SURVEY OF OPHTHALMOLOGY VOLUME 47 • NUMBER 4 • JULY–AUGUST 2002

ELSEVIER

MAJOR REVIEW

Management of Traumatic Hyphema

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Abstract. Hyphema (blood in the anterior chamber) can occur after blunt or lacerating trauma, after intraocular surgery, spontaneously (e.g., in conditions such as rubeosis iridis, juvenile xanthogranuloma, iris melanoma, myotonic dystrophy, keratouveitis (e.g., herpes zoster), leukemia, hemophilia, von Willebrand disease, and in association with the use of substances that alter platelet or thrombin function (e.g., ethanol, aspirin, warfarin). The purpose of this review is to consider the management of hyphemas that occur after closed globe trauma. Complications of traumatic hyphema include increased intraocular pressure, peripheral anterior synechiae, optic atrophy, corneal bloodstaining, secondary hemorrhage, and accommodative impairment. The reported incidence of secondary anterior chamber hemorrhage, that is, rebleeding, in the setting of traumatic hyphema ranges from 0% to 38%. The risk of secondary hemorrhage may be higher in African-Americans than in whites. Secondary hemorrhage is generally thought to convey a worse visual prognosis, although the outcome may depend more directly on the size of the hyphema and the severity of associated ocular injuries. Some issues involved in managing a patient with hyphema are: use of various medications (e.g., cycloplegics, systemic or topical steroids, antifibrinolytic agents, analgesics, and antiglaucoma medications); the patient's activity level; use of a patch and shield; outpatient vs. inpatient management; and medical vs. surgical management. Special considerations obtain in managing children, patients with hemoglobin S, and patients with hemophilia. It is important to identify and treat associated ocular injuries, which often accompany traumatic hyphema. We consider each of these management issues and refer to the pertinent literature in formulating the following recommendations. We advise routine use of topical cycloplegics and corticosteroids, systemic antifibrinolytic agents or corticosteroids, and a rigid shield. We recommend activity restriction (quiet ambulation) and interdiction of non-steroidal anti-inflammatory agents. If there is no concern regarding compliance (with medication use or activity restrictions), follow-up, or increased risk for complications (e.g., history of sickle cell disease, hemophilia), outpatient management can be offered. Indications for surgical intervention include the presence of corneal blood staining or dangerously increased intraocular pressure despite maximum tolerated medical therapy, among others. (**Surv Ophthalmol 47**:297–334, 2002.

Key words. Amicar • aminocaproic acid • corneal blood staining • Cyclokapron • eye trauma • glaucoma • hyphema • optic atrophy • prednisone • sickle cell disease • tranexamic acid

Hyphema (blood in the anterior chamber) can occur after blunt or lacerating trauma, or after intraocular surgery.[94,123,144,174,184,189,190,204] Hyphema can occur spontaneously in conditions such as rubeosis iridis (e.g., associated with diabetic retinopathy, central retinal vein occlusion, carotid occlusive disease, or chronic retinal detachment), vascular tufts at the pupillary margin, juvenile xanthogranuloma, iris

0039-6257/02/$–see front matter
PII S0039-6257(02)00317-X

melanoma, myotonic dystrophy, keratouveitis (e.g., herpes zoster), leukemia, hemophilia, thrombocytopenia, or Von Willebrand disease.[5,10,14,17,24,29,40,43,45,105,118,128] Hyphema also occurs in association with the use of substances that alter platelet or thrombin function (e.g., ethanol, aspirin, warfarin).[95,103,171]

In this review, we consider the management of hyphemas that occur after closed globe trauma. Despite the fact that much has been written on this subject, the management of patients with traumatic hyphema is controversial.[11,119,162,167,168] Some issues confronting the physician managing a patient with hyphema are: use of medications (e.g., cycloplegics, systemic or topical steroids, antifibrinolytic agents, analgesics, and antiglaucoma medications); restriction of the patient's activity; use of a patch and shield; identification of criteria by which patients can be assigned to outpatient vs. inpatient management (e.g., age, systemic disease, intraocular pressure, associated injuries, follow-up compliance); medical vs. surgical management; and management of patients with sickle cell disease/trait or hemophilia and hyphema. Another important issue in the management of traumatic hyphema is the identification and treatment of associated ocular injuries, as the presence of hyphema is a hallmark of severe injury. In most patients, the cause of poor vision after resolution of the hyphema is the associated injury and not the hyphema itself[35,98,142,145,158,185,203] (Table 1). In the review that follows, we will consider each of these management questions and will refer to the pertinent literature in formulating a recommendation.

I. Mechanisms of Hemorrhage and Blood Resorption

In urban medical centers, approximately two-thirds of traumatic hyphemas result from blunt trauma and one-third from lacerating injury.[65,186]

Blunt injury is associated with antero-posterior compression of the globe and simultaneous equatorial globe expansion. Equatorial expansion induces stress on anterior chamber angle structures, which may lead to rupture of iris stromal and/or ciliary body vessels with subsequent hemorrhage.[210] Secondary hemorrhage, also termed *rebleeding*, may be due to clot lysis and retraction from traumatized vessels.

TABLE 1

Primary Causes of Visual Acuity Chronically Worse than 20/40 after Traumatic Hyphema

Study	Hyphema	Associated Injury
Gilbert and Jensen[71]	2/14 (14%)	12/14 (86%)
Gregersen[85]	1/13 (8%)	12/13 (92%)
Read and Goldberg[161]	11/33 (33%)	22/33 (67%)

Lacerating injury can also be associated with direct damage to blood vessels and hypotony, both of which can precipitate hyphema. Hyphema after intraocular surgery can be due to granulation tissue in the wound margin or due to damaged uveal vessels (e.g., from surgical trauma or from intraocular lens-induced uveal trauma).[94,123,144,174,184,189,190,204] This mechanism should be considered in patients with a history of ocular surgery who present with apparent traumatic hyphema.

In conditions such as rubeosis iridis (e.g., associated with proliferative diabetic retinopathy, central retinal vein occlusion, carotid occlusive disease, or chronic retinal detachment), juvenile xanthogranuloma, iris melanoma, iris leiomyosarcoma, myotonic dystrophy, and vascular iris tufts, iris vessel fragility may predispose to hyphema.[10,14,17,24,29,40,43,105,118] Minor trauma might precipitate hyphema in this setting.

Spontaneous hyphema can also occur in patients using drugs that alter platelet or thrombin function (e.g., aspirin, alcohol, warfarin) and in patients with blood dyscrasias.[3,14,45,95,103,118,171] Some patients with uveitis (particularly in the setting of herpes zoster uveitis) develop spontaneous hyphema.[5] For example, we have seen patients with acute retinal necrosis develop hyphema (Fig. 1). In children without a history of trauma, if there is no evidence of a predisposing ocular or systemic disease or medication, then the possibility of child abuse should be considered.

Duke-Elder proposed that hyphema absorption might occur through the anterior surface of the iris.[59] Several groups have shown that erythrocytes leave the anterior chamber via the trabecular meshwork as relatively intact, undamaged cells.[30,32,77,78,91,177] Uncomplicated hyphemas usually clear within approximately 1 week.

II. Epidemiology

The mean annual incidence of hyphema is approximately 17 per 100,000 population.[4] In one study, the mean annual incidence for male and female patients was 20 and 4 per 100,000 population, respectively.[99] The peak incidence is between ages 10–20 years.[15,63,68,70,79,98,106,140,143,161,175] The average age of patients is less than 25 years.[63,68,70,98,99,106,143,173,216] The majority (~80%) of hyphema patients are males probably because most cases develop after trauma.[63,68,70,98,99,106,140,143,173,175,197,199,208,216] In one study, 44% of traumatic hyphemas occurred on the street (during assaults), and 12% occurred at work or during athletics.[158] Similar findings have been reported by other investigators[63,65,70,173,175,183,186] but not by all,[98,99,143,147,211] which may reflect the local customs and environment of the various reporting medical centers. Presumably, one could reduce the incidence at work or athletics by using protective devices. Preven-

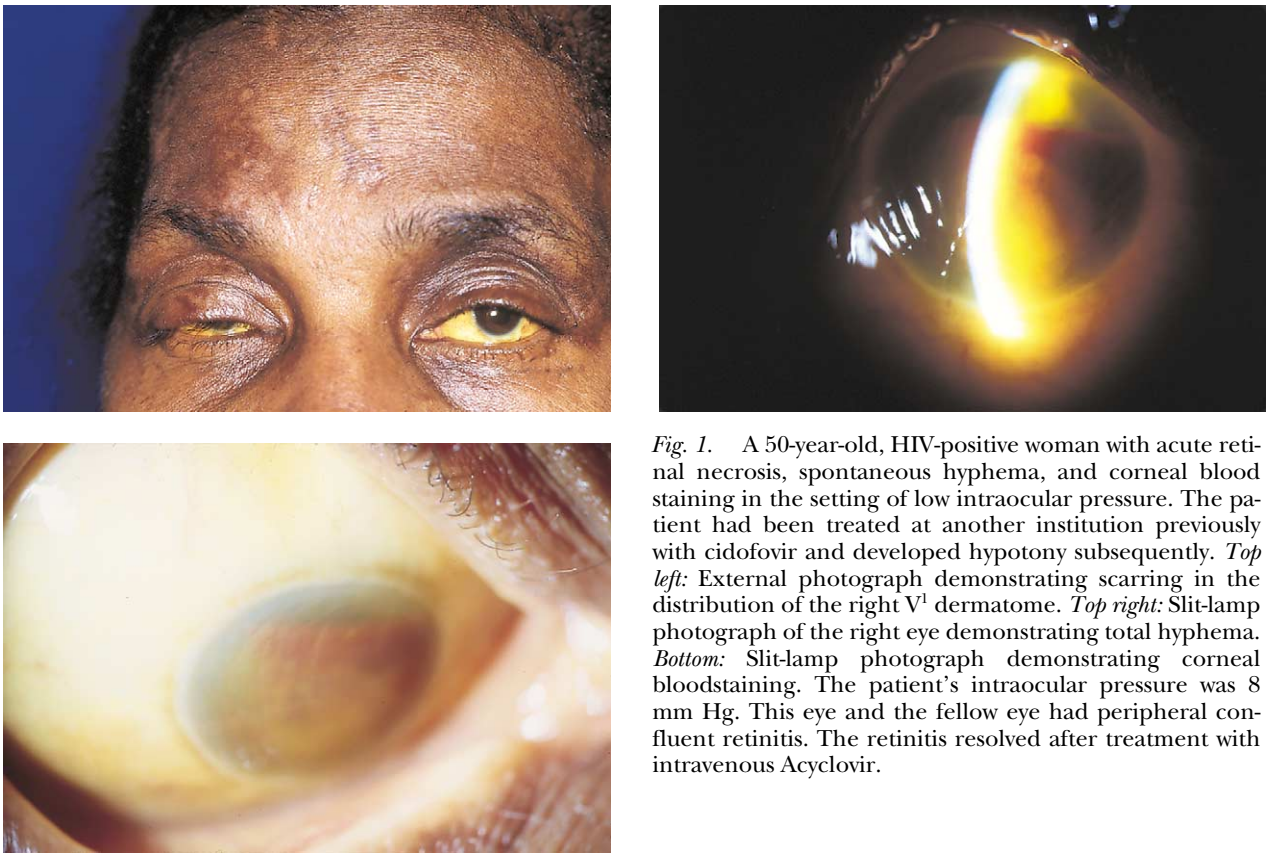

Fig. 1. A 50-year-old, HIV-positive woman with acute retinal necrosis, spontaneous hyphema, and corneal blood staining in the setting of low intraocular pressure. The patient had been treated at another institution previously with cidofovir and developed hypotony subsequently. *Top left:* External photograph demonstrating scarring in the distribution of the right V^1 dermatome. *Top right:* Slit-lamp photograph of the right eye demonstrating total hyphema. *Bottom:* Slit-lamp photograph demonstrating corneal bloodstaining. The patient's intraocular pressure was 8 mm Hg. This eye and the fellow eye had peripheral confluent retinitis. The retinitis resolved after treatment with intravenous Acyclovir.

tion in other settings, for example, motor vehicle accident–associated hyphema due to airbag deployment, would be much more difficult.[57,136] Projectile injuries tend to account for a greater proportion of hyphema-related injuries among children than adults, and blows to the eye tend to account for a greater proportion of hyphema-related injuries among adults than children.[186]

There probably are race-related differences in the rate of secondary hemorrhage. Patients reported in the Scandinavian literature appear to have a substantially lower incidence of rebleeding after traumatic hyphema compared to patients reported from centers (mostly urban) in the United States and Great Britain (Tables 2 and 3). Spoor et al found that secondary hemorrhage was significantly more frequent in African-American patients than in Caucasian patients.[186] Some studies confirm this finding,[32,47,49,108,110,141,149,179] but not all.[34,42,65,99,106,161,166,193] Some investigators[19,141] suggest that the incidence of secondary hemorrhage in African-Americans is specific to those with sickle cell hemoglobinopathy, but others[34,49,110,149,179,186] do not. In a report on Iranian patients, the control rebleeding rate was 26%,[157] which resembles that in North American urban populations. In a report on Lebanese patients, the rebleeding rate was 27%.[173] Some of these outcomes may be due to racial differences in iris melanin content, which may play a role in hyphema resorption. Lai et al found that injecting melanin into a rabbit eye with a Nd-YAG–induced hyphema prolonged resorption and influenced the rate of rebleeding.[111] Histopathologically the trabecular meshwork was mechanically obstructed by melanin-laden macrophages, which would explain the prolonged presence of the hyphema. There was no clear histologic explanation for the increased rate of rebleeding. The authors speculated that inflammation and early clot lysis are mediated by melanin.

III. Complications

In general, visual prognosis and complications are substantially worse in the setting of total hyphema as opposed to subtotal hyphema.[28,159] For example, recovery of good visual acuity (i.e., better than 20/50) following hyphema clearance occurred in 104/137 (76%) patients in one study.[161] In the setting of total hyphema, however, good visual recovery (>20/50) occurred in only 7/20 (35%) patients.[161]

A. INCREASED INTRAOCULAR PRESSURE

Approximately one-third of all hyphema patients exhibit increased intraocular pressure.[48] In the setting of traumatic hyphema, intraocular pressure may

TABLE 2

Incidence of Rebleeding with Traumatic Hyphema: Non Scandinavian Literature

Investigator	Incidence of Rebleeding	Investigator	Incidence of Rebleeding
Agapitos et al[4]	24/316 (8%)	Kushner[106]	16/100 (16%)
Bedrossian[13]	1/58 (2%)	Kutner et al[108]	3/13 (23%)
Britten[26]	6/54 (11%)	Laughlin[114]	18/49 (37%)
Cassel et al[34]	16/100 (16%)	Lawrence et al[115]	11/108 (10%)
Cole and Byron[42]	30/100 (30%)	Leone[117]	25/121 (21%)
Coles[44]	57/235 (24%)	Loring[121]	17/56 (30%)
Crawford et al[45]	16/127 (13%)	McGetrick et al[130]	7/21 (33%)
Crouch and Frenkel[47]	9/27 (33%)	Nasrullah and Kerr[141]	9/99 (9%)
Crouch et al[49]	12/54 (22%)	Ng et al[143]	40/462 (9%)
Darr and Passmore[50]	15/109 (14%)	Rahmani et al[158]	21/80 (26%)
Deans et al[52]	24/316 (8%)	Rakusin[159]	36/370 (10%)
Eagling[60]	12/67 (18%)	Read and Goldberg[161]	30/137 (22%)
Edwards and Layden[63]	64/184 (35%)	Shammas and Matta[173]	34/127 (27%)
Ferguson and Poole[66]	35/200 (18%)	Shea[175]	16/113 (14%)
Fritch[69]	3/50 (6%)	Skalka[179]	34/250 (14%)
Geeraets et al[70]	10/152 (7%)	Smith[180]	6/27 (22%)
Gilbert and Jensen[71]	15/117 (13%)	Spaeth and Levy[183]	10/46 (22%)
Gillan[72]	8/35 (23%)	Spoor et al[185]	7/43 (16%)
Goldberg[73]	12/41 (29%)	Spoor et al[186]	40/188 (21%)
Gorn[79]	24/195 (12%)	Teboul et al[191]	2/46 (4%)
Henry[89]	35/204 (17%)	Thomas et al[193]	25/156 (16%)
Howard et al[92]	5/50 (10%)	Thygeson and Beard[194]	13/34 (38%)
Kearns[98]	13/314 (4%)	Volpe et al[203]	3/56 (5%)
Kennedy and Brubaker[99]	18/248 (7%)	Wilson et al[212]	15/59 (25%)
Kraft et al[104]	1/25 (4%)	Wilson et al[211]	26/105 (25%)

These studies report the rate of secondary hemorrhage in a variety of clinical settings. Thus, some patients may have been treated with agents that may increase (e.g., aspirin) or decrease (e.g., topical corticosteroids) the rate of secondary hemorrhage compared to untreated patients. The racial composition of the patients also varies among the studies. Some studies excluded patients with microscopic hyphemas or patients who presented more than one day after injury. These variations may underlie the wide range of secondary hemorrhage rates reported.

be elevated for several reasons. Acutely, the pressure may be elevated due to the following: 1) occlusion of the trabecular meshwork by clot, inflammatory cells, or erythrocytic debris; or 2) pupillary block secondary to a collar button-shaped clot involving both the anterior and posterior chambers. The intraocular pressure varies unpredictably with the size of the hyphema. For example, patients with sickle cell disease can have high intraocular pressure with relatively small hyphema volume. This caveat not withstanding, it is generally true that the larger the hyphema volume, the greater the likelihood of increased in-

TABLE 3

Incidence of Rebleeding After Traumatic Hyphema: Scandinavian Literature

Investigator	Incidence of Rebleeding
Bengtsson and Ehinger[15]	7/171 (4%)
Bramsen[22]	9/135 (7%)
Gregersen[85]	11/200 (6%)
Mortensen and Sjolie[140]	3/56 (5%)
Ohrstrom[145]	4/167 (2%)
Oksala[147]	12/128 (9%)
Sjolie and Mortensen[178]	4/44 (9%)
Uusitalo et al[198]	9/126 (7%)
Varnek et al[200]	12/130 (9%)
Zetterstrom[219]	4/59 (7%)

