Microwave cyclodestruction: evaluation on human eyes

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Abstract

Aims—The study was set up to evaluate the effect of microwave cyclodestruction on human eyes.

Methods—Two human eyes were studied. For treatment a horn shaped 5.8 GHz microwave applicator and fibre optic thermometry were used. Just before enucleation, the rectangular (2×3 mm) microwave aperture was placed onto the conjunctiva at a position 1–2 mm posterior to the corneal scleral limbus. Each of three to four treatment spots was targeted to receive a thermal dose of 54°C for 1 minute. Clinical, gross, and histopathological evaluations were performed.

Results—Clinical evaluations of the treatment sites (immediately after microwave application) revealed no evidence of conjunctival or scleral damage. Trace fluorescein 2% uptake was noted within the targeted zones. The first eye was sectioned along the equatorial axis. Examination of the ciliary body and pars plana revealed whitening of the ciliary processes and depigmentation. Histopathological evaluations revealed ciliary epithelial necrosis with pigment dispersion. The vascularity of the ciliary processes showed focal disruption and haemorrhage. The underlying ciliary muscle and sclera appeared to be unaffected. No other findings could be attributed to microwave cyclodestruction.

Conclusion—The results of this phase I toxicity study suggest that microwave heating can be used to damage preferentially the epithelial layers of the human ciliary body.

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evaluations of microwave conjunctivosclerocyclothermia have shown it capable of inducing ciliary body haemorrhages in normal rabbit eyes (with relative sparing of the conjunctiva and sclera).^{16 17} Chorioretinal and ciliary body destruction have resulted in reductions of intraocular pressure in an experimental model of glaucoma.¹⁷ We have attributed these effects to the energy deposition characteristics of microwaves, our microwave delivery system, and the relatively low level thermometry controlled heating used for microwave cyclothermia.^{16 17}

This study presents the results of microwave cyclodestruction performed on two eyes just before enucleation for posterior uveal melanoma. We describe the clinical, gross, and histopathological effects of microwave cyclodestruction on human eyes.

Patients and methods

Before treatment, a USA FDA investigational device exemption no G840196, North Shore University Hospital investigational review board approval, and informed consent were obtained. Each patient was made aware of the number of previously treated patients, the possible risks associated with microwave cyclothermia, and the absence of known benefits associated with treatment of their eyes.

Each patient was diagnosed as having a posterior uveal melanoma. Before surgery, their clinical diagnosis was based on a history, and a complete eye examination including ophthalmoscopy and ultrasonography.¹⁸ A survey for metastatic disease was found to be negative for each patient.

MICROWAVE CYCLOTHERMIA DEVICE

As described in our previous study, treatments involved the use of a horn shaped 5.8 GHz microwave rectangular wave guide applicator.¹⁷ Thermometry was performed with a Luxtron 3000 temperature monitoring system (Luxtron Corp, Santa Clara, CA, USA) with fibreoptic heat sensing probes. Before each treatment, a USA National Bureau of Standards mercury in glass thermometer was used to calibrate the fibreoptic thermometers.

MICROWAVE CYCLOTHERMIA TREATMENT

Under general anaesthesia, treatment involved placing the rectangular (2×3 mm) aperture of the microwave applicator onto the conjunctiva at a position 1–2 mm posterior to the corneal scleral limbus. Each of three to four treatment spots was targeted to receive a thermal dose of

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Ciliary body destruction has played an important role in the treatment of refractory glaucoma.^{1–3} Cyclocryotherapy was the clinical standard until the late 1980s when interest in other methods including therapeutic ultrasound and several new laser techniques were investigated.^{3–14} Since morbidity associated with cyclodestruction has included conjunctival scleral adhesions, corneal scleral thinning, hyphaema, cataract, vitritis, vitreous haemorrhage, retinal detachment, fibroproliferative retinopathy, cystoid macular oedema, hypotony, and sympathetic ophthalmia.^{1–10 15} Side effects have largely defined cyclodestruction as a last alternative therapy for refractory glaucomas.

