Enzymatic Lysis In Hyphema With Glaucoma In Children; Experimental Study And Case Reports*

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Enzymatic lysis of ocular blood blot has been attempted and reported since 1951. It is believed that the enzymes lyse fibrin and cells or enhance the activity of plasmin. Critical evaluation of most reports on the use of proteolytic enzymes as therapeutic agents has been hampered by such reports being based on empirical observations, meager scientific data and uncontrolled clinical observations in diseases where the natural course is extremely variable, despite the design of “carefully controlled, double-blind” studies which have no foundation of quantitation suitable to the extremely varied situations studied. Treatment of total hyphema with secondary glaucoma following trauma or surgery remains difficult, so that in 1963, Cole and Byron (*) advised “conservatism,” and the use of intravenous urea to lower intraocular pressure.

Treatment of three cases of hyphema with glaucoma in children in a short period of time, using oral streptokinase-streptodornase (Varidase®)*** with repeated paracentesis, as suggested in 1953 by O'Rourke and Leopold (2), with complete recovery,

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***Varidase (Lederle), brand of streptokinase-dornase was obtained through the courtesy of R. John F. Renshaw, M.D.
led to an experimental study in rabbits.

Experimental Materials: Albino rabbits weighing approximately 2 kg. were used. Strepto-kinase-streptodornase (2000 U/ml) was given twice daily intramuscularly post-operatively in treated animals. Alternate animals did not receive enzyme, as control. Under pentobarbital intravenous anesthesia, blood was drawn from the heart or ear artery. 0.2 ml aqueous humor was withdrawn by 27 guage needle, and immediately replaced with the just previously drawn blood to fill the anterior chamber. 24 hours later, an oblique incision into the cornea (keratotomy), 2 mm. from the limbus was made with a #11 Bard-Parker blade, and the wound lips depressed to permit drainage. The wound was reopened daily by depressing the lips with a spatula. No irrigation was done. 1% tetracaine anesthesia. Results: The anterior chamber of all treated rabbits was entirely clear of blood by the third day; untreated (no enzyme) rabbits had clots persisting as long as ten days. Photos were taken daily.

Case 1. (MS) Pt. was admitted to hospital on 11-22-62 after being struck in right eye with a hard baseball. There was ecchymosis and hyphema filling all but the far periphery of the anterior chamber. Tension was (38) (Schiottz). Vision LP & P. Conservative treatment with bedrest, patching, dichlorphenamide 25 mg. orally q.i.d., pilocarpine 2% q. 3 hrs., and streptokinase-strepto-dornase, one table q.i.d., resulted in a clear eye and tension of 20 (Schiottz), with a small clot inferiorly and on the iris at 1 o'clock. On 11-25, total hyphema was found, but tension was normal. (Pt. was found to be striking his eye with his fist). Tension rose on the following day to 27 (S), and then to 50 (S). Intravenous injection of urea (1g./kg) promptly lowered tension to 15 (S), but rose to 43 in a few hours, with no clearing of blood. On 12-2, peripheral keratotomy was done, and the chamber immediately cleared with escape of bloody aqueous. Vision was LP, with a poor fundus reflex due to blood in the vitreous. He was discharged with preparations for dexamethasone eye drops (0.1% soln.), and 0.75 mg. tablets to be taken three times a day, and streptokinase-dornase four tablets daily. On Jan. 8, vision was 20/20 with correction. Pt. was 12 yrs. of age.

Case 2. (KT). This 8 yr. old white female had congenital nystagmus with poor vision (20/100 Rt.; 20/70 Left), and had been a premature baby. She had been treated for strabismus by surgery at age 3, with cosmetically straight eyes. The right eye was myopic, but vision was not improved by glasses. She was first seen on Oct. 21, 1963 with pain in the right eye, tension of 60 (Schiottz), and a shallow chamber with narrow angle. Medical treatment with dichlorphenazine 25 mg. orally q.i.d., pilocarpine 2%-eserine 1/4% q 2 hrs. reduced the pressure to normal levels. On Oct. 26, despite treatment with pilocarpine 1%, and acetazolamide 62.5 mg. b.i.d., the acute glaucoma recurred with tension of 59 (S), shallow anterior chamber, domed pupil, and pain. Intravenous injection of urea (1 gm/kg) lowered the intraocular pressure to 10 (S), and gonioscopy revealed a closed angle. Surgery was advised and performed (Peripheral iridectomy). A small amount of bleeding occurred at surgery, but the anterior chamber was found to be full of blood the following day. Strepto-kinase-streptodornase (table one q.i.d.) was given orally. Tension became hard (0 with 10 gm. wt. Schiottz), and irrigation with thrombolytic was contemplated. Under local anesthesia, keratotomy was done, and a trial with saline irrigation removed the blood completely. Hemorrhage recurred two days later, and was evacuated by depressing the wound lips of the keratotomy. The eye became clear the following day, with tension "soft," and uneventful recovery to preoper-
tive vision of 20/70, with normal pressure. Followup until Jan. 1965 has revealed normal pressure and the same vision, with no acute attacks.

