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Red Laser Cyclophotocoagulation for Treatment of Therapy-resistant Glaucoma

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Academic dissertation

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Contents

Abbreviations

CAI	carbonic anhydrase inhibitor
CPC	cyclophotocoagulation
cw	continuous-wave
ECCE	extracapsular cataract extraction
EG	exfoliation glaucoma
fr	free-running
ICCE	intracapsular cataract extraction
IOL	intraocular lens
IOP	intraocular pressure
J	Joule
mo	month
mW	milliwatt
n.d.	not done
Nd	neodymium
Nd:YAG	neodymium:yttrium-aluminium-garnet
nm	nanometer
n.s.	not statistically significant
NVG	neovascular glaucoma
pc	posterior chamber
ppv	pars plana vitrectomy
SD	standard deviation
VA	visual acuity
W	Watt
y	year
YAG	yttrium-aluminium-garnet

List of original publications

This thesis is based on the following original publications, which are referred to in the text by Roman numerals:

I Raivio VE, Immonen IJR, Laatikainen LT, Puska PM. Transscleral Contact Krypton Laser Cyclophotocoagulation for Treatment of Posttraumatic Glaucoma. J Glaucoma 2001;10:77-84.

II Raivio VE, Immonen IJR, Puska PM. Transscleral Contact Krypton Laser Cyclophotocoagulation for Treatment of Glaucoma in Children and Young Adults. Ophthalmology 2001;108:1801-1807.

III Raivio VE, Immonen IJR, Puska PM. Transscleral Red Laser Cyclophotocoagulation Combined with Limited Anterior Retinal Cryocoagulation in Neovascular Glaucoma. *Submitted* 2001.

IV Raivio VE, Vesaluoma MH, Tervo TMT, Immonen IJR, Puska PM. Corneal Innervation, Corneal Mechanical Sensitivity, and Tear Fluid Secretion after Transscleral Contact 670 nm Diode Laser Cyclophotocoagulation. J Glaucoma 2002; *in press*.

1. Introduction

Glaucoma is an ocular disease causing atrophy of the optic nerve head. The chief risk factor of optic nerve head damage is intraocular pressure (IOP), and treatment by medication, laser procedures and incisional surgery aims at lowering the IOP to a level at which no further damage will occur.

The IOP is determined by the balance between the production of aqueous humour in the ciliary body and the outflow of aqueous humour via the trabecular meshwork and by the uveoscleral pathway. All treatment options aimed at lowering the IOP affect one or both of the above.

Cyclodestruction aims at lowering the IOP by reducing production of the aqueous humour in the ciliary body, and alteration of the vascular supply of the ciliary body probably acts as a synergistic mechanism. (van der Zypen et al. 1989, Schlote et al. 2001a) Further, experimental studies suggest that cyclodestruction may also enhance uveoscleral outflow owing to postoperative inflammation or disruption of the neuroepithelial barrier at the level of the pars plana. (Schubert et al. 1989a, Schubert et al. 1990, Liu et al. 1994)

Cyclodestruction is used in patients in whom IOP cannot be controlled by the maximum tolerable medical therapy and in whom filtration surgery is likely to fail, has failed or is not feasible (Mastrobattista et al. 1996, Chen et al. 1999), but it has also been proposed as first-line therapy in primary open-angle glaucoma. (Egbert et al. 2001) Cyclodestruction rather than filtration surgery, is also used in eyes with limited visual potential and for relief of pain in eyes with no visual potential. (Mastrobattista et al. 1996, Stewart et al. 1996, Chen et al. 1999) It is used in patients who, for medical reasons, are unable to undergo filtration surgery or in those who decline surgical treatment. (Stewart et al. 1996, Chen et al. 1999) Previously, cyclocryocoagulation was the means most widely used for cyclodestruction but owing to the high rate of complications and the unpredictable effect of treatment, it has fallen into disfavour.

The first laser widely used for cyclophotocoagulation (CPC), was the 1064 nm Neodymium:YAG (Nd:YAG), operating in the pulse mode. However, especially in the long term, the result of the treatment was unpredictable, with a high incidence of post-operative pain, hypotonia, phthisis bulbi and visual loss. (Schuman et al. 1990a, Trope et al. 1990, Schuman et al. 1992, Al-Ghamdi et al. 1993, Shields et al. 1993, Baez et al. 1994, Shields et al. 1994, Dickens et al. 1995, Zhou Wei et al. 1996)

Later, improvements in the use of the Nd:YAG included employing the laser in the continuous-wave (cw) mode, using a longer application time (up to 2 seconds) and a contact probe. However, the theoretical disadvantage of the Nd:YAG remained: it is less than optimally absorbed by the melanin in the pars plicata of the ciliary body.

The absorption of light energy by melanin increases with a decrease in wavelength. (Rol et al. 1990) Thus, more recently, the 810 nm infrared diode laser has been adopted for CPC. The 647 nm krypton and the 670 nm diode red lasers have an even higher affinity for the pigment epithelium, and thus are more selectively absorbed by the target tissue than the infrared Nd:YAG and the 810 nm diode lasers. It has been shown that the red krypton laser, with poorer scleral transmission, but better absorption by the pigment epithelium than the Nd:YAG, produced more cyclodestruction at similar power settings. (Immonen et al. 1993) Furthermore, the long application time, 10 seconds, of red laser CPC allows the use of very low intraocular power levels as compared with the laser modalities previously used for CPC.

This study was designed to examine the usefulness of and the complications with the red 647 nm krypton laser for CPC in the treatment of the difficult posttraumatic glaucoma and of refractory glaucoma in children and young adults. The combination of red laser CPC with limited anterior retinal cryocoagulation was studied in recalcitrant neovascular glaucoma. The effect of red laser CPC on the corneal innervation and the parameters related to it was also studied in eyes undergoing 670 nm diode CPC.

2. Review of the literature

2.1. Glaucoma

2.1.1. Definition

Glaucoma is an optical neuropathy characterized by a specific pattern of damage to the optic nerve head and the visual field, which represents the final common pathway resulting from various conditions that can affect the eye. (Ritch et al. 1996).

2.1.2. Treatment options

Treatment is currently aimed at reducing the IOP to an individual target pressure. This is achieved by medical therapy, laser treatment or incisional surgery.

Medical therapy lowers the IOP by decreasing the production of aqueous humour, by increasing the conventional outflow of the aqueous humour, and also by increasing its outflow via the uveoscleral route. In patients who are not helped by the maximal tolerated glaucoma medication, argon laser trabeculoplasty (Wise et al. 1979) is performed to obtain further reduction of IOP by increasing the facility of aqueous outflow. Trabeculectomy (Cairns 1968), with its numerous modifications, produces a guarded fistula between the anterior chamber and the subconjunctival space. (Traverso et al. 1987) It is used in cases where non-invasive therapy has failed, or is unsuitable (e.g. when compliance with medical therapy is a problem), when appropriate medical therapy is not available, or when the target pressure required cannot be reached with medications or laser treatment, and when the IOP is so high at presentation that other forms of therapy are unlikely to be successful. (Watson et al. 1981, Jay et al. 1988, Migdal et al. 1994) In selected cases, to prevent postoperative conjunctival scarring with resultant failure of filtration and to reach a low target pressure, antimetabolites are used at the site of trabeculectomy. (Khaw et al. 1996)

The use of glaucoma implant surgery is generally reserved for patients in whom filtering surgery with antimetabolites has failed or for patients with excessive conjunctival scarring due to previous surgery, who have a very high risk of failure of trabeculectomy or where filtration surgery would have been technically difficult. (Fellenbaum et al. 1994, Coleman et al. 1995, Mills et al. 1996) Future research will establish the place of non-penetrating filtration procedures, such as deep sclerectomy and viscocanalostomy, in the field of glaucoma surgery. (Schwenn et al. 1998, Stegmann et al. 1999, Mermoud et al. 1999)

The aim of cyclophotocoagulation is to reduce the production of aqueous humour by ablating the epithelium of the ciliary processes in the pars plicata of the ciliary body. (Beckman et al. 1972, Schuman et al. 1990b, Liu et al. 1994, Stewart et al. 1996). The conventional role of transscleral cyclophotocoagulation has been in those refractory cases in which all other treatments, including incisional surgeries, have been tried and have failed (Wilson 2001, Semchyshyn et al. 2002) Patients typically are those who have a high IOP that cannot be controlled by medication or previous surgery, or who would be poor surgical candidates or who decline surgical treatment. (Chen et al. 1999) Cyclodestruction, instead of filtration surgery, is also used in eyes with limited visual potential and for relief of pain in eyes with no visual potential. (Mastrobattista et al. 1996, Stewart et al. 1996, Chen et al. 1999)

2.2. Cyclodestruction

2.2.1. The pre-laser era of cyclodestruction

Cyclodestruction aims at causing atrophy in the secretory non-pigmented ciliary epithelium of the pars plicata of the ciliary body and thus reducing the production of aqueous humour. (Stewart et al. 1996) The early cyclodestructive procedures included non-penetrating cyclodiathermy introduced by Weve in 1933 (Weve 1933), penetrating cyclodiathermy developed by Vogt in 1936 (Vogt 1936), and cycloelectrolysis evaluated by Berens in 1949 (Berens et al. 1949). In 1950, Bietti suggested freezing as a method for producing ciliary body damage. (Bietti 1950) Krwawicz studied the action of low temperature on various ocular structures, including the ciliary body. (Krwawicz 1966) DeRoetth reported that cyclocryotherapy was effective in treating patients with open-angle glaucoma. (DeRoetth 1968) In a study by Bellows et al. in 1973, approximately 75% of patients with open-angle glaucoma followed for more than a year had IOPs of 19 mmHg or less. (Bellows et al. 1973)

In 1985, Shields reported that cyclocryocoagulation resulted in adequate pressure control in 64% of neovascular glaucomatous eyes, but that 17% progressed to phthisis bulbi and 69% had profound loss of visual acuity (VA). (Shields et al. 1985) Also, because of the postoperative pain and the significant incidence of postoperative inflammation, which occasionally leads to extensive posterior synechiae and chronic flare (Stewart et al. 1996), this treatment has fallen into disfavour despite attempts to modify the procedure in order to reduce the complications. (Lehtinen et al. 1968)

2.2.2. Cyclophotocoagulation

History

In 1961, Weekers et al. employed light as the cyclodestructive element, using the transscleral application of xenon arc photocoagulation over the ciliary body. (Weekers et al. 1961) However, it was the introduction of the laser, a source of monochromatic and coherent light, that eventually led to the clinical application of cyclophotocoagulation.

In 1969, Smith and Stein, and Vucicevic et al. reported the use of the first laser CPC, using a ruby and a neodymium (Nd) laser in rabbits. (Smith et al. 1969, Vucicevic et al. 1969) In human subjects, Beckman et al. reported the use of the ruby laser for transscleral CPC in 1972, that of the Nd:glass in 1973, and that of the 1064 nm Nd:YAG in 1985. (Beckman et al. 1972, Beckman et al. 1973, Beckman 1985) It was only after the better availability of the Nd:YAG laser that the use of CPC became widespread.

The Nd:YAG laser can be used for CPC in a free-running thermal mode, which is delivered in short pulses, or in a continuous-wave mode, in which the laser emits radiation continuously over time. (Stewart et al. 1996) In the beginning of the previous decade, the use of the cw-810 nm diode laser for CPC began. (Balles et al. 1990, Naguib et al. 1990, Assia et al. 1991, Brancato et al. 1991, Hennis et al. 1992) The 810 nm diode laser incorporates two light-emitting diodes with a combined wavelength of 810 nm. (Stewart et al. 1996) Most recently, the cw-647 nm krypton (Immonen et al. 1994, Kivelä et al. 1995) and the cw-670 nm diode (Immonen et al. 1996) have been adopted for CPC.

Laser delivery to the ciliary body

Laser energy can be delivered to the ciliary body by various routes. The laser beam emitted from a slit-lamp delivery system travels through air and through the sclera to reach the target tissue. This so-called

transscleral non-contact method has nowadays mostly been abandoned. The method most widely used today is the transscleral contact method, in which the laser light is delivered via a fibreoptic probe which is placed on the sclera. When circumstances allow for the visualization of the ciliary processes, cyclophotocoagulation can also be performed by delivering laser energy across the plane of the pupil (Kim et al. 1999) or by using an intraocular endolaser with or without an endoscope. (Shields et al. 1985, Pastor et al. 2001)

Scleral transillumination

To achieve ablation of the ciliary processes by transscleral cyclophotocoagulation, it is important to place the laser beam in a correct location over the ciliary body. (Hampton et al. 1988, Allingham et al. 1990, Brancato et al. 1990, Schuman et al. 1991, Bloom et al. 1992, Marsh et al. 1993, Brancato et al. 1994) The site of the ciliary body is not uniform for all eyes, and the position in relation to the limbus may vary with the axial length. (Frieling et al. 1995) Thus, scleral transillumination (Sharkey et al. 1994) is recommended to locate the anterior edge of the ciliary processes. Transillumination is reported to be used routinely in every case deemed to be an important step. (Bloom et al. 1997, Mistlberger et al. 2001, Kirwan et al. 2002) Some surgeons, however, limit the use of scleral transillumination to cases with atypical ciliary body anatomy, such as occurs in congenital glaucoma, or to those with anatomic limbal abnormalities. (Bock et al. 1997, Spencer et al. 1999)

Non-contact CPC

Non-contact Nd:YAG laser CPC is delivered without the use of a contact probe with the patient sitting at the laser slit lamp. A contact lens can be used to blanch the conjunctiva, but no histological difference was found in the ciliary body lesion when a contact lens was used as compared with a treatment without it. (Simmons et al. 1990). The most effective destruction of the pars plicata was achieved with applications located 1 to 1.5 mm behind the limbus (1 mm temporally and nasally and 1.5 mm superiorly and inferiorly), using an energy of 7 to 8 J. (Hampton et al. 1988) Lower IOPs were achieved with fewer retreatments in eyes treated at 1.5 mm instead of 3 mm posterior to the limbus. (Crymes et al. 1989) No substantial difference in the gross appearance of the lesions was noted between the tangential and perpendicular approaches for the same treatment distance. (Hampton et al. 1988)

The treatment guidelines published by Schuman and Puliafito recommend a 360° treatment with 8 applications per quadrant, sparing the 3 o´clock and 9 o´clock positions, with an energy of 8 J, an application time of 20 ms, and maximum offset. (Schuman et al. 1990a) The parameters remain the same for the retreatment, except that the number of applications should be half the previous number. Comparison of initial treatments at 180° and 360° showed that control of IOP was achieved more slowly with the 180-degree treatment, which required more treatment sessions, but that the final IOP results in the two groups were similar. (Hardten et al. 1993)

Contact CPC

The contact probe

Contact CPC is delivered with a fibreoptic probe, which eliminates the problems of aiming and focusing encountered with the non-contact method. The G-probe (Iris Medical Instruments Inc; Mountain View, CA, USA) with a 600 µm fibre, a curved footplate to match the scleral curvature, and a 0.7 mm protrusion of the fibre-optic tip beyond the contact surface indenting the conjunctiva and sclera, and enhancing laser transmission, is widely used for 810 nm diode CPC. (Gaasterland et al. 1992, Kosoko et al. 1996, Bloom et al. 1997, Spencer et al. 1999, Egbert et al. 2001, Mistlberger et al. 2001, Schlote 2001b, Kirwan et al. 2002) The probe is designed so that the distance from the surgical limbus need not be measured. (Mastrobattista et

al. 1996) When the probe is placed at the limbus, the laser beam is directed at a distance of 1.2 mm posterior to the limbus, parallel to the visual axis. (Kosoko et al. 1996) The applications can be spaced at half the width of the 2-mm G-probe tip by aligning the lateral edge of the probe on the centre of the last application. This technique produced burns located in the ciliary processes, as seen in autopsy eyes. (Gaasterland et al. 1992, Feldman et al. 1997)

Brancato et al. published a fibre-optic delivery system with a 365 µm fibre and a contact probe with a 3 mm tip placed tangentially to the corneoscleral limbus, thus centering the laser beam at a predetermined distance of 1.5 mm posteriorly from the limbus. (Brancato et al. 1994) This probe is adapted for both Nd:YAG and 810 nm diode CPC. For Nd:YAG CPC, Bloom et al. used a rounded, 1.5-mm, tipped probe. (Bloom et al. 1992) For CPC with the 647 nm krypton laser, a 1000 µm fibre and a contact probe with a 1200 µm ball tip were used. (Immonen et al. 1994).

Contact Nd:YAG laser CPC

The technique described by Brancato et al. produced well-defined cyclophotocoagulation as shown by histological examinations: the authors recommended that the energy should not be higher than 5 to 6 J. (Brancato et al. 1994) Bloom et al. used 5 J, performed transillumination of the eye to determine the location of the ciliary body, and placed the anterior edge of the laser probe perpendicularly on the sclera to correspond to the anterior edge of the illuminated ciliary body. (Bloom et al. 1992) Histological observations in the same study showed that placing the probe at an angle as little as 15° off the perpendicular led to destruction of less than optimal sites (Bloom et al. 1992) Along with probe orientation and the distance from the limbus, the amount of pressure applied with the contact probe should be kept stable in order to minimize the variation in coagulation intensity and lesion size. (Fankhauser et al. 1992, Echelman et al. 1995)

In contact CPC, less energy is needed than in non-contact laser use. The treatment guidelines published by Schuman and Puliafito recommend a 360° treatment with 8 applications per quadrant, sparing the 3 o´clock and 9 o´clock positions, with a power of 7 W and an application time of 0.7 s. (Schuman et al. 1990a) The parameters for the retreatment remain the same, except that the number of applications should be half of the original number.

Contact 810 nm diode laser CPC

The technique of the contact 810 nm diode laser CPC is similar to that of the contact Nd:YAG laser CPC. (Mastrobattista et al. 1996) Currently used treatment parameters include a power of 1.25 to 3 W, an application time of 1.5 to 2 s and a total of 10 to 40 applications, usually sparing the 3 o´clock and 9 o´clock positions. (Kosoko et al. 1996, Bloom et al. 1997, Spencer et al. 1999, Egbert et al. 2001, Schlote et al. 2001b) It is common to perform 360° treatments, although some authors recommend sparing one or two quadrants of the ciliary body to avoid hypotonia. (Kosoko et al. 1996, Spencer et al. 1999) The number of applications and degrees treated can also be individualized according to each case (Bloom et al. 1997, Yap-Veloso et al. 1998) The parameters and the extent of treatment may remain the same or may be reduced for the retreatment (Bloom et al. 1997, Yap-Veloso et al. 1998), or a different 90° from that in the initial treatment is left untreated. (Spencer et al. 1999)

Contact Red Laser CPC

The protocol of the contact red laser CPC is described in detail in this book in the Methods -section on page 32.

Laser transmission and absorption

The effect of CPC depends on the absorption of the transmitted laser energy by the melanin granules, which are highly concentrated in the pigment epithelium of the ciliary body (Beckman et al. 1972, Cantor et al. 1989, Schubert et al. 1989b) The energy absorbed is degraded into heat, which leads to thermal damage resulting in the denaturation of proteins and inactivation of enzymes. (Vassiliadis 1989)

Transscleral irradiation must travel through the conjunctiva, the sclera, and the highly vascularized ciliary muscle before reaching the ciliary pigment epithelium. When the laser wavelength is well transmitted and at the same time effectively absorbed by the ciliary pigment epithelium, the desired interactions can be obtained at the target site with minimal effects elsewhere. (Vassiliadis 1989) When the sclera is thinned pathologically, transmission is better and will result in exaggerated effects and vice versa. (Rol et al. 1990, Kirwan et al. 2002)

Absorption of laser energy by melanin takes place in pigmented cells, which are found particularly on the inner scleral surface (lamina fusca) (Vogel et al. 1991), by the melanin in the pigmented lesions in the conjunctiva, by the melanin dispersed throughout the ciliary muscle, and by the melanin in the ciliary body pigment epithelium. (Nemati et al. 1996). The role of tissue pigmentation in cyclodestruction was demonstrated both experimentally and in enucleated human eyes previously treated with cyclophotocoagulation. (Cantor et al. 1989, Ferry et al. 1995) No visible histopathological effect was detected after non-contact pulsed Nd:YAG CPC in albino rabbit eyes where there was minimal or no pigmentation of the ciliary body stroma or ciliary epithelium. (Cantor et al. 1989) In contrast, in Dutch-belted rabbit eyes, where there was heavy pigmentation of both the ciliary body stroma and pigmented ciliary epithelium, there was marked destruction of the ciliary body after CPC performed at similar energies in the same study.

