Histologic Evidence of Orbital Inflammation from Retrobulbar Alcohol and Chlorpromazine Injection: A Clinicopathologic Study in Human & Rat Orbits

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Purpose: Retrobulbar injections of alcohol and chlorpromazine are used for the treatment of blind, painful eyes. There have been reports of inflammation after retrobulbar injections of these agents, but the histologic effects are not well characterized. A clinical case with histopathologic confirmation of inflammation after retrobulbar alcohol injection led the authors to develop a rat model to examine these effects.

Methods: Adult Lewis rats were given retrobulbar injections of either 0.1 ml of absolute alcohol or 25 mg/ml chlorpromazine in the right orbit, and 0.1 ml of saline in the left orbit as a control. Rats were euthanized, perfused, and postfixed at 1 to 2 weeks after injection. Exenterated orbital tissue was sectioned for histologic staining. Slides were reviewed by a masked ocular pathologist who evaluated the level of orbital inflammation.

Results: Histopathology demonstrated foci of granulomatous inflammation in the orbit of the patient and similar inflammation in the rat orbits injected with retrobulbar alcohol. In the chlorpromazine group, only 1 rat demonstrated small foci of inflammation, while the control orbits injected with saline showed no inflammation. On blinded qualitative analysis, the orbits receiving retrobulbar alcohol had greater inflammation than the orbits receiving either saline or chlorpromazine.

Conclusions: Our findings in this preclinical pilot study suggest that retrobulbar alcohol injections incite significant orbital inflammation, whereas retrobulbar chlorpromazine induces little or no inflammation. This potential inflammatory response should be considered when selecting an agent for pain management, particularly if future orbital surgery is anticipated.

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Management of the blind, painful eye is a problem frequently encountered by comprehensive ophthalmologists as well as glaucoma, vitreoretinal and oculoplastic specialists.[1] A number of treatment modalities are available, including medical therapy with topical agents or bandage contact lenses, neurolytic therapy with agents injected into the retrobulbar space, such as alcohol and chlorpromazine, and surgery to remove the eye.[1] In certain cases, patients cannot undergo enucleation or evisceration because of coexisting medical conditions or because of cultural or religious objections.[1] Retrobulbar injection therapy may be an effective therapeutic choice for these individuals. However, little is known about the histologic effects of these injections on the orbital tissues.

The application of retrobulbar alcohol to treat eye pain has been documented since the early 1900s, and has been advocated as a good option for pain management.[1,2] In most of the patients, retrobulbar alcohol is effective in reducing pain but its effects may be temporary, lasting on average 6 months.[1–3] Initial studies on the effects of retrobulbar alcohol in a rabbit model suggested an increase in orbital fibroblasts and, in most cases, induction of neurotrophic keratopathy.[4] Chlorpromazine, an antipsychotic medication, has been advocated as an alternative to alcohol for the treatment of the blind, painful eye.[5] It is typically delivered as a 1 ml retrobulbar injection at a concentration of 25 mg/ml.[5] Some surgeons have reported fewer side effects and a longer duration of action with the use of chlorpromazine, although there are potential systemic toxicities with the use of this agent including blood dyscrasias and anaphylaxis.[6] While these side effects have not been observed after retrobulbar injection, a recent report demonstrated systemic absorption of the medication with resultant dizziness and palpitations following orbital injection.[7]

Importantly, there have been case reports of orbital inflammation and fibrosis after use of both of these agents, suggesting they may have long-lasting effects on the orbital tissues.[8–11] Orbital fibrosis is of particular concern, as it is thought that fibrotic changes may make subsequent removal of the eye more difficult, may limit the viability of the socket after eye removal, and may impede extraocular motility and thus limit motility of an ocular prosthesis. Recently, investigators demonstrated enhancement of retrobulbar tissues on MRI in a patient who received retrobulbar alcohol,[12] suggesting a possible acute inflammatory response. Here, the authors present histologic evidence of acute inflammation in a patient who underwent enucleation for a blind painful eye after failing to have improvement from retrobulbar alcohol. To examine these findings further, the authors directly compared the histologic effects of retrobulbar alcohol and chlorpromazine on the orbit in an animal model of retrobulbar injection.

