EXTENDED REPORT

Effect of tranexamic acid on early postvitrectomy diabetic haemorrhage; a randomised clinical trial

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Aims: To evaluate the effect of tranexamic acid on early postvitrectomy haemorrhage in diabetic patients.
Methods: In a clinical trial, 62 diabetic patients scheduled for vitrectomy were randomly assigned to two groups. The treatment group (32 eyes) received two doses of tranexamic acid (10 mg/kg) shortly before and after the operation intravenously, continued orally for 4 days (20 mg/kg/8 hours). The control group (30 eyes) received no medication. Both media clarity and visual acuity were compared during 4 weeks.
Results: Four weeks after surgery visual acuity was low ($\leqslant$1 metre counting fingers) in 21.4%, moderate ($>$1 metre counting fingers but$<$20/200) in 14.3%, and good ($\geqslant$20/200) in 64.3% of the treated group. Corresponding figures in the control group were 26.1%, 26.1%, and 47.8%, respectively. These differences were of no statistical significance. The ratio of mild to severe vitreous haemorrhage during the first 4 days and after 4 weeks was 79% to 21% and 82% to 18% in the treatment group and 76.7% to 23.3% and 78.3% to 21.7% in the control group respectively, which showed no statistically significant difference.
Conclusion: Tranexamic acid, with the method of administration in this study, had no effect on reducing early postvitrectomy haemorrhage in diabetic patients.

Early vitreous haemorrhage, within a week after vitrectomy, is a common complication in diabetic patients, with an incidence of 29–75%.[1] It may cause severe visual impairment (especially important in monocular patients), interfere with examination and laser therapy, induce ghost cell glaucoma,[2] increase need for vitrectomy,[3] and stimulate the growth of epiretinal membranes and fibrous tissue.

Antifibrinolytic drugs, like tranexamic acid and EACA (ϵ-aminocaproic acid), inhibit clot lysis through interference with plasmin action.[1] The haemostatic effect of EACA has been proved in different types of operations such as prostatectomy, dental, cardiac, and orthopaedic operations.[4 5] In addition, the role of these drugs in decreasing rebleeding in hyphaema is clear.[2]

These two medications have been used after vitrectomy for diabetic patients in two separate studies and good results were observed in one of them.[6 7] The present study evaluated the effect of tranexamic acid on early vitreous haemorrhage after vitrectomy in diabetic patients with proliferative retinopathy.

MATERIALS AND METHODS

This randomised clinical trial was conducted on diabetic patients scheduled for vitrectomy for advanced retinopathy including non-clearing vitreous haemorrhage, tractional retinal detachment, and progressive fibrovascular proliferation. All registered patients were fully informed of the side effects of tranexamic acid.

After complete history taking and ophthalmic examination, laboratory tests were performed for each enrolled patient that included blood cell and platelet counts, serum creatinine and fasting blood sugar level, prothrombin and partial thromboplastin time. Exclusion criteria consisted of history of cataract surgery or vitrectomy, haemodialysis, pregnancy, history of disorders such as deep vein thrombosis, myocardial infarction, or cerebrovascular accidents.

Before surgery, patients were randomly assigned to receive tranexamic acid or no medication. In the case group, the first drug administration (10 mg/kg intravenously) was performed just before transferring the patient to the operating room. The second tranexamic acid intravenous injection was performed after surgery with the same dose. From the day after vitrectomy, the medication was continued orally in the form of 250 mg capsules (20 mg/kg every 8 hours) for 4 days during hospitalisation. The drug dosage was adjusted according to serum creatinine level (table 1).

Table 1 Tranexamic acid dosage adjustment according to serum creatinine level

Creatinine level (mg/dl)	Intravenous (mg/kg)	Oral (mg/kg)
2.83–1.36	5	15 (twice daily)
5.66–2.84	2.5	15 (daily)
>5.66	1.7	5 (daily)

Standard three port vitrectomy was performed for all patients under local or general anaesthesia. Only Ringer's solution was used to avoid the anticoagulative effect of citric acid present in balanced salt solution. Additional procedures like endolaser, membrane dissection, etc, were performed if needed. Intraoperative bleeding was controlled by either raising intraocular pressure or endodiathermy. If use of an internal tamponade such as air, gas, or silicone oil was mandatory, that case would be excluded from the study. Blood pressure was monitored during hospitalisation including operation time. Eye pressure was checked at the end of the surgery with the Schiotz device. The surgeons were masked to the randomisation.