With an increase in laser wavelength, transmission through the sclera increases and scleral scattering decreases (Figure 1). (Rol et al. 1990, Vogel et al. 1991) If contact application is used and pressure is applied to the sclera by the fibre-optic probe, scleral transmission is increased and scleral scattering is reduced (Figure 2). (Rol et al. 1990, Vogel et al. 1991) The absorption of laser energy by melanin decreases with increasing wavelength in the infrared region (Figure 3). (Vassiliadis et al. 1989) The lasers with better absorption by the pigment epithelium produce more cyclodestruction at similar power settings, despite their poorer scleral transmission, as compared with those more efficiently transmitted but less efficiently absorbed. (Assia et al. 1991, Brancato et al. 1991, Immonen et al. 1993)

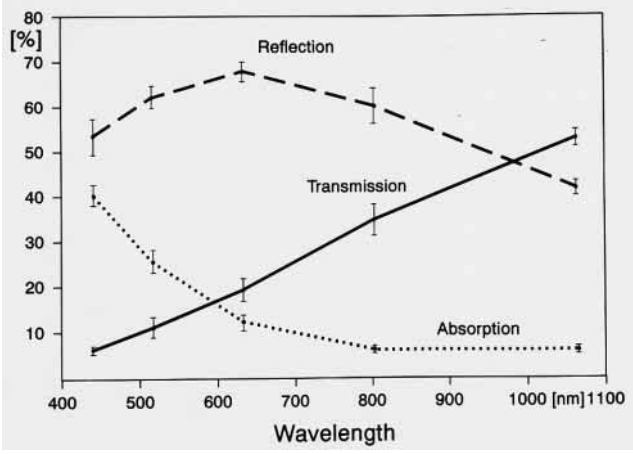

Figure 1. Total reflection, absorption, and transmission of the human sclera, plotted as a function of laser wavelength. The error bars represent the standard deviation of the measurement values. (From: Vogel et al. Optical properties of human sclera, and their consequences for transscleral laser applications. Lasers Surg Med 1991;11:334.)

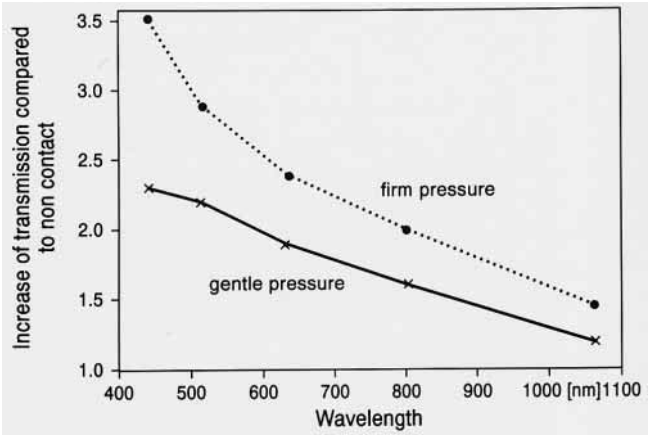

Figure 2. Ratio of the scleral transmission values with and without fibre contact, plotted as a function of laser wavelength. The ratio was determined for gentle and firm pressure of the fibre tip against the scleral surface. (From: Vogel et al. Optical properties of human sclera, and their consequences for transscleral laser applications. Lasers Surg Med 1991;11:334.)

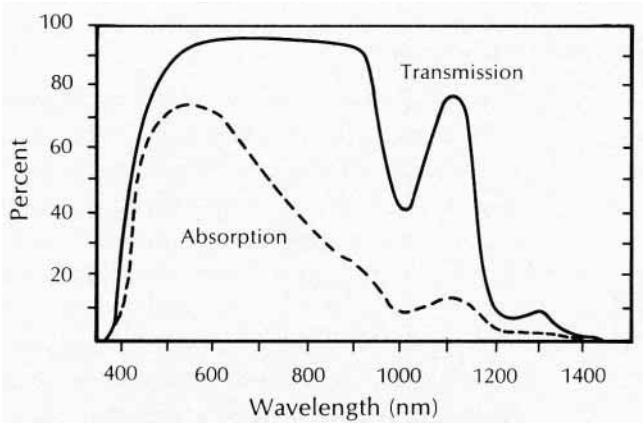

Figure 3. Ocular media transmission and absorption of the retinal pigment epithelium and choroid. (From: Vassiliadis A. Laser sources and ocular effects. In: L´Esperance FA. Ophthalmic Lasers, 3rd ed. St.Louis: C.V. Mosby Company, 1989.)

Mechanisms of IOP decrease

The accepted aim of CPC is ablation of the epithelium of the ciliary processes in the pars plicata of the ciliary body to reduce the production of aqueous humour.(Beckman et al. 1972, Schuman et al. 1990a, Liu et al. 1994, Stewart et al. 1996). However, transscleral and transpupillary photocoagulation of the pars plana or an even more posterior site was also shown to decrease the IOP in the rabbit, the monkey, and the human eye (Schiødte 1982, Schubert et al. 1989a, Liu et al. 1994) Non-contact Nd:YAG laser photocoagulation of the pars plana increased the outflow in enucleated human and porcine eyes, which was considered to relate to the pars plana transscleral outflow, facilitated by disruption of the neuroepithelial barrier. (Schubert et al. 1990) In monkeys, coagulation of the pars plana with the contact Nd:YAG laser resulted in enhancement of uveoscleral outflow, which was not demonstrable after pars plicata coagulation in the same study. (Liu et al. 1994) The increase in the outflow facility after cyclocryocoagulation supports the view that non-conventional outflow pathways are increased after cyclodestruction. (Duy et al. 1987)

In the monkey eye, contact Nd:YAG laser photocoagulation at the equator produced a decrease in IOP which was closely related to the breakdown of the blood-ocular barrier observed as flare (Schubert et al.

1989a), and contact Nd:YAG CPC either in the pars plicata or in the pars plana produced a significant decrease in IOP corresponding to the degree of inflammation in the anterior chamber. (Liu et al. 1994) Inflammatory mediators such as prostaglandin $F_{2\alpha}$ enhance aqueous drainage via the uveoscleral pathway (Crawford et al. 1987) and are currently also adopted for therapeutic use in glaucoma.

The alteration of ciliary body vascularization demonstrated after contact 810 nm diode laser CPC probably acts as a synergistic mechanism for decreasing IOP. (Pablo et al. 1997, Schlote et al. 2001a)

Morphological changes observed in the ciliary body epithelium, the stroma and the ciliary body vasculature

The Nd:YAG laser

With pulsed Nd:YAG CPC, energy levels ranging from 4.4 to 9 J were effective in producing appropriate lesions in the ciliary body. A blister-like elevation of the ciliary epithelium was described early after treatment. (Devenyi et al. 1987, Hampton et al. 1988, Blasini et al. 1990, Ferry et al. 1995) Destruction of the non-pigmented and pigmented epithelium was seen and the pigmented epithelium was more vulnerable to laser energy. (Marsh et al. 1993, Ferry 1995 et al.) In the peripheral zones of individual treatment sites, the epithelium lining the crests of the ciliary processes survived the treatment, in contrast to the valleys between the crests. Hyperplasia of the non-pigmented epithelium occurred later. (Marsh et al. 1993) Occlusion of the capillaries of the ciliary processes was also detected. (Marsh et al. 1993)

A videographic recording technique and light microscopy were used in a study comparing tissue responses to three Nd:YAG lasers with different durations of exposure, modes of laser, and various energy levels: a pulsed contact laser with a duration of 0.75 ms; a pulsed non-contact laser with a duration of 20 ms; and a continuous-wave contact laser with durations of 700 and 2000 ms. (Prum et al. 1992) Both pulsed lasers caused mild whitening of the pigment epithelium with frequent vapourization and explosive tissue disintegration, typically most marked with the 0.75-ms pulsed laser. In contrast, the continuous-wave laser produced prominent tissue whitening and puckering, seen histologically as convolution of the epithelium and coagulation of the stroma, called a shrinkage-like lesion. (Prum et al. 1992)

The 810 nm diode laser

In gross examination of human cadaver eyes, the transscleral non-contact 810 nm diode laser caused homogeneous blanching of the ciliary processes and ciliary body shrinkage at an energy of 1.2 J. (Hennis et al. 1991) Using a transscleral contact technique, the 818 nm or the 850 nm diode laser produced no visible damage to the ciliary body at exposures of less than 2 J in human autopsy eyes. (Schuman et al. 1991) A 2 to 3 J exposure produced mild whitening and 4 to 5 J exposures more intense whitening of the pars plicata. Energies higher than 5 J frequently produced explosive tissue damage. (Schuman et al. 1991) With the use of ultrasound in living eyes, detachment of the ciliary body was observed in the early postoperative period. (Werner et al. 1998)

Microscopically, transscleral contact 810 nm diode CPC at an energy level of 3.9 and 5.2 J resulted in moderate thermal damage to the ciliary body and coagulative necrosis of the ciliary pigmented and unpigmented epithelial layers in a human eye treated shortly before a planned enucleation. (Brancato et al. 1994) At 7.8 J of energy, wide disorganization of the ciliary processes and marked thermal coagulation of the ciliary body bulk with vacuolization and swelling of collagen fibres were noted. (Brancato et al. 1994) With the contact 818 nm and the 850 nm diode CPCs, evidence of thermal coagulation of the ciliary body stroma and stromal vasculature was found and coagulation necrosis was more intense with longer exposure times. (Schuman et al. 1991) At 4 to 5 J, disruption of the pigmented and non-pigmented epithelium and intense coagulation of the ciliary body stroma were seen. Marked rarefication in the capillary network within the treatment areas in the pars plicata and pars plana was demonstrated using vascular casts in the rabbit after

transscleral contact 810 nm diode laser. (Schlote et al. 2001a) Thermal coagulation of the stromal vasculature was also histologically evident in the rabbit after transscleral contact 810 nm diode laser. (Pablo et al. 1997)

During continuous-wave laser application, an audible pop is produced when the threshold between coagulation and explosive tissue disintegration is exceeded, representing an intraocular uveal micro-explosion. (Prum et al. 1992) Audible pops are associated with more severe postoperative inflammation and increased risk of postoperative hyphema. (Rebolleda et al. 1998) Investigations concerning dosage problems of transscleral CPC aim at finding a more suitable clinical method for evaluating the amount of laser-induced tissue destruction. (Preußner et al. 1997, Rosenow et al. 1999)

The Visible Red Lasers

The transscleral contact 647 nm krypton laser at 0.25 to 0.5 J in the rabbit eye produced thinning of the pigmented and non-pigmented layers of the ciliary body and some extracellular dispersion of pigment granules. (Immonen et al. 1993) At higher energies in the same study, more widespread destruction was detected, with occasional bleeding under the ciliary body. These findings were similar to the continuous-wave Nd:YAG lesions at approximately double the energy in the same study. Autopsy findings in an eye treated with the transscleral contact 647 nm krypton laser CPC at 3.7 J (power 0.37 W and duration of application 10 s) showed confluent scars straddling the posterior pars plicata and the anterior pars plana, and the posterior processes had totally disappeared. (Kivelä et al. 1995) Dispersed pigment engulfed by clumplike cells was abundant within the subepithelial stroma.

The transscleral contact 670 nm diode laser in the rabbit eye at 0.5 to 1 J (0.2 W, 2.5 and 5 s, respectively) produced grey discoloration of the ciliary body epithelium with some shrinkage of the ciliary processes. (Immonen et al. 1996) Histological examination demonstrated the disappearance of the non-pigmented and pigmented epithelium and pigment dispersion in the photocoagulated areas. The histological changes observed recently after use of a clinical 670 nm diode laser CPC at 4.3 J (power 0.43 W and duration of application 10 s) in a human eye are essentially identical to those decribed after use of a clinical transscleral contact 647 nm krypton laser CPC at 3.7 J. (Kivelä et al. 1995, Tarkkanen 2001, personal communication, to be published)

Morphological changes observed elsewhere

The conjunctiva

In the conjunctiva, white lesions that fade within 24 to 48 hours appear at the site of laser application after the use of the clinical non-contact Nd:YAG CPC (Schuman et al. 1990a, Shields et al. 1994). With use of the contact lens, these conjunctival burns are smaller and tissue disruption is rare. (Shields et al. 1994) Following contact Nd:YAG CPC, the treated eye generally shows less conjunctival coagulation. (Schuman et al. 1990a) Mild burns on the conjunctival surface resolving 24 hours to one week after treatment are described after contact 810 nm diode CPC. (Kosoko et al. 1996, Bloom et al. 1997, Gupta et al. 1997, Schlote et al. 2001b, Kirwan et al. 2002) No signs of conjunctival burns were seen after transscleral contact 647 nm krypton CPC. (Immonen et al. 1994)

The sclera

Scleral reactions have been produced at energies above those producing a desired effect in the ciliary body epithelium in experimental cyclophotocoagulation in cadaver eyes (Schuman et al. 1991), in a human eye that was soon to be enucleated (Brancato et al. 1994), and in the rabbit eye. (Immonen et al. 1993) Heat-induced homogenization of the scleral lamellae near the damaged ciliary body occurred after both contact transscleral Nd:YAG and contact transscleral 810 nm diode laser treatment at 6.6 J, an amount of energy

above the recommended level. (Brancato et al. 1994) Superficial scleral damage was observed after contact transscleral 818 nm and 850 nm diode laser treatment at a high energy of 8 J. (Schuman et al. 1991) In the rabbit, with a thinner sclera than that of the human eye, the 810 nm diode laser, with a lower energy of 1.8 J per application, produced scleral coagulation at the treatment site. (Pablo et al. 1997) After the transscleral contact 647 nm krypton and the cw-Nd:YAG CPC in rabbits, oedema and cell infiltrates were detected in the sclera at the site of the lesions produced by energies above 1 J. (Immonen et al. 1993) Defocusing the non-contact pulsed Nd:YAG laser progressively less than the maximum of 9 was associated with progressively greater tissue disruption on the external surface of the sclera. (Hampton et al. 1988)

After a failed clinical non-contact pulsed Nd:YAG CPC, (Marsh et al. 1993) and a failed clinical contact 810 nm diode CPC, (Walland et al. 1998), no evidence of scleral damage was present on examination of enucleated eyes. In a larger histopathological series of nine eyes treated with contact 810 nm diode CPC, scleral scarring was detected in three eyes. (McKelvie et al. 2002) Focal areas of oedema in the deep sclera were observed in one study of eyes enucleated after non-contact pulsed Nd:YAG CPC. (Ferry et al. 1995) In a previously treated human autopsy eye, the krypton laser was shown to produce clinically efficient cyclophotocoagulation without histopathological scleral damage. (Kivelä et al. 1995)

Clinically, focal scleral thinning was detected in a 30-year-old patient treated with the non-contact Nd:YAG laser CPC. (Fiore et al. 1989) More recently, scleral perforation was reported after 810 nm contact CPC in an eye with scleral thinning following cataract surgery. (Sabri et al. 1999) Further, scleral staphyloma developed in an eye with a previous posterior pole choroidal melanoma, and focal thinning of the sclera was noted in a previous sclerotomy site after 810 nm contact CPC. (Bhola et al. 2001)

The ciliary muscle

The ciliary muscle and the inner connective tissue layer of the ciliary body were markedly atrophic in an autopsy eye previously treated with transscleral contact 647 nm krypton laser CPC. (Kivelä et al. 1995) Loss of some of the inner layers of the ciliary muscle also developed after clinical non-contact pulsed Nd:YAG CPC, but there was a moderate amount of haemorrhage within the central layers of the ciliary muscle. (Marsh et al. 1993) In another study of eyes enucleated after non-contact pulsed Nd:YAG CPC, the ciliary muscle was always severely damaged. (Ferry et al. 1995)

When the tissue responses of the cw contact Nd:YAG laser and the cw contact 810 nm diode laser were videographically and histologically compared, the Nd:YAG produced coagulation and disruption of the ciliary epithelium and little effect on the underlying ciliary muscle, whereas the 810 nm diode laser had less effect on the ciliary epithelium but caused a significant coagulative response in the ciliary muscle. (Simmons et al. 1994) However, the laser power was 2 to 3 times higher in the Nd:YAG-treated eyes, although a similar application time of 2 seconds was used in both laser modalities. In enucleated eyes that had been previously treated with the 810 nm diode CPC, the ciliary muscle was extensively destroyed. (McKelvie et al. 2002)

The iris, the lens, the intraocular lens and the zonules

The peripheral iris was affected, when tangentially or perpendicularly oriented non-contact pulsed Nd:YAG at 4 to 8 J was performed at 0.5 mm from the limbus in human autopsy eyes. (Hampton et al. 1988) When contact 818 nm and 850 nm diode CPC at 2.7 J were performed in human cadaver eyes, placing the probe perpendicularly with its anterior edge 0.5 mm posterior to the limbus, focal disruption of the posterior pigment epithelium of the peripheral iris resulted. (Schuman et al. 1991) In this position, exposure times of 3 seconds or longer produced an iridectomy with focal disruption of the lens capsule. Clinically, anterior displacement of the laser beam can result in peripheral iris damage (McKelvie et al. 2002) and subsequent pupillary distorsion. (Schlote et al. 2000, Bhola et al. 2001) These observations further emphasize the importance of careful orientation and location of the ciliary processes with scleral transillumination.

In contrast, no significant thermal effect at the intraocular lens (IOL) haptic or the capsular bag in pseudophakic eyes or on the crystalline lens in phakic eyes was seen in cadaver eyes when a 780 to 830 nm

non-contact diode laser was applied perpendicularly at 0.5, 1, or 2 mm from the limbus. (Hennis et al. 1991). In that study, the power used was 1.0 to 1.2 W and the pulse duration 0.7 to 1.0 s, resulting in a low total energy of 0.7 to 1.2 J. In two experimental studies of noncontact Nd:YAG CPC, IOL haptic damage occurred only at the maximum energy of 8.8 J delivered 1 mm posterior to the limbus (Blomquist et al. 1990, Assia et al. 1991) The krypton CPC with its long duration of 10 s and power of 0.37 W, performed on the ciliary processes at approximately 2 mm from the limbus as determined by transillumination, produced no damage to the lens, the iris, the anteriormost ciliary processes or the adjacent zonules. (Kivelä et al. 1995)

Sympathetic ophthalmia

There are few occasional case reports of sympathetic ophthalmia after non-contact and contact Nd:YAG CPC in the literature. (Edward et al. 1989, Brown et al. 1990, Lam et al. 1992, Pastor et al. 1993, Bechrakis et al. 1994) However, in all the reported cases with histological confirmation of sympathetic ophthalmia, the exciting eye had previously undergone incisional surgery (trabeculectomy or cataract extraction) or cyclocryocoagulation, all of which are possible exciting events triggering sympathetic ophthalmia. (Sabates 1988, Minckler 1989)

The retina

Retinal detachment was reported in one adult patient after non-contact Nd:YAG CPC. (Geyer et al. 1993) However, two cyclocryocoagulations had already been performed previously in this eye. In children, retinal detachment and subsequent phthisis in the majority of the same cases were discovered in 4% to 10% of eyes after contact Nd:YAG CPC (Phelan et al. 1995) and 810 nm diode CPC. (Bock et al. 1997, Izgi et al. 2001, Kirwan et al. 2002)

Mechanisms of treatment failure

Ciliary epithelial regeneration, reversal of increased uveoscleral outflow, reversal of inflammation, and revascularization of the ciliary body (van der Zypen et al. 1989, Schlote et al. 2001a) have been investigated in order to explain the gradual recovery of IOP in a proportion of the patients treated with CPC.

Moderate hyperplasia of the non-pigmented and pigmented ciliary epithelium was noted in an eye enucleated 8 weeks after a failed non-contact pulsed Nd:YAG CPC. (Marsh 1993) In the treatment areas, the epithelium was spindle-shaped and multilayered.

