

Long-term outcome of transscleral diode laser cyclophotocoagulation in refractory glaucoma.

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ABSTRACT

Background: Long-term outcome and complications of diode laser cyclophotocoagulation (DCPC) may be important, since eyes once treated with DCPC are less likely to be subjected to other types of interventions in the further follow-up.

Methods: Retrospective review of 131 eyes of 127 patients treated from 2000 through 2004. Success was defined as IOP at last visit 6–21 mmHg; hypotony: IOP \leq 5 mmHg.

Results: Mean follow-up (FU) was 30.1 \pm 16.7 months. Mean number of treatment sessions per eye was 1.54, 89% of the eyes having one or two sessions; overall re-treatment rate: 38.9%. Mean total laser energy delivered per eye: 133.9 \pm 73.7 J; mean energy per treatment episode: 86.8 \pm 22.0 J. Eyes with 3 or more treatments (11%) had a significantly larger proportion of post-traumatic glaucoma, and patients were significantly younger. All eyes had refractory glaucomas on maximal medication, neovascular glaucoma (NVG) representing the largest subgroup (61%). IOP decreased from 36.9 \pm 10.7 mmHg pre-treatment to 15.3 \pm 10.4 mmHg at the end of FU. Success was noted in 69.5% (91 eyes), failure (non-response) in 13%. Hypotony occurred in 17.6% eyes, of which 74% had NVG. Hypotony developed after mean 19.3 \pm 11.0 months, range 6–36; with 96% of these eyes having received only 1 or 2 treatments; delivered energy did not differ from the one in the successful eyes.

Conclusions: DCPC is an efficient treatment for refractory glaucoma. Hypotony, the most common complication, may develop as late as 36 months post-treatment. Diagnostic category and age seem to influence the outcome stronger than laser protocol and delivered energy.

INTRODUCTION

Cyclodestructive procedures have an established place in the management of high-pressure glaucoma, particularly in advanced cases, refractory to other treatment modalities.[1-5] The transscleral cyclophotocoagulation with the diode laser has gained popularity and practically replaced the cryo method, but also the Nd:YAG laser method, due to comparable efficacy and increased safety and tolerability. It is, however, known that the therapeutic effect can be lost over time, and that non-responsiveness makes repeated treatments necessary in a considerable number of cases.[6-12] Data about dose- and laser protocol-related pressure response and complications vary considerably in the literature. Parameters such as total delivered energy per eye, number of laser burns per session, combination of pulse power and pulse duration, sparing or not sparing a portion of the circumference have been analyzed with varying, partially contradictory results.[13-15] Although several long-term observations have been published[16-18], the majority of the data in the literature refer to mean follow-up periods up to 1 year[9-12, 14, 15, 19, 20], which may influence the results. Long-term aspects of this treatment method may be important, since eyes treated with cyclophotocoagulation are less likely to be subjected to other types of interventions in the further follow-up.

The purpose of this study was to retrospectively analyze the long-term safety and efficacy of diode CPC in eyes with refractory glaucoma in a tertiary clinical center.

METHODS

Retrospective chart review was performed of all patients that had undergone diode laser cyclophotocoagulation (DCPC) over a period of five years (2000 through 2004) at the Department of Ophthalmology at the University Hospital in Bern, Switzerland. Data were collected about patient demographics, diagnosis, glaucoma medication, IOP course, complications, visual acuity, and laser parameters.

DCPC was indicated in refractory cases, when IOP control could not be achieved with maximal tolerated topical and systemic (oral acetazolamide) medication in glaucoma eyes having undergone (or not suitable for) conventional filtering or drainage surgery, and when severely elevated IOP was causing discomfort and pain in terminal glaucoma.

Treatment was conducted under topical (retrobulbar injection of 3.5 ml of 20% mepivacain) or general anaesthesia using the continuous wave semi-conductor diode laser (810 nm) and the fiber optic Iris G-probe (OcuLight SLx, IRIS Medical Instruments, Inc., Mountain View, CA). Transillumination to localize the ciliary body band was not used routinely, but according to surgeon's preference – in approximately 15% of the cases, when ciliary body location was uncertain. The footplate of the G-probe was placed according to the transillumination results or, routinely, about 0.5 mm behind the limbus and moderate pressure was exerted. There was no standard treatment protocol. In practically all cases, 270 degrees of the circumference were treated and either the supero-temporal or the superior sector (the site of previous surgeries) was spared. Pulse duration was fixed at 2 seconds. Pulse power and the number of burns varied from case to case and among the surgeons. In general, pulse power was set at 1750 or 2000 mW to start with and was either maintained throughout the procedure or adjusted according to the audible 'pops'. Postoperatively, an antibiotic/steroid ointment was instilled and the eye patched over night. Antibiotic/steroid eye drops were prescribed 5 times daily for one week, and the pre-operative glaucoma medication continued. Eyes were examined on the next day, at one and four weeks, and then according to the clinical picture. When a pressure-lowering effect was

noted, the hypotensive medication was reduced gradually, starting with oral acetazolamide. CPC was repeated (re-treatment) if the IOP response was inadequate, after a minimum interval of 4 weeks.

