Urokinase in the management of traumatic hyphaema

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There is no general agreement in the literature on the correct management of traumatic hyphaema*—even about such minor points as whether to pad the injured eye only or to pad both eyes, and whether to use a miotic or mydriatic or not. It was therefore decided in 1966 to treat a controlled series of cases of traumatic hyphaema with various pre-selected regimes. This prospective study was undertaken at Baragwanath Hospital and extended over 3 years (1966–1969), when 370 consecutive cases were examined and treated. A detailed report of this study is to be published elsewhere. One of the major findings was that the prognosis was directly related to the size of the hyphaema (Table I). The problem of management thus mainly concerns the three-quarters to full hyphaemas, since, in our experience, those occupying half the volume of the anterior chamber or less have a good prognosis irrespective of the type of treatment and even with no treatment at all.

Table I *Traumatic hyphaema treated according to size*

Size	<i>Less than half of volume of anterior chamber</i>		<i>More than half of volume of anterior chamber</i>	
	<i>No.</i>	<i>Per cent.</i>	<i>No.</i>	<i>Per cent.</i>
No. of cases	213		157	
Raised intraocular pressure	8	3.8	133	84.7
Incidence of complications	47	22.0	123	78.3
Final vision of 6/18 or better	166	78.0	44	28.0

This paper reports our experience with the use of Urokinase as a fibrinolytic agent in twenty cases of full hyphaema, associated with large blood clots in the anterior chamber, which could not be washed out with saline.

There have been many reports of the use of fibrinolytic substances†, but these dealt with only eight cases or less, with no attempt to compare the results with those of other forms of treatment. None of the patients had previously been treated by anterior chamber wash-out with saline.

Materials and methods

In the early part of the study before Urokinase was available, the effect of conservative as against surgical management was investigated, 98 cases selected at random were treated conservatively‡ and 59 cases by immediate anterior chamber wash-out with saline through a small corneal incision.

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*Rychener (1944), Laughlin (1948), Thyesson and Beard (1952), Duke-Elder (1954), Sorsby (1964), MacDonald (1964), Oksala (1967) Darr and Passmore (1967)

†Pierse and Le Grice (1963, 1964), Scheie, Ashley, and Burns (1963), Heath (1966)

‡Conservative treatment comprised rest in bed, pad to the injured eye, topical antibiotic, cycloplegic, and miotic, and Diamox

SURGICAL TECHNIQUE

Incision

This was made with a von Graefe knife through the peripheral part of the cornea, 1–2 mm. in front of the limbus. The incision was slanted within the corneal stroma so that suturing was unnecessary, and was extended to about 15°. The posterior lip of the incision was depressed with an iris repositor to evacuate the fluid blood from the anterior chamber.

Irrigation

Saline from a 2 ml. syringe with a blunt cannula was then introduced into the anterior chamber through the incision; care was taken to keep the tip of the cannula just within the incision and directed away from both the corneal endothelium and the lens capsule, *i.e.* over the iris and parallel to it. The anterior chamber was then gently irrigated with saline until it was free of blood.

UROKINASE

This was used in twenty cases in which anterior chamber wash-out with saline had failed to evacuate large blood clots. In eight cases, the patients were returned to the ward after anterior chamber irrigation with saline and were assessed the following day. They were then subjected to a second anterior chamber wash-out with Urokinase through the same incision. In the other twelve cases, Urokinase was used at the first operation after irrigation with saline had failed to remove blood clot.

The Urokinase was supplied fresh in ampoules by Leo Laboratories as a lyophilized powder and used soon after delivery. If some delay before use is anticipated, the Urokinase should be stored in a refrigerator. 5,000 units Urokinase solution was made up by mixing the powder with 2-ml. sterile distilled water. The anterior chamber was irrigated slowly, with 0.3 ml. Urokinase solution and this was left *in situ* for 3 minutes and then washed out with saline. This procedure was repeated five times. With each introduction of Urokinase the clot became more friable and easier to disperse. If any residual clot was present at the end, 0.3 ml. Urokinase was left in the anterior chamber for 24–48 hours. This caused no harmful effects, and every small clot which remained in the anterior chamber after operation had dissolved completely within 48 hours.

Results

These were assessed by the following criteria in the twenty cases in which saline irrigation was unsuccessful:

- (1) Rate of dispersal of blood from the anterior chamber;
- (2) Incidence of complications of the hyphaema;
- (3) Final visual acuity.

(1) Rate of dispersal of blood

In the eight patients in whom Urokinase was used on the next day, it was found that the blood clot had remained the same size and that the intraocular pressure was elevated.

With the use of Urokinase, the blood clot absorbed completely on the operating table in four cases.

In a further four cases it had dissolved before the first post-operative dressing on the first day, and in five more cases within 3 days.