Evidence of epithelial regeneration was found in one eye studied by Walland et al., who examined two eyes enucleated after a previous failed contact 810 nm diode laser CPC. (Walland et al. 1998) The regenerated epithelium was presumed from its appearance to be nonfunctional, and no histological explanation for the rise in IOP was provided. In one of these eyes, the laser was delivered too posteriorly, and the short-lived IOP reduction probably represented the reversal of an early increase in uveoscleral outflow. (Walland et al. 1998)

Examination of vascular casts of the rabbit ciliary body 12 weeks after contact 810 nm diode CPC showed short vessel sprouts at the margins of the laser burns in the pars plana and the pars plicata. (Schlote et al. 2001a) With a similar technique, regeneration of the capillary network was observed seven months after Nd:YAG CPC in the rabbit eye, but regeneration was mostly incomplete (van der Zypen et al. 1989). Further studies are needed to investigate the vascular regeneration process during longer periods of observation. (Schlote et al. 2001a)

Clinical outcome of cyclophotocoagulation

Heterogeneous glaucoma population

In unselected glaucoma patients after the 810 nm diode laser CPC, success rates of 48% to 85% have been obtained (Table 1). (Kosoko et al. 1996, Bloom et al. 1997, Wong 1997 et al. Werner et al. 1998, Yap-Veloso et al. 1998, Spencer et al. 1999, Threlkeld et al. 1999, Mistlberger et al. 2001, Schlote et al. 2001b) Comparable success rates (71% to 87%) have been reported after operations with a glaucoma drainage device performed in similar patients with glaucoma. (Airaksinen et al. 1990, Noureddin et al. 1992, Lloyd et al. 1994, Välimäki et al. 1998, Krishna et al. 2001) With the Nd:YAG CPC, performed with either the non-contact or the contact method, the success rate was 39% to 79% (Brancato et al. 1989, Hampton et al. 1990, Schuman et al. 1992, Al-Ghamdi et al. 1993, Hawkins et al. 1993). With the contact krypton CPC, success was achieved in 73% of eyes. (Immonen et al. 1994)

Hypotonia rates of 0% to 15%, (Brancato et al. 1989, Schuman et al. 1990c, Al-Ghamdi et al. 1993, Shields et al. 1994) and rates of phthisis bulbi from 0% to 11% have been reported after Nd:YAG CPC. (Trope et al. 1990, Schuman et al. 1992, Shields et al. 1994, Baez et al. 1994, Dickens et al. 1995, Zhou Wei et al. 1996) After 810 nm diode laser CPC, hypotonia was reported in 0% to 15% and phthisis in 0% to 2%. (Hawkins et al. 1993, Kosoko et al. 1996, Werner et al. 1998, Yap-Veloso et al. 1998, Youn et al. 1998, Spencer et al. 1999, Threlkeld et al. 1999, Walland 2000, Schlote et al. 2001b) After glaucoma implant surgery, 0% to 6% developed phthisis. (Lloyd et al. 1992, Noureddin et al. 1992, Lloyd et al. 1994, Krishna et al. 2001)

Visual acuity decreased in 7% to 65% of eyes after Nd:YAG CPC. (Trope et al. 1990, Schuman et al. 1992, Al-Ghamdi et al. 1993, Baez et al. 1994, Shields et al. 1994, Dickens et al. 1995, Zhou Wei et al. 1996, Youn et al. 1998) After 810 nm diode CPC, similarly, 18.7% to 38% lost vision (Youn et al. 1998, Yap-Veloso et al. 1998, Spencer et al. 1999, Threlkeld et al. 1999, Mistlberger et al. 2001b) After implant surgery, visual deterioration occurred in 24% to 38% of patients. (Airaksinen et al. 1990, Lloyd et al. 1994, Välimäki et al. 1998)

Posttraumatic glaucoma

When needed in addition to medical therapy, filtering procedures (Mermoud et al. 1996) and glaucoma implant operations (Välimäki et al. 1998) are less frequently successful in patients with angle-recession glaucoma than in those with chronic open-angle glaucoma. Posttraumatic conjunctival and scleral abnormalities may even prevent incisional surgical procedures. (Mermoud et al. 1993a, Mermoud et al. 1993b) In filtration surgery without antimetabolites, the cumulative probability of survival of the IOP was 52% at 1 year, 32% at 3 years, and 8% at 5 years in angle-recession glaucoma in contrast to 89%, 84% and 76% in primary open-angle glaucoma, respectively. (Mermoud et al. 1993a)

Trabeculectomy with antimetabolites resulted in more successful cases at 3 and 6 months in angle-recession glaucoma than trabeculectomy without antimetabolites or Molteno implantation. (Mermoud et al. 1993b) However, severe bleb-associated complications occurred in 15% of patients treated with 5-fluorouracil or mitomycin C. (Mermoud et al. 1993b)

In previously published series of cyclophotocoagulation, the proportion of eyes with posttraumatic glaucoma has ranged from 0% to 15%. (Hampton et al. 1990, Schuman et al. 1992, Hawkins et al. 1993, Al-Ghamdi et al. 1993, Baez et al. 1994, Immonen et al. 1994, Shields et al. 1994, Brancato et al. 1995, Bloom et al. 1997, Wong et al. 1997, Kosoko et al. 1996, Zhou Wei et al. 1996, Werner et al. 1998, Spencer et al. 1999, Therkeld et al. 1999, Schlote et al. 2001b). The published success rate in heterogeneous glaucoma populations after CPC has ranged from 39% to 85%. (Brancato et al. 1989, Hampton et al. 1990, Schuman et al. 1992, Hawkins et al. 1993, Al-Ghamdi et al. 1993, Immonen et al. 1994, Brancato et al. 1995, Bloom et al. 1997, Wong et al. 1997, Werner et al. 1998, Spencer et al. 1999, Therkeld et al. 1999, Schlote et al. 2001b)

Author, year, reference number	n	Laser modality	Contact/ non-contact (c/nc)	Power/ spot (W)	Application time (s)	Mean/ median follow-up (months)	IOP limit of success (mmHg)	IOP success	Reduction in mean IOP	Definition and rate of visual decrease	Hypotonia	Phthisis
Hampton et al 1990	106	fr-YAG	nc	350-400	0.02	11	7-20	51 %		47% (def.2)	9 %	
Trope and Ma 1990*	28	fr-YAG	nc	90-225	0.02	21.9	< 21	62.5 %	58 %	65 % (def 001)		10.7 %
Baez et al 1994	128	fr-YAG	nc	250-350	0.02	36.9			56 %			0 %
Shields et al 1994	500	fr-YAG	nc	200-400	0.02	24			65%**	46% (def.1)	8 %	0.1 %
Dickens et al 1995	173	fr-YAG	nc	mean.360	0.02	30.5	< 23	65 %	51 %	40 % (def.1)		6.9 %
Youn 1996	479	fr-YAG	nc	200-400	0.02	22				39.5 % (def.1)	8 %	
Schuman et al 1992	116	cw-YAG	c	7-9	0.7	19	3-22	39 %	54.8 %	47 % (def.01)	8%*****	
Kosoko et al 1996	27	810 diode	c	1.5-2.0	2	17.9	< 23****	52 %	44 %	30 % (def.01)	4 %	0 %
Bloom et al 1997	210	810 diode	c	1.5	1.5	10	< 22	66 %	41 %	29 % (def.001)	1 %	0.5%
Wong 1997	33	810 diode	c	1.8-2.0	0.3-0.5	9.4	2-21	48 %	40 %	24% (def.?)		0 %
Werner et al 1998	106	810 diode	c	1.4-1.8	2	15.3			28 %		0 %	0 %
Yap-Veloso et al 1998	43	810 diode	c	1.4-2.75	2	10	< 22***	68 %	52 %	22% (def.01)		2 %
Spencer et al 1999	58	810 diode	c	2	2	16.8			65.6 %			0 %
Threlkeld et al1999	47	810 diode	c	1.5-2.5	2	9	< 21	81 %	58 %	38% (def.1)	15 %	
Immonen et al 1994	57	krypton	c	0.4-0.5	10	6	8-24	73 %	45 %		2 %	0 %
Brancato et al 1989	23	cw-YAG	c	4.0	0.5	8.6	< 26	66.6 %		13 % (def.?)	0 %	0 %
Schuman et al 1990c	140	cw-YAG	c	7-9	0.7	3.2	5-22	59 %	39 %	7 % (def.01)	3 %	
Al-Ghamdi et al 1993	47	fr-YAG	nc			13	< 26	79 %		8 % (def.1)	15 %	
Mistlberger et al 2001	206	810 diode	c	1.75-3.0	2	9.2	< 23	73 %	40 %	18.7% (def. 01)		1.9 %

* No retreatments in eyes that were initially well controlled

** Mean final IOP reduction

*** IOP < 22 mmHg and reduction in IOP of 20% or more

**** IOP < 23 mmHg or reduction in IOP of 20% or more, cumulative probability of IOP success at 2 years

***** Hypotonous or phthisical

def. 001 VA decrease of 1 or more Snellen lines

def. 01 VA decrease of more than 1 Snellen line

def.1 VA decrease of more than 1 Snellen line or a change in low-vision category

Table 1. Reviewed data published on transscleral cyclophotocoagulation in heterogeneous glaucoma populations.

In most studies of CPC, detailed information on the few posttraumatic patients included is limited. According to the available data, IOP success after CPC tends to be lower in the refractory posttraumatic glaucoma population than in an average glaucoma population. (Baez et al. 1994, Bloom et al. 1997, Schlote et al. 2001)

Glaucoma in children and young adults

In previously published series of CPC in young patients, Bock et al. reported a success rate of 50% in young patients treated with a transscleral contact 810 nm diode laser. (Bock et al. 1997) Phelan and Higginbotham also achieved a success rate of 50% in paediatric glaucoma patients treated with transscleral contact Nd:YAG laser CPC. (Phelan et al. 1995) Izgi et al. had an IOP success rate of 78% in paediatric glaucoma patients after 810 nm diode CPC. (Izgi et al. 2001) In a similar but larger study (n=77) published recently, Kirwan et al. reported IOP success in 72% 1 year and in 51% two years after 810 nm diode CPC. (Kirwan et al. 2001) In most previous reports on CPC, paediatric patients were not analysed separately from adult patients.

Phthisis was reported in 0% (Izgi et al. 2001), 4% (Kirwan et al. 2002), and 5% (Bock et al. 1997) of eyes using a 810 nm contact diode laser, and in 10% (Phelan et al. 1995) of eyes using a contact Nd:YAG laser. Bock et al. noted a decline in vision in 18% of eyes and Phelan and Higginbotham in 40%. (Bock et al. 1997, Phelan et al. 1995) Izgi et al. found no VA decrease after CPC in paediatric eyes, most patients representing other than the refractory secondary glaucomas, as in the study by Kirwan et al., in which 8% lost vision after CPC. (Izgi et al. 2001, Kirwan et al. 2002)

As shown in Table 2, the success rates obtained after CPC are in the same range as those obtained with other surgical treatment modalities in unselected paediatric populations.

Author	Reference number	n	Glaucoma subtype	Patient age (years)	Surgical method	Length of follow-up (mean, months)	Definition of IOP success (mmHg)	Success rate
Beauchamp et al 1979	2	22	prim. and sec.	0.8 - 20	TRE	18	< 25	50 %
Sturmer et al 1993	11	113	prim. and sec.	11 - 49 **	TRE	38	< 22	54 %
Mandal et al 1997	4	19	mainly prim.	0.7 - 18	TREcM	20	< 21	95 %
Al-Hazmi et al 1998	5	150/254*	98% prim. cong.	2 - 7	TREcM	> 12	> 3, < 21	39 %
Susanna et al 1995	24	98	mainly prim. cong.	1 - 30	TREcM	15	> 4, < 22	67 %***
Beck et al 1998	25	60	mainly sec.	0.1 - 17	TREcM	30	< 22	60 %
Munoz et al 1991	26	53	inf.	< 12	Molteno	18	< 22	68 %
Hill et al 1991	27	65	inf. and sec.	< 21	Molteno	23	< 22	62 %
Eid et al 1997a	28	18	mainly sec.	< 18	Tube-shunt	> 24	> 6, < 22	44%****
Lloyd et al 1992	29	16/96*	prim. and sec.	< 13	Molteno	49	> 5, < 22	56%*****

*The number of children treated versus the number of all eyes in the study.
**No difference in treatment success according to the age of the patients.
***All patients, success positively correlated with increasing age.
****After revision operations
*****After second plate implantation

prim. = primary
sec. = secondary
cong. = congenital
inf. = infantile

TRE = trabeculectomy
TREcM = trabeculectomy with Mitomycin C

Table 2. Reviewed data published on filtration and implant glaucoma surgery in young patients.

Neovascular glaucoma

In neovascular glaucoma, filtering procedures with or without antimetabolites, glaucoma implant operations, implant operations combined with pars plana vitrectomy (Sinclair et al. 1982, Mincler et al. 1988, Lloyd et al. 1991, Mermoud et al. 1993b, Tsai et al. 1995, Eid 1997b, Scott et al. 2000), and CPC have all been used. (Hampton et al. 1990, Trope et al. 1990, Schuman et al. 1992, Baez et al. 1994, Immonen 1994 et al., Seah et al. 1994, Shields et al. 1994, Tsai et al. 1996, Youn et al. 1996, Bloom et al. 1997, Di Staso et al. 1997, Eid et al. 1997b, Oguri et al. 1998, Youn et al. 1998, Yap-Veloso et al. 1998, Spencer et al. 1999, Threlkeld et al. 1999) Filtration surgery has little chance of success unless the stimulus for new vessel formation is eliminated. (Wand 1996) After retinal panphotocoagulation, regression of inflammation and of iris neovascularization takes 3 to 4 weeks. (Wand 1996)

In the published studies of CPC, the IOP success rates have ranged from 33% to 86% (Table 3). In most of these studies it was not stated whether iris neovascularization was brought to halt. Comparable success rates (35% to 67%) were reported in studies of filtration and implant surgery in neovascular glaucoma (Table 4). (Allen et al. 1982, Minckler et al. 1988, Lloyd et al. 1991, Mermoud et al. 1993, Tsai et al. 1995)

The decrease in VA after Nd:YAG CPC was shown to be high in eyes with neovascular glaucoma, partly as a result of hypotonia and phthisis. With the contact or non-contact Nd:YAG CPC, phthisis bulbi of up to 19%, and visual loss of up to 56% have been reported in neovascular glaucoma (Table 3) (Hampton et al. 1990, Trope et al. 1990, Schuman et al. 1992, Shields et al. 1994, Youn et al. 1996) VA decreased in 24% in a study of 810 nm diode CPC (Oguri et al. 1998). Studies on filtration and implant surgery in neovascular glaucoma also show a high incidence of visual decrease, of up to 62%, and of phthisis, of up to 24%. (Table 4) (Allen et al. 1982, Minckler et al. 1988, Lloyd et al. 1991, Mermoud et al. 1993c, Tsai et al. 1995)

Corneal complications after cyclophotocoagulation

Several corneal complications have been described in the literature after cyclophotocoagulation with a Nd:YAG or a 810 nm diode laser. They include corneal burns, corneal decompensation, epithelial defects, bacterial ulcers, neurotrophic ulcers, band keratopathy, corneal graft failure, or an ulcer at a corneal graft. (Baez et al. 1994, Dickens et al. 1995, Flaxel et al. 1997, Ayyala et al. 1998, Johnson et al. 1998, Walland et al. 1998, Yap-Veloso et al. 1998, Jennings et al. 1999) Corneal complications are especially likely to occur in patients with predisposing ocular conditions, such as neovascular glaucoma in patients with diabetes or after central retinal vein occlusion, preoperative epithelial oedema or dystrophic calcification of the cornea, a corneal graft, or chronic ocular inflammation. (Flaxel et al. 1997, Ayyala et al. 1998, Johnson et al. 1998, Walland et al. 1998, Yap-Veloso et al. 1998)

Corneal nutrition, surface maintenance and repair are dependent on healthy sensory innervation. (Beuerman et al. 1980, Beck et al. 1992) Sensory denervation may lead to punctate neurotrophic keratitis or even widespread corneal epithelial detachment. (Beck et al. 1992) In transscleral treatments in the ciliary region, the long posterior ciliary nerves lying in the suprachoroidal space and conducting sensory impulses from the cornea (Müller et al. 1997) are susceptible to damage. (Bietti 1972, Wener et al. 1973, Martin et al. 1988) After 810 nm diode laser CPC, Johnson et al. found qualitative changes in the structure of the nerve fibres by transmission electron microscopy in a rabbit model: the 810 nm diode laser CPC appeared to cause disruption of the myelin nerve sheaths, and damaged keratocytes were also observed in the tissue samples. (Johnson et al. 1999) They did not find any quantitative histological changes in corneal nerve density.

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Table 3. Reviewed data published on transscleral cyclophotocoagulation in neovascular glaucoma.

Author, year, reference number	n*	Laser modality	Contact/ non-contact (c/nc)	Power/ spot (W)	Application time (s)	Mean/ median follow-up (months)	IOP limit of success (mmHg)	IOP success	Reduction in mean IOP	Definition and rate of visual decrease	Hypotonia	Phthisis
Hampton et al 1990	27/106	fr-YAG	nc	350-400	0.02	11				38% (def.2)		
Trope and Ma 1990**	16/28	fr-YAG	nc	90-225	0.02	21.9	< 21	62.5 %				19 %
Baez et al 1994	12/128	fr-YAG	nc	250-350	0.02	36.9			56 %			0 %
Shields and Shields 1994	130/500	fr-YAG	nc	200-400	0.02	24			65%***	46% (def.1)		
Youn et al 1996	119/479	fr-YAG	nc	200-400	0.02	22				49.6 % (def.1)		
Oguri et al 1998	**9**	fr-YAG	nc	350	0.02	26.4	< 23	56 %		56% (def.2)		0 %
Youn et al 1998	18/95	fr-YAG	nc	260-390	0.02	10.4						
Schuman et al 1992	26/116	cw-YAG	c	7-9	0.7	19	3-22	39 %	54.8 %		19 %	
Seah et al 1994	8/16	cw-YAG	c	8	0.2-0.5	9.8				50% (def.3)	0 %	0 %
Oguri et al 1998****	**5**	cw-YAG	nc	7	1.5	16.8	< 23	33 %		44% (def.1)		11 %
Oguri et al 1998****	**4**	cw-YAG	c	4	1		< 23					
Bloom et al 1997	25/210	810 diode	c	1.5	1.5	10			53 %			0 %
Oguri et al 1998	**21**	810 diode	c	2	2	15.6	< 23	86 %		24% (def.2)		0 %
Yap-Veloso et al 1998	9/43	810 diode	c	1.4-2.75	2	10	< 22	75 %	68 %			11 %
Youn et al 1998	13/95	810 diode	c	1.75-3	2							
Spencer and Vernon 1999	6/58	810 diode	c	2	2	16.8			65.6 %			0 %
Threlkeld and Johnson 1999	9/47	810 diode	c	1.5-2.5	2	9	< 22	78 %			56 %	
Immonen et al 1994	9/57	krypton	c	0.4-0.5	10	6	< 25	50 %	45 %		2 %	0 %
Di Staso et al 1997*****	**12**	krypton	c	0.4-0.5	10	6	8-25	50 %	58 %	100% (def.1)	0 %	0 %
CPC combined with transscleral retinal coagulation												
Flaxel et al 1997	**9**	810 diode	c	1.5	1.5	14	< 21	78 %			33 %	
present study (all eyes)	**13**	krypton	c	0.37-0.4	10	21.3	< 22	62 %	47.7%	54% (def.2)	0 %	0 %
present study (therapeutic eyes)	**7**	krypton	c	0.37-0.4	10	21.3	< 22	86 %	62.4%	57% (def.2)	0 %	3 %
present study (all eyes)	**17**	670 diode	c	0.43-0.45	10	13.1	< 22	71 %	51.5%	47% (def.2)	3 %	0 %
present study (therapeutic eyes)	**12**	670 diode	c	0.43-0.45	10	13.1	< 22	92 %	61.8%	33% (def.2)	3 %	0 %

In studies including multiple glaucoma subtypes, IOP success, visual decrease, hypotonia and phthisis rates are those calculated for neovascular glaucomatous eyes only.

Definitions (def.) of visual decrease:
1 = visual decrease of more than one Snellen line or a change in low vision category.
2 = visual decrease of more than 2 Snellen lines or a change in low vision category.
3 = loss of light preception.

* The proportion of neovascular glaucomatous eyes versus the number of all eyes in the study.
** No retreatments in eyes that were initially well controlled.
*** Mean final IOP reduction.
**** Cw-YAG group results are reported as a whole.
***** Including palliative treatments.

Author	n	Surgical method	Length of follow-up (mean, months)	Definition of IOP success (mmHg)	IOP Success rate	Visual decrease definition	Visual decrease	Phthisis
Allen et al 1988	24	filtering surgery	22.8	< 21****	67 %	> 1 line ******	46 %	8 %
Tsai et al 1995	34	5-FU filtering surgery	12.5**	< 22	65 %	> 2 lines	53 %	24 %
Mincler et al 1988	15/79*	Molteno	20.2***	< 22	47 %	> 1 line	33 %	6 %
Mermoud et al 1993c	60	Molteno	24.7	< 22	35 %*****	not given	62 %	18 %
Lloyd et al 1991	10	Molteno & ppv	18.0	< 22	60 %	> 1 line ******	60 %	0 %

IOP = intraocular pressure
5-FU = 5-fluorouracil
ppv = pars plana vitrectomy

* the proportion of neovascular glaucomatous eyes in the study
** median (the successful eyes)
*** complete failures excluded
**** plus 2 eyes in the mid-20s
***** eyes with loss of light perception excluded
****** or a change in the low vision category.

Table 4. Reviewed data published on filtration and implant surgery in neovascular glaucoma.

