

Surgery for normal tension glaucoma

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Abstract

The long term follow up of surgery in normal tension glaucoma is presented. One eye of 18 patients with bilateral progressive disease underwent fistulising surgery. Over follow up periods ranging from 2 to 7 years (50% \geq 5 years) the operated eye showed on average a 30% reduction in intraocular pressure (IOP). This was associated with a marked difference in the rate and number of retinal locations showing a progressive decline in retinal function, suggesting some protective function for lowering IOP in patients with normal tension glaucoma.

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Normal tension glaucoma is the term given to patients with open angle glaucoma whose intraocular pressure (IOP) lies within the normal range.^{1 2} These patients may comprise a pathogenetic subset of the open angle glaucomas, because they suffer from progressive visual field loss as do patients with 'high tension' glaucoma, a number of therapeutic options have been considered. The most important of these options is lowering of IOP to low normal levels.

Any investigation of the effects of treatment on the rate or type of visual field progression must take into account the inherent variability of response (inter and intratest) that exists within each of us. The simplest way to overcome this variability is to treat one eye and measure the response against the untreated eye. The treatment options that avoid a potential effect on the contralateral eye are limited. Fistulising surgery to one eye minimises the risk of a crossover effect. We report on the long term results of surgery to one eye in a group of patients with bilateral progressive normal tension glaucoma.

Patients and methods

Patients were selected from the normal tension glaucoma clinic at Moorfields Eye Hospital for consideration of surgery to one eye if they had the following factors.

Normal tension glaucoma. Normal tension glaucoma was present in both eyes (each patient/eye complied with the following diagnostic criteria):

(1) Mean untreated IOP of <21 mm Hg on 24 hours phasing with no individual IOP exceeding 24 mm Hg.^{1 3}

(2) 'Typical' glaucomatous cupping to be present (that is, each optic disc to have enlargement of the orifice to the optic cup with overall thinning of the rim plus or minus focal notching. Cup pallor disparity, whereby the extent of the pallor exceeded the cup area, was not considered to be a diagnostic sign.

(3) 'Nerve fibre bundle' type of visual field defect, and at least one locus on a central 24 degree field to be depressed by >10 dB.

(4) No other cause for the visual loss. (Each patient had undergone a computed tomography scan of the optic nerves and chiasm, which had been reported upon as not showing signs for a space occupying lesion.)

(5) Each patient had open angles on gonioscopy.

(6) No patient gave a history of topical steroid usage.

Visual loss. A similar, if not symmetrical amount of visual loss was present in both eyes. (In practice, both eyes showed reproducible visual field defects on perimetry which occupied a similar area of the visual field.)

Visual field. The patients had to be adequate performers on computer assisted perimetry, visual field responses being limited to $<20\%$ fixation errors, and $<30\%$ false positive errors. No restriction was placed on the number of false negative errors.

Other eye disease. There had to be no other eye disease, specifically, no cataract (excluded on the basis of central acuity), or macular degeneration.

Visual acuity. Central acuity had to be $\geq 6/9$ with/without correction.

Patients fulfilling the above criteria were invited to undergo fistulising surgery to the eye with greater area of visual field loss, on the understanding that if a detectable differential rate of visual loss developed between the two eyes then the other eye could undergo the same treatment.

VISUAL FIELD PROGRESSION

Preoperatively, progression was defined either as the development of a defect exceeding 5 degrees in diameter on a 1-4 isoptre using kinetic perimetry with the Goldmann perimeter (two patients), or the development of individual locations showing a significant depression by analysis with the STATPAC-2 program on the Humphrey perimeter. A comparison between the two eyes of the mean

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Table 1 Summary of clinical characteristics of the patients

Patient No	Age (years)*	Follow up (years)†	IOP‡ (mm Hg)		IOP change proportions§ (%)	
			SE	NE	SE	NE
1	67	6	18	11	-49	-0
2	64	4	19	18	-42	20
3	54	3	19	18	-34	0
4	61	6	16	15	-11	16
5	54	4	20	20	-41	-5
6	43	2	17	18	-33	-3
7	62	4	14	16	-26	-9
8	62	4	18	18	-32	2
9	71	4	14	15	-27	-3
10	56	5	19	19	-22	-8
11	76	4	16	20	-37	-5
12	65	6	18	17	-27	-3
13	63	6	17	16	-48	4
14	47	4	20	21	-6	-10
15	65	6	20	19	-26	-5
16	66	4	18	18	-51	2
17	48	6	15	15	-27	0
18	44	6	13	16	-26	-8

IOP=intraocular pressure; SE=surgery eye; NE=non-surgery eye.

