

RAPID CLINICAL REPORT

ADVERSE EFFECTS ASSOCIATED WITH THE ABSENCE OF HYALURONIDASE IN ANESTHESIA FOR CATARACT SURGERY

Issued February 13, 2001

Background:

Hyaluronidase (Wydase®) is a medical preparation of highly purified bovine testicular enzyme. The enzyme hydrolyzes hyaluronic acid, which usually limits diffusion by binding cells together. Thus, it is believed that hyaluronidase increases permeability and promotes the spread of local anesthetic. This accelerates the onset of akinesia, and also helps to reduce the increase in intraocular pressure that can be seen after peribulbar block. In 1986, hyaluronidase was reported in the literature to enhance the diffusion of ocular anesthesia, and since then, has been widely used in injections of local anesthesia for cataract surgery and other ophthalmic surgeries. In 1999, Wydase® was used in approximately 750,000 procedures.

In 1998 and 2000, shortages of Wydase® surfaced, and ophthalmologists coped by utilizing smaller concentrations, or switching to a different type of block such as sub-Tenon's infusion or to topical anesthesia which don't require the use of hyaluronidase. Complications occurring in the absence of Wydase® have been anecdotally reported, including diplopia and greater orbital swelling.

Status of Wydase™:

In January 2001, Wyeth-Ayerst announced that it would not resume manufacturing Wydase®. The drug has been in limited supply since Wyeth-Ayerst voluntarily closed its manufacturing facility to address quality assurance issues. Its current supply is in controlled inventory and is anticipated to last until April 2001. Unless another drug manufacturer assumes production, Wydase® will be unavailable permanently. Some ophthalmologists are turning to local compounding pharmacies to obtain hyaluronidase as an alternative to Wydase®. However, there are no uniform national standards for the production of drugs in compounding pharmacies.

Evidence of Effects of Hyaluronidase:

Does the addition of hyaluronidase to local blocks produce better akinesia?

In October, 1998, the federal Agency for Healthcare Research and Quality contracted with the Johns Hopkins University Evidence-based Practice Center (EPC) to prepare an evidence report on the management of local anesthesia and sedation for cataract surgery.¹ The EPC, led by Principal Investigator, Oliver Schein, M.D., MPH, performed a comprehensive literature search, abstracted key data for constructing evidence tables, and graded the evidence in each study. The grading scale for evidence consisted of A (good), B (fair), C (poor) and I (insufficient).

The Evidence Report, issued in September 1999, identified the following question: Is there evidence that adding hyaluronidase to local blocks produces better akinesia than not adding hyaluronidase? Six studies in the literature addressed this question. The report concluded that, “while several studies compared hyaluronidase with placebo, few reported data on the effect of using hyaluronidase on pain control. On average, hyaluronidase appeared to produce better akinesia than placebo, but the results of studies addressing this issue were inconsistent, with several studies finding no benefit. In addition, hyaluronidase consistently took two to three fewer minutes to produce akinesia than control, but the difference was not always statistically significant.”(Evidence Grade:C).

Does the use of hyaluronidase prevent the occurrence of postoperative strabismus following retrobulbar or peribulbar anesthesia?

A MEDLINE literature search performed in February 2001 did not yield any studies documenting a protective effect of hyaluronidase against postoperative strabismus, or a causal relationship between the absence of hyaluronidase and the occurrence of diplopia. A known, but relatively rare, complication of cataract surgery is strabismus. This can be caused by inadvertent injection of the local anesthetic into an extraocular muscle.² Initially, the extraocular muscle, most commonly the inferior rectus muscle, is injured and becomes paretic from the myotoxic effect of the anesthetic, presenting as diplopia. In many patients, this heals over days to weeks. In some elderly patients, however, paresis is followed by localized fibrosis of the muscle. Over the next few weeks, the diplopia worsens, in the opposite direction, and persists. This condition can usually be corrected by eye muscle surgery.

