Efficacy of sulodexide as adjunct in trabeculectomy. A two-year randomized clinical study

L. Quaranta, S. Bettelli, E. Gandolfo

Glaucoma Centre of the Eye Clinic, University of Brescia

Introduction

One of the main causes of failure in antiglaucomatous filtering surgery is to be found in fibroblast proliferation and in a subconjunctival fibrosis at the filtering bleb.

The processes of surgical wound repairing after a trabeculectomy operation include initially an increase in vascular permeability with a leakage of plasmatic proteins. These proteins may accumulate and unite at the aqueous humour filtration area, together with blood from the surrounding tissues. These aggregates, which involve primarily the deep sclerectomy area, constitute the framework for the subsequent migration of inflammatory cells and fibroblasts. The ultimate object of antiglaucomatous filtering operations is the obtainment of a subconjunctival aqueous humour filtering through the deep sclerectomy zone. The perviousness of that zone and the diffusion of the aqueous humour through the subconjunctival spaces are obtained by means of the continuous flow of the aqueous humour itself and its fibrinolytic properties.

Notwithstanding primary trabeculectomy success rates are of the order of 75–85% in Caucasian subjects, the last few years have seen the advent of antiproliferative drugs, such as 5-fluorouracil and mitomycin C, which have optimized the success rates of the operation. And although those drugs have certainly improved success expectations of a trabeculectomy, there are many side effects to their use. These complications, sometimes very serious and with extremely invalidating potency towards the visual function, have, however, always limited their use to selected cases, or, anyway, to relegate them to subspecialists of glaucomatous pathology.

Sulodexide (SDX) is a highly purified preparation containing a heparinic fraction with a high affinity for antithrombin III (80%) and a dermatan fraction with affinity for the cofactor II of heparin (20%). Sulodexide has been shown to possess a fibrinolytic activity expressed through the inhibitor of t-PA and the inhibitor of the plasminogen activator (PAI-1). It has also been shown to have an anti-aggregating pharmacological activity manifested through an inhibition of the leukocytic pathway of platelet aggregation.

On the basis of these presuppositions as to the failure of filtering surgery, we have considered it conceptually justified to plan a randomized clinical trial on the possible efficacy of SDX in preventing antiglaucomatous filtering surgery failure.

Patients and Methods

Between April and June of 1997, 42 consecutive patients were recruited, each with primary open-angle glaucoma, uncompensated by maximal medical therapy and, therefore, candidates for trabeculectomy surgery. The criteria for inclusion included:

1. no previous eye surgery;
2. intraocular pressure (IOP) ≥22 mmHg in hypotensive topical therapy (IOP calculated as the mean of the two highest values recorded during a diurnal pressure curve from 0800 hours to 1800 hours measured every 2 hours by Goldmann applanation tonometry;
3. availability for the checks according to the investigation protocol. A standard technique trabeculectomy operation was carried out, all by the same surgeon (LQ) under peribulbar anaesthesia. A limbus-based conjunctival flap with an 8–9 mm posterior cut to the limbus was made and, then, a careful haemostasis of the episcleral vessels with a moist cautery.

After sculpting a rectangular surface wedge of sclerotomy, about half the thickness of the sclera and 3×4 mm in size, a deep sclerotomy wedge 1×2 mm was excised. A basal iridectomy was then performed. The scleral wedge was closed with two separate stitches (one on each apex of the rectangular wedge of surface sclerotomy) in nylon 10-0. The conjunctiva and Tenon's capsule were closed, both at the same time, with a continuous suture in polyglactin (Vicryl) and the anterior chamber was re-formed with a balanced saline solution. After closure, the conjunctiva was tested for tightness to liquid flow. In all cases, a subconjunctival injection of 1.5 mg of betamethazone acetate was given at the inferior conjunctival fornix at the end of the operation.

The patients were then medicated and discharged with a topical therapy: dexamethazone 0.2% eyedrops, tobramycin 0.3% eyedrops, six times daily and tropicamide 0.1% eyedrops twice daily, for a period of six weeks.

In accordance with the standard schedule in routine use in our glaucoma centre, pressures were taken six hours after the operation and then once daily for the first week thereafter. Scleral suture lysis was done if necessary always within the first post-operative week.

At this point, the eyes were randomly

Table 1. General characteristics of the groups studied.

Variable	Trabeculectomy with		p
	Sulodexide	5-FU	
Age (years)	57.8±10.8	63±13.5	0.525*
Pre-op IOP (mmHg)	26±4.4	28±4.5	0.159*
Medical treatment period			
Antiglaucomatous (years)	7.51±1	7±1.5	0.211*
Pre-op pilocarpine	7	6	1†
Pre-op β-blockers	13	12	1†
β-blockers in contralateral eye	32	19	1†
Glaucoma type:			
Pigmented	3	3	
Open-angle	19	16	0.465†

IOP=Intraocular pressure. *=Student's t-test †=Fisher test.