Microwave heating may offer a method to damage the ciliary body with minimal damage to the conjunctiva and sclera.^{16 17} Preclinical

Figure 1 The horn shaped microwave applicator placed on the conjunctiva during treatment. The heat sensing fibreoptic thermal probe (arrow) was juxtaposed between the aperture of the microwave applicator and the conjunctiva.

54°C for 1 minute. Microwave power was turned on only when the applicator was in contact with the conjunctiva. During treatment a fibreoptic probe was placed onto the conjunctiva beneath the aperture of the microwave applicator (Fig 1). Temperatures were monitored continuously. The use of fibreoptic thermometry avoided self heating induced temperature artefacts which have been noted with thermocouple thermometry.¹⁹

Results

CASE 1

A 47-year-old male patient was referred with a 4 week history of decreased visual acuity and yellow discoloration of objects seen from his left eye. Ophthalmic examination was significant for a visual acuity of 20/60 in the left eye. No conjunctival, scleral, or anterior segment abnormalities were noted. Ophthalmoscopy revealed a pigmented juxtafoveal tumour which measured 6×6 mm in basal dimensions. Its posterior margins were 0.5 mm from the fovea and 3 mm from the edge of the optic nerve. Orange pigment was noted over the tumour's surface. An overlying non-rhegmatogenous neurosensory detachment extended both into the fovea and inferiorly into the retinal periphery. Standardised ultrasonography was performed and an apical tumour height of 2.7 mm with low internal reflectivity was noted.¹⁸ B scan ultrasonography revealed a dome-shaped choroidal tumour without evidence of scleral invasion or extrascleral tumour extension. A metastatic survey was found to be negative.

After the clinical diagnosis of choroidal melanoma was made, the risks and benefits of observation, enucleation, and radiotherapy were discussed. He refused participation in the Collaborative Ocular Melanoma Study because of a strong preference for enucleation.

He agreed to be the first person to be treated with microwaves specifically for cyclodestruction.

Microwave cyclothermia was performed on four areas, each 1–2 mm posterior to the corneal scleral limbus. No conjunctival or scleral changes were observed at 54°C for 1 minute. Immediately after hyperthermic treatment, enucleation was performed. The eye was hand carried to the pathology department where it was immediately sectioned along the equatorial meridian. From an intraocular perspective an evaluation of the anterior segment revealed four cyclothermia spots. Microwave cyclodestruction appeared to cause a whitening of the ciliary processes within the ovoid treatment zone (Fig 2). No evidence of pigment epithelial detachment was visualised. In that heat related cataracts can be acute in onset, it was significant to note that there was no evidence of heat related lenticular opacities. The sclera and vitreous also appeared to be within normal limits.

Histopathological evaluation of the targeted zone revealed focal ciliary body destruction. The main histopathological feature was near total disruption of the non-pigmented and pigmented ciliary epithelium, leading to pigment dispersion with no apparent damage to the underlying muscle or sclera (Fig 3). Lesions were characterised by focal areas of epithelial blistering, and pigment dispersion (Fig 4). The ciliary and iris pigment epithelial detachment was thought to be an artefact of sectioning. Beneath the application site, the sclera and ciliary muscle appeared to be unaffected. No intraocular complications could be attributed to the use of microwave cyclodestruction. A mixed cell-type choroidal melanoma with minimal scleral invasion was noted in the region of the macula.

CASE 2

A 68-year-old patient was referred for an evaluation of a juxtapapillary tumour in her left eye. Ophthalmic examination revealed a visual acuity of 20/50 in the right eye and 20/300 in the left. No external manifestations of tumour were noted on inspection of the globe. A trace afferent pupillary defect was noted in the left

Figure 2 Gross photograph of microwave cyclodestruction applied 1–2 mm from the limbus. White blanching with pigment dispersion is seen within the targeted zone (arrow). The pseudovascular pattern within the pupil resulted from blood staining of the 4×4 cm gauze on which the specimen rested during photography.

