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Acupuncture for glaucoma

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Abstract

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DECLARATIONS OF INTEREST

No financial conflicts of interest have been declared, and the authors declare that they do not have any association with any parties who may have vested interests in the results of this review.

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Background—Glaucoma is a multifactorial optic neuropathy characterized by an acquired loss of retinal ganglion cells at levels beyond normal age-related loss and corresponding atrophy of the optic nerve. Although many treatments are available to manage glaucoma, glaucoma is a chronic condition. Some patients may seek complementary or alternative medicine approaches such as acupuncture to supplement their regular treatment. The underlying plausibility of acupuncture is that disorders related to the flow of Chi (the traditional Chinese concept translated as vital force or energy) can be prevented or treated by stimulating relevant points on the body surface.

Objectives—The objective of this review was to assess the effectiveness and safety of acupuncture in people with glaucoma.

Search methods—We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* 2012, Issue 12), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to January 2013), EMBASE (January 1980 to January 2013), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to January 2013), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (January 1937 to January 2013), ZETOC (January 1993 to January 2013), Allied and Complementary Medicine Database (AMED) (January 1985 to January 2013), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov), the WHO International Clinical Trials Registry Platform (IC-TRP) (www.who.int/ictrp/search/en) and the National Center for Complementary and Alternative Medicine web site (NCCAM) (http://nccam.nih.gov). We did not use any language or date restrictions in the search for trials. We last searched the electronic databases on 8 January 2013 with the exception of NCCAM which was last searched on 14 July 2010. We also handsearched Chinese medical journals at Peking Union Medical College Library in April 2007.

We searched the Chinese Acupuncture Trials Register, the Traditional Chinese Medical Literature Analysis and Retrieval System (TCMLARS), and the Chinese Biological Database (CBM) for the original review; we did not search these databases for the 2013 review update.

Selection criteria—We included randomized controlled trials (RCTs) in which one arm of the study involved acupuncture treatment.

Data collection and analysis—Two authors independently evaluated the search results and then full text articles against the eligibility criteria. We resolved discrepancies by discussion.

Main results—We included one completed and one ongoing trial, and recorded seven trials awaiting assessment for eligibility. These seven trials were written in Chinese and were identified from a systematic review on the same topic published in a Chinese journal. The completed trial compared auricular acupressure- a nonstandard acupuncture technique- with the sham procedure for glaucoma. This trial is rated at high risk of bias for masking of outcome assessors, unclear risk of bias for selective outcome reporting, and low risk of bias for other domains. The difference in intraocular pressure (measured in mm Hg) in the acupressure group was significantly less than that in the sham group at four weeks (−3.70, 95% confidence interval [CI] −7.11 to −0.29 for the right eye; −4.90, 95% CI −8.08 to −1.72 for the left eye), but was not statistically different at any other follow-up time points, including the longest follow-up time at eight weeks. No statistically significant difference in visual acuity was noted at any follow-up time points. The ongoing trial

was registered with the International Clinical Trials Registry Platform (ICTRP) of the World Health Organization. To date this trial has not recruited any participants.

Authors' conclusions—At this time, it is impossible to draw reliable conclusions from available data to support the use of acupuncture for the treatment of glaucoma. Because of ethical considerations, RCTs comparing acupuncture alone with standard glaucoma treatment or placebo are unlikely to be justified in countries where the standard of care has already been established. Because most glaucoma patients currently cared for by ophthalmologists do not use nontraditional therapy, clinical practice decisions will have to be based on physician judgments and patient preferences, given this lack of data in the literature. Inclusion of the seven Chinese trials in future updates of this review may change our conclusions.