METHODS

Case Subject

An 80-year-old woman presented following blunt trauma after a fall with a total hyphema of the right eye. Despite maximal medical and surgical

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therapy, the intraocular pressure remained elevated and the vision deteriorated to no light perception. Three months after the trauma and decline in vision, she experienced chronic eye pain. The patient did not want the eye enucleated, and therefore underwent a series of 2 retrobulbar injections of alcohol 1 month apart to relieve the pain. Despite the injections, she did not achieve sufficient pain relief, and subsequently underwent enucleation 2 months after the second alcohol injection. The enucleation specimen was sent for routine surgical pathology processing, and tissue sections stained by hematoxylin and eosin (H&E) were examined by an ocular pathologist.

Rat Retrobulbar Injections

All animal experiments were conducted in accordance with the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Visual Research, and approved by the Institutional Animal Care and Use Committee at the University of Pennsylvania. For the alcohol experiment (Group 1), 5 adult male Lewis rats were sedated using inhalational isoflurane anesthesia. Using a 30-gauge needle, 0.1 ml of 100% alcohol was injected into the retrobulbar space of the right orbit. In the left orbit, 0.1 ml of sterile phosphate buffered saline was injected into the retrobulbar space as a control. For the chlorpromazine experiment (Group 2), 3 adult male Lewis rats were sedated using the same protocol, but injected with 0.1 ml of 25 mg/ml chlorpromazine into the right orbit only. All rats awoke from anesthesia without complication. Each rat received topical ophthalmic antibiotic ointment every 48 hours following injection.

Orbital Histology

Methods for fixation and exenteration of orbital tissues were adapted from prior studies.[13] One week after injection, 3 of the rats in Group 1 were anesthesized and euthanized by cardiac perfusion with 4% paraformaldehyde. After perfusion, each rat was decapitated and the head was further fixed in 10% formalin. One week later, the 2 remaining rats from Group 1 and the 3 rats in Group 2 were euthanized and perfused in the same manner.

Two weeks after euthanizing and fixation, each orbit was carefully exenterated with an 11-blade scalpel and placed in 10% formalin. The exenteration specimens were embedded in paraffin after tissue processing. Inferior, mid-, and superior orbital sections were obtained and stained with H&E for histologic examination.

Six representative slide specimens from the inferior, middle, and superior aspect of each orbit were examined from 2 rats in each of the specimens injected with alcohol, chlorpromazine, or saline for a total of 12 slides in each of the 3 categories. An ocular pathologist examined the slide specimens and qualitatively evaluated each sample in a blinded fashion to assess the extent of orbital inflammation.

RESULTS

The enucleation specimen from the patient who received retrobulbar alcohol injections demonstrated focal fat necrosis and inflammatory cells adjacent to the optic nerve. There were also giant cells in the tissues adjacent to the globe in the specimen showing signs of granulomatous inflammation (Fig. 1).

Similar orbital inflammation was found in rats injected with retrobulbar alcohol. At both 1 and 2 weeks postinjection, the orbits treated with retrobulbar alcohol had severe inflammatory changes that included foci of granulomatous inflammation, fat necrosis, and atrophy of the Harderian gland (Figs. 2 and 3) observed on assessment of histologic sections of the orbit by a masked ocular pathologist. The pathologist could not distinguish between sections from rats euthanized 1 week after injection as compared to those euthanized 2 weeks after injection, suggesting there was no difference in the level or distribution of inflammation. Thus, the decision was made to euthanize all rats in the chlorpromazine group at the 2-week time point.

In the rats that received retrobulbar chlorpromazine, there was scant evidence of orbital inflammation (Fig. 4). However, 1 rat did have periocular alopecia and exhibited systemic symptoms of dehydration and lethargy. The rat was provided rehydration therapy and survived until the date of euthanization. In this rat, the orbital tissues showed minimal signs of acute inflammation.

The control orbits treated with retrobulbar saline injections had scant evidence of inflammation (Fig. 5). There was no difference in the level of inflammation in these samples between rats euthanized at 1 or 2 weeks after injection, similar to the orbits in the alcohol group. Qualitative analysis of 12 representative slide specimens from each of the alcohol, chlorpromazine, and saline groups showed much more severe inflammation in the alcohol group. The group of slides from rats injected with chlorpromazine showed scant foci of inflammation and were similar in appearance to the orbits injected with saline.

