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Experimental study on drug therapy of "traction retinal detachment" after posterior penetrating eye injury in the rabbit

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Abstract. In an experimental study on rabbits, a standarized eye injury was created by using the "pars-plana incision model." Subsequently, the effect of intravenous application of dexamethasone and penicillamine on traction retinal detachment was investigated. The two drugs were applied in varying concentrations and combinations (single and combined use in varying intervals), followed by a 3-month control period without medication. Clinical and histological findings showed that intravitreal instillation of 1.2 mg dexamethasone reduces the incidence of retinal detachment from 46% to 27%. Higher concentrations of dexamethasone, as well as the use of penicillamine or a combination of both substances, proved to enhance traction retinal detachment.

Introduction

Traction retinal detachment after posterior penetrating eye injury is still a major cause of blindness (Johnston 1971; Eagling 1974, 1975, 1976; Faulborn and Birnbaum 1974; Faulborn et al. 1977; Schmidt and Pedersen 1981), despite surgical treatment with pars plana vitrectomy. Vitrectomy itself can cause serious complications, including secondary hemorrhage (Faulborn et al. 1977; Heimann and Paulmann 1982), retinal lesions (Michels and Ryan 1975), traumatic cataract (Ghartey et al. 1980), and fibrous proliferation from the sclerotomy (Pülhorn et al. 1977; Kreiger et al. 1977; Paulmann and Behrendt 1980).

Several animal models have been described to study the effect of drugs on proliferative vitreoretinoopathy. The "cell injection model" (Müller-Jensen and Mandelcorn 1975; Algvere and Kock 1976; Sugita et al. 1980; Trese et al. 1980; Radtke et al. 1981; Fastenberg et al. 1982) has been used for various drug therapy (Tano et al. 1980a, b; Binder 1981, 1983; Blumenkranz et al. 1982; Wiedemann et al. 1983). The "double perforation model" (Topping et al. 1979) has been used for therapy with dexamethasone (Tano et al. 1981), penicillamine (Weiss and Belkin 1981) and β-aminopropionitrile (Moorhead 1983). The "pars plana incisional model" (Cleary and Ryan 1979a, b) has been used only for therapy with 5-fluorouracil (Mein and Blumenkranz 1982).

We report on therapy of traction retinal detachment in this model with dexamethasone and penicillamine in various doses and in combination, with repeated intravitreal injections over 6 weeks and with a subsequent 3-month period of observation (Behrens-Baumann 1983).

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Material and methods

A total of 135 pigmented, male rabbits were used, which weighed about 3.6 kg each. Each group primarly consisted of 15 animals. Some rabbits died between days 9 and 16 postoperatively. These eyes were enucleated for histological examination but otherwise excluded from the experiment. For final evaluation in some groups, therefore, there remained only 11, 13 and 14 animals, respectively.

All animals were anesthetized with ketamine (Ketanest) and xylazine (Rompun) and operated on under sterile conditions. An 8-mm scleral incision 2.5 mm from the limbus was produced with Graefe's knife and corneal scissors. After excision of prolapsed vitreous, the wound was closed with 14–16 interrupted sutures of 10-0 nylon. The fundus was examined by indirect ophthalmoscopy and scleral indentation to exclude any eye with retinal damage. An injection of the group-specific drugs (Table 1) and 0.4 ml autologous blood was done with a 27-gauge cannula between the sutures. Finally, atropine drops were instilled in the cul-de-sac for prophylaxis of iritis (Algvere et al. 1981).

The experimental design is demonstrated in Table 1. All groups had the same operation but different drugs (water-soluble dexamethasone phosphate or penicillamine) and different doses of the drugs (2.4 mg and 1.2 mg dexamethasone and 10 mg and 5 mg penicillamine, respectively). Intravitreal injection of the group-specific drug was repeated postoperatively at different intervals in some groups to evaluate whether or not repeated treatment is successful in fibroblastic inhibition.

After a 3-month interval without therapy, the animals were killed with an overdose of Ketanest and Rompun and the eyes enucleated. The cornea was perforated at 12 o'clock with a 1.2 mm trephine and the globe fixed in 3% glutaraldehyde for 48 h. The eyes were sectioned through the optic nerve and the wound for gross examination. After embedding in paraffin, serial sections of 6 μm thickness were made and stained with hematoxylin and eosin, periodic acid-Schiff, Masson trichrome and Prussian blue. The examiner of the sections (M.V.) did not know the prior treatment of the eye.