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TABLE 4

Incidence of Glaucoma after Traumatic Hyphema: Effect of Rebleeding

Investigator	Incidence of Glaucoma *without* Rebleeding	Incidence of Glaucoma *with* Rebleeding
Cole and Byron[42]	14%	60%
Darr and Passmore[50]	0%	67%
Gregersen[84, 85]	3%	45%
Henry[89]	14%	51%
Kitazawa[101]	7%	67%
Leone[117]	4%	36%
Loring[121]	2%	59%
Shea[175]	2%	25%
Thygeson and Beard[194]	0%	54%

traocular pressure.[44,159] Secondary hemorrhage is often associated with increased intraocular pressure (Table 4). In the setting of a total hyphema, a normal or low intraocular pressure should alert one to the possibility of a ruptured globe.[160] An initial period of elevated intraocular pressure can be followed, however, by a period of normal or low intraocular pressure even in the absence of a ruptured globe, provided that a secondary hemorrhage does not occur.[46,60,92] (This period of temporarily reduced pressure may be due to decreased aqueous humor production and may play a role in predisposing patients to secondary hyphema, particularly as the normal process of clot lysis proceeds.[46,60,92])

The incidence of late-onset glaucoma in eyes with a history of traumatic hyphema ranges from 0–20%.[18,26,195,196] Glaucoma developing days to years after the inciting injury can arise from damage to the trabecular meshwork (often associated with angle recession), descemetization and fibrosis of the trabecular meshwork, siderosis of the trabecular endothelium, or peripheral anterior synechia formation leading to secondary angle closure glaucoma.[80] The incidence of angle recession after eye trauma ranges from 20–94%.[26,33,92,97,161,195,196] The possibility of developing glaucoma in an eye with angle recession appears to be related to the extent of angle recession. The greater the circumferential extent of angle recession, the greater the chance of subsequently developing glaucoma, particularly if more than 180° of the anterior chamber angle is involved.[9,125,138,195,196] If extensive, posterior synechiae, which can form as a result of inflammation, also can cause secondary angle-closure glaucoma. Ghost-cell glaucoma, caused by dehemoglobinized erythrocyte diffusion from the vitreous cavity into the anterior chamber weeks to months after a vitreous hemorrhage, can be associated with a khaki-colored hyphema and is another cause of late-onset intraocular pressure elevation after trauma.[31]

In patients without a history of sickle cell disease, we routinely manage elevated intraocular pressure medically with beta-adrenergic antagonists (e.g., timolol, levobunolol, or betaxolol) or alpha-2 adrenergic agonists (e.g., apraclonadine or brimonidine). If these medications are inadequate, topical or systemic carbonic anhydrase inhibitors (e.g., dorzolamide, brinzonamide, methazolamide, or acetazolamide) are added. If these measures are ineffective, isosorbide, oral glycerin, or intravenous mannitol is administered. We do not recommend pilocarpine use in these patients for three reasons. First, pilocarpine may increase vascular permeability and promote fibrin deposition in an already inflamed eye. Second, the possibility of iridolenticular adhesions and seclusio pupillae may be greater with a miotic pupil. Third, fundus examination is impaired. Prostaglandin (e.g., latanoprost) use in the management of increased intraocular pressure associated with traumatic hyphema is not yet reported. In our practice, prostaglandins usually are not employed in this setting because of a presumed increase in the inflammatory response.

B. PERIPHERAL ANTERIOR SYNECHIAE

Persistence of the hyphema for more than 1 week can result in the formation of peripheral anterior synechiae (PAS). In one study, PAS (circumferentially $\leq 180°$) were encountered in five eyes in which the hyphema remained longer than eight days.[161] The hyphema occupied more than half the anterior chamber volume in four of these cases and about one-third of the anterior chamber in volume in the remaining case. The incidence of PAS increased with size and duration of visible hyphema greater than 8 days. Posterior synechiae also can form. Presumably, synechia formation is the result of inflammation or clot organization.

C. OPTIC ATROPHY

In the setting of traumatic hyphema, optic atrophy tends to occur as a result of elevated intraocular pressure or due to optic nerve contusion. In a prospective study, Read and Goldberg found that 8/137 (6%) eyes had optic atrophy characterized by pallor without glaucomatous cupping.[161] In 5 (4%) eyes transient intraocular pressure elevation was noted, and optic atrophy without cupping was attributed to this pressure elevation. In 3 (2%) eyes, no period of elevated intraocular pressure was detected. The latter cases may represent traumatic optic neuropathy secondary to short posterior ciliary artery damage caused by optic nerve contusion. Of the 5 eyes with optic atrophy and elevated pressures, 3 had total hyphemas. Although the data underlying these conclusion are limited, the risk of optic atrophy related to elevated intraocular pressure appears to be greater if the pressure is allowed to remain at 50 mm Hg or more for 5 days or 35 mm Hg or more for 7 days, in otherwise healthy individuals.[161] In these eyes optic nerve head cupping does not develop with optic nerve atrophy as it does in chronic glaucoma patients. Patients with sickle cell disease/trait can develop optic atrophy with smaller intraocular pressure elevations (see below).

D. CORNEAL BLOODSTAINING

The incidence of traumatic hyphema-associated corneal bloodstaining varies from 2–11%.[28,44,161,173] Among patients with total hyphema, however, the incidence is substantially higher, ranging from 33–100% in two studies.[161,173] Corneal bloodstaining tends to occur in the setting of larger hyphemas, re-

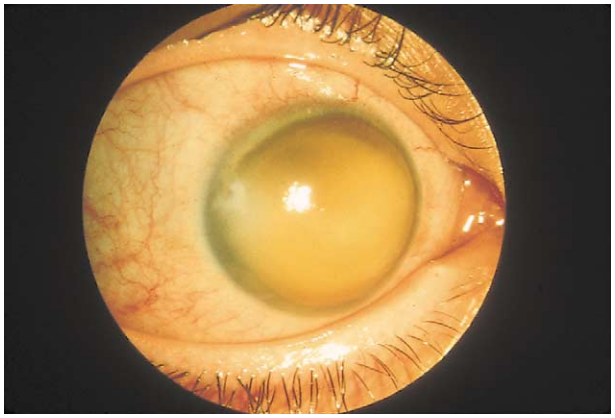

Fig. 2. Diffuse corneal bloodstaining. Note that there is less blood staining near the limbus. This opacity can cause amblyopia in susceptible patients.

bleeding, prolonged clot duration, sustained increased intraocular pressure, and corneal endothelial cell dysfunction (Fig. 2).[28,58,124,161,173] Corneal bloodstaining can occur, however, with a less than total hyphema,[28,161] and, in the setting of endothelial dysfunction, in the presence of low or normal intraocular pressure.[16,28,90,160,161,194] Corneal endothelial damage associated with traumatic disruption of Descemet's membrane or with mechanical damage induced during surgery can lead to corneal bloodstaining.[82,132] Corneal bloodstaining can cause decreased visual acuity after hyphema resolution and can cause deprivation amblyopia in infants and children.[28]

Because Read and Goldberg found that corneal bloodstaining was more likely to occur in patients with a total hyphema associated with intraocular pressure >25 mm Hg and ≥6 days duration, these investigators recommend that one manage such eyes surgically by day 6 if the hyphema does not resolve below 50%.[160,161]

The earliest sign of corneal bloodstaining is a straw yellow discoloration of the deep stroma, which should be distinguished from the light reflected off the surface of the blood clot in the anterior chamber. One clue to the presence of bloodstaining vs. reflected light is the presence of greater stromal discoloration centrally than peripherally. Early signs of corneal bloodstaining include the presence of tiny yellowish granules in the posterior third of the corneal stroma or blurring of the fibrillar appearance of the corneal stroma.[46,160] Crouch and Crouch believe that these early biomicroscopic signs precede gross blood staining by 24–36 hours, and they suggest that clot evacuation at this stage can prevent gross staining with corneal clearing in 4–6 months.[46] As indicated above, even if the intraocular pressure is normal, it is important to perform daily slit-lamp examination to detect corneal bloodstaining. The opacity usually clears from the periphery toward the center, and the process can require 2 or 3 years.[4,28,58,90,129,173] The blood product protoporphyrin has been identified by Gottsch and coworkers as a phototoxic compound in the anterior chamber of patients with hyphema and has been demonstrated to photosensitize the endothelium experimentally.[81,82] Endothelial cell decompensation or degeneration is the earliest event in the pathogenesis of corneal bloodstaining.[81,82,129] Mechanical disruption of the endothelium may play a role in the pathogenesis of endothelial decompensation, but photosensitization of the endothelium by hemoglobin-derived porphyrins in the presence of ambient light may also disrupt endothelial function.[82] For this reason, we agree with Gottsch's suggestion that patching eyes with longstanding hyphemas may reduce the chance for corneal bloodstaining.[80]

Pathologically, endothelial degeneration and eosinophilic deposits distributed throughout the stroma characterize corneal bloodstaining.[129,132] The latter aggregates of hemoglobin or hemoglobin breakdown products, seen ultrastructurally as electron-dense deposits, are located primarily within the stromal lamellae. Both hemoglobin and hemosiderin are concentrated in the central corneal stroma.[129,132] Ultrastructural studies and energy dispersion analysis of x-rays indicate that hemoglobin tends to be extracellular between collagen fibrils, and hemosiderin tends to be in the keratocyte cytoplasm.[129,132] Free hemoglobin particles tend to be concentrated more posteriorly, and hemosiderin granules are concentrated more anteriorly. In the areas of staining, keratocytes show hemoglobin and hemosiderin accumulation as well as vacuolization and necrosis, particularly if overloaded with hemoglobin.[132] Messmer et al noted that the posterior stroma also tends to be hypocellular compared to the anterior stroma.[132] In two studies of acutely stained corneas, the epithelium was intact, stained diffusely positive for iron, and contained intracellular hemosiderin and extracellular hemoglobin accumulation.[129,155]

As noted above, in both acutely stained and clearing corneas, the endothelium exhibits areas of discontinuity and degeneration.[129,132] Descemet's membrane is intact. Hemoglobin particles are located within as well as on Descemet's membrane. X-ray dispersive analysis demonstrates the presence of iron within Descemet's membrane as well as throughout the stroma and within the epithelium.

Messmer et al posited the following mechanism for corneal bloodstaining.[132] First, hemoglobin is released from erythrocytes in the anterior chamber, diffuses across Descemet's membrane, and aggregates focally within the membrane as well as within the stromal lamellae. Second, the keratocytes phago-

cytize and metabolize hemoglobin, producing intracellular hemosiderin. Excess intracellular hemosiderin/hemoglobin induces keratocyte necrosis, with attendant decreased cellularity of the posterior stroma. Third, released hemosiderin is phagocytized by keratocytes in the anterior stroma.

McDonnell et al found that most clearing occurred from the periphery toward the center, and the demarcation between cleared and stained corneal stroma was abrupt both clinically and histopathologically.[129] Cleared stroma lacked extracellular hemoglobin deposits, although keratocytes in these areas did contain hemosiderin.[129] In contrast to the studies of Yoshimura et al and Kanai et al, Pouliquen and Desvignes, McDonnell et al, and Messmer et al did not observe macrophages in areas of corneal bloodstaining.[96,129,132,155,218] Yoshimura et al noted macrophages in the stroma where new blood vessels were formed, but corneal bloodstaining in this case was secondary to intracorneal hemorrhage in the setting of interstitial keratitis.[218]

Based on these findings and the lack of macrophages in stained cornea, McDonnell et al proposed that corneal bloodstaining clears by diffusion.[129] The experimental work of Gottsch et al indicates that hemoglobin is phagocytized by keratocytes and degraded to hemosiderin.[82] McDonnell et al noted an area of clear anterior stroma underlying stained epithelial cells and proposed that epithelial cell shedding might also clear the anterior corneal stroma of hemoglobin pigment.[129]

Both Pouliquen and Desvignes and McDonnell et al found intact stromal lamellae in bloodstained corneas despite vacuolization and degeneration of keratocytes in areas of extensive hemoglobin deposition.[129,155] McDonnell et al noted that keratocytes in the cleared areas of cornea appeared intact ultrastructurally and that the stroma was hypocellular in areas where partial clearing had occurred. McDonnell et al suggested that keratocyte loss was due to iron toxicity and that repopulation of the stroma occurred as fibrocytes grew into the stroma from the periphery.[129] As a result, they concluded that corneal stromal changes produced by bloodstaining probably were reversible.

McDonnell and coworkers pointed out that molecular hemoglobin has a diameter of 64 Å, and, according to Maurice, there is approximately 60 Å between corneal stromal collagen fibrils available for diffusion.[126,129] They suggested that corneal edema occurring in the setting of endothelial dysfunction (secondary either to elevated intraocular pressure or to direct insult due to trauma) would increase the intrafibrillar distance, permitting diffusion of hemoglobin into the cornea. After intraocular pressure lowering, the cornea can deturgesce, resulting in a reduction in the intrafibrillar distance rendering diffusion of the hemoglobin molecule out of the corneal stroma a relatively slow process.

E. SECONDARY HEMORRHAGE

Secondary hemorrhage is present if the size of the hyphema increases, if a layer of fresh blood is noted over the older, darker clot in the anterior chamber, or if dispersed erythrocytes appear over the clot after the blood has settled. Total and near total hyphemas, which often appear dark red, may become bright red at the clot periphery as the clot dissolves.[46,161] This change in color due to clot lysis should be distinguished from secondary hemorrhage.[161,215] Rebleeding can cause a substantial increase in the size of the hyphema. For this reason, rebleeding can be associated with complications such as increased intraocular pressure, corneal bloodstaining, optic atrophy, and peripheral anterior synechiae. Edwards and Layden reported that surgical intervention was required in 1/120 (0.8%) patients without secondary hemorrhage vs. 10/64 (16%) patients with secondary hemorrhage.[63] In another retrospective study, Thomas et al[193] also found that patients with rebleeding had a higher incidence of surgical intervention (i.e., in 14/44 [32%] with rebleeding vs. 1/131 [0.7%] patients without rebleeding), commonly under general anesthesia (9/14 [64%] patients). Eyes with total hyphemas were even more likely to require surgery than the eyes with subtotal hyphemas. In a prospective randomized double blind study, Kutner et al found that 2/3 (67%) patients with secondary hemorrhage vs. 0/31 patients without secondary hemorrhage required surgical intervention.[108] Considering the relatively high incidence of surgical intervention for complications of rebleeding, the risks of surgery (including general anesthesia) may justify the use of a treatment that significantly reduces the incidence of rebleeding. Secondary hemorrhage can occur following even a microscopic hyphema.[4,117] Although some studies report a greater likelihood of secondary hemorrhage with larger hyphemas,[4,34,44,63,99,173,186,213] others report no clear relationship between the initial size of the hyphema and the incidence of secondary hemorrhage.[68,79,89,98,106,108,115,117,143,149,161,176,183,193] Thus, one should consider the use of medications to reduce the likelihood of rebleeding regardless of the hyphema size.

F. ACCOMMODATIVE IMPAIRMENT

Theriault reviewed the records of 30 patients who had traumatic hyphema.[192] Average follow-up was 29.6 months. He observed that in measuring near point of accommodation, 2 (7%) had reading disability requiring asymmetric spectacle correction of

greater than 2.5 diopters. Thus, evaluation of accommodative amplitude may be important when following these patients.

IV. Medical Management to Prevent Rebleeding

A. PHARMACOLOGIC THERAPY

1. Antifibrinolytic Agents

Pandolfi et al suggested using ε-aminocaproic acid to prevent intraocular hemorrhage in 1966.[150] In most studies, antifibrinolytic agents (i.e., tranexamic acid and ε-aminocaproic acid) significantly lower the rate of rebleeding after traumatic hyphema and also may delay clot resorption (Tables 5 and 6).[65,130,137,149,197–200]

A generally small but consistent difference in the rebleeding rate between control and tranexamic acid treatment groups has been reported (Table 5). In the North American literature there is strong evidence that ε-aminocaproic acid (Amicar [Lederle Laboratories, American Cyanamid Company, Pearl River, NY]) decreases the rate of rebleeding after traumatic hyphema (Table 6).

ε-aminocaproic acid is a water-soluble antifibrinolytic agent that resembles the amino acid lysine.[1,2,146] Normally, plasmin binds to lysine molecules in the fibrin clot via a lysine binding site. Amicar competitively inhibits fibrin clot digestion by occupying plasmin's lysine binding site. Also, ε-aminocaproic acid competitively inhibits activating substances in plasma that convert plasminogen to plasmin, perhaps by binding to plasminogen and preventing its binding to fibrin, even after activation to plasmin.[6] Through these mechanisms, ε-aminocaproic acid stabilizes the fibrin clot, thus preventing rebleeding while permanent vessel repair takes place. Amicar is absorbed in the gastrointestinal tract, reaches peak plasma levels in three hours, and is excreted primarily via the kidneys with a clearance rate approximately 75% of the glomerular filtration rate.[154] The dose of Amicar must be adjusted for patients with renal failure. Relatively low doses will inhibit fibrinolysis in the urine. Thus, Amicar can precipitate renal colic in patients with renal failure or even mild cases of hemophilia,[154] and its urinary antifibrinolytic activity can persist even after the serum concentration is subtherapeutic. Active intravascular clotting and known allergy to ε-aminocaproic acid are contraindications to the use of Amicar. Relative contraindications to Amicar use include a history or predisposition to thrombosis, hematuria of upper renal tract origin, renal failure, and hemophilia. Amicar is an FDA pregnancy category C drug, and it is not known whether it crosses the placenta or is found in breast milk.[152]

Tranexamic acid (Cyklokapron [Pharmacia]) also resembles lysine and is similar to ε-aminocaproic acid in mechanism of action. It is similarly absorbed by the gastrointestinal tract (30–50%), reaches peak concentration in three hours, and is excreted mostly by the kidneys, so the dose must be adjusted in renal failure. Overdoses (3–40 times recommended human dose for 6 days to a year) in laboratory animals have caused focal areas of retinal atrophy. There have been no reports of retinal atrophic changes in human clinical trials. A branch retinal artery occlusion has been described 5 days after starting the drug.[151] Central retinal vein occlusion has been asso-

TABLE 5

Effect of Tranexamic Acid on Rebleeding after Traumatic Hyphema

Investigator	Incidence of Rebleeding	
	Control	Tranexamic Acid
Bramsen[22a]	9/135 (7%)	1/72 (1%)
Bramsen[23]	ND	0/75 (0%)
Clarke and Noel[36]	ND	0/21 (0%)[b]
Deans et al[52a]	24/316 (8%)	5/163 (3%)
Mortensen and Sjolie[140a]	3/56 (5%)	0/64 (0%)
Rahmani et al[158a]	21/80 (26%)	8/80 (10%)
Uusitalo et al[197a]	21/219 (10%)	1/121 (1%)
Uusitalo et al[198]	3/55 (6%)	0/58 (0%)
Vangsted and Nielsen[199]	0/53 (0%)[b]	0/59 (0%)[b]
Varnek et al[200a]	12/130 (9%)	2/102 (2%)

ND = Not done.

