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Trabeculectomy combined with β irradiation for congenital glaucoma

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Abstract

Sixty-six eyes with congenital glaucoma were subjected to trabeculectomy between July 1975 and June 1989 are presented. Thirty-one were treated with β irradiation at the time of surgery with a strontium-90 applicator; 35 were not treated with β irradiation. The usual dose was 750 rad. Analysis was limited to three years because of the shorter follow-up of the irradiated eyes. Failure in the two groups was compared statistically. When failure was categorised as IOP >21 mm Hg, β irradiation was found to be significantly protective with an adjusted risk ratio of 0·31 (95% confidence interval 0·11–0·90, p<0·05). Failure categorised as the need for additional medical treatment or further surgery showed significant protection with an adjusted risk ratio of 0·33 (confidence interval 0·12–0·94, p<0·05). Multiple regression models were used for the analysis of intraocular pressure; β irradiation was associated with a significantly lower IOP at six months, one year, and three years (p<0·05). Other factors identified as being associated with a reduced failure rate or lower IOP were: no previous topical glaucoma medications: age over seven years; lack of previous surgery involving the conjunctiva. The results indicate that β irradiation may have a beneficial effect on the prognosis of trabeculectomy in children with congenital glaucoma. However, because of the retrospective and observational nature of the study, the results must be regarded as tentative.

Many children with congenital glaucoma respond adequately to one or more surgical procedures of goniotomy or trabeculotomy.[1] A persistent or recurrent rise in intraocular pressure (IOP) may necessitate filtration surgery even though trabeculectomies in children have less satisfactory results than in older patients.[2 3] The results of surgery may also be worse depending on the type of glaucoma and on previous surgery.[2 4] Among the important causes of failure is the cessation of filtration due to fibrous tissue formation in the region of the scleral flap.

In adults adjunct therapy may improve the results of surgery by limiting the wound healing response and reducing the formation of fibrous tissue. Topical steroids significantly improve the results of trabeculectomy in patients with primary open angle glaucoma and primary acute angle glaucoma.[5] 5-Fluorouracil reduces the number of failures in patients with a poor prognosis but is also associated with complications such as corneal epithelial defects[6] and wound leaks.[7 8] In addition the frequent subconjunctival injections make the use of 5-fluouracil impracticable in children.

β Irradiation has been used intermittently in glaucoma fistulising surgery for many years,[9-16] but all reports were of small numbers of patients, and the irradiation tended to be used in mixed groups of patients with poor prognosis. There are no convincing data from these studies to suggest that β irradiation improves control of the IOP, and so the technique has not gained popularity.

Animal studies on the effect of irradiation on the healing of skin wounds[17] showed reduced numbers of fibroblasts and reduced collagen, and the fibroblast activity was delayed. Animal studies on fistulising surgery[10 18] and corneal or scleral wounds[19-21] have also demonstrated reduced fibroblast proliferation and reduced collagen formation, so that the authors speculate that irradiation may benefit fistulising surgery. In addition the bleb survival was extended in rabbits.[18]

In this report the results of 66 trabeculectomies performed in children with congenital glaucoma are presented; 31 of these procedures were accompanied by treatment with β irradiation. In this retrospective analysis we show that a statistically significant improvement in IOP control was achieved in the group treated with β irradiation, and the rate of failure was significantly reduced. The retrospective collection of data from a period of 14 years means that variables other than β irradiation may have been changing. An attempt has been made to incorporate some of these into the analysis, but the study cannot take account of all factors which might influence the results of surgery.

Materials and methods

All patients aged 18 years or less with congenital glaucoma who were attending Moorfields Eye Hospital under the care of NSCR and had a trabeculectomy between July 1975 and June 1989 were identified. Data were collected from the hospital notes. One eye only from each patient was entered into the analysis.

The surgery in each case was performed by one surgeon (NSCR). Those eyes which had trabeculectomies prior to 1984 did not have β irradiation. There was a short transition period of changing management, but after 1985 all eyes were treated. In those eyes treated with β irradiation a strontium-90 applicator, semicircular in shape and measuring 5·5 mm in radius, was applied immediately after the end of the surgical procedure while the patient was still anaesthetised. It was positioned over the conjunctiva at the operation site with the anterior edge of the applicator at the limbus. The usual dose was 750 rads except for one eye which had 500 rads.

Since the two groups of irradiated or non

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Table 1 The risk factors which were divided into categories for analysis, and the definition of each of the categories

	Group 1				Group 2			
	Definition	*No β*	*β*	*Total*	*Definition*	*No β*	*β*	*Total*
Age at surgery	<7 yr	15	19	34	≥7 yr	20	12	32
Number of previous conjunctival operations	0	27	27	54	>0	8	4	12
Number of topical glaucoma medications	0	13	17	30	>0	22	14	36
Preoperative IOP	<30	7	13	20	≥30	28	18	46
Preoperative corneal diameter	≤13·5	17	12	29	>13·5	10	11	21
Preoperative cup/disc ratio	≤0·8	11	14	25	>0·8	18	5	23
Preoperative visual acuity	≤6/36	22	20	42	>6/36	13	11	24
Number of steroid applications (drops) postoperatively	≤140	23	18	41	>140	9	12	21

irradiated eyes were not running concurrently, it is important to establish the factors other than β irradiation which might affect the surgery. The available data varied between patients depending on their age. For example, visual acuities were not available in the youngest patients; data on corneal diameters were available only in younger age groups; and visual fields were only available in older patients. In addition many children had advanced glaucoma prior to surgery, some with medial opacities with corresponding low visual acuities and offering poor views of the optic discs. All these factors contributed to a reduction in the overall useful data and meant that the main parameters used to assess the effect of β irradiation were the IOP and time of failure.