Table 1. Experimental design with frequency of retinal detachment. The three columns at the right show the observed side effects of the drugs

Group	Operation and intravitreal injection of 0.1 ml (A–E) or 0.05 ml (F–I)	Repeated intravitreal injection (in weeks)						Retinal detachment (%)	Neovascularization	Pigment alteration	Cataracta matura (non-traumatic)
		1	2	3	4	5	6				
A ($n=13$)	NaCl, 0.9%	−	+	−	+	−	+	46	0	0	0
B ($n=14$)	Soluble dexamethasone, 2.4 mg	−	+	−	+	−	+	80	2	3	6
C ($n=14$)	Penicillamine, 10 mg	−	+	−	+	−	+	93	0	3	1
D ($n=15$)	Combination of B and C	−	+	−	+	−	+	100	5	6	6
E ($n=15$)	Combination of B and C	+	+	+	+	+	+	87	4	5	8
F ($n=15$)	Soluble dexamethasone, 1.2 mg	−	+	−	+	−	+	27	0	3	3
G ($n=11$)	Penicillamine, 5 mg	−	+	−	+	−	+	87	1	2	1
H ($n=15$)	Soluble dexamethasone, 1.2 mg	−	−	−	−	−	−	33	0	2	0
I ($n=13$)	Penicillamine 5 mg	−	−	−	−	−	−	80	0	1	0

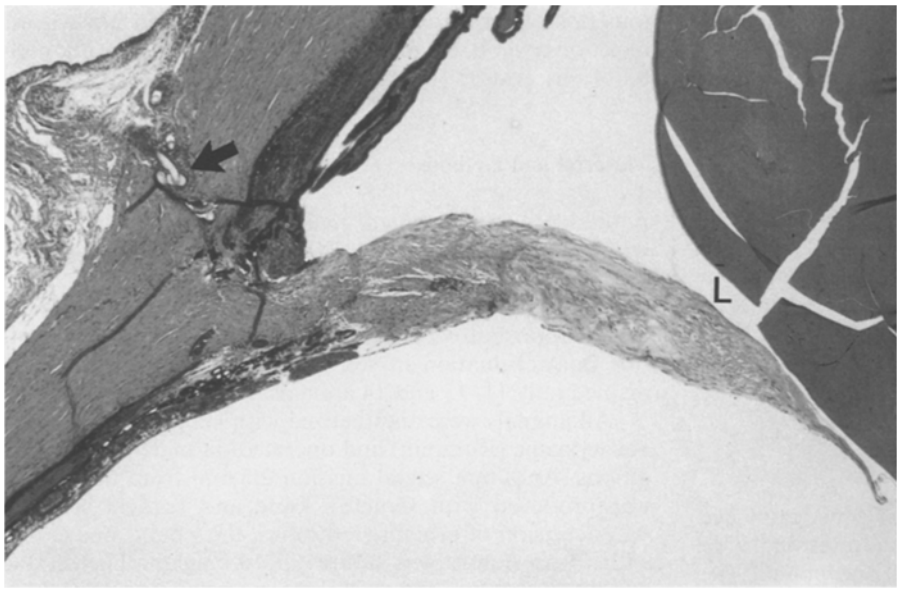

Fig. 1. From the inner aspect of the perforation scar, which is marked by sutures (*arrow*), a fibroblastic membrane extends up to the posterior surface of the lens (*L*). The perforation defect of the choroid and retina is filled by connective tissue (histology no. 276, group H, hematoxylin and eosin, ×12.8)

Results

Clinical results

Provisional diagnosis of retinal detachment was made via indirect ophthalmoscopy when the media were not opaque. The definite diagnosis was made histologically when one quadrant or more was detached. The histologically proved detachment rate in the control group was 46% and decreased only in low-dose dexamethasone groups F and H (Table 1). However, this is not statistically significant. Penicillamine and the combination of both substances produced an increasing incidence of retinal detachment up to 100%.

The complications (Table 1, three right columns) involved the retinal vessels with neovascularization in the area of the optic disc and the medullated nerve fibers. In some animals pigment alterations were observed: first, atrophy of the retinal pigment epithelium and second, black pigment clumps in the vitreous, which could easily be differentiated from blood clots. Another side effect was the development of cataracts. In 11 additional cases there were histologically proven traumatic cataracts due to an unintentional lesion of the lens during the surgical manipulation. In all cases with cataract the fundus was clinically not visible.

Histological description

In five eyes a postoperative vitreous abscess had developed. All intraocular structures were densely infiltrated by polymorphonuclear leukocytes. These eyes were excluded from the experiment. In all eyes with retinal detachments the detachments ranged from total to one quadrant. All of these were traction detachments due to proliferation of connective tissue from the area of the perforation (Fig. 1).

The proliferation of fibroblasts in the vitreous cavity was particularly noteworthy. Fibroblastic proliferation into the vitreous cavity of animals in group A (control group) was contiguous with the inner aspect of the wound and discrete. The 10/0 ethilon sutures caused a mild lymphocytic infiltration. In all cases the wound revealed a perfectly smooth adaptation. In those areas where the choroid and in a few cases also the retina were perforated, the defect was filled by collagenous connective tissue. In the cases with perforated retina there was no retinal detachment caused by the trauma.