INDEX TERMS Medical Subject Headings (MeSH)

Acupuncture Therapy [*methods]; Acupuncture, Ear; Glaucoma [*therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans

PLAIN LANGUAGE SUMMARY

Acupuncture as a treatment modality for patients with glaucoma

Glaucoma is a condition that damages the optic nerve and affects primarily the side vision. It is a major cause of blindness worldwide. Although many treatments are available, including eye drops, laser treatment, and surgical procedures, some patients may seek complementary or alternative medicine approaches such as acupuncture to supplement their regular treatment. This review aimed to evaluate available evidence in the findings of randomized controlled trials to assess whether acupuncture is useful and safe in treating patients with glaucoma. We included in the review one completed and one ongoing trial, and we recorded seven trials (all published in Chinese) awaiting assessment for eligibility. The completed trial was conducted in Taiwan among 33 patients. This trial compared auricular acupressure- a nonstandard acupuncture technique- versus a sham procedure (which is a fake procedure designed to resemble the real one) for glaucoma. The trial measured intraocular pressure and visual acuity during an eight-week follow-up period. The quality of this trial was not high. According to the findings of this trial, auricular acupressure lowers intraocular pressure by around 4 mm Hg for the right eye and around 5 mm Hg for the left eye at four weeks, but not significantly effective at any other time points or for any other visual outcomes. The safety of acupuncture was not examined in this trial. To date, the ongoing trial "Acupuncture for Glaucoma" has not recruited any participants. On the basis of currently available evidence, the benefit and harm of acupuncture as a therapeutic modality for glaucoma cannot be established. Inclusion of the seven Chinese trials that are awaiting assessment for eligibility in the future may change our conclusions.

BACKGROUND

Introduction—Glaucoma is a multifactorial optic neuropathy characterized by an acquired loss of retinal ganglion cells at levels beyond normal age-related baseline loss and corresponding atrophy of the optic nerve (AAO 2010). Glaucoma affects primarily peripheral vision and is asymptomatic in its earlier stages. It is one of the leading causes of irreversible blindness worldwide (Friedman 2004; Quigley 2006; Tsai 2005).

Glaucoma is classified on the basis of anatomic features as open-angle (where the anterior chamber angle of the eye remains open) and angle-closure (with closure of the anterior chamber angle). Glaucoma is considered primary if the eye has no preexisting disease. Secondary forms of glaucoma are caused by various ocular or systemic diseases such as pigment dispersion syndrome and ocular trauma.

Epidemiology—More than two million people in the United States are living with glaucoma; 80,000 of these individuals are legally blind as a result of the disease (Friedman 2004; Lee 2005; Martin 1985). It was estimated that 60.5 million people were affected by glaucoma in 2010, and bilateral blindness were present in 4.5 million people with open-angle glaucoma (OAG) and in 3.9 million people with angle-closure glaucoma (Quigley 2006). The prevalence of glaucoma is higher in the elderly, in persons of African descent, and in people with diabetes, hypertension, or myopia (Lee 2005; Quigley 2006).

Description of the condition

Primary open-angle glaucoma (POAG) is the most common type of glaucoma (Friedman 2004). POAG usually has an insidious onset and progresses slowly and painlessly, affecting one or both eyes. Because central vision is relatively unaffected until late in the disease, visual loss generally progresses without symptoms. Diagnosis of POAG is based on evidence of optic nerve damage presented as a structural abnormality of the optic disc or retinal nerve fiber layer, or as the presence of characteristic abnormalities in the visual field. Additional criteria include a normal appearing open anterior chamber angle and absence of secondary causes of glaucoma. Although most glaucoma patients exhibit increased intraocular pressure (IOP) upon repeated measurement, some may have IOP that is within the average range (AAO 2010).

Patients may present with acute elevation of IOP, when the entire circumference of the anterior chamber angle is obstructed suddenly. Intermittent closure of the anterior chamber angle may lead to chronic angle-closure glaucoma (AAO 2010).

Diagnosis of angle-closure can be achieved by gonioscopy, which is an examination of the structure and width of the anterior chamber angle. Angle-closure glaucoma is reserved for eyes in which glaucomatous optic neuropathy or visual field defect is evident in the presence of angle-closure.

Description of the intervention

Treatment options—Current treatments for glaucoma are directed at lowering IOP because IOP is the only known risk factor that can be treated with the beneficial effect of

reducing progression of visual field loss (AGIS 2000; CNTGSG 1998; Gordon 2002; Heijl 2002).