*When surgery done.

†When last visual field examined after the surgery.

‡Average of IOPs before the surgery.

§Proportion of IOP change after surgery = $(IOP_{pos} - IOP_{prs}) / IOP_{prs} \times 100$.

prs=pre-surgery; post=post-surgery.

deviation for these 16 patients has been set out in Table 1. The PROGRESSOR program was not used for this analysis as in some cases there were insufficient visual fields. Ethical constraints prevented waiting for additional visual fields once there was some indication for progression.

Postoperatively all patients were examined with the Humphrey perimeter (Humphrey Instruments Inc, Palo Alto, CA, USA) using the 24-2 program. Progression was identified using the PROGRESSOR program previously reported on.⁴ Changes in the visual field were checked in two ways: (a) number of locations showing change, and (b) rate of change at progressing locations.

Visual fields were repeated at least three times per year. Real time analysis using the PROGRESSOR program identified, within the

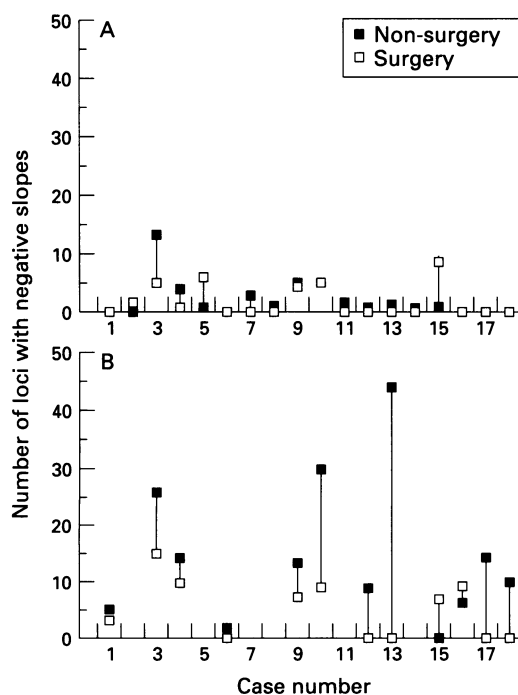


Figure 1 The number of significant negative regression slopes at 3 (A) and 5 (B) years respectively for the operated and unoperated eyes.

central 24 degrees, retinal locations which showed positive or negative linear regression slopes significant at the $p < 0.05$ level. Because, within the central 10 degrees, such slopes may occur even with minimal loss the smallest rate of change was set at ≥ 1 dB per year – that is, $\times 10$ the age related annual sensitivity loss.⁵ Locations which maintained significant regression slopes on ≥ 2 tests were said to be progressing (in practice this was rarely found before the fourth field). For those progressing slopes the rate of progression measured as dB/year loss was noted.

SURGERY

The eye selected for surgery underwent a guarded fistulising procedure (trabeculectomy) without antiproliferative treatment. Topical steroids and antibiotics were given for up to 6 weeks afterwards. No other treatments (and no hypotensive agents) were given to either eye before or after surgery.

POSTOPERATION

Visual field testing was resumed from 3 months postoperation; it continued with at least three tests per year thereafter.

VISUAL FIELD ANALYSIS

Visual field analysis as described above was carried out at each visit. Preliminary data at a mean of 2 years follow up have already been presented.⁶

Results

Eighteen patients have undergone surgery to one eye. Follow up has been for a mean of 5.06 (range 2–7 years). The average preoperative IOP was 17.28 (range 13–20) mm Hg in the surgery group and 17.22 (range 11–20) mm Hg in the non-surgery group. The percentage fall in IOP was 31.39% in the surgery group and 0.83% in the non-surgery group. One patient received systemic β blockers for a period during the study.