The time of failure was defined in two separate ways: (1) The time that the IOP was first above 21 mm Hg, even if subsequent measurements were less than 21 mm Hg. (IOP data were only collected after 3 months.) (2) The time that glaucoma medications were started or further glaucoma surgery was required.

STATISTICAL ANALYSIS

One eye only for each patient was included in the analysis; if both eyes were operated on at different times, then only the right eye was entered into the study. If an eye had more than one trabeculectomy at Moorfields Eye Hospital, then only the first procedure was entered.

Eyes were grouped into those whose treatment included irradiation and those not so treated. Differences between the groups were analysed with independent sample t tests for continuous variables, and χ^2 or Mann-Whitney test for categorical variables.

A correlation matrix was calculated for all variables to identify any large intercorrelations.

Kaplan-Meier survival curves were calculated for the whole study population for each of the failure categories using different variables as the grouping factor. Multivariate survival analysis used Cox's proportional hazards model.[22,23]

The IOP data were analysed by means of a multiple regression model at each time point.[24] Variables were entered into the model by forward, stepwise selection if the 'probability to enter' was less than or equal to 0·05. Additional factors were then forced into the model to test their effect. An explanation of Cox's proportional hazards and multiple regression techniques may be found elsewhere.[22-24]

For the Kaplan-Meier and multiple regression analysis grouped data rather than continuous variables were used. Groupings are shown in Table 1. For both types of model several different models were calculated initially. From these models it was possible to determine those variables which were not significantly affecting the model but which had missing values. A missing value in a variable leads to the exlusion of that eye from the entire analysis. If reasonable, these variables were excluded so that the final model had the maximum number of procedures in it.

The data used for the Cox proportional hazards and multiple regression models were confined to the first three years, because only two of the procedures which were accompanied by β irradiation had a longer follow-up than three years.

Results

We identified 112 trabeculectomy procedures which were performed during the 14-year period on children with congenital glaucoma aged 18 years or less. The hospital records of six of these patients were not found, and in a further six there was no follow-up because patients were returned to the care of the referring ophthalmologist immediately after surgery. Two patients had peroperative choroidal haemorrhages which were unrelated to the use of β irradiation and were therefore excluded. Of the patients undergoing the remaining 98 procedures 66 (66 eyes) fitted the entry criteria. Only one operation per patient was entered to reduce bias by entering both eyes of the same patient or the same eye twice; if both eyes were operated upon, the right eye was always entered. Most of the eyes had had

Table 2 The previous surgical procedures. Eyes had up to a maximum of five previous operations prior to the trabeculectomy entered into the study

Operation:	*1st*	*2nd*	*3rd*	*4th*	*5th*	*Total*
No β irradiation at time of surgery						
Goniotomy	23	10	3	1	1	38
Trabeculotomy*	3	1				4
Trabeculectomy*	2	1				3
Scheie*	1					1
Cyclocryotherapy	2					2
Cycloanaemation*	1	1				2
Other	1	1				2
With β irradiation at time of surgery						
Goniotomy	23	11	1			35
Trabeculotomy*	1	2	1			4
Trabeculectomy*						0
Scheie*						0
Cyclocryotherapy						0
Cycloanaemation*						0
Other	2	2	1			5

*Procedures which were included in the category of 'previous procedures involving the conjunctiva'.

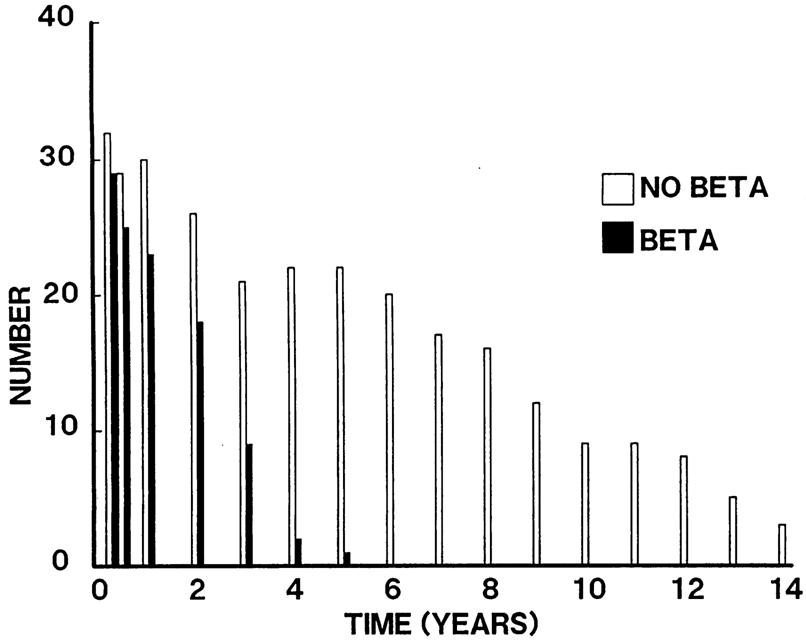

Figure 1 Graph showing the number of eyes (patients) with data available for analysis at each time point. Data was collected at 3 months, 6 months, one year and every year thereafter.

previous surgery at Moorfields Eye Hospital or the referring hospital, and some eyes had had previous surgery affecting the conjunctiva (Table 2). Only the first trabeculectomy performed at Moorfields Eye Hospital was entered.