Pharmacologic therapy—Treatment of glaucoma usually begins with topical antiglaucoma medications. First-line medical treatment has consisted of a topical beta-blocker that reduces IOP by decreasing aqueous humor formation or a topical prostaglandin analog that increases the uveoscleral outflow of aqueous humor (AAO 2010; Marquis 2005; van der Valk 2005). These agents are used as initial treatment because they are effective, have relatively few ocular adverse effects, and can be used once or twice daily without affecting pupil size or accommodation. Second-line drugs include alpha-agonists and topical carbonic anhydrase inhibitors (AAO 2010; Lee 2005). These medications may cause ocular irritation and must be used twice or three times daily. Parasympathomimetic (miotic) agents such as pilocarpine are considered third-line treatment options (AAO 2010; Lee 2005). These agents affect pupil size or accommodation, are used two to four times daily, and are reserved for use in patients who do not respond to other topical antiglaucoma medications. Medical interventions for POAG are the subject of a published Cochrane systematic review (Vass 2007).

Laser therapy—An alternative or additive treatment to glaucoma medication is laser trabeculoplasty (AAO 2010). Laser trabeculoplasty lowers IOP by mechanically stimulating the trabecular meshwork to reduce its resistance to the outflow of aqueous humor (Lee 2005). A Cochrane review on laser trabeculoplasty for OAG has been published (Rolim de Moura 2007).

Incisional surgery—If the patient's IOP cannot be controlled with medications, incisional filtering surgery can be considered (AAO 2010). Filtering surgery reduces IOP by creating a new channel that improves the outflow of the aqueous humor. Trabeculectomy is the most commonly performed surgical procedure. An opening created in the anterior chamber angle allows the aqueous humor to flow from the anterior chamber into a space beneath the conjunctiva under the surface of the eye. The most common problem associated with this surgery is the growth of scar tissue, which may cause an obstruction in this artificial channel that blocks aqueous humor drainage, and the IOP-lowering effect may decrease gradually with time. Other vision-threatening complications include overfiltration, hypotony, bleeding, and infection.

In addition to trabeculectomy, nonpenetrating surgical procedures such as viscocanalostomy and deep sclerectomy have been developed. These techniques avoid full-thickness penetration into the anterior chamber of the eye. Fewer complications have been reported, but their effectiveness in lowering IOP may be limited compared with that of trabeculectomy (Netland 2001). A Cochrane systematic review comparing medical and surgical interventions for glaucoma has been published (Burr 2012).

Glaucoma drainage devices—Tube and plate drainage devices could be used to maintain drainage of aqueous humor in spite of subconjunctival scarring (Burr 2012; Lim 1998). Glaucoma drainage devices are usually recommended in cases where trabeculectomy

is unlikely to succeed. A Cochrane systematic review of these devices has been published (Minckler 2006).

Other procedures—Alternative microsurgical procedures performed on the trabecular meshwork such as trabecular aspiration, goniocurettage, laser trabecular ablation, and trabeculotomy have been described as means of lowering IOP in OAG. These techniques are not widely used, and their safety and effectiveness are not known (Burr 2012). Although many treatments are available, glaucoma is a chronic condition for which no cure is known. Some patients may seek complementary or alternative medicine such as acupuncture to supplement their regular treatment.

Acupuncture—Acupuncture is a branch of traditional Chinese medicine that has been used for more than 2000 years in the treatment of various illnesses. In traditional Chinese medicine, the body is seen as representing a delicate balance of two opposing and inseparable forces: yin and yang. Yin represents the cold, slow, or passive principle, and yang represents the hot, excited, or active principle. An imbalance in these two opposing forces is associated with blockage in the flow of Chi (vital force or energy), which leads to various illnesses. Chi flows along pathways known as meridians with acupuncture points on the human body that connect with them (NCCAM 2007). The underlying philosophy of acupuncture is that disorders related to the flow of Chi can be prevented or treated by stimulating the relevant acupuncture points on the body surface. These points are stimulated typically by inserting needles; however, related techniques such as manual (acupressure), electrical, or laser stimulation of acupuncture points are often included under this term (Rhee 2002).