Success was defined as IOP at last visit between 6 and 21 mmHg, or IOP of 22-26 mmHg and pressure reduction of at least 30% compared to pre-treatment, with or without topical medications. Decrease of number of medications was also considered (for example, pre-op 20 mmHg with 4 topically applied substances and a systemic carboanhydrase inhibitor, post-op 17 mmHg with two topical preparations only). Hypotony was considered when $IOP \leq 5$ mmHg. The delivered laser energy (joules, J) was calculated per pulse (pulse power in watts multiplied by pulse duration in seconds), per treatment session (pulse energy multiplied by the number of laser burns), and per eye (all treatment sessions added).

To evaluate the outcome, following parameters were calculated (in percentage of total): response rate (successful and hypotony eyes taken together), success rate, hypotony rate, re-treatment rate (eyes with more than one treatment). Statistical analysis was performed with SPSS for Windows, version 13.0. Parameters were compared using the unpaired t-test and the Mann-Whitney test. The distribution of diagnosis between subgroups was compared with the Kruskal-Wallis test. Differences were considered significant when $p < 0.05$. Data were reported as mean \pm standard deviation, range minimum–maximum.

RESULTS

During the 5 years considered in the study, a total of 181 eyes of 176 patients were treated with DCPC. A total of 268 treatment sessions were carried out, two thirds (67.5%) being initial cyclodiode treatments, one third (32.5%) re-treatments. The number of treatments per year ranged between 42 and 65, mean 53.6. A mean of 36 new eyes (initial treatments) were registered per year.

Fifty eyes had to be excluded because the documented follow-up was less than 5 months. Thus, 131 eyes of 127 patients with a follow-up of 5 or more months were included in the statistical analysis. There were 62 female and 65 male patients with mean age of 69.51 ± 15.21 , range 8 – 92 years, including only 7 patients under the age of 40. Mean follow-up was 2.5 years or 30.1 ± 16.7 months (range 5–75 months). The distribution of the eyes according to the follow-up period is given in **figure 1**. For these 131 eyes, 202 treatment sessions were carried out, a mean of 1.54 sessions per eye. Eighty-nine percent of the eyes had one or two, 11% three or more treatments (**table 1**). The three subgroups –with one (n=80), two (n=37), and three or more (n=14) cyclodiode treatments– were compared for age (Mann-Whitney test) and distribution of glaucoma diagnosis (Kruskal-Wallis test, adjusted for ties). There was no significant difference between the first two groups for any of the parameters. The patients in the third subgroup were significantly younger ($p < 0.001$), and had significantly more post-traumatic glaucomas ($p < 0.01$) than the other two subgroups. The difference in the distribution of the other glaucoma types did not reach statistical significance.

No of treatment sessions	No of eyes	Percentage	Follow-up (months)	Age (years)	NVG	Post VR	Trauma	ACG	POAG	XFG	PKP	Uveitis	Cong	Other sec gl
1	80	61.1%	26.1±15.1	72.8±10.9	55	6	-	1	3	8	3	1	2	2
2	37	28.2%	33.4±14.7	68.1±19.5	19	4	2	-	2	3	-	2	-	4
3	10	7.6%	36.7±20.6											
4	3	2.3%	64.0±10.2	54.7±15.5	6	3	4	1	-	-	-	-	-	-
6	1	0.8%	60.3											
Total	131	100%	30.1±16.7	69.5±15.2	80	13	6	2	5	11	3	3	2	6

Table 1. Distribution of the eyes by number of treatment sessions and diagnosis.

Legend: NVG, neovascular glaucoma; Post VR, glaucoma post vitreo-retinal surgery; ACG, chronic angle-closure glaucoma; Trauma, post-traumatic glaucoma; POAG, primary open-angle glaucoma; XFG, pseudoexfoliation glaucoma; PKP, glaucoma secondary to penetrating keratoplasty; Uveitis, uveitic glaucoma; Cong, congenital glaucoma; Other sec gl, secondary glaucomas of other etiologies (untreated retinal detachment, complicated intraocular surgery, irido-corneal-endothelial syndrome)

Fifty-one eyes have received more than one cyclodiode session (re-treatment rate 38.9%). Mean period between the initial and the second session (first re-treatment) was 5.35 ± 8.22 months (range 0.5 – 45.7 months). There were 5 eyes that were re-treated before the completion of the first 4 weeks, because of very high IOP. Almost 50% (25/51) of the re-treatments occurred within the first 2 months, and almost 70% (35/51) within the first 4 months (**figure 2**). For the whole group, IOP decreased from 36.9 ± 10.7 mmHg before initial DCPC to 15.3 ± 10.4 mmHg at the end of follow-up, a highly significant reduction of 55.5% ($p < 0.001$) (**figure 3**). The mean number of antiglaucoma medications decreased significantly from 2.97 ± 1.36 pre-treatment to 1.39 ± 1.36 at the end of follow-up ($p < 0.001$) (**figure 4**). Success was noted in 69.5% (91 eyes), failure (non-response) in 13.0% (17 eyes), and hypotony in 17.6% (23 eyes, of which 13 with phthisis). The overall response rate was 87%. **Figure 5** presents survival curves for the pressure response to DCPC treatment.