One article in the literature described the occurrence of diplopia cases when hyaluronidase was not available. In a retrospective chart review, Brown et al. found 25 cases of transient or permanent diplopia, submitted by 8 different surgeons.³ Of these eyes, 10 had peribulbar injections, and 13 had retrobulbar injections. The injected volume of anesthetics ranged from 3 to 10 cc, with an average of 6.2 cc. For 4 of these surgeons with 11 cases, the known incidence of iatrogenic postoperative diplopia was zero, and in the other cases, a baseline incidence could not be obtained. Other factors (such as volume of anesthetic injected, technique, anesthetic mixture, etc.) did not appear to be significant,

although a quantitative analysis was not described. The authors postulated that in the absence of hyaluronidase, either the anesthetic was in longer contact with the extraocular muscle and caused toxicity, or that increased intraorbital pressure led to decreased blood flow and ischemic injury to the muscle.

In response to this article, a group of 2 cataract surgeons and 1 neuro-ophthalmologist reported that they experienced 10 cases of postoperative diplopia.⁴ Once hyaluronidase was available again, they reported that no more cases of diplopia occurred. However, another surgeon reported that in a chart review of approximately 7,000 cases performed using retrobulbar block without hyaluronidase, there was zero incidence of iatrogenic diplopia.^{5,6}

Additional Questions:

1. What is the incidence of iatrogenic postoperative strabismus in cases using hyaluronidase and in cases not using hyaluronidase?
2. Does the addition of hyaluronidase protect against the occurrence of postoperative strabismus? If so, what is the mechanism of action?
3. What is the incidence of other potential adverse effects, e.g., more pain, less akinesia, more orbital swelling, in cases using hyaluronidase and in cases not using hyaluronidase?
4. What are the outcomes of alternative techniques that do not use hyaluronidase, i.e., pain, akinesia, strabismus?

Expert Comments:

David L. Guyton, M.D.

We do not yet know for certain whether the absence of hyaluronidase in retrobulbar or peribulbar anesthesia increases the risk for post-operative strabismus, but the accumulating evidence is bothersome. Anecdotally, I have seen four cases of significant strabismus in the past month from anesthetic myotoxicity, four times the usual rate in my adult strabismus practice, two each from two different surgeons. Each of these surgeons had stopped using hyaluronidase because of its unavailability.

Estimates of the incidence of post-operative strabismus from anesthetic myotoxicity, even with hyaluronidase, have been in the 1 in 500 range. This complication is probably related more to injection technique than to the presence or absence of hyaluronidase, but it occurs in the hands of even the most experienced surgeons, and hyaluronidase may provide a safety margin. The best evidence suggests that intramuscular injection of the anesthetic is the culprit. Perhaps hyaluronidase speeds diffusion of the anesthetic from the muscle tissue.

Sub-Tenon infusion of anesthetic with a blunt cannula is a good alternative to retrobulbar or peribulbar blocks. In older individuals, Tenon's capsule is thin, providing little barrier to posterior diffusion of the anesthetic. Pain relief is excellent, and akinesia is usually good. With the patient sedated, the conjunctiva is nicked in one of the inferior quadrants, between muscles, about 5–6 mm from the limbus. Scissors are used to spread into the sub-Tenon space, and 2–3 cc of anesthetic are infused into this space using a blunt cannula. Care should probably be taken not to inject the anesthetic against resistance to avoid creating a loculated "cyst" of anesthetic, the pressure from which was probably responsible for the one case of central retinal artery occlusion I have seen with this technique. In other words, pull back slightly if the anesthetic does not flow freely from the tip of the blunt cannula. An added and welcome advantage of sub-Tenon infusion is avoidance of retrobulbar hemorrhage.

Samuel Masket, M.D.

Although the evidence-based literature does not lend strong support for the routine use of Wydase® (hyaluronidase, Wyeth) there is a definite clinical impression of its efficacy among the profession. Anterior segment surgeons who prefer injection anesthesia suggest that the onset of anesthesia is more rapid and that excess orbital pressure dissipates quickly when the agent is added to the anesthetic mixture. Moreover, there has been concern regarding an increased incidence of postoperative diplopia when Wydase® has been unavailable. It appears that there is a dichotomy between clinical practice and the available literature. Eye surgeons will need to consider alternative methods for ocular anesthesia.

This information is designed to inform ophthalmologists and their patients of current clinical developments in a summary fashion, and does not reflect a position or policy of the American Academy of Ophthalmology or its Board of Trustees. This information is time-limited, and based solely on a summary review of articles available as of February 2001. The material provided is informational only, and is not intended to be a basis for diagnosis, treatment or any other clinical application.

References:

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February 2001



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