Corneal morphology and corneal subbasal innervation can be evaluated *in vivo* with a tandem scanning confocal microscope (TSCM, Model 165A, Tandem Scanning Corporation, Reston, VA, USA). (Cavanagh et al. 1993, Linna et al. 1997) In human eyes treated with LASIK, an automated microkeratome creates a continuous incision and a flap in the central cornea, resulting in nerve damage, which is visible *in vivo* with the confocal microscope. Corneal nerve damage after LASIK also results in low corneal sensitivity (Linna et al. 2000) and a reduced rate of basic tear secretion (Yu et al. 2000) as tear fluid secretion, too, is under neural control. (Dartt 1994, Meneray et al. 1998)

To the best of my knowledge, no profound studies of the possible dry eye syndrome after cyclophotocoagulation have been performed

3. Aims of the study

The purpose of the present study was to evaluate the clinical applicability of long-pulsed visible red laser cyclophotocoagulation to the treatment of therapy-resistant glaucoma, -more specifically,

to evaluate the usefulness and complications of the 647 nm krypton red laser CPC in posttraumatic glaucoma, (I)

to evaluate the usefulness and complications of the 647 nm krypton red laser CPC in children and young adults with glaucoma, (II)

to evaluate the usefulness and complications of combining limited anterior retinal cryocoagulation with CPC performed with the 647 nm krypton or the 670 nm diode red laser in the treatment of neovascular glaucoma, (III)

to investigate whether 670 nm diode red laser CPC has an effect on corneal morphology when studied by *in vivo* confocal microscopy, on the density of corneal subbasal nerves, on corneal mechanical sensitivity, and on the rate of tear fluid secretion. (IV)

4. Patients and Methods

4.1. Patients

This investigation comprised all the patients with the particular glaucoma subtypes studied who had received cyclophotocoagulation treatment in Helsinki University Eye Hospital (Studies I and II), all those with neovascular glaucoma who had received a combined CPC and limited anterior retinal cryocoagulation (Study III), and 10 glaucoma patients enrolled for CPC with the 670 nm diode laser (Study IV).

The indication for cyclophotocoagulation was uncontrolled glaucoma despite maximal tolerated medication. The procedure was performed as an alternative to filtration or implant glaucoma surgery. Its purpose was to preserve vision (therapeutic treatment) or to prevent ocular pain due to high IOP in an eye with no visual potential (palliative treatment), as stated in the medical chart by the referring or the treating ophthalmologist. Of the patients who had received CPC in both eyes, one eye was chosen randomly for statistical analysis in all the studies.

The indication for retinal cryocoagulation was retinal ischaemia, as demonstrated by iris neovascularization, and persisting after full panphotocoagulation or found to be untreatable by transpupillary panphotocoagulation.

All the study protocols were reviewed by the Ethics Committee of Helsinki University Eye and Ear Hospital. Informed consent was obtained from all the patients in Study IV. In Studies I, II and III, follow-up data were gathered from the files of Helsinki University Eye Hospital, other hospitals, and private ophthalmologists after the signed permission of the particular patient.

4.1.1. Transscleral Contact Krypton Laser Cyclophotocoagulation for Treatment of Posttraumatic Glaucoma (I)

The criterion for inclusion was a previously performed krypton laser CPC in patients with posttraumatic glaucoma. The criterion for exclusion was a concurrent ocular incident, possibly affecting IOP. One patient was excluded from the study because of recent ocular trauma, with a giant retinal tear and detachment, and another patient because of a recently detected central retinal vein occlusion and neovascular glaucoma. One patient received a second injury to the treated eye after the one-month follow-up and his subsequent IOP data were excluded from the analysis. The study comprised 18 consecutive patients (7 females and 11 males) treated with krypton laser CPC in Helsinki University Eye Hospital from August 1991 to January 1996 for therapy-resistant posttraumatic glaucoma.

The mean age of the patients at the time of the first CPC was 56.6 (range, 21 to 89) years. The types of the initial ocular trauma (classified according to the Birmingham eye trauma terminology system by Kuhn et al. (Kuhn et al. 1996)) are shown in Table 5. All patients had a therapeutic treatment indication. The first CPC treatment was performed 7 days to 30.5 years (mean 8.1 years) after the ocular injury. Fourteen eyes (77%) had undergone previous ocular procedures, which are shown in Tables 6 and 7.

Type of ocular trauma	**Eyes**	**%**
Contusion injury	8	44
Rupture of the globe	5	28
Penetrating injury	4	22
Perforating injury	1	6
Total	18	100

Table 5. Types of ocular trauma of the patients included in Study I.

Glaucoma Procedures	**Eyes**	**%**
Argon laser trabeculoplasty	4	22
670 nm diode laser CPC	1	6
Trabeculectomy once	1	6
Posterior sclerotomy	1	6
Cyclocryocoagulation (twice in one eye)	1	6
A previous glaucoma procedure performed	**8**	**44**

Table 6. Glaucoma procedures previously performed on the patients included in Study I.

Other than Glaucoma Procedures	**Eyes**	**%**
Suturing of the wound after the initial trauma	10	56
Extirpation of prolapsed uveal tissue	3	17
Lens extraction	9	50
IOL implantation	6	33
Anterior vitrectomy	3	17
Pars plana vitrectomy (three times in one eye)	4	22
Scleral buckling (twice in one eye)	5	28
Penetrating keratoplasty	1	6
One or more previous procedures performed	**12**	**67**

Table 7. Previous ophthalmic procedures other than glaucoma procedures performed on the patients included in Study I.

4.1.2. Transscleral Contact Krypton Laser Cyclophotocoagulation for Treatment of Glaucoma in Children and Young Adults (II)

The criterion for inclusion was a previously performed krypton laser CPC in patients younger than 20 years of age with glaucoma. Inclusion in the study was dependent on a length of follow-up of at least one month. Exclusion criteria were a previously performed cyclodestructive procedure (cyclocryotherapy, four eyes, and 670 nm diode laser CPC, one eye), and a concurrent ocular condition during follow-up possibly affecting IOP. One patient was excluded from the study because of recent ocular trauma, a giant retinal tear, and detachment, and another patient because of a fulminantly growing retinoblastoma with closed-funnel retinal detachment.

The study comprised 22 patients (9 females and 13 males) under 20 years of age treated with krypton laser CPC in Helsinki University Eye Hospital from December 1991 to March 1998 for therapy-resistant glaucoma. Twenty patients had a therapeutic treatment indication whereas two patients had a palliative treatment indication. The mean age of the patients at the time of the first CPC was 10.5 years (range, 11 months to 19.4 years). The glaucoma diagnoses of the patients are shown in Table 8. Sixteen eyes (73%) had already undergone 1 to 8 previous laser or surgical procedures, which are listed in Tables 9 and 10.

Glaucoma diagnosis	**Eyes**	**%**
Secondary glaucoma	**19**	**86**
- due to aphakia after congenital cataract extraction	7	32
- due to chronic uveitis	6	27
- due to ocular trauma	2	9
a contusion	1	4.5
a penetrating injury	1	4.5
- due to intraocular developmental abnormalities	4	18
Aniridia	2	9
Klippel-Trénaunay-Weber syndrome	1	4.5
Sturge-Weber syndrome	1	4.5
Neovascular glaucoma	**1**	**4.5**
- due to total retinal detachment	1	4.5
Infantile glaucoma	**1**	**4.5**
Juvenile glaucoma	**1**	**4.5**
Total	**22**	**100**

Table 8. Glaucoma diagnoses of the patients included in Study II.

Glaucoma Procedure	**Eyes**	**%**
Trabeculectomy once	3	14
Trabeculectomy twice	1	5
Trabeculectomy three times	1	9
Glaucoma implant operation once	2	9
Glaucoma implant operation twice	2	9
Glaucoma implant revision twice	1	5
Glaucoma implant revision five times	1	5
Liberation of pupillary adhesions	1	5
Surgical peripheral iridectomy	1	5
Nd:YAG laser iridotomy once	2	9
Nd:YAG laser iridotomy twice	1	5
A previous glaucoma procedure performed	**10**	**45**

Table 9. Glaucoma procedures previously performed on the patients included in Study II.

Other than Glaucoma Procedures	**Eyes**	**%**
Cataract extraction with no accompanying procedures	4	18
Cataract extraction with IOL implantation	1	4.5
Cataract extraction with anterior vitrectomy and/or peripheral iridectomy and/or membranectomy	6	27
Discision of a secondary cataract	2	9
Liberation of pupillary adhesions	1	4.5
Optic iridectomy	1	4.5
Suturation of a penetrating corneal wound	1	4.5
A previous procedure other than glaucoma procedures performed	**11**	**50**

Table 10. Previous ophthalmic procedures other than glaucoma procedures performed on the patients included in Study II.

4.1.3. Transscleral Red Laser Cyclophotocoagulation Combined with Limited Anterior Retinal Cryocoagulation in Neovascular Glaucoma (III)

The criterion for inclusion was a previously performed krypton or 670 nm diode laser CPC combined with anterior retinal cryocoagulation for neovascular glaucoma. Exclusion criteria were a previously performed cyclodestructive procedure (cyclocryotherapy, two patients), the use of both laser CPC modalities in the patient (10 patients) and a concurrent ocular condition during follow-up possibly affecting IOP. The study comprised 30 patients (21 females and 9 males) treated with the krypton laser (13 patients) or the 670 nm diode laser (17 patients) CPC, followed by anterior retinal cryocoagulation for neovascular glaucoma in Helsinki University Eye Hospital from April 1994 to March 2000.

The mean age of the patients at the time of the first CPC was 75.0 (range, 42 to 90) years. Three eyes had had chronic open-angle glaucoma, two exfoliation glaucoma, and one posttraumatic glaucoma (due to ocular contusion) before neovascular glaucoma was detected. Neovascular glaucoma was caused by central retinal vein occlusion in 23 (77%) eyes, by diabetic retinopathy in six (20%) eyes, and by occlusive disease of the carotid artery in one (3%) eye. Retinal photocoagulation had been commenced in four (13%) eyes and panphotocoagulation had been performed in seven (23%) eyes, but 19 (63%) eyes had not received any retinal laser ablation. Fifteen eyes (50%) had already undergone one to three laser or surgical procedures, which are shown in Tables 11 and 12.

Glaucoma Procedures	**Eyes**	**%**
Nd:YAG laser iridotomy	4	13
Argon laser trabeculoplasty once	2	7
Argon laser trabeculoplasty twice	2	7
Trabeculectomy	1	3
A previous glaucoma procedure performed	**7**	**23**

Table 11. Glaucoma procedures previously performed on the patients included in Study III.

Other than Glaucoma Procedures	**Eyes**	**%**
Phacoemulsification and IOL implantation	7	23
Phacoemulsification, anterior vitrectomy and IOL implantation	1	3
Planned ECCE and anterior vitrectomy	1	3
Retinal cryocoagulation and encirclement procedure	1	3
Suturation of a penetrating corneal wound	1	3
One or more previous procedures performed	**10**	**33**

Table 12 . Previous ophthalmic procedures other than glaucoma procedures performed on the patients included in Study III.

4.1.4. Corneal Innervation, Corneal Mechanical Sensitivity, and Tear Fluid Secretion after Cyclophotocoagulation with the Transscleral Contact 670 nm Diode Laser (IV)

The criterion for inclusion was a planned 670 nm diode laser CPC for treatment of glaucoma. Exclusion criteria included a cloudy cornea due to such causes as high IOP or scarring, eyes with manifest anterior segment disease or with a corneal graft, and also patients with diabetes, rheumatoid arthritis, amyloidosis, or a history of herpetic eye disease. The study comprised 10 patients (6 females and 4 males) enrolled for 670 nm diode laser CPC in Helsinki University Eye Hospital from September 1999 to May 2000 for therapy-resistant glaucoma.

The mean age of the patients at the time of the first CPC was 73.8 (range, 67 to 85) years. The glaucoma diagnoses of the patients are shown in Table 13. Seven (70%) of the patients had undergone previous ophthalmic procedures, which are given in Tables 14 and 15.

Glaucoma diagnosis	**Eyes**	**%**
Exfoliation glaucoma	**5**	**50**
Primary open-angle glaucoma	**3**	**30**
Secondary glaucoma	**2**	**20**
- due to aphakia	1	10
- due to episcleral venous congestion	1	10
Total	**10**	**100**

Table 13 . Glaucoma diagnoses of the patients included in Study IV.

Glaucoma Procedure	**Eyes**	**%**
Trabeculectomy	2	20
Argon laser trabeculoplasty	5	50
Nd:YAG laser iridotomy	1	10
Krypton laser CPC	1	10
A previous glaucoma procedure performed	**5**	**50**

Table 14. Glaucoma procedures previously performed on the patients included in Study IV.

Other than Glaucoma Procedures	**Eyes**	**%**
ECCE and posterior chamber lens implantation	1	10
Phacoemulsification and posterior chamber lens implantation	1	10
A previous procedure other than glaucoma procedures performed	**2**	**20**

Table 15. Previous ophthalmic procedures other than glaucoma procedures performed on the patients included in Study IV.

4.2. Methods

4.2.1. Clinical ophthalmological examination

In Studies I, II and III, follow-up data were gathered in a retrospective chart review. Follow-up data were assessed within 2 weeks postoperatively and at one, 3, 6, 9 and 12 months, and thereafter every 6 months, after the patients´ first CPC treatment. The last follow-up available for each patient after one or more CPCs but no other glaucoma procedures constituted the end-point (Studies I, II, III). In the prospective Study IV, follow-up data were assessed within 10 days and at one month, which was the end-point in that study.

Refraction was assessed with the lens correction achieving the best visual acuity. VA was measured using standard Snellen acuity charts at 5 metres. IOP was measured with the Goldmann applanation tonometer, and in very young patients with a SchiØtz or Tono-Pen (Mentor Inc, Norwell, MA, USA) tonometer. Biomicroscopy was performed with the slit lamp (Haag-Streit, Bern, Switzerland). The amount of iris neovascularization was assessed during biomicroscopy.

4.2.2. Cyclophotocoagulation

CPC was performed under periocular anaesthesia. Ninety pecent of the CPC treatments were performed by Päivi Puska, MD, permanent senior ophthalmic consultant in the glaucoma service of Helsinki University Eye Hospital, and 10% were performed by other seniors in the research group. With the patient in the supine position, the ciliary body was identified by transillumination. For krypton CPC, the Lasertek 41 AKTrKr krypton laser unit (Dual Laser Oy, Helsinki, Finland) and, for the 670 nm diode CPC, a prototype 670 nm diode laser unit (Dual Laser Oy, Helsinki, Finland) was used. CPC was performed using a 1000 µm fibre and a contact probe with a 1200 µm ball tip (Laser Peripherals, Inc., Minnetonka, MN, USA / Dual Laser Oy, Helsinki, Finland), focusing the beam 2 mm in front of the probe in the air. For approximately 1 second before and during each application, the sclera was compressed with the probe. The power used was 0.3 to 0.5 W with the krypton and 0.43 to 0.45 W (Scientec Calorimeter Bolden, CO, USA) with the 670 nm diode laser and the exposure time was 10 seconds.

According to the general treatment protocol, the first treatment was applied to the inferior 180° of the ciliary body. If needed, a second treatment was given to the temporal 180°, a third treatment to the inferior nasal 90° and superior temporal 90°, a fourth treatment again to the inferior 180°, and a fifth treatment again to the temporal 180°. Thus, the superior nasal 90° of the ciliary body was left intact in an attempt to avoid hypotonia. In practice, the extent of the CPC was individualized according to the preoperative IOP, the preoperative glaucoma medication, the target pressure (therapeutic vs. palliative treatment), and the surgical anatomy of the eye. Approximately 10 applications were applied to the ciliary body per quadrant, avoiding the 9 and 3 o'clock positions. (Schuman et al. 1990)

In Study I, a mean number of 1.9 ± 1.2 treatments was performed per eye. Repeated CPC treatments were given to 44% of the eyes. A total number of 34 treatments were performed. The second CPC was performed a mean of 3.3 ± 2.4 (range one to 32) months since the first treatment. Two eyes (11%) received 2, 3 eyes (17%) 3, 2 eyes 4 (11%), and one eye (6%) 5 treatments. Of the 10 patients that were treated once, the treated area involved two quadrants in 8 eyes and four quadrants in 2 eyes of the ciliary body. In these 2 eyes, the treatments covered the whole 360° of the ciliary body. Of the 8 patients that received multiple treatments, the total treated area involved two quadrants in one eye, three quadrants in 4 eyes and four quadrants in 3 eyes, covering up to 315° of the ciliary body.

In Study II, a mean number of 2.3 ± 1.6 treatments was performed per eye. Two or more CPCs were given to 14 eyes (64%). The second CPC was performed after a mean interval of 5.5 ± 7.3 (range, 1 to 30) months since the first treatment. Eight eyes (36%) were treated once, seven eyes (32%) twice, four eyes (18%) 3 times, two eyes (9%) 4 times, and one eye (5%) eight times. Applications covered 90° to 360° of the pars plicata of the ciliary body, with approximately 10 applications per quadrant. Of a total of 50 treatments, four (8%) were applied to one quadrant, 32 (64%) to two quadrants, nine (18%) to three quadrants, and five (10%) to four quadrants of the ciliary body. Only in two eyes did the applications cover the full 360°.

In Study III, a mean number of 1.4 ± 0.7 CPC treatments were performed per eye, and two or more CPCs were given to eight eyes (27%). The second CPC was performed after an interval of 2.9 ± 3.2 (range, 1 to 10) months since the first treatment. Five eyes (17%) were treated twice, and three eyes (10%) three times. At each treatment, the applications covered 90° to 270° of the pars plicata of the ciliary body. Of the total of 41 CPC treatments, one (2%) was applied to one quadrant, 22 (54%) to two quadrants, and 17 (41%) to three quadrants of the ciliary body. In one case (2%) the treated area was not mentioned. Of the eight patients who received multiple treatments, the total treated area involved three quadrants in seven eyes and four quadrants in one eye, covering up to 300° of the ciliary body. Because of the higher retreatment rate in the 670 nm diode group (seven of 17 eyes vs. one of 13 eyes), the total area treated after all CPCs was larger in that group.

To prevent a postoperative IOP rise, the patients were given one drop of 1% apraclonidine (Iopidine®, Alcon, Fort Worth, TX, USA), and/or carbonic anhydrase inhibitors (CAI) and/or osmotic agents were administered pre- and postoperatively. After treatment, the patients used antibiotic-steroid drops 4 to 5 times a day for 3 to 4 weeks. Glaucoma medication was adjusted according to the pressure response.

4.2.3. Limited anterior retinal cryocoagulation

Limited anterior retinal cryocoagulation was performed once in each eye. Eighty percent of the procedures were performed by Docent Paula Summanen, MD, permanent senior ophthalmic consultant in the vitreoretinal service of Helsinki University Eye Hospital, and 20% were performed by other seniors in the research group. One to two rows of cryoapplications (Mira Ophthalmic Cryo CR 4000, Waltham, MA, USA) at -85°C and 15 to 40 in number, were applied transsclerally to 360° of the retina immediately posterior to the ora serrata. In 28 eyes (93%), cryocoagulation was performed under indirect ophthalmoscopic control. In these eyes, each application was interrupted at the earliest sign of retinal blanching. In two eyes, media clarity was insufficient for visual control during treatment. In these eyes, the applications were placed at a distance of 7 to 8 mm measured from the limbus with an application time of 5 to 7 seconds.

Retinal cryocoagulation was performed in 22 eyes (73%) in the same session as the first CPC, in four eyes (13%) in the same session as a subsequent CPC, and in four eyes (13%) separately from the CPC (in one eye 2 months before a single CPC, 1 day after a single CPC in the second eye, 9 months after a single CPC in the third eye, and 2 months after a third CPC in the fourth eye). In one eye, posterior sclerotomy was performed during one treatment session.

4.2.4. Definitions of success and failure

IOP success was defined as an IOP level of 8 to 21 mmHg or a decrease in IOP of more than 30% following one or more CPC treatments, but no other glaucoma procedures. IOP failure was defined as an IOP level of < 8 or > 21 mmHg and a decrease in IOP of 30% or less following one or more CPC treatments, but no other glaucoma procedures. IOP failure was also defined to occur if the patient underwent additional glaucoma procedures other than a repeated CPC.

In terms of alleviating ocular pain with CPC combined with limited anterior retinal cryocoagulation (Study IV), success was based on subjective assessment by the patient and was defined as the patient not complaining of pain during the follow-up visit, as recorded in the charts. Failure was defined as the patient complaining of pain during the follow-up visit, as recorded in the charts.

