

Hypersensitivity reaction to hyaluronidase following peribulbar anesthesia: a case series

Hyaluronidase (HA) is a common additive to local anesthetic eye blocks because it catalyzes the hydrolysis of hyaluronic acid, a major component of connective tissue. This increases tissue permeability, thereby increasing the dispersion and, as a consequence, efficacy of local anesthetics.¹ Adverse reactions to HA occur rarely, with an incidence of at least 1 per 2000.² This case series describes 6 patients who suffered hypersensitivity reactions following the administration of peribulbar anesthesia (PA) containing HA.

Two patients suffered anaphylactic reactions (defined as a severe, potentially fatal systemic allergic reaction that occurs suddenly after exposure to an allergy-causing substance),³ with 1 patient requiring emergency intubation. One patient developed severe orbital inflammation, orbital compartment syndrome, and permanent no-light-perception (NLP) vision. Three patients presented with milder orbital inflammation and no long-term sequelae.

All patients presented in this series underwent intradermal skin testing (IDST) with a concentration of 1.5 IU/mL, in keeping with the testing guidelines of the Australian and New Zealand Anaesthetic Allergy Group. Each patient's IDST was for all substances to which the patient was exposed intraoperatively, and all tested positive to HA alone. The cases are reported herein, with information on patient demographics, previous exposure, operation performed, anesthetic use, management, and patient outcomes presented in Table 1.

After administration of anesthetic, the first patient (case 1) immediately developed tachycardia, hypotension (~60/30 mm Hg), a fall in oxygen saturation to less than 80% as well as generalized flushing, piloerection, and mild swelling at the injection site. A diagnosis of a type I immediate-type hypersensitivity reaction was made. The procedure was abandoned, general anesthesia-induced and urgent airway management was performed. Intravenous adrenaline boluses (total of 850 µg) and aggressive intravenous fluid replacement were given. The patient was subsequently admitted to the intensive care unit for 24 hours, where she required ongoing inotropic support. Extubation occurred after 6 hours, and the patient was transferred to the ward, where she was treated with oral prednisolone and loratadine for 2 days before being discharged. The patient had a full recovery.

Over the 30 minutes proceeding PA, the second patient (case 2) developed periorbital inflammation (Fig. 1), subjective nasal congestion, and chest tightness. Subsequently, systolic blood pressure dropped from 140 to 95 mm Hg, and urticaria developed over the chest and back. Treatment consisted of oral antihistamine (loratadine 10 mg),

nebulized salbutamol, intravenous dexamethasone (8 mg), and intravenous Hartmann's solution. Surgery was abandoned, and the patient was transferred to the emergency department, where 25 mg of intramuscular promethazine and 100 mg of intravenous hydrocortisone were administered. He was admitted overnight and given a further 25 mg of oral prednisone that evening before being discharged the next morning on oral antihistamine.

Ten minutes after PA block, the third patient (case 3) suffered localized/periorbital edema and erythema that slowly spread to involve the entire face. There were no systemic manifestations. The procedure was abandoned, and the symptoms resolved over the next 12 hours without treatment.

In the fourth patient (case 4), the vitrectomy was completed without complication. Eighteen hours after the procedure at the day 1 postoperative appointment, a mild periorbital inflammatory reaction was noted. A review was scheduled for the next day. Over the next 12 hours, the patient noted deteriorating vision. At the next postoperative visit (48 hours after surgery), the patient had NLP, a dense relative afferent pupillary defect, 4 mm of proptosis, and an intraocular pressure above 50 mm Hg. No systemic symptoms developed. A diagnosis of orbital compartment syndrome was made, and an urgent lateral canthotomy/cantholysis was performed. The patient was admitted to hospital and given intravenous antibiotics, as well as high-dose intravenous steroids (3 days of 250 mg qid methylprednisolone), to empirically treat both HA-induced orbital inflammation and orbital cellulitis. Despite these measures, vision was not restored.

In the fifth patient (case 5), the operation was completed successfully, but within 1 hour of surgery, the patient developed painless periorbital inflammation as well as urticaria to his thorax. He had no systemic symptoms. Intravenous hydrocortisone (100 mg) and oral antihistamine were given before the patient was transferred to the local emergency department, where he was given a further 300 mg of intravenous hydrocortisone with intravenous antihistamine 1 hour later. The patient's symptoms subsided that day, and he was discharged home the same evening. Recovery was full.