Mild uveitis within the first two weeks of treatment was observed frequently and was considered a common postoperative reaction rather than a complication. During the long-term follow-up in this study, by far the most frequent complication (17.6%; 23/131) was hypotony, 74% of these eyes having neovascular glaucoma. Hypotony occurred on a mean of 19.3 ± 11.0 months after the initial treatment, range 6–36 months. Other complications included: prolonged uveitis 1, severe dry eye 1, hyphema 1, vitreous hemorrhage 1, keratitis/band keratopathy 4. It was not always clear-cut whether the complication was related to the cyclodiode treatment itself or to the complexity of eye pathology (for example, corneal failure in an eye with several intraocular surgeries and periods of very high IOP with corneal edema). No cases of endophthalmitis or sympathetic ophthalmia were observed.

When the whole study group and the entire follow-up period were considered, 45.8% of the eyes (60/131) achieved a successful IOP control after the first cyclodiode treatment, and 9.2% (12/131)

developed hypotony, i.e. 72 eyes responded to a single treatment. Following the second DCPC session, additional 17.6% (23 eyes) gained control, but also another 7.6% (10 eyes) progressed to hypotony. Thus, after one or two treatment sessions, the IOP response rate was 80.2%, consisting of 63.4% with reasonable IOP control, and 16.8% with an 'overshoot' leading to hypotony. A third cyclodiode session added another 7 eyes (5.3%) to the successful ones. There were three eyes with a total of 4 DCPC sessions – one gained control (IOP 10 mmHg without medication), one developed hypotony (IOP 4 mmHg), and one was non-responsive. One traumatic eye has been treated 6 times with DCPC during 5 years, but the pressure was still 26 mmHg.

The mean total energy delivered per eye was 133.9 ± 73.7 J. When the energy delivered during the first session in the 72 responding eyes (92.5 ± 22.5 J) was compared with the energy in the 59 non-responding eyes (77.2 ± 19.5 J), a significant difference was found ($p < 0.001$). Also, 75% of the responding eyes have received laser energy of 80.0 J and higher during the first DCPC; this proportion being 49% in the non-responding eyes. However, the above relation was no longer observed after the second DCPC session: the total energy from the initial and the re-treatment in the 33 responding eyes (166.7 ± 30.4 J) did not differ from that in the 18 non-responding eyes (161.1 ± 27.3 J), $p = 0.52$. Interestingly, when the energy delivered during the first DCPC to the success eyes ($n = 60$) and to the hypotony eyes ($n = 12$) was compared, no difference was noted, $p = 0.93$. The same was true, when the successful and the hypotony eyes after one re-treatment were compared, implicating that the occurrence of hypotony was not directly correlated with the laser energy.

Diagnosis distribution is given in **table 2**. The highest failure rate (the lowest response rate) was noted for eyes with traumatic glaucoma and pseudoexfoliation glaucoma (Kruskal-Wallis, adjusted for ties, $p < 0.01$). It is to be noted that 90% of XFG were very advanced cases with vision of hand motions to light perception. Traumatic glaucoma and glaucoma post VR surgery had significantly higher number of treatments per eye compared with the other groups ($p < 0.05$; unpaired t-test and Mann-Whitney test). The differences between the other groups did not reach statistical significance. Hypotony was observed in NVG, glaucoma post vitreo-retinal surgery, and secondary glaucoma of other etiologies. Neovascular glaucoma comprised with 61.1% the largest diagnostic subgroup. The subcategories of NVG are listed in **table 3**; no statistically significant difference was noted.

Diagnosis	No of eyes	% of total	Response		Non-response	No of sessions per eye	Mean (SD) Total Energy (J)	Mean (SD) Energy First Treatment (J)
			Success	Hypotony	Failure			
NVG	80	61.1	56	17	7	1.4	123.9 (62.6)	86.5 (20.1)
Post-VR surgery	13	9.9	10	3		1.9	158.8 (79.7)	86.8 (20.1)
Traumatic gl	6	4.6	3		3	3.2	273.4 (132.0)	75.7 (12.9)
Uveitic gl.	3	2.3	3			1.7	117.0 (23.8)	68.8 (20.7)
Post keratoplasty	3	2.3	2		1	1.0	83.3 (47.3)	83.3 (47.3)
Other sec glaucomas	6	4.6	2	3	1	1.6	131.2 (44.3)	86.8 (20.1)
Cong gl	2	1.5	2			1.0	110.0 (14.1)	110.0 (14.4)
CACG	2	1.5	2			2.0	250.0 (127.3)	120.0 (56.6)
POAG	5	3.8	5			1.4	135.0 (47.3)	84.1 (33.4)
XFG	11	8.4	6		5	1.3	103.7 (42.3)	83.9 (19.8)
Total	131	100	91	23	17	1.54	133.9 (74.0)	85.7 (22.5)

Table 2. Distribution of diagnosis.

