INTRODUCTION

Hyaluronic acid (HA) cosmetic injection is a minimally invasive and nonsurgical, rejuvenating therapy used in China and overseas. It is effective and nonsurgical and significantly reduces downtime. HA could be used as a soft tissue filler given its glycosaminoglycan structure, which promotes water retention and consequently volumizes and outlines the skin contour. With the rapidly growing application of HA injections, the numbers of reported cosmetic injection complications have also incrementally increased. The incidence of HA embolism has increased markedly in recent years. HA embolism can lead to serious complications such as blindness, eye and eyelid movement disorders, skin necrosis, and cerebral embolism. However, there is a lack of robust clinical evidence regarding the benefits of treatment of HA embolism with intra-arterial thrombolytic therapy (IATT).

METHODS

In the present study, we enrolled 45 patients with decreased visual acuity, including 40 patients with symptoms of vision loss and eight patients with symptoms of intracranial embolism. The patients underwent emergency IATT via hyaluronidase and papaverine injections, followed by conventional sequential therapy.

RESULTS

In the 45 patients with symptoms of vision loss, 16 (36%) exhibited improvements in final visual acuity, even when the clinical application of the thrombolytic treatments was performed beyond the recommended window for optimal treatment. The facial skin necrosis of all patients was restored to near normal appearance. Notably, for eight patients with suspected symptoms of intracranial infarction we performed cerebral angiography and IATT, and in two patients obtained partial recanalization of the obstruction, the symptoms of heavy headache and binocular distension pain were improved in one patient with intracranial embolism after IATT treatment.

CONCLUSION

Our results indicate that IATT is feasible for patients with vision loss induced by HA embolism. IATT combined with conventional sequential therapy was beneficial in the recovery from other serious HA embolism complications. Nevertheless, the underlying pathophysiological mechanism needs to be clarified in future animal experiments.

KEYWORDS
artery occlusion, HA injection complication, intra-arterial thrombolytic therapy

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increased. Although localized injection site reactions may be temporary, skin ecchymosis, edema, local pain, and even severe complications have persistently been reported. Among these complications, arterial occlusion (shown in Figure 1) is a rare but devastating condition that can lead to skin necrosis or blindness, or even intracranial embolism. Unless it is managed appropriately, the resulting vision loss might be irreversible. Intra-arterial thrombolytic therapy (IATT) is regarded as a viable treatment strategy for vessel embolism and is considered an appropriate option for treating the complications of HA injections. In the current study, we aimed to evaluate the efficacy of IATT in cases with HA facial cosmetic injection embolisms. Therefore, we retrospectively reviewed the cases of 45 patients with severe vision loss, ocular motility disorder, ptosis, and skin lesions, along with intracranial embolism attributed to HA facial cosmetic injections. All the patients received emergency IATT on admission. In this study, we assess our treatment methods along with the associated efficacy, in order to better manage the serious complications caused by HA facial injections.

2 | METHODS

We retrospectively reviewed the case history of patients diagnosed with ophthalmic artery and/or retinal artery occlusion on account of cosmetic facial HA injections, and who underwent IATT along with transfemoral cerebral angiography at our department of hospital between January 1, 2017, and December 31, 2018.

We performed MRI and CT to exclude intracranial infarction or hemorrhage prior to IATT. Shortly after strict control of IATT contraindications, such as hypertension, coagulopathy, intracranial and external hemorrhaging, and obtaining written informed consent, it was considered for the majority of patients who presented within 24 h after symptom onset.