[a]No-treatment cohort studied retrospectively. Tranexamic acid treatment cohort studied prospectively.

[b]Cohort was treated with topical steroids as well.

TABLE 6

Effect of ε-Aminocaproic Acid on Rebleeding after Traumatic Hyphema

Investigator	Incidence of Rebleeding	
	Placebo	ε-Aminocaproic Acid
Crouch and Frenkel[47]	9/27 (33%)	1/32 (3%)
Crouch et al[49]	12/54 (22%)	2/64 (3%)[a]
Kraft et al[104]	1/25 (4%)	2/24 (8%)
Kutner et al[108]	3/13 (23%)	0/21 (0%)
McGetrick et al[130]	7/21 (33%)	1/28 (4%)
Spoor et al[186]	40/187 (21%)[b]	6/54 (11%)
Teboul et al[191]	2/46 (4%)	1/48 (2%)
Volpe et al[203]	3/56 (5%)[c]	3/63 (5%)
Wilson et al[211]	15/59 (25%)[a]	1/46 (2%)

[a]Topical as well as systemic Amicar was used. The incidence of secondary hemorrhage was 1/35 (3%) and 1/29 (3%) among the topical and systemic Amicar treatment groups, respectively.

[b]Historical control group.

[c]The no Amicar treatment group is composed of historical as well as prospectively randomized controls.

TABLE 7

Meta-Analysis: Effect of Tranexamic Acid on the Rate of Secondary Hemorrhage

Study	Statistic		
	From Fisher's Exact Test 1-tailed p	For Stouffer's Combined Test z	For Fisher's Combined Test $-2\log_e p$
Bramsen[22]	0.0828	−1.386481472	4.982654435
Deans et al[52]	0.0341	−1.823682396	6.756915789
Mortensen and Sjolie[140]	0.0987	−1.288995009	4.631340665
Rahmani et al[158]	0.0064	−2.489286999	10.10291458
Uusitalo et al[197]	0.0006	−3.238965292	14.83716181
Vangsted and Nielsen[199]	0.1121	−1.215435077	4.376727898
Varnek et al[200]	0.1171	−1.189609975	4.289454017

Fisher's Combined Test

$$\sum(-2\log_e p) = 49.97716919$$
$$df = 14$$
$$p_{FC} = 0.00000616$$

Stouffer's Combined Test

$$\sum Z_C = -12.63245622$$
$$\sqrt{N} = 2.645751311$$
$$Z_{Combined} = -4.774619658$$
$$p_{SC} = 0.000001$$

The results of the clinical trials cited above comparing the effects of tranexamic acid on the rate of secondary hemorrhage were analyzed using meta-analytic[214] techniques. These studies were selected based on the availability of data from both control and treatment groups within a given study. A 1-tailed (since the direction was already known) probability value was calculated for each 2 by 2 contingency table (Treatment vs. Outcome) using Fisher's exact test. These probabilities were then combined into an over-all, combined probability using both:

Fisher's Combined Test

Where minus 2 times the sum of the natural log of the p values ($-2*\sum\log_e p$) is distributed as χ^2 with 2*n degrees of freedom, where n is the number of tests combined and p is the one-tailed probability associated with each test.

Stouffer's Combined Test

Where each probability value is converted to a z score before combining the z's according to the following equation:

$$Z_{combined} = \sum z_i / \sqrt{N}$$

Where $Z_{combined}$ is the overall z score, and N is the number of tests combined. A combined p value (assuming normality) was then calculated for $Z_{combined}$.

ciated with tranexamic acid use.[181] In vitro, the antifibrinolytic potency is approximately five to 10 times that of ϵ-aminocaproic acid. Tranexamic acid crosses the placenta and is found in breast milk at 1% of the maternal circulation concentration and is considered to be a FDA pregnancy category B drug.[53] Tranexamic acid has similar contraindications and relative contraindications as Amicar. Neither oral tranexamic acid nor oral ϵ-aminocaproic acid is label-indicated for the treatment of hyphema in the United States.

In 4 prospective studies (3 from the same institution), Amicar was found to decrease the incidence of rebleeding from 22–33% to 0–4% (Table 6).[47,108,130,149] In the studies by Crouch and Frenkel,[47] McGetrick et al,[130] and Palmer et al,[149] children as well as adults were included (age range: 3 to 50 years). In the study by Kutner et al,[108] children less than 7 years of age were excluded from randomization. The studies by Crouch and Frenkel, McGetrick et al, and Palmer et al took place in an urban setting. Crouch and Frenkel had 38/59 (64%) African-American and 21/59 (36%) Caucasian patients. McGetrick et al had 34/49 (69%) African-American, 10/49 (20%) Hispanic, and 5/49 (10%) Caucasian patients. Palmer et al had 31/59 (53%) African-American, 12/59 (20%) Hispanic, and 16/59 (27%) Caucasian patients. Kutner et al's study differs in that 29/34 (85%) of the patients were Caucasian.[108] Thus, these studies indicate that Amicar effectively prevents rebleeding regardless of age or race. It may be useful to note that clot dissolution following Amicar discontinuation can mimic a secondary hyphema, but the dissolved cells appear khaki-colored and not red.[56]

The study of Crouch and Frenkel included eight patients with sickle cell trait or sickle cell disease, and these patients appeared to respond as well as the others in the study group. The studies by McGetrick et al, Palmer et al, and Kutner et al, however, excluded patients with hemoglobin S. In addition, in the studies by McGetrick et al and Palmer et al, topical steroids were used indiscriminately, and patients were treated with cycloplegic-mydriatic agents, whereas in the study of Kutner et al, no patient was treated with cycloplegic-mydriatic agents or steroids. All patients were treated as in-patients in the previously cited four studies, and patients were treated at a dose of 100 mg Amicar/kg body weight by mouth every 4 hours up to a maximum dose of 30 g/day for a total of 5 days.[47,108,130,149] Palmer et al randomized some patients to a 50 mg/kg every 4 hours dose regimen.[149] In summary, Amicar appears to be effective in decreasing the incidence of rebleeding in African-Americans, Caucasians, and Hispanics, in children and adults, and in males as well as females. Although the effectiveness of Amicar in patients with sickling hemoglobinopathies has not been proven, we suspect that such patients can be treated with Amicar safely.

Some studies have found Amicar ineffective in reducing the risk of secondary hemorrhage (Table 6). Teboul et al found a low rebleeding rate in both the treatment and placebo groups and attributed this rate and the apparent ineffectiveness of Amicar to the fact that African-American patients constituted only 4% of the study population.[191] Of note, the duration of hospital stay and clot resorption time were both increased significantly in the Amicar treatment group. Kraft and coworkers found that among 49 patients (ages 3–18 years) randomly assigned to receive either 100 mg/kg Amicar or placebo, there was no significant benefit on the rate of secondary hemorrhage, and hyphemas in the Amicar-treated group cleared significantly more slowly (mean 5.3 days vs. 2.6 days among controls).[104] Other investigators also have observed that time for clot lysis may be prolonged with Amicar use.[65,108,130,149] (Tranexamic acid also delays the clearance of hyphemas.[197–200]) In contrast to the studies cited above, Kraft et al[104] and Teboul et al[191] did not find Amicar to be effective in children (see below). Among patients examined within 1 day of injury, Volpe et al found the rate of secondary hemorrhage to be 5% (3/63) among patients treated with Amicar and 5% (3/56) among non-treated patients.[203] A separate group of patients examined more than 1 day after injury had a 39% (5/13) rate of secondary hemorrhage. (Some of the patients presenting more than 24 hours after injury were treated with Amicar, but the report does not indicate which of the 5 were so treated.) The rebleeding rate among untreated patients is rather low in these studies, but children do not appear to have a lower secondary hemorrhage rate than adults.[4,44,63,68,115,121,161,175,186] In the studies of Kraft et al and Volpe et al, the patient populations were predominately Caucasian.[104,203] Also, topical corticosteroids were used in one study,[203] and this medication may have altered the incidence of secondary hemorrhage (see below). Aylward et al[11] reported a meta-analysis of six randomized, controlled, clinical trials involving the use of aminocaproic acid[47,104,108,130] and tranexamic acid.[199,200] The results confirmed a beneficial effect of systemic antifibrinolytic agents on the rate of secondary hemorrhage (but not on final visual acuity). Fisher's combined (FC) test and Stouffer's combined (SC) test were used for a meta-analysis of the data in Tables 5 and 6.[214] Both tests (Table 7) indicated that the decreased incidence of rebleeding associated with tranexamic acid use is highly statistically significant ($p < 0.0001$ [FC] and $p < 0.0001$ [SC]). Both tests (Table 8) indicated that the decreased incidence of rebleeding associated with ϵ-aminocaproic acid is highly statistically significant ($p < 0.0001$ [FC] and $p < 0.0001$ [SC]).

Amicar has some undesirable systemic side effects. McGetrick et al, DeBustros et al, and Kutner et al found that nausea, vomiting, or diarrhea occurred in approximately 25% of the patients receiving this medication.[51,108,130] These side effects seem to be related to the medication, as they resolve with the removal of the drug. The 6–18% incidence of postural hypotension is of concern because this side effect might limit the feasibility of outpatient hyphema management. Other reported side effects include pruritus, muscle cramps, rash, nasal stuffiness, arrhythmia, and confusional states.[104,108] Rhabdomyolysis and myoglobinuria are infrequent complications of ϵ-aminocaproic acid therapy, but they tend to occur after a prolonged course of therapy (e.g., 6 weeks) at doses of 24–36 g/day.[25,27,122] As noted above, Amicar can precipitate acute renal failure in patients with even mild hemophilia.[154] The possibility of cardiac muscle damage should be considered when skeletal myopathy occurs. Adverse effects of Amicar not reported in the ophthalmic literature include teratogenicity and thromboembolic events.[152] Nausea and vomiting may be due to local irritation of the gastrointestinal tract, since these side effects are not seen after intravenous drug administration. Most side effects, however, are probably related to plasma ϵ-aminocaproic acid levels.[149] In addition to being more potent than Amicar, oral tranexamic acid may have less frequent gastrointestinal side effects.[52]

In this regard, it may be important to note that the prospective randomized study of Palmer et al showed that a lower dose regimen (50 mg/kg every 4 hours up to a maximum dose of 30 gm/day) was:

TABLE 8

Meta-Analysis: Effect of ϵ-Aminocaproic Acid on the Rate of Secondary Hemorrhage

Study	Statistic		
	From Fisher's Exact Test 1-tailed p	For Stouffer's Combined Test z	For Fisher's Combined Test $-2\log_e p$
Crouch and Frenkel[47]	0.002	−2.878150553	12.4292162
Crouch et al[49]	0.0015	−2.967717592	13.00458034
Kraft et al[104]	0.8901	1.227060693	0.232842926
Kutner et al[108]	0.0478	−1.666567186	6.081459279
McGetrick et al[130]	0.0077	−2.422821126	9.7330699
Spoor et al[186]	0.0627	−1.532498572	5.538787663
Teboul et al[191]	0.4839	−0.040367922	1.45175401
Volpe et al[203]	0.6026	0.260082516	1.013003305
Wilson et al[211]	0.0006	−3.238965292	14.83716181

Fisher's Combined Test

$$\sum(-2\log_e p) = 64.32187543$$
$$df = 18$$
$$p_{FC} = 0.00000040$$

Stouffer's Combined Test

$$\sum Z_C = -13.25994504$$
$$\sqrt{N} = 3$$
$$Z_{Combined} = -4.4199817$$
$$p_{SC} = 0.000005$$

The results of the clinical trials cited above comparing the effects of ϵ-aminocaproic acid on the rate of secondary hemorrhage were analyzed using meta-analytic[214] techniques. These studies were selected based on the availability of data from both control and treatment groups within a given study. A 1-tailed (since the direction was already known) probability value was calculated for each 2 by 2 contingency table (Treatment vs. Outcome) using Fisher's exact test. These probabilities were then combined into an over-all, combined probability using both:

Fisher's Combined Test
where minus 2 times the sum of the natural log of the p values ($-2*\Sigma\log_e p$) is distributed as χ^2 with 2*n degrees of freedom, where n is the number of tests combined and p is the one-tailed probability associated with each test, and the

Stouffer's Combined Test
where each probability value is converted to a z score before combining the z's according to the following equation:

$$Z_{combined} = \Sigma z_i / \sqrt{N}$$

where $Z_{combined}$ is the overall z score, and N is the number of tests combined. A combined p value (assuming normality) was then calculated for $Z_{combined}$.

1) effective in preventing rebleeding (1/26 [4%] in the 50 mg/kg vs. 5/33 [16%] in the 100 mg/kg q4 hours groups), 2) produced peak, trough, and mean Amicar blood levels within the range of inhibition of plasmin formation, and 3) was associated with a significantly lower incidence of dizziness and hypotension than the 100 mg/kg dose (0/26 vs. 5/33 [15%]).[149] The incidence of the dizziness and hypotension appeared to be unrelated to age. The incidence of nausea or vomiting was similar in each group (5/26 [20%] vs. 9/33 [27%]) in the 50/mg/kg-group and 100 mg/kg-group, respectively) and typically responded to prochlorperazine edisylate (5–10 mg PO or IM q6 hours). When Amicar is used, one should consider taking precautions regarding the development of dizziness, hypotension, nausea, and/or emesis (e.g., use of bathroom with assistance, pretreatment with prochlorperazine).

Loewy et al examined the antifibrinolytic activity of Amicar in the plasma and aqueous humor of rabbits after systemic administration.[120] After a 50 mg/kg intravenous bolus, aqueous humor ϵ-aminocaproic acid levels peaked at roughly 60 minutes (13 mg/dl), and aqueous antifibrinolytic activity increased ~1.6–1.8-fold over control. A 100 mg/kg IV bolus produced higher aqueous levels (34 mg/dl) and greater antifibrinolytic activity (2.5-fold increase). The investigators noted that although the peak aqueous humor concentration in the 50 mg/kg group was less than half that of the 100 mg/kg

group, the rates of antifibrinolytic activity were quite comparable (490 s vs. 683 s).[120] This result may mean that Amicar inhibition of fibrinolysis is saturable. These data corroborate the clinical effectiveness of the 50 mg/kg q4 hours dose regimen.

Amicar produces significant inhibition of plasminogen activation at plasma levels of 1.3 mg/dl, and plasma levels of 1.3 mg/dl are effective in inhibiting systemic fibrinolysis.[86,131] Peak and trough plasma Amicar levels were roughly 13 mg/dl and 5 mg/dl (at 240 minutes) after a 50 mg/kg intravenous bolus in Loewy et al's study and 8 mg/dl and 6 mg/dl in the clinical study of Palmer et al.[120,149] This result may mean that even lower doses of Amicar are effective clinically provided that the dose interval is adjusted. Thus, there is a real possibility that Amicar could be of practical utility in outpatient hyphema management provided low enough doses can be used that are both therapeutically effective and associated with a low incidence of side effects.

To reduce the systemic effects of oral of ε-aminocaproic acid, topical administration of ε-aminocaproic acid has been examined. Allingham et al determined that the greatest aqueous concentrations of topical ε-aminocaproic acid were obtained with a carboxypolymetheylene (58 mg/ml) preparation.[8] This preparation, applied topically every 6 hours, effectively reduced the incidence of secondary hemorrhage in an animal model.[7] Using knowledge of the concentrations of ε-aminocaproic acid needed to achieve a therapeutic effect, Ehlers et al determined the optimum combination to be 30% ε-aminocaproic acid: 2% carboxypolymethylene.[64] In a prospective, randomized, double-masked, multicenter trial, Crouch at al found that topically (0.2 ml of the gel applied in the inferior fornix every 6 hours) and systemically administered ε-aminocaproic acid were equally effective.[49] In this study, the topical ε-aminocaproic acid group had a 3% (1/35) incidence of secondary hemorrhage compared to a 3% (1/29) incidence in the systemic ε-aminocaproic acid group and a 22% (12/54) incidence in the control group. The topical ε-aminocaproic acid-treatment group had a final visual acuity of 20/40 or better in 30/35 (86%) patients compared with 20/69 (69%) patients in the systemic-treatment group and 23/43 (53%) patients in the control group. Four (11%) patients reported a conjunctival or corneal foreign body sensation, and transient punctate corneal staining was observed in three (9%) patients. Systemic side effects were observed in 1 (3%) adult patient compared to 5 (17%) of 29 patients taking systemic ε-aminocaproic acid. The 10-fold increase in the serum levels in the systemically-treated ε-aminocaproic acid group compared with the topically-treated group accounts for the different incidence of side effects.[49] The control group consisted of patients who refused entry to the study, which could create selection bias, but there was an equal distribution of initial hyphema size, patient demographics, and initial visual acuity among the three cohorts. A recent randomized, double-blind, placebo-controlled study found rebleeding occurred in 2/24 (8%) eyes treated with topical ε-aminocaproic acid and in 8/27 (30%) placebo-treated eyes.[153] This difference was not statistically significant. In summary, it appears that topical and systemic ε-aminocaproic acid provides comparable protection from rebleeding. There is, however, no available commercial formulation of topical ε-aminocaproic acid currently.

To prevent a transient rise in intraocular pressure following discontinuation of Amicar, it may be useful to taper the medication.[56,203,211] The presence of active intravascular clotting is a contraindication to Amicar use. It may be hazardous to use Amicar in the presence of renal insufficiency (for which dosage must be reduced), hemophilia,[139] possibly hepatic insufficiency (one reported case of death due to intracranial hemorrhage associated with hepatic and cardiac necrosis at a total dose of 26 g [2 g every 6 hours]), pregnancy (during which teratogenic effects may occur), and, possibly, total hyphemas. (The effect of delayed clot lysis on the incidence of corneal bloodstaining is unestablished.)