4.2.5. In vivo confocal microscopy

The central corneal morphology was examined and the subbasal innervation in the central and inferior perilimbal cornea was evaluated of three of the eyes without previous intraocular surgery or transscleral treatments with a tandem scanning confocal microscope (TSCM, Model 165A, Tandem Scanning Corporation, Reston, VA, USA). *In vivo* confocal microscopy was performed before CPC and at 3 days and 1 month postoperatively. The confocal microscopy was performed by Docent Minna Vesaluoma, MD, of the cornea study group of Helsinki University Eye Hospital. Before the examination, one drop of 0.4% oxybuprocaine hydrochloride (Oftan Obucain®, Santen Oy, Tampere, Finland) was applied to the cornea and one drop of 2.5% hydroxymethylcellulose gel (Goniosol®, IOLAB Pharmaceuticals, Claremont, CA, USA) to the lower surface of the objective. After the examination, the gel was washed from the ocular surface, using artificial tears (Tears Naturale®, Alcon, Puurs, Belgium). During the examination, the patient fixated on a bright object with the contralateral eye to minimize eye movements. The objective lens of the microscope was adjusted to give an *en face* view of the anterior keratocytes. The setup and operation of the confocal microscope has been described previously. (Møller-Pedersen et al. 1997) A 24X, 0.6 NA variable working distance objective lens was used. With this lens, the field of view is 450 µm x 360 µm, and the z axis resolution is 9 µm. Images were detected using a Dage VE1000 Sit System low-light level camera (Dage-MTI Inc., Michigan City, IN, USA) and recorded on SVHS tape (Fuji Magnetics GmbH, Kleve, Germany). Video images of interest were digitized, using a PC-based imaging system with custom software (University of Texas, Southwestern Medical Center at Dallas, TX, USA), and printed, using an Epson Stylus Color 800 printer (Seiko Epson Corporation, Nagano, Japan).

4.2.6. The measurement of corneal sensitivity

The mechanical sensitivity of the four quadrants (superonasal, superotemporal, inferotemporal, and inferonasal) and the central cornea was tested before treatment and at 3 days and 1 month postoperatively, using a Cochet-Bonnet aesthesiometer (Luneau, Paris, France). The nylon monofilament had a diameter of 0.08 mm. The patients were asked to fixate on an object 3 metres distant. Each area was tested, beginning with a maximal filament length of 60 mm, which was sequentially reduced by 5-mm intervals. Two to three positive responses to three consecutive touches were recorded as a positive result. The longest filament length in mm resulting in a positive response was considered to be the corneal sensitivity threshold in the area tested.

4.2.7. The measurement of the rate of tear fluid secretion

The Schirmer basic secretion tear test (Whatman #41, CooperVision, San German, PR, USA) with topical anaesthesia was performed for measurement of the basic tear fluid secretion before treatment and at 1 month postoperatively. Five minutes after installation of oxybuprocaine hydrochloride eye drops, a Schirmer filter paper strip was placed in the lower temporal fornix of the eye, avoiding any irritation. The patient was then asked to keep both eyes gently closed for 5 minutes. The amount of wetting of the paper strip was then measured with a millimeter ruler.

4.2.8. Statistical methods

For the analyses in Studies I, II, and III, data were extracted from reviewed patient charts and statistical analyses were performed, using the NCSS 2000 statistical software program (NCSS Statistical Software, Kaysville, UT, USA). Pre- and postoperative IOP levels were compared, using the Wilcoxon signed rank test. Pre- and postoperative glaucoma medications were compared, using the McNemar test and the Wilcoxon signed rank test.

For the analyses in Study I, The Kruskall-Wallis one-way ANOVA on ranks test was used to analyze differences in IOP outcome, in the duration of the treatment effect in the different glaucoma subtypes, and in the change in IOP according to the number of quadrants treated. The Mann-Whitney U test was used to analyze the extent to which the effect of the treatment depended on the patient´s age and on the total treatment energy. The effect of the pre- and postoperative IOPs and of the mean length of follow-up on the visual outcome was analyzed with the Mann-Whitney U test. The effects on visual outcome of the mean number of glaucoma medications, the amount of CAI used, and the number of treatments given were analyzed with Fisher´s exact test.

In Study III, the Mann-Whitney U test and the Fisher´s exact test were used to analyze the differences between the krypton and the 670 nm diode laser treatment groups.

For the analysis in Study IV, data were extracted completing data forms prospectively. Statistical analyses were performed using SPSS for Windows, ver. 7.0 (SPSS, Chicago, IL, USA). The paired samples *t* test was performed for comparison of the paired pre- and postoperative data for each individual eye.

Differences were considered statistically significant when $P < 0.05$ in all analyses. Missing data were not substituted by any method. Only one eye of each patient was included in the statistical analyses. Statistical consultation was provided by Timo Pessi, M.Sc., statistician at the Department of Computer Services in Helsinki University Hospital.

5. Results

5.1. Transscleral Cyclophotocoagulation with the Contact Krypton Laser for Treatment of Posttraumatic Glaucoma (I)

5.1.1. Success of IOP

With one or more CPCs but no other glaucoma procedures, the IOP decreased from the baseline mean (± SD) of 32.6 ± 12.8 to 23.6 ± 10.3 mmHg (n=17) at one month ($P < 0.01$), to 21.8 ± 7.5 mmHg (n=13) at 3 months ($P < 0.05$), to 22.5 ± 7.6 mmHg (n=13) at 6 months ($P < 0.01$), and to 19.6 ± 10.5 mmHg (n=18) at the last control visit (3 weeks to 73 months, mean 19.4 ± 21.2 months after the first cyclophotocoagulation, $P < 0.01$). The mean IOP decreased by 40%.

At the last control visit, the IOP success rate (an IOP of 8 to 21 mmHg or a decrease in IOP > 30%) was 67%. All the three eyes with pretreatment IOP < 22 mmHg maintained this IOP level after treatment, but none achieved greater than a 30% IOP reduction. If these three eyes are classified as treatment failures, the success rate decreases to 50%. Surgical success rates during follow-up for various IOP criteria are given in Table 16. The proportions of eyes with success and failure of IOP during follow-up and the cumulative proportion of eyes that were lost to follow-up are shown in Figure 4.

	Baseline	<10 days	1 month	3 months	6 months	last control
Number of eyes	18	16	18	16	16	18
< 25 mmHg	5 (28 %)	14 (88%)	9 (50%)	9 (56%)	10 (63%)	14 (78%)
< 22 mmHg	3 (17 %)	10 (63%)	8 (44%)	8 (50%)	9 (56%)	12 (67%)
< 17 mmHg	0 (0 %)	6 (38%)	5 (28 %)	3 (19%)	2 (13%)	7 (39%)
> 30 % decrease in IOP		10 (63%)	7 (39%)	8 (50%)	6 (38%)	8 (44%)
> 30 % decrease in IOP or IOP < 22 mmHg		13 (81%)	10 (56%)	10 (63%)	10 (63%)	12 (67%)
6-24 mmHg	5 (28 %)	14 (88%)	9 (50%)	9 (56%)	10 (63%)	13 (72%)
6-21 mmHg	3 (17 %)	10 (63%)	8 (44%)	8 (50%)	9 (56%)	11 (61%)
8-21 mmHg	3 (17 %)	10 (63%)	7 (39%)	8 (50%)	9 (56%)	10 (56%)
8-16 mmHg	0 (0 %)	6 (38%)	4 (22%)	3 (19%)	2 (13%)	5 (28 %)

Eyes treated with other glaucoma procedures after CPC were considered to be failures. Two patients had missing IOP values at 10 days and one patient at 3 months. One patient got a second injury to the treated eye after the one month follow-up and his subsequent IOP data were excluded from the analysis. Another patient died 4 months postoperatively.

Last follow up = The last check-up visit for which intraocular pressure data are available (mean, 19.4 ± 21.2 months after the initial cyclophotocoagulation). For eyes that received other additional glaucoma procedures, the last available intraocular pressure before such an operation was used.

Table 16. Surgical success rates with different IOP criteria during follow-up after one or more krypton cyclophotocoagulations but no other glaucoma procedures.

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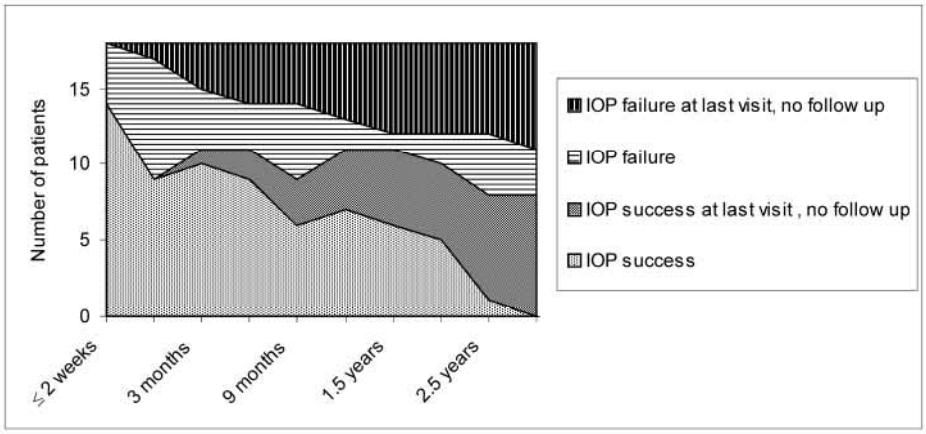

Figure 4. The proportions of eyes with success and failure of IOP during follow-up in Study I. The cumulative proportions of eyes with success and failure of IOP that were no longer in follow-up at the time point in question are also shown.

Definition of success of IOP: an IOP level of 8 to 21 mmHg or a decrease in IOP of > 30% from the baseline. Instead of missing values, the previous value observed in a particular patient was carried forward.

Other glaucoma procedures than a repeated CPC were performed on 4 patients. One eye was treated with trabeculectomy at one month, one with cyclocryocoagulation at one month, and 2 with glaucoma implant surgery: one at 3 weeks and the other at 15 months after the first CPC. IOP and other data measured after additional glaucoma procedures were excluded from the analysis. During follow-up, phacoemulsification with IOL implantation was performed in one eye at 5 months and intracapsular cataract extraction (ICCE) and anterior vitrectomy with IOL implantation at 18 months in one eye.

5.1.2. Glaucoma medication

At baseline (n=18), 17 patients (94%) had glaucoma medication, and 12 (67%) received peroral CAI in addition to topical treatment. At the last control visit, 15 of the 18 patients (83%) had glaucoma medication after one or more CPCs, and 7 (39%) used peroral CAI with topical medication. The median number of topical glaucoma medications was 2 preoperatively and 1 at the last control visit. The median daily dose of CAI was 250 mg preoperatively and 0 mg at the last control visit. The reduction in glaucoma medication during the follow-up did not reach statistical significance.

5.1.3. Visual acuity

An increase in VA of more than 2 Snellen lines or a change in low vision category was found in 4 patients (22%). The reason for this was the correction of a refractive error in one patient, visual recovery after the initial trauma in 2 patients and phacoemulsification with IOL implantation at 5 months in one patient, in whom VA had been within one Snellen line during follow-up before the cataract operation.

A decline in VA of more than 2 Snellen lines or a change in low vision category occurred in 3 eyes during the follow-up period. The decline in VA was due to punctate corneal epitheliopathy at the last control visit of one patient with no such findings at previous visits, to a dry corneal epithelium in the second eye with fluctuation of vision, and the development of phthisis in the third eye. In 2 of these eyes, the decline in VA was considered to be potentially CPC-related.

5.1.4. Complications

Postoperative complications, their frequencies and whether or not they were transient are shown in Table 17. No conjunctival burns or fibrinoid reactions were seen, nor did the patients report significant postoperative pain requiring systemic analgesics. Corneal punctate epitheliopathy or dry eye was seen after 2 treatments (6%). After the third treatment of one eye, the cornea appeared permanently dry. One eye with silicone oil in the anterior chamber developed corneal opacification after delayed healing of a corneal epithelial defect one month after CPC and mild anterior chamber irritation chronically thereafter. One eye showed small patches of scleral thinning in the treatment area after the third CPC.

One patient had macular oedema at the first examination after a contusion injury. It disappeared within a week, but developed again 5 days after CPC (21 days after the initial trauma). The oedema resolved again completely and the patient gained 20/20 vision during follow-up.

Hypotonia (IOP < 6 mmHg) was seen in one eye with perforating injury and four subsequent posterior segment operations with silicone oil injection. An IOP of 6 mmHg was first measured at one month postoperatively (the CPC covered 360° of the ciliary body), but when the glaucoma medication was reduced, the IOP returned to normal in this patient within 3 months after CPC. However, 2 years postoperatively, hypotonia (IOP of 5 to 7 mmHg) again developed without glaucoma medication. At the last follow-up at 5 years and 3 months postoperatively, the IOP in this patient was 6 mmHg.

Hypotonia and phthisis developed in another eye with a contusion injury, lens subluxation and vitreous prolapse into the anterior chamber. This eye had received 3 CPCs covering 315° of the ciliary body within 7 months, the first treatment 2 days after the initial injury. An IOP of one mmHg developed one month after the last CPC. After 4 months of hypotonia, the IOP returned to 6 mmHg and after 7 months to 12 mmHg. Four months later (11 months after the last CPC) ICCE, anterior vitrectomy and anterior chamber lens implantation were performed. Before the cataract operation, the IOP had been 22 mmHg without glaucoma medication. Five months after cataract surgery, hypotonia (an IOP of one mmHg) again developed and phthisis bulbi followed 2 years and 2 months after the last CPC.

Complication	*** Transient**	**Treatments (%)**
Dry eye or corneal punctate epitheliopathy		2 (6)
Corneal epithelial erosion and subsequent opacification		1 (3)
Corneal marginal ulcer	*	1 (3)
Mild anterior uveitis	*	13 (38)
Macular oedema (previously posttraumatic oedema)	*	1 (3)
Mild scleral thinning		1 (3)
Hypotonia (IOP < 6 mmHg)	*	1 (3)

Complication	*** Transient**	**Eyes (%)**
Phthisis bulbi		1 (6)

Table 17. Complications after 34 cyclophotocoagulation treatments with the krypton laser in 18 eyes of 18 patients with posttraumatic glaucoma. See text for a more detailed descriptions of some patients.

5.2. Transscleral Cyclophotocoagulation with the Contact Krypton Laser for Treatment of Glaucoma in Children and Young Adults (II)

5.2.1. Success of IOP

Preoperatively, the mean IOP was 35.0 ± 7.9 mmHg (n=22). After one or more CPCs, the mean IOP decreased to 21.5 ± 8.7 mmHg (n=22) at 1 month ($P < 0.001$), to 23.4 ± 8.6 mmHg (n=18) at 3 months ($P < 0.001$), to 25.0 ± 12.1 mmHg (n=19) at 6 months ($P < 0.01$), to 22.1 ± 9.1 mmHg (n=16) at 1 year ($P < 0.01$), to 22.6 ± 10.3 (n=11) at 2 years ($P < 0.01$), and to 26.2 ± 10.5 mmHg (n=22) at the last follow-up visit (1 to 74 months, mean 27.1 ± 21.9 months after one or more CPCs but no other glaucoma procedures, $P < 0.01$).

At the last control visit, the IOP success rate (an IOP of 8 to 21 mmHg or a decrease in IOP > 30%) was 64%. Surgical success rates during follow-up for various IOP criteria are given in Table 18. The proportions of eyes with IOP success and failure during follow-up and the cumulative proportions of eyes that were lost to follow-up are shown in Figure 5.

The total number of quadrants of the ciliary body treated did not correlate statistically with the IOP results. The difference in IOP outcome or in the means of the follow-up time after one or more CPCs in eyes with congenital glaucoma (n=7), eyes with uveitic glaucoma (n=6) and the other eyes with various other glaucoma diagnoses (n=9) was not statistically significant.

The mean duration of the treatment effect (IOP < 22 mmHg or IOP reduction > 30%) of all patients´ first CPC was 6.8 ± 10.5 months (median 2.0 months, range, no effect to 35 months). None of the three diagnostic groups had longer or shorter treatment effects than any other. The longest treatment effects were shown by two uveitic eyes (31 to 35 months), one post-traumatic glaucomatous eye (24 months) and one eye operated on for congenital cataract (20 months). Within the follow-up period, five of the 22 eyes still showed a treatment effect after only one CPC (two uveitic eyes, one eye with juvenile glaucoma, one post-traumatic glaucomatous eye, and one eye operated on for congenital cataract). Nor was there a statistically significant difference in the treatment effect between patients treated with a higher- and with a lower-than-median amount of energy (70 J, range, 44 to 113 J). There was no statistically significant difference in the mean duration of the treatment effect between 11 patients older than and 11 patients younger than the median age of 10 years.

Additional glaucoma procedures were performed on nine eyes (see Table 19). For eyes that received other additional glaucoma procedures, the last available IOP before such an operation was used in the calculations. During follow-up, Nd:YAG laser capsulotomy was performed in one patient at 7 months and cataract extraction was performed in another patient at 2 years.

	Baseline	1 month	3 months	6 months	1 year	2 years	last follow-up
Number of eyes*	n=22	n=22	n=19	n=21	n=20	n=18	n=22
IOP criterion							
< 25 mmHg	1(4%)	16(73%)	10(53%)	11(52%)	10(50%)	8(44%)	9(41%)
< 22 mmHg	0(0%)	13(59%)	7(37%)	8(38%)	8(40%)	7(39%)	9(41%)
6-21 mmHg	0(0%)	12(55%)	6(32%)	8(38%)	8(40%)	7(39%)	9(41%)
8-21 mmHg	0(0%)	12(55%)	6(32%)	7(33%)	8(40%)	7(39%)	9(41%)
6-24 mmHg	1(4%)	15(68%)	9(47%)	11(52%)	10(50%)	8(44%)	9(41%)
8-24 mmHg	1(4%)	15(68%)	9(47%)	10(48%)	10(50%)	8(44%)	9(41%)
>30% decrease in IOP		16(73%)	10(53%)	13(62%)	9(45%)	9(50%)	13(59%)
>30% decrease in IOP or IOP< 22 mmHg		16(73%)	10(53%)	13(62%)	9(45%)	9(50%)	14(64%)

*The total number of eyes at each time point gives the number of eyes deemed as successes at the given time point plus the number of patients regarded as failures at the given time point or at any previous time point. The number excludes eyes lost to follow-up (one eye after 1 month with an IOP of 16 mmHg, and three additional eyes after 1 year with last recorded IOPs of 10, 16 and 25 mmHg). The IOP data of two patients were missing at 3 months and that of one patient was missing at 1 year.

Last follow up = The last check-up visit for which IOP data are available (mean, 27.1 ± 21.9 months after the initial CPC). Of eyes that received other additional glaucoma procedures, the last available IOP before such an operation was used.

Table 18. Number and proportion of eyes on a specific intraocular pressure (IOP) level during follow-up after one or more cyclophotocoagulations (CPC) but no other glaucoma procedures.

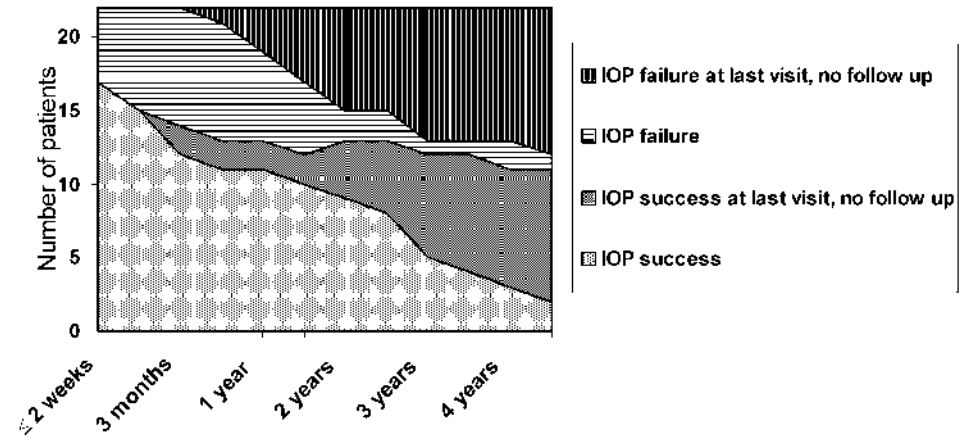

Figure 5. The proportions of eyes with success and failure of IOP during follow-up in Study II. The cumulative proportions of eyes with success and failure of IOP that were no longer in follow-up at the time point in question are also shown.

Definition of success of IOP: an IOP level of 8 to 21 mmHg or a decrease in IOP of > 30% from the baseline. Instead of missing values, the previous value observed in a particular patient was carried forward.

Procedure	**Eyes (%)**	**Time after the initial CPC (months)**
Trabeculectomy	2 (9%)	3 and 8
Implant surgery	4 (18%)	4, 11, 13, and 33
Nd:YAG laser iridotomy	2 (9%)	8 and 20
670 nm diode laser CPC	1 (5%)	62

Table 19. Additional procedures performed for glaucoma during follow-up after one or more CPCs in the eyes in Study II.