Three patients (three procedures) were removed at a later date. Two patients had an ocular injury which ultimately led to the loss of all vision, and one patient died. These patients were not treated as failures but as if they had been lost to follow-up at the time of the injury/death.

Table 3 Comparison of the preoperative risk factors in the β irradiated and non-β -irradiated eyes by the t test. No=number of eyes with available data

	No β			β			
	No	Mean	SD	No	Mean	SD	p
Age at diagnosis if glaucoma	34	1·8	2.6	29	1·1	2·2	0·27
Age at trabeculectomy	35	7·7	4·0	31	5·1	4·2	0·011
No of previous operations	35	1·5	0·9	31	1·4	0·9	0·868
No of previous operations of conjunctiva	35	0·29	0·6	31	·13	0·3	0·189
No of previous glaucoma drop applications	35	1162	2832	31	303	760	0·16*
No of different previous glaucoma medications	35	0·83	0·7	31	0·55	0·7	0·117
Preoperative IOP	35	33·6	6·7	31	28·8	5·6	0·003
Preoperative cup/disc ratio	29	0·9	0·2	19	0·79	0·1	0·043
Preoperative corneal diameter	27	13·4	1·0	23	14·0	1·0	0·035

*Mann-Whitney test. Mean=mean for each eye.

Table 4 Comparison of the preoperative risk factors in the β irradiated and non-β-irradiated eyes by χ^2 analysis. Number/total indicates the number in that subgroup and the total of all eyes with available information for that particular subgroup

	No β		β		
	Number total	%	Number total	%	p
Caucasian	34/35	97·1	30/30	100	1·00
Male	19/35	54·3	21/31	67·7	0·40
Right eye	27/35	77·1	19/31	61·3	0·26
Isolated trabecular dysgenesis	22/35	62·9	22/31	70	0·66
Iridocorneal dysgenesis	5/35	14·3	0/31	0	0·08
Aniridia	1/35	2·9	1/31	3·2	1·00
Sturge-Weber	2/35	5·7	6/31	19·4	0·19
Neuro-fibromatosis	5/35	14·3	1/31	3·2	0·26
Visual acuity	28/35		17/31		0·31*

*Mann-Whitney test

Table 5 Comparison of the preoperative risk factors in the β irradiated and non-β-irradiated eyes by χ^2 analysis. The table structure is similar to that of Table 4. Conjunctival flaps were either limbal or fornix based

	No β		β		
	Number total	%	Number total	%	p
New site for surgery	35/35	100	31/31	100	NA
Sutures to scleral flap	33/34	97·1	31/31	100	1·0
Vitreous loss	1/35	2·9	0/31	0	1·0
Fornix based conj. flap	14/30	46·7	31/31	100	0·000

The 66 eyes used in the analysis had surgery over a period of 14 years with variable length of follow-up (Fig 1). Those which had trabeculectomies prior to 1984 did not have β irradiation. There was a short transition period of changing management, but after 1985 all eyes were treated. *T* Test and χ^2 calculations for pre-, per-, and postoperative factors are given in Tables 3 to 6 and show several significant differences between the two groups.

Part of the correlation matrix is shown in Table 7 and identifies all pairs of factors which have a significant correlation.

The differences between the groups treated or not treated with β irradiation and the correlating variables all occur in potential risk factors, so the statistical analysis needs to control for these confounding variables.

The graphs for the Kaplan-Meier estimation for the two categories of failure with β irradiation used as the stratification factor are shown in Figs 2 and 3. These graphs suggest separation of the groups, but they do not take into account other factors which might affect the success or failure. To examine the effects of other risk factors and the interaction of these factors a Cox proportional hazards model was established for each of the two failure categories.

In the Cox proportional hazards models the preoperative visual acuity, cup-disc ratio, corneal diameter, type of conjunctival flap, and postoperative steroid regimen were found to reduce markedly the numbers available for analysis because of missing values for different eyes. Preoperative visual acuity data were available only for older children, and since inclusion would confine the analysis to that group only it was excluded. Preoperative cup-disc ratios and postoperative steroid regimens were categorised to form approximately equal groups. The groups so formed had doubtful clinical relevance, and since they were found to have no particular effect on the models in the initial analyses they were excluded.