Despite the fact that ε-aminocaproic acid and tranexamic acid have been shown to decrease the incidence of rebleeding (Tables 5 and 6), they have no consistent statistically proven beneficial effect on visual outcome in the setting of traumatic hyphema.[11] Fisher's combined (FC) test and Stouffer's combined (SC) test were used for a meta-analysis of data in Tables 5 and 6.[214] Both tests (Table 9) indicated that tranexamic acid use is not associated with a statistically significant benefit on visual outcome ($p < 0.148$ [FC] and $p < 0.098$ [SC]). Both tests (Table 10) indicated that ε-aminocaproic acid use is not associated with a statistically significant benefit on visual outcome ($p < 0.0625$ [FC] and $p < 0.135$ [SC]). The lack of proven benefit on visual outcome has led some clinicians to refrain from using these agents in managing traumatic hyphema.[11,98,191,203,119] One should not conclude, however, that these results necessarily mean that there is no real visual benefit to the use of antifibrinolytic agents in patients with traumatic hyphema. To demonstrate that the absence of a statistically significant difference in outcome (e.g., visual acuity) means that two groups actually had "the same" outcome, a study must be designed with the power to detect a clinically important difference.[20,61,107] To design such a study, one must take into account the variability of the outcome in question, the sample size, and the chosen level of significance.

TABLE 9

Meta-Analysis: Effect of Tranexamic Acid on Visual Outcome

Study	Statistic		
	From Fisher's Exact Test 1-tailed p	For Stouffer's Combined Test z	For Fisher's Combined Test $-2\log_e p$
Rahmani[157]	0.1693	−0.956933945	3.55216598
Rahmani[158]	0.1343	−1.106291165	4.015358351
Mortensen[140]	0.7733	0.749757874	0.514176415
Uusitalo[198]	0.3775	−0.312053317	1.948369421
Vangsted[199]	0.1028	−1.265757419	4.549939852

Fisher's Combined Test

$$\sum(-2\log_e p) = 14.58001002$$
$$df = 10$$
$$p_{FC} = 0.14814060$$

Stouffer's Combined Test

$$\sum Z_C = -2.891278$$
$$\sqrt{N} = 2.236068$$
$$Z_{Combined} = -1.2930188$$
$$p_{SC} = 0.098002$$

The results of the clinical trials cited above comparing the effects of tranexamic acid on visual outcome were analyzed using meta-analytic[214] techniques. These studies were selected based on the availability of visual acuity data from both control and treatment groups within a given study. A 1-tailed (since the direction was already known) probability value was calculated for each 2 by 2 contingency table (Treatment vs. Outcome) using Fisher's exact test. These probabilities were then combined into an over-all, combined probability using both:

Fisher's Combined Test

where minus 2 times the sum of the natural log of the p values ($-2*\Sigma\log_e p$) is distributed as χ^2 with 2*n degrees of freedom, where n is the number of tests combined, and p is the one-tailed probability associated with each test, and the

Stouffer's Combined Test

where each probability value is converted to a z score before combining the z's according to the following equation:

$$Z_{combined} = \Sigma z_i / \sqrt{N}$$

where $Z_{combined}$ is the overall z score, and N is the number of tests combined. A combined p value (assuming normality) was then calculated for $Z_{combined}$.

Several factors may account for the lack of statistically proven benefit of antifibrinolytic agents (or corticosteroids, as detailed below) on visual outcome. First, the major determinant of final visual acuity in the setting of traumatic hyphema is usually an associated ocular injury and not the hyphema itself.[35,98,142,145,158,185,203] Read and Goldberg, for example, found that poor visual outcome could be attributed directly to the hyphema in approximately 10% of patients.[160,161] Second, a commonly held view that rebleeding per se *drastically* alters the visual prognosis does not seem to be substantiated by our review of the literature (Table 11 and references[98,99,108,193,197,203]), although Rahmani et al did find that 15/43 (35%) patients with rebleeding and 16/195 (8%) patients without rebleeding had final visual acuity of 6/120 or less ($p < 0.001$).[158] Review of published data indicates that rebleeding does seem to be associated with a mildly worse visual prognosis. Fisher's combined (FC) test and Stouffer's combined (SC) test were used for a meta-analysis of data in Table 11.[214] Both tests (Table 12) indicated that the lower likelihood of achieving visual acuity 20/50 or better associated with rebleeding is highly statistically significant ($p < 0.0001$ [FC] and $p < 0.0001$ [SC]). One interpretation of the higher risk of decreased vision associated with rebleeding, the lower risk of rebleeding associated with antifibrinolytic or corticosteroid use, and the apparent lack of association between the use of these agents and improved visual prognosis, is that rebleeding is associated with another independent variable that alters visual prognosis. Another interpretation is that the mere occurrence of rebleeding does not confer a worse visual prognosis and that only a subset of patients with secondary hemorrhage have a worse visual prognosis specifically due to rebleeding. If this were the case, one might expect that a relatively large number of pa-

TABLE 10

Meta-Analysis: Effect of ϵ-Aminocaproic Acid on Visual Outcome

Study	Statistic		
	From Fisher's Exact Test 1-tailed p	For Stouffer's Combined Test z	For Fisher's Combined Test $-2\log_e p$
Crouch[49]	0.0031	−2.736996976	11.55270633
Kraft[104]	0.8595	1.078076366	0.302808908
Kutner[108]	0.4788	−0.05316565	1.472944611
McGetrick[130]	0.2708	−0.610396	2.612749476
Volpe[203]	0.4408	−0.148941126	1.638328042

Fisher's Combined Test

$$\sum(-2\log_e p) = 17.57953737$$
$$df = 10$$
$$p_{FC} = 0.06248420$$

Stouffer's Combined Test

$$\sum Z_C = -2.4714234$$
$$\sqrt{N} = 2.236068$$
$$Z_{Combined} = -1.1052541$$
$$p_{SC} = 0.134525$$

The results of the clinical trials cited above comparing the effects of ϵ-aminocaproic acid on visual outcome were analyzed using meta-analytic[214] techniques. These studies were selected based on the availability of visual acuity data from both control and treatment groups within a given study. A 1-tailed (since the direction was already known) probability value was calculated for each 2 by 2 contingency table (Treatment vs. Outcome) using Fisher's exact test. These probabilities were then combined into an over-all, combined probability using both:

Fisher's Combined Test

where minus 2 times the sum of the natural log of the p values ($-2*\sum\log_e p$) is distributed as χ^2 with 2*n degrees of freedom, where n is the number of tests combined, and p is the one-tailed probability associated with each test, and the

Stouffer's Combined Test

where each probability value is converted to a z score before combining the z's according to the following equation:

$$Z_{combined} = \sum z_i / \sqrt{N}$$

where $Z_{combined}$ is the overall z score, and N is the number of tests combined. A combined p value (assuming normality) was then calculated for $Z_{combined}$.

tients would have to be followed in order to prove a statistically significant association between a decrease in the incidence of rebleeding and an improvement in visual outcome.

Visual outcome may be related closely to hyphema volume. For example, Edwards and Layden found that final visual acuity declined as a function of hyphema volume, regardless of whether that volume was achieved on presentation or after rebleeding.[63] Other investigators have reported similar or compatible results.[44,142,147,159,161,193,194] (The incidence of glaucoma also appears to be related to the volume of blood in the anterior chamber.[44,159]) Although Rahmani et al did not find an association between hyphema volume and visual outcome, they excluded patients with "black ball" (i.e., total) hyphemas, patients with definite rebleeding before admission, and patients referred more than 48 hours after the trauma from their study, which may have biased the results.[158]

If the hypothesis that visual outcome is directly related to hyphema volume is true, then one can understand why it has been difficult to demonstrate a visual benefit with the use of Amicar, for example, despite its proven benefit in decreasing the incidence of rebleeding. Most hyphemas occupy less than one third of the anterior chamber volume and even after rebleeding occupy less than one-half of the anterior chamber.[52,63,68,98,130,158,161,186,211] In studies that have assessed the efficacy of Amicar, the majority of patients had less than one-third of the anterior chamber filled with blood even after rebleeding. Compared to the initial hyphema, however, the probability of a secondary hemorrhage becoming total is much greater.[52,161,193] Thus, to the extent that secondary hemorrhage is associated with a substantial increase in the volume of blood in the anterior chamber, it probably is associated with a worse visual prognosis. Because most hyphemas, both primary

TABLE 11

Effect of Secondary Hemorrhage on Visual Outcome

Investigator	Final Acuity 20/50 or Better: *without* Rebleeding	Final Acuity 20/50 or Better: *with* Rebleeding
Agapitos et al[4]	160/176 (91%)[a]	17/22 (77%)[a]
Coats et al[39]	20/22 (91%)	3/3 (100%)[a]
Edwards and Layden[63]	59/120 (49%)	36/64 (56%)
Fritch[69]	34/47 (72%)[b]	0/3 (0%)[b]
Gilbert and Jensen[71]	85/102 (83%)	10/15 (67%)
Gregersen[84,85]	180/189 (95%)	9/11 (82%)
Leone[117]	84/96 (88%)	20/25 (80%)
Loring[121]	29/39 (74%)	9/17 (53%)
Shea[175]	75/84 (89%)	10/16 (63%)
Spaeth and Levy[183]	39/65 (60%)[a]	12/20 (60%)[a]
Spoor et al[185]	34/36 (94%)	5/7 (71%)
Thygeson and Beard[194]	18/21 (86%)	7/13 (54%)

[a]These cohorts had final visual acuity of 20/30 or better.
[b]These cohorts had final visual acuity of 20/40 or better.

and secondary, do not result in greater than 50% filling of the anterior chamber, they are not commonly associated with decreased visual acuity. Therefore, study of a very large number of patients might be necessary to demonstrate a visually significant outcome with the use of antifibrinolytic agents.

2. Corticosteroids

Trauma-induced breakdown of the blood-ocular barrier might enhance the diffusion of some plasma proteins into the anterior chamber, including plasminogen, thus increasing the risk of secondary hemorrhage.[145,150] By stabilizing the blood-ocular barrier and by directly inhibiting fibrinolysis, corticosteroids might reduce the risk of secondary hemorrhage. Yasuna postulated that steroid-induced reduction of uveitis might decrease the tendency of congested uvea to rebleed.[217]

The first reports demonstrating that corticosteroids reduce the incidence of secondary hemorrhage after traumatic hyphema involved the use of topical medications (Table 13). Oksala reported that topical corticosteroids (Decadron [dexamethasone sodium phosphate, Merck] 3–6 times daily) reduced the incidence of secondary hemorrhage.[147] In this study, patients with hyphemas 4 mm in height or greater were not treated with steroids, and it is not clear what the incidence of secondary hemorrhage was among patients treated with and without steroids. In a prospective study, Zetterstrom showed that topical Decadron drops (5 times daily) reduced the incidence of secondary hemorrhage among patients permitted quiet ambulation vs. those treated with bed rest but no topical corticosteroids.[219] In a retrospective review of 462 patients treated over 10 years, Ng et al found a statistically significant decrease in the frequency of secondary hemorrhage among patients treated with topical steroids.[143] A 5% (11/215) rebleeding rate was calculated for the group of patients treated with topical steroids (with or without cycloplegics) vs. a 12% (29/247) rebleeding rate for the group treated without topical steroids (with or without cycloplegics). These investigators did not report the dose of the topical steroids.[143] In retrospective studies, Fong[68] and Gorn[79] also found that topical steroids significantly reduced the risk of secondary hemorrhage. (Fong concluded that the observed reduction in rebleeding risk was subject to reverse causality bias due to selection of patients with more severe hyphemas for treatment and initiation of steroids in some patients after rebleeding had occurred.[68]) Although Agapitos et al observed a lower rebleeding rate among patients treated with topical corticosteroids (Table 13), they concluded that the effect was not statistically significant.[4] However, their statistical analysis may be flawed.[168] A nonrandomized retrospective study by Witteman et al did not find a reduced incidence of secondary hemorrhage associated with topical steroid use.[213] Most (99%) of the patients were Caucasian, which may underlie the low rebleeding rate observed in both the treatment and observation groups. The steroid preparation and dose were not reported.

Evidence demonstrating the effectiveness of topical steroids in preventing secondary hemorrhage is not as strong as that demonstrating the effectiveness of systemic Amicar, which has been shown to be effective in prospective, randomized, controlled clinical trials conducted at more than one medical center (Table 6). Nonetheless, we suspect topical steroids are effective based on the following reasoning. Robust evidence demonstrates that systemic and topical ϵ-aminocaproic acid reduce the incidence of secondary hemorrhage in traumatic hyphema (Ta-

TABLE 12

Meta-Analysis: Effect of Secondary Hemorrhage on Visual Outcome

Study	Statistic		
	From Fisher's Exact Test 1-tailed p	For Stouffer's Combined Test z	For Fisher's Combined Test $-2\log_e p$
Agapitos et al[4]	0.0645	−1.518055797	5.48218011
Coats et al[39]	0.9999	3.719469532	0.00020001
Fritch[69]	0.046	−1.684938979	6.158227765
Leone[117]	0.1199	−1.175487796	4.242194434
Spoor et al[185]	0.1153	−1.198814061	4.320435703
Spaeth and Levy[183]	0.143	−1.06693733	3.889821297
Thygeson and Beard[194]	0.16	−0.994457423	3.665162927
Shea[175]	0.0139	−2.200104063	8.551732878
Gregersen[84,85]	0.5992	0.25127747	1.024319694
Gilbert and Jensen[71]	0.1177	−1.186563168	4.279232529
Loring[121]	0.0509	−1.636190063	5.955784711
Edwards and Layden[63]	0.00000031	−5.36441803	29.97338708

Fisher's Combined Test	Excluding Ref 63
$\sum(-2\log_e p) = 77.54267914$	47.56929206
$df = 24$	22
$p_{FC} = 0.00000015$	0.00123633
Stouffer's Combined Test	
$\sum Z_C = -14.05521971$	−8.690801678
$\sqrt{N} = 3.4641016$	3.31662479
$Z_{Combined} = -4.0573924$	−2.620375299
$p_{SC} = 0.000025$	0.004392

The results of the clinical trials cited above comparing the effects of secondary hemorrhage on visual outcome were analyzed using meta-analytic[214] techniques. These studies were selected based on the availability of visual acuity data from both control and treatment groups within a given study. A 1-tailed (since the direction was already known) probability value was calculated for each 2 by 2 contingency table (Treatment vs. Outcome) using Fisher's exact test. These probabilities were then combined into an over-all, combined probability using both:

Fisher's Combined Test

where minus 2 times the sum of the natural log of the p values ($-2*\sum\log_e p$) is distributed as χ^2 with 2*n degrees of freedom, where n is the number of tests combined, and p is the one-tailed probability associated with each test, and the

Stouffer's Combined Test

where each probability value is converted to a z score before combining the z's according to the following equation:

$$Z_{combined} = \sum z_i / \sqrt{N}$$

where $Z_{combined}$ is the overall z score, and N is the number of tests combined. A combined p value (assuming normality) was then calculated for $Z_{combined}$.

ble 6). Systemic prednisone appears to be as effective as systemic Amicar (see below).[65] It is therefore biologically plausible that in the correct dose and with the proper formulation, topical steroids should be able to reduce the incidence of rebleeding. Many studies (but not all) indicate that this conclusion is correct (Table 13). More studies may be needed to define the minimal effective dose and optimal steroid preparation. Topical administration of steroids would eliminate some of the possible side effects of systemic steroids (e.g., hyperosmolar, hyperglycemic non-ketotic coma) and of Amicar (e.g., nausea, vomiting, orthostatic hypotension). We do not know whether, in principle, topically applied steroids and ϵ-aminocaproic acid should be equally effective. Topical steroids, however, are readily available, and topical ϵ-aminocaproic acid is not.

Prednisone appears to reduce the incidence of secondary hemorrhage after traumatic hyphema (Table 13). Yasuna first reported the effectiveness of systemic prednisone (40 mg/day in divided doses for adults and 0.6 mg/kg/day in children) in preventing secondary hemorrhage.[217] His treatment protocol included complete bed rest, sedation as needed, binocular eye pads, and no local ocular medications. (Romano has referred to the latter fea-

TABLE 13

Effect of Topical and Systemic Corticosteroids on Rebleeding after Traumatic Hyphema

Investigator	Incidence of Rebleeding	
	"Control"	Corticosteroids
Agapitos et al[4]	11/79 (14%)	13/237 (5%) (T)
Farber et al[65a]	4/56 (7%) (A)	4/56 (7%) (S)
Gorn[79]	6/98 (6%)	1/52 (2%) (T)
Kennedy and Brubaker[99]	15/203 (7%)	3/45 (7%) (T)
Ng et al[143]	29/247 (12%)	11/215 (5%) (T)
Ohrstrom[145]	ND	4/167 (2%) (T)
Rahmani et al[158a]	21/80 (26%) (P)	14/78 (18%) (S)
Rakusin[159a]	2/24 (8%)[b]	1/13 (8%) (T)
Romano[165]	ND	0/34 (0%) (S)
Romano and Phillips[167]	ND	0/24 (0%) (S)
Rynne and Romano[169]	12/38 (32%)	1/18 (6%) (S)
Spoor et al[185a]	4/20 (20%) (P)	3/23 (13%) (S)
Witteman et al[213]	5/200 (3%)	8/171 (5%) (T)
Witteman et al[213]	9/318 (3%)	5/53 (9%) (S)
Yasuna[217]	9/50 (18%)	0/50 (0%) (S)
Zetterstrom[219a]	4/59 (7%)	0/58 (0%) (T)

S = systemic prednisone; T = topical corticosteroid; P = placebo; A = Amicar; ND = not done.
[a]Prospective, randomized study.
[b]controls were treated with topical chloramphenicol 0.5% (21 cases) or no antibiotic (3 cases).

ture as the "no touch" protocol although tonometry was done initially at least.[167]) In a double-blind prospective randomized study, Spoor et al found no significant difference in the incidence of rebleeding or final visual acuity between the placebo- and prednisone-treatment groups.[185] Although the dose of prednisone was identical to the dose used in uncontrolled studies that had shown a beneficial effect, the duration of steroid treatment was different. Spoor treated with prednisone for no longer than 7 days (in order to eliminate the need for steroid tapering). If the hyphema resolved earlier than 7 days after presentation, the steroids were discontinued. Previous investigators, however, continued steroid treatment for a full 5 days regardless of whether or not the hyphema cleared.[169,217] The lack of full 5-day treatment and possible lack of statistical power in the study by Spoor and co-workers may account for the discrepancy in results.[164] Also, as part of the management plan, Yasuna[217] and Rynne and Romano[169] recommended that no local ocular medications be administered, which may also play a role in reducing the frequency of secondary hemorrhage.

In a nonrandomized retrospective study, Witteman did not find systemic steroid use associated with a lower incidence of secondary hemorrhage.[213] The steroid dose used was not reported. The authors stated that patients prescribed systemic steroids tended to have the more severe hyphemas. Also, some patients not receiving systemic steroids were treated with topical steroids, which may have lowered the rebleeding rate in the comparison group.