Table 1 shows the clinical characteristics. From year 2 there was a progressive divergence in the visual field performance of the eyes in operated and non-operated groups. A greater number of deteriorating locations existed in the unoperated group and they did so at a faster rate (Figures 1–5, Tables 2 and 3).

Discussion

This paper has shown that in a small group of patients with progressive normal tension glaucoma fistulising surgery to one eye was associated with fewer progressing retinal locations, and that those locations that did progress did so at a slower rate. As this has implications for the management of this condition a number of points need clarification first. These include:

(a) were the study patients typical for all normal tension glaucomas?

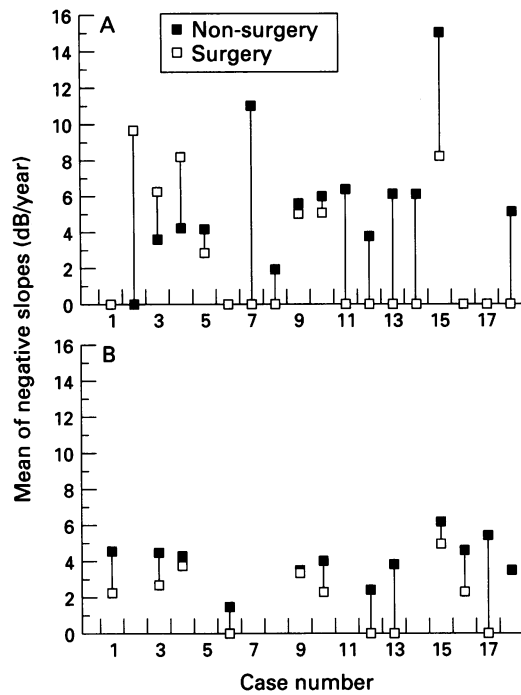


Figure 2 The mean loss (dB/year) for 3 (A) and 5 (B) years respectively for the operated and unoperated eyes.

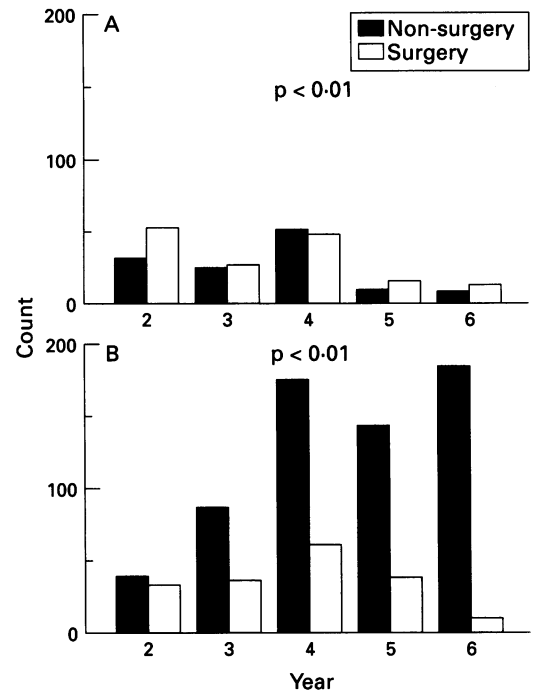


Figure 3 The total number of significantly improving (A) and deteriorating (B) slopes for all operated and unoperated eyes for years 2-6 of follow up.

(b) was true progression identified by the test method. Did the non-random selection invalidate the results?

(c) can the results be extrapolated to all patients with normal tension glaucoma?

(d) was the IOP lowering sufficient?

(e) was the effect related to the postoperative IOP?

WERE THE PATIENTS 'TYPICAL'?