Figure 3 Arrowheads show site of microwave application. There was no apparent damage to the underlying sclera or ciliary muscle (haematoxylin and eosin, $\times 15$).

eye. Slit-lamp biomicroscopy was showed no evidence of conjunctival or scleral abnormalities. Moderate nuclear sclerotic lenticular opacities were noted in both eyes. Indirect ophthalmoscopy revealed a juxtapapillary choroidal tumour arising from the superonasal choroid. It was noted to hang over and obscure the optic nerve. A subtotal non-rhegmatogenous retinal detachment with a small amount of vitreous haemorrhage was also noted. When standardised ultrasonography was performed, the A scan revealed an apical tumour height of 6.6 mm with low internal reflectivity. B scan demonstrated the tumour's juxtapapillary location, collar button configuration and 12×10 mm basal dimensions. No evidence of extrascleral tumour extension or intraneural invasion were noted.

After the clinical diagnosis of choroidal melanoma was made, the risks and benefits of observation, enucleation, and radiotherapy were discussed. She was not eligible for participation in the medium tumour arm of the Collaborative Ocular Melanoma Study because of her tumour's close proximity to the optic nerve. Because she was a poor candidate for radiotherapy, enucleation was recom-

Figure 4 Note that both the non-pigmented and pigmented ciliary epithelium (arrows) and posterior pigmented layer of the iris are artefactually detached. The microwave induced ciliary body lesions were characterised by multifocal areas of pigment epithelial detachment and pigment dispersion. Most subepithelial tissues within the treatment zone appeared normal (haematoxylin and eosin, $\times 25$).

mended as treatment for her choroidal melanoma.²⁰ She agreed to volunteer the use of her eye possibly to help others with glaucoma.

Under general anaesthesia microwave cyclothermia (54°C for 1 minute) was performed on three areas. Applications were placed on the temporal, superior, and inferior bulbar conjunctiva. Each spot was located 1–2 mm posterior to the corneal scleral limbus. No conjunctival or scleral changes were observed. Though a small subconjunctival haemorrhage was noted within one of the treatment zones, we could not distinguish whether it was from treatment or the trauma of application of the antenna (Fig 5). Fluorescein 2% was instilled and trace uptake was noted in a rectangular pattern consistent with the size of the aperture of the applicator (Fig 5). Enucleation was performed immediately after hyperthermic treatment.

Histopathological evaluation revealed a selective necrosis of the ciliary epithelium with pigment dispersion. In some areas there was spillover onto the peripheral iris and adjacent pars plana. The affected epithelium was present only as a thin band of nondescript tissue. In these areas the subepithelial tissue appeared compressed or thinned. The underlying tissues showed little damage. Ciliary muscle and sclera were normal. The tumour contained primarily epithelioid melanoma cells. Though the melanoma was in contact with the optic nerve, no extrascleral or subarachnoid extension was noted.

Discussion

Techniques used to destroy the ciliary body can be characterised by their patterns of energy transfer into the eye with distinct tissue reactions. For example, topically applied transscleral cyclocryotherapy has been associated with conjunctival oedema, damage to the ciliary body stroma, intraocular pigment dispersion, and inflammation.^{2,3} Since a therapeutic ultrasound beam induces most of its heating at the level of the acoustically dense sclera, it has been associated with scleral thinning.^{4,10,12} Though the energy deposition of neodymium:YAG cyclophotocoagulation

Figure 5 External photograph shows fluorescein uptake within the treated areas (arrow). These lesions were not visible without topical fluorescein 2%.