The fibroblasts were present along vitreous strands acting as a scaffold and extended in some instances to the posterior surface of the lens (Fig. 2). The peripheral retina was involved by the progressing fibroblasts in different

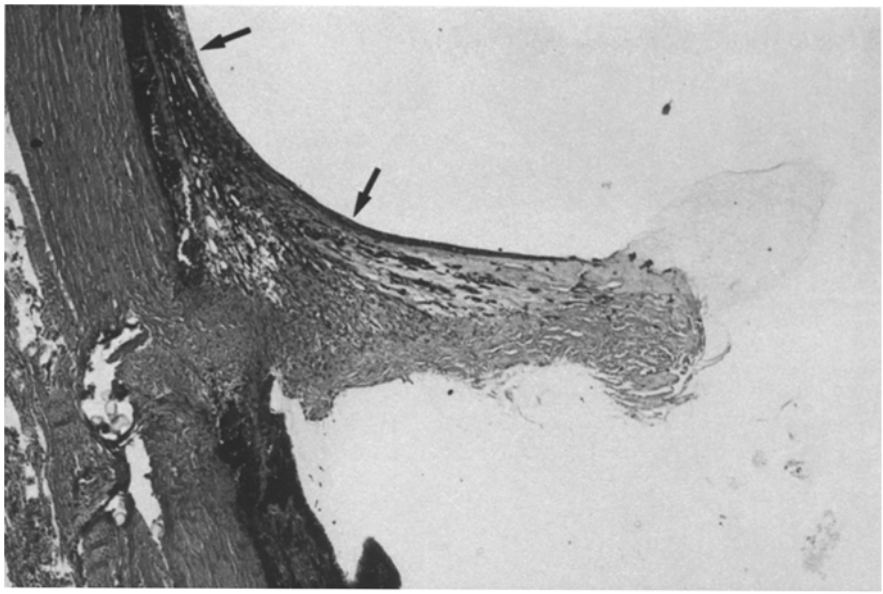

Fig. 2. Vitreous strands are used as a scaffold for the fibroblastic proliferation. The peripheral retina (*arrows*) and the retinal pigment epithelium are pulled into the vitreous cavity by the proliferating fibroblastic membrane without causing retinal detachment (histology no. 275, group H, hematoxylin and eosin, ×12.8)

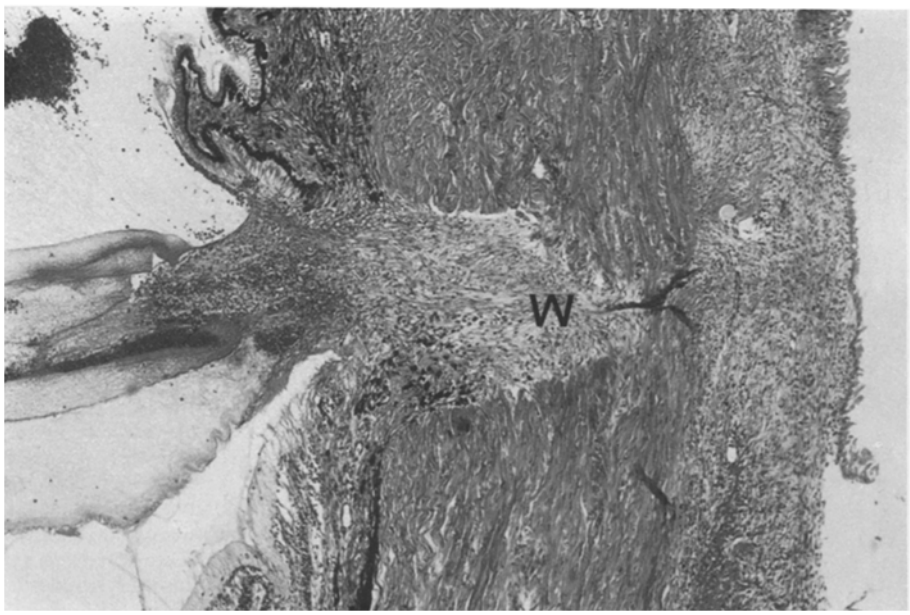

Fig. 3. Nine days after the perforation injury, the perforation wound (*W*) is not completely adapted. The defect is filled by fibroblastic proliferation, which continues into the hemorrhagic, condensed vitreous (histology no. 269, group G, hematoxylin and eosin, ×12.8)

ways. In several slides the retina was adherent to the connective tissue and was pulled into the vitreous together with the retinal pigment epithelium without being detached. In one instance a schisislike splitting of the retina could be observed.