The type of conjunctival flap (limbal or fornix based) had marked collinearity with irradiation treatment and was thought to be an important risk factor which should be kept in the models to ensure that the improved results associated with irradiation were not in fact due to the type of conjunctival flap.[25] In the Cox proportional hazards models the type of conjunctival flap was

Table 6 Comparison of the postoperative risk factors in the β irradiated and non-β-irradiated eyes by t test analysis. The table structure is similar to that of Table 3

	No β			*β*			
	No	Mean	SD	No	Mean	SD	p
Total number of postoperative steroid drops	32	34	15·3	30	35	10·3	·692

Table 7 Part of correlation table showing all the significant correlations between paired risk factors. No other risk factors were found to correlate significantly

	Treatment with β irradiation	*Age <7 years*	*Age of diagnosis*	*Corneal diam. >13·5 mm*	*Previous conjunctival surgery*
Previous topical treatment		0·40**			
Preop. IOP >30 mm Hg		0·44**			
Limbal based conjunctival flap	−0·61*				
Postop. steroid >140 drops		0·36**			−0·35*
Preop. cup/disc >0·8	−0·35*				
Previous surgery			−0·33*	0·43*	

*p<0·01. **p<0·001. Pairwise calculations.

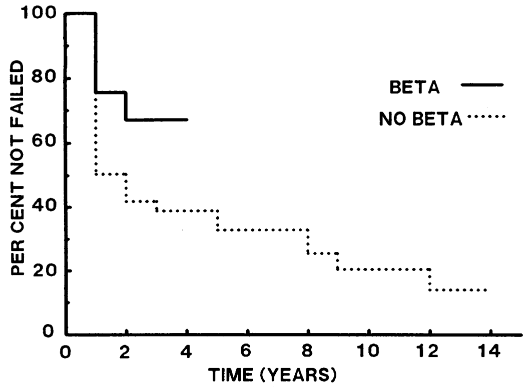

Figure 2 Kaplan-Meier survival curve. Failure is categorised as the time at which the IOP was first above 21 mm Hg.

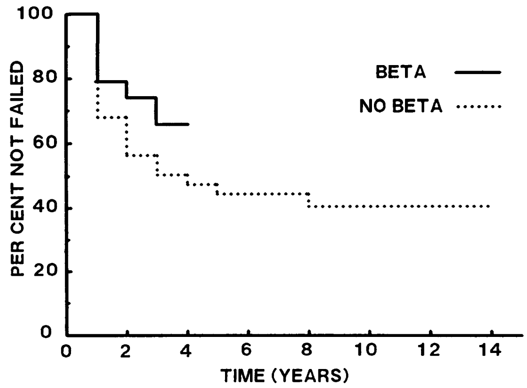

Figure 3 Kaplan-Meier survival curve. Failure is categorised as the time at which further medical or surgical treatment was required to control the IOP.

the last factor to enter each model. It was not a significant factor, but it did influence the p values of the other factors already in the model. It was therefore considered necessary to include this risk factor, though the eyes available for analysis were reduced from 66 to 61 because of missing values. The final Cox proportional hazards models for the two failure categories are shown in Tables 8 and 9.

The difference in IOP with only β irradiation used as the stratification factor is shown in Fig 4. The multiple regression models which include significant factors only are summarised in Table 10. These significant factors were identified by the forward, stepwise selection if the probability to enter was less than or equal to 0·05. The models suggest that treatment with β irradiation has a highly significant effect in improving the quality of IOP control at all time points except three months. However, these models do not take account of the other factors which affect the IOP, even if these other factors are not significant themselves. Therefore the same risk factors that were used in the Cox proportional hazards models were forced stepwise in order of significance until all factors were entered into the model.

The significance of treatment with β irradiation was reduced at each time point in these new models, but remained significant (p<0·05) except at two years. The new models are summarised in Table 11. In these models the effect of preoperative medical treatment maintained its original pattern of significance at three and six months and one year, though the significance was reduced from its previous levels. The significance of the type of conjunctival flap and effect of previous conjunctival surgery was lost (p>0·05) in the new model. Table 11 shows the order in which the variables entered the models and the p value of each. Multiple regression does not provide information in any absolute terms about the relative importance of independent variables (that is, hazard ratios), so further details are not included.

The main postoperative complications were related to the increase in IOP and the need for further treatment. A list of other early and late complications is given in Table 12.

Discussion

This analysis suggests that treatment of the trabeculectomy site with β irradiation at the time of surgery has a beneficial effect in children with congenital glaucoma. Failure categorised by a rise in IOP above 21 mm Hg showed that β irradiation was significantly protective with an adjusted risk ratio of 0·31 (95% confidence interval 0·11–0·90, p<0·05). Failure categorised as the need for additional medical treatment or further surgery showed significant protection with an adjusted risk ratio of 0·33 (confidence interval 0·12–0·94, p<0·05).

Irradiation was associated with a significantly improved quality of IOP control at six months, one year, and three years (p<0·05). It was not significant at three months or two years. These IOP results included eyes on additional glaucoma treatment, which was greater amongst the non-irradiated eyes, but excluded eyes which had undergone further surgery.