The exact mechanism of the effects of acupuncture is far from clearly delineated. People have tried to explain how acupuncture works within the framework of Western medicine. Of the different mechanisms of action proposed (Cho 2006; Moffet 2006), the dominant one suggests that acupuncture stimulates the release of neurochemicals (usually endogenous opioids or serotonin). “Gate theory” or segmental effects is another proposed mechanism for analgesia. In the “gate theory,” sensory input from acupuncture blocks or interferes with nociceptive pain signals at the spinal level. In addition, involuntary body functions may be regulated by the autonomic nervous system. Examples of such functions include heart rate, blood pressure, postmenopausal vasomotor symptoms, and respiration. By incorporating the results from studies on different body systems treated with acupuncture, a model termed the broad sense hypothalamus-pituitary-adrenal (BS-HPA) axis was proposed recently. This model hypothesizes that the central nervous system is essential for processing the effects of acupuncture by modulating the autonomic nervous system, the neuroimmune system, and hormone regulation. Different mechanisms proposed so far might be viewed as part of an elaborate interaction among different systems of the body.

Animal models and small samples of human studies have explored ocular effects associated with acupuncture. Studies have reported potentially beneficial effects of IOP reduction, improvement in central visual acuity, increased ocular blood flow, preservation of normal waveform characteristics of multifocal electroretinography (mfERG), alteration of visual

function tested by the visual evoked potential (VEP), and increased retinal nerve growth factor (Chan 2005; Chu 2002; Naruse 2000; Pagani 2006; Sagara 2006).

Why it is important to do this review

A cross-sectional study among the US population in 1998 indicated that the prevalence of the use of acupuncture among people reporting use of complementary medicine for glaucoma was 1.8% (1/54) (Rhee 2001; Rhee 2002). A comprehensive collection and summary of currently available clinical trials will provide the best evidence to determine whether acupuncture is effective and safe in treating glaucoma.

OBJECTIVES

The objective of this review was to assess the effectiveness and safety of acupuncture compared with other treatments, no treatment, or placebo in patients with glaucoma.

METHODS

Criteria for considering studies for this review

Types of studies—We included in this review randomized controlled trials (RCTs) and quasi-RCTs.

Types of participants—We included trials enrolling participants of any age and sex with any type of glaucoma, as diagnosed in the included studies.

Types of interventions—We defined *acupuncture* as the stimulation of acupuncture points by any methods, including needle insertion, acupressure, and surface electrical and laser stimulation. We included studies that compared acupuncture therapy with other treatments, no treatment, or placebo for treating any type of glaucoma. We also included studies that compared different types of acupuncture therapy, as well as studies in which acupuncture in combination with another treatment was compared with the other treatment alone.

Types of outcome measures—Primary outcomes

The primary outcome for this review was the difference between treatment groups regarding changes in the visual field when the follow-up visual field was compared with the baseline visual field, as measured by any methods defined in the methodology of the included trial.

Secondary outcomes: Secondary outcomes for this review were:

1. Reduction of IOP.
2. Change in visual acuity.
3. Progression of optic disc damage or nerve fiber layer loss.

The timing of the outcome assessment was:

1. Short term: outcomes up to one year.

2. Long term: longer than one year.

Adverse effects: We planned to include all systemic and ocular adverse effects related to either acupuncture or other treatments as reported in the included studies. Specific adverse effects of interest were:

1. Pain and bleeding due to placement of the acupuncture needle.
2. Reduction in visual acuity.
3. Cataract formation.
4. Infection.
5. Punctured organs.
6. Legal blindness (visual acuity of 20/200 or worse in the better eye with corrective lenses, or visual field restriction to 20 degrees diameter or less (tunnel vision) in the better eye).

Quality of life measures: We planned to summarize quality of life data by any validated measures presented in included trials.

Economic data: We planned to summarize cost-benefit analyses and other data on economic outcomes.

Follow up: We did not impose any restrictions based on the length of follow-up.

Search methods for identification of studies

Electronic searches—We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 12, part of *The Cochrane Library* www.thecochranelibrary.com (accessed 8 January 2013), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to January 2013), EMBASE (January 1980 to January 2013), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to January 2013), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (January 1937 to January 2013), ZETOC (January 1993 to January 2013), Allied and Complementary Medicine Database (AMED) (January 1985 to January 2013), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov), the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en) and the National Center for Complementary and Alternative Medicine web site (NCCAM) (http://nccam.nih.gov). We did not use any language or date restrictions in the search for trials. We last searched the electronic databases on 8 January 2013 with the exception of NCCAM, which was last searched on 14 July 2010. See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), LILACS (Appendix 4), CINAHL (Appendix 5), ZETOC (Appendix 6), AMED (Appendix 7), *m*RCT (Appendix 8), ClinicalTrials.gov (Appendix 9), the ICTRP (Appendix 10) and NC-CAM (Appendix 11).

We searched the Chinese Acupuncture Trials Register, the Traditional Chinese Medical Literature Analysis and Retrieval System (TCMLARS), and the Chinese Biological Database (CBM) for the original review; we did not search these databases for the 2013 review update.

Searching other resources—We searched the reference lists of the trials included. We used the Science Citation Index to search for studies that cited the included trials. An ad hoc manual search of Chinese medical journals *(Beijing Journal of Traditional Chinese Medicine, Shanghai Journal of Traditional Chinese Medicine, Liaoning Journal of Traditional Chinese Medicine, Zhejiang Journal of Medicine, Jiangxi Journal of Traditional Chinese Medicine, Journal of Clinical Acupuncture, Shanghai Journal of Acupuncture, Chinese Journal of Practical Ophthalmology)* was conducted by Dr. Yuanbo Liang and colleagues at Peking Union Medical College Library.

Data collection and analysis

Selection of studies—Two authors independently assessed the titles and abstracts obtained by the searches. We classified each citation as "definitely exclude," "unclear," or "definitely include." We obtained full text of all potentially or definitely related articles and determined their final eligibility. We resolved discrepancies between the two authors through discussion. We documented the excluded studies and the reasons for exclusion (*see* Characteristics of excluded studies).

Data extraction and management—Two authors independently extracted study characteristics and data for the primary and secondary outcomes onto paper data collection forms developed by the Cochrane Eyes and Vision Group. We resolved discrepancies through discussion. One author entered all data into Review Manager (Review Manager 2012). The second author independently checked the data entered.

Assessment of risk of bias in included studies—Two authors independently assessed included studies for four types of bias. We rated each domain as at low, high, or unclear risk of bias in accordance with Chapter 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

1. Selection Bias: Selection bias, in the context of RCT, refers to "systematic differences between baseline characteristics of the groups that are compared (Higgins 2011)." We assessed the method of sequence generation and allocation concealment.

2. Performance Bias: Performance bias refers to "systematic differences between groups in the care that is provided (Higgins 2011)." We examined masking of outcome assessment, in which persons responsible for assessing outcomes were unaware of the assigned intervention. In our opinion, masking of participants and care providers may not be feasible in trials on this topic, and hence is not used as a measure of quality.

3. Attrition bias: Attrition bias refers to "systematic differences between groups in withdrawals from a study (Higgins 2011)." We assessed follow-up times and losses to follow-up in each group. We examined reasons for losses to follow-up (e.g., withdrawals,

dropouts, protocol deviations) and how losses of participants were handled. We also assessed whether the analysis was conducted on an intention-to-treat basis, that is, whether participants were analyzed in the group to which they were randomly assigned.

4. Detection bias: Detection bias refers to "systematic differences between groups in how outcomes are determined (Higgins 2011)." We examined masking of outcome assessment.

Data synthesis—We followed the guidelines in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011) pertaining to data synthesis. For dichotomous outcomes, we planned to calculate a summary risk ratio. For continuous outcomes, we planned to calculate the mean difference. Before combining the data, we planned to assess clinical and methodologic heterogeneity by examining the characteristics and methodologic quality of each trial. To assess the amount of statistical heterogeneity, we planned to use forest plots, results of the Chi^2 test for statistical heterogeneity, and the value of I^2. If no substantial statistical heterogeneity is detected (i.e., I^2 value less than 50%), and if no clinical or methodologic heterogeneity is noted among trials, we planned to combine the results in a meta-analysis using a random-effects model. A fixed-effect model will be used if is three or fewer trials are used. If substantial heterogeneity is present, we will not combine study results but will present them in a tabulated summary.

Sensitivity analysis—We planned to conduct sensitivity analyses to examine the impact of exclusion of studies of lower methodologic quality if at least two studies were included.

RESULTS

Description of studies

Results of the search—The initial electronic searches revealed 28 distinct titles and abstracts, of which two appeared to be relevant and underwent review of the full articles. We excluded both studies (Kumar 1994; Nesterov 1997) because they were not RCTs. We identified 13 reports through handsearching, none of which met our inclusion criteria. An updated search in March 2010 yielded 15 abstracts and two clinical trials. None were relevant to the scope of the review. The updated search in January 2013 yielded 14 abstracts and one ongoing trial. We also identified one systematic review on the same topic published in a Chinese journal before submitting the current version of review for publication. From this systematic review, we recorded seven trials, all written in Chinese, awaiting assessment for eligibility (see Characteristics of studies awaiting classification table). We plan to assess the final eligibility of these seven trials in our next update. For this update, we included one completed (Her 2010) and one ongoing (JPRN 2009) RCT in the review.

Included studies—Her 2010 compared auricular acupressure, a nonstandard acupuncture technique, versus a sham procedure for glaucoma in 33 patients: 16 patients with 28 glaucoma eyes in the acupressure group, and 17 patients with 32 glaucoma eyes in the sham group. We described details of this trial in the Characteristics of included studies table.

Types of participants: The trial included 33 participants 30 years of age or older who had primary open-angle glaucoma, chronic angle-closure glaucoma, normal tension glaucoma,

ocular hypertension, or secondary glaucoma in one or both eyes and had been treated for at least one year.

The trial excluded patients if they had the following surgeries or conditions: laser trabeculoplasty or filtering surgery for glaucoma in the past, persistent ocular inflammation within the past year, use of any systemic medication that affects the IOP within three months, end-stage glaucoma with impending phthisis bulbi, or no detectable IOP because of poor psychological condition.

Types of interventions: Participants were randomly assigned to the auricular acupressure group or the sham group. Patients in the acupressure group received "stimulator tapping" and massage of the "auricular points (kidney, liver, and eye) over the right ear at our first course of outpatient clinic." Tapping stimulation was administered. Over a four-week period, patients regularly massaged their ears using thumb and index finger "twice per day for nine minutes each time (three minutes/each point)." At four weeks' follow-up, patients stopped acupoint tapping and no further massages were given. Patients in the sham group received "stimulator tapping but no massage at the sham auricular points." All other treatment modalities were the same as those used for the acupressure group.

Types of outcomes: The trial assessed IOP, uncorrected visual acuity, and best corrected visual acuity before and after the massage at the patient's first clinic visit and at one, two, three, four, and eight weeks' follow-up. The trial report did not provide between-group comparisons related to any outcomes. The trial did not discuss any complications or adverse events reported in the two treatment groups.

The ongoing trial "Acupuncture for Glaucoma (JPRN 2009)" is registered with the ICTRP. To date, no participant has been recruited into this trial.

Excluded studies—See Characteristics of excluded studies table for further details.

Risk of bias in included studies

Her 2010 did not provide enough information on the study design. We contacted the authors and assessed the risk using information provided by the authors. We rated the trial as follows: at low risk of bias for random sequence generation, allocation concealment, and masking of participants (performance bias); at high risk of bias for masking of outcome assessors (detection bias); and at unclear risk of bias for selective outcome reporting. No loss to follow-up was reported in this trial. Details of the trial design are available in the Risk of bias in included studies table.