These changes were minute in groups A, F, and H and increased in intensity and spread according to the increasing percentage of retinal detachment in the other groups. In the most pronounced cases a cyclitic membrane with metaplastic bone formation, Ringschwiele, and complete traction detachments were present. No retinal tears could be seen in any of the cases. No remnants of the postoperatively injected blood into the vitreous could be seen except for an occasional hemosiderin-laden macrophage.

An unintentional lesion in the lens during the surgical manipulations had no appreciable influence on the development of a cyclitic membrane. The development of a cataract was seen most frequently in group E, which received a combination of 2.4 mg dexamethasone and 10 mg penicillamine seven times.

At the base of the fibroblastic proliferation at the inner base of the perforation a reactive proliferation of the retinal pigment epithelium was frequently seen. Usually these were arranged in ring-shaped, tubular structures, which blended into the fibroblastic membrane.

The origin of the fibroblastic intravitreal proliferation could not be clearly defined. In some cases the fibroblastic membrane obviously developed from the scleral part of the wound. In other cases it developed from the choroid. In some instances the fibroblastic proliferation developed from the sclera as well as from the choroid.

Two animals died 9 days after the perforating injury. Enucleation was performed to study the early stage of the fibroblastic proliferation. At the inner aspect of the perforation wound, fresh blood was visible which extended into the condensed vitreous strands (Fig. 3). This blood was fol-

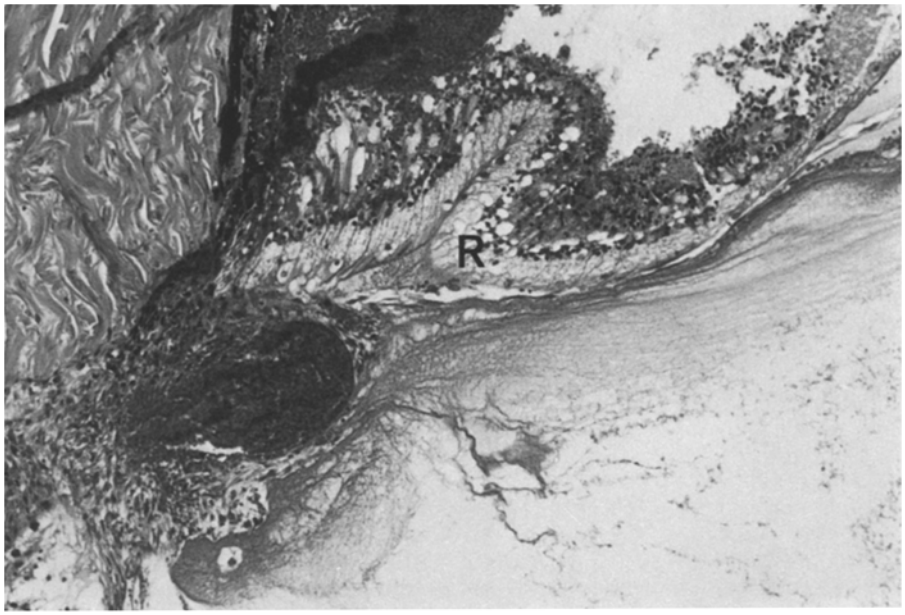

Fig. 4. In this case, the retina (*R*) forms a fold that is adherent to the condensed hemorrhagic vitreous base. This formation of a peripheral retinal fold seems to be dependent on the intimate adherence of the vitreous base to the peripheral retina (histology no. 268, group G, hematoxylin and eosin, ×32)

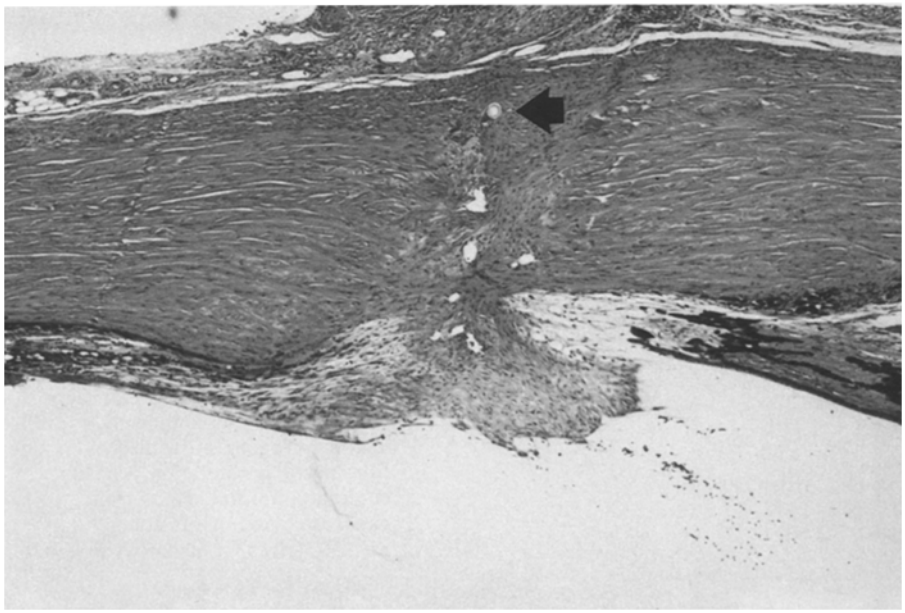

Fig. 5. The scleral scar with remnants of the suture (*arrow*) reveals mild fibroblastic proliferation from the inner aspect. This scar tissue fills the defect within the choroid. There is only very limited proliferation into the vitreous (histology no. 3039, group A, hematoxylin and eosin, ×12.8)