Apart from β irradiation, another strong factor determining the outcome of surgery was the use of topical medications prior to surgery. This was a significant factor which increased the incidence of failure in both of the failure categories. Failure categorised by a rise in IOP above 21 mm Hg showed an adjusted risk ratio of 5·56 (95% confidence interval 1·77–17·44, p<0·01), and failure categorised by medical treatment or further surgery showed an adjusted risk ratio of 7·24 (confidence interval 2·01–26·07, p<0·01). The use of preoperative topical glaucoma medications reduced the quality of IOP control at three months, six months, and one year (p<0·05). This supports the findings of recent

Table 8 Cox proportional hazards model with each of the listed factors forced into the model. The hazard ratio for each factor takes into account the effect of each of the factors and adjusts for confounding variables

	Coefficient	SE	p Value	Hazard ratio	95% confidence limits	
Treatment with irradiation	−1·16	(0·54)	0·031	0·31	0·11	0·90
Previous topical treatment	1·71	(0·58)	0·003	5·56	1·77	17·44
Previous conjunctival surgery	−1·36	(0·70)	0·052	0·26	0·06	1·01
Age >7 years at surgery	−1·13	(0·53)	0·034	0·32	0·11	0·92
Isolated trabecular dysgenesis	0·24	(0·46)	0·60	1·28	0·52	3·15
Female	−0·31	(0·47)	0·501	0·73	0·29	1·83
Limbal based conj. flap	0·19	(0·50)	0·702	1·21	0·45	3·24
Preop. IOP >30 mm Hg	−0·12	(0·56)	0·836	1·12	0·37	3·39
	Deviance =		187.48			
Likelihood ratio statistic on	8 DF =		22.39, p=0·004			
	Number=61					

Table 9 Cox proportional hazards model for failure=further surgery or medical treatment

	Coefficient	SE	p Value	Hazard ratio	95% confidence limits	
Previous topical treatment	1·98	(0·65)	0·002	7·24	2·01	26·07
Previous conjunctival surgery	−1·5	(0·72)	0·038	0·22	0·05	0·92
Age >7 years at surgery	−1·64	(0·63)	0·009	0·19	0·06	0·66
Treatment with irradiation	1·1	(0·53)	0·038	0·33	0·12	0·94
Preop. IOP >30 mm Hg	0·81	(0·6)	0·175	2·24	0·7	7·21
Female	−0·73	(0·5)	0·151	0·48	0·18	1·3
Isolated trabecular dysgenesis	0·71	(0·48)	0·137	2·03	0·8	5·16
Limbal based conj. flap	−0·63	(0·54)	0·250	0·53	0·18	1·55
	Deviance =		158·87			
Likelihood ratio statistic on	8 DF =		21·02, p=0·007			
	Number=61					

Table 10 Multiple regression model of factors influencing the postoperative IOP. The model contains only those factors which were significant. The effect of other risk factors is not included, which inappropriately exaggerates the beneficial effect of β irradiation, as shown by the high p values in this table compared with Table 11

IOP at:	3 mth	6 mth	1 yr	2 yr	3 yr
Treatment with β irradiation		<0·001	<0·005	<0·01	<0·05
Previous topical glaucoma treatment	<0·05	<0·005	<0·05		
Limbal based conj. flap	<0·01				
Previous conjunctival surgery					<0·05

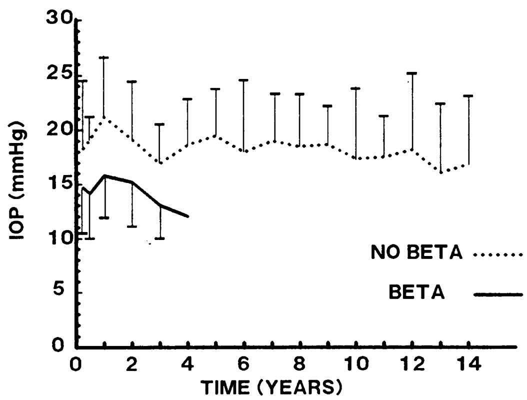

Figure 4 The mean postoperative IOP of eyes treated or not treated with β irradiation. The first post-operative IOP is at three months.

studies in adults which suggest that early surgery (as opposed to surgery following failure of medical treatment) may improve the final surgical outcome.[23 26]

Another significant factor in the Cox proportional hazards models was the age at surgery. Children older than 7 years had a lower hazard ratio than patients less than 7. For failure categorised as IOP >21 mm Hg the adjusted risk ratio=0·32 (95% confidence interval 0·11–0·92, p<0·05). For failure categorised as further medical treatment or surgery the adjusted risk ratio=0·19 (95% confidence interval 0·06–0·66, p<0·05). This supports the findings of previous publications that younger patients do not do so well as older.[2]

Previous surgery involving the conjunctiva also significantly increased the risk of failure in the model of failure categorised as the need for further surgery or medical treatment, adjusted risk ratio=0·22 (95% confidence interval 0·05–0·92, p<0·05).

The study suffers from a number of problems which affect retrospective studies. In particular several of the pre- and peroperative risk factors in the patients treated and not treated with β irradiation were not equal, and the analysis was complicated by multicollinearity. The correlations reflect a change in management of these patients over 14 years. β Irradiation was used in the later years only; surgery began to be used at an earlier stage rather than medical treatment; children were operated upon with trabeculectomy at a younger age; and the type of conjunctival flap changed from limbal based to fornix based. All these variables affect the hazard ratios, and yet they significantly correlate with each other. It is because of these correlations and interactions that the analysis requires such complex models to be calculated which control for confounding variables.

The most important of the identified correlating risk factors was the association between treatment with β irradiation and the type of conjunctival flap (limbal or fornix based). However, β irradiation was repeatedly the more significant factor in the models, and the type of conjunctival flap was not shown to have a significant effect in either of the categories of failure. It entered the multiple regression models after β irradiation (except at three months) and was not significant at any time point.

