ischemic skin complication cases reported using at least one type of microdermabrasion or laser treatment, of which five cases reported complete resolution. The timing of follow-up and the extent of skin damage may explain these varied outcomes. Although not used in the case reports of this review, topical treatments such as growth factors and vitamin C should also be considered to supplement laser treatments[35]. Early and consistent intervention is recommended for best results. It is also

important to advise the patient that underlying collagen production is a slow process and satisfactory results may take 10-12 months to achieve[35].

Summary of management recommendations

There is not a gold standard for treating vascular complications following CaHA injections. While prevention is the best strategy, it is also important to have a management plan prepared to quickly respond to these potential complications. The timing of management could mean the difference between recovery and a permanent deficit. As a result, this review presents the following management recommendations derived from the findings of this review, current literature[31,35,44,61-63] proposed protocols for HA-associated intraarterial occlusions[8], and the authors' personal experiences.

Skin tissue ischemia: discoloration, mottling, extraordinary pain, etc.

1. If acute, stop the injection and attempt aspiration before withdrawing the needle

2. Assess capillary refill time by gently compressing the skin of the affected area for 5 s

    a. normal refill time is 3-4 seconds or less

    b. If refill time is greater than 4 seconds, proceed to the next steps

3. Administer the following as soon as possible:

    a. Apply warm compresses and gently massage the area for 5 minutes every hour

    b. Flood the area with hyaluronidase 600 units per 1cc of CaHA injected

        i. If reperfusion is not noted, repeat every 2 h up to 4 times

    c. Administer the following as soon as possible:

        i. Oral aspirin 500-650 mg plus antacid (If contraindicated, consider subcutaneous LMWH)

        ii. Oral prednisone 50-60 mg

        iii. Oral pentoxifylline 40 mg

        iv. Oral PDE5 inhibitor 20 mg

4. If circulation is restored, follow-up weekly up to 4 weeks

    a. If vascular compromise persists or is delayed, proceed to the next steps

5. Continue treatments:

a. Oral aspirin 75 mg daily for 3-5 days

b. Oral prednisone taper over 7 days

c. Oral PDE5 inhibitor 20 mg for 3-5 days

d. Wound care and debridement as needed

6. Consider supplementing with the following:

a. HBOT 1-2 sessions per day up to 10 days

b. Topical and systemic antibiotics

c. Antivirals (especially if the patient has a history of Herpes simplex)

d. Red LED light as soon as 2 days after event

e. Bipolar radiofrequency, microdermabrasion, and/or laser resurfacing treatments for scarring as needed

Retinal ischemia: vision loss, ocular pain, etc.

1. If acute, stop the injection and attempt aspiration before withdrawing the needle

2. Immediately prepare transport to a hospital or known ophthalmologist - there is an approximate window of 60-90 min for recirculation before permanent vision loss

a. Document visual acuity for each eye, injection time, product(s) used, injection site(s), volume administered, and any in-office medications administered

3. Until transfer:

a. Apply firm pressure to the affected eye(s) for 10-15 s, then release for 3-5 s, repeat until transfer

b. Carbogen rebreathing with paper bag

c. Administer oral aspirin 650 mg plus antacid (If contraindicated, consider subcutaneous LMWH)

d. Administer 2 drops to the affected eye(s) of either ophthalmic Timolol 0.5% OR Brimonidine 1%

e. Consider sublingual NTG

4. In hospital:

a. Intravenous (IV) dexamethasone 1 g

b. IV acetazolamide 500 mg

c. Consider:

i. Central nervous system (CNS) imaging

ii. Systemic anti-coagulant

iii. IV prostaglandin E1 analog

iv. Within the first 8 h, a 90-min session of HBOT at 3 atm

v. Retrobulbar flush of hyaluronidase 2-4 mL (150-200 units/mL)

vi. Anterior chamber paracentesis

vii. Neodymium: yttrium-aluminum-garnet (Nd-YAG) laser

5. Discharge:

a. 1-2 drops to the affected eye(s) 4 times a day for 7 days of ophthalmic Timolol 0.5% OR Brimonidine 1%

b. Consider:

i. Oral aspirin 75 mg daily for 3-5 days

ii. HBOT 1-2 sessions per day up to 10 days

iii. Ophthalmic antibiotic drops

6. In addition to ophthalmology, consider consulting neurology and plastic surgery

7. Follow-up with the patient for dermatological care as needed

Limitations

There were many limitations to this systemic review. There was no homogeneity in the presentation, management, or follow-up time of the case reports and the experimental studies. In the cases with visual complications, a few did not report the initial visual acuity of their patient, and fewer authors reported data that indicated a basic eye examination was completed. Thus, this review could not infer a cause-and-effect relationship, a common limitation with descriptive studies. Lastly, these findings cannot be generalized as the information generated from these case reports is not representative of the entire population.

In conclusion, vascular complications following CaHA injections are seemingly rare but often associated with devastating outcomes. There is no gold standard for treating CaHA-associated complications, and even though this review outlines recommendations, there is no known universally effective management plan for these complications. Preventative measures remain the best practice. When vascular occlusions do occur,

early recognition and prompt treatment are paramount to minimizing consequences. If there are any ocular symptoms following CaHA injections, immediate referral to an ophthalmologist is highly recommended.

DECLARATIONS

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Authors' contributions

Made substantial contributions to the concept of this article; the acquisition, analysis, and interpretation of data for this article; and the drafting of this article: Lindgren AL, Welsh KM

Availability of data and materials

The data that support the findings of this study were derived from resources detailed in the text. The details of these resources are available in the "References" section of this text and can be sourced from PubMed, Medline, SCOPUS, EMBASE, Google Scholar and/or Google search engine. Additionally, data are available from the corresponding author, Welsh KM, upon reasonable request.

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Conflicts of interest

Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The authors made every effort to ensure the best possible quality, integrity, and impartiality of the information in this review. The authors discussed and mitigated risks and potential harm to the human participant referred to in the case report. The authors respect the confidentiality and anonymity of the included participant, ensured participation was voluntary, and obtained informed consent to be included in this text from the participant.

Consent for publication

Informed, voluntary consent was obtained from the included patient for use of the information and materials (such as photograph) included in this review.

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