5.2.2. Glaucoma medication

At baseline (n=22), 20 eyes (91%) had glaucoma medication, and four patients (18%) received peroral CAI in addition to topical treatment. At the last follow-up visit, after one or more CPCs but no other glaucoma procedures, 17 eyes (77%) were on glaucoma medication ($P < 0.05$) and four patients (18%) were using peroral CAI. The median number of topical glaucoma medications pre- and postoperatively was 2.

5.2.3. Visual acuity

An increase in VA of more than two Snellen lines or a change in the low vision category was found in one patient (5%) after correction of refractive error, and in another patient (5%) after visual recovery from ocular trauma.

A decline in VA of more than two Snellen lines or a change in the low vision category occurred in four (18%) of the 22 eyes. The reason for this was progression of pre-existing lens opacification and band keratopathy (one eye), progression of a pre-existing cyclitic membrane (one eye), postoperative exacerbation of chronic uveitis (one eye), and progression of pre-existing, posttraumatic corneal decompensation and uveitis (in one eye). In five patients, the change in VA could not be evaluated because of lack of co-operation.

Nd:YAG laser capsulotomy was performed in one patient at 7 months and cataract extraction was performed in another patient at 2 years. Before these procedures, VA had been within one Snellen line during follow-up in both eyes.

5.2.4. Complications

Postoperative complications and events, their frequencies and whether they were transient are given in Table 20. No conjunctival burns were seen. Ten (20%) cases of corneal punctate epitheliopathy or dry cornea were transiently noted (four within 2 weeks, one at 1 month and five at 3 to 5 months). Band keratopathy progressed in three (14%) eyes: in two aniridic eyes with progressive corneal subepithelial and stromal degeneration before the CPC, and in one uveitic eye. Subtle transient (4 to 5 months) subepithelial corneal opacification or infiltration developed in one epikeratophacic eye and in one uveitic eye. Mild limbal vessel growth with no progression was seen at 1 month in an eye after four previous intraocular operations. Scleral thinning developed in the treatment area in two patients: after a single treatment in one eye of a 13-year-old patient with uveitic glaucoma and after each of two treatments in one eye of an 11-year-old patient operated on for congenital cataract.

After one CPC treatment (2%), transient hypotonia (an IOP of 3 to 6 mmHg) was seen for 6 months in an eye with a preoperative cyclitic membrane. The eye had previously been operated on for congenital cataract and secondary glaucoma (two implant operations). A shallow anterior chamber developed 5 to 6 months postoperatively in two eyes with preoperative uveitis and cyclitic membranes. No cases of phthisis bulbi were seen.

Complication	*** Transient**	**Treatments (%)**
Dry eye or corneal punctate epitheliopathy	*	10 (20)
Subtle subepithelial corneal opacification or infiltrates	*	2 (4)
Mild limbal vessel growth		1 (2)
Marked ciliary injection (uveitic eyes)	*	2 (4)
Minor anterior uveitis	*	8 (16)
Moderate anterior uveitis (uveitic eyes)	*	2 (4)
Shallow anterior chamber		2 (4)
Fibrinoid reaction (preoperative hyphema in one eye)	*	2 (4)
Oval pupil	*	1 (2)
Minor anterior vitritis	*	3 (6)
Scleral thinning		3 (6)
Hypotonia (IOP 3 to 6 mmHg)	*	1 (2)
Disturbance of near vision	*	1 (2)
Postoperative pain	*	2 (4)

Complication	*** Transient**	**Eyes (%)**
Progression of band keratopathy		3 (14)
Progression of a pre-existing subcapsular cataract		4 (18)

Table 20. Complications after 50 cyclophotocoagulation treatments with the krypton laser in 22 eyes of 22 children and young adults. See text for more detailed descriptions of some patients.

5.3. Transscleral Cyclophotocoagulation with the Red Laser Combined with Limited Anterior Retinal Cryocoagulation in Neovascular Glaucoma (III).

There were no statistically significant differences between the krypton and the 670 nm diode groups in the patients´ age, sex, glaucoma medication, extent of retinal photocoagulation pre- or postoperatively, perioperative additional glaucoma medication, amount of total energy used in the first CPC (72.5 ± 11.7 (range, 57.0 to 96.2) J and 80.4 ± 21.8 (range, 38.7 to 116.1) J, respectively) or extent of the area treated in the first CPC. Because of the higher retreatment rate in the 670 nm diode group where 7 eyes (41%) were retreated compared with one retreated eye (8%) in the krypton group, the total area treated after all CPCs was larger and the total amount of energy delivered per eye was higher in the 670 nm diode laser group ($P < 0.05$).

5.3.1. Success of IOP

With one or more CPCs and an anterior retinal cryocoagulation, the mean IOP decreased from a preoperative level of 44.0 ± 12.5 (range, 22 to 70) mmHg (n=30) to 22.1 ± 15.8 (range, 0 to 72) mmHg (n=30) at the last follow-up, which was at a mean of 16.8 ± 13.8 months (median 11.5, range, 1 to 45 months) after the initial CPC ($P < 0.0001$). In the krypton and 670 nm diode groups, the mean IOPs at baseline were 45.1 ± 12.2 (range, 25 to 64) and 43.1 ± 13.1 (range, 22 to 70), respectively, decreasing to 23.6 ± 16.6 (range, 5 to 72), and 20.9 ± 15.6 (range, 0 to 58). The last control visit took place at a mean of 21.3 ± 14.4 (range, 4 to 43) months after the initial CPC in the krypton group, and 13.1 ± 12.7 (range, 1 to 45) months after the initial CPC in the 670 nm diode group. These differences between the two groups were not statistically significant.

In the patients with a therapeutic treatment indication (n=19), the IOP decreased from a preoperative mean level of 40.9 ± 11.8 (range, 22 to 62) mmHg to 15.6 ± 5.9 (range, 5 to 26) mmHg (n=19) ($P < 0.001$) at the last follow-up, which was a mean of 14.0 ± 12.2 (range, 1 to 43) months after the first CPC. At the last control visit in these 19 patients, the IOP success rate (an IOP of 8 to 21 mmHg or a decrease in IOP > 30%) was 95%. The IOP success rates of these 19 patients during follow-up, using various IOP criteria, are given in Table 21, and the proportions of these eyes with IOP success and failure during follow-up and the cumulative proportions of eyes that were lost to follow-up are shown in Figure 6. At the last follow-up, all the patients (n=30) were pain-free.

	Baseline	< 10 days	1 month	3 months	6 months	1 year	last follow-up
Number of eyes* IOP criterion	n=19	n=19	n=18	n=14	n=11	n=9	n=19
< 25 mmHg	2 (11%)	14 (74%)	13 (72%)	14 (100%)	9 (82%)	8 (89%)	17 (89%)
< 22 mmHg	0 (0%)	11 (58%)	12 (67%)	13 (93%)	9 (82%)	8 (89%)	17 (89%)
5-21 mmHg	0 (0%)	10 (53%)	10 (56%)	13 (93%)	9 (82%)	8 (89%)	17 (89%)
8-21 mmHg	0 (0%)	10 (53%)	10 (56%)	12 (86%)	8 (73%)	8 (89%)	15 (79%)
5-24 mmHg	2 (11%)	13 (68%)	11 (61%)	14 (100%)	9 (82%)	8 (89%)	17 (89%)
8-24 mmHg	2 (11%)	13 (68%)	11 (61%)	13 (93%)	8 (73%)	8 (89%)	15 (79%)
> 30% decrease in IOP		14 (74%)	13 (72%)	11 (79%)	7 (64%)	9 (100%)	17 (89%)
> 30% decrease in IOP or IOP < 22 mmHg		15 (79%)	14 (78%)	14 (100%)	9 (82%)	9 (100%)	18 (95%)
> 30% decrease in IOP or IOP 8 to 21 mmHg		15 (79%)	14 (78%)	14 (100%)	9 (82%)	9 (100%)	18 (95%)

*The total number of eyes at each time point gives the number of eyes deemed as successes at the given time point plus the number of eyes regarded as failures at the given time point, or at any previous time point. The number excludes eyes lost to follow-up (two eyes after 1 month with an IOP of 17 and 20 mmHg, 3 eyes after 3 months (5, 12, and 14 mmHg), and five eyes after 6 months (5, 10, 17, 18, and 20 mmHg). The IOP data of one patient at 1 month, of three patients at 3 months, and of three patients at 6 months, were missing.

Last follow up = The last check-up visit for which intraocular pressure data are available (mean, 14.0 ± 12.2 months after the initial cyclophotocoagulation). For eyes that received other additional glaucoma procedures, the last available intraocular pressure before such an operation was used.

Table 21. Number and proportion of eyes in the therapeutic group on a specific intraocular pressure (IOP) level during follow-up after one or more cyclophotocoagulations (CPC) but no other glaucoma procedures.

Glaucoma procedures other than repeated CPC treatments, were not performed during the follow-up. Phacoemulsification and IOL implantation were performed in one eye at 2 months, Nd:YAG laser capsulotomy in one eye at 12 months, and pars plana vitrectomy and silicone oil injection for traction retinal detachment in one eye at 9 months after the first CPC. By the last follow-up, 15 eyes (50%) had received retinal panphotocoagulation.

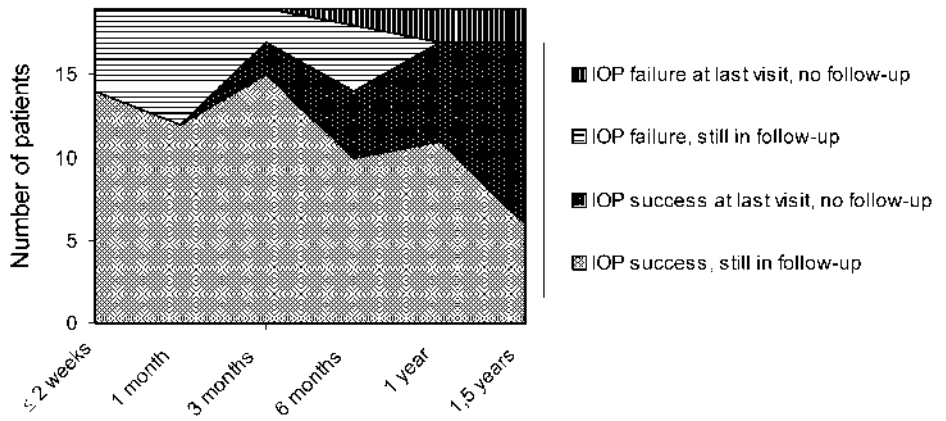

Figure 6. The proportions of eyes with IOP success and failure during follow-up (n=19, patients with a therapeutic treatment indication) in Study III. The cumulative proportions of eyes with success and failure of IOP that were no longer in follow-up at the time point in question are also shown.

Definition of success of IOP: an IOP level of 8 to 21 mmHg or a decrease in IOP of > 30% from the baseline. Instead of missing values, the previous value observed in a particular patient was carried forward.

5.3.2. Glaucoma medication

At baseline (n=30), 26 (87%) patients were on glaucoma medication. Eighteen (60%) patients took topical glaucoma medication only, and eight (27%) were taking systemic CAI with topical treatment. At the last follow-up visit (n=30), after one or more CPCs but no other glaucoma procedures, 20 (67%) patients were on glaucoma medication. Of these, one patient (3%), as compared with eight (27%) at baseline, was using peroral CAI ($P < 0.05$). Preoperatively, the median number of topical glaucoma medications was 2, and postoperatively 1 ($P < 0.05$).

5.3.3. Regression of iris neovascularization and resolution of vitreous haemorrhage

In 13 (43%) cases, iris neovascularization regressed or disappeared during follow-up. All three eyes with preoperative vitreous haemorrhage preventing retinal photocoagulation showed resolution of the haemorrhage, enabling fundus examination at or before the last follow-up.

5.3.4. Visual acuity

In four (21%) of the 19 eyes of the patients with an indication for therapeutic treatment, an increase in VA of more than two Snellen lines or a change in the low vision category was found: after the IOP had decreased and corneal epithelial oedema had resolved (three eyes), and after Nd:YAG laser capsulotomy (one eye). Before capsulotomy, VA had been within one Snellen line during follow-up.

In 15 (50%) of all eyes and in eight (42%) of the 19 eyes of the patients with an indication for therapeutic treatment, a decline in VA of more than two Snellen lines or a change in the low vision category occurred. In

the patients with an indication for palliative treatment, the reason for the visual decline was high IOP and progression of the coexisting retinal disease. In those with an indication for therapeutic treatment, the reason was progression of the retinal disease (five eyes), progression of a pre-existing lens opacification (two eyes), and vitreous haemorrhage and intermittent poor control of glaucoma despite an IOP within the normal range at the last follow-up (one eye).

One patient was operated on for cataract at 2 months, but VA deteriorated owing to the progression of the coexisting retinal disease. Before cataract operation, VA had been within one Snellen line during follow-up.

5.3.5. Complications

Postoperative complications, their frequencies and whether they were transient are given in Table 22. The two laser treatment groups did not differ significantly in the number or severity of the complications noted.

No conjunctival burns were seen. Of the four cases (9%) of dry eye, three were transient. One was seen at 3 days and three were seen during the first 3 months. One of these eyes, with no light perception (palliative treatment), had a persistently elevated IOP and corneal epitheliopathy. The patient requested enucleation, which was performed 8 months postoperatively.

Complication	*** Transient**	**Treatments (%)**
Postoperative pain	*	3 (7)
Lid oedema	*	1 (2)
Sugillation	*	3 (7)
Ciliary injection	*	8 (18)
Chemosis	*	19 (42)
Dry eye	*	4 (9)
Corneal dellen	*	1 (2)
Corneal epithelial erosion	*	1 (2)
Corneal epithelial erosion and subsequent haze, precipitates, and prolonged anterior uveitis		1 (2)
Corneal epithelial oedema	*	1 (2)
Folding of Descemet´s membrane	*	1 (2)
Mild anterior uveitis	*	18 (40)
Fibrinoid reaction	*	3 (7)
Hyphaema	*	3 (7)

Complication	*** Transient**	**Eyes (%)**
Progression of a pre-existing cataract		2 (7)
Late vitreous haemorrhage (at 2 to 33 months)		5 (17)
Traction retinal detachment		1 (3)
Hypotonia (IOP of 5 mmHg)		1 (3)
Phthisis bulbi		1 (3)

Table 22. *Complications after a total of 45 treatment sessions in 30 eyes of 30 patients with neovascular glaucoma in Study III. See text for more detailed descriptions of some patients.*

Anterior chamber haemorrhage was seen after three treatments (7%): in one eye with previous spontaneous anterior chamber haemorrhages, and in another eye peroperatively following posterior sclerotomy (hypotonia caused bleeding from neovascular vessels of the iris). The third case only occurred 1 month postoperatively. Three (7%) fibrinoid reactions were seen, two in eyes with an anterior chamber haemorrhage, and in one eye 3 months after treatment.

One eye (3%) had an IOP of 5 mmHg without glaucoma medication at the last follow-up (at 3 months). The only case of phthisis developed gradually during 39 months. During follow-up, one eye (3%) with proliferative diabetic retinopathy was operated on at 9 months for traction retinal detachment.

5.4. Corneal Innervation, Corneal Mechanical Sensitivity, and Tear Fluid Secretion after Transscleral Cyclophotocoagulation with the Contact 670 nm Diode Laser (IV)

5.4.1. Morphology of the central cornea

In the central corneas, the outer and basal epithelial cells were normal in shape and reflectivity at all examinations. (Li et al. 1997, Møller-Pedersen et al. 1997, Rosenberg et al. 2000a, Vesaluoma et al. 2000) The anterior keratocyte nuclei were clearly discernible in all the corneas, although in two of them the anterior matrix was less transparent than in healthy eyes of young individuals (Original Article IV, Figure 2A). Keratocyte activation, described as brightly reflecting keratocyte nuclei and visible cell processes, (Møller-Pedersen et al. 1997, Vesaluoma et al. 2000) was not observed after the treatment. In all cases following the 670 nm diode laser CPC, the posterior stroma appeared normal, and did not reveal any changes in morphology. The endothelial cells were regularly distributed and appeared hexagonal in shape.

5.4.2. The subbasal nerves of the central cornea

In the pretreatment images, the central corneal nerve fibre bundles forming the subbasal nerve plexus appeared less abundant than in normal young individuals (Original Article IV, Figure 2B). (Rosenberg et al. 2000b) In the best images with most nerve fibre bundles, the central corneas of the patients exhibited only one to three long nerve fibre bundles. Their course was not normal, as short nerve fibre bundles, not found in the normal subbasal corneal innervation, were also occasionally observed, and some of the long nerves were not straight (Original Article IV, Figure 2C). However, the nerve counts had not decreased during the follow-up; in fact, in one case, more bundles were observed at 1 month than at earlier time points (Original Article IV, Figures 2B-D). No particular changes in the morphology or density of the nerve fibre bundles were detected during the follow-up. Images of central stromal nerve trunks could be visualized at all examinations and appeared normal (Original Article IV, Figure 2E).

5.4.3. The subbasal nerves of the inferior perilimbus

In the inferior perilimbal area, both long and short subbasal nerve fibre bundles were observed, but, in this area also, the images remained unchanged at all time points. In one cornea, small, round, highly reflecting cells, presumably of inflammatory origin, were connected to the short nerve fibre bundles at all examinations (Original Article IV, Figure 2 F).

5.4.4. Corneal sensitivity

Comparison of the pre- and postoperative data for each corneal area in each individual eye showed that there was no statistically significant change in the mechanical sensitivity values in any of the corneal areas examined (P > 0.05). (Table 23).

	Baseline (n = 10)	3 days (n = 9)	one month (n = 9)
Superonasal	54.5 ± 8.3 (40.0 to 60.0)	56.7 ± 6.6 (40.0 to 60.0) (n.s.)	55.0 ± 5.0 (45.0 to 60.0) (n.s.)
Superotemporal	56.5 ± 5.8 (45.0 to 60.0)	57.2 ± 3.6 (50.0 to 60.0) (n.s.)	58.3 ± 2.5 (55.0 to 60.0) (n.s.)
Inferotemporal	58.0 ± 6.3 (40.0 to 60.0)	58.9 ± 2.2 (55.0 to 60.0) (n.s.)	57.8 ± 3.6 (50.0 to 60.0) (n.s.)
Inferonasal	55.5 ± 8.3 (35.0 to 60.0)	57.2 ± 6.7 (40.0 to 60.0) (n.s.)	57.8 ± 3.6 (50.0 to 60.0) (n.s.)
Central	55.5 ± 8.3 (35.0 to 60.0)	57.2 ± 3.6 (50.0 to 60.0) (n.s.)	57.2 ± 5.7 (45.0 to 60.0) (n.s.)

Table 23. The mean ± SD (range) mechanical sensitivity of the central cornea and its four quadrants of ten glaucomatous eyes preoperatively and after 670 nm diode laser cyclophotocoagulation.

5.4.5. Tear fluid secretion

On comparing the pre- and postoperative data for each individual eye, there was no statistically significant change in the results of the Schirmer basic secretion tear test (P > 0.05) (Table 24). Before treatment, the eyes were classified into three categories according to the test readings (Fingeret et al. 1990): those with normal values (> 10 mm), those with borderline values (5 to 10 mm), and those with pathological values (< 5 mm). One month after treatment, three eyes showed no change in category, four eyes showed a change to a lower category and two showed a change to a higher category.

Patient	**Results of the Schirmer basic secretion tear test** (the amount of wetting of the filter paper strip in mm)		
	Baseline	*1 month*	*Change in category*
1	3	9	Higher
2	5	2	Lower
3	5	22	Higher
4	14	9	Lower
5	33	24	No change
6	12	4	Lower
7	2	0	No change
8	6	9	No change
9	18	n.d.	
10	12	6	Lower
Mean	11.0	9.4	
SD	9.6	8.3	

Table 24. Results of the Schirmer basic secretion tear test at baseline and at 1 month after 670 nm diode laser cyclophotocoagulation.