lowed by a delicate formation of fibroblasts which infiltrated the condensed vitreous. In one case the peripheral retina formed a fold that was adherent to one of the condensed vitreous strands, which blended with the perforating wound (Fig. 4).

Discussion

Drug therapy to prevent traction retinal detachment after posterior penetrating eye injury is desirable to replace or enhance pars plana vitrectomy. The rationale for using dexamethasone is its ability to inhibit proliferation of fibroblasts (Cornman 1951; Grossfeld and Ragan 1954; Ruhman and Berliner 1965, 1967; Rozen and Chernin 1965; Pratt and Aronow 1966) and to inhibit synthesis of the collagen in these cells (Haferkamp 1980). Penicillamine prevents cross-linking of collagen fibers (Amiel et al. 1977; Nimni and Bavetta 1965; Nimni 1979) and inhibits activity of fibroblasts (Müller et al. 1971; Junge et al. 1974; Priestley 1980). To test the efficiency of drug therapy, several models have been developed.

The main disadvantage of the "cell injection model" (Müller-Jensen and Mandelcorn 1975; Algvere and Kock 1976) is the lack of vitreous loss or blood in the vitreous, which, however, frequently occurs in penetrating eye injuries. Blood produces strand formation of the vitreous (Oguchi 1913; Freilich et al. 1966; Constable et al. 1973; Constable 1975; Swann 1977). Hemoglobin induces proliferation of hyalocytes and RPE cells (Burke and Smith 1981; Burke et al. 1981). After fibrinolysis (Forrester et al. 1976) and extracellular hemolysis, the cell fragments are phagotized by invading macrophages (Constable 1977; Forrester et al. 1978a, b; Forrester and Grierson 1980). Blood, therefore,

is important for producing the sequelae of eye injury, not the injury itself.

In preliminary experiments (Behrens-Baumann 1983) we tested the "double perforation model" (Topping et al. 1979). In all cases the injected substances left the vitreous cavity through the star-sphaped wound, which could not be closed water-tight. In addition, the strand formation varied considerably in nontreated eyes.

In contrast, the "pars plana incisional model" (Cleary and Ryan 1979a, b) seems to be the best in simulating posterior penetrating eye injury (Behrens-Baumann 1983). There is vitreous loss, blood in the vitreous, and a water-tight wound to leave the intravitreal drugs in place. In this model we then compared dexamethasone with penicillamine. To evaluate the most efficient medical treatment for fibroblastic inhibition different doses as well as repeated intravitreal injections were used.

Our histopathologic results corresponded to those of Cleary and Ryan (1979a, b). In contrast to human eyes, the nonpigmented ciliary epithelium of the rabbit does not participate in membrane formation (Winthrop et al. 1980). The other intraocular reactions of the rabbit eye, however, can be well compared with those of the human eye.

In all cases, proliferation of fibroblasts had developed and extended along the vitreous fibers into the vitreous cavity. The proliferation was very limited (Fig. 5) in the control group and the group with low-dose dexamethasone and increased in the high-dose groups to a cyclitic epiretinal membrane with total retinal detachment. Thus, fibrous proliferation seems to cause the retinal detachment.

With increasing extension of the developing intravitreal fibroblastic membrane, traction was exerted on the peripheral retina. From our histopathologic specimens it appeared that the fibroblastic proliferation developed from the choroid underneath the peripheral retina and pulled the attached retina into the vitreous cavity (Figs. 3 and 4). Within this fibroblastic membrane, which with increasing maturity becomes collagenous, myofibroblasts have been demonstrated with the electron microscope in the rhesus monkey (Cleary et al. 1980). It would be reasonable to assume that these cells, through their contraction, cause a contraction of the collagenous membrane and cause massive traction on the retina. This traction also becomes relevant for the retinal pigment epithelium with ring-shaped tubular proliferations. The retinal pigment epithelium that may lead to epi- and retroretinal membranes in man did not appear to play a significant role in the rabbit eye.