Legend: Abbreviations as in table 1. All eyes with traumatic glaucoma had 2 or more CPC sessions (range 2-6); re-treatment rate 100%. Congenital glaucoma: both eyes of the same patient with glaucoma fere absolutum, aphakia and high myopia. Chronic angle closure glaucoma: two eyes of two patients; the one with 3 filtering surgeries and penetrating keratoplasty because of bulous keratopathy; the other with microphthalmus, status post filtering surgeries, cataract extraction; and trisomy 21.

Diagnosis	No of eyes	% of total	Response		Non-response	No of sessions per eye	Mean (SD) Total Energy (J)	Mean (SD) Energy First Treatment (J)
			Success	Hypotony	Failure			
NVG diabetes	38	47.5	29	6	3	1.4	113.2 (46.1)	84.3 (18.4)
NVG vein occl	34	42.5	25	6	3	1.4	133.0 (75.8)	90.9 (20.3)
NVG artery occl	2	2.5	1	1		2.0	148.8 (29.4)	61.8 (19.5)
NVG other	6	7.5	1	4	1	1.5	131.1 (78.8)	88.2 (20.2)
NVG all	80	100	56	17	7	1.4	123.9 (62.6)	86.5 (20.1)

Table 3. Composition of the subgroup of 80 eyes with neovascular glaucoma (NVG).

DISCUSSION

The results of this study confirm that refractory glaucoma can be managed on long-term (up to 6 years) with single or repeated cyclodiode treatments, the overall pressure-lowering response rate being 87%, and the overall success rate approximately 70%. The outcome seems to be related to the type of glaucoma, the longevity of observation, the definition of success and, to a lesser extent, the laser parameters and delivered energy. **Figure 6** compares several larger studies published recently and allows some general conclusions: In high-pressure glaucoma, an IOP decrease of 35% to 55% and a significant reduction in the number of medications can be expected. The response rate after one treatment and one re-treatment is roughly 80%. This is particularly true for advanced, refractory cases. DCPC as primary interventional treatment and in primary glaucoma seems to be associated with less IOP decrease and less reduction of medication, although, also, with less re-treatments (*Grueb et al*, *Kramp et al*). In mixed cohorts, the proportion of neovascular glaucoma cases is relevant for the overall outcome. Comparing the four studies with intractable glaucomas (last four in fig 6), it is to be noted that *Pucci et al* have used a very restrictive laser protocol with low power-settings and, particularly, low number of burns per treatment session. Although their reported overall success does not differ significantly from the other three studies, *Pucci et al* had the lowest percentage of IOP reduction, the highest postoperative IOP, and the highest re-treatment rate, this despite a very high proportion of primary glaucoma in their cohort. This may be due to the low-energy protocol used.

Hypotony was the most common long-term complication in our study (17.6%). This complication was observed only in three diagnostic categories, neovascular glaucoma, glaucoma post vitreo-retinal surgery, and secondary glaucoma of other etiologies (table 2), which is in accordance with other published reports (*Murphy et al 2003*). Studies with cohorts comprising different diagnostic categories, mainly primary glaucomas, have reported significantly lower hypotony rates (*Pucci et al*, *Grueb et al*, *Kramp et al*). *Murphy et al* noted a hypotony rate of 15.6% in a large subgroup of 122 eyes with NVG. Their definition of hypotony was “less than 5 mmHg”. If we adjust our criterion accordingly, the hypotony rate in our NVG subgroup becomes 17.5% (14/80), which is well comparable with that reported by *Murphy et al*.

We analyzed various parameters for association with hypotony. However, hypotony incidence did not depend upon the laser energy delivered during initial DCPC treatment, and did not increase (i.e. remained stable) after the second treatment. Eyes developing hypotony have not received higher energies or more re-treatments compared with eyes maintaining normal IOP. Half of the eyes complicating to hypotony (12 of 23) have had only one DCPC session, the other 10 eyes two, and only one eye had 4 sessions. Hypotony occurred on a mean of 19.3 months after the initial treatment, as early as 6 and as late as 36 months. Mean age was not significantly different between the subgroups with hypotony, successful pressure control, and pressure non-response. In conclusion, an overshoot reaction to cyclodiode and development of hypotony cannot be predicted in an individual case, but should be expected in 15 to 20% in neovascular glaucoma, and in even higher percentage in glaucoma post vitreo-retinal or other intraocular surgeries. Longer follow-up is likely to be associated with new cases of hypotony and phthisis. The intention to reduce hypotony risk by using lower laser power and fewer applications per treatment should be weighed against the possible lower response rate.

The overall re-treatment rate (all eyes with more than a single DCPC) was 39%, younger patients, post-traumatic cases, and glaucoma post VR surgery tending to need higher number of repetitions. Although the bulk of first re-treatments took place within 4 months of initial DCPC, more and more initially successful eyes had to be re-treated over time. Regardless of this trend, it does not appear possible to define an “average duration of cyclodiode success”, since more than 50% of the eyes

controlled with a single treatment had a follow-up over 2 years (i.e., significantly longer than the average time to re-treatment), 25% over 3 years, with the longest follow-up of a successful IOP control after a single treatment being 5.5 years in this study cohort.