By definition the patients suffered from primary open angle glaucoma with normal IOPs. They did not have evidence for high myopia or congenital abnormality, and had no other cause for their visual loss. They were considered typical of the patients attending the normal tension glaucoma clinic at Moorfields, and agree with previous descriptions.¹

Table 2 Summary of visual field progression (SE)

Year	No of pairs	Number of negative slope		t test* p Value	dB of negative slope		t test p Value
		Non-surgery	Surgery		Non-surgery	Surgery	
2	18	0.6 (0.33)	1.0 (0.4)	0.26	3.3 (1.2)	3.5 (1.3)	0.91
3	18	2.2 (0.73)	1.9 (0.6)	0.62	4.3 (0.9)	2.5 (0.8)	0.12
4	15	5.7 (1.4)	2.3 (0.6)	0.03	3.4 (0.6)	2.5 (0.6)	0.26
5	12	14.5 (0.6)	5.0 (1.4)	0.03	3.9 (0.3)	1.8 (0.5)	0.00
6	9	15.9 (4.9)	4.3 (1.5)	0.07	2.9 (0.3)	1.5 (0.3)	0.02

*t Test for paired samples for SPSS (win 6.0).

Table 3 Summary of mean deviation (MD) of Humphrey visual fields

	Pre-surgery			Post-surgery			p Value
	Range	MD		Range	MD		
		Mean	SD		Mean	SD	
Non-surgery	-1.4, -25	-11.2	7.3	-1, -29	-15.5	7.7	0.001
Surgery	-9, -28	-17.2	5.7	-10, -27	-18.1	6.0	0.221

HAD TRUE 'PROGRESSION' OF THE VISUAL FIELD DEFECT OCCURRED?

An acceptable definition of visual field progression is the appearance of a new defect consisting of ≥ 2 spots ≥ 0.5 dB below the age matched normal level, or the deepening of a pre-existing defect by 0.5 dB; and for these changes to persist on retesting at 1 week and at 3/12.⁷ This approach aims to bypass some of the inherent variability seen on visual field testing, but limits the sensitivity of detectable change (particularly in the central visual field where reproducibility on retesting is much higher).⁵

The PROGRESSOR program only analyses significant regression slopes, therefore variability has already been taken into account. By insisting on two or more consecutive significant slopes (which, in this study were 3-4/12 apart), the effect of a single spurious result is minimised. Linear regression analysis was chosen because it gave the best fit on the decay of retinal sensitivity in untreated normal tension glaucoma patients.⁸ A minimal rate of decay 10 times the age related rate was chosen to ensure clinical as well as statistical significance. This method of identifying deterioration has been shown to correlate well with the 'probability plot' for change in the STATPAC-2 program.⁹ The test locations are treated as independent units. Although cluster analysis of retinal locations has been used to enhance test sensitivity, it has not been shown to have a conclusive superiority over single point analysis. It is possible, however, that a combination of linear regression and cluster analysis could give greater sensitivity than is at present available.

ARE THE RESULTS EXTRAPOLATABLE TO ALL CASES OF NORMAL TENSION GLAUCOMA?
The results presented refer only to a small

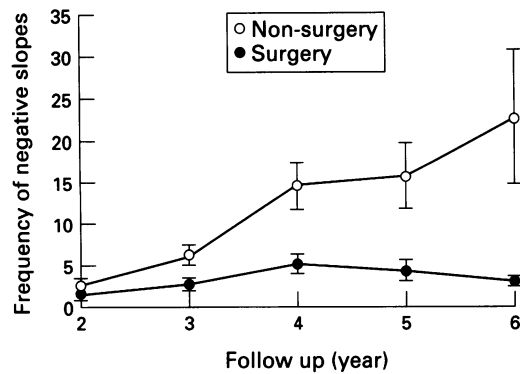


Figure 4 Visual field loss (no of negative regression slopes) in normal tension glaucoma. The difference in the number of progressing locations between operated and unoperated eyes.

cohort of patients. It would be unreasonable to expect every patient to behave in the same way. In her analysis of a large group of patients with normal tension glaucoma, Gjeissen subdivided her patients into several subtypes and considered whether the behaviour could be different between groups.¹⁰ If that was the case then some of her subtypes could be expected to respond better to IOP lowering than others. Patients at Moorfields Eye Hospital show a striking range in the rate of deterioration of points in their visual field. Some patients over years of follow up appear to deteriorate slowly, if at all on kinetic testing¹¹ as well as static testing. This apparent lack of change agrees well with and others.^{12 13} Clearly, surgical treatment should not be offered to patients whose visual fields appear stable.