After a particular ophthalmologic testing, a microcatheter was inserted into the femoral artery, and digital subtraction angiography (DSA) along with IATT was performed. In brief, DSA was performed at the proximal bifurcation of the internal and external carotid arteries with a DSA angiography machine, and IATT was subsequently performed after written informed consent was obtained. DSA was performed in the proximal part of the internal and external carotid artery bifurcation by using an angiography machine (Philips, FD20). After ocular artery dysplasia was detected, a microcatheter (Stride 2.6-Fr, ASAIHI, INTECC; the swan neck catheter and Carnelian 1.8 catheter in wheat Ruitong Ltd.; TOKAI MEDICAL, PRODUCTS, INC.) was placed in the proximal part of the ophthalmic artery, and a thrombolytic agent (hyaluronidase) and vasodilator (papaverine) were slowly injected with mechanical disruption with a micro-guidewire (Streaming 0.14, 0.18 microguidewire, ASAHI INTECC) to distally dislodge the emboli. The hyaluronidase dose ranged from 500 units and 1500 units, whereas the papaverine dose ranged up to 30 mg. We retrospectively analyzed patient demographic data and clinical features, in light of the DSA images. We performed cerebral angiography by localizing the embolic obstruction site on the ophthalmic angiogram; subsequently, the pattern of distal angiographic runoff was labeled with an external carotid angiogram, in accordance with the skin necrosis lesion.

Following HA embolization, the patients were promptly administered oxygen via inhalation. Multi-layered hyaluronidase injections were put into effect at the primary embolism area to dissolve the HA that was stacked under the skin and to reduce the local tension. Moreover, vacuum sealing drainage dressing was used in the patients who had facial skin wounds on the cutaneous necrosis, significantly promoting repair of the wounds. Expectant treatments were performed: glucocorticoid pulse therapy (methylprednisolone sodium succinate [1000 mg, ivgtt [>30 min], q.i.d., 3 days) treatment for edema (mannitol, 125 ml [25 g], ivgtt, q6 h; Melilotus extract tablet, 50–100 mg, po, t.i.d.); and neurotrophic treatment (mouse nerve growth factor for injection, 20 μg, qn; mecobalamin injection, 0.5 mg, ivgtt, q.i.d., 90 days). A few individual patients received postfrontal injection depending on their specific conditions (20 mg tobramycin and 2.5 mg dexamethasone). Moreover, the compound anisodine hydrobromide (2 ml, q.i.d.) was injected in the temples. According to the degree of conjunctival edema, prednisolone acetate eye drops, levofloxacin, and deproteinized calf blood extract eye gel were selectively used. Scavenging of oxygen radical treatment used edaravone. Patients with intracranial vascular embolism, as detected via MRI, were administered edaravone to remove the oxygen free radicals, butylphalide to protect the mitochondria, and dehydration treatment with glycerin fructose to

FIGURE 1 Schematic drawings of the vascular anatomy with the ophthalmic artery and its branches. The yellow lines indicate the optic nerve and posterior wall of the eyeball. The presumed injection content level is shown as a solid round (HA)
reduce cranial pressure. Most patients could not adapt to the convalescence of visual impairment, insomnia, and other depressive symptoms, and hence, the psychological team administered drugs and other psychological interventions. The patients were followed-up for 1 month to 1 year (mean follow-up: 3 months).

3 | RESULTS

3.1 | Demographics

In this study, we included 45 patients with HA occlusion of the ophthalmic artery after cosmetic facial injection, including 39 young women and six men (mean age, 26 years). All 45 patients had impaired unilateral and bilateral vision (right eye in 10, left eye in 22, and both eyes in 3). The nasion area was the most common injection site of HA (49%, 22/45), which give rise to ophthalmic artery occlusion. The second common site was the frontal area (42%, 19/45), followed by the glabella (n = 2), and temporal area (n = 1). 83% (20/24) patients did not receive immediate IATT after embolism occurred, but received treatment with vasodilatory agents, glucocorticoid therapy, or neurotrophic drugs in the other hospital. They had no significant improvement in visual acuity. However, eight patients with intracranial embolism presented to our hospital directly following symptom onset, and received emergency IATT and cerebral angiography along with other symptomatic treatments.

