A Comparison of CW Nd:YAG Contact Transscleral Cyclophotocoagulation with Cyclocryopexy

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The cyclodestructive and inflammatory effects of CW Nd:YAG contact laser were compared to those of conventional cryopexy. CW Nd:YAG light transmitted by fiber optic cable and sapphire crystal was applied transsclerally to the ciliary body of pigmented and albino rabbits. Cyclocryopexy was given to a comparable second group. The intraocular pressure (IOP), flare, iritis, cells and conjunctival hyperemia were monitored clinically up to 3 weeks. The breakdown of the blood-aqueous barrier and time course of ocular inflammation was similar for both modalities and IOP was −12.2 ± 4.2 mm Hg for laser cyclopxy and −15.1 ± 5.4 mm Hg for cyclocryopexy at 3 weeks. Ciliary body lesions were noted in both groups. Overall, albino rabbits showed less histological damage and faster recovery of IOP. Contact cyclocphotocoagulation and cyclocryopexy can be considered models of ocular injury. The similarities in ocular irritative response suggest a similar pathophysiologic mechanism underlying the pressure behavior in both thermal mode injuries. Invest Ophthalmol Vis Sci 30:536-542, 1989

Cyclodestruction is generally achieved by applying thermal energy across the intact sclera. Commonly employed modalities are cryopexy,1,9 diathermy,2 noncontact laser light,3,10 ultrasound4 and, most recently, contact transscleral laser using argon, krypton5 and CW Nd:YAG6 light. The desired end result in cycloablation is a decrease in intraocular pressure thought to be due to reduced aqueous production,2,7-9 vascular compromise,2,9 a reduction in ciliary epithelial surface,7,10 ciliary body atrophy3,10 or, in addition, an increase in uveoscleral outflow.8 Cycloablation by definition destroys intraocular tissues. According to current thinking, destruction has to be effective, controlled and specific to minimize side effects. It is therefore the purpose of this study to compare the pressure-lowering and tissue effects of contact transscleral photocoagulation to transscleral cryopexy in an animal model. Pigmented and albino rabbits were juxtaposed to examine the effects of uveal pigmentation on IOP for both laser and cryopexy groups. Finally the time course of post-treatment inflammation was recorded for each group. Our results indicate that both transscleral laser photocoagulation and transscleral cryopexy are models of ocular injury whose tissue effects and irritative response are phenotypically similar, suggesting a similar pathomechanism underlying the pressure reduction.