In addition to these identifiable factors there may have been other unidentified and unmeasurable factors affecting the patient selection, surgery, or postoperative management. The retrospective collection of the data means that the models cannot adequately control for all confounding variables, and despite the complex statistical analysis it is not possible to be certain that β irradiation is an important factor as opposed to some other unmeasured confounding variable. Therefore the conclusion that β irradiation improves the prognosis for trabeculectomy in children with congenital glaucoma must be regarded as tentative.

DOSE OF β IRRADIATION

The dose of β irradiation used in each case was 750 rads except in one of the early cases, which had 500 rads. The results in this report demonstrate that 750 rads has a significant effect without an increased incidence of complications, but the ideal dose is not known. Higher doses have been reported to cause a variety of side effects, including ocular irritation immediately following treatment, delayed or persistent

Table 11 Multiple regression model of factors influencing the postoperative IOP, with each of the listed risk factors forced into the model. The level of significance shown in Table 9 has been reduced with the inclusion of other risk factors which are also influencing the results, though they are not themselves significant

	3 Months			*6 Months*			*1 Year*			*2 Years*			*3 Years*		
	Ord	*B*	*p*	*Ord*	*B*	*p*	*Ord*	*B*	*p*	*Ord*	*B*	*p*	*Ord*	*B*	*p*
Treatment with irradiation	5	−2·0	0·26	*1*	*−3·5*	*0·012*	*1*	*−4·3*	*0·04*	1	−4·3	0·06	*1*	*−5·2*	*0·02*
Previous topical treatment	2	3·5	0·04	*2*	*3·0*	*0·02*	*2*	*−4·1*	*0·04*	2	4·5	0·14	8	−1·2	0·65
Limbal based conj. flap	1	2·6	0·21	8	1·9	0·89	4	2·0	0·37	7	0·6	0·79	7	−1·5	0·46
Isolated trabecular dysgenesis	3	2·4	0·12	4	0·9	0·42	8	1·8	0·69	3	−3·0	0·17	4	−2·7	0·25
Female	4	−1·2	0·4	5	−0·4	0·73	5	−1·8	0·30	8	0·4	0·82	6	2·3	0·30
Previous conj. surgery	6	−2·4	0·23	3	−1·7	0·24	3	−2·3	0·33	4	−1·7	0·58	2	−4·8	0·09
Preop. IOP >30 mm Hg	8	−0·8	0·63	6	−0·6	0·63	7	1·8	0·36	6	0·8	0·73	3	0·0	0·99
Age >7 years at trabeculectomy	7	−1·6	0·35	7	0·6	0·63	6	−2·0	0·34	5	−1·4	0·64	5	3·5	0·24

Ord=order of entry into the model. B=partial regression coefficient. Those p values in italic are <0·05.

Table 12 Summary of the postoperative complications in the eyes which were or were not treated with β irradiation

	No Irradiation Number=35	*β Irradiation Number=31*
Early complications		
Shallow anterior chamber	18 (51·4%)	10 (32·3%)
Hyphaema	13 (37·1%)	10 (32·3%)
Low IOP	8 (22·9%)	6 (19·4%)
Choroidal detachment	3 (8·6%)	3 (9·6%)
Late complications		
Cystic bleb	–	5 (16%)
Cataract surgery	1 (2·9%)	1 (3·2%)
Corneal decompensation	1 (2·9%)	–
Keratoplasty (iridocorneal dysgenesis)	1 (2·9%)	–
Retinal detachment	1 (2·9%)	1 (3·2%)
Corneal abscess	1 (2·9%)	–
Endophthalmitis	–	1 (3·2%)
Band keratopathy	2 (5·7%)	–

irritation, telangiectasis causing haemorrhage, ischaemic areas, loss of lashes, late corneal ulceration and 'epidermalisation' of the conjunctiva.[27] Cataracts may form with high doses.[27-31] Cataracts have been estimated to occur at doses above 2000 to 4000[29] and 3000 rep to be a non-cataractous dose when used in the treatment of pterygia.[30] Cataracts were identified in 38% of 71 patients followed up for 5–21 years with doses of 6460–90 000 rads,[31] but lens opacities have also been recorded at lower doses and were identified in 19% of 83 eyes at 4–8 years with 1800–2200 rads for pterygia.[32] Doses of 20 000 rads have also caused telangiectasis, lipid infiltration of the cornea, and corneal thinning.[31] All these doses are higher than the 750 rads used in the majority of patients in this report.

In animal studies in rabbits doses of 2500 rads produce an increased survival time of the blebs, but the blebs are extremely thin.[18] The thin blebs may be undesirable and suggest that 2500 rads may be too high in man.

In the children treated with β irradiation in this report no children developed cataracts which were thought to be associated with the irradiation, and they did not develop irritable eyes or telangiectasia. A list of complications in both treated and untreated groups is given in Table 12. The retrospective collection of these data means that some of it is unreliable, particularly the early postoperative complications. Despite these reservations it is interesting to note that the recorded incidence of early complications is similar in each group.

The late complications of corneal decompensation (one leading to a corneal abscess), band keratopathy, retinal detachments, and the need for corneal or cataract surgery reflect the poor health of these eyes rather than the consequences of trabeculectomy or β irradiation. There is no suggestion that treatment with β irradiation causes or worsens these problems.