In a double-blind randomized prospective clinical trial of Amicar vs. oral prednisone involving 112 patients, Farber et al found that the rebleeding rate for each group was 7% (4/56).[65] Fifty-six patients received a 5-day course of 40 mg oral prednisone adjusted for weight in 2 divided doses daily, for patients over 60 kg body weight, or a dose of 0.6 mg/kg/day for patients weighing less than 60 kg. Fifty-six patients received a 5-day course of 50 mg/kg Amicar every 4 hours up to 30 g/day. Patients with sickle cell trait/disease, intravascular coagulopathy, gastric ulcer, diabetes mellitus, intoxicated patients, patients with blood in the stool, and pregnant patients were excluded from the study. All patients were admitted to the hospital. Neither topical steroids nor aspirin were used. There was no untreated control group in this study. There were no differences in the patient populations, including representation of African-Americans, who constituted 53% (59/112) of the study population. There were no differences in admission or final visual acuity.[65] This study confirmed prior reports by Yasuna[217] and Rynne and Romano[169] and showed that oral prednisone is as effective as oral Amicar in reducing the incidence of rebleeding after traumatic hyphema. Because of the lack of a "no treatment" control group, the study does not prove that either therapy is more effective than no treatment in this population. In this study, approximately 42% of patients in the Amicar group and 75% of patients in the prednisone group exhibited no hyphema on discharge, indicating that one potential advantage of steroid use is faster clot resorption.

A prospective placebo-controlled randomized clinical trial in an Iranian population by Rahmani et al included 238 patients in whom hyphema developed after blunt trauma.[157,158] The patients were randomized to one of three groups: oral placebo (80 patients), oral tranexamic acid at 75 mg/kg/day divided in three doses (80 patients), or oral prednisone at 0.75 mg/kg/day in three divided doses (78 patients). Medicines were discontinued at 5 days if no rebleeding occurred. Patients with total hyphema, penetrating injury, immediate need for intraocular surgery, referral later than 48 hours after injury, bleeding disorder, recent aspirin or anticoagulant use, pregnancy, use of topical steroids, renal insufficiency, peptic ulcer disease, or definite rebleeding before admission were excluded from study. No patients had medication discontinued because of side effects. Rebleeding occurred in 43/238 (18%) patients: 8/80 (10%) of the tranexamic acid-treated group, 14/78 (18%) of the prednisone-treated group, and 21/80 (26%) of the placebo-treated group. The rebleeding rates of tranexamic acid and placebo treatment groups were significantly different. There was no statistically significant difference in rebleeding rate between the prednisone- and placebo-treatment groups nor between the prednisone- and tranexamic acid-treatment groups. There was no statistical difference in admission or discharge visual acuity, age, initial and discharge intraocular pressure, rate of hyphema clearance, duration of hospital stay, nor day of rebleed. (Visual acuity of 6/60 or less at the time of discharge was significantly associated with rebleeding, initial visual acuity of 6/60 or less, retinal damage, and male gender.) Final visual acuity had no significant statistical association with age, use of oral prednisone or tranexamic acid, or size of hyphema. Six eyes required surgical intervention, but the treatment groups to which the patients were assigned is not clear.[158] It is not clear why prednisone had no statistically significant effect in this study, but this study does have a placebo-treated control group that was lacking in the study of Farber et al.[65] Like the study of Farber et al,[65] however, this study showed that the incidence of rebleeding among the antifibrinolytic- and steroid-treated groups was not significantly different. Perhaps oral steroids are somewhat less effective than tranexamic acid in preventing secondary hyphema. Alternatively, limitations in the statistical power of the study may underlie the failure to demonstrate that the difference in outcome between prednisone- and placebo-treatment groups was statistically significant.[163]

Fisher's combined (FC) test and Stouffer's combined (SC) test were used for a meta-analysis of data in Table 13.[214] Both tests (Table 14) indicated that the decreased incidence of rebleeding associated with corticosteroid use is highly statistically significant ($p < 0.0001$ [FC] and $p < 0.0149$ [SC]). They also (Table 15) indicated that corticosteroid use is not associated with a statistically significant benefit on visual outcome ($p < 0.584$ [FC] and $p < 0.519$ [SC]).

3. Conjugated Estrogens

Premarin (conjugated estrogen, Wyeth-Ayerst) can increase prothrombin concentration and decrease antithrombin activity.[16] Two nonrandomized consecutive case series indicate that Premarin can reduce the likelihood of secondary hemorrhage.[73,211] A double-blind randomized prospective study by Spaeth and Levy found no difference between the incidence of rebleeding in 10/46 (22%) control patients vs. 10/39 (26%) estrogen-treated patients.[183] These investigators used Premarin 5 mg intramuscularly in children younger than 5 years of age, 10 mg intramuscularly in children under 10 years of age, and 20 mg intravenously in all other patients, daily for 5 days. A small subset of patients underwent clotting studies, and no differences between Premarin and placebo-treated patients were found.

4. Mydriatic and Miotic Agents

Rakusin examined whether the use of mydriatics, miotics, or both influences the outcome of traumatic hyphema.[159] He found no significant difference in the incidence of rebleeding, in the final visual acuity, in the rate of clot absorption, or in the incidence of complications regardless of whether the patient was using a mydriatic, a miotic, neither, or both. In a retrospective study, Gilbert and Jensen showed that the use of topical atropine sulfate 3% was unassociated with a worse visual prognosis in eyes with or without secondary hemorrhage.[71] Other retrospective studies indicate that cycloplegics have no positive or adverse effect on outcome.[44,68,143] Gorn found that cycloplegics might reduce the likelihood of secondary hemorrhage, particularly among patients using aspirin.[79] Because patients with traumatic hyphema commonly have iridocyclitis, we prescribe a cycloplegic agent (atropine 1% once per day) to relieve photophobia and to prevent formation of posterior synechiae. We prefer atropine because once-a-day dosing reduces the amount of ocular manipulation needed, which may reduce the chance of secondary hemorrhage.

5. Aspirin

In a retrospective analysis, Crawford et al demonstrated that the incidence of rebleeding is increased by aspirin regardless of the hyphema volume.[45] Patients using aspirin had a secondary hemorrhage rate of 39% (12/31) vs. 4% (4/96) among patients

TABLE 14

Meta-Analysis: Effect of Corticosteroids on the Rate of Secondary Hemorrhage

Study	Statistic		
	From Fisher's Exact Test 1-tailed p	For Stouffer's Combined Test z	For Fisher's Combined Test $-2\log_e p$
Agapitos et al[4]	0.0172	−2.115348252	8.12569179
Farber et al[65]	0.6419	0.363542085	0.886645501
Gorn[79]	0.2331	−0.728675786	2.912575466
Kennedy and Brubaker[99]	0.5816	0.205989181	1.083944706
Ng et al[143]	0.0118	−2.263586794	8.879311495
Rahmani et al[158]	0.1435	−1.064727257	3.882840488
Rakusin[159]	0.7223	0.589686806	0.650629428
Rynne and Romano[169]	0.0287	−1.900252755	7.101716312
Spoor et al[185]	0.4181	−0.206756567	1.744069281
Witteman et al[213]	0.9224	1.421403795	0.16155262
Witteman et al[213]	0.9922	2.418128133	0.015661158
Yasuna[217]	0.0013	−3.011518857	13.29078203
Zetterstrom[219]	0.0614	−1.543126018	5.580690888

Fisher's Combined Test

$$\sum(-2\log_e p) = 54.31611116$$
$$df = 26$$
$$p_{FC} = 0.00092608$$

Stouffer's Combined Test

$$\sum Z_C = -7.8352423$$
$$\sqrt{N} = 3.6055513$$
$$Z_{Combined} = -2.1731052$$
$$p_{SC} = 0.014886$$

The results of the clinical trials cited above comparing the effects of corticosteroids on the rate of secondary hemorrhage were analyzed using meta-analytic[214] techniques. These studies were selected based on the availability of data from both control and treatment groups within a given study. A 1-tailed (since the direction was already known) probability value was calculated for each 2 by 2 contingency table (Treatment vs. Outcome) using Fisher's exact test. These probabilities were then combined into an over-all, combined probability using both:

Fisher's Combined Test

where minus 2 times the sum of the natural log of the p values ($-2*\Sigma\log_e p$) is distributed as χ^2 with 2*n degrees of freedom, where n is the number of tests combined, and p is the one-tailed probability associated with each test, and the

Stouffer's Combined Test

where each probability value is converted to a z score before combining the z's according to the following equation:

$$Z_{combined} = \Sigma z_i / \sqrt{N}$$

where $Z_{combined}$ is the overall z score, and N is the number of tests combined. A combined p value (assuming normality) was then calculated for $Z_{combined}$.

not using aspirin. A subsequent retrospective study by Gorn demonstrated that the incidence of rebleeding among aspirin users was 47% (16/34) vs. 5% (3/59) among patients who did not use aspirin.[79] The difference between Tylenol (acetaminophen, McNeil)-treated and control groups was not statistically significant (Table 16). A randomized, controlled, prospective study by Marcus et al showed 3/23 (13%) patients given aspirin (500 mg PO, TID for 5 days) and 2/28 (7%) patients not given aspirin rebled. The difference between the two groups was not statistically significant, however.[125] It seems prudent to avoid using aspirin and non steroidal anti-inflammatory analgesic medications in this setting despite the conflicting evidence concerning aspirin's effect on the incidence of secondary hemorrhage.

In summary, there is strong evidence that systemic as well as topical medications, including corticosteroids, ϵ-aminocaproic acid, and tranexamic acid, decrease the risk of rebleeding among patients with traumatic hyphema. In most published studies, use of these medications has not conferred a definite visual benefit in association with the reduced frequency of secondary hemorrhage, but methodological prob-

TABLE 15

Meta-Analysis: Effect of Steroids on Visual Outcome

Study	Statistic		
	From Fisher's Exact Test 1-tailed p	For Stouffer's Combined Test z	For Fisher's Combined Test $-2\log_e p$
Rakusin[159]	0.9	1.281550794	0.210721031
Rahmani[157]	0.19	−0.877896582	3.321462414
Romano[167]	0.29	−0.553384325	2.475748712
Spoor[185]	0.64	0.358459147	0.892574205
Rahmani[158]	0.46	−0.100433226	1.553057579

Fisher's Combined Test

$$\sum(-2\log_e p) = 8453563941$$
$$df = 10$$
$$p_{FC} = 0.58462346$$

Stouffer's Combined Test

$$\sum Z_C = +0.10829581$$
$$\sqrt{N} = 2.236068$$
$$Z_{Combined} = +0.04843136$$
$$p_{SC} = 0.519314$$

The results of the clinical trials cited above comparing the effects of corticosteroids on visual outcome were analyzed using meta-analytic[214] techniques. These studies were selected based on the availability of data from both control and treatment groups within a given study. A 1-tailed (since the direction was already known) probability value was calculated for each 2 by 2 contingency table (Treatment vs. Outcome) using Fisher's exact test. These probabilities were then combined into an over-all, combined probability using both:

Fisher's Combined Test

where minus 2 times the sum of the natural log of the p values ($-2*\sum\log_e p$) is distributed as χ^2 with 2*n degrees of freedom, where n is the number of tests combined, and p is the one-tailed probability associated with each test, and the

Stouffer's Combined Test

where each probability value is converted to a z score before combining the z's according to the following equation:

$$Z_{combined} = \sum z_i / \sqrt{N}$$

where $Z_{combined}$ is the overall z score, and N is the number of tests combined. A combined p value (assuming normality) was then calculated for $Z_{combined}$.

lems such as small sample size may underlie this fact. Depending on the patient's age (e.g., elderly with a history of orthostatic hypotension), associated illnesses (e.g., hyperglycemia with diabetes mellitus), and the clinical care setting (inpatient vs. outpatient), either ϵ-aminocaproic acid, tranexamic acid, or corticosteroids can be used to reduce the chance of secondary hemorrhage. In our practice, we usually prescribe topical corticosteroids (e.g., prednisolone acetate 1% QID) to reduce intraocular inflammation. (If a child is uncooperative, however, it may be wise to use systemic medications only.) In addition, either systemic prednisone or systemic Amicar is used in most cases, depending on specific features of the case (Table 17). We suspect that tranexamic acid (e.g., 25 mg/kg PO, TID for 5 days) would serve well in circumstances in which we prefer ϵ-aminocaproic acid, but we have no clinical experience with this therapeutic modality. We also recommend the use of a long-acting cycloplegic (e.g., atropine 1%) to prevent synechia formation and relieve photophobia. Acetaminophen or codeine is used as an analgesic, and aspirin and non-steroidal anti-inflammatory analgesic medications are not used. Although we feel that this approach to medical management is justified based on the results published in the scientific literature, we note that a properly designed cost-benefit analysis of the approach has not yet been published. Furthermore, it is important to note that antifibrinolytic and anti-inflammatory agents have no statistically proven benefit on visual outcome. This fact, combined with known cost and potential risk, has led some experts to avoid the use of these medications.[11,98,191,203,119]

B. BED REST VERSUS AMBULATION MANAGEMENT

Some physicians place patients with traumatic hyphema at bed rest, hoping to minimize the chance for secondary hemorrhage. Two controlled studies,

TABLE 16

Aspirin and the Incidence of Rebleeding after Traumatic Hyphema

Treatment	Incidence of Rebleeding	
	Gorn[79]	Marcus[125]
Aspirin	16/34 (47%)	3/23 (13%)
Acetaminophen	2/13 (15%)	—
Neither Aspirin nor Acetaminophen	3/59 (5%)	2/28 (7%)

however, have demonstrated that there is no clear advantage conferred by managing patients with strict bed rest. Rakusin reported that the incidence of rebleeding among those treated with bed rest was 4% (1/26) whereas no patient treated with quiet ambulation experienced a secondary hemorrhage.[159] Read and Goldberg reported the incidence of rebleeding to be 18% (12/66) among those treated with bed rest, bilateral patching, elevation of the bed (30°), and sedation as opposed to 25% (18/71) among those treated with quiet ambulation, patching of the traumatized eye only, elevation of the bed (45°), and no sedation (Table 18). Differences between the groups were not statistically significant.[161] Each cohort's visual acuity outcomes also were similar. Thus, there appears to be no benefit conferred by limiting activity limited to strict bed rest compared to the alternative of quiet ambulation in a hospital setting.

Vangsted and Nielsen reported a prospective randomized study of bed rest vs. ambulation.[199] Exclusionary criteria were: only microscopic hyphema present; age less than 8 years; lapse of more than 24 hours between injury and presentation; or history of renal disease, blood dyscrasia, thrombotic disease, or pregnancy. One cohort was confined to bed rest for 6 days, and the other was permitted ambulation in the clinic and received tranexamic acid (25 mg/kg PO, TID × 7 days). Both cohorts received topical atropine 1% QD and dexamethasone TID as well as monocular patching. Visual outcomes were slightly worse in the group assigned to bed rest, but vision was impaired in these patients due to associated injuries and not complications of the hyphema per se.

Wright et al compared two different cohorts at two different times, hospital bed rest (retrospective, uncontrolled) vs. hospital ambulation (prospective, uncontrolled), in patients with hyphemas filling less than one-third of the anterior chamber.[216] The cohorts were well matched demographically and with respect to trauma severity. The investigators found that 4/37 (11%) patients in the bed rest group and 7/36 (19%) patients in the ambulatory group experienced a rebleed. Despite an almost 50% increase in frequency of secondary hemorrhage, this difference was not statistically significant. The final visual acuity and length of hospital stay were nearly identical in the two cohorts.[216] A number of studies indicate that bed rest provides no advantage over ambulatory management, but in many cases the ambulatory group was, as noted above, also treated with tranexamic acid and/or topical steroids (Table 18).

For most patients, it appears that there is no clear advantage to prescribing bed rest instead of quiet ambulation as long as the environment can be controlled. Children may represent a subset of patients in whom bed rest may be preferable to ambulation in a hospital setting, if there is a question of control.

C. EFFECT OF EYE PATCHING

In a prospective randomized double-blind study, Rakusin demonstrated that bilateral patching, unilateral patching, and no patching appear to be associated with the same visual outcome.[159] We recommend that patients with hyphema wear a metal or hard plastic shield at all times (including sleep) to prevent further trauma to the injured eye. Gottsch et al suggested that patients with longstanding hyphema who may have prolonged light exposure might be at risk for developing endothelial dysfunction and corneal bloodstaining.[81] Patching of these patients' affected eyes may be prudent.

D. OUTPATIENT HYPHEMA MANAGEMENT

Most published reports on the effectiveness of outpatient hyphema management are retrospective and uncontrolled (Table 19). In a non-randomized retrospective analysis, Clever reported his experience with 20 patients.[37] All had less than one-third of the anterior chamber filled with blood. Six (75%) of eight managed as inpatients had final visual acuity of 20/40 or better, and 10 of 10 managed as outpatients had similar results. One patient in each group developed a secondary hemorrhage. Of note, 2 of the patients admitted to the hospital were subsequently lost to follow-up whereas none of the cases treated as outpatients was lost to follow-up. Mortensen and Sjolie reported a non-randomized study in which 56 consecutive patients were treated with bed rest for 5 days as inpatients, and 64 consecutive patients were treated with tranexamic acid (25 mg/kg, PO, TID for 6 days), no bed rest, and as outpatients.[140] Exclusionary criteria for outpatient treatment included: age less than 12 years, increased intraocular pressure, or hemorrhage preventing a retinal examination. Although these criteria would tend to render the inpatients a more severely injured group, the two cohorts appeared well matched with regard to accompanying injuries. Fifty-two

TABLE 17

Suggestions for Use of Amicar[a] vs. Systemic Prednisone[b] in Prevention of Rebleeding

Clinical Setting	Amicar	Prednisone
Children	Not preferred	Preferred[c]
Diabetes Mellitus	Preferred	Not preferred
Hemophilia	Contraindicated	Preferred
Nausea	Not preferred	Preferred
Ocular or systemic infection	Preferred	May be contraindicated
Ocular or systemic thrombosis	Contraindicated	Preferred
Peptic ulcer disease	Preferred	Not preferred
Pregnancy	May be contraindicated	Preferred
Renal failure	Not preferred	Preferred
Ruptured Globe	Preferred	Not preferred initially[d]
Sickle cell trait/disease	?Preferred	Not preferred
Syncope	Not preferred	Preferred
Total hyphema	Not preferred	Preferred[e]

[a]Dose: 50 mg/kg po every 4 hours × 5 days up to maximum of 30 g daily.