3.2 | Clinical manifestations

In total, 89% (40/45) patients presented with sudden visual loss immediately and ophthalmodynia during HA injection, along with the inability to open eyes, dizziness, nausea, emesis, severe headache, and skin numbness. Moreover, 18% (8/45) of patients showed intracranial infarction on cerebral angiography. As for visual acuity deficit, 25 patients exhibited ablepsia (no light perception [NLP]) during their first presentation at our hospital. However, four patients did exhibit light perception (LP). All patients exhibited mydriasis with a pupil diameter >5 mm and exhibited ptosis. Forty-one patients presented with ocular motility disorders. In particular, 43 patients showed skin lesions in the corresponding region of artery occlusion, which manifested as pale, piebald, or necrotic. Of concern, 68.89% (31/45) of embolized patients received hyaluronic acid injection before and after menstruation or even during menstruation.

3.3 | Analysis of the therapeutic effect of IATT

Following IATT, the recanalization of the ophthalmic artery and its branches could be clearly observed on DSA (Figure 2). Meliorative retinal blood supply and arterial recanalization were observed via fundus color photography (Figure 3). Moreover, visual acuity of 36% (16/45) of patients was immediately improved after IATT. The visual acuity of these 16 patients continued to improve following sequential comprehensive treatment. In addition, IATT significantly improved skin necrosis and skin ecchymosis, and normal skin appearance was restored in all patients. A few superficial scars remained in some patients.

3.4 | Intracranial embolism and hemorrhage after recanalization

Intra-arterial thrombolytic therapy and cerebral angiography were performed in eight patients with intracranial infarction. Table 1 summarizes the demographic characteristics, clinical characteristics, and cerebral angiography results of these patients. The patients were
mostly female and young (average age, 26 years). They received facial fillers in the glabella area and/or the dorsum of the nose for rhinoplasty. All the patients had diffuse occlusion, including complete occlusion of the ophthalmic artery or branch occlusion. Skin necrosis was noted in six of eight patients after HA injection, and all patients were treated with hyaluronidase injection subcutaneously without any severe skin scarring. All the patients presented to our department within 10 h after symptom onset and underwent IATT on the same day. However, the outcomes of thrombolysis were unfavorable, as only two patients underwent partial recanalization of the obstruction (Table 1). Moreover, the visual acuity was not objective in the end, because, in the final evaluation, five patients had NLP, two had LP, and one exhibited perception of hand motion (HM).

In one patient with intracranial embolism after IATT treatment, the symptoms of heavy headache and binocular distension pain had improved, although fundus examination in this case exhibited poor retinal vascular development. After 2 days, the patient was again treated with IATT, and the clinical symptoms had alleviated. After 3 days, the patient experienced paroxysmal headache and progressive aggravation, and emergency head CT indicated multiple cerebral hemorrhages on the left side of the frontal, parietal, and temporal area (Figure 4A,C,E), as well as <5 ml of bleeding and no marked deviation of the midcourt line. Therefore, conservative treatment with moderate dehydration, fluid infusion, and nerve nutrition support therapy was administered, and CT showed stable hemorrhagic focus after 3 days and absorption of the hemorrhagic focus after 1 week (Figure 4B,D,F).

3.5 | Typical case

One of the patients underwent HA injection in the nasion for rhinoplasty, and after 26 h, she received IATT for HA embolization. Her initial thromboembolic symptoms included intense pain in the left eye, nausea, and vomiting. She arrived at our hospital with severe symptoms. Her left vision acuity had decreased to LP 15 min after the HA injection. Moreover, her left eye exhibited complete ptosis, eyeball fixation, conjunctival hyperemia, and edema. In addition, skin ecchymosis was clearly seen in the frontal area, root of the nasal area, and under the left eyelid (Figure 5A,B), and skin necrosis was noted in the zygomatic facial area (Figure 5C). We immediately performed IATT and general sequential therapy. The patient’s headaches and ocular discomfort improved immediately after treatment. Finally, her visual acuity improved from LP to normal (vision acuity: 1.0). In addition, no ptosis of the eyelid was observed after IATT, and conjunctival edema had recovered. Ocular motility disorders had recovered with slight strabismus. The skin lesions were completely healed and only superficial scars remained (Figure 5D).