Effects of interventions

In the existing literature, the term *acupuncture* embraces a variety of stimulation techniques including different types of acupuncture needles used, electrical or laser stimulation with or without needle acupuncture, application of moxibustion with acupuncture, and acupressure without needling. In addition, different acupuncture points or groups of points and different intensity, duration, and frequency or repetition rate of stimulation were studied under the

same category of acupuncture. This clinical heterogeneity made comparisons or analyses of studies on acupuncture almost impossible.

Her 2010 did not report between-group comparisons for any outcomes examined in the trial. We re-analyzed data reported at four weeks and eight weeks.

At four weeks- the time point at which acupressure treatment stopped- comparison of the acupressure group with the sham group revealed that the between-group difference in IOP (measured in mm Hg) was −3.70 (95% confidence interval (CI) −7.11 to −0.29; P = 0.044) for the right eye and −4.90 (95% CI −8.08 to −1.72; P = 0.006) for the left eye. The difference in uncorrected visual acuity (UCVA, measured in logMAR) was −0.01 (95% CI −0.24 to 0.22; P = 0.932) for the right eye and −0.04 (95% CI −0.27 to 0.19; P = 0.747) for the left eye. The difference in best corrected visual acuity (BCVA, measured in logMAR) was 0.10 (95% CI −0.06 to 0.26; P = 0.236) for the right eye and 0 (95% CI −0.14 to 0.14; P = 1.000) for the left eye.

At eight weeks- the longest follow-up time point in the study- comparison of the acupressure group with the sham group revealed that the between-group difference in IOP was −1.30 mm Hg (95% CI −4.78 to 2.18; P = 0.474) for the right eye and −2.30 mm Hg (95% CI −5.73 to 1.13; P = 0.202) for the left eye. The difference in UCVA was −0.03 logMAR (95% CI −0.27 to 0.21; P = 0.812) for the right eye and −0.16 logMAR (95% CI −0.43 to 0.11; P = 0.261) for the left eye. The difference in BCVA was −0.04 logMAR (95% CI −0.09 to 0.17; P = 0.565) for the right eye and −0.04 logMAR (95% CI −0.18 to 0.10; P = 0.589) for the left eye.

No statistically significant difference in IOP or visual acuity was noted at any other follow-up time points.

We did not conduct a meta-analysis for this review because we found only one completed RCT.

Our search revealed a few case series of small sample size. We believed it would be inappropriate to summarize the results from these case series because the search strategy employed was not designed to identify nonrandomized studies. In addition, the methodologic limitations made it impossible to quantify the magnitude of the effect.

DISCUSSION

Acupuncture, which originated in China more than 2000 years ago, is one of the oldest medical procedures in the world (NCCAM 2007). Over the past two decades, acupuncture has grown in popularity in the United States and in other Western countries. According to the 2002 National Health Interview Survey (Barnes 2004), 8.2 million US adults had used acupuncture, and 2.1 million had used it during the previous year.

In accordance with this trend, some glaucoma patients may seek acupuncture as a supplement or an alternative to their traditional glaucoma management. One completed trial suggests that although IOP in the acupressure group was statistically lower than that in the

sham group at four weeks' follow-up, the difference was not statistically significant at any other follow-up time points, including the longest follow-up time (eight weeks). Further, the difference in visual acuity between the two groups was not statistically significant at any follow-up time points. These results should be interpreted carefully because the trial was rated as at high risk of bias for masking of outcome assessors. Inadequate masking of outcome assessors may introduce information bias. All together, the limited information from RCTs highlights the gap in existing evidence. The effectiveness of acupuncture as a therapeutic modality for glaucoma could not be firmly established at this point. Inclusion of the seven Chinese trials that are classified as "awaiting assessment in the future" may change this conclusion.

AUTHORS' CONCLUSIONS

Implications for practice

At this time, it is impossible to draw reliable conclusions from the available data to support the use of acupuncture for the treatment of glaucoma. Most glaucoma patients currently cared for by ophthalmologists do not use nontraditional therapy; therefore clinical practice decisions will have to be based on physician judgments and patient preferences, given this lack of data in the literature.