6. Discussion

6.1. Cyclophotocoagulation

Cyclophotocoagulation has been widely used in therapy-resistant glaucoma. (Schuman et al. 1990a) In an Ophthalmic Technology Assessment (OTA) by the American Academy of Ophthalmology (AAO) (Pastor et al. 2001) based on the current literature, it was found that cyclophotocoagulation (based on Level III evidence) is indicated for patients with refractory glaucoma in whom trabeculectomy or tube shunt procedures have failed, patients with minimal useful vision and elevated IOP, patients who have no visual potential and need pain relief, and patients with complicated glaucoma and conjunctival scarring from previous surgery. It may be useful for patients whose general medical condition precludes invasive surgery (i.e. filter or tube) and is useful in emergency situations, such as the acute onset of neovascular glaucoma. (Pastor et al. 2001)

6.1.1. Methodological considerations and qualities of the laser

In this study, we placed the laser probe on the anterior edge of the illuminated ciliary body and held it perpendicular to the sclera. This individualized technique has been shown to destroy the ciliary ridges optimally (Bloom et al. 1992, Kivelä et al. 1995) Two reports of treatment failures after contact 810 nm diode CPC performed with the G-probe placed at the limbus revealed lesions situated more posteriorly than intended in the pars plana. (Walland et al. 1998, Barkana et al. 2002) Walland et al. studied autopsy eyes and concluded that the lack of flexibility of the standard G-probe suggested that, in eyes at the extremes of size, an individualized technique should be considered instead. (Walland et al. 1998) Barkana et al. viewed the ciliary body as they performed endoscopic CPC after three transscleral CPC treatments. Scleral transillumination had only been applied in the repeat treatments. The authors concluded that scleral transillumination did not correctly reflect the anatomy of the elongated ciliary processes since many laser-induced scars were noted in the pars plana. However, it is not known which of the burns were performed with the assistance of transillumination and which without it.

The choice of the laser type has been based on the scleral transmission of the laser used. Since scleral transmission increases at longer wavelengths, (Vogel et al. 1991) the lasers most frequently employed in clinical practice have been the infrared 810 nm diode and the 1064 nm Nd:YAG lasers. (Hampton et al. 1990, Schuman et al. 1992, Shields et al. 1994, Dickens et al. 1995, Kosoko et al. 1996, Bloom at al 1997, Werner et al. 1998, Yap-Veloso et al. 1998, Spencer et al. 1999, Threlkeld et al. 1999, Schlote et al. 2001b, Mistlberger et al. 2001)

When a transscleral contact laser application is used while simultaneously compressing the sclera with the probe, the scleral transmission is increased, especially at shorter wavelengths, by 2.5-fold with the krypton laser and by 1.5-fold with the cw-Nd:YAG laser. (Vogel et al. 1991) In non-contact applications, the scleral transmission is 24% for 670 nm, 36% for 810 nm, and 50% for 1064 nm. (Vogel et al. 1991) From the available data (Rol et al. 1990, Vogel et al. 1991) it can be extrapolated that, with the 670 nm laser using contact application and pressure on the sclera, 43% of the energy is transmitted and the rest is reflected, with little absorption by the sclera. The corresponding scleral transmission with contact application for the 810 nm diode and the 1064 nm Nd:YAG laser is about 60%. (Rol et al. 1990, Vogel et al. 1991) On the other hand, the absorption of light by the pigment epithelium is 66% at 670 nm, as compared with 37% at 810 nm and 12% at 1064 nm, (Vassiliadis 1989) compensating for the poorer scleral transmission of the red 670 nm diode laser. Thus the energy of the red lasers, with high affinity for the pigment epithelium, is more selectively absorbed by the pars plicata than that of the infrared lasers.

Our previous experimental and clinical experience has suggested that the red krypton at 647 nm is a promising wavelength for transscleral CPC. (Immonen et al. 1993, Immonen et al. 1994) To produce comparable lesions in the pars plicata of the rabbit eye, the contact krypton laser requires only half of the energy that is needed with the contact cw-Nd:YAG laser. (Immonen et al. 1993) Although clinically similar IOP responses, with similar or smaller total energies per session, are obtained with the red lasers than with the infrared Nd:YAG laser, the poorer scleral transmission and better absorption by melanin with the red lasers indicates that less energy enters the eye with the red lasers, and even less energy reaches the vitreous and the retina at the contralateral wall of the eye. This may be of practical importance, since, in the case of non-contact Nd:YAG CPC, it has been calculated that the resulting retinal exposure to energy may even exceed the threshold for retinal damage. (Myers et al. 1998)

The total energy applied with the red CPC is similar to that of the 810 nm diode CPC, but these two modalities differ in principle. In red laser CPC, the power at the scleral surface is 0.35 to 0.43 W and the duration of one laser exposure with the red CPC is 10 seconds. In the 810 nm diode CPC, the corresponding values are in the region of 1.5 to 2.0 W and 1.5 to 2.0 seconds. (Yap-Veloso et al. 1998, Flaxel et al. 1997, Oguri et al. 1998) From the powers mentioned above and the scleral reflectance values given by Rol et al. (Rol et al. 1990), it can be estimated that the amount of energy traversing the sclera during one CPC application is about 1.4 J/s with the 810 nm CPC, and 0.2 J/s with the 670 nm diode CPC.

Further, the duration of the laser exposure with the red laser CPC, 10 seconds, is longer than in other modalities of transscleral laser CPC. This allows for the lower power of the laser, and explosive reactions in the ciliary body are avoided. On the other hand, the long duration allows more heat to be spread from the pigment epithelium to other parts of the ciliary body, resulting in less selective coagulation of the pigment epithelium than is suggested by the absorption characteristics of the wavelength used. However, the cooling effect of the highly vascularized ciliary body may limit the spreading of heat, especially at the very low intraocular power levels used in the red laser CPC.

As a result of the low power and the long duration of application, parts of the ciliary body lesion may be warmed to levels above 43°C without being coagulated. Such a hyperthermic effect may induce apoptosis in the cellular components of the ciliary body (Mainster et al. 2000) instead of the necrosis that occurs after coagulative lesions. It is known that, as compared with necrotic cell death, the inflammatory reaction following apoptosis is minimal. (Papermaster et al. 1995, Mainster et al. 2000). The hyperthermia produced in the lesions by the low-power, slow-burn laser may partly explain the mild postoperative uveitis and the fact that pain is rarely observed after this treatment modality as compared with cyclocryocoagulation and Nd:YAG CPC. (Stewart et al. 1996, Jennings et al. 1999)

6.2. Transscleral Cyclophotocoagulation with the Contact Krypton Laser for Treatment of Posttraumatic Glaucoma (I)

In this study, the first krypton CPCs were performed a mean of 8.1 years (7 days to 30.5 years) after the initial ocular injury, which was an open globe injury in 56% of eyes and a contusion injury in 44% of eyes. Seventy-seven percent of patients had already undergone previous ocular surgery and glaucoma procedures had been done on 44% of the eyes before CPC.

The IOP success rate (an IOP of 8 to 21 mmHg or a decrease in IOP > 30%) was 67%. All three eyes with pretreatment IOP < 22 mmHg maintained this IOP level after treatment, but none achieved greater than a 30% IOP reduction. If these three eyes are classified as treatment failures, the success rate decreases to 50%. The heterogeneity of eyes in different studies makes comparison of the CPC outcomes difficult, but it appears that our result is within the 39% to 85% in some previously published studies of heterogeneous glaucoma populations after CPC. (Brancato et al. 1989, Hampton et al. 1990, Schuman et al. 1992, Al-Ghamdi et al. 1993, Hawkins et al. 1993, Immonen et al. 1994, Brancato et al. 1995, Bloom et al. 1997, Wong et al. 1997, Werner et al. 1998, Spencer et al. 1999, Therkeld et al. 1999, Schlote et al. 2001b) The success of IOP after CPC tends to be lower in trauma patients than in an average glaucoma population: In a study of 93 eyes, Schlote et al. reported an IOP success rate of 54.5% for 14 trauma eyes compared with that of 90% for eyes with primary open-angle glaucoma. (Schlote et al. 2001b) In this study, after krypton CPC,

the mean IOP decreased by 40%. With the non-contact Nd:YAG CPC, Baez et al. (Baez et al. 1994) reported a decrease in mean IOP of 22% in posttraumatic glaucoma (n=8), which showed the least hypotensive effect in a study of 128 eyes. In that study, a decrease in mean IOP of 56% was achieved in neovascular glaucoma, although the posttraumatic patients required more treatment sessions per eye (3.6 treatments vs. 1.3 treatments within 2 years).

After contact 810 nm diode CPC, the mean percentage IOP reduction in posttraumatic glaucoma (n=14) was 33% in a study of 210 eyes, at the lower end of all the glaucoma subgroups included (29% in anterior dysgenesis to 53% in neovascular glaucoma) (Bloom et al. 1997). In contrast, in a study of 58 eyes, also with the 810 nm diode CPC, Spencer and Vernon obtained a reduction of 57% in mean IOP in trauma patients (n=5). (Spencer et al. 1999) They obtained a lower postoperative mean IOP in posttraumatic glaucoma compared with that of all treated eyes which may be due to the small number of trauma patients analyzed in their study.

To reach an acceptable IOP, repeated CPC treatments were needed in 8 of the 18 eyes in the posttraumatic eyes (44%) in the present study. In a general glaucoma population evaluated by Bloom et al. (mean follow-up time 10 months), 102 of the 210 eyes (49%) were retreated, and in that of Immonen et al. (mean follow-up time 6 months), 8 of the 62 eyes (13%) were retreated. (Immonen et al. 1994, Bloom et al. 1997)

In posttraumatic glaucoma, conjunctival and scleral abnormalities may prevent incisional glaucoma surgery. The outcome of a filtration procedure (Mermoud et al. 1996) or implant surgery (Välimäki et al. 1998) in traumatized eyes is modest, mainly because of the increased healing response due to intraocular inflammation, previous intraocular operations, and the young age of trauma patients. Vitreous incarceration into the filtering site or at the tube in a posttraumatic aphakic eye may also block the outflow. In filtration surgery without antimetabolites, the cumulative probability of survival in angle-recession glaucoma was 52% at 1 year, 32% at 3 years, and 8% at 5 years. (Mermoud et al. 1993a)

In angle-recession glaucoma, trabeculectomy with antimetabolites resulted in more successful cases at 3 and 6 months than trabeculectomy without antimetabolites or Molteno implantation. (Mermoud et al. 1993b) The mean reduction in IOP was also largest in the antimetabolite group (59% as compared with 36% and 41%). However, when the surgical outcome for each operation was compared, using the log-rank test, no statistically significant difference was found. In 15% of patients treated with 5-fluorouracil or mitomycin C, there were severe bleb-associated complications as compared with 0% after trabeculectomy and 0% after implant surgery. (Mermoud et al. 1993b)

The IOP results in the present study and those of eyes with angle-recession glaucoma only cannot be directly compared (Mermoud et al. 1993b, Mermoud et al. 1993a), as, in the latter studies, eyes with partial or total dislocation of the lens and eyes with angle closure due to peripheral anterior synechiae had been excluded. Most of the patients in our study had suffered from open globe injuries with multiple reconstructive procedures subsequently.

In the present study, the median number of topical glaucoma preparations, preoperatively was 2 and at the last control visit, 1. The median daily dose of CAI and the proportion of patients taking it was reduced during the follow-up. This reduction did not reach statistical significance. In the literature, there are no available data concerning the change in medical therapy of posttraumatic patients only, but our result is in accord with the results reported by Schlote 2001b et al. for 810 nm diode CPC in a general glaucoma population. (Schlote 2001b et al.) As in the present study, patients were able to discontinue CAI after 810 nm diode CPC. (Bloom et al. 1997, Mistlberger et al. 2001) The mean total number of glaucoma medications was reduced in some studies of 810 nm diode CPC (Kosoko et al. 1996, Wong et al. 1997, Werner et al. 1998, Yap-Veloso 1998, Spencer et al. 1999, Therkeld et al. 1999, Pucci et al. 2001). In some studies made after Nd:YAG CPC in a general glaucoma population, the mean number of medications was reduced, but the statistical significance of the change was not always tested (Brancato et al. 1989, Hampton et al. 1990, Trope and Ma 1990, Al-Ghamdi et al. 1993, Hennis et al. 1993) In some reports the number of medications remained unchanged. (Hawkins et al. 1993) However, after filtering and implant surgery in angle-recession glaucoma, the need for additional glaucoma medication was statistically significantly reduced. (Mermoud et al. 1993b, Mermoud et al. 1993a)

In the present study, 3 of 18 eyes (17%) showed a decline in VA after a mean follow-up time of 19.4 months. We consider the visual loss in 2 eyes to be potentially CPC-related. After Nd:YAG CPC, using

varying criteria, VA decreased in 7% to 65% of eyes. (Trope et al. 1990, Schuman et al. 1992, Al-Ghamdi et al. 1993, Shields et al. 1993, Baez et al. 1994, Shields et al. 1994, Dickens et al. 1995, Zhou Wei et al. 1996, Youn et al. 1998) Similarly, after 810 nm diode CPC, 18.7% to 38% lost vision. (Yap-Veloso et al. 1998, Youn et al. 1998, Spencer et al. 1999, Mistlberger et al. 2001) Studies indicate that postoperative visual loss after Nd:YAG CPC is correlated with hypotonia, neovascular glaucoma and a long follow-up time. (Schuman et al. 1992, Youn et al. 1996). After filtering or implant surgery with or without antimetabolites, 26% of posttraumatic patients had a decrease in vision. (Mermoud et al. 1993b)

In the present study, one patient (6%) developed phthisis bulbi, but only 2 years and 2 months after the last CPC and 5 months after complicated cataract surgery, before which the IOP had been within the normal range. No other patient ended up with an IOP permanently less than 6 mmHg. In the series of Immonen et al. (Immonen et al. 1994), hypotonia (4 mmHg < IOP < 8mmHg) was seen in 4% and phthisis bulbi in no eyes treated with krypton laser CPC.

After 810 nm diode laser CPC, hypotonia was reported in 0% to 15% and phthisis in 0% to 2%. (Hawkins et al. 1993, Kosoko et al. 1996, Yap-Veloso et al. 1998, Youn et al. 1998, Spencer et al. 1999, Walland 2000, Schlote et al. 2001b) After Nd:YAG CPC, hypotonia rates of 0% to 15%, (Schuman et al. 1990c, Al-Ghamdi et al. 1993, Shields et al. 1993, Shields et al. 1994) and rates of phthisis bulbi of 0% to 11% (Trope et al. 1990, Schuman et al. 1992, Shields et al. 1993, Baez et al. 1994, Shields et al. 1994, Dickens et al. 1995, Zhou Wei et al. 1996 Threlkeld et al. 1999) have been reported in a general glaucoma population. After glaucoma implant surgery, 0% to 6% developed phthisis. (Lloyd et al. 1992, Noureddin et al. 1992, Lloyd et al. 1994, Krishna et al. 2001)

In the present study, postoperative inflammation was mild. The eyes appeared reasonably unaffected with no signs of conjunctival injury. In one patient, scleral thinning was found on the treatment area after the third CPC. No significant postoperative pain, fibrinoid reactions, intraocular haemorrhages, or permanent posterior segment complications were detected.

6.3. Transscleral Cyclophotocoagulation with the Contact Krypton Laser for Treatment of Glaucoma in Children and Young Adults (II)

In young glaucoma patients, medical glaucoma treatment has only a limited effect. Surgical treatment options include goniotomy, trabeculotomy, trabeculectomy, or combined trabeculotomy-trabeculectomy. (Luntz 1996, Costa et al. 1993) The success of filtration and implant surgery (Munoz et al. 1991, Hill et al. 1991, Eid 1997a) is lowered by the thick Tenon´s capsule, the strong healing response, and, in some patients, by scarring of the conjunctiva after previous operations. (Beauchamp et al. 1979, Stürmer et al. 1993) Performing a glaucoma filtration procedure or implant surgery in buphthalmic eyes is complicated by the stretching and thinning of the coats of the eye, the low scleral rigidity, and the failure of the stretched zonules to provide a normal suspension for the lens or support for the vitreous. (Beauchamp et al. 1979) Previous ocular operations resulting in conjunctival adherence to the sclera also carry a worse prognosis for a successful filtering bleb. (Beauchamp et al. 1979, Stürmer et al. 1993)

Trabeculectomy with antimetabolites is performed in children in eyes in which conventional procedures have failed, but also as a primary procedure. (Susanna et al. 1995, Mandal et al. 1997, Beck et al. 1998, Al-Hazmi et al. 1999) When previous incisional surgery has failed or in cases considered unlikely to be controlled with other treatment modalities, transscleral CPC (Phelan et al. 1995, Bock et al. 1997, Izgi et al. 2001, Kirwan et al. 2002) and endoscopic CPC (Neely et al. 2001, Barkana et al. 2002) have been performed.

Twenty of 22 eyes in this series had difficult secondary glaucoma. In these eyes, 21 unsuccessful filtering and/or implant glaucoma operations and revisions, and 16 other intraocular operations had already been performed before the krypton CPC.

After one or more krypton CPC treatments, an IOP of 8 to 21 mmHg was obtained in nine (41%) and an IOP of 8 to 21 mmHg or a reduction in IOP of > 30% in 14 (64%) of 22 eyes at the last follow-up visit. Our IOP success rate is comparable with that of most previous studies in young patients, but lower than that of

most adult series treated with CPC. (Phelan et al. 1995, Bock et al. 1997, Immonen et al. 1994, Youn et al. 1996, Bloom et al. 1997, Kirwan et al. 2002) The better outcome in the adult population implies that paediatric patients are less responsive to CPC treatment. However, Izgi et al. found no statistically difference in the IOP survival rate between adult (n=26) and paediatric (n=15) glaucoma patients after 810 nm diode CPC, but the number of eyes in that study may have been small for the purpose of comparison. (Izgi et al. 2001)

In children, repeated treatments were needed in 64% of the eyes in the present study and in 56% to 70% of the eyes in other studies. (Phelan et al. 1995, Bock et al. 1997, Kirwan et al. 2002) Retreatments are needed less often in adults, for only 13% of the eyes were retreated in the study of adult glaucoma by Immonen et al., using the krypton laser, and in 49% of the eyes in the study of Bloom et al. (Bloom et al. 1997), using the 810 nm diode laser. Izgi et al. found no significant difference in the retreatment rate between paediatric patients and adults, but, again, the numbers in that study may have been small for the purpose of comparison. (Izgi et al. 2001)

Irrespective of the surgical modality used (CPC, filtration or implant surgery), the treatment of glaucoma in children and young adults is challenging. Although higher success rates have been reported in selected series (mainly in those of primary glaucomas), success rates obtained in unselected paediatric populations are in the same range irrespective of the treatment modality used (Table 2). (Beauchamp et al. 1979, Hill et al. 1991, Munoz et al. 1991, Lloyd et al. 1992, Stürmer et al. 1993, Susanna et al. 1995, Eid et al. 1997a, Mandal et al. 1997, Al-Hazmi et al. 1998, Beck et al. 1998)

In the present study, there was a statistically significant reduction in the number of eyes using glaucoma medication at the last follow-up visit compared to baseline, but the median number of topical glaucoma medications pre- and postoperatively was 2. The mean number of medications was statistically significantly reduced in the study of Izgi et al. (Izgi et al. 2001), but others reported that CPC did not enable reduction of the number of medications in childhood glaucoma. (Phelan et al. 1995, Bock et al. 1997, Kirwan et al. 2002)

In the present study, VA decreased by more than two Snellen lines or there was a change in the low vision category in 18% of eyes during the follow-up time. In view of the severity of the multiple concomitant conditions in these eyes, it is difficult to decide how far CPC was responsible for the observed decline in VA. Izgi et al. found no VA decrease after CPC in paediatric glaucoma, but most of the eyes in his study had congenital glaucoma. (Izgi et al. 2001) In the study by Kirwan et al., also comprising fewer cases of secondary glaucoma than our study, 8% lost vision after CPC. (Kirwan et al. 2002)

In young patients, the interpretation of the effect of CPC is complicated by the imprecise nature of VA measurement, especially at the low levels of vision, and visual maturation during follow-up. (Izgi et al. 2001, Kirwan et al. 2002) After the contact 810 nm diode CPC for paediatric glaucoma, Bock et al. noted a decline in vision in 4 (18%) of 22 eyes and Phelan et al., after using the contact Nd:YAG laser, noted a decline in 4 (40%) of 10 eyes. (Phelan et al. 1995, Bock et al. 1997)

In the present study, no eyes ended up in permanent hypotonia or phthisis bulbi. In other paediatric glaucoma series, using a 810 nm contact diode laser, phthisis was reported in 0% (Izgi et al. 2001), 4% (Kirwan et al. 2002), and 5% (Bock et al. 1997), and, using a contact Nd:YAG laser, in 10%. (Phelan et al. 1995) The absence of chronic hypotonia and phthisis in our series may be due to the fact that, even in patients with multiple treatment sessions, we generally avoided treating 360° of the ciliary body.