4 | DISCUSSION

Although the reported incidence of intra-vascular complications of HA injection procedures has been increasing, the incidence may be even higher due to potential underreporting as a result of legal concerns. The most critical complication in these cases is blindness or even hemiplegia due to the facial HA injection. Hayreh et al indicated that the retinal circulation needs to be restored within 60–90 min to prevent total blindness. The onset time of IATT thrombolytic therapy after HA injection and the degree of vascular embolism were associated with a higher likelihood of vascular recanalization and vision improvement, both of which are important prognostic factors. IATT helped increase the blood supply to the ophthalmic artery and aided in the recanalization of the peripheral branches. Our previous study confirmed that patients experienced long-term embolization (≥26 h) before IATT even though they ultimately showed...
| No. | Age | Sex | Eye | Site    | Dose | Diagnosis | Skin Necrosis | MRI Brain | Findings                      | Time to IAT | Thrombolysis                                      | Pupillary reaction baseline/final | Visual acuity baseline/final | Follow-up Period |
|-----|-----|-----|-----|---------|------|-----------|--------------|-----------|--------------------------------|-------------|-------------------------------------------------|-------------------------------|--------------------------|------------------|
| 1   | 24  | F   | L   | Nose    | 0.2 ml| OAO       | Y            | Normal    | Diminished                     | 6 h         | HAase 1500 U + papaverine 30 mg/Recanalization fail | N/N                           | NLP/NLP                | 3 mo             |
| 2   | 24  | F   | L   | Nose    | Unknown| OAO       | Y            | MCA       | Preserved                      | 7 h         | HAase 1500 U + papaverine 30 mg/Recanalization fail | Weak/Weak                     | NLP/NLP                | 3 mo             |
| 3   | 35  | F   | L   | Frontal | Unknown| OAO       | Y            | Normal    | Preserved                      | 10 h        | HAase 1500 U + papaverine 30 mg/Recanalization fail | N/N                           | NLP/NLP                | 3 mo             |
| 4   | 29  | F   | L   | Frontal | Unknown| OAO       | Y            | Normal    | Diminished                     | 8 h         | HAase 1500 U + papaverine 30 mg/Recanalization fail | Weak/Weak                     | NLP/NLP                | 6 mo             |
| 5   | 19  | F   | R   | Nose    | 0.7 ml| OAO       | Y            | Normal    | Preserved                      | 2 h         | HAase 1500 U + papaverine 30 mg/partial recanalization | Y/Y                           | LP/HM                   | 6 mo             |
| 6   | 21  | F   | L   | Frontal | Unknown| OAO       | Y            | Normal    | Diminished                     | 5 h         | HAase 1500 U + papaverine 30 mg/Recanalization fail | N/N                           | NLP/NLP                | 6 mo             |
| 7   | 19  | M   | L   | Nose    | Unknown| OAO       | N            | Normal    | Preserved                      | 6 h         | HAase 1500 U + papaverine 30 mg/partial recanalization | Weak/Weak                     | NLP/LP                   | 6 mo             |
| 8   | 35  | F   | R   | Temple  | Unknown| OAO       | N            | Normal    | Preserved                      | 5 h         | Hyaluronidase 1500 U + papaverine 30 mg/partial recanalization | N/N                           | NLP/LP                   | 6 mo             |

Note: The patients were totally injected in the injection esthetic filling area with subcutaneous hyaluronidase immediately after the onset of visual symptoms by the people who performed the HA injection.

Abbreviations: ECA, external carotid artery; F, female; HA, hyaluronic acid; HAase, hyaluronidase; HM, hand motion; IAT, intra-arterial thrombolysis; L, left; MCA, middle cerebral artery; MRI, magnetic resonance imaging; NLP, no light perception; OAO, ophthalmic artery occlusion; R, right.
improvement in vision. However, the premise is that these patients were light-sensitive on admission to our hospital, thereby indicating that some of the retinal nerve cells were still alive. Moreover, during the IATT procedure, we found that the key point to the improvement of vision loss for long time embolization patient is that the ophthalmic artery and retinal arteries were not completely occluded, which could have served as a basis for vision improvement. After the ophthalmic artery was recanalized with IATT, we continued treatment with glucocorticoids, dehydration, and neurotrophic agents, as well as other general symptomatic therapies, which markedly postponed the deterioration of patients’ illness, alleviated tissue edema and inflammation, and protected the injured retinal nerve cells. We strongly believe that these sequential treatments contributed to the increased survival of visual cells.