[b]Dose: 0.6–0.75 mg/kg po/day in 2 divided doses × 5 days up to a maximum of 40 mg daily.

[c]Amicar is probably effective in children, but some studies suggest it is not (see text). More importantly, it may be easier and safer to administer systemic prednisone rather than topical predisone to children as a means of reducing intraocular inflammation (depending on the patient's ability to cooperate).

[d]May be contraindicated if infection is present. Once it is clear that infection is not present, prednisone may be preferred as a means of reducing intraocular inflammation as well as reducing the risk of secondary hemorrhage.

[e]In the setting of a total hyphema, corticosteroids might be particularly helpful in reducing the likelihood of peripheral anterior synechia formation. Also, it is not clear to us that rebleeding can occur in the setting of a total hyphema.

(93%) of 56 inpatients and 56 (88%) of 64 outpatients achieved visual acuity of 20/30 or better. Whereas none of the outpatients had a secondary hyphema, three (5%) of the inpatients did.

In another study, Sjolie and Mortensen treated 44 consecutive patients without antifibrinolytic drugs and as outpatients.[178] Children under 12 years of age were included but were hospitalized and allowed ambulatory privileges. Patients were instructed not to read, not to exert themselves, and to return for examination on the fifth and twelfth days after presentation and at any time should visual loss or pain occur. Eleven patients were admitted for increased intraocular pressure, "serious lesions of the iris," vitreous hemorrhage, or "lesions of the retina." Admitted patients were permitted ambulatory activity. Four (9%) of 44 patients had secondary hyphemas. Apparently, no patient was lost to follow-up.

Bramsen reported the results of a retrospective uncontrolled study of outpatient traumatic hyphema management.[21] Only patients with macroscopic hyphemas were studied. All patients were treated with oral tranexamic acid (25 mg/kg PO, TID for 6 days). From 1 January 1977 to 13 December 1977, 78 patients were admitted to the hospital for 5 days and were mobile without an eye bandage. From 1 January 1978 to 1 October 1978, 85 patients were admitted on the day of referral, instructed in the proper administration of the medication, and discharged the following day with permission to resume normal work and activity. Overall, 8/78 (10%) inpatients and 4/85 (5%) outpatients did not return for follow-up appointments. No secondary hemorrhages occurred among the inpatient cohort or among the 81 "outpatients" who returned for follow-up. The two treatment groups had similar visual acuity outcomes.

A retrospective uncontrolled study by Wilson et al assessed outpatient management of microscopic hyphemas without other severe eye injuries in an urban setting.[212] Of the initial 80 patients, only 62 re-

TABLE 18

Traumatic Hyphema: Bed Rest vs. Inpatient Ambulatory Management

	Incidence of Rebleeding	
Investigator	Bed Rest	Ambulation
Bramson[23,22]	1/72 (1%)[a,b]	0/75 (0%)[a,b]
Kennedy and Brubaker[99]	17/221 (8%)[a]	1/26 (4%)[a]
Rakusin[159]	1/26 (4%)	0/26 (0%)
Read and Goldberg[161]	12/66 (18%)	18/71 (25%)
Uusitalo et al[197]	21/219 (10%)[b]	1/95 (1%)[c]
Vangsted and Nielson[199]	0/53 (0%)[d]	0/59 (0%)[c,d]
Wright et al[216]	4/37 (11%)[a,b]	7/36 (19%)[a]
Zettterstrom[219]	4/59 (7%)	0/58 (0%)[d]

[a]Retrospective study.

[b]Historical controls.

[c]Treated with tranexamic acid.

[d]Treated with topical desamethasone 3–5 times daily.

TABLE 19

Inpatient (IP) vs. Outpatient (OP) Hyphema Management

Investigator	Rebleeding Rate		Final Visual Acuity		Loss to Follow-Up
	OP	IP	OP	IP	OP
Bramsen[21]	0/85 (0%)[a]	0/78 (0%)[a]	75/84 (89%) · 20/40	64/78 (82%) · 20/40	4/85 (5%)
Clarke and Noel[36]	0/21 (0%)	ND	ND	ND	ND
Clever[37]	1/10 (10%)	1/10 (10%)	10/10 (100%) · 20/40	6/8 (75%) · 20/40	0/10 (0%)
Coats et al[39]	3/25 (12%)	ND	22/25 (88%) · 20/40	ND	0/25 (0%)
Kennedy and Brubaker[99]	5/54 (9%)	13/194 (7%)	ND	ND	ND
Mortensen and Sjolie[140]	0/64 (0%)[a]	3/56 (5%)	56/64 (88%) · 20/30	52/56 (93%) · 20/30	0/64 (0%)
Shiuey and Lucarelli[176]	5/147 (3%)	6/119 (5%)	141/147 (96%) · 20/30	ND	3/147 (2%)
Sjolie and Mortensen[178]	4/44 (9%)	ND	43/44 (98%) · 20/30	ND	0/44 (0%)
Willaims et al[208]	3/34 (9%)	ND	ND	ND	9/43 (21%)
Wilson et al[212]	4/62 (4%)	ND	ND	ND	18/80 (23%)
Witteman et al[213]	2/109 (2%)	11/262 (4%)	ND	ND	0/109 (0%)

[a]These patients were treated with tranexamic acid.
ND = not done.

turned for a minimum of 5 days follow-up (23% dropout rate). Patients were given atropine three times a day and a protective shield. Timolol was given for increased intraocular pressure (>24 mm Hg). Among those who returned for follow-up visits, 4/62 (6%) patients developed a secondary hemorrhage. The true rebleeding rate among the patients is unknown, however, due to the lack of complete follow-up. In general, those who experienced a secondary hemorrhage had higher intraocular pressure compared to those who did not. The authors concluded that most microscopic hyphemas could be treated on an outpatient basis. They suggested that patients with increased intraocular pressure or those believed to have an increase risk of rebleeding might benefit from inpatient management. Limitations of this study include the following: failure to characterize the racial composition of the patient population, failure to note initial vs. final visual outcome, and the high dropout rate.

Williams et al, in an uncontrolled prospective study, managed 43 patients with small hyphemas (less than one-third anterior chamber volume) as ambulatory outpatients.[208] Patients returned every day (average 4.3 times) for observation, but 9/43 (21%) defaulted from follow-up. There was no topical or systemic treatment. Three patients developed a secondary hemorrhage. Limitations of the study include the facts that the final visual acuity was not recorded, there was no control group, and a large number of patients were lost to follow-up. The rebleeding rate (9% among the 34 patients followed-up), however, was comparable to that observed in other studies.

Shiuey et al conducted a retrospective analysis of outpatient treatment of hyphema in a predominantly white population.[176] The study group of 154 outpatients was compared to a historical control of 119 inpatients with hyphema from the same institution. (Of the inpatient cohort, 63 [53%] received oral ϵ-amino caproic acid.) Seven (5%) study patients were admitted at presentation due to decreased vision (2 patients), rebleeding at presentation (2 patients), increased intraocular pressure (1 patient), and uncomplicated hyphema with anticipated poor compliance (2 patients). Of the 147 remaining patients managed as outpatients, 6 (4%) were subsequently admitted. One (0.6%) patient was admitted for intractably elevated intraocular pressure, and 5 (3%) additional patients were admitted after rebleeding. All patients diagnosed with rebleeding at presentation or at follow-up were admitted and started on Amicar (50 mg/kg orally every 4 hours). Patients were treated uniformly pharmacologically (including topical prednisolone acetate 1% QID), and surgically as necessary. Patients were instructed to maintain strict bed rest, elevate the head of the bed, wear a Fox eye shield, and avoid aspirin and non-steroidal anti-inflammatory agents. There were no differences between the study and historical groups in overall rebleeding rate or in rebleeding rate among patients who received or did not receive ϵ-aminocaproic acid.[176] The rebleeding rates of the study group and the historic control group were 4.5% and 5.0%, respectively ($p > 0.05$). The rebleeding rates of the study patients initially treated as outpatients and the historic control group were 3.4% and 5%, respectively ($p > 0.05$). The rebleeding rates of study patients who did not receive Amicar and the subset of historic control patients who did were 3.3% and 4.8%, respectively ($p > 0.05$). A total of 96% of study patients achieved a final best corrected visual acuity of 20/30 or better. Causes of a final documented visual acuity worse than 20/30 included loss of patient to follow-up before reso-

lution of the hyphema (in 3/147 [2%] patients), traumatic cataract (2 [1%] patients), macular hole (1 patient), and macular degeneration (1 patient). The authors concluded that in their predominantly Caucasian patient population, close outpatient follow-up of traumatic hyphemas was safe and effective. Hospitalization for hyphema did not appear to decrease the rate of rebleeding, and decreased vision in the setting of traumatic hyphema generally resulted from co-morbidities not affected by inpatient management. The authors estimated an 80% cost reduction associated with outpatient vs. inpatient management. (Outpatient management was relatively intensive with an average of 4.6 visits in the first 2 weeks after presentation for patients who were not admitted.)

Clarke and Noel reported the results of outpatient management involving 21 patients, aged 4 to 15 years, with microscopic (19 cases) or "rim" (two cases) hyphemas.[36] The protocol included quiet activity at home for 7 days, use of a shield, topical steroid-antibiotic ointment therapy (TID for 7 days), and tranexamic acid (25 mg/kg PO, TID up to a maximum dose of 1,500 mg PO TID). Eighteen patients were Caucasian, 2 were of mixed race, and 1 was black. Limitations of the study include the lack of a prospective control group, no information regarding visual outcome in the study group, and no information concerning loss to follow-up despite "some difficulty" ensuring adequate follow-up.

Coats et al reported a retrospective study of 25 children less than 16 years of age with hyphemas occupying less than one-third of the anterior chamber.[39] Treatment included a protective shield (25 [100%] patients), bed rest/inactivity (21 [84%] patients), topical cycloplegia (20 [80%] patients), topical corticosteroids (24 [96%] patients), antiglaucoma medications (7 [28%] patients), and Amicar (5 [20%] patients). Sixteen (64%) of the patients were Caucasian, six (24%) were African-American, and 3 (12%) were of other races. Secondary hemorrhage occurred in 3 (12%) patients. One (17%) of 6 African-Americans had a rebleed, and 2 (13%) of 16 Caucasians had a rebleed. All 3 eyes with secondary hemorrhage had final visual acuity of 20/30 or better. Apparently, no patient was lost to follow-up. The authors emphasized that one should consider outpatient management only if the parents and child were likely to comply with medical recommendations and keep follow-up appointments. Similar consideration was to be given to patients with time delay before presentation, penetrating ocular injuries, markedly elevated intraocular pressure, and monocular status.

Witteman et al reported the results of a large collaborative, retrospective outpatient hyphema management study.[213] Outpatients had daily slit-lamp examinations, and inpatients were generally examined at the bedside. These investigators found no difference in the incidence of rebleeding between inpatients and outpatients for less than total hyphemas. Overall, the incidence of rebleeding was lower for outpatients than for inpatients. Regardless of the hyphema size at presentation, outpatient management did not increase the risk of secondary hemorrhage. A very low rebleeding rate, 13/371 (4%), was observed. Limitations in the study design include: non uniform management of the in- and outpatient groups; nonrandomized assignment to in- and outpatient groups; small numbers of outpatients in the severe hyphema group (8 cases with hyphemas occupying 50–100% of the anterior chamber among outpatients vs. 22 such cases among inpatients); lack of visual acuity data; and the applicability of these data to urban centers. Regarding the applicability of these data to urban centers, only 0.8% of the study population was African-American, and patient follow-up was excellent.

Follow-up in an urban population might not be as good as that obtained by Shiuey et al and Witteman et al. The low rebleeding rate they observed is important. The incidence of rebleeding after traumatic hyphema may be different among Caucasians and African-Americans, as noted above. If this hypothesis is correct, it might be difficult to generalize on the results of Shiuey et al and Witteman et al, particularly in urban areas within the United States. In summary, although Shiuey et al and Witteman et al's studies have provided evidence that one can treat some patients with hyphemas safely as outpatients, they may not be directly applicable to all urban populations in the United States nor to all children.

Romano has pointed out that patient compliance may be a major factor limiting the effectiveness of outpatient management.[162] He has suggested the following strategies to ensure patient compliance with medication delivery, activity limitations, and follow-up appointments. First, review the medication schedule several times with the caregiver/patient, and put the medication schedule in tabular form with a space for the caregiver/patient to enter the date and time of drug administration. Second, have the prescriptions filled for the patient, if possible, and have the staff instruct the caregiver/patient in applying the medications. The staff should observe and critique the technique. Third, insist that the caregiver/patient bring the medicines with them to each follow-up visit. At this time, the staff can assess whether the medications are being used (e.g., count pills, determine the volume of fluid in bottles). Fourth, to ensure adequate follow-up, have office staff call the patient's home the night before each scheduled follow-up visit to remind them of the appointment. If the patient fails to return for follow-up, the treating physician should make a

concerted effort to contact the patient (e.g., by telephone, certified mail, even directing the police to the patient's home).

V. Sickle Cell Hemoglobinopathy and Clotting Disorders: Special Considerations

A. SICKLE CELL HEMOGLOBINOPATHY

Medical and surgical management of elevated intraocular pressure in patients with sickle cell hemoglobinopathy differs in some respects from the management of patients with normal hemoglobin. Patients with sickle cell disease or trait have a higher incidence of increased intraocular pressure, optic nerve atrophy, and secondary hemorrhage in the setting of traumatic hyphema compared to non-sickle cell patients.[41,47,49,108,110,141,149,186,205] Sickle cell trait in children, for example, has been described as a risk factor for rebleeding, increased intraocular pressure, and permanent visual impairment.[141] A retrospective analysis of 99 eyes in children with traumatic hyphema found a rebleeding rate of 9% (9/99).[141] All nine cases occurred in sickle cell trait-positive patients. In other words, 64% (9/14) of the sickle cell trait–positive children experienced rebleeding. These patients were more likely to have elevated intraocular pressure. They also had worse visual outcome when non–hyphema-related injuries were excluded. Fibrinolysis may be enhanced in patients with sickle cell trait, which could predispose to secondary hemorrhage.[87] In the setting of sickle cell disease or trait, the size of the hyphema may not be a reliable indicator of the subsequent clinical course. For example, there is a poor correlation between hyphema size and the ease with which intraocular pressure is controlled.[53]

Goldberg has shown that patients with sickle cell trait exhibit more erythrocyte sickling in the aqueous humor than in venous blood.[74,75] Rabbit eyes injected with human erythrocytes capable of sickling manifest more prolonged hyphemas and more severe increases in intraocular pressure than rabbit eyes injected with normal human erythrocytes.[76,77] Presumably, sickled erythrocytes are less able to pass through the outflow channels of the trabecular meshwork than are normal erythrocytes,[77,78] which is analogous to the inability of "ghost erythrocytes" to pass through the outflow channels.[32]

Increased intraocular pressure is poorly tolerated in patients with sickle cell disease as evidenced by the fact that central retinal artery occlusion has followed the formation of small hyphemas in young individuals with sickling hemoglobinopathy.[134,156,182] Flow in the central retinal artery of sickle cell patients may be impaired significantly at intraocular pressures greater than 40 mm Hg.[156] In the study of Crouch and Frenkel, the two patients who developed optic atrophy in the setting of traumatic hyphema, both of whom had sickle cell trait, had intraocular pressures varying between 35 and 39 mm Hg (for 2 and 4 days, respectively).[47] Thus, even patients with sickle cell trait are susceptible to vascular occlusion at relatively low intraocular pressures and at higher pressures of relatively brief duration.

The increased susceptibility to mildly elevated intraocular pressure may be due to stagnation of blood in small vessels, excessive deoxygenation of erythrocytes, erythrostasis, sickling, increased blood viscosity, and further reduction in blood flow.[74] This cascade of events could result in arteriole occlusion by sickled erythrocytes. Also, to the extent that increased intraocular pressure decreases anterior chamber perfusion, it may contribute to increased anterior chamber sickling, which would also serve to further increase intraocular pressure.

These observations have led Goldberg to suggest that one avoid medical treatments that promote sickling when managing patients with sickle cell trait/disease and hyphema.[74] Repeated or excessive dosages of hyperosmotic/diuretic agents (e.g., glycerin, isosorbide, mannitol) should be avoided, as they may cause hemoconcentration and increased blood viscosity in the ocular microvasculature. Systemic carbonic anhydrase inhibitors not only promote hemoconcentration but also induce systemic acidosis, which is known to exacerbate erythrocyte sickling.[67] Besides lowering the aqueous humor pH, acetazolamide increases the concentration of ascorbic acid in the aqueous humor, and ascorbate may exacerbate the sickling process itself possibly by acting as a reducing agent.[12,74] Methazolamide creates less systemic acidosis than acetazolamide, and it may increase the pH of the aqueous humor slightly. If a systemic carbonic anhydrase inhibitor is needed, we recommend using methazolamide instead of acetazolamide in managing patients with traumatic hyphema and sickling hemoglobinopathy.

Dorzolamide applied locally decreases aqueous outflow but does not produce systemic acidosis.[113,207] In clinical trials, no acid-base or electrolyte disturbances were reported with dorzolamide use. Although we are unaware of data from human studies, an overdose potentially could produce an electrolyte imbalance, an acidotic state, and other possible side effects. There is a theoretical risk of anterior chamber acidosis; however, there are no studies documenting anterior chamber acidosis caused by dorzolamide. The lack of systemic acidosis may be attractive, particularly in sickle cell disease patients, but there is no study proving safety of topical dorzolamide in sickle cell disease patients with hyphema.

Vernot et al suggested that epinephrine might promote deoxygenation of the anterior chamber in

sickle cell patients and recommended that it not be used in managing increased intraocular pressure in such patients.[202] These investigators, however, were unable to demonstrate a difference in the intraocular pressure or percentage of sickled erythrocytes in epinephrine- and placebo-treated rabbit eyes.