In conclusion, diode cyclophotocoagulation is an efficient treatment for refractory glaucoma.

Diagnostic category and age seem to influence postoperative course and outcome stronger than laser protocol and delivered energy. Neovascular glaucoma and glaucoma secondary to intraocular surgery are associated with higher incidence of hypotony, while post-traumatic, pseudoexfoliation glaucoma, and younger age tend to be less responsive to cyclodiode treatment.

LEGENDS

** The legends of the tables are given below each table incorporated in the text. Figures 1-5 are self-explanatory and do not need legends.

Figure 1. Distribution of the study eyes in % according to the follow-up period.

Figure 2. Time (in months) to the first cyclodiode re-treatment.

Figure 3. Intraocular pressure (IOP) pre- and post-treatment

Figure 4. Change in medication in the course of follow-up

Figure 5. Kaplan-Meier survival curves for the pressure response to diode laser cyclophotocoagulation, single and repeated treatments.

Figure 6. Comparison of seven recent studies with mid- and long-term follow-up of eyes treated with diode laser cyclophotocoagulation.

Legend (Fig 6):

* Calculated, based on the data in the paper; † calculated according to table 2 in the paper; ‡ only one eye was re-treated; ** see the definition of success and the end IOP.

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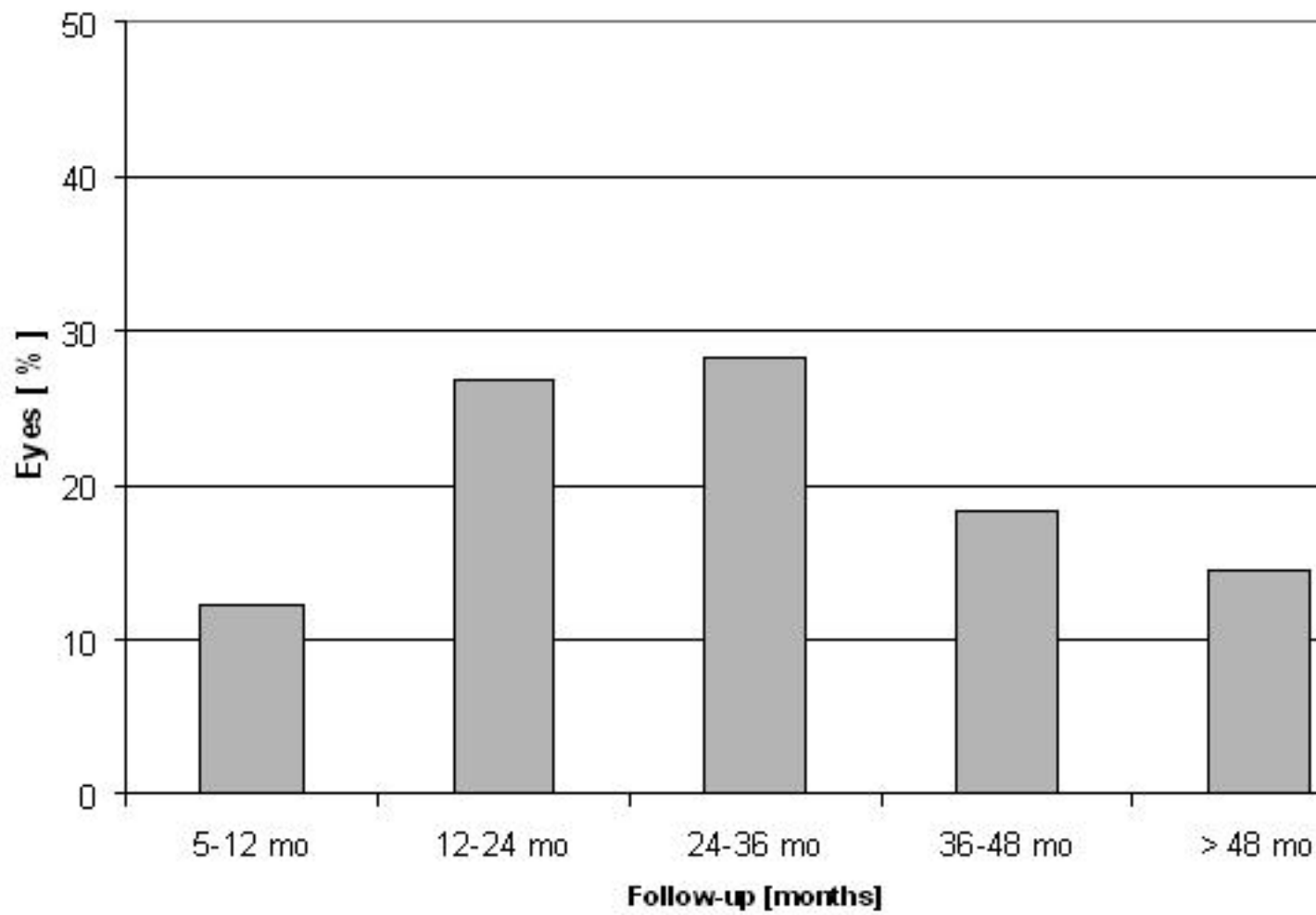
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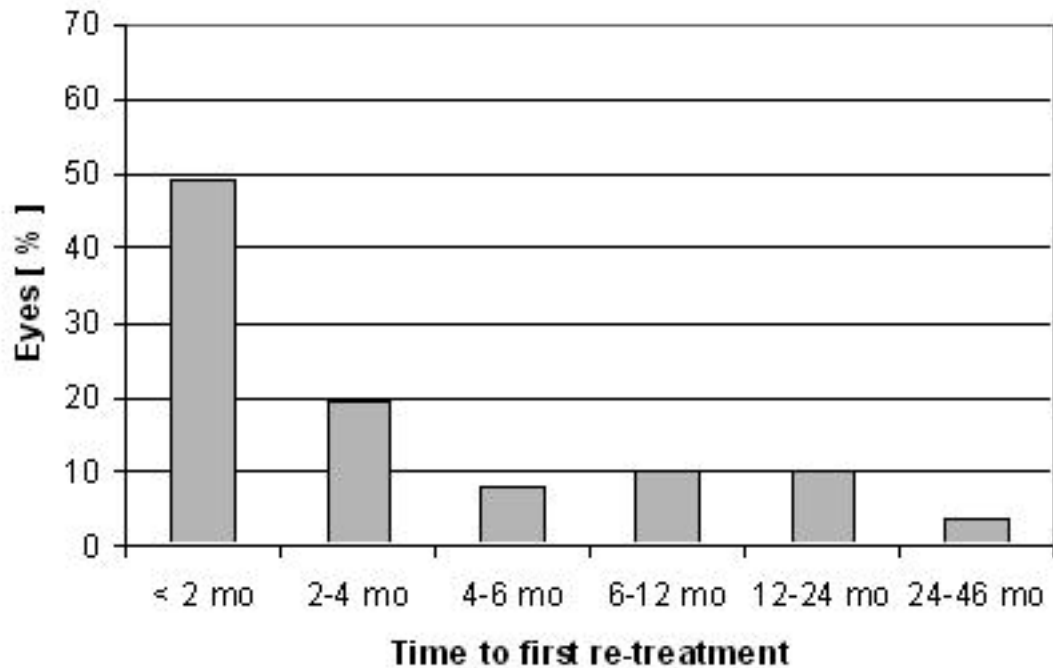
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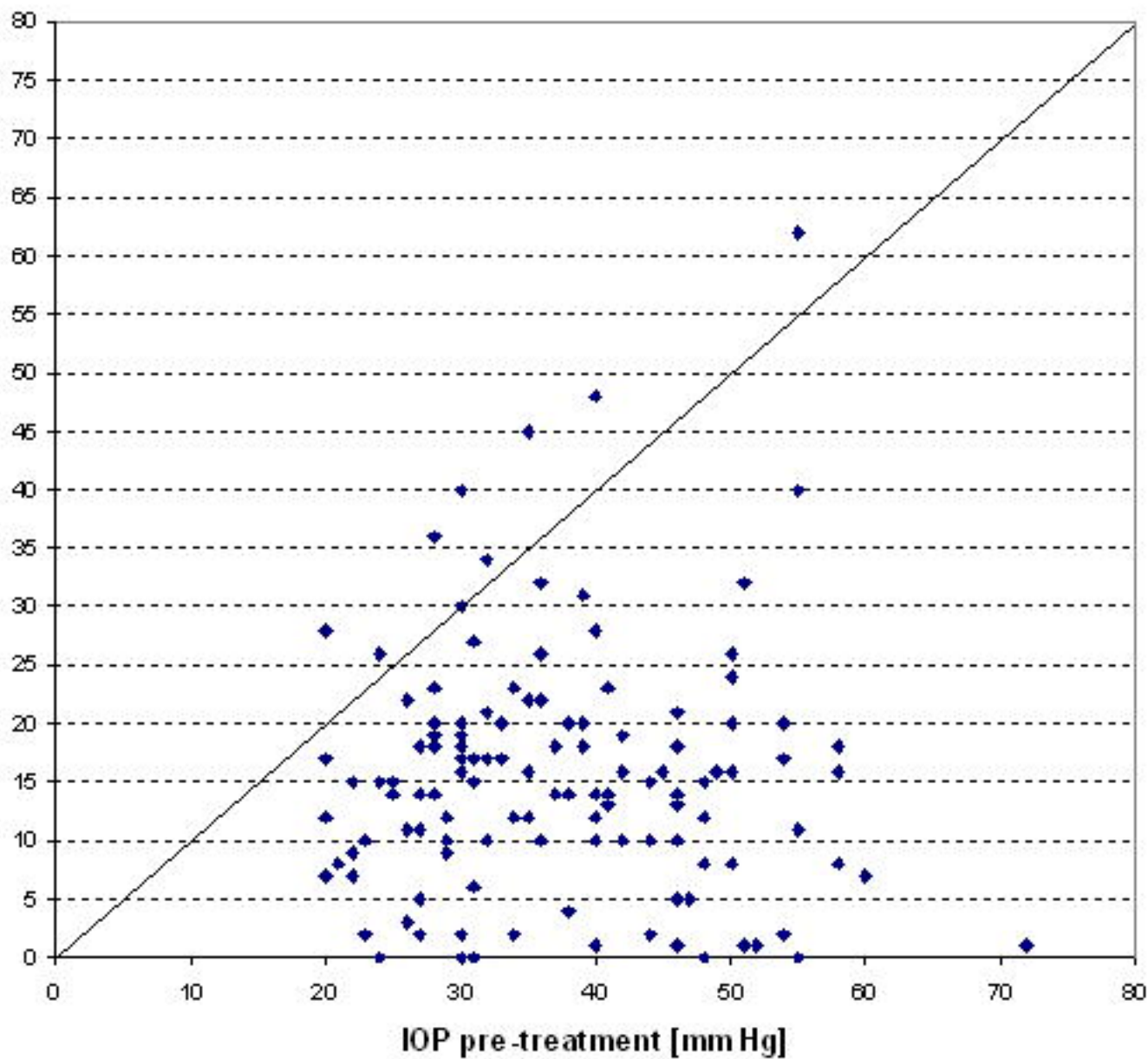
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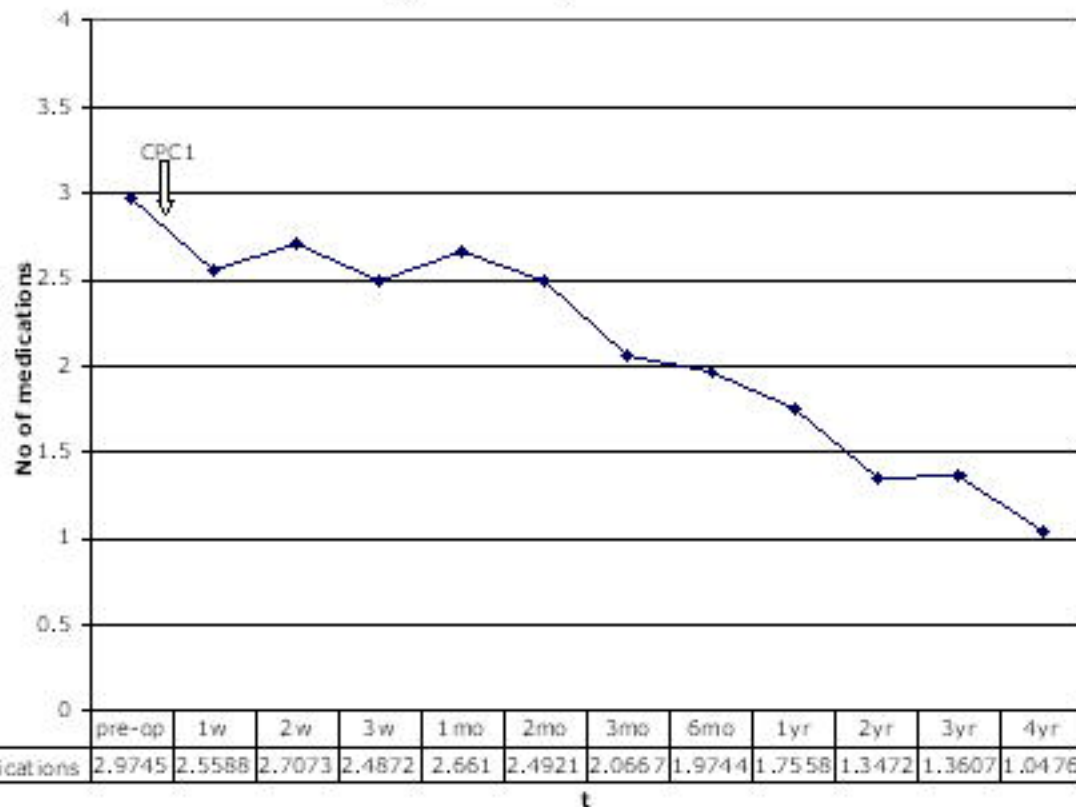