In our experimental study the penicillamine groups had a higher detachment rate than the control group. This is in contrast with the results of Weiss and Belkin (1981), who used the "double perforation model." Their method has already been criticized by Machemer (1981). The combination of dexamethasone and penicillamine and the high dose of dexamethasone (2.4 mg) produces a high detachment rate, too. The exact mechanism is not clear and cannot be determined in an in vivo system. Possibly the vehicle is the reason for this form of toxicity. On the other hand, it may be a question of therapeutic and toxic level of the pharmacon, as known from cardiac glycosides. We speculate that there is a stronger inhibition of the macrophages than the fibroblasts. Macrophages seem to be more sensitive to corticosteroids (Jessop et al. 1973). Erythrophagocytosis is, therefore, decreased. This leads to continuous stimulation of fibroblasts by hemoglobin (Constable 1977; Forrester et al. 1978a, b; Forrester and Grierson 1980). In the control group, the proportion of macrophages and fibroblasts is obviously disturbed to a lower degree, followed by less proliferation of fibroblasts. We assume a dose-response relationship.

In fact, the groups with low-dose dexamethasone (1.2 mg) had a lower detachment rate (27%) than the 2.4 mg dexamethasone groups (80%) $P<0.05$ (chi-square). The low dose of dexamethasone reduced the incidence of detachment from 46% down to 27% in the control group. However, this is not statistically significant. When one extrapolates the low dosage of dexamethasone used for our experimental animals (1.2 mg per rabbit eye) to the low dosage appropriate for a human eye, the approximate amount is 2.5 mg.

Hübner (1982) injected 3.0 mg dexamethasone into the human eye without seeing any side effects. In posterior penetrating eye injuries, then this maximal dexamethasone dosage should, therefore, be applied intravitreally at the end of the primary wound closure. Higher doses do not result in better final results but in more severe side effects.

References

Abrams GW, Topping TM, Machemer R (1979) Vitrectomy for injury. The effect on intraocular proliferation following perforation of the posterior segment of the rabbit eye. Arch Ophthalmol 97:743–748

Algvere P, Kock E (1976) Experimental fibroplasia in the rabbit vitreous. Retinal detachment induced autologous fibroblasts. Graefe's Arch Clin Exp Ophthalmol 199:215–222

Algvere P, Jonsson V, Svedbergh B (1981) Vascular damage in the anterior uvea induced by intravitreal autogenous blood. Graefe's Arch Clin Exp Ophthalmol 217:273–283

Amiel D, Akeson WH, Harwood FL, Schmidt DA, Mechanic GL (1977) Effect of low dosage schedule of D-penicillamine on collagen cross-linking in a nine week immobilized rabbit knee. Connect Tissue Res 5:179–183

Behrens-Baumann W (1983) Tierexperimentelle Untersuchungen zur medikamentösen Behandlung der massiven periretinalen Proliferation (MPP) nach penetrierender Augenverletzung. Habilitationsschrift, Göttingen

Benson WE, Machemer R (1976) Severe perforating injuries treated with pars plana vitrectomy. Am J Ophthalmol 81:728–739

Binder S, Riss B, Skorpik C, Kulnig W (1983) Inhibition of experimental intraocular proliferation with intravitreal 5-fluouracil. Graefe's Arch Clin Exp Ophthalmol 221:126–129

Binder S (1981) Gibt es eine medikamentöse Alternative in der Behandlung der massiven periretinalen Proliferation? Klin Monatsbl Augenheilkd 179:483–485

Blumenkranz MS, Ophir A, Claflin AJ, Hajek A (1982) Fluorouracil for the treatment of massive periretinal proliferation. Am J Ophthalmol 94:458–467

Burke JM, Smith JM (1981) Retinal proliferation in response to vitreous hemoglobin or iron. Invest Ophthalmol 20:582–592

Burke JM, Sipos E, Cross HE (1981) Cell proliferation vitreous hemoglobin. Invest Ophthalmol 20:575–581

Cleary PE, Ryan SJ (1979a) Experimental posterior penetrating eye injury in the rabbit. I. Method of production and natural history. Br J Ophthalmol 63:303–311

Cleary PE, Ryan SJ (1979b) Method of production and natural history of experimental posterior penetrating eye injury in the rhesus monkey. Am J Ophthalmol 88:212–220

Cleary PE, Minckler DS, Ryan SJ (1980) Ultrastructure of traction retinal detachment in rhesus monkey eyes after a posterior penetrating ocular injury. Am J Ophthalmol 90:829–845

Colemann DJ (1982) Early vitrectomy in the management of the severely traumatized eye. Am J Ophthalmol 93:543–551