We suggest the following protocol for patients with sickle cell disease/trait who have traumatic hyphema and elevated intraocular pressure. Use timolol as the primary topical agent. (Timolol does not appear to have a significant effect on anterior chamber oxygenation, which may be important in this setting.[148]) Add topical brimonidine or apraclonidine if an additional agent is needed. If a further agent is necessary, use topical dorzolamide before using methazolamide. A hyperosmotic agent should be used infrequently, for example, only once every 24 hours, and as a last resort to avoid surgery. (Repeated use of hyperosmotic agents mandates routine evaluation of blood electrolytes [e.g., to detect hyponatremia] and monitoring for orthostatic hypotension.) Surgical evacuation of the hyphema should be considered at lower intraocular pressures than proposed in the management of hyphema in the non-sickle cell patient. Because sickle cell trait occurs in 8–9% of the African-American population, we recommend that a sickle prep (Sickledex) or hemoglobin electrophoresis be performed for all African-American patients who present with hyphema. Deutsch et al have suggested that one consider surgical intervention if the intraocular pressure averages more than 24 mm Hg over any consecutive 24-hour period despite maximum tolerated medical therapy.[54] In addition, if the intraocular pressure increases transiently and repeatedly above 30 mm Hg, surgery should be considered.[54] In their study of 22 patients with sickle cell trait and hyphema, 14 patients (64%) maintained an intraocular pressure low enough that only medical therapy was required (average intraocular pressure less than 25 mm Hg with none recorded higher than 30 mm Hg after the first 24 hours). Except for 1 (5%) patient, the average time needed to bring the pressure under medical control was less than 24 hours. Only 1 (13%) of the 8 surgically treated eyes' intraocular pressure was controlled within 24 hours. These investigators concluded that if a patient's condition is amenable to medical therapy alone, consistent reduction of the intraocular pressure to less than 30 mm Hg will probably be achieved within the first 24 hours. If the intraocular pressure repeatedly exceeds 30 mm Hg in the first 24 hours, the pressure is unlikely to be controlled at a later time. We concur with the recommendations of Deutsch et al but recognize that clinicians must use judgment in applying the results of this retrospective clinical report to the management of any particular patient.

B. CLOTTING DISORDERS

Traumatic hyphema can be the presenting feature of hemophilia.[88] Activated partial thromboplastin time (APTT) is sometimes used to screen for hemophilia A. The APTT can be normal despite low factor VIII:C levels under conditions of stress, which can result in failure to diagnose the condition.[62] Thus, if there is a family history of hemophilia, it may be prudent to directly measure the factor VIII level in a patient with hyphema, as a factor VIII deficiency alters the course of management.

Morsman and Holmes[139] reported a 9-year-old hemophiliac boy who sustained a traumatic hyphema with secondary hemorrhage. The authors noted that when managing such patients, one should correct the clotting disorder and observe the patient closely to detect and treat complications such as secondary hemorrhage with increased intraocular pressure. If ocular trauma has occurred, an ophthalmologist should examine the patient at the slit lamp, if possible, to detect a microscopic hyphema. The deficient clotting factor should be administered as soon as possible after the injury. The authors recommended that in the presence of even minor signs of intraocular hemorrhage, the patient should be admitted to the hospital, and the deficient clotting factor (or cryoprecipitate) should be infused regularly during the high-risk period for secondary hemorrhage (i.e., the first 5 to 7 days after the injury). If the patient must undergo surgery to evacuate the hyphema, it may be worthwhile to provide replacement therapy sufficient to restore levels of clotting factor levels to 100% of normal during the procedure.[102]

Patients with even mild cases of hemophilia may be at increased risk for acute renal failure if treated with ϵ-aminocaproic acid.[154] Pitts et al suggested that asymptomatic urinary clotting may be common in hemophiliacs, and this process may be exacerbated with ϵ-aminocaproic acid administration.[154] Hallet et al reported treatment of traumatic hyphema in a 12-year-old boy having factor VIII:C deficiency with desmopressin acetate (DDAVP, Aventis). DDAVP, which increases plasma levels of factor VIII activity in patients with hemophilia and von Willebrand's disease Type I, appeared to precipitate further bleeding despite correction of the factor VIII:C to normal, possibly due to the vasodilation induced by the therapy. Bleeding was effectively treated with recombinant factor VIII concentrate. The authors suggested that DDAVP may be contraindicated in mild hemophilia and von Willebrand patients for treatment of traumatic hyphema. Although one might safely undertake prophylaxis against secondary hemorrhage in such patients with topical or systemic corticosteroids, it is not clear that these agents would be effective in the setting of hemophilia.

In patients with intraocular hemorrhage and severe thrombocytopenia, one must balance the risks of platelet infusion (e.g., hepatitis) against those of recurrent intraocular hemorrhage.[3]

In general, it is prudent to manage patients with blood dyscrasias and intraocular hemorrhage in conjunction with a hematologist.

VI. Management of Hyphema in Children

DeRespinis et al found that the most common admitting diagnosis in children sustaining ocular trauma was hyphema (81/258 [31%]).[53] Traumatic hyphemas in children tend to be associated with the same spectrum of ocular injuries as adults,[4,39,104,117,203] but assaults constitute a smaller proportion of the cases and injuries with missiles (e.g., balls, stones, toys, BBs) a greater proportion.[39,117]

Children do not appear to have a lower secondary hemorrhage rate than adults (Tables 2 and 3 and references[4,44,63,68,115,121,161,175,186]). Agapitos et al, for example, observed rebleeding in 24/316 (8%) children in a Caucasian urban community. Most (294/316 [93%]) of the hyphemas were grade 1 or less. Of the patients who rebled, 17/22 (77%) had a final visual acuity of 20/30 or better, and among those who did not rebleed, 160/176 (91%) had final visual acuity of 20/30 or better. A higher secondary hemorrhage rate was not present in younger children. In this study topical steroids were used in an uncontrolled manner, and systemic treatments were not used.[4] One study showed that children, especially those younger than 6 years old, have an increased incidence of rebleeding after traumatic hyphema.[166] African-American children may have a higher incidence of rebleeding than Caucasian children (see below).

To identify risk factors associated with higher rates of ocular complications in children with traumatic hyphema, Lai et al analyzed the outcomes in 40 children.[110] Inclusion criteria in this retrospective study included children (age $\leq$ 18 years) who were admitted to the hospital within 48 hours of a closed-globe injury leading to hyphema. Of the 40 children, 20 were African-American, 1 was Asian-American, and 19 were Caucasian. Five (25%) of the 20 African-American children had sickle cell trait, and 1 (5%) had sickle cell anemia. The rate of secondary hemorrhage was statistically higher in the African-American population ($p = 0.05$), but no statistical difference existed between the rate of secondary hemorrhage in patients with and without sickle cell hemoglobinopathy. Sickle cell hemoglobinopathy was associated with a higher intraocular pressure at presentation ($p = 0.03$) and during inpatient follow-up ($p = 0.02$). The authors concluded that in the setting of traumatic hyphema, African-American children appear to be at greater risk for developing a secondary hemorrhage and that sickle cell hemoglobinopathy increased the risk of intraocular pressure elevation, but it did not seem to increase the risk of rebleeding beyond that associated with race. They cautioned that larger studies are needed to validate these observations.

The treatment of children with traumatic hyphema has been controversial.[167] Some studies have assessed the value of antifibrinolytic and systemic corticosteroid therapy in children with hyphemas.[47,52,104,130,149,164,169,191,197] Systemic tranexamic acid appears to reduce the incidence of secondary hemorrhage in children. Deans et al, for example, observed rebleeding in 24 (8%) of 316 patients in a retrospectively analyzed no-treatment cohort and in five (3%) of 163 patients in a prospectively studied tranexamic acid-treatment cohort.[52] Topical steroids and cycloplegics were used indiscriminately, and there were no side effects noted in the treatment group. The difference in secondary hemorrhage rates was statistically significant.[52] In a mixed retrospective and prospective analysis of 340 cases, Uusitalo et al observed rebleeding in 21/214 (10%) patients treated with bed rest only and in 1/121 (0.8%) patients treated with systemic tranexamic acid.[197] The tranexamic acid-treatment cohort was divided into bed rest and quiet ambulation groups. Rebleeding occurred in 0/26 and 1/95 (1%) patients assigned to bed rest and quiet ambulation, respectively. Steroids were not used. No treatment side effects were noted, and the final visual acuities were similar in the different groups.

As noted earlier, published results generally indicate that both systemic prednisone and Amicar are effective in children, although the data are not entirely consistent. Kraft et al[104] and Teboul et al[191] did not, for example, find Amicar effective in children. Kraft et al treated 49 children (4 African-American, 45 Caucasian) with 100 mg/kg of Amicar every 4 hours for 5 days (maximum dose 30 gm/day).[104] Topical steroids were not used. Rebleeding occurred in 2 of 24 (8%) Amicar-treated patients and in 1 of 25 (4%) placebo-treated patients. Nausea occurred in 8 of 24 (33%) patients treated with Amicar. The investigators concluded that Amicar conveyed no beneficial effect.[104] In a prospective double-blind randomized study of a predominantly white population by Teboul et al, 94 children were randomized to Amicar 100 mg/kg PO every 4 hours ($n = 48$) or placebo ($n = 46$) for 5 days.[191] Patients with a history of sickle cell anemia, hepatic, renal or cardiac diseases, coagulopathy, recent aspirin ingestion, impending surgery, and pregnant patients were excluded. Eighty-eight (94%) of 94 patients had a hyphema occupying less than one-third of the anterior chamber,

and no patient had a hyphema occupying more than one-half the anterior chamber. One (2%) of 48 patients treated with Amicar and 2 (4%) of 46 patients treated with placebo experienced a secondary hemorrhage. These investigators concluded that the use of ϵ-aminocaproic acid could not be justified.[191]

Nonetheless, several prospective randomized controlled studies including children have demonstrated the effectiveness of Amicar in reducing the incidence of secondary hemorrhage.[47,130,149] We recommend use of Amicar or prednisone routinely in children with hyphema (Tables 17 and 20). Both the apparent efficacy of systemic and topical steroids in reducing the incidence of secondary hemorrhage and the commonly accepted value of steroids in attenuating the sequelae of intraocular inflammation (which often accompanies ocular trauma) lead us to prefer the use of systemic steroids with or without topical steroids, rather than Amicar, in managing children with traumatic hyphema, independent of whether they are managed as inpatients or outpatients. Although tranexamic acid probably reduces the incidence of secondary hemorrhage in children, currently it is unavailable for use in the United States.

Some evidence indicates that there is no difference in visual outcome or rebleeding rate among children assigned to bed rest vs. quiet ambulation.[15,36,161,178,197] Traditionally, hospitalization has been recommended for the first 5 to 7 days after the injury.[4,52,63,65,98,143,149,166,169,186,191,193] In properly selected patients, outpatient management may be safe, but the data are limited. As noted above, Clarke and Noel treated 21 children with microscopic and rim hyphemas as outpatients with systemic tranexamic acid.[36] No patient experienced a secondary hemorrhage. In a retrospective study, Coats et al reported on the results of outpatient management of 25 children less than 16 years old with hyphemas filling less than one-third of the anterior chamber.[39] As noted above, three (12%) of 25 patients experienced a secondary hemorrhage (one of whom used Amicar), and one required surgical clot evacuation. Two of these patients were Caucasian, and one was African-American. One of the patients with secondary hemorrhage did not use topical corticosteroids. All patients had final visual acuity of 20/40 or better except 3 (12%) with concurrent vision-limiting ocular injuries/disorders. Final visual acuity was 20/30 or better in all patients with secondary hemorrhage.

Thus, published studies indicate that outpatient management of children with hyphema can be safe. At present there are no published prospective randomized clinical trials that provide firmly established criteria for recommending admission vs. outpatient treatment of traumatic hyphema in children. The treating physician must use his/her clinical judgment based on the features of the case. We recommend hospital admission for children if there are concurrent injuries mandating admission; if the hyphema is large (e.g., ≥ 50% of anterior chamber volume); if the intraocular pressure is elevated; if the patient has sickle cell disease/trait or a clotting diathesis; if there was a time delay before presentation; or if there is a concern regarding medication delivery, compliance with activity restrictions, ability to return for follow-up, or safety of the home environment (Table 20). If the treatment of children with hyphema differs from adults in any respect, it is that one must give special consideration to the safety of the home environment with regard to activity restrictions, medication delivery, and adequacy of follow-up if outpatient management is contemplated. Thus, the treating physician must assess both the parent(s) and the child. One hyphema complication unique to the pediatric population is the development of amblyopia, which can occur as a result of corneal bloodstaining.[28]

VII. Surgical Management

Rakusin compared medical with surgical treatment of hyphemas.[159] He found that the surgically treated cohort had a higher proportion with absorption in 1 week. The medically treated cohort had better final visual acuity and a lower incidence of complications. In one study, 20 patients (11 with primary total hyphemas and 9 with secondary hemorrhage that developed total hyphema) were randomized to either medical or surgical management.[160] If possible, the treating physicians waited 4 days before assigning patients to the medical or surgical cohort. This plan was based on a study of clot lysis, which showed that at 4 days the clot was sufficiently organized to be expressed as a single mass and yet not so organized that the clot periphery was adherent to the anterior chamber angle.[215] The surgical technique used was an ab externo corneal section of 90° under a limbus-based flap with preplaced sutures.[172] The clot was removed by a combination of spontaneous extrusion and gentle manual expression with a muscle hook. Residual clot was removed with Weck sponges, and the corneal-scleral section was irrigated with balanced salt solution. Instrumentation of the anterior chamber was not performed at anytime during the procedure. Criteria for crossover from medical to surgical treatment were as follows: intraocular pressure greater than 60 mm Hg for 48 hours despite maximum medical therapy (1 case); microscopic corneal blood staining (3 cases), or 8 days of total hyphema greater than 75% (4 cases). Overall, 8 patients were managed medically, and 12 were managed surgically. Four (33%) of these 12 pa-

TABLE 20

Management of Traumatic Hyphema: Authors' Recommendations

1. Obtain complete history.	•Ocular: amblyopia, corneal disease (e.g., Fuchs' dystrophy), glaucoma •Systemic disease (e.g., sickle cell disease/trait, blood dyscrasia, thrombotic disorder, pregnancy, renal disease) •Medications (e.g., warfarin, aspirin) •Details of injury
2. Identify and treat associated injuries and conditions.	•Complete eye exam (except gonioscopy, scleral depression) if possible •Echography, CAT-scan, MRI as needed •Consultation (e.g., neurosurgical) as needed •Perform sickle hemoglobin screening in all African American patients and coagulation studies and pregnancy test in selected patients
3. Initiate medical management.	•Cycloplegic (e.g., atropine 1%QD) •Topical corticosteroid (e.g., prednisolone acetate 1% QID) if systemic steroid not used •Topical or systemic IOP-lowering medications as needed •Analgesic and antiemetic medications as needed (no nonsteroidal anti-inflammatory medications used) •Correct clotting disorder, if present •Rigid shield •Patch (if there is a concern regarding corneal blood staining) but beware of inducing amblyopia and/or strabismus in children •Elevate head of bed ∼30°
4. Administer systemic medication to decrease risk of secondary hemorrhage.	•Amicar or Prednisone, depending on clinical setting (see Table 17) •Clotting factor (for hemophilia) •Plateletes (for severe thrombocytopenia)
5. Examine patient daily at the slit lamp if possible.	•Record visual acuity, intraocular pressure, corneal clarity, hyphema height •Defer gonioscopy (if possible) and scleral depression •Measure IOP more often in selected patients (e.g., sickle cell disease/trait, pre-existing glaucomatous optic atrophy, elevated IOP)
6. Consider outpatient management.	•No associated ocular injury mandating admission •Hyphema ⩽ 1/2 anterior chamber volume •IOP satisfactory •No blood dyscrasia •Home environment safe •Patient can comply with activity limitations •Medications can be administered properly •No concern regarding reliable follow-up (e.g., no time delay before presentation)
7. Consider surgery (irrigation, vitrectomy, trabeculectomy) to evacuate clot.	•Microscopic corneal blood staining present •Risk of optic atrophy/CRAO (e.g., sickle cell disease/trait and IOP averages ⩾ 25 mm Hg for ⩾ 24 hours or spikes repeatedly > 30 mm Hg, IOP ⩾ 60 mm Hg for 2 days or ⩾ 50 mm Hg for ⩾ 4 days, presence of pre-existing glaucomatous optic atrophy and "unacceptable" IOP) •Risk of corneal blood staining (e.g., 4 days after onset of total hyphema, >1/2—total hyphema with IOP ⩾ 25 mm Hg for ⩾ 6 days) •Risk of synechia formation (e.g., ⩾ 50% hyphema for ⩾ 8 days)

IOP = intraocular pressure; CRAO = central retinal artery occlusion.

tients had surgical intervention within 4 days of the onset of the hyphema (1 for elevated intraocular pressure and 3 for corneal bloodstaining). Another 4 (33%) of the 12 underwent surgery at 8 days due to inadequate hyphema clearance. Four (33%) patients underwent surgery at 4 days according to protocol. Among those treated medically, 5 (63%) of eight patients retained vision of 20/200 or better

whereas only 4 (33%) of 12 surgically treated patients retained visual acuity of 20/200 or better. In the latter cohort, only 1 (25%) of the 4 patients who underwent crossover to surgical treatment 8 days into the study retained visual acuity of 20/200 or better. Visual prognosis of those who underwent surgery within 4 days of hyphema onset was equally poor with 1 (25%) of 4 patients having vision of 20/200 or better. Two (50%) of the 4 patients assigned to medical treatment who cleared sufficiently at 4 days to be removed from surgical consideration ultimately retained vision of 20/40 or better as compared to 1 (25%) of the 4 comparable patients in the surgical treatment group. The findings indicate that medical management of total hyphemas is preferable for the initial 4 days if one can control intraocular pressure satisfactorily with medications and if there is no corneal blood staining. One should interpret these results cautiously. In most cases, currently available microsurgical instrumentation[55,127,133,188] offers a superior approach compared to manual clot expression and other enzyme-based techniques that have been suggested.[93,100,109,112,116,170,187,209]

Read and Goldberg and Deutsch et al developed the following empirical criteria for surgical intervention.[54,161] Hyphema evacuation is recommended in the following cases:

1. A patient has sickle cell disease or trait and if the mean intraocular pressure is greater than 24 mm Hg over the first 24 hours or if the intraocular pressure spikes repeatedly over 30 mm Hg.
2. In non-sickling patients, if the intraocular pressure is greater than 60 mm Hg for 2 days (to prevent optic atrophy).
3. The intraocular pressure is greater than 25 mm Hg with a total hyphema for 5 days (to prevent corneal bloodstaining).
4. There is microscopic corneal bloodstaining.
5. The hyphema fails to resolve to less than 50% of the anterior chamber volume by 8 days (to prevent peripheral anterior synechiae formation).

In general, we follow similar empirical criteria for surgical intervention (Table 20). We tend to recommend surgery earlier in cases with elevated intraocular pressure despite maximal medical therapy and in cases of non-resolving total hyphema.