All patients were hospitalised after surgery and for 4 days, all had bed rest in a semi-sitting position. Complete examination was performed during the admission period, and 1 week and 4 weeks after surgery. The degree of intravitreal haemorrhage was scaled according to the diabetic

Abbreviations: EACA, ϵ-aminocaproic acid; IOP, intraocular pressure; PT, prothrombin time; PTT, partial thromboplastin time

Table 2 Intravitreal haemorrhage scaling according to the diabetic retinopathy vitrectomy study

Description	Grade
No vitreous haemorrhage	0
Mild vitreous haemorrhage with visible fundus details	1
Moderate vitreous haemorrhage with no visible fundus details but with an orange fundus reflex	2
Severe vitreous haemorrhage with no retinal details and no orange fundus reflex	3

retinopathy vitrectomy study grading system (table 2).[8] For statistical analysis, eyes with grade 0 or 1 haemorrhage were classified as mild, and cases with grade 2 or 3 as severe haemorrhage.

Visual acuity was also graded into low ($\leqslant$1 metre counting fingers), moderate (more than 1 metre counting fingers but less than 20/200), and good ($\geqslant$20/200). The amount of vitreous haemorrhage and visual acuity were compared between the two groups at three different times: hospitalisation period (according to the mean of 4 days), after 1 week and 4 weeks. All the examiners were masked to patients' allocation into each group.

This clinical trial was approved by the review board/ethics committee of the ophthalmic research centre.

Statistical analysis

Taking into account the reported 70% incidence of postvitrectomy diabetic haemorrhage and reducing this to 35% as our main goal, a minimal sample size of 32 eyes in each group was required to detect a significant difference at the two sided 5% level with a study power of 80%.

Independent samples *t* test was employed for evaluating quantitative variables. The χ^2 test was used to compare the severity of preoperative and postoperative vitreous haemorrhage and visual acuity levels. Statistical level of significance was preset at 0.05. Data were analysed using SPSS 9.

RESULTS

Sixty two eyes of 62 patients (32 cases and 30 controls) were included in the study. Some relevant individual and clinical characteristics of each group are presented in table 3. It may be noted that both groups were similar in all factors except for age. Mean age of the treatment group was 6 years older than the controls ($p = 0.04$).

Means of probable confounding factors are shown in table 4. All of the mentioned parameters displayed no significant difference between the groups except mean intraocular pressure at the first week.

The presence and severity of vasoproliferative or fibroproliferative changes at the time of surgery were also similar in both groups (data not shown).

Visual acuity levels, evaluated at three different times, are presented for each group separately in table 5. There was no significant statistical difference at any of the examination intervals.

Overall, visual acuity during the first 4 days was low in 22 eyes (35.5%), moderate in 28 eyes (42.5%), and good in 12 eyes (19.4%). Corresponding figures with correction after 4 weeks were 12 eyes (23.5%), 10 eyes (19.6%), and 29 eyes (56.9%) respectively.

Severity of vitreous haemorrhage is presented in table 6. The prevalence of severe vitreous haemorrhage in the treated and observation groups was 6/32 versus 7/30 , 3/27 versus 4/27, and 4/27 versus 5/23 after 4 days, 1 week, and 4 weeks, respectively. No statistically significant difference was observed between the two groups.

Overall, the presence and severity of retinal neovascularisation were similar in eyes with either mild or severe postoperative haemorrhage during the first 4 days. Although eyes with mild postvitrectomy haemorrhage had more severe fibrovascular changes, this difference was not significant ($p = 0.052$). The amount of haemorrhage during the first 4 days in both groups had no correlation with intraoperative bleeding or performing membrane dissection.

Early postoperative vitreous haemorrhage was correlated with the presence of fresh preoperative vitreous haemorrhage. Of eyes with mild postoperative haemorrhage 61.2% (30 of 49) had fresh preoperative haemorrhage; however, 92.3% (12 of 13 eyes) of eyes with severe postoperative haemorrhage had such a finding ($p = 0.03$).

No evidence of thrombotic or thromboembolic complications was seen in the treated group. Among the cases, three complained of nausea, two of vomiting, and one of diarrhoea. One of the controls also reported nausea.

DISCUSSION

This clinical trial showed that tranexamic acid did not reduce early vitreous haemorrhage or improve visual acuity after vitrectomy in patients with proliferative diabetic retinopathy.