Constable IJ (1975) Pathology of vitreous membranes and the effect of hemorrhage and new vessels on the vitreous. Trans Ophthalmol Soc UK 95:382–386
Constable IJ (1977) Vitreous membrane formation. In: McPherson A (ed) New and controversial aspects of vitreoretinal surgery. C.V. Mosby, St. Louis, pp 53–58
Constable IJ, Oguri M, Chesney CM, Swann DA, Colman RW (1973) Platelet-induced vitreous membrane formation. Invest Ophthalmol 12:680–685
Conway BP, Michels RG (1978) Vitrectomy techniques in the management of selected penetrating ocular injuries. Ophthalmology 85:560–583
Cornman J (1951) Selective damage to fibroblasts by desoxycortiosterone in cultures of mixed tissues. Science 113:37–39
Eagling EM (1974) Ocular damage after blunt trauma to the eye. Br J Ophthalmol 58:126–140
Eagling EM (1975) Perforating injuries involving the posterior segment. Trans Ophthalmol Soc UK 95:335–339
Eagling EM (1976) Perforation injuries of the eye. Br J Ophthalmol 60:732–736
Fastenberg DM, Diddie KR, Sorgente N, Ryan SJ (1982) A comparison of different cellular inocular in an experimental model of massive periretinal proliferation. Am J Ophthalmol 93:559–564
Faulborn J, Birnbaum F (1974) Netzhautoperationen in Verbindung mit der Versorgung schwerer perforierender Verletzungen. Klin Monatsbl Augenheilkd 164:111–116
Faulborn J, Atkinson A, Olivier D (1977) Primary vitrectomy as a preventive surgical procedure in the treatment of severely injured eyes. Br J Ophthalmol 61:202–208
Forrester JV, Grierson J (1980) Repair in the rabbit vitreous after hemorrhage. In: Naumann GOH, Gloor B (eds) Wundheilung des Auges und ihre Komplikationen. Bergmann, Munich, pp 389–394
Forrester JV, Edgar W, Prentice CRM, Forbes CD, Williamson J (1976) Intravitreal fibrinolyses in experimental vitreous hemorrhage. Exp Eye Res 22:181–188
Forrester JV, Lee WR, Williamson J (1978a) The pathology of vitreous hemorrhage. I. Gross and histological appearences. Arch Ophthalmol 96:703–710
Forrester JV, Grierson J, Lee WR (1978b) Comparative studies of erythrophagocytosis in the rabbit and human vitreous. Graefe's Arch Clin Exp Ophthalmol 208:143–148
Freilich DB, Lee PF, Freeman HM (1966) Experimental retinal detachment. Arch Ophthalmol 76:432–436
Ghartey KN, Tolentino FI, Freeman HM, McMeel JW, Schepens CL, Aiello LM (1980) Closed vitreous surgery. XVII. Results and complications of pars plana vitrectomy. Arch Ophthalmol 98:1248–1252
Grossfeld H, Ragan C (1954) Action of hydrocortisone on cells in tissue culture. Proc Soc Exp Biol Med 86:63–68
Haferkamp O (1980) Allgemeine Pathologie der Wundheilung. In: Naumann GOH, Gloor B (eds) Wundheilung des Auges und ihre Komplikationen. Bergmann, Munich, pp 11–20
Heimann K, Paulmann H (1977) Vitrectomy after perforating injuries. Mod Probl Ophthalmol 18:242–244
Heimann K, Paulmann H (1982) Vitrektomie in der Verletzungschirurgie. In: Jacobi KW (ed) Aktuelle Ophthalmologie. Deutscher Ärzte-Verlag, Cologne, pp 17–31
Hübner H (1982) Intravitreale Steroidinjektion. Fortschr Ophthalmol 79:236–238
Hutton WL, Snyder WB, Vaiser A (1976) Vitrectomy in the treatment of ocular perforating injuries. Am J Ophthalmol 81:733–739
Jessop JD, Vernon-Roberts B, Harris J (1973) Effects of gold salts and prednisolone on inflammatory cells. I. Phagocytic activity of macrophages and polymorphs in inflammatory exsudates studied by a 'skin-window' technique in rheumatoid and control patients. Ann Rheum Dis 32:294–300
Johnston S (1971) Perforating eye surgery: a five year survey. Trans Ophthalmol Soc UK 91:895–921
Junge U, Perings E, Lubrich E (1974) Hemmung von Fibroblastenkulturen durch D-Penicillamin. Klin Wochenschr 52:749–796
Kreiger AE, Straatsma BR, Foos RY (1977) Incisional complications in pars plana vitrectomy. Mod Probl Ophthalmol 18:210–223
Machemer R (1981) Correspondence. Am J Ophthalmol 92:133
Mein C, Blumenkranz M (1982) Antiproliferative agents in traumatic detachment. ARVO abstracts. Invest Ophthalmol Vis Sci [Suppl] 22:234
Michels RG, Ryan SJ (1975) Results and complications of 100 consecutive cases of pars plana vitrectomy. Am J Ophthalmol 80:24–29
