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Topical aminocaproic acid to prevent rebleeding in cases of traumatic hyphema

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PURPOSE. *To determine the effect of topical aminocaproic acid on the incidence of rebleeding after traumatic hyphema.*

PATIENTS AND METHODS. *This randomized double blind clinical trial investigated 132 consecutive cases of traumatic hyphema referred to the emergency room of Farabi Eye Hospital in 1998-1999. The patients were randomly divided into three groups: Group 1 received cycloplegic drops only. Group 2 received cycloplegic drops and 2% carboxy polymethylene (CPM) gel as placebo. Group 3 was treated with cycloplegic drops and 25% aminocaproic acid (ACA) in CPM gel (supplied by Messrs. Sina Darou). All patients were treated for five days on an outpatient basis, with a two-week follow-up. The incidence of rebleeding, time needed for clot absorption, and complications of hyphema were recorded and analyzed using the chi-square and Student's t-tests and logistic regression modeling.*

RESULTS. *Rebleeding occurred in 8 eyes of 52 patients in group 1 (15.4%), 7 eyes of the 39 patients in group 2 (17.9%) and 5 eyes of the 41 patients in group 3 (12.2%). This difference was not significant. The time needed for clot absorption in groups 1, 2 and 3 was respectively 9.5±3.9, 9.3±4.2 and 11.15±4.7 days, the difference between group 3 and the other two groups being statistically significant ($p<0.04$).*

CONCLUSIONS. *Topical 25% ACA is not effective in reducing the incidence of rebleeding and lengthens the time needed for clot absorption. (Eur J Ophthalmol 2003; 13: 57-61)*

KEY WORDS. *Aminocaproic acid, Traumatic hyphema, Rebleeding*

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INTRODUCTION

Secondary hemorrhage follows traumatic hyphema in 3-30% (1) of untreated patients 2-5 days after the initial injury and significantly increases the risk of visual impairment in the traumatized eye (1,2). Secondary hemorrhage is more severe than the initial hemorrhage and the visual prognosis is worse (2). The incidence of corneal bloodstaining, elevated intraocular pressure with resulting optic atrophy, posterior and anterior synechiae are all higher after secondary hemorrhage (1-7).

Aminocaproic acid (ACA), an antifibrinolytic agent, retards lysis by preventing plasmin from binding to lysine molecules in the fibrin clot. ACA, acting as a lysine analogue, competitively inactivates plasmin by occupying the lysine-binding site on plasmin that normally binds to fibrin. ACA also binds to plasminogen,

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preventing its activated form (plasmin) from attaching to fibrin. These effects stabilize the clot vessel wall interface, reducing the potential for secondary hemorrhage (2).

Various studies have shown that systemic ACA at doses from 50 to 100 mg/kg every 4 hours for five days significantly reduces the incidence of secondary bleeding (2, 8, 9, 10). In a randomized, double-blind, prospective trial Crouch and Frenkel found that the incidence of secondary hemorrhage was reduced to 3% compared with 33% in placebo-treated eyes (11,8).

The secondary bleeding mostly occurs because of lysis and contraction of the fibrin plug in the injured vessels. Management with ACA for five days before the primary fibrin clot is absorbed would give time for repair of the vascular lumen and prevent secondary bleeding.

The systemic side-effects of oral ACA include nausea, vomiting, vertigo, headache, postural hypotension, muscle cramps, skin rash and itching, asthma, and cardiac arrhythmia (9-11). A study on New Zealand White rabbits found that topical ACA in carboxyl polymethylene gel reduced the rate of rebleeding (14). The drug concentration in the anterior chamber remains the same with oral and topical use. Crouch et al (12, 14), in a prospective, double-masked, multicenter trial on 64 patients, found topical ACA was as effective as systemic ACA in reducing secondary hemorrhage (2).

Since only one study has been done in humans, we designed the present study, conducted from 1998 to 1999, to investigate the exact effect of topical ACA in carboxy polymethylene gel, in reducing the incidence of secondary bleeding in patients with traumatic hyphema referred to the Farabi Eye Hospital, in Tehran (Iran).

MATERIALS AND METHODS

One hundred and fifty-five patients with non-penetrating traumatic hyphema were recruited in a sequential randomized double-blind clinical trial. Patients meeting the following criteria were excluded: penetrating ocular injury, delay in referral to the hospital of more than 24 hours, previous surgery on the affected eye, history of bleeding disorders, recent ingestion of aspirin or anticoagulants, pregnancy, microscopic hyphema, black-ball hyphema and trauma to the affected eye during the follow-up. All cases were managed as outpatients.