The sixth patient (case 6) had received numerous regular intravitreal injections of bevacizumab to treat diabetic macular edema. Because of her severe anxiety, these injections were given under sedation with PA containing HA. After each injection, the patient noted periorbital edema that resolved without treatment over a few days. The severity of her periorbital edema gradually worsened with each injection. The patient was consequently referred for allergy testing.

HA hypersensitivity reactions can be broadly divided into local and systemic reactions, although both can occur simultaneously. They also can be classified according to the speed of onset of symptoms. Immediate-type hypersensitivity reactions tend to be mediated by immunoglobulin E, whereas

Table 1—Summary of cases and patient demographics

Case	Age (y)/Sex	Prior HA Exposure	Type of Operation	Anesthetic Used	HA Dose (IU)	Management	Outcome	IDST Positive to HA Only
1	41/F	No	PK	Lignocaine 2%, ropivacaine 1%	150	Procedure abandoned, GA + intubation, IV adrenaline + IV fluids, ICU admission, oral steroids + antihistamine	Full recovery	Yes
2	53/M	Uncertain	DMEK	Ropivacaine 1%	300	Procedure abandoned, oral antihistamine, IV fluids + IV steroids, oral steroids	Full recovery	Yes
3	65/M	Yes	Excision of pterygium + ACG	Ropivacaine 1%	500	Procedure abandoned	Full recovery	Yes
4	82/M	Yes	Vx + laser	Ropivacaine 1%, lignocaine 2%	300	Lateral canthotomy, IV steroids + IV antibiotics, oral steroids + antibiotics	NLP	Yes
5	51/M	No	Phaco + IOL	Unknown local	Unknown dose	IV steroids + IV antihistamine	Full recovery	Yes
6	44/F	Yes	IVI*	Ropivacaine ± lignocaine	Varying doses	None	Full recovery	Yes

HA, hyaluronidase; IDST, intradermal skin testing; PK, penetrating keratoplasty; GA, general anesthetic; IV, intravenous; ICU, intensive care unit; DMEK, descemet membrane endothelial keratoplasty; ACG, autoconjunctival graft; Vx, vitrectomy; Phaco, phacoemulsification; NLP, no light perception; IOL, intraocular lens; IVI, intravitreal injection

delayed-type hypersensitivity reactions tend to be mediated by immunoglobulin G. With either type of reaction, there may or may not be a history of prior sensitization to the specific allergen.⁴

As reflected in this case series, the most commonly reported local hypersensitivity HA reaction is orbital and periorbital inflammation. This may manifest as either an immediate- or a delayed-type reaction and may present with signs such as periorbital edema and erythema, chemosis, proptosis, and ophthalmoplegia. Rarely, as seen in the fourth patient in this series, this inflammation can be severe, resulting in orbital compartment syndrome and vision-threatening optic nerve ischemia.⁵



Fig. 1—Image of the second patient conscious with extensive periorbital inflammation spreading to the face, chest rash, and oxygen mask on during anaphylactic reaction. Dot on the forehead marks operative side.

If orbital inflammation owing to HA develops immediately following administration of the periorbital anesthetic, an important differential diagnosis is a retrobulbar hemorrhage. Irrespective of the underlying causes of orbital compartment syndrome, prompt canthotomy/cantholysis is warranted to preserve vision. We also recommend administering systemic steroids in this situation to treat the possibility of HA hypersensitivity.

If the orbital inflammation presents less acutely, an important differential diagnosis is orbital cellulitis. Delay in the correct diagnosis can result in irreversible loss of vision. A reasonable approach to this diagnostic dilemma is the concurrent use of antibiotics and corticosteroids because the possibility of orbital cellulitis is difficult to exclude.

Because hypersensitivity reactions to HA can be associated with significant morbidity and potential mortality, the safe future management of patients who have suffered a perioperative allergic event requires a thorough investigation of the reaction. Skin testing is indicated in all patients in whom the clinical history may be consistent with a diagnosis of perioperative anaphylaxis and also should be considered in less severe immediate-type hypersensitivity reactions.

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Footnotes and Disclosure

The authors have no proprietary or commercial interest in any materials discussed in this article.