Only two cases took longer than 1 week to absorb completely (one in 7 days and one on the 9th postoperative day), and it was felt that in these cases a higher concentration of Urokinase was necessary to dissolve the blood clot. This was achieved by using 10,000 units (2 ampoules) dissolved in 2 ml. sterile distilled water. In one case, in which 5,000 units Urokinase had had no effect, immediate irrigation with 10,000 units succeeded in dissolving the clot completely.

A comparison between the group of full hyphaemas treated conservatively, those irrigated with saline alone, and those irrigated with saline plus Urokinase shows that the rate of absorption of blood from the anterior chamber (Figure) was slowest in the first group, more rapid in the second, and markedly accelerated in the last.

FIGURE Rate of absorption of blood from anterior chamber

With conservative treatment only 35 per cent. of hyphaemas had absorbed within 1 week, whereas with saline irrigation 62 per cent. and with Urokinase irrigation 90 per cent. had absorbed completely within 1 week.

(2) Incidence of complications

The incidence of major complications before treatment (Table II) was least in the group treated conservatively, greater in the group treated with saline washout, and highest in the group treated with Urokinase.

Table II Incidence of major complications before and after treatment

Treatment		Anterior chamber irrigation					
		Conservative		With saline		With saline plus Urokinase	
		No.	Per cent.	No.	Per cent.	No.	Per cent.
Corneal blood staining	Before treatment	27	27.6	29	49.2	2	60
	After treatment	21	21.6	10	16.9	2	10
Raised intraocular pressure	Before treatment	85	85.8	56	94.9	20	100
	After treatment	49	49.7	12	20.3	1	5
Clotting in anterior chamber	Before treatment	19	19.6	29	49.2	20	100
	After treatment	33	33.7	21	37.9	2	10
Total cases		98		59		20	

The effect of the type of treatment in reducing the incidence of complications is seen most markedly in the group treated with Urokinase (where blood staining of the cornea was reduced from 60 per cent. before treatment to 10 per cent. after treatment, raised intraocular pressure from 100 to 5 per cent., and fibrous membrane formation occurred in only two cases (10 per cent.) although all the cases in this group had large anterior

chamber blood clots). The reduction of complications was also marked, although less so, in the group treated with saline, and least in the group treated conservatively. In fact, from a 20 per cent. incidence of blood clotting in the anterior chamber at the start of treatment, fibrous membrane formation occurred in 33.7 per cent. of these cases; blood clotting must have occurred while these patients were receiving conservative treatment.

The relative incidence of minor complications in the three groups is essentially similar (Table III).

Table III *Incidence of minor complications*

<i>Treatment</i>	<i>Conservative</i>		<i>Anterior chamber irrigation</i>			
			<i>With saline</i>		<i>With saline plus Urokinase</i>	
	<i>No.</i>	<i>Per cent.</i>	<i>No.</i>	<i>Per cent.</i>	<i>No.</i>	<i>Per cent.</i>
Pigment on endothelium	15	15.5	10	16.9	3	15
Pigment on lens capsule	10	10.5	6	10.2	2	10
Pigment on vitreous	3	3.3	3	5.1	2	10
Posterior synechiae	15	15.5	11	18.6	2	10
Peripheral anterior synechiae	2	2.2	0		0	
Cholesterol crystals	3	3.3	0		0	
Total cases	98		59		20	

(3) *Final visual acuity (Table IV)*

The final visual acuity is poor in all three groups, irrespective of the type of treatment. The acuity recorded is that observed on discharge. As such, it is partly related to the presence of associated ocular injuries which depend on the severity of the initial injury rather than on the type of treatment. Their presence is often not diagnosed until the hyphaema has absorbed and their treatment is of necessity delayed.

Table IV *Final visual acuity*

<i>Treatment</i>	<i>Conservative</i>		<i>Anterior chamber irrigation</i>			
			<i>With saline</i>		<i>With saline plus Urokinase</i>	
	<i>No.</i>	<i>Per cent.</i>	<i>No.</i>	<i>Per cent.</i>	<i>No.</i>	<i>Per cent.</i>
6/18 or better	33	33.7	11	18.9	4	20
6/24 to 6/60	11	11.2	11	18.9	5	25
Less than 6/60	54	55.1	37	62.2	11	55
Total cases	98		59		20	

The associated ocular injuries were essentially the same in all three groups (Table V, over-leaf) and this may explain the similarity in visual acuity.