Table 2. Post-operative intraocular pressure (IOP) values in mmHg±SD.

Variable	Trabeculectomy with Sulodexide (range)	Trabeculectomy with 5-FU (range)	p*
IOP after (months):			
2	15.00±2.1 (9–19)	15.00±2.8 (8–20)	1
6	13.20±1.3 (7–16)	12.75±1.6 (10–16)	0.327
12	15.50±2.2 (9–19)	14.80±2.4 (10–19)	0.336
18	12.70±3.22 (8–20)	13.25±2.5 (10–21)	0.550
24	14.25±3.32 (8–22)	13.80±2.7 (10–21)	0.640

*=Student's t-test.

assigned to treatment with 5-FU (19 eyes) and SDX (22 eyes). The two groups were comparable insofar as the variables:

1. risk factors for trabeculectomy failure (age, antiglaucomatous therapy period, previous treatment with parasympathicomimetics, treatment with β-blockers, glaucoma type) and
2. β-blockers in the contralateral eye were concerned (Table 1)

In neither group was any therapy modification with β-blockers made in the contralateral eye, nor were any hypotensive therapies given in the operated eye for the whole period of the study.

The eyes were to receive at random 5 subconjunctival injections of 5-FU or SDX at days 10, 17, 24, 31 and 38 after the operation. The injection cycle was fixed by external circumstances to start at 10 days after the operation, so that it should not interfere with scleral suture lysis. In both groups, the subconjunctival injections were made at the inferior fornix. So far as the 5-FU was concerned, 5 injections were given of 0.1 ml at the concentration of 50 mg/ml, care being taken to inject as far as possible from the ingress point of the needle. This protocol was adopted that the total dose administered be 25 mg of 5-FU, which is very like the total quantity of the drug shown to be efficacious in primary trabeculectomies (29 mg). The SDX treatment comprised 5 subconjunctival injections of 0.1 ml of the drug at a concentration of 300 USL/ml. This was a quite arbitrary dosage in that there is nothing in the literature concerning experience of this type of SDX use. Moreover, the same total volume of fluid in each treatment was deemed desirable so that there should be no possible interactions on the result due to mechanical conjunctiva-peeling difference caused by the volume of fluid injected. The same injection technique was used for SDX, too. In both groups, after injection, the drug left in the hole made by the needle was washed out with 100 ml of saline solution.

Before each injection, the presence of any complications presumably associated with 5-FU or SDX administration was evaluated.

After 2, 6, 12, 18 and 24 months, all the patients of the two groups were tested for their IOPs by tonometric curve (Goldmann applanation tonometer, measurements every two hours from 0800 hours to 1800 hours). The presence of any complications associated with the operation and/or the pharmacological treatment in use was noted at the same intervals.

For IOP statistical analysis, the mean of the two highest values found in the tonometric curve was evaluated.

The statistical analysis of the data was made by the Fisher test and Student's t-test.

The power for all the hypotheses tested was >0.78 and all the statistical tests were two-tailed with $\alpha=0.05$ and the confidence interval calculated at 95% (BMDP computer program release 7.0).

Results

All the 41 patients enrolled for the study completed the 24-month follow-up.

In the 5-FU group, 11 eyes out of the 19 operated were scleral suture lysed, in the SDX group, 10 out of the 22 eyes operated (scleral suture lysis always took place in the first post-operative week, leaving only one of the two sutures).

No ocular complications were found in 16 cases (73%) in the SDX group and in 12 (63%) of the 5-FU group. In 6 cases (32%) of the 5-FU group a superficial punctate keratopathy was found, none in the SDX group. In 6 cases (27%) of the SDX group, there was found a modest subconjunctival haemorrhagic suffusion, while there was only one (5%) in the 5-FU group, associated with a superficial punctate keratopathy. In all the cases, there was an extremely modest bleeding, which resolved within 7–10 days.

In the 5-FU group, 2 cases of aqueous leaking from a conjunctival operculum were found at 8 months and 13 months after the operation. These two cases required surgical repair of the bleb with suture of the ruptured area of the filtration bleb with 2–3 separate Vicryl 10–0 stitches.

No significant differences between the two groups were found in the IOP at any of the checks (Table 2, Fig. 1).