We reconfirmed from a previous study that the occlusion of the ophthalmic artery was improved, and the occluded ophthalmic artery was recanalized after superselective ophthalmic artery IATT. The ocular motility and eyelid movement of the patients improved significantly within hours and days after IATT, and gradually recovered. Following IATT in our study, the ptosis healed in all 45 patients. The ocular motility limitations were ameliorated to different degrees in these patients; in particular, ocular motility limitation had healed in 40 patients and ameliorated in five patients. Patients undergoing HA injections more commonly exhibit skin necrosis than those undergoing other filler injections. In this study, IATT combined with glucocorticoids and other sequential treatment significantly improved skin necrosis and skin ecchymosis, with only a few superficial scars in some patients.

With regard to the mechanism underlying vascular embolism due to facial injections, three hypotheses have been proposed extracranial compression, vasospasm, and vascular embolism. Several scholars have proposed that occlusion was probably caused by retrograde embolism with the HA injection. In particular, the supratrochlear and supraorbital arteries are identified as one possible pathway for retrograde embolism in the glabellar region, and the anastomosis of the dorsal nasal artery and angular artery could be a potential entryway for the nasally injected embolic HA particles. Accordingly, the results at this stage discourage HA injections into the glabellar area, nasal dorsum, and even nasolabial fold. In the present study, we concluded that the nasion is the most frequently targeted region for complications related to HA cosmetic injection. Most (68.89%; 31/45) embolized patients received hyaluronic acid injection before and after menstruation or even during menstruation. We speculate that blood vessel dilation during menstruation increased the incidence of vascular embolism.

Furthermore, we found that in eight cases of intracranial infarction, only one patient exhibited bleeding after IATT. An analysis of the mechanism of intracranial hemorrhage after embolization suggests that after intracranial infarction, the infarcted peripheral vascular ischemia and spasm cause distal nutritional necrosis in the blood vessel walls and form small aneurysms, and the subsequent fracture results in bleeding. Second, the lesions and denaturation of the embolic tube wall in patients...
with intracranial embolism, as well as the increase in intracranial pressure during thrombolytic agent injection, can lead to vascular rupture and bleeding in the infarcted region. Third, the routine administration of anticoagulant could be one of the causes of bleeding. In addition, secondary embolization occurred in three of 45 patients, possibly due to blood flow acceleration after recanalization and the dissociation of some incomplete small HA emboli into the distal small artery. Therefore, we suggest that patients should be closely monitored after IATT, particularly for symptoms such as headache, eye pain, or vision loss. In cases exhibiting these conditions, physicians should first consider the possibility of secondary embolism. Cerebral angiography can provide additional detailed information on blood flow in the ophthalmic artery and the surrounding orbital area, which cannot be covered by fundus fluorescein angiography. Prompt imaging was ensured to determine the infarct site, and DSA and IATT were performed again to effectively reduce the incidence of limb disorders caused by intracranial infarction.

In conclusion, we found that timely IATT is effective for ocular artery embolism caused by facial HA injections. Moreover, earlier IATT can increase the likelihood of vision improvement. In addition, patients with intracranial infarction should be closely monitored after thrombolysis, particularly for the occurrence of bleeding. In fact, patients should also be carefully observed over the 2 days after IATT, especially for the occurrence of secondary embolism, and IATT should be performed when necessary. Thus, effective symptomatic treatment including early use of glucocorticoid, multiple local injections of hyaluronidase, oxygen therapy, dehydration therapy, and neurotrophic drug administration were an essential part of this treatment procedure.

**ETHICS STATEMENT**

This study was approved by our hospital. The study adhered to the tenets of the Declaration of Helsinki. The study needed informed consent for participation.
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