Case 3. (DC). This 6 yr. old white female injured her left eye when it was struck with a plastic dart on 2-27-63. A small 3 mm. hyphema cleared with bed rest, sedation and streptokinase-dornase tablets q.i.d. Total hyphema recurred on 3-2-1963, and on 3-5, tension was "hard" (0 reading, 10 gm. Schiotz). Keratotomy was done under local anesthesia (tetracaine 1%), and a small amount of bloody aqueous escaped. On the following day, it was possible to irrigate out the bulk of the blood using normal saline. On Mar. 7, tension was again elevated, and the wound lips were reopened when a small amount of fresh blood was found. On March 8, tension was 24 (S), and the anterior chamber cloudy, but was clear with tension normal by Mar. 11, with no further surgical treatment. Tension 11 (S), vision 20/20. Followup for one year with same findings.

Discussion
Jukofsky (3) reported on intraocular use of streptokinase-dornase in 1951. In 1952, Friedman (4) reported marked irritation and cyclitic membranes on intraocular use so that local reactions associated with this route of administration were discouraging, but did not inhibit further studies. Sacks-Wilner et al., (5) reported adverse local reactions. O'Rourke and Leopold (6) reported the inability to lyse rabbit blood, and advised paracentesis and flushing of the anterior chamber with saline. Scheie et al., (16,17) studied and introduced the use of fibrinolysin (Plasmin) for anterior chamber irrigation, but this frequently required prolonged washing. Plasmin is a proteolytic enzyme with a pronounced tendency to destroy fibrin, but it will also lyse fibrinogen, casein and gelatin. It does not attack albumin, but it can destroy some of the clotting proteins (Factor V or VII) if used in large doses. Several investigators have indicated that the effective thrombolytic principle in streptokinase-plasmin mixtures was the streptokinase itself (7).

Hurwitz (8) and Wright (9) found oral streptokinase to have no effect on traumatic hyphema. Chandra and Guptra (10) in a "double-blind" study found buccal "Varidase" to be a "useful" adjunct in treatment of intraocular hemorrhage. Desvignes et al (11) reported marked edema of the cornea, persisting for at least 10 days in a rabbit experiment in which human blood was injected intracamerally, followed by enzyme irrigation for 50 minutes. They believe that human blood was more toxic and irritating. (Podos et al(12) demonstrated lysis of human blood clots in total hyphema in rabbit anterior chambers, but noted residual corneal opacities in all eyes treated after 7 hours, and diminution of effect in clots 35 and 60 hours old.

Studies using various techniques for quantitation of blood (13,14,15) have indicated increased rate of disappearance from the anterior chamber with use of the enzyme. A new hypotonic approach to cell lysis in the anterior chamber was reported by Binder(16) who suggests irrigation with distilled water (maximum 2 ml.)

The use of repeated drainage of anterior chamber contents probably produces increased concentration of enzyme through production of secondary aqueous humor, with a high concentration of blood serum constituents. The lack of effect in simple hyphema is probably due to lack of entry into the eye. It was noted above that in treatment of thrombotic processes elsewhere in the body, that large doses are necessary, even when used in areas with large blood supply, while the blood-aqueous barrier serves to limit entry of protein constituents from the blood.
Keratotomy was performed in these children under local anesthesia with little difficulty. It was not necessary to completely remove all blood to resolve the glaucoma or favor blood absorption. This type of treatment is suggested only when glaucoma is associated with the hyphema. It is necessary to reiterate the difficulty in transferring animal data to human patients without reservation, and the problem of controls in the cases reported.

Summary

Streptokinase-dornase has been reported to be effective in lysing blood clots by many authors, when introduced in sufficient dose levels. Anterior chamber hemorrhages are anatomically situated so that penetration of the enzyme is limited, and local use damaging. The clinical and experimental results presented suggest that keratotomy with repeated reopening of the wound results in the entry of secondary aqueous humor containing adequate levels of enzyme to be effective in lysing clots, so that they may be successfully removed by drainage alone or by irrigation with normal saline or anterior chamber-type fluids, with minimal trauma, with favorable results in resolving glaucoma and conserving vision.

REFERENCES:


