Sensory stimulation for lowering intraocular pressure, improving blood flow to the optic nerve and neuroprotection in primary open-angle glaucoma

Edith Rom

ABSTRACT
Primary open-angle glaucoma is a group of optic neuropathies that can lead to irreversible blindness. Sensory stimulation in the form of acupuncture or ear acupressure may contribute to protecting patients from blindness when used as a complementary method to orthodox treatment in the form of drops, laser or surgery. The objective of this article is to provide a narrative overview of the available literature up to July 2012. It summarises reported evidence on the potential beneficial effects of sensory stimulation for glaucoma. Sensory stimulation appears to significantly enhance the pressure-lowering effect of orthodox treatments. Studies suggest that it may also improve blood flow to the eye and optic nerve head. Furthermore, it may play a role in neuroprotection through regulating nerve growth factor and brain-derived neurotrophic factor and their receptors, thereby encouraging the survival pathway in contrast to the pathway to apoptosis. Blood flow and neuroprotection are areas that are not directly influenced by orthodox treatment modalities. Numerous different treatment protocols were used to investigate the effect of sensory stimulation on intraocular pressure, blood flow or neuroprotection of the retina and optic nerve in the animal model and human pilot studies. Objective outcomes were reported to have been evaluated with Goldmann tonometry, Doppler ultrasound techniques and electrophysiology (pattern electroretinography, visually evoked potentials), and supported with histological studies in the animal model. Taken together, reported evidence from these studies strongly suggests that sensory stimulation is worthy of further research.

INTRODUCTION
Glucoma is a group of diseases defined by progressive optic nerve degeneration that results in visual field loss and may eventually lead to irreversible blindness.1 2 Some consider glaucoma a systemic disease, but this has not yet led to treatment strategies.3 4 The axons of the retinal ganglion cells (RGC) connect the eye to the brain (figure 1)5 through the optic nerve. This is the anatomical manifestation of the eye being part of the CNS. This anatomical continuity and the similarities at the molecular level are why glaucoma is increasingly considered together with other neurodegenerative conditions such as dementia.6–9

Known risk factors for glaucoma are increased rate of apoptosis (programmed cell death) of the RGC,4 10–13 abnormal blood flow of the eye and optic nerve14–17 and an abnormal sensitivity to, or increase in, intraocular pressure (IOP). Glaucoma may occur and progress even with normal IOP. Presently, the only treatable risk factor is the IOP 5 6 18–20

Primary open-angle glaucoma (POAG) is the commonest cause of irreversible blindness worldwide with an estimated prevalence of over 60 million, 4.5–8.4 million of whom are blind.21–25 The most common cause of blindness is cataract (estimated 18 million people), which is reversible by a routinely performed operation. In contrast to POAG, macular degeneration (3 million persons) leaves the peripheral retina intact and therefore does not lead to complete blindness. POAG, although painless and initially asymptomatic, may eventually obliterate the whole visual field.
Reduction of IOP through pharmacological and/or surgical methods is the mainstay of conventional treatment, and both have seen impressive progress over past decades. Numerous large-scale trials such as the Early Manifest Glaucoma Trial (EMGT), Collaborative Normal Tension Glaucoma study (CNTG), Collaborative Initial Glaucoma Treatment Study (CIGTS), and the Advanced Glaucoma Intervention Study (AGIS) have shown that lowering the IOP slows the progression of the condition in a significant proportion of patients. The disease-slowing effect is independent of the initial level of IOP elevation, which is particularly relevant for so-called normal tension glaucoma. The target IOP is generally 30% lower than the presenting IOP.

Sensory stimulation in the form of acupuncture/acupressure appears to have the potential to address all three areas of interest: IOP, blood flow and regulation of apoptosis. This article is a narrative summary of the literature discussing the effect of sensory stimulation on these three areas, with the aim of suggesting possible lines and evidence-based rationale for research into acupuncture as a possible treatment modality for open-angle glaucoma.

ACUPUNCTURE LITERATURE

The databases Cochrane Library, PubMed, Scopus, World-of-Knowledge and CINAHL were searched to July 2012 using the terms: (a) acupuncture OR acupressure OR auricular acupuncture OR ear acupuncture OR electro-acupuncture; and (b) glaucoma OR open-angle glaucoma OR intraocular pressure OR IOP OR ocular hypertension.

The search produced 88 articles, which was reduced to 83 articles after exclusion of duplicates. Fifty-two articles were excluded as they were in non-European languages without an English abstract or were not relevant, so 31 articles or English language abstracts were accessed. Hand-searching for related articles resulted in two more relevant articles.

Two systematic reviews included the Cochrane review by Law and Li and the systematic review by Gao et al. Both concluded that no large-scale randomised controlled trials were to be found in the literature. Lack of evidence does not equal proof of lack of effect. The review by Rhee et al found no evidence to encourage or discourage the use of acupuncture for glaucoma. Only a minority of patients (1.8%) in a tertiary referral centre for glaucoma were using acupuncture. Sold-Darseff et al express the opinion that acupuncture is of no use for organic disease.

Of the research articles seeking to establish evidence at the level of case series/cohort studies or randomised trials, five articles investigated the effect of sensory stimulation on IOP, three articles explored the blood flow to the eye and optic nerve and three looked at neuroprotection and optic nerve function in response to sensory stimulation. The aim of the clinical and electrophysiological studies was to investigate the clinical effects, not the mechanisms. In...
Contrast, Pagani et al.\textsuperscript{16} looked at the potential mechanisms protecting the RGC in the murine model, highlighting the role of the nerve growth factor (NGF) and its receptor. The evidence presented in the accessible literature is summarised in this article.

Abstracts supportive of the idea that sensory stimulation may be useful in glaucoma are summarised in table 1.

### INTRAOCULAR PRESSURE (IOP)

IOP is considered to be dependent on ocular perfusion pressure\textsuperscript{28,38} with the autonomic nervous system\textsuperscript{40} and the opioid system\textsuperscript{41} among others, also exerting their influence. IOP represents the balance of the production of fluid in the eye through active and passive mechanisms and the outflow of fluid from the eye.\textsuperscript{43} Active mechanisms in the intraocular fluid dynamics involve carbonic anhydrase in the ciliary body and adrenergic receptors.\textsuperscript{44-47} Passive mechanisms may be dependent on vascular status and resistance of surrounding tissues.\textsuperscript{48}

While it is not clear how acupuncture would lower the IOP, several small-scale studies describe this effect.

### Acupuncture on IOP in the animal model

Chu et al.\textsuperscript{22} found in the animal model (rabbit) that the reduction of IOP after electroacupuncture (0.1 – 3 Hz, 0.1 – 1 V for 0.5 – 1 h) near the sciatic nerve was associated with decreased levels of noradrenaline and dopamine and increased levels of naloxone-reversible opioids in the aqueous humour as well as with lowered IOP.

### Acupuncture and IOP in the human

In humans, Uhrig et al.\textsuperscript{20} treated 18 patients with glaucoma or ocular hypertension with one 20 min session of manual acupuncture, eliciting de qi sensation (LR3, LI4, GB37). IOP was significantly reduced 15 min and 24 h after the treatment. His choice of points was informed by Traditional Chinese Medicine (TCM) theory, but partly coincides with the segments stimulated by Chu et al in rats. Some of the distal points stimulate segments L5/S1 and thereby appear to have an influence on the parasympathetic system.\textsuperscript{49}

Kurusu et al.\textsuperscript{38} reported a pilot study on 11 patients with medically controlled glaucoma. Applying manual acupuncture following a standard protocol (manual acupuncture, no de qi aimed at, 2 × 15 min BL2, ST2, Taiyang, ST36, GB20, KI3, LR3, SP6, BL18, BL23), they found a cumulative effect of the treatment over 4 weeks with twice weekly treatment. Follow-up at 5 weeks showed a reduction in IOP to 81.4%. Incidentally, visual acuity and ocular comfort were also improved.

Ewert and Schwanzit\textsuperscript{11} randomised 50 patients to standard care or standard care plus manual acupuncture according to TCM criteria: distal points SP6, KI3, GB39, LI4, LR2 or LR3 and local points Yuyao, BL1, TE23, Taiyang and Yintang. Ten sessions were given over 8 weeks and a significant reduction in IOP occurred in the acupuncture-treated group. Interestingly, the IOP actually went up after the first and second sessions. The authors suggest that this initial rise in IOP may be explained by sympathetic activation due to apprehension about the procedure and minor discomfort due to needling. Only after the third session did they observe a noticeable IOP-lowering effect. The difference between the two groups was still present after 12 months. Compliance with medication was also improved in the acupuncture-treated group. It is therefore debatable whether the long-term effect is due to the acupuncture or to better compliance. In Germany patients have to pay an extra fee for acupuncture which might have introduced further bias. Ewert et al. found no effect on IOP in normal controls—that is, in participants without elevated IOP and without glaucoma.

Meira-Freitas et al.\textsuperscript{12} similarly found that acupuncture had no effect on the IOP in 30 healthy volunteers. Whereas Ewert et al. chose the acupuncture points according to TCM diagnosis, Meira-Freitas et al. offered one session of 20 min manual acupuncture on BL1, GB1 and GB14 as standard protocol. The lack of effect on IOP may be due to any of the following factors: the protocol was undertreating, the

### Table 1

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Details</th>
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<tbody>
<tr>
<td>Sun et al.</td>
<td>Experimentally high IOP for 28 days reversed by trabeculectomy in rabbits; compared with observation. Expression of Bcl-xL and BDNF in rabbit retina increased after acupuncture (Qiuhou, GB20, LR2 bd; Vitamin B12 and 1 injection)</td>
</tr>
<tr>
<td>Zhou et al.</td>
<td>Acute high IOP (30, 50, 70 mm Hg for 2 h), then 2 weeks daily EA (BL2 and ST36); recovery of some RGC (histological examination) only for exposure to 30 and 50 mm Hg with EA, 32 rabbits</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>EA (LI4, L3, GB37) significantly lowered IOP (p&lt;0.05), blood pressure, heart rate, vascular resistance unchanged; 10 anaesthetised dogs</td>
</tr>
<tr>
<td>Yasuno et al.</td>
<td>EA (BL10-G820 and GB21-SI13, 15 min, 1 Hz, intensities to cause muscle contraction). Choroidal blood flow increased in 11 healthy humans (laser speckle method); no change in IOP, blood pressure, ocular perfusion pressure</td>
</tr>
<tr>
<td>Steuhl et al.</td>
<td>EA near sciatic nerve (GB30) lowered IOP and elevated vitreal endorphin levels (reversible by naloxone); normal rabbits</td>
</tr>
<tr>
<td>Naruse et al.</td>
<td>Optic nerve head blood flow increased (8–32%) significantly (p&lt;0.01) in 10 patients with normal tension glaucoma but not in 10 healthy volunteers after ear acupuncture</td>
</tr>
</tbody>
</table>

BDNF, brain-derived neurotrophic factor; EA, electroacupuncture; IOP, intraocular pressure; RGC, retinal ganglion cells.
treatment would best be individualised, the treatment can only regulate a situation that needs regulation (ie, that is abnormal) or the volunteers had IOP that was normal for them.

Her et al\textsuperscript{10} showed in their sham-controlled study of 33 patients with medically well-controlled glaucoma that pressure massage twice daily to the auricular points Liver, Kidney and Eye induced lowering of IOP by up to an additional 15\%. 1 mm alloy balls were unilaterally placed and alternated weekly between right and left ears for 4 weeks. The lowest documented IOP was after 3–4 weeks, with a significant difference between the real points and the sham points. Sham points chosen in the control group were shoulder, wrist and jaw. Four weeks after discontinuation of the ear stimulation the IOP returned to previous levels.

The recognised conventional treatment pathway—lowering of the IOP—may be responsive to sensory stimulation.

**OCULAR BLOOD FLOW**

Acupuncture may improve the blood flow to the eye in POAG. There is ample evidence that acupuncture improves blood flow to various organs and sites (eg, ovaries, skin and muscle, brain\textsuperscript{49–53}). On a molecular level, regulation of the blood flow within tissues appears to be associated with a change of local mediators such as substance \(\mathrm{P}\), nitric oxide, endothelin, calcitonin gene-related peptide.\textsuperscript{54–57} All of these have been shown to be influenced by acupuncture. On a systemic level, autonomic activation leads to dilation of the vessels and therefore increased blood flow due to reduced vascular resistance.\textsuperscript{58} Tsuru et al suggest that local effects increase local blood flow through polymodal receptors while central effects of acupuncture increase stroke volume and cardiac outflow, at the same time decreasing total peripheral resistance.\textsuperscript{59} Litscher et al\textsuperscript{13, 14} used Doppler ultrasound to examine the blood flow of the middle cerebral artery and the supratrochlear artery, a branch of the ophthalmic artery that supplies the optic nerve. They found that manual acupuncture with \textit{de qi} activation for 20 min to local points BL2, Yuyao, GB1, TE23 and, according to TCM theory, vision-related points GB37 and SI6 increases the blood flow to the supratrochlear artery but not to the middle cerebral artery. In contrast, stimulation of the peripheral points PC6, CV6, ST36 and SP6 increased the blood flow to the middle cerebral artery but not to the supratrochlear artery. Takayama et al\textsuperscript{15} used colour Doppler ultrasound in 11 patients with medically controlled glaucoma after manual acupuncture with \textit{de qi} sensation intended (BL2, Taiyang, ST2, ST36, SP6, KI3, LR3, GB20, BL18, BL23) and found a significant increase in blood flow in the short posterior ciliary arteries. Pagani et al\textsuperscript{16} (see also below) used electroacupuncture on Royal College of Surgeons (RCS) rats with retinitis pigmentosa. The treated rats showed increased vascularity of the retina compared with the non-treated eyes on histological sections.

**APOPTOSIS AND NEUROPROTECTION**

Glaucomatous optic neuropathy appears to take place through apoptosis of the RGCs. Mechanisms to explain apoptosis most often mentioned and studied are excitotoxicity, mitochondrial dysfunction, protein misfolding, oxidative stress, inflammation and neurotrophins.\textsuperscript{6} w13 w60 For each of these mechanisms there are examples in the acupuncture literature.\textsuperscript{w61–w65} Important examples of the neurotrophins are NGF and brain-derived neurotrophic factor (BDNF); both play a role in neuroprotection and both have been associated with acupuncture.\textsuperscript{25} Pagani et al looked at the neuroprotective effects of electroacupuncture in RCS rats. This strain of rats has the genetic defect leading to optic atrophy related to retinitis pigmentosa. Young rats were treated for 11 days with electroacupuncture at 2 Hz, 1.5–2 mA, bilaterally in biceps brachii and biceps femoris for 25 min. The retinas were then examined histologically and immunohistochemically. They showed increased neurotrophins (NGF, BDNF) and alterations in the neurotrophin receptors (NGF receptor tyrosine kinase A, TrkA), increased vascularisation and less degenerate architecture compared with control retinas.

Reduction of the rate of apoptosis through application of NGFs and other neurotrophins, or their respective receptors, is the declared aim of newer treatment mechanisms.\textsuperscript{w62–w69} There are now numerous suggestions that the potential neuroprotective effect of sensory stimulation may be achieved through reduction of the inflammatory drive and oxidative stress, regulation of neurotrophins, growth factors and, possibly uniquely, their receptors. All those markers of apoptosis are measurable.

Miyake et al,\textsuperscript{w70} Oono et al\textsuperscript{w71} and Morimoto et al\textsuperscript{w72} described the neuroprotective or even recuperative effect of transcorneal electrical stimulation on the optic nerve. The effect and mechanism may be comparable to the application of electroacupuncture across the orbit.

The multitude of proposed apoptotic mechanisms indicates that we do not yet clearly understand the complex processes underlying apoptosis in glaucoma.

**CLINICAL RELEVANCE OF NEUROPROTECTION ASSESSED BY ELECTROPHYSIOLOGY**

Electrophysiology is used to assess the optic nerve function objectively.\textsuperscript{w73} Pattern electroretinography (PERG),\textsuperscript{w74} multifocal electroretinography,\textsuperscript{w75} w76 and visually evoked potentials (VEP)\textsuperscript{w77 w78} have been used to study glaucoma (figure 2). They are similar to the more familiar EEG in that they record electrical potentials that are created by nerve activity. They all require considerable time, skill and sophisticated equipment so...
that they are used as research tools only. In clinical routine, the automated visual field test serves as a surrogate outcome for optic nerve mass response. The N95 component of the PERG is reduced in POAG. It has been reported to recover after lowering the IOP. This improvement in objective electrophysiological tests is thought to represent an objective measure for improved function of the RGC under treatment. Electrophysiology may be abnormal even before a visual field defect is detectable.

The VEP, in contrast, documents latency between stimulus exposure and vision-related activity in the occipital cortex. The small change in latency reported 15 min after manual acupuncture on LR3, SP6, GB20, GV20, Yintang and BL2 by Sagara et al in healthy volunteers may not be clinically relevant. In contrast, Chan et al found a significant improvement in the VEP after electroacupuncture in rats. After inducing glaucoma with laser ablation of the trabecular meshwork, they found the amplitude of the multifocal ERG reduced when compared with rats without induced glaucoma. After electroacupuncture with 2 Hz three times a week for 4 weeks on Yuyao and ST2, the N/P ratio normalised, indicating improved optic nerve function after treatment. Treatment with 100 Hz did not induce any improvement in optic nerve function. Electrophysiology describing amplitude and latency can therefore be an objective marker for changes in optic nerve function.

In summary, while Western medical and surgical treatment often achieves lowering of the IOP in patients with glaucoma, it does not address any other risk factors and a proportion of patients still progress to blindness. It appears that sensory stimulation may contribute to normalising IOP and blood flow to the eye and optic nerve as well as having a neuroprotective effect through both regulating neurotrophins and their receptors. Sensory stimulation may contribute to prevent progression of visual field defects and thereby delay blindness. Even if the full picture is not yet clear, as clinicians we should give serious consideration to investigating sensory stimulation as an inexpensive and safe method complementary to our standard treatments.

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REFERENCES

Figure 2 Examples of normal electroretinogram and visually evoked potentials.


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