The eye selected for surgery was considered to have the more severe visual field defect. It could be argued that this prejudiced the results against the operated eye in view of the findings of others that the response to treatment (for high tension glaucoma) is more easily detected in eyes with 'early' disease (less severe visual field defects^{14 15}). Conversely, it could be argued that with fewer normal locations there was less change of detecting progression. Analysis of individual locations showed that significant negative slopes could be identified even if the 'start defect' was 20 dB loss. As progression often occurs around the sides of an absolute defect then the larger the initial defect the greater the chance of progression being detected.

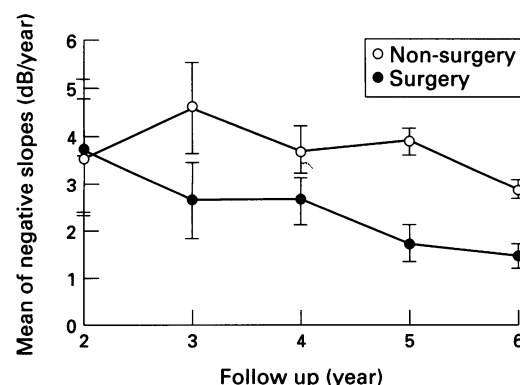


Figure 5 The difference in the rate of loss (dB/year) in the operated and unoperated eyes from years 2-6.

The case for IOP playing a significant role in the progression of visual field defects in normal tension glaucoma was enhanced when it was pointed out by Cartwright and Anderson¹⁶ and Crighton *et al*¹⁷ that IOP asymmetry existed in these patients, the higher IOP existing in the eye having the more severe disease. This asymmetry has since been shown to exist for the patients in our clinic.¹⁸ Additionally an increase in IOP with time has been noted.¹⁹ Although it could be said that the IOP change was a consequence rather than a cause of the disease, these findings suggest that it is at least a risk factor.

WAS THE IOP LOWERING SUFFICIENT?

What level of IOP lowering should be aimed for in treating NTG?

For high tension glaucoma a target IOP of 17 mm Hg has been suggested.²⁰ This was the average starting IOP for our cohort. Surgery lowered the IOP to 11-12 mm Hg and the 5 mm Hg difference between the two eyes was associated with a detectable difference in the amount of visual field progression after 2 years. The mean treated IOP was 11-12 mm Hg. It could be argued that a still lower IOP, without causing hypotony maculopathy, could have been even more beneficial. At present the only way to achieve these IOP levels is by means of fistulising surgery, although in the future prostaglandin analogues may achieve the same long term effect. A worrying trend for the patients in our study was that there was a slight tendency for the IOP to rise after about 5 years. This process, if continued, could restart visual field progression again and may require further treatment.

This is not the first paper to advocate fistulising surgery for Normal Tension Glaucoma. Bloomfield²¹ and more recently de Jong *et al*²² considered it as a useful treatment. More recently a collaborative low tension glaucoma study has been started in the USA which includes surgery as one of the therapeutic options although the authors suggest that a similar percentage lowering of IOP can be achieved with medical treatment in some patients over the short term.²³ Antiproliferative drugs were not used in the eyes reported on here. However, the IOP levels were obtained in eyes without noted risk factors for failure. The presence of any of these factors may necessitate antiproliferative use.

AT WHAT STAGE DID CESSATION OF PROGRESSION OCCUR?

An earlier analysis of changes occurring in this cohort 2 years after surgery could not detect differences between the operated and non-operated eyes. The effects of IOP lowering may have occurred by that time but could not be detected. This may be because the sensitivity of the field analysis depends on the number of points, and that any differences present at 2 years after surgery could not be detected using only five to six tests. More frequent perimetry may well have allowed earlier

detection of a difference than was found in our patients. Alternatively a lag period may exist before changes in rate of loss occur after alterations in treatment.

Conclusion

From the evidence presented we suggest that eyes with progressive normal tension glaucoma may have the rate of their visual field loss slowed or halted by long term lowering of the IOP to subnormal levels. In the absence of universally applicable medical methods to achieve these target pressures we consider that this will involve fistulising surgery. In many eyes with NTG these target pressures will only be achieved with the use of antiproliferative drugs. Because many years may pass before progression occurs, or can be detected we do not consider that surgery should be performed on making the diagnosis, but only when unequivocal progression has occurred.

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