DISCUSSION

Retrobulbar injections of alcohol or chlorpromazine have long been advocated for the treatment of the blind, painful eye.[1,2] This treatment modality is efficacious for treating pain; however, its analgesic benefit is often temporary, and there are limited studies of its histologic effects on the orbital tissues. In a clinical case, a patient who received retrobulbar alcohol and then subsequently

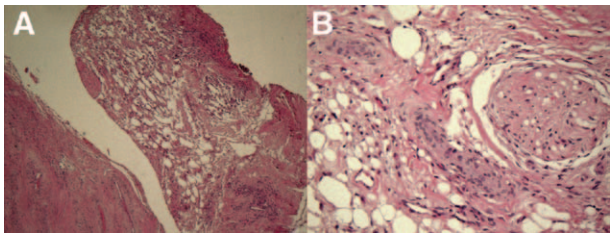

FIG. 1. **A** & **B**, Hematoxylin and eosin-stained enucleation specimen from clinical case depicting areas of fat necrosis adjacent to the optic nerve 2 months after retrobulbar alcohol injection (**A**, original magnification, 50×) with giant cells (**B**, original magnification, 200×).

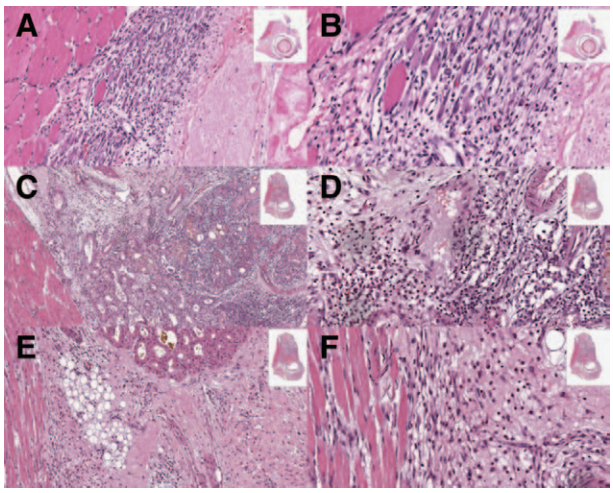

FIG. 2. Hematoxylin and eosin-stained rat orbital specimens injected with alcohol demonstrate evidence of inflammation 1 week after injection. Inflammatory infiltrate surrounding muscles at low (**A**, original magnification, 10×) and on higher magnification (**B**, 20×). Inflammation also surrounding muscle and glandular soft tissue (**C**, 4×) and on higher magnification (**D**, 20×) in another alcohol-injected rat orbit. Inflammation within intraconal fat and adjacent to the optic nerve (**E**, 10×) and on higher magnification (**F**, 20×) from another region of the orbit shown in (**C**) and (**D**). *Inset* in **upper right** of each photograph shows a nonmagnified (1×) scan of the entire orbital tissue examined, and the *red box* indicates the region shown in the photograph.

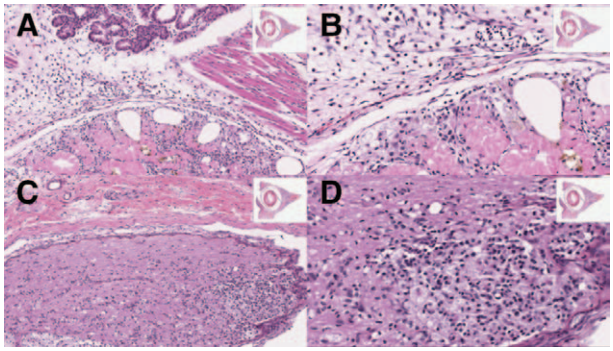

FIG. 3. Hematoxylin and eosin-stained rat orbital specimens injected with alcohol demonstrate evidence of inflammation 2 weeks after injection. Inflammatory infiltrate surrounding muscles and glandular tissues (**A**, 10×) and on higher magnification (**B**, 20×). Inflammation within the optic nerve (**C**, 10×) and on higher magnification (**D**, 20×) from another region of orbit shown in (**A**) and (**B**).