IOP at the end of follow-up [mm Hg]

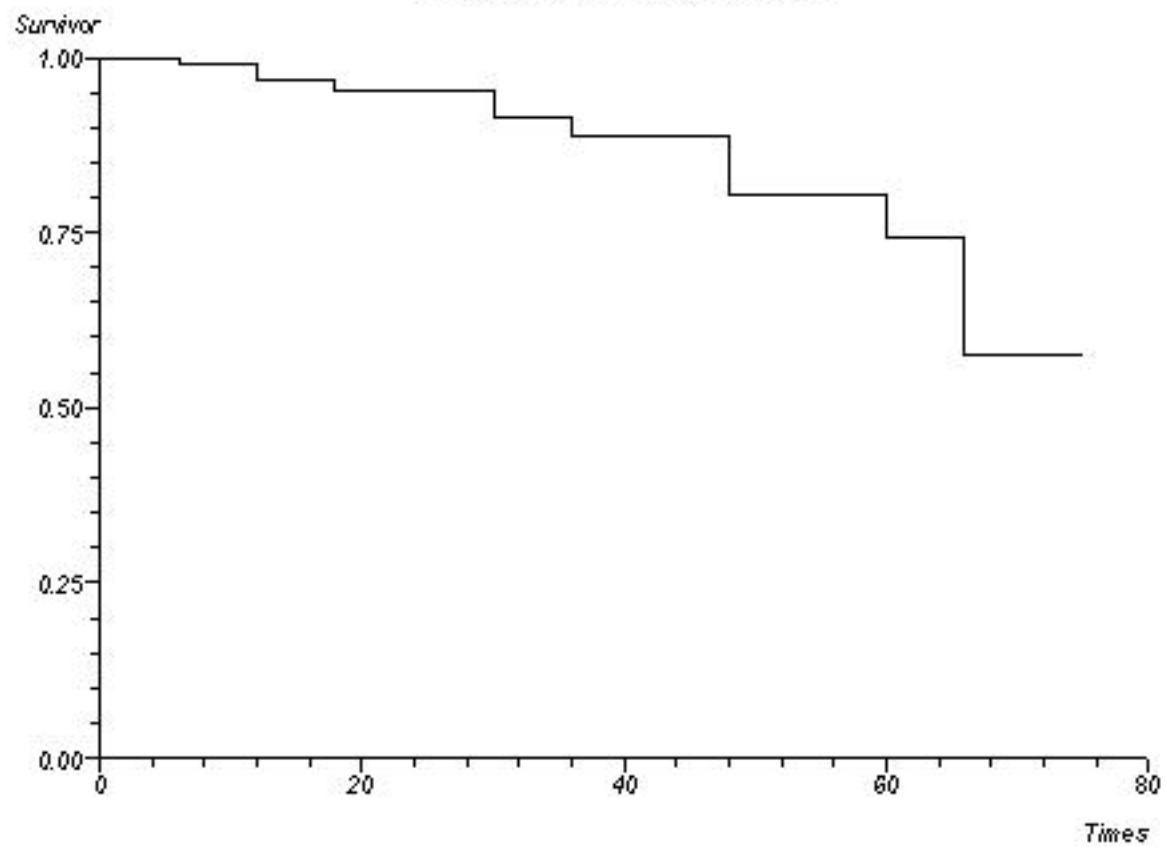


IOP pre-treatment [mm Hg]

Change in antiglaucomatous medication



Survival Plot (PL estimates)



Study	Country	Follow up (mo)	No of eyes	Diagnosis	% Refractory glaucomas	% Neovasc glaucoma	% Primary glauc	Mean IOP pre-treatm	Mean IOP end of FU	% IOP reduction	Overall success rate	Definition of success	Re-treatment rate	Response rate after 1st CPC	Response rate after 2nd CPC	No of treatments per eye	No of treatm (range)	No of burns per treatm episode	Mean energy per treatment episode [J]	Mean total energy per eye (J)	VA stable	VA improved	VA worsened
Kramp et al. 2002	Germany	13.9	193	Primary and sec gl		6.2%	64.8%*	24.6	19.3	21.5%*	76.4%	10 - 22 mmHg	21.2%	68.9%		1.3	1 - 6	24-30	92.4 *	120.1 *			
Grueb et al. 2006	Germany	24.0	90	Primary gl		0%	100%	21.0	16.0	23.8%	36.7%	4 - 18 mmHg	30.0%			1.3	1 - 3	15-20	80.0	104.0 *			
Ansari & Gandhewar 2006	UK	12.5	74	Refractory and non-refr gl		50%	31%	40.3	21.1	45.1%	82.0%	30% reduction	1.4% [‡]	82%**		1.01	1 - 2	30 (4.5)	124.1 *	124.1 *			
Noureddin et al. 2006	Lebanon	13.7	36	Refractory glaucoma	100%	16.6%	25%	35.8	19.1	53%	72.2%	≤ 21 mmHg	25.0%			1.25	1 - 2	26 - 28	121.5 *	151.9 *	44%	33%	22%
Murphy et al. 2003	UK	17.0	263	Refractory glaucoma	100%	46.4%	18.6%	40.7	17.7	52.6%	79.5%	5 - 21 mmHg	34.2%	58.9%	81.3%	1.5	1 - 7	-	104.1	155.2	75%	5%	20%
Pucci et al. 2003	Italy	26.0	120	Refractory glaucoma	100%	12.5%	52.5%	30.4	20.3	35%	76% [†]	≤ 21 mmHg	45.8%	54.1%		1.7	1 - 5	10 (1.8)	43.6 *	75.2 *	55%	21%	24%
Iliev & Gerber (this study)	Switzerland	30.1	131	Refractory glaucoma	100%	61.1%	12.2%	37.7	15.3	55%	69.5%	6 - 21 mmHg	38.9%	55.0%	80.2%	1.54	1 - 6	22 (5.6)	86.8	133.9	55%	11%	34%



Long-term outcome of transscleral diode laser cyclophotocoagulation in refractory glaucoma.

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