Moorhead LC (1983) Effects of β-aminoproprionitrile after posterior penetrating injury in the rabbit. Am J Ophthalmol 95:97–109
Müller US, Wagner H, Wirth W, Junge-Hülsing G, Hauss WH (1971) Die mesenchymsuppressive Wirkung von D-Penicillamin. Arzneimittelforsch 21:679–683
Müller-Jensen K, Mandelcorn MS (1975) Membrane formation by autotransplanted retinal pigment epithelium (RPE). Mod Probl Ophthalmol 15:228–234
Nimni ME (1979) Penicillamine and collagen metabolism. Scand J Rheumatol [Suppl] 28:71–78
Nimni ME, Bavetta LA (1965) Collagen defect induced by penicillamine. Science 150:905–907
Oguchi C (1913) Über die Wirkung von Blutinjektionen in den Glaskörper nebst Bemerkungen über die sog. Retinitis proliferans. Graefe's Arch Clin Exp Ophthalmol 84:446–520
Paulmann H, Behrendt K (1980) Experimentelle Pars-plana-Vitrektomie: Folgerungen für die klinische Praxis. Ber Dtsch Ophthalmol Ges 77:587–591
Pilkerton AR, Rao NA, Marak GE, Woodward SC (1979) Experimental vitreous fibroplasia following perforating ocular injuries. Arch Ophthalmol 97:1707–1709
Pratt WB, Aronow L (1966) The effect of glucocorticoids on protein and nucleic acid synthesis in mouse fibroblasts growing in vitro. J Biol Chem 241:5244–5250
Priestley GC (1980) Changes in the growth and metabolism of cells cultured from normal, sclerotic and rheumatoid connective tissue brought about by D-penicillamine and by sodium salicylate. J Invest Dermatol 74:413–417
Pülhorn G, Teichmann KD, Teichmann I (1977) Intraocular fibrous proliferation as an incisional complication in pars-plana vitrectomy. Am J Ophthalmol 83:810–814
Radtke ND, Tano Y, Chandler D, Machemer R (1981) Simulation of massive periretinal proliferation by autotransplantation of retinal pigment epithelial cells in rabbits. Am J Ophthalmol 91:76–87
Rozen VB, Chernin LS (1965) Effects of different doses of glucocorticoids on the growth of monolayer cultures of connective tissue. Fed Proc 24:T861–862
Ruhmann AG, Berliner DL (1965) Effect of steroids on growth of mouse fibroblasts in vitro. Endocrinology 76:916–927
Ruhmann AG, Berliner DL (1967) Influence of steroids on fibroblasts. II. The fibroblast as an assay system for topical anti-inflammatory potency of corticosteroids. J Invest Dermatol 49:123–130
Ryan SJ, Allen AW (1979) Pars-plana vitrectomy in ocular trauma. Am J Ophthalmol 88:483–491
Schmidt P, Pedersen B (1981) Perforating eye injuries. Visual results after 5 years. Acta Ophthalmol (Copenh) 59:949–958
Sugita G, Tano Y, Machemer R (1980) Intravitreal autotransplantation of fibroblasts. Am J Ophthalmol 89:121–130
Swann DA (1977) On the integrity of vitreous structure. In: Freeman HM (ed) Vitreous surgery and advances in fundus diagnosis and treatment. Appleton-Century-Crofts, New York, pp 3–14
Tano Y, Sugita G, Abrams G, Machemer R (1980a) Inhibition of intraocular proliferations with intravitreal corticosteroids. Am J Ophthalmol 89:131–136
Tano Y, Chandler DB, Machemer R (1980b) Treatment of intraocular proliferations with intravitreal triamcinolone acetonide. Am J Ophthalmol 90:810–816

Tano Y, Chandler DB, McCuen BW, Machemer R (1981) Glucocorticosteroid inhibition of intraocular proliferation after injury. Am J Ophthalmol 91:184–189

Topping TM, Abrams GW, Machemer R (1979) Experimental double-perforating injury of the posterior segment in rabbit eyes. The natural history of intraocular proliferation. Arch Ophthalmol (Chicago) 97:735–742

Trese MT, Spitznas M, Foos RY, Hall MO (1980) Experimental tractional retinal detachment in rabbits. Clinical picture and histopathologic features. Graefe's Arch Clin Exp Ophthalmol 214:213–222

Weiss JF, Belkin M (1981) The effect of penicillamine on posttraumatic vitreous proliferation. Am J Ophthalmol 92:625–627

Wiedemann P, Kirmani M, Santana M, Sorgente N, Ryan AJ (1983) Control of experimental massive periretinal proliferation by daunomycin: dose-response relation. Graefe's Arch Clin Exp Ophthalmol 220:233–235

Winthrop SR, Cleary PE, Minckler DS, Ryan SJ (1980) Penetrating eye injuries: a histopathological review. Br J Ophthalmol 64:809–817

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