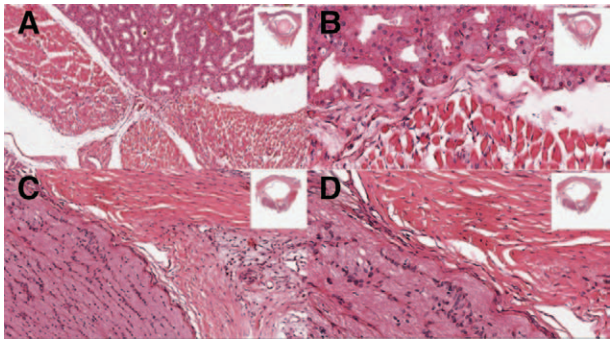

FIG. 4. Hematoxylin and eosin-stained rat orbital specimens injected with chlorpromazine demonstrate minimal inflammatory cell infiltrate 2 weeks after injection (**A**, 10×) and on higher magnification (**B**, 20×). Scant inflammatory cells infiltrating orbital fat adjacent to the optic nerve (**C**, 10×) and on higher magnification (**D**, 20×).

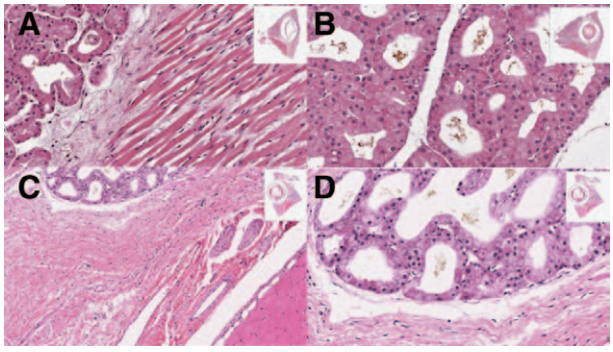

FIG. 5. Hematoxylin and eosin-stained orbital specimens injected with saline demonstrate no inflammation in the orbital muscle and glandular tissues 1 week after injection (**A**, 20×) or in a separate sample in the glandular tissues (**B**, 20×). Two weeks after injection, no inflammation was observed in the orbital soft tissues (**C**, 4×) and on higher magnification (**D**, 20×).

underwent enucleation 2 months after the last alcohol injection had evidence of fat necrosis and signs of inflammation in the orbit adjacent to the optic nerve. Oculoplastic specialists have postulated that retrobulbar alcohol may cause orbital fibrosis and may complicate subsequent enucleation[11]; thus, the authors examined whether similar inflammatory changes in the orbit are a consistent finding by using an animal model of retrobulbar injection. Our results in this pilot study suggest that retrobulbar alcohol is associated with significant orbital inflammation unlike control orbits injected with saline in a rat animal model. Orbits injected with retrobulbar chlorpromazine did not demonstrate severe orbital inflammation but 1 rat experienced systemic dehydration. These preliminary results suggest that retrobulbar alcohol may induce more orbital inflammation than chlorpromazine. The ability to detect these differences further suggests that this rat model is useful for examining orbital changes in response to retrobulbar injections.

The current case findings are consistent with the limited number of reported cases available, which also found orbital inflammation following retrobulbar injections of alcohol or chlorpromazine.[8–11] These cases have included isolated reports in which the patient had typically received multiple injections of 1 or both agents. In addition, the detection of chlorpromazine within the systemic circulation following retrobulbar injection has been reported.[7] It is possible that the same toxicity that impacted this patient may also have induced the observed systemic side effects of dehydration and lethargy in 1 of our experimental animals. However, our study is limited by the fact that the serum chlorpromazine level was not measured.

Results of the current pilot study suggest that retrobulbar alcohol injections may lead to more severe orbital inflammation than retrobulbar chlorpromazine. This finding may have clinical utility for ophthalmologists and oculoplastic specialists should removal of the eye be necessary. Chlorpromazine may represent a safer alternative for the orbital tissues, but potential systemic side effects should be considered and future studies are needed to further elucidate the effects of these agents.

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