The increased incidence of cystic blebs in the irradiated eyes is an important observation. The apparent incidence of 16% of eyes developing cystic blebs following β irradiation is not the clinical impression. The category of cystic bleb can cover a wide spectrum from minor to grossly cystic with extreme thinning. Eyes treated with 750 rads of β irradiation tends to develop blebs which are not cystic, are slightly elevated, and are not inflamed. If the bleb wall does become thin or cystic, then it is of minor degree only with 750 rads in children. There were no cases of perforated blebs or persistent wound leak in eyes treated with irradiation. We believe that the retrospective collection of these observations has provided unreliable data which do not reflect the true situation. The eyes which were not treated with β irradiation were treated at a time when it was still common to see the cystic blebs that followed the Scheie procedure. An eye which might be defined today as cystic may not have been considered to be cystic in the post-Scheie era.

TIMING OF IRRADIATION

To our knowledge no studies have been performed which consider the ideal time to apply the irradiation to the trabeculectomy site. The options are: prior to surgery; at the time of surgery; some time after surgery; and in fractionated doses. In experimental skin wounds in rats[17 33-35] 1000 r given 1 to 30 days before the incision, incision had no perceptible effect on wound healing, but immediately, 24 hours, and 48 hours after incision radiation retarded healing, though at no time did it affect the final scar. The most marked delay was observed with treatment at 24 hours. The difference in effect depends on the stage of mitosis of the cell.[36] The cell is most sensitive to irradiation during mitosis itself. It is relatively resistant during the G_1 phase, but radiosensitivity returns during the late G_1 and early synthetic phase (S) and early G_2 phases. The greatest effect in skin wounds at 24 hours reflects the activity of transcription and mitosis of the fibroblasts at this time. It is interesting to note how rapidly the state of the fibroblasts must change following surgical injury, because radiotherapy one day prior to incision does not influence the repair, and yet treatment immediately after incision does have an effect.[33 34]

In fistulising surgery, particularly in children,

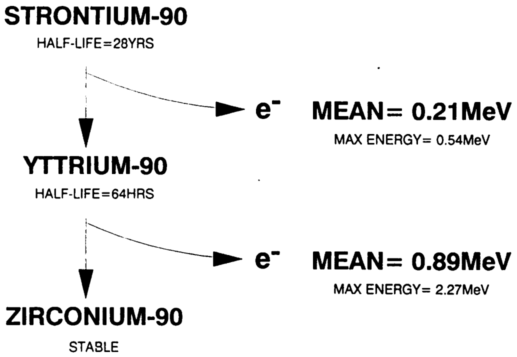

Figure 5 Decay path of strontium-90 showing emission and energy of β particles which are electrons of negligible mass and one negative charge, and therefore rapidly slowed down when passing through tissues.

the application of the radiation source is very convenient immediately after surgery. The operating theatre is a restricted area and therefore handling radioactive sources in the theatres is simplified. The child is already anaesthetised, and the operative procedure is extended by less than five minutes. Treatment at 24 to 48 hours or in fractionated doses would require further sedation in children.

An important consideration during treatment is the effect of a raised, aqueous filled bleb at the site of application. Strontium-90 emits β particles which are electrons of negligible mass, one negative charge, and therefore rapidly slowed down when passing through tissues. Strontium-90 decays to yttrium-90 which decays to zirconium-90, which is stable.[32] The β rays of yttrium-90 have the greatest energy, with a mean of 0·89 MeV (Fig 5). Electrons of 2 MeV have a maximum range of about 1 cm of water, with a rapid fall off in penetration below the surface. Application of the β source to a raised bleb will give maximal treatment to the elevated conjunctiva, less to the fluid filled contents of an elevated bleb, and still less to the episclera and sclera. Since the episclera is an important source of fibroblasts following fistulising surgery, it is undesirable to place an additional barrier (the fluid filled bleb) between the β source and the tissue. It follows that a more satisfactory and consistent dose (and the most convenient) will be achieved immediately after the end of the surgical procedure when the patient is asleep and the bleb has not yet formed.