The source of early postvitrectomy diabetic haemorrhage is retained blood in the vitreous cavity or rebleeding from cut edges of fibrovascular tissue during surgery. Some methods

Table 3 Individual and clinical characteristics of 62 patients (%)

Characteristics	Control (n = 30)	Treated (n = 32)	p Value
Age (years)	50.53 (SD 11)	56.9 (SD 11)	0.04
Sex			
Male	16 (53.3)	19 (59.4)	NS
Female	14 (46.7)	13 (40.6)	
History of systemic hypertension	17 (56.7)	18 (58.1)	NS
Preoperative vision			
Low	14 (46.7)	19 (59.4)	NS
Moderate	8 (26.07)	9 (28.1)	NS
Good	6 (20)	4 (12.5)	NS
Presence of preoperative NVI*	1 (3.3)	2 (6.25)	NS
Fresh preoperative VH†	19 (63.3)	23 (71.9)	NS
Membrane dissection	22 (73.3)	23 (71.9)	NS
Intraoperative bleeding	21 (72.4)	20 (62.5)	NS
Applying endodiathermy	3 (10)	6 (18.8)	NS

*Neovascularisation of the iris.
†Vitreous haemorrhage.
NS, not significant.

Table 4 Confounding factors in the study groups (SD)

Confounding factors	Treated (n = 32)	Control (n = 30)	p Value
Preoperative serum creatinine (mg/dl)	1.2 (0.59)	1.3 (0.89)	NS
Preoperative platelet count (10^6/l)	227 838	209 100	NS
Preoperative PT (s)	13.5 (2.9)	13.6 (3.6)	NS
Preoperative PTT (s)	38.6 (11)	38.5 (9)	NS
End of surgery IOP (mm Hg)	15.9 (4)	14.8 (6)	NS
Intraoperative blood pressure			
systolic (mm Hg)	143 (17)	134 (24)	NS
diastolic (mm Hg)	83 (8)	81 (12)	NS
Postoperative blood pressure			
systolic (mm Hg)	131 (18)	132 (14)	NS
diastolic (mm Hg)	76 (8)	76 (8)	NS
Postoperative IOP			
first day (mm Hg)	20 (6)	17 (5)	0.037
first week (mm Hg)	16 (6)	13 (5)	NS
fourth week (mm Hg)	17 (7)	15 (5)	NS

PT, prothrombin time; PTT, partial thromboplastin time; IOP, intraocular pressure; NS, not significant.

used to decrease this complication are: (1) adding thrombin to the irrigation fluid during surgery, which decreased bleeding time during the operation[9 11]; (2) use of sodium hyaluronate (Healon) intravitreally at the end of the surgery to mechanically prevent dispersion of haemorrhage[12 13]; (3) injection of silicone oil to prohibit the spread of coagulative elements[14]; (4) fluid exchange with air or gas to produce tamponade, however one study showed an opposite result.[15]

The main cause of early postoperative haemorrhage is lysis of the clot, which is usually formed at the edges of cut vessels or dissected fibrovascular tissue during surgery. Therefore, antifibrinolytic drugs that inhibit clot lysis might decrease rebleeding. In the present study, we preferred to use tranexamic acid rather than EACA, because of its lower dosage and less side effects.

Both groups in our study were matched according to basic and confounding factors except in two aspects, age, and IOP at 1 week. On average, treated patients were 6 years older than controls. Although this difference was statistically significant, it could not have been an important confounding factor clinically. Contrary to the present study, average age in the treated group was 10 years lower in the study performed by Laatikainen *et al*.[6] Since in both studies tranexamic acid had no beneficial effect, these two papers could complement each other regarding the confounding factor of age.

We believe that the 3 mm Hg difference in the average first week IOP has no clinical importance either. In addition, IOP before and after the first week, showed no meaningful difference. There is also a low probability that increased IOP in the treated group was caused by tranexamic acid; as far as we know, such a side effect has not previously been reported.

To the best of our knowledge, antifibrinolytic agents had been evaluated for postoperative vitreous haemorrhage in only two studies.[6 7] In 1987, Laatikainen *et al* performed a similar study with tranexamic acid on fewer patients (31 cases). They administered the first dose at the end of the operation and the second one 12 hours later. However, in our study, cases received the first dose before going to the operating room and the second on returning. Although rates of vitreous haemorrhage in their study were 44% in treated patients versus 60% in controls, the difference was not significant.[6] No important side effect was seen in either of these studies with tranexamic acid, and they both concluded that this drug had no effect on early postvitrectomy vitreous haemorrhage and final visual acuity.