Treatment consisted of 30° head elevation, protection of the involved eye with a metal shield and homatropine drops three times a day as cycloplegic. Patients were instructed to avoid taking aspirin, but were allowed acetaminophen.

The patients were randomly divided into three groups. Group 1 (control, n=52) received cycloplegic drops only; group 2 (n=39) received the cycloplegic and 2% carboxy-polymethylene gel as placebo, two drops every six hours; group 3 (n=41) received the cycloplegic and a 25% ACA in 2% carboxypolymethylene gel applied in the inferior fornix of the involved eye, two drops every six hours. Patients were treated for five days and followed-up for two weeks. Information on age, sex, cause, time and type of trauma was collected.

All patients underwent a complete ophthalmologic examination. Clinical information including the initial visual acuity (Snellen's chart), initial intraocular pressure (aplanation tonometry), initial bleeding (using the Haag-streit 900 biomicroscope), indirect fundus ophthalmoscopy findings, and associated ocular injuries were recorded. Patients were then examined daily for seven days and on the 14th day after ocular trauma the examination included visual acuity, grading of hyphema, secondary bleeding, intraocular pressure, corneal blood staining, drug toxicity, and indirect fundus ophthalmoscopy (B-scan ultrasonography was done initially when details of the fundus were obscured). The ophthalmologist who examined the patients did not know if they were treated or not.

Patients randomly assigned to receive the drops were given the preparation labelled with a code. Data were collected using SPSS for Windows software. Univariate and multivariate (logistic regression modeling) analyses were done.

RESULTS

A total of 155 patients entered the trial; 23 were lost to follow-up and were omitted from the final analysis, which included 14 patients from the first group, five from the second, and four from the third. There was no significant differences between the three groups

in terms of age, sex, side affected, initial amount of hyphema, initial and final visual acuity and initial and final intraocular pressure (IOP) (Tab. I, Fig. 1). Rebleeding occurred between the second and fourth day after ocular injury (mean 3 days) in 20 patients, 8 in group 1 (15.4%), 7 in group2 (17.8%) and 5 in group 3 (12.2%) (Tab. II). In group 3 (n=41) who received ACA, clot absorption took 11.1 days compared to 9.3 days in group 2 (n=39) and 9.5 days in group 1 (n=52).

Rebleeding in the different groups was analyzed to assess the factors associated with a high risk, such as age, amount of hyphema, initial IOP and initial visual acuity. The effects of different factors on the incidence of rebleeding were estimated by logistic regression (Tab. III). No factor had any real effect on the rate of rebleeding, except for a moderate effect of visual acuity less than 20/200 (OR= 2.8, 95% CI 0.8-10.0) compared to visual acuity of 20/40 or greater.

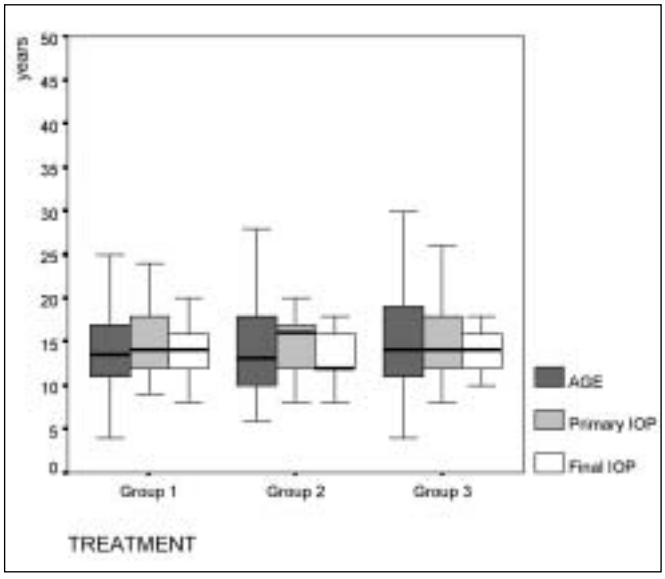

Fig. 1 - *Distribution of age, primary and final IOP.*

TABLE I - SEX, EYE AFFECTED, DEGREE OF HYPHEMA AND VISUAL ACUITY OF PATIENTS WITH TRAUMATIC HYPHEMA, No. (%)