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1 Shaffer RN, Hoskins HD. Goniotomy in the treatment of isolated trabeculodysgenesis (primary congenital (infantile) developmental glaucoma). Montgomery lecture. *Trans Ophthalmol Soc UK* 1983; **103**: 581–5.
2 Gressel MG, Heuer DK, Parrish RK. Trabeculectomy in young patients. *Ophthalmology* 1984; **91**: 1242–6.
3 Beauchamp GR, Parks MM. Filtering surgery in children: barriers to success. *Ophthalmology* 1979; **86**: 170–80.
4 Inaba Z. Long term results of trabeculectomy in the Japanese: an analysis by life table method. *Jpn J Ophthalmol* 1982; **26**: 361–73.
5 Starita RJ, Fellman RL, Spaeth GL, Poryzees EM, Greenidge KC, Traverso CE. Short- and long-term effects of postoperative corticosteroids on trabeculectomy. *Ophthalmology* 1985; **92**: 938–46.
6 The Fluorouracil Filtering Surgery Study Group. Fluorouracil filtering surgery study one year follow up. *Am J Ophthalmol* 1989; **108**: 625–35.
7 Heuer DK, Parrish RK, Gressel MG, *et al.* 5-Fluorouracil and glaucoma filtering surgery. *Ophthalmology* 1986; **93**: 1537–46.
8 Knapp A, Heuer DK, Stern GA, Driebe WT. Serious corneal complications of glaucoma filtering surgery with postoperative 5-fluorouracil. *Am J Ophthalmol* 1987; **103**: 183–7.
9 Iliff CE. Surgical control of glaucoma in the Negro. *Am J Ophthalmol* 1984; **27**: 731–8.
10 Friedenwald JS. Some problems in diagnosis and treatment of glaucoma. *Am J Ophthalmol* 1959; **33**: 1523–38.
11 Cohen LB, Graham TF, Fry WE. Beta irradiation. As an adjunct to glaucoma surgery in the Negro. *Am J Ophthalmol* 1959; **47**: 54–61.
12 Iliff CE, Haas JS. Posterior lip sclerotomy. *Am J Ophthalmol* 1962; **54**: 688–93.
13 Ogino N, Masuda H, Abe Y. Beta irradiation in filtering operations. *Nippon Ganka Gakkai Zasshi* 1966; **70**: 1834–9.
14 Cameron ME. Beta irradiation as an adjunct to surgery in refactory glaucoma. *Trans Aust College Ophthalmol* 1970; **2**: 53–60.
15 Cameron ME. Thrombotic glaucoma successfully treated. *Trans Ophthalmol Soc UK* 1973; **78**: 537–47.
16 Miller MH, Joseph NH, Wishart PK, Hitchings RA. Lack of beneficial effects of intensive topical steroids and beta irradiation of eyes undergoing repeat trabeculectomy. *Ophthalmic Surg* 1987; **18**: 508–12.
17 Grillo HC, Potsaid MS. Studies in wound healing: IV. Retardation of contraction by local x-irradiation, and observations relating to the origin of fibroblasts in repair. *Ann Surg* 1961; **154**: 741–50.
18 Miller MH, Grierson I, Unger WG, Hitchings RA. The effect of topical dexamethasone and postoperative beta irradiation on a model of glaucoma surgery in the rabbit. *Ophthalmic Surg* 1990; **21**: 44–54.
19 McDonald JE, Wilder HC. The effect of beta radiation on corneal healing. *Am J Ophthalmol* 1955; **40**: 170–80.
20 Anton M, Riebel O. Influence of beta rays on the healing of corneo-scleral wounds. *Scr Med Fac Med Brun* 1961; **34**: 293–6.
21 Tanaka N, Yutaka U. Effect of beta irradiation on the trephine wound in rabbit cornea. *Nippon Ganka Gakkai Zasshi* 1962; **66**: 1090–6.
22 Seigel DG. Cox regression analysis in clinical research. *Arch Ophthalmol* 1990; **108**: 888–9.
23 Lavin MJ, Wormald RPL, Migdal C, Hitchings RA. Influence of prior therapy on the success of trabeculectomy. *Arch Ophthalmol* 1990; **108**: 1543–8.
24 Seigel D. Regression. *Arch Ophthalmol* 1987; **105**: 185–6.
25 Shuster JN, Krupin T, Kolker AE, Becker B. Limbus vs fornix based conjunctival flap in trabeculectomy. *Arch Ophthalmol* 1984; **102**: 361–2.
26 Jay JL, Murray SB. Early trabeculectomy versus conventional management in primary open angle glaucoma. *Br J Ophthalmol* 1988; **72**: 881–9.
27 Hughes WF. Beta irradiation therapy in ophthalmology. *Trans Am Ophthalmol Soc* 1952; **50**: 469–549.
28 Sallmann LV, Munoz CM, Drungis A. Effects of beta irradiation in the rabbit lens. *Arch Ophthalmol* 1953; **50**: 727–36.
29 McDonald JE, Hughes WF, Peiffer VG. Beta radiation cataracts. *Arch Ophthalmol* 1955; **53**: 248–59.
30 Hilgers JHC. Strontium-90 β-irradiation, cataractogenicity, and pterygium recurrence. *Arch Ophthalmol* 1966; **76**: 329–33.
31 Barron A, McDonald JE, Hughes WF. Long-term complications of beta irradiation therapy in ophthalmology. *Trans Am Ophthalmol Soc* 1970; **68**: 113–28.
32 Bahrassa F, Datta R. Postoperative beta radiation treatment of pterygium. *Int J Radiat Oncol Biol Phys* 1983; **9**: 679–84. wounds in rats following postoperative irradiation. *Radiology* 1933; **20**: 102–8.
33 Pohle EA, Ritchie G, Wright CS. Studies of the effect of roentgen rays on the healing of wounds. *Radiology* 1931; **16**: 445–60.
34 Pohle EA, Ritchie G. Studies of the effects of roentgen rays on the healing of wounds. II. Histological changes in skin
35 Grillo HC. Origin of fibroblasts in wound healing. An autoradiographic study of inhibition of cellular proliferation by local x-irradiation. *Ann Surg* 1963; **157**: 453–67.
36 Walter JB, Israel MS. *General pathology*. 5th ed. Edinburgh: Churchill Livingstone, 1979.