There is a high incidence of vitreous haemorrhage and traumatic cataract in full hyphaemas, and it may thus be difficult to assess the underlying retina and choroid, so that the incidence of retinal oedema, retinal tears, retinal detachment, and choroidal tears is probably much higher than is shown here. These two injuries are mainly responsible

Table V *Associated ocular injuries*

<i>Treatment</i>	<i>Conservative</i>		<i>Anterior chamber irrigation</i>			
			<i>With saline</i>		<i>With saline plus Urokinase</i>	
	<i>No.</i>	<i>Per cent.</i>	<i>No.</i>	<i>Per cent.</i>	<i>No.</i>	<i>Per cent.</i>
Vitreous haemorrhage	50	50	30	51	9	45
Traumatic cataract	26	26	22	37	10	50
Dislocated lens	6	6	4	7	2	10
Traumatic iritis	24	24	9	15	2	10
Iris sphincter tears	6	6	1	1.7	1	5
Iridodialysis	4	4	0		1	5
Angle contusion	21	21	17	28	5	25
Retinal oedema	3	3	2	3.4	2	10
Retinal tears	5	5	2	3.4	2	10
Retinal detachment	1	1	2	3.4	2	10
Choroidal tears	1	1	0		0	
No injury	28	28	4	6.7	1	5
Total cases	98		59		20	

for the poor visual acuity. In the group treated conservatively there is a significantly higher incidence of traumatic iritis than in the other two groups.

Discussion

Early surgery is important in the management of full hyphaemas (Rakusin and Kuming, 1969). Factors against continued conservative treatment include:

- (1) The slow rate of absorption.
- (2) The small effect on lowering the incidence of complications—in fact the results suggest that clotting had occurred while patients were actually receiving conservative treatment.
- (3) The high incidence of traumatic iritis.

With traumatic hyphaemas which occupy more than three-quarters of the volume of the anterior chamber, two clinical types are recognizable, one in which the blood is mainly fluid and one in which it is clotted. In the first type blood is easily washed out with saline, but in our experience, only 45 per cent. of cases of the second type can be easily treated with saline alone. In large hyphaemas irrigation with saline succeeded in increasing the rate of absorption and decreasing the incidence of complications, but two disturbing features were noted:

- (1) A high incidence (36 per cent.) of fibrous membrane formation. This presumably occurred as a result of organization of clots which could not be evacuated with saline.
- (2) In many cases (38 per cent.) the clot took longer than 1 week to absorb.

Obviously saline irrigation alone is often inadequate and fibrinolysis is required to dissolve the blood clot.

The ability of urine to dissolve a thrombus had long been recognized, but the active principle, Urokinase, was first isolated and purified by Ploug and Kjeldgaard (1957). This protein of human origin is entirely non-antigenic. It is a plasminogen activator and

converts plasminogen to plasmin which digests fibrin. In the twenty cases in which Urokinase was used, it markedly increased the rate of absorption of blood from the anterior chamber and decreased the incidence of complications.

The results in patients treated conservatively and those treated with saline irrigation can be compared, but, it is not strictly accurate to include the group treated with Urokinase. These patients formed a highly selected group of the most severely traumatized eyes (in which there was a 100 per cent. incidence of large blood clot formation in the anterior chamber and of raised intraocular pressure and a 60 per cent. incidence of corneal blood staining) in whom saline irrigation had failed. They form a group, in fact, acting as its own control, since in each patient saline was used unsuccessfully before Urokinase. They compare very favourably with the other groups, in which the trauma was less severe (as suggested by the lower incidence of glaucoma, corneal blood staining, and blood clot formation before treatment was started).

We feel that Urokinase has a significant role in the management of large traumatic hyphaema associated with large anterior chamber blood clots, and urge that it should be readily available in the operating theatre when saline irrigation is to be performed, so that it may be used immediately in difficult cases, so avoiding the need for a second surgical operation.

Our suggested schedule for the management of large traumatic hyphaemas is shown in Table VI.

Table VI *Management of three-quarters to full hyphaema*

(1) *Conservative treatment*

Should *not* be continued for longer than 48 hours without definite improvement (*i.e.* I.O.P. normal and blood absorbing).

(2) *Surgery*

(A) *Anterior chamber irrigation with saline*

Good response—when blood remains fluid
—in 45 per cent. of clotted hyphaemas

(B) *Anterior chamber irrigation with saline plus Urokinase*

Immediately after washout with saline in cases in which blood clot remains in anterior chamber

Summary

In twenty patients who sustained traumatic hyphaemas occupying the whole of the anterior chamber together with large blood clots unsuccessful irrigation of the anterior chamber with saline was followed by the use of Urokinase. There was an increased rate of absorption and fewer complications than in two groups of similar hyphaemas treated conservatively or by irrigation with saline alone.

Early irrigation with saline should be performed in cases of traumatic hyphaemas occupying more than three-quarters of the volume of the anterior chamber, and Urokinase should be available for immediate use if saline alone is ineffective.

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