Variable	Group 1 (n=52)	Group 2 (n=39)	Group 3 (n=41)
Sex* (male)	48 (92)	34 (78)	35 (85)
Eye* (right)	25 (48)	18 (46)	23 (56)
Hyphema level*:			
< 1/4 of AC	39 (75)	31 (79/5)	34 (83)
1/4 - 1/2 of AC	13 (25)	7 (18)	7 (17)
> 1/2 of AC	0	1 (2/5)	0
Initial Visual Acuity*:			
20/20-20/40	34 (65.5)	27 (68.5)	32 (78)
20/50-20/100	9 (17.5)	4 (10.5)	2 (5)
< 20/200	9 (17.3)	8 (15.4)	7 (13.4)

*= Difference between groups not significant at 5% level
AC= Anterior chamber

TABLE II - INCIDENCE AND TIME OF ONSET OF REBLEEDING, TIME TAKEN FOR CLOT ABSORPTION IN ANTERIOR CHAMBER (AC)

Variable	Group 1 (n=52)	Group 2 (n=39)	Group 3 (n=41)
Rebleeding, no. (%)*	8 (15.4)	7 (17.8)	5 (12.2)
Time of rebleeding,* days (mean, SD)	3 (0.8)	3 (0.8)	3.2 (0.5)
Duration of AC clot absorption** days (mean, SD)	9.5 (3.9)	9.3 (4.2)	11.1 (4.7)

*= Not significant at 5% level
**= Significant difference between group 3 and both other groups ($p<0.04$)

TABLE III - ADJUSTED ESTIMATES OF EFFECTS OF DIFFERENT FACTORS ON REBLEEDING*

Factor	Relative risk	95% CI
Therapy group:		
Group 1	1	Reference
Group 2	0.7	0.2-2.5
Group 3	0.9	0.2-3.4
Visual acuity:		
≥ 20/40	1	Reference
20/200 to 20/40	2.9	0.5-17.7
≤ 20/200	2.8	0.8-10.0
Age	0.9	0.8-1.0
Initial IOP	1.1	1.0-1.2
Degree of hyphema	0.7	0.2-2.5

IOP= Intraocular pressure

The type of treatment also did not appear to affect the incidence of rebleeding, but the clot in the anterior chambler was absorbed on average two days later in the group treated with ACA (P<0.04).

DISCUSSION

In a double-blind controlled trial we studied the effect of a topical 25% solution of ACA in patients with traumatic hyphema. Though ACA did not appear to affect the rate of rebleeding, the time needed for clot absorption in the anterior chamber was significantly (20%) longer in the group receiving ACA.

This is not consistent with Crouch's report in 1997 that ACA drops could prevent rebleeding in patients with traumatic hyphema (3% compared to 22%) (1, 2). In Crouch's study, the ACA concentration was 30% and the dose 0.2 ml, equal to three drops every six hours, in the form of gel in the lower cul de sac, while in our study the drug concentration was 25%, and the dose was two drops every six hours - also as a gel - which might explain the different results of the two studies. It was because of technological shortages in our country that the manufacturer could not produce a 30% solution of ACA.

Another finding was that the ACA drops markedly prolonged the time for clot absorption in the anterior chamber. As regards the drug mechanism that prevents the adhesion of plasmin to the fibrin clots, delaying the lysis of the clots, it seems that the penetration of the drop into the anterior chamber should have some effect on the rebleeding system. Our study showed that in groups 1 and 2, given respectively the regular and placebo protocols, the rate of rebleeding was significantly higher in patients with visual acuity less than 20/200 than in those with 20/40 or greater. This confirms the findings of Fong (1994) (15), and Rahmani (1999) (20), who reported that patients with vision lower than 20/200 had a higher risk of rebleeding than those with the vision better than 20/200.

The correlation between the amount of initial bleeding and the possibility of rebleeding was also investigated in some studies (15-18). In the study by Rahmani this correlation was not confirmed (20). The present study also indicates that the rate of initial bleeding has no influence on the risk of rebleeding. Our investigation did show a significant association between the primary IOP and rebleeding (OR = 1.1, 95% CI 1.0-1.2), which is consistent with the results of Rahmani (20).

Conclusion: We were not able to show any effect of topical ACA on the rate of rebleeding in patients with traumatic hyphema, but there was some lengthening of the time needed for clot absorption.

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