Materials and Methods

Male and female Dutch-Belted and New Zealand White albino rabbits (1.5–3 kg) were placed in rabbit boxes without restraint. The ARVO Resolution on the Use of Animals in Research was followed. One drop of 0.5% proparacaine hydrochloride (Alcon Laboratories, Fort Worth, TX) was applied topically to each conjunctival sac. A floating tip pneumotonometer (Alcon Laboratories) calibrated with the standard calibrator (Alcon)19 was used to measure the IOP in conscious animals. Five in vivo baseline measurements and observations were then made on each eye to characterize the time course of inflammation, as described previously.20 Briefly, aqueous flare and cellular response in the anterior chamber were assessed using a slit lamp. The response was rated from 0 to 3+: 0: no tindall effect; 1+: slight tindall effect; 2+: moderate to dense tindall effect; 3+: dense tindall effect with fibrin clots. Iris hyperemia was rated from 0 to 3+: 0: no cells apparent; 1+: few cells; 2+: many cells and 3+: cell clumps. Pupillary diameter was measured with a pupil gauge in millimeters. Conjunctival effects were rated grossly. 1+: conjunctival hyperemia only; 2+: hyperemia and chemosis of the bulbar conjunctiva,
and 3+: prolapsing conjunctival chemosis and upper lid swelling. After these baseline observations, the animals were anesthetized with intramuscular ketamine hydrochloride (100 mg/ml) and acepromazine 10 mg/ml. For all animals in this study, the anesthesia was identical. Twelve animals each were assigned to the laser group or cryopexy group. Half of each group of rabbits was albinotic and the other half pigmented. CW Nd:YAG light (1.0-5 W) was generated by a self-calibrating laser unit (SLT, Malvern, PA) and transmitted through a quartz fiber-optic cable. A pencil-shaped handpiece carried a rounded sapphire crystal measuring 2.2 x 1.5 mm. The right eye of each animal was gently proptosed. The crystal was brought into conjunctival contact just posterior to the limbus in opaque sclera and the beam was directed toward the opposite ora serrata. This was done to assure irradiation of the ciliary processes which are found in an anterior retroiridal position in the rabbit (Fig. 2a,b). Thirty applications were given for 360° with 1.5 J being the mean for pigmented rabbits and 2.5 J for albino rabbits at a constant exposure of 0.5 sec. Signs of irradiation in pigmented animals were a mild contraction and discoloration of the iris root with an occasional popping sound whenever the energy was selected too high. In a second group of 12 animals, a cryo unit (Keeler-Amoils, Acu 220, Bromhall, PA) was connected by a cable to a handheld probe with a tip measuring 2.2 mm in diameter. The right eye of each rabbit was gently proptosed and the tip of the cryo probe was brought into conjunctival contact just posterior to the limbus. Six applications of confluent cryopexy were given to the superior limb. Each application was carried out for 60 sec at -80°C. A circular ice ball formed including the limbal arcades and 0.5 mm of clear cornea. Following the laser or cryopexy treatment, intraocular pressure readings and the other biomicroscopic observations were repeated, immediately after the injury and at one-half hour, 1, 2, 4, 7, 24 hr, 2, 3, 5, 7, 10, 14, 17, 19, 20 and 21 days. The last three measurements on days 19, 20 and 21 were averaged to obtain a more objective end point at 3 weeks. For each data point the mean and standard deviation of the difference of experimental and control eyes were calculated. Under full anesthesia, rabbits were sacrificed at 21 days using intravenous T-61 euthanasia solution (Hoechst, Somerville, NJ). The eyes were enucleated. Aqueous was removed using a tuberculin syringe and aqueous and vitreous were stored for later analysis. The eyes were fixed in cold 10% formaldehyde solution for a minimum of 1 week and dissected and photographed using a dissecting microscope. Sections of tissue containing lesions were embedded in paraffin, sectioned for light microscopy and stained with Hematoxilin and Eosin.

Results

Biomicroscopic Observations

Ocular response to contact CW Nd:YAG cyclophotocoagulation: Following photoagulation in albino rabbits the IOP rose only minimally (Fig. 1a), accompanied by minimal flare (Fig. 1b) and iris hyperemia (Fig. 1f). There was no cellular or conjunctival reaction.

In pigmented rabbits the IOP reached +12.3 ± 5.3 mm Hg at 30 min, fell and reached a second peak at 2-3 hr (Fig. 1a). The highest isolated increase in IOP recorded was +22 mm Hg at 1 hr. Compared to the control eye, the laser-treated eye became hypotensive at 1 day, reached a minimum in IOP at 3 days, and had an average reduction of IOP of -12.2 ± 4.2 mm at 3 weeks. Maximum aqueous flare was reached at 2 hr, was maintained until day 5 and decreased thereafter (Fig. 1b). Pupillary miosis was maximal immediately postoperatively (Fig. 1e). Iritis and aqueous cells followed the time course of aqueous flare (Fig. 1f,g). Mild conjunctival hyperemia was noted from day 1-10 (Fig. 1h).

Ocular response to cryopexy: Following cyclocryopexy the IOP rose immediately in both albino and pigmented rabbits reaching a peak of 19.3 ± 12.9 mm Hg at 30 min (Fig. 1c). The highest isolated pressure increase recorded in a pigmented rabbit was +41 mm Hg at 30 min. The pressure fell in pigmented rabbits and reached a second peak at 2-4 hr (Fig. 1c). On the average, pressures fell below control pressures at 1-2 days, reached a minimum IOP at 5 days and increased thereafter. At 3 weeks, the average pressure was -5.4 ± 5.9 mm Hg in the albino group and -15.1 ± 5.4 mm Hg in the pigmented group, a difference that is statistically significant. Even though maximum flare was present in both pigmented and albino rabbits at 7 hr, the recovery of flare was faster in albino rabbits, parallelling the faster return of IOP to normal levels (Fig. 1d).