A beneficial effect of EACA on early vitreous haemorrhage was reported in 1985 in study by de Bustros *et al* on 96 patients.[7] The potency of this drug is 10 times less than tranexamic acid, so it must be administered in much higher doses. In spite of some side effects (nausea, vomiting, and diarrhoea in 21% and postural hypotension in 6%), there was no need for discontinuation of the drug in any of their cases. The study concluded that EACA reduced postvitrectomy haemorrhage in the first 4 days ($p = 0.002$); however, no significant difference was noted in the second and sixth weeks. The authors believed that disappearance of intergroup difference was in part caused by rebleeding in treated patients after EACA was discontinued, and spontaneous clearing of haemorrhage in untreated eyes. They concluded that although EACA could not decrease the recurrence of bleeding, its ability to reduce vitreous haemorrhage during the early postoperative period permits better evaluation of the fundus during this crucial time when media clarity is required for detection of retinal detachment or performing laser therapy.

Since the mechanism of these drugs is inhibition of clot lysis, they would not have any effect unless bleeding has already happened. As a result, it is logical to expect their effect only in cases with bleeding during vitrectomy, but the statistical analysis was not able to show any benefit, even in such cases. In Laatikainen's study also, even though bleeding and need for diathermy were more common in the control group, the incidence of vitreous haemorrhage was greater in the first week in the treated patients.[6]

Among all probable confounding factors, only fresh vitreous haemorrhage before surgery affected the first 4 day

Table 5 Visual acuity levels at three different times in each group (%)

	Visual acuity								
	1st 4 days			1st week			4th week		
	Low	Mod	Good	Low	Mod	Good	Low	Mod	Good
Treated	11 (34.4)	16 (50)	5 (15.6)	9 (31)	11 (37.9)	9 (31)	6 (21.4)	4 (14.3)	18 (64.3)
Control	11 (36.7)	12 (40)	7 (23.3)	7 (25.9)	10 (37)	10 (37)	6 (26.1)	6 (26.1)	11 (47.8)
Total	22 (35.5)	28 (45.2)	12 (19.4)	16 (28.6)	21 (37.5)	19 (33.9)	12 (23.5)	10 (19.6)	29 (56.9)

Table 6 Vitreous haemorrhage severity compared between groups at three different intervals (%)

	Vitreous haemorrhage severity					
	1st 4 days		1st week		4th week	
	Mild	Severe	Mild	Severe	Mild	Severe
Treated	26 (81.3)	6 (18.8)	24 (88.9)	3 (11.1)	23 (85.2)	4 (14.8)
Control	23 (76.7)	7 (23.3)	23 (85.2)	4 (14.8)	18 (78.3)	5 (21.7)
Total	49 (79)	13 (21)	47 (87)	7 (13)	41 (82)	9 (18)

bleeding. Such an effect is an expected finding, because fresh vitreous haemorrhage implies activity of retinopathy with more predisposition to bleeding.

When evaluating the effect of tranexamic acid on early postvitrectomy haemorrhage in diabetic patients some factors must be kept in mind:

(1) The role of improper clot formation as a result of coagulopathy in diabetic patients who might already have a renal problem.

(2) Inadequate drug dose or intraocular drug concentration. Although drug concentration is low in the vitreous cavity at the end of surgery, it seems that the fibrinolysis is more active at the vessel side than the vitreous side of a clot. Therefore, blood drug concentration must be more important.

(3) Short drug administration period. Most bleedings occur after the hospitalisation period (the first 4 or 5 days), at which time the drug is discontinued and has no more effect. In de Bustros's study, the benefit of drug was shown only during its administration and repeat bleeding occurred after its discontinuation. Therefore, they recommended a longer period of drug administration.[7]

(4) Some instances of early vitreous haemorrhage are merely the result of dispersion of pre-existing blood in the vitreous cavity and not because of rebleeding after clot lysis. We should remind ourselves that all of our patients were phakic and complete clearing of the peripheral vitreous cavity from blood was impossible.

(5) Because of dysfunction of coagulative and fibrinolytic systems in diabetics (especially in cases with renal failure), the effect of tranexamic acid may be different in these patients. Moreover, drug effect may differ specifically in the eye compared to other organs.

(6) Although attempts were made to control for confounding for both groups, their effects could not be ignored completely. Two of these factors were blood pressure rise after surgery both with general or local anaesthesia (noting that most of our patients were hypertensive) and coagulative disorders. As a result, administration of a drug with only relative inhibitory effect on clot lysis may not have had the ability to compete with such factors, with greater potential to induce bleeding.

In conclusion, we would not recommend tranexamic acid for decreasing postvitrectomy diabetic vitreous haemorrhage . Further studies with other drugs may be suggested.

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