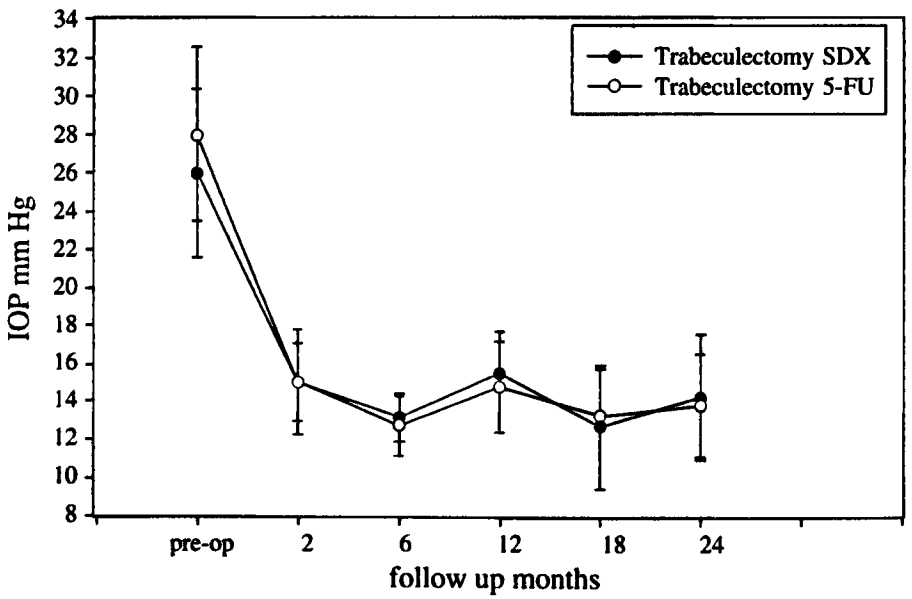

Fig. 1.

Discussion

It would seem from the results of this randomized clinical study the use of SDX as adjunct in trabeculectomy operations ensures a success rate comparable with that of 5-FU.

Notwithstanding the IOP levels of the two groups are comparable, however, the data of the investigation point up that major ocular complications were found only in the 5-FU group. This type of complication, perforation of the filtering bleb, as we found in two cases, is one of the more common side effects associated with the use of 5-FU and, in fact, on the basis of its activity of antimetabolite, 5-FU exerts a suppressive action on Tenon's capsule fibroblastic population proliferation in the filtering bleb area. This fibroblastic suppressive activity may conduce to a marked thinning of the conjunctiva in the filtering bleb zone, inducing a delay of the surgical wound cicatrization in the early post-operative phase, or a conjunctival perforation in the late post-operative phase, induced by the pressure exerted by the aqueous humour at the filtering bleb.

In addition, still concerning the 5-FU antiproliferative activity, whenever it might come in contact with the corneal epithelial surface (reflux from the needle ingress hole after subconjunctival injection), which is a high turnover cell layer, there may be proliferation defects of the epithelial cells themselves, with alterations more or less severe of corneal trophism (surface punctate keratopathy, persistent epithelial defects).

From what is known about its reparative processes that regulate the cicatrization of the sclero-conjunctival layers after a trabeculectomy operation, this randomized clinical trial has shown that a success rate can be obtained comparable with primary trabeculectomy plus post-operative 5-FU with the use post-operatively of a fibrinolytic drug, SDX, administered subconjunctivally. This is a fact that may arouse a certain interest when one considers that no complications were found associated with the use of SDX and, furthermore, IOP values at 2 years are practically the same as those in the group treated with 5-FU. It also seems important to point out that the modulation of the fibrinogen cascade in the early post-operative phases would seem able to prevent the fibroblastic organization and, hence, the possible failure of this surgery.

In conclusion, the data obtained gives evidence that the post-operative treatment with SDX in primary trabeculectomy furnishes success rates and IOP levels comparable with those obtained with 5-FU but without the side effects typical of this antimetabolite.

Further studies are necessary, however, to define the more ideal dosages of SDX for this type of application.

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Post-trabeculectomy hypotension and hypoathalamia: efficacy of treatment with ibopamine eyedrops

S. Di Giulio, C. De Stefano, B. Boccassini, G. Boccassini

C.T.O. Hospital, Rome – Oculistics Division

Among the post-operative complications of trabeculosclerectomy, we can certainly count hypotension and bulbar hypoathalamia two of the most to be feared because of their causing serious secondary effects: corneal oedema, irido-corneal adherence, cataract, choroid detachment, papillary oedema, as well as non-formation of the filtering bleb.

Those complications, where not attributable to surgical error or to a dehiscence of the wound or to bleb hyperfiltration are certainly to be related to ciliary secretion block, a probable consequence of the surgical trauma and/or previous pharmacological therapies.

These mishaps prove to be, moreover, not easy or quick to resolve with the traditional therapeutic protocol based on local and/or systemic steroids associated with cycloplegic mydriatics.

With the above-described pathogenetic mechanism of hypotension in mind, we thought to try a therapeutic protocol which would use ibopamine eyedrops together with the other drugs for its property of inducing mydriasis without cycloplegia and principally to stimulate the dopaminergic D1 receptors of the ciliary bodies, thus increasing aqueous humour production markedly.

We chose 8 patients affected by POAG, uncompensated with maximal, local medical therapy and untreated surgically or parasurgically within the preceding six months, on whom we had performed trabeculosclerectomy and who had had an ocular tension on the first day below 6 mmHg with absence or reduction of anterior chamber depth associated or unassociated with reduced or no formation of a filtering bleb and/or choroid detachment.

These 8 patients we put into two