The surgical approach used depends on the clinical setting and, to some degree, the training of the surgeon. To lower intraocular pressure acutely, an anterior chamber paracentesis can be performed at the slit lamp under topical anesthesia if the patient can cooperate. With a sterile lid speculum in place and after sterilizing the ocular surface with topical povidone iodine, a 0.5-inch 30-gauge needle attached to a tuberculin syringe is introduced at the limbus. While the surgeon holds the syringe in place, the assistant aspirates bloody aqueous humor slowly. This approach will not be effective if most of the anterior chamber is filled with clot.

Definitive clot evacuation is done in the operating room. We prefer the following approach. A clear corneal incision is created near the limbus just superior to the horizontal meridian on the side of the surgeon's non-dominant hand. A bent 23-gauge needle is introduced through this incision for balanced salt solution infusion. The infusion pressure is adjusted to 30–40 mm Hg. (One avoids prolonged periods of high intraocular pressure, however, particularly if the patient has sickle cell disease/trait.) The vitrectomy probe is introduced into the anterior chamber through a second clear corneal incision near the limbus just superior to the horizontal meridian on the opposite side. The vitrectomy probe's cutting port is occluded with clot. Working at low suction (~50 mm Hg), to avoid anterior chamber collapse, the surgeon first attempts to aspirate liquefied blood. Solid clot is engaged with the probe, drawn centrally (if the hyphema occupies less than 50% of the anterior chamber volume), and excised by activating the cutting action of the probe (200–1200 cycles/second depending on the vitrectomy machine used). The cutting port is not directed towards the crystalline lens, particularly while the cutting-suction mode is activated. One increases the suction on the vitrectomy probe as needed to engage the clot and occlude the port while simultaneously avoiding sudden anterior chamber collapse. The availability of modern vitrectomy instruments that permit "shaving" of the clot with minimal tendency for anterior chamber collapse (e.g., the Accurus machine by Alcon) probably lessens the risk of this part of the procedure. We leave in the eye clot that adheres firmly to the iris. Clear corneal incisions parallel to the iris are preferred to avoid contact between the intraocular instruments and the iris and crystalline lens. Divided instrumentation is preferred because it offers the surgeon better control over anterior chamber volume and permits instrument removal without sudden intraocular pressure lowering, which can precipitate intraocular hemorrhage. If intraocular bleeding occurs intraoperatively, one can control it in several ways. First, one increases the infusion pressure to 60–70 mm Hg for 3 to 5 minutes.[188] Second, one can infuse Healon into the anterior chamber to clear the view. If bleeding persists and the bleeding site is identified, the site can be diathermized using a 23-gauge blunt unipolar endodiathermy needle or bimanual bipolar diathermy.[133] At the end of the procedure, the limbal incisions are closed with 10-0 nylon suture. One per-

forms a peripheral iridectomy if there is concern regarding the development of pupillary block post operatively or if the iris prolapses and cannot be reposited.

We recognize that the surgeon's training will influence the approach used and that other approaches are effective. For example, one can perform irrigation and, if necessary, aspiration of the anterior chamber blood with the Simcoe irrigation-aspiration probe leaving any firmly adherent clot in the eye. The incision depends on the preference of the surgeon. Incisions can be made at the limbus or can be of a scleral tunnel-type (3 mm in width and 1–2 mm posterior to the limbus) with a limbal paracentesis site located in a position that will be accessible postoperatively. Alternatively, two clear cornea incisions can be made and bimanual technique using the Simcoe probe and a separate infusion line can be employed. We feel the bite-by-bite cutting action of the vitrectomy probe offers a superior way to remove clot in a controlled manner. As noted above, we also feel that divided instrumentation offers greater control over anterior chamber volume. Compared to scleral tunnel incisions, clear corneal incisions seem less likely to predispose to contact between the instruments and the crystalline lens, particularly if a collar button clot with pupillary block is present, and the iris-lens diaphragm is displaced anteriorly.

If the intraocular pressure is elevated primarily because of dispersed red blood cells, one can irrigate the anterior chamber in the following way. A 0.5-inch 27–30-gauge needle attached to an infusion line is introduced through clear cornea superior to the horizontal meridian on the side of the surgeon's dominant hand. A 0.5-inch 27–30-gauge needle attached to a tuberculin syringe without the plunger is introduced through clear cornea on the opposite side. This system permits slow controlled irrigation of the anterior chamber and uses self-sealing incisions.

In our experience, a trabeculectomy is done uncommonly because removing the red blood cells from the anterior chamber usually lowers the intraocular pressure to a level that can be managed medically. If necessary, a trabeculectomy can be done under more controlled circumstances later. Furthermore, a trabeculectomy may lower the pressure excessively and may create complications such as choroidal effusion or ciliary body shutdown, which may predispose to secondary hemorrhage due to hypotony. Nevertheless, trabeculectomy can be an effective intervention,[83,206] particularly in patients with total hyphema, very high intraocular pressure, and particular susceptibility to intraocular pressure-induced damage (e.g., pre-existing glaucomatous optic atrophy, sickle cell disease/trait). Also, if corneal bloodstaining severely compromises the view of the anterior chamber, a trabeculectomy may offer the safest approach to management. A standard technique is used. A 4×4 mm^2 limbus-based 0.33–0.5-thickness scleral flap extending approximately 1 mm into clear cornea is fashioned under a limbus-based conjunctival flap. At the anterior edge of the scleral flap, a 3–4-mm wide full-thickness incision is made at the limbus. Tissue comprising the posterior lip of the incision is excised using free hand dissection (e.g., with right-angled Vannas scissors) or a Kelly Descemet's punch. Liquefied blood is irrigated from the anterior chamber (e.g., by infusing balanced salt solution into the anterior chamber via a separate limbal paracentesis site), and a peripheral iridectomy is made. It may be appropriate to make the ostium somewhat larger than normal if the retained clot is large. The scleral flap is closed with 10-0 nylon sutures. The conjunctiva is closed using running, locked 9-0 vicryl suture on a vascular needle (BV 100-3). The scleral sutures are lysed after surgery as needed. Verma found that trabeculectomy alone did not lower the intraocular pressure satisfactorily and reported that trabeculectomy combined with manual clot extraction through a large incision was effective and safe.[201] Angled McPherson forceps were used to extract clot through a 120° limbal incision.[201]

Interventions in the operating room are performed under general anesthesia in children and under local or general anesthesia in adults.

VIII. Conclusions and Recommendations

In summary, we believe that previously reported observations justify the following approach to the management of traumatic hyphema (Table 20).

First, one should obtain a complete history. The patient should be questioned regarding a personal or family history of glaucoma, corneal endothelial disease (e.g., Fuchs's dystrophy), anticoagulant use, blood dyscrasia (such as sickle cell disease, leukemia, or Von Willebrand's disease), bleeding diathesis (e.g., hemophilia), aspirin/nonsteroidal anti-inflammatory drug use, thrombotic disorder, or any malignancy. If the patient is using a drug such as aspirin or coumadin, the possibility of its discontinuation should be discussed with an internist or pediatrician. If the patient is African-American or might have sickle cell disease or sickle trait, a sickle prep followed by hemoglobin electrophoresis should be obtained. If clinically indicated (e.g., apparently spontaneous hyphema), patients with hyphema should have complete blood cell count, platelet count, prothrombin time, activated partial thromboplastin time, and measurement of bleeding time. Liver function tests and electrolytes, including blood urea nitrogen and creatinine, should be obtained in patients before treatment with systemic medications

such as Amicar. If hemophilia is present, Amicar should not be used. Women of childbearing age should have a pregnancy test done before instituting treatment with Amicar or Cyclokapron as pregnancy is a relative contraindication to the use of these medications. As a matter of standard practice, one should record the details of the injury (e.g., location and date of occurrence, use of protective eye wear or glasses, history of abnormal vision in the involved eye, history of fluctuating vision subsequent to the injury). If one suspects child or spousal abuse, social service representatives should be contacted.

Second, one should identify and treat all associated ocular and corporeal injuries. Identification of ocular injuries requires complete eye examination including assessment of visual acuity, extraocular motility, consensual pupillary response testing, and, if fundus visualization is possible, dilatation and indirect ophthalmoscopic examination (without scleral depression). Evaluation of touch sensation in the area innervated by the maxillary division of the trigeminal nerve may reveal hypesthesia indicative of an orbital blowout fracture, which often accompanies hyphemas.[135] We do not recommend gonioscopy until approximately 2 weeks after the injury to avoid inducing secondary hemorrhage. In selected cases, the evaluation will also include careful ultrasound examination of eye for early detection of retinal detachment, intraocular foreign body, or globe rupture, CAT-scan examination if orbital injuries are suspected, and MRI if optic nerve injury is suspected. Although the mechanism is not known, patients with hyphema may be somnolent.[38] In the setting of head trauma associated with hyphema, it may be necessary to obtain CAT or MRI studies (as well as neurosurgical consultation) to rule out intracranial injury as the cause of altered mental status.

Third, medical management is initiated. A mydriatic is provided to relieve photophobia and to prevent seclusio pupillae. We prefer atropine 1% because it is effective with once-a-day dosing. A topical corticosteroid (e.g., prednisolone acetate 1% QID) is administered to reduce intraocular inflammation, the risk of peripheral anterior and posterior synechiae, and the risk of secondary hemorrhage. (If systemic corticosteroids are used, topical steroids probably are not needed.) The patient is examined with slit lamp biomicroscopy at least once a day if at all possible. (Occasionally patient agitation induced by the examination may be deemed a greater risk than that posed by the hyphema depending on the degree of patient cooperation, hyphema size, and other features of the clinical setting.) The cornea is evaluated carefully for the development of bloodstaining. Topical beta-adrenergic antagonists, topical alpha-adrenergic agonists, and topical carbonic anhydrase inhibitors are used as needed to control intraocular pressure. Oral methazolamide (10 mg/kg/day in three divided doses up to a maximum dose of 50 mg PO TID) or acetazolamide (in adults, 20 mg/kg/day in four divided doses up to a maximum dose of 250 mg PO QID); in children, 5–10 mg/kg/day in 4 divided doses may also be used. (In patients with sickling hemoglobinopathies, we prefer methazolamide.) We have found that systemic carbonic anhydrase inhibitors are somewhat more effective in lowering intraocular pressure than topical preparations. If needed, glycerin (1–1.5 gm/kg orally) or isosorbide (1.5 gm/kg orally) or intravenous mannitol (1.5 gm/kg administered over approximately 45 minutes) can be used every 6 hours (for 24 hours), but these agents are used only once in 24 hours in sickle cell disease/trait patients. Systemic hyperosmotic agents are usually used to stabilize the patient before surgery and generally are not employed for more than 24 hours. Hyperosmotic agents may be contraindicated in patients with congestive heart failure. Their use in patients with urinary tract obstruction should be considered carefully. Excessive use of hyperosmotic agents can result in hyponatremia and/or hyperglycemia (i.e., with glycerin). Thus, urine output, blood urea nitrogen, serum creatinine, serum electrolytes, and blood glucose (in the case of glycerin) should be monitored if one uses these agents. We avoid use of pilocarpine or latanoprost. Topical epinephrine probably should be avoided in patients with sickling hemoglobinopathies. Topical carbonic anhydrase inhibitors may have the potential to cause anterior chamber acidosis, which may be a factor in the treatment of sickle cell patients. The literature has not supported or refuted this possibility. The decision to use topical carbonic anhydrase inhibitors therefore is based on the clinical judgment of the treating physician. A rigid shield is worn over the injured eye at all times. Occlusive tape or an occlusive patch is applied to the perforated eye shield or a non-perforated shield is used if there is a concern regarding corneal bloodstaining. An occlusive dressing may increase the risk of acquired strabismus or amblyopia in children, however. Activity is limited to quiet ambulation. The head of the bed is elevated approximately 30° above the horizontal to promote settling of the hyphema. Acetaminophen (10–20 mg/kg every 4 hours up to a maximum dose of 650 mg per dose) is used as an analgesic, unless there is a contraindication (e.g., liver disease). Codeine or oxycodone is used should additional analgesia be required, provided that patient has no contraindication. Narcotics are used sparingly due to the risk of nausea and altered mental status.

Fourth, depending on the clinical setting (Table 17), the patient is treated with systemic Amicar (50

mg/kg PO every four hours, total dose ≤ 30 g/day) or Prednisone (0.6–0.75 mg/kg/day in divided doses up to 40 mg/day) for 5 days. (If Cyclokapron is available, it may be used at a dose of 25 mg/kg PO, TID up to a maximum daily dose of 1500 mg PO TID for 5 days.) Compazine (prochlorperazine) may be added for the treatment of nausea, should it develop. Adults usually are treated with 5–10 mg PO TID–QID, or 5–10 mg IM every 4 hours, or 25 mg PR BID. Children usually are treated with 2.5 mg PO/PR QD–BID (20–29 pound weight, not to exceed 7.5 mg/day), or 2.5 mg PO/PR BID–TID (30–39 pound weight, not to exceed 10 mg/day), or 2.5 mg PO/PR TID or 5 mg PO/PR BID (40–85 pound weight, not to exceed 15 mg/day). Although we have no reason to believe that prednisone is less effective than Amicar among patients with sickle cell disease/trait, data demonstrating efficacy in this patient population have been reported in prospective randomized studies of Amicar use.[47,49] Farber et al excluded such patients from enrollment in their prospective randomized trial comparing prednisone and Amicar treatment.[65] After discontinuation of the antifibrinolytic agent, the patient should be monitored carefully for increased intraocular pressure, which can be created by clot lysis. Some clinicians feel that tapering the medication can reduce the likelihood of this complication. Patients with hemophilia should receive factor replacement therapy. Platelet therapy should be considered for patients with severe thrombocytopenia.

Fifth, each day the patient is examined carefully with special attention directed to the visual acuity, the presence of corneal bloodstaining, the size of the hyphema, and the intraocular pressure. (As noted above, particularly when treating uncooperative patients, clinicians must balance the risks associated with careful examination against the potential benefits.) Hyphema height is recorded in millimeters. The intraocular pressure is measured daily with applanation tonometry. If there is likelihood of developing glaucoma (e.g., sickle cell patients or hyphema more than three-fourths the volume of anterior chamber), if the ability to tolerate increased intraocular pressure is compromised (e.g., patients with sickle cell disease/trait or known glaucomatous optic atrophy), or if the intraocular pressure is elevated, the pressure should be measured more often (e.g., every 6–12 hours) at a frequency indicated by the judgment of the treating physician. Indirect ophthalmoscopy should be performed as soon as media clarity allows to detect retinal tears, vitreous hemorrhage, or macular pathology. In most cases, scleral depression should be postponed until several weeks after the injury to avoid precipitating secondary hemorrhage. Gonioscopy is done approximately 2 to 6 weeks after the injury. Earlier gonioscopy may be necessary if the patient has hypotony and the possibilities of cyclodialysis cleft vs. ruptured globe must be distinguished. If angle recession is detected or if there is a family history of glaucoma, but the intraocular pressure is normal, the patient is seen for pressure checks annually or biannually. Otherwise, the intraocular pressure is checked annually or every two years.

Sixth, we offer outpatient hyphema management to adults in the following situation: 1) no associated ocular injury mandating admission to the hospital, 2) hyphema occupying ≤ one-half the anterior chamber volume, 3) satisfactory intraocular pressure (e.g., ≤ 35 mm Hg with no history of glaucomatous optic atrophy or sickle cell trait/disease), 4) no history of blood dyscrasia or bleeding diathesis, 5) no concern regarding the safety of the home environment, 6) no concern regarding the patient's ability to comply with activity limitations, 7) no concern regarding the ability to administer medications properly, and 8) no concern regarding reliable follow-up. Otherwise, the patient is admitted for observation. Activity is limited to quiet ambulation. The head of the bed is elevated (approximately 30°) to promote settling of the hyphema, and the involved eye is protected with a rigid, perforated shield to allow binocular vision unless there is a concern regarding corneal bloodstaining as noted above. Generally, children are admitted, but exceptions are made on an individual basis according to the criteria outlined above. Patients with sickle cell trait or disease usually are admitted so that their intraocular pressure can be checked more than once a day.

Seventh, if surgical intervention is required (Table 20), the approach is tailored to the needs of the patient and the training of the surgeon as outlined above.

Unresolved issues in the management of traumatic hyphema remain. These include the following:

1. Does the use of antifibrinolytic agents, systemic prednisone, or any other agent that reduces the rate of secondary hemorrhage confer a visually significant benefit for patients with traumatic hyphema?
2. What is the minimal effective dose with which topical prednisolone acetate reduces the frequency of secondary hyphema?
3. Is a particular antirebleeding agent preferable in specific clinical circumstances (e.g., are systemic prednisone and Amicar equally effective in patients with sickle cell disease)?
4. Is the combination of Amicar or tranexamic acid and prednisone (topical or systemic) more effective than either agent alone? (A retrospective analysis of published data indicates that

combining topical and systemic steroid therapy does not have an additive benefit.[168])

5. Which patients are most suited to outpatient management?

We suspect that the answers to these questions will be obtained only through large multicenter randomized prospective clinical trials the design of which takes into account the different tendencies for complications to occur among different ethnic groups. A cost-benefit analysis of such data could then lead to establishment of rational regionally based public health policy regarding traumatic hyphema management.

Method of Literature Search

Medline was the database used for the literature search conducted in preparation of this article. All articles in Medline up to April 2001 were reviewed using one or combination of the following key words: *hyphema, amino caproic acid, tranexamic acid.* Relevant articles in English, French, Italian, and Spanish were reviewed and included in this review. In addition, relevant articles cited in these references were reviewed references, and those thought to be of relevance were also included in this review.

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Supported in part by Research to Prevent Blindness, Inc., the New Jersey Lions Eye Research Foundation, and the Eye Institute of New Jersey. The authors have no proprietary or commercial interest in any product mentioned or concept discussed in this article. The authors thank Dr. Rudy Wagner for reviewing sections of the manuscript dealing with management of pediatric patients.

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Outline

I. Mechanisms of hemorrhage and blood resorption
II. Epidemiology
III. Complications
  A. Increased intraocular pressure
  B. Peripheral anterior synechiae
  C. Optic atrophy
  D. Corneal bloodstaining
  E. Secondary hemorrhage
  F. Accommodative impairment
IV. Medical management to prevent rebleeding
  A. Pharmacological therapy
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VI. Management of hyphema in children
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VIII. Conclusions and recommendations