In our study, postoperative inflammation was mostly mild. There was no significant postoperative pain requiring systemic analgesics, or intraocular haemorrhages, or permanent complications in the posterior segment. The eyes appeared reasonably unaffected, except those with chronic uveitis, which required more postoperative cortisone eye drops. No signs of conjunctival injury were detected. Scleral thinning developed in two eyes: one of these had received one CPC at a distance of 4 mm from the limbus (with obvious incorrect localization of the pars plicata region) in the pars plana, where the pigment epithelium is closer to the sclera than in the pars plicata, probably thus contributing to absorption of more energy by the sclera. The other eye was a microphthalmic aphakic eye treated with CPC at a distance of 1.5 mm from the limbus. Possibly, anterior segment anomalies in this eye contributed to the abnormal scleral absorption of the laser energy. No reports comparing the penetration and absorption of laser energy through the human eye in children are available, but focal scleral thinning was also detected earlier in a 30-year-old man treated with the Nd:YAG laser CPC. (Fiore et al. 1989) More recently, scleral perforation was reported after 810 nm contact CPC in an eye with scleral thinning following cataract surgery. (Sabri et al. 1999)

In other studies of CPC in young patients, postoperative complications were also few. (Kirwan et al. 2002, Phelan et al. 1995, Izgi et al. 2001, Bock et al. 1997) However, retinal detachment and subsequent phthisis in the majority of the same cases were discovered in 4% to 10%. (Kirwan et al. 2002, Phelan et al. 1995, Izgi et al. 2001, Bock et al. 1997) Kirwan et al. further repored that two of the three paediatric patients with postoperative retinal detachment had previously been treated with Nd:YAG CPC. In adults, retinal detachment is a known complication of Nd:YAG CPC. (Geyer et al. 1993)

6.4. Transscleral Cyclophotocoagulation with the Red Laser Combined with Limited Anterior Retinal Cryocoagulation in Neovascular Glaucoma (III)

In neovascular glaucoma, there is no ideal surgical procedure. (Sivak-Callott et al. 2001) Despite successful control of IOP, the visual prognosis remains poor because of the severe underlying disease process. The patients with neovascular glaucoma in this study were of advanced age (mean, 75.0 years) with high preoperative IOPs (mean, 44.0 mmHg) and poor VA (unrecordable with the Snellen charts in 90% of the patients). In the majority (77%) of the eyes, neovascular glaucoma was caused by a previous occlusion of the central retinal vein. In 19 eyes, the combined procedure was performed to achieve an IOP within the normal range and to preserve vision. In 11 eyes, it was performed to decrease the IOP to a tolerable level and relieve ocular pain in an eye with no visual potential.

6.4.1. Retinal Cryocoagulation

In the management of neovascular glaucoma, the cornerstone is retinal panphotocoagulation. (Krill et al. 1971, Laatikainen 1977, Flanagan et al. 1983). Transpupillary retinal photocoagulation can be performed with a slit-lamp delivery system or with indirect ophthalmoscopy. If media opacities or retinal haemorrhages are present, the 647 nm krypton laser and the 810 nm diode laser will frequently be more effective than the argon laser. (Wand 1996)

In eyes with neovascular glaucoma, fundus visibility is often decreased because of corneal decompensation, poor mydriasis, cataract, and/or vitreous haemorrhage, which prevent transpupillary laser treatment of the retina. (Lloyd et al. 1991, Mermoud et al. 1993c, Tsai et al. 1996, Flaxel et al. 1997) In cases of inadequate visualization, transscleral anterior retinal cryocoagulation (Sihota et al. 1991, Knapp et al. 1997) and transscleral retinal photocoagulation (Tsai et al. 1996, Flaxel et al. 1997) are viable treatment options. Preoperatively in this study, it had been possible to perform transpupillary retinal panphotocoagulation in only 23% of eyes, but, even in these eyes, active iris neovascularization persisted. Thus, the only means of decreasing the ischaemic stimulus was considered to be transscleral cryocoagulation of the anterior retina.

Retinal cryocoagulation is known to induce more breakdown of the blood-retinal barrier than retinal laser photocoagulation (Jaccoma et al. 1985, Inoue et al. 2001), especially if the freezing time is long or if the same site is frozen repeatedly. (Singh et al. 1986) Excessive breakdown of the blood-eye barrier is connected with fibrinoid reactions and proliferative vitreoretinopathy. To minimize these reactions, we limited the number of applications to 15 to 40 per treatment and set the applications no further than 1 to 2 rows behind the ora serrata. In 93%, fundus visibility was sufficient for ophthalmoscopic monitoring of the retinal freezing, which was interrupted at the first sign of retinal blanching.

6.4.2. Outcome of the combined procedure

In this study, the decrease in mean IOP of 50% was comparable with that of other transscleral laser CPC modalities in neovascular glaucoma (Table 3). In the published studies, the IOP success rates have ranged from 33% to 86%. It is difficult to compare these results with those of the present study, because of the

differences in the patient characteristics and the definition of IOP success. It appears, however, that the IOP successes with the combined procedure with the krypton and 670 nm diode lasers in our study, 62% and 71% (using a definition of IOP < 22 mmHg for the purpose of comparison) and in particular those of the therapeutic group, 86% and 92%, are high compared with those published for the CPC in neovascular glaucoma (Table 3). The IOP responses in the krypton laser and the 670 nm diode laser groups were equal, but the retreatment rate was higher in the 670 nm diode group. In 43% of cases, iris neovascularization regressed or disappeared.

In a study by Flaxel et al., transscleral retinal 810 nm diode laser photocoagulation was combined with the 810 nm diode laser CPC, and an IOP of < 22 mmHg was obtained in six out of nine eyes and hypotonia developed (IOP of 0 to 2 mmHg) in three eyes. (Flaxel et al. 1997) All eyes showed regression of rubeosis, and one eye showed complete resolution of rubeosis. In both the two eyes treated similarly by Tsai et al., an IOP of < 22 mmHg and the regression of rubeosis was achieved in both eyes. (Tsai et al. 1996)

In neovascular glaucoma, filtration surgery has a poor chance of success unless the stimulus for new vessel formation is eliminated. (Wand 1996) Studies on filtration and implant surgery in neovascular glaucoma show success rates of 35% to 67% (Table 4, Allen et al. 1982, Minckler et al. 1988, Lloyd et al. 1991, Mermoud et al. 1993c, Tsai et al. 1995) but also a high incidence of visual decrease (up to 62%) and phthisis (up to 24%). Tube surgery compared favourably with the non-contact Nd:YAG CPC (360° treatment in 83% of the eyes) in terms of IOP control (the mean final reduction in IOP in the two groups was equal), visual outcome (baseline VA was significantly worse in the CPC group), and hypotonia (3/24 eyes in the tube surgery group vs. 6/24 eyes in the CPC group) in neovascular glaucoma. (Eid et al. 1997b) Randomized clinical comparisons of tube surgery and contact CPC with other laser modalities are not as yet available.

In the present study, the reduction in use of CAI after treatment was statistically significant. At the last follow-up, one patient (3%), as compared with eight (27%) at baseline, was using peroral CAI. During follow-up, the median number of topical glaucoma medications was also reduced from 2.0 to 1.0 in both laser treatment groups, but this reduction was not statistically significant. After fr-YAG (n=9), cw-YAG (n=9), or 810 nm diode (n=21) CPC in neovascular glaucoma eyes only, Oguri reported a result similar to ours. (Oguri et al. 1998) However, use of CAI was not separately reported in that study.

In our study, VA decreased during the follow-up time in 15 (50%) of 30 eyes and, of these, seven eyes progressed to no light perception. The reasons for the decrease in vision were a high IOP and progression of the retinal disease in seven eyes with no visual potential, in which the treatment was palliative. In the eight eyes in which the treatment was therapeutic, the causes of visual deterioration were progression of the retinal disease (five eyes), progression of cataract (two eyes), and vitreous haemorrhage with intermittent high IOP (one eye). Thus, the decline in vision seemed not to be treatment-related in our study. This is in agreement with the results of Egbert et al. in eyes with primary open-angle glaucoma. (Egbert et al. 2001) In their study, they found equal rates of visual decrease (23%) in the eyes after primary 810 nm diode CPC and in the control fellow eyes that were receiving medical therapy only. Similarly, in the study of Hamard et al., a decrease in VA, noted in 34% of eyes treated with 810 nm diode CPC, was not related to cyclodestruction. (Hamard et al. 1997) In the present study, VA was very poor preoperatively (unrecordable with the Snellen charts in 90% of the patients), which may have caused fluctuation and unreliability in visual testing.

After Nd:YAG CPC, the decrease in VA was shown to be high, up to 56%, in eyes with neovascular glaucoma, partly as a result of hypotonia and phthisis. (Hampton et al. 1990, Schuman et al. 1992, Youn et al. 1996) In the study of Oguri et al. (Oguri et al. 1998) in neovascular glaucomatous eyes treated with the 810 nm diode CPC, 24% lost vision. An additional 14% of the eyes in that study already had no light perception at baseline. Studies of filtration and implant surgery in neovascular glaucoma also show a high incidence of visual decrease, up to 62% (Table 4). (Allen et al. 1982, Minckler et al. 1988, Lloyd et al. 1991, Mermoud et al. 1993c, Tsai et al. 1995)

In the present study, only one eye (3%) developed phthisis 39 months after the CPC and another eye had an IOP of 5 mmHg at the last follow-up visit. This low incidence of hypotonia and phthisis may be due to the fact that, even after multiple treatments, we generally left one quadrant of the ciliary body untreated. Most complications after treatment were mild and transient (Table 22). Hypotonia and phthisis are well-known complications of cyclodestructive treatments, described especially after cyclocryotherapy (Klemm et al. 1995, Heuring et al. 1998) and Nd:YAG CPC. With the contact or non-contact Nd:YAG CPC, phthisis bulbi of up to 19% have been reported in neovascular glaucoma (Table 3) (Trope et al. 1990, Schuman et al. 1992,

Shields et al. 1994, Youn et al. 1996), but neovascular glaucoma was also shown to be an independent risk factor for these complications. (Hampton et al. 1990, Schuman et al. 1992, Youn et al. 1996) After filtration and implant surgery in neovascular glaucoma, phthisis was reported in 0% to 24% of eyes. (Table 4)

6.5. Corneal Innervation, Corneal Mechanical Sensitivity, and Tear Fluid Secretion after Transscleral Cyclophotocoagulation with the Contact 670 nm Diode Laser (IV)

6.5.1. In vivo confocal microscopy

After 670 nm diode laser CPC, sequential *in vivo* confocal microscopic examinations of the subbasal nerve plexus in the central and inferior limbal areas of the three corneas studied, at the level of resolution allowed by the methodology, did not reveal any significant reduction in nerve density. However, it should be noted that with *in vivo* confocal microscopy, bundles of nerve fibres are viewed, rather than single fibres (Müller et al. 1996, Müller et al. 1997), and, therefore, with this technique, the absence of single nerve fibres among the bundles cannot be discerned. The confocal microscopic examination can also be criticised for the fact that only a very limited area of the cornea (360 µm x 450 µm) can be evaluated at one time. As most of the stromal nerves run obliquely to the surface and cannot be easily visualized by *in vivo* confocal microscopy, stromal nerve density was not evaluated.

Before treatment, the patients already showed a reduced number of subbasal nerve fibre bundles, which may have been due to their advanced age. The confocal microscopic images of the subbasal nerves in the healthy cornea, published earlier, represent those of younger individuals. (Rosenberg et al. 2000b, Vesaluoma et al. 2000) Glaucoma and the prolonged use of glaucoma medication can also be speculated to have played a role. However, none of the three patients examined by confocal microscopy had undergone any previous intraocular surgical procedures or transscleral treatments that would have affected the corneal nerves.

Bearing in mind the limitations of the confocal microscopic technique, we conclude that our present findings concerning the corneal nerves are in accord with those previously reported by Johnson et al. (Johnson et al. 1999). Using anticholinesterase staining, Johnson et al. did not find any quantitative histological changes in corneal nerve density after the 810 nm diode laser CPC in a rabbit model. However, qualitative changes in the structure of the nerve fibres were revealed in their study by transmission electron microscopy: The 810 nm diode laser CPC appeared to cause disruption of the myelin nerve sheaths, and damaged keratocytes were also observed in the tissue samples. We did not detect any keratocyte activation or particular damage to the keratocytes in the central cornea by *in vivo* confocal microscopy after 670 nm diode laser CPC.

6.5.2. Corneal sensitivity and tear fluid secretion

Comparison of the pre- and postoperative data for each corneal area in each individual eye showed that there were no statistically significant changes in the mechanical sensitivity values in any of the corneal areas examined.

Since tear secretion is under neural control, (Dartt 1994, Meneray et al. 1998) we expected that, if CPC induced a sensory deficit, the amount of the basic tear secretion would diminish, as was shown to happen after laser in situ keratomileusis (LASIK) by Yu et al. (Yu et al. 2000) Of our patients, two had changed to a higher Schirmer value category. Four of our patients had changed to a lower Schirmer value category, but, in the cornea next to the treated part of the ciliary body, the sensitivity remained unchanged. There was no

systematic trend towards worsening of the Schirmer value, and since the Schirmer basic secretion tear test excludes reflex tear production, it might be expected that the variability of these results would be less than that of the total secretion.

The clinical course of the eyes studied was unremarkable. Patient 3 showed transient corneal punctate staining with fluorescein at 3 days, but no reduction in tear fluid secretion, no deterioration in corneal sensitivity, and no change in the corneal subbasal nerves during follow-up.

Given the small sample size in this investigation, further controlled studies with larger numbers of patients are desirable to definitively rule out the possibility of corneal nerve damage after transscleral contact 670 nm diode CPC.

7. Summary and conclusions

Today, it appears reasonable to consider that, in addition to destroying the epithelium and capillaries of the ciliary processes (Marsh et al. 1993), cyclodestruction contributes to the increase in uveoscleral outflow of aqueous humour due to loss of the blood-aqueous barrier within the laser-induced scar. (Schubert 1989a, Schubert 1990, Liu et al. 1994) The results of this study reveal the outcome of transscleral red laser CPC in therapy-resistant glaucoma. The protocol with low laser power and a long duration of application diverges from the other treatments commonly used for CPC. In transscleral cyclophotocoagulation, the importance of careful peroperative localization of the pars plicata, using scleral transillumination must be stressed.

The study comprised the patients with therapy-resistant posttraumatic glaucoma who were treated with krypton red laser CPC at the Department of Ophthalmology, Helsinki University Eye Hospital, the aim being to evaluate the usefulness and complications of this procedure in posttraumatic glaucoma. There were altogether 18 eyes of 18 patients, aged 56.6 ± 23.0 years. The indication for CPC was uncontrolled glaucoma despite maximal tolerated medication. The procedure was performed as an alternative to filtration or implant glaucoma surgery. Follow-up data were gathered in a retrospective chart review. After one or more krypton CPCs, but no other glaucoma procedures, the mean IOP decreased by 40% from the preoperative level of 32.6 ± 12.8 mmHg to 19.6 ± 10.5 mmHg at the last control visit 19.4 ± 21.2 months postoperatively. The IOP success rate (an IOP of 8 to 21 mmHg or a decrease in IOP > 30%) was 67%. There were three eyes with pretreatment IOP < 22 mmHg which all maintained this IOP level after treatment, but none achieved greater than a 30% IOP reduction. If these three eyes are classified as treatment failures, the success rate decreases to 50%. This is within the success rates of CPC published of heterogeneous glaucoma populations. Repeated treatments were needed in 44% of eyes. The median number of topical glaucoma medications and the median daily dose of CAI was reduced during follow-up but the reduction did not reach statistical significance. Seventeen percent of eyes showed a decline in VA. One (6%) case of phthisis occurred. The results of this study suggest that transscleral krypton red laser CPC is a useful procedure for lowering IOP in posttraumatic glaucoma. It is reasonably safe for the eye and can be repeated when necessary.

Patients under 20 years of age with therapy-resistant glaucoma treated with the krypton red laser CPC at the Department of Ophthalmology, Helsinki University Eye Hospital, were included in the study to evaluate the usefulness and complications of the procedure in children and young adults with glaucoma. The study comprised 22 eyes of 22 patients, aged 10.5 ± 5.6 years. The indication for cyclophotocoagulation was uncontrolled glaucoma despite maximal tolerated medication. The procedure was performed as an alternative to filtration or implant glaucoma surgery. Follow-up data were gathered in a retrospective chart review. After one or more krypton CPC treatments, the mean IOP decreased by 25% from a preoperative level of 35.0 ± 7.9 to 26.2 ± 10.5 mmHg at the last control visit 27.1 ± 21.9 months postoperatively. IOPs of 8 to 21 mmHg were obtained in 41% and the IOP success rate (an IOP of 8 to 21 mmHg or a decrease in IOP of > 30%) at the last follow-up visit was 64%. Our IOP result is comparable with that of most previous studies in young patients, but lower than in most adult series treated with CPC. Success rates similar to ours have been obtained in unselected paediatric populations independently of the surgical treatment modality used. Repeated treatments were needed in 64% of the eyes. The number of patients using glaucoma medication at the last follow-up visit was reduced compared to the baseline ($P < 0.05$). VA decreased in 18% of eyes during the follow-up time. No permanent hypotonia, phthisis bulbi, or devastating CPC-related complications were noted. The results of this study suggest that the transscleral krypton red laser CPC is a reasonably safe procedure for lowering IOP in children and young adults with difficult glaucomas, but that multiple treatments may be needed.

Patients with therapy-resistant neovascular glaucoma treated with the krypton red laser (13 patients) or the 670 nm diode laser (17 patients) CPC followed by anterior retinal cryocoagulation at the Department of Ophthalmology, Helsinki University Eye Hospital, were included in the study to evaluate the usefulness and complications of this combined procedure in neovascular glaucoma. The study comprised 30 eyes of 30 patients, aged 75.0 ± 12.1 years. The indication for CPC was uncontrolled glaucoma despite maximal tolerated medication. The CPC was performed as an alternative to filtration or implant glaucoma surgery.

The indication for retinal cryocoagulation was retinal ischaemia, as demonstrated by iris neovascularization, and persisting after full panphotocoagulation or found to be untreatable by transpupillary panphotocoagulation. In 11 eyes with no visual potential, the combined treatment was performed to relieve pain (palliative group). In 19 eyes the treatment was performed to preserve vision (therapeutic group). Follow-up data were gathered in a retrospective chart review. After one or more CPC treatments and one retinal cryocoagulation, the mean IOP at the last follow-up 16.8 ± 13.8 months postoperatively had decreased by 50% from the preoperative level of 44.0 ± 12.5 mmHg to 22.1 ± 15.8 mmHg. In the therapeutic group, an IOP of 8 to 21 mmHg was obtained in 79% of eyes. The IOP success rate (an IOP of 8 to 21 mmHg or a decrease in IOP of more than 30%) for all eyes was 87% and, that for the therapeutic group, 95%. These IOP successes with the krypton and the 670 nm diode red laser in our study are high compared with those published for CPC with other laser modalities or those for filtration and implant surgery in neovascular glaucoma. The IOP responses in the krypton laser and the 670 nm diode laser groups were equal, but the retreatment rate was higher in the 670 nm diode group. Repeated CPC treatments were needed in 27% of the eyes. In 43% of cases, iris neovascularization regressed or disappeared. At the last follow-up, 3% of patients, as compared with 27% at baseline, was using peroral CAI ($P < 0.05$). VA decreased in 50% of all eyes and in 42% of the eyes with a therapeutic treatment indication. At the last follow-up, there was one case (3%) of hypotonia and one case (3%) of phthisis. The results of this study suggest that, in neovascular glaucoma, transscleral contact krypton or 670 nm diode red laser CPC combined with transscleral limited anterior retinal cryocoagulation is an efficient means for lowering the IOP and inducing regression of iris neovascularization. During the follow-up, the underlying retinal disease causes a decrease in VA in a significant proportion of patients.

Ten patients with therapy-resistant glaucoma enrolled for 670 nm diode laser CPC at the Department of Ophthalmology, Helsinki University Eye Hospital, were included in the study to investigate whether the 670 nm diode red laser CPC has an effect on corneal morphology and the density of corneal subbasal nerves as studied by *in vivo* confocal microscopy, on corneal mechanical sensitivity, and on the rate of tear fluid secretion. The study comprised 10 eyes of 10 patients aged 73.8 ± 6.4 years. The CPC was performed as an alternative to filtration or implant glaucoma surgery. Follow-up data were gathered prospectively. *In vivo* confocal microscopy, with special attention to corneal morphology and the density of the subbasal nerves in the central and inferior perilimbal cornea, was performed in three eyes preoperatively, and at 3 days, and 1 month postoperatively. Corneal mechanical sensitivity was tested in all eyes preoperatively, and at 3 days, and at 1 month postoperatively, using a Cochet-Bonnet aesthesiometer. The rate of tear fluid secretion was measured in all eyes preoperatively and 1 month postoperatively, using the Schirmer basic secretion tear test. After treatment, *in vivo* confocal microscopy did not reveal any changes in any of the corneal layers or in the corneal subbasal nerves, nor was there any statistically significant change in the mechanical sensitivity values in any part of the cornea or in the Schirmer basic secretion tear test result (paired samples *t* test, $P > 0.05$). The results of this study suggest that transscleral CPC with the 670 nm diode red laser does not impair corneal innervation.

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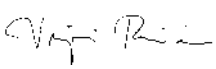

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