Table 1 Effects of cyclodestructive techniques on ocular tissues

Treatment method	Conjunctiva	Sclera	Ciliary body	Ciliary epithelium	Lens	Vitreous
Cryotherapy	Yes	Yes	Yes	Yes	Yes	Yes
Nd:YAG laser	Yes	Yes	Yes	Yes	No	No
Ultrasound	Yes	Yes	Yes	Yes	No	No
Diode laser	N/A	No	Yes	Yes	No	No
Microwave	Yes	No	No	Yes	No	No

Yes=effects commonly observed on clinical or histopathological evaluation; No=no effects commonly observed on clinical or histopathological evaluation; N/A=no mention of effect in literature. Data as reported in references 10, 12, 36, 38, 39, 40, 44, and 45.

has been reported to emanate from the ciliary body out towards the sclera, wedge-shaped spots of scleral necrosis and rounded conjunctival lesions are evidence of ectopic energy deposition.⁸ Non-contact therapies also suffer from alterations in energy absorption based on the angle of incidence of the incident beam. Another factor is that ultrasound and laser cyclodestruction techniques do not use thermometry as a method of titrating thermal dose; instead they have relied on the variables of power and treatment duration.^{8 14}

Microwaves have been used to treat intraocular tumours, create chorioretinal scars for retinopexy, and to destroy the ciliary body.^{16 17 21-26} These heat delivery systems have exploited the advantages characteristic of microwave energy deposition, the tissue sparing effects of low level heating over time, and the safety of temperature control (thermometry). We have noted that relatively low level heating over time has been well tolerated by the sclera.²⁵⁻²⁸

Advantages of microwaves are that tissues with relatively low water content (for example, the conjunctiva and sclera) should absorb less energy than those tissues with relatively high water content (for example, ciliary body and vitreous).²⁹⁻³⁴ Water content must be analysed not only by percentage of water per gram of tissue, but also by the amount of that tissue within the treated zone. Energy deposition can also be modulated by frequency selection where higher frequencies offer less intraocular penetration. Lastly, it is important to note that microwave technology and components are relatively inexpensive.

Slowing the rate of irradiation has been shown to decrease heat related side effects found in normal tissues.¹³ Rather than choosing to deposit enough energy to damage the ciliary body in less than 1 second, we lowered the rate of microwave heating to 1 minute. This may explain (in part) why we noted relative sparing of the conjunctiva and sclera.

Thermal dose can be defined as a measured temperature over a period of time. Based on our preclinical evaluations and experience with the treatment of patients with uveal melanomas we chose to treat to a temperature of 54°C for a 1 minute period.²⁴⁻²⁶ At this level we expected to cause damage within and posterior to the ciliary body. Measuring surface temperature during treatment also allowed us to define the thermal dose and prevent overdosing.

The lesions created by microwave cyclodestruction appeared remarkably similar to diode laser lesions described by Brancato and Hennis

(Table 1).^{13 35} Our histopathological studies have also indicated that like the diode laser and non-contact neodymium:YAG laser, microwave cyclodestruction appeared to damage preferentially the epithelial layers at the level of the pars ciliaris.^{13 36-39} Unlike neodymium:YAG cyclophotocoagulation or therapeutic ultrasound, we noted relative sparing of the underlying stroma and collagen lamellae (Table 1).^{8 10 12 37-44} Microwave cyclodestruction induced no evidence of lens effects in both our phakic patients. In that microwaves preferentially heat high water content tissues, we would not expect intraocular lens haptic distortion as has been noted with laser therapy.⁴⁵

Owing to the presence of intraocular malignancies in these patients, it was not possible to obtain information on longer term effects such as pigment dispersion or vascular occlusions. We performed immediate clinical and histopathological evaluations of microwave cyclodestruction on human eyes. These studies have revealed that ciliary body destruction can be achieved with relative sparing of the conjunctiva, sclera, and lens.

PTF holds United States patent no 5 272 301 titled, 'Thermostatically controlled microwave used for treatment of internal tissue of the eye', issued on 21 December 1993.

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