Miosis was more pronounced in pigmented rabbits than in albino rabbits undergoing cryopexy (Fig. 1i) or pigmented rabbits undergoing laser treatment (Fig. 1e). Iritis and aqueous cells followed the time course of aqueous flare (Fig. 1jk). As expected, following cryopexy, the conjunctival reaction was pronounced. Albino rabbits had the most conjunctival chemosis and lid swelling (Fig. 1e).
Morphologic Observations

Cyclolaser in albino eyes: All eyes were grossly and histologically normal.

Cyclolaser in pigmented eyes: Grossly, all pigmented eyes showed fine limbal neovascularization and pupillary anisochoria in five of six eyes. Mild, diffuse and focal lens opacities were seen in five of six eyes, posterior synechiae in two eyes. On cut surface ciliary body lesions were identified with great ease extending circumferentially (Fig. 2c). The ciliary body processes were flattened and covered by superficial fibrous tissue attached to the lens equator. The anterior vitreous was condensed. Retroliral lesions were seen in all eyes associated with iris atrophy and corectopia. Histologically, compared to a control (Fig. 2b) there was disorganization and atrophy of the fibrovascular ciliary body and iris stroma (Fig. 2d). The lining epithelium, where present, formed a bilayer of pleomorphic cells. The sclera showed an area of compression which was hypercellular compared to controls.

Cyclocryopexy in pigmented eyes: Grossly, corneal edema and corectopia were noted in two of six eyes, while mild cataracts were present in all. Grossly, the ciliary processes were slightly atrophic. Only after removal of the lens was segmental atrophy of the fine retroiridal ciliary processes apparent in all eyes (arrow, Fig. 2g). The anterior vitreous was condensed. Histologically, there was mild stromal and epithelial disorganization and moderate epithelial pleomorphism (Fig. 2h). The retroiridal processes were either thickened or had completely disappeared.

Discussion

Our histological studies show that both contact transscleral laser and transscleral cryopexy are effective anatomic cyclodestructive modalities. There was more scleral effect with contact laser application, however, in this study, as in another long-term study...
Fig. 1. (continued) Effects of CW Nd:YAG contact laser (e-h) and cryopexy (i-l) applied just posterior to the limbus of rabbits on pupillary diameter (e, i), iridal (f, j), cellular (g, k) and conjunctival response (h, l). Each point is based on the mean of the difference of 6 experimental and control eyes ± SD. (---) albino rabbit, (—) pigmented rabbit.

using higher energy levels scleral necrosis and perforation were not observed.\(^{21}\) The IOP was also lowered in the rabbit. According to current thinking, the goal of ablation is the destruction of an aqueous-producing target tissue,\(^{1,3,9,11-18}\) sparing the surrounding tissues to minimize inflammation and other unavoidable side effects. Preliminary experiments indicated that the degree of destruction and of resulting inflammation could be titrated to be the same in both laser photopexy or cryopexy, depending on the amount of energy applied. Both cryopexy and contact laser are contact techniques. There appears to be more control in a contact energy delivery, even though this may also be personal preference.\(^{22}\) For the laser, it is of note that the energies applied are about one-half of the energies used in the noncontact mode, which in itself may reduce side effects. There are theoretical advantages in delivering less energy, well focused, to target tissues and nowhere else. The laser as compared to cryopexy has a spot size of 1 mm, cryopexy of 7-8 mm, due to the spreading effect and ultrasound of approximately 3 mm.\(^{4}\) If there were agreement about the target tissue, (how posterior to the limbus, how much penetration, retrofocus), exact focus might be a definite advantage of the contact laser.

In our experiment, after injury, both modalities showed a bimodal IOP rise which was larger in extent for cryopexy, reaching in excess of 40 mm Hg as compared to the control eye. This initial hypertensive response may not be unique to the laser or cryopexy since a biphasic hypertensive response had also been noted after topical application of nitrogen mustard to the rabbit eye and has been shown to be mediated both neurogenically and by prostaglandins.\(^{20}\) An initial IOP rise after cryopexy has been described in the rabbit,\(^{8,10,23,24}\) in primates\(^{25}\) and in humans,\(^{25-28}\) and therefore is not unique to the rabbit. Similarly, our results show an initial pressure rise following contact laser photocoagulation in the rabbit. In the current literature on noncontact laser cyclophotocoagulation there is no report of a pressure rise in any species.\(^{3,17,29-32}\) It seems unlikely that a pressure rise after cyclophotocoagulation is unique to the rabbit and it is our unpublished experience that a pressure rise after noncontact laser does occasionally occur in humans. It is of interest that after ciliary body insonification in humans a transient pressure elevation had been noted in 10% of patients\(^{33}\) and was also reported after nonpenetrating cyclodiathermy.\(^{34}\) If at all present, the initial IOP rise after laser often may be blocked by topical or retrobulbar anesthesia or may
Fig. 2. Gross (a, c, e, g) and microscopic (b, d, f, h) findings 3 weeks after ablation: pigmented control (a, b), laser cyclopaexy of pigmented eyes (c, d), cyclopaexy of pigmented eyes (e, f), and albino eyes (g, h). Magnification of histologic sections X10.

go unnoticed if it occurs hours later. Clinical trials of contact laser and other cycloablation will have to examine the possibility of an early IOP rise and its possible effect on a compromised optic nerve.

Similar to our results, 24 hr after treatment most eyes reported elsewhere became hypotensive coincident with maximal flare, regardless of whether the insult was cryopexy, noncontact contact laser,2 diathermy3 or ultrasound.4, 4,31 The time course of recovery reported was remarkably similar for most species and modalities. Minimum pressures were reached between 5 days and 2 weeks and then there was slow recovery towards normal pressures, its rate often reflecting the severity of the initial insult.2, 7, 10, 23, 36

In our experiments, albino eyes showed less anatomic cyclodestruction after cryopexy, and even though maximal breakdown of the blood–aqueous barrier (BAB) and low IOP were present, recovered faster after cryopexy. This clinical phenomenon has been termed “pigment effect” by de Roetth37 and has been confirmed mostly in the rabbit for cryopexy,7, 36, 38 and diathermy.18 The role of uveal pigmentation in ruby and Nd: YAG noncontact lasers has not been studied in a large series and remains controversial.29

The behavior of the IOP in our experiments mirrored the rise and recovery of flare, ie, lowest tensions were associated with maximal breakdown of the BAB, a phenomenon noted by others for cryopexy,7, 10, 24, 35, 36 and for noncontact cyclophocoagulation.3, 30, 31 Hypotony associated with protracted uveitis has been described following ultrasound.4 Some authors have regarded iridocyclitis a “complication,” others have appreciated its relationship to the length of pressure lowering following cryopexy,10, 36 and also following noncontact xenon photocoagulation in humans,38 ruby noncontact photocoagulation in humans30, 31 and noncontact Nd:YAG laser in rabbits.17 The breakdown of the BAB and its partial recovery seems to be one of the important characteristics of ablation.10, 24, 36 After treatment it appears that the BAB is never again fully restored and chronic flare even months or years after treatment is occasionally found after cryopexy11, 39 and noncontact laser.31 A morphological basis for this phenomenon in the primate has been provided by Quigley, who emphasized the permanently altered ultrastructure.11

In conclusion, transscleral cycloablation by contact laser or cryopexy have in common a scarred ciliary body and a bimodal pressure rise preceding prolonged hypotension which is related chronologically and quantitatively to a nonspecific ocular irritative response. Even though there are marked species differences in the response of the eye to trauma,40-42 the main features of the response of the rabbit eye are found in reports on ablation in other species, including humans. In our experiment the inflammation was caused by actual cyclodestruction resulting in histological defects in the neuroepithelium and possibly long-term breakdown of the BAB at the ciliary body level. The similarities in the ocular irritative response suggest a similar pathophysiological mechanism underlying the pressure behavior in both thermal mode injuries and may provide a basis for further clinical investigation.

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References