Implications for research

Because of ethical considerations, RCTs comparing acupuncture alone with standard glaucoma treatment or placebo are unlikely to be justified in the near future in countries where the standard of care has already been established. However, trials in which acupuncture in combination with another glaucoma treatment is compared with the other glaucoma treatment alone might be of interest. It would be valuable for researchers and clinicians who are experienced in acupuncture to agree on certain basic standards for administration of acupuncture in clinical trials. Adequate data on IOP, central visual acuity, contrast sensitivity, visual field changes, optic nerve and retinal nerve fiber layer analysis, ocular blood flow, pattern electroretinography (PERG), multifocal ERG, visual evoked potential (VEP), multifocal visual evoked potential (mfVEP), potential harms, visual-related quality of life, and economic outcomes will facilitate appropriate evaluation of the effectiveness and safety of acupuncture.

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APPENDICES

Appendix 1. CENTRAL search strategy

#1	MeSH descriptor Glaucoma
#2	MeSH descriptor Ocular Hypertension
#3	MeSH descriptor Intraocular Pressure
#4	(pressure near ocular) and (increas* or elevat* or high*)
#5	glaucoma*
#6	MeSH descriptor Acupuncture
#7	acupuncture therapy
#8	acupuncture or acupressure
#9	(electro next stimulat*) or (electro next acupuncture)
#10	(#1 OR #2 OR #3 OR #4 OR #5)
#11	(#6 OR #7 OR #8 OR #9)
#12	(#10 AND #11)

Appendix 2. MEDLINE (OvidSP) search strategy

1	randomized controlled trial.pt.
2	(randomized or randomised).ab,ti.
4	dt.fs.
5	randomly.ab,ti.
6	trial.ab,ti.
7	groups.ab,ti.
8	or/1–7 1155275
9	exp animals/
10	exp humans/
11	9 not (9 and 10)
12	8 not 11 999260
13	exp glaucoma/
14	exp ocular hypertension/
15	exp intraocular pressure/
16	((increas$ or elevat$ or high$) adj3 ocular adj3 pressure).tw.
17	glaucoma$.tw.

18 or/13–17

19 exp acupuncture/

20 exp acupuncture therapy/

21 (acupuncture or acupressure).tw.

22 (((electro adj1 stimulat$) or electro) adj1 acupuncture).tw.

23 or/19–22

24 18 and 23

25 12 and 24

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville (Glanville 2006).

Appendix 3. EMBASE (OvidSP) search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1–5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/

21. exp latin square design/

22. or/12–21

23. 22 not 10

24. 23 not 11

25. exp comparative study/

26. exp evaluation/

27. exp prospective study/

28. (control$ or prospectiv$ or volunteer$).tw.

29. or/25–28

30. 29 not 10

31. 30 not (11 or 23)

32. 11 or 24 or 31

33. exp glaucoma/

34. exp intraocular hypertension/

35. exp intraocular pressure/

36. ((increas$ or elevat$ or high$) adj3 ocular adj3 pressure).tw.

37. glaucoma$.tw.

38. or/33–37

39. exp acupuncture/

40. (acupuncture or acupressure).tw.

41. (((electro adj1 stimulat$) or electro) adj1 acupuncture).tw.

42. or/39–41

43. 38 and 42

44. 32 and 43

Appendix 4. LILACS search strategy

acupuncture and glaucoma

Appendix 5. CINAHL (EBSCO) search strategy

S11 S6 AND S10

S10 S7 OR S8 OR S9 OR S10

S9 TX acupuncture or acupressure

S8 (MH “Medicine, Chinese Traditional+”)

S7 (MH “Acupuncture+”)

S6 S1 OR S2 OR S3 OR S4 OR S5

S5 TX high* n3 ocular pressure

S4 TX elevat* n3 ocular pressure

S3 TX increas* n3 ocular pressure

S2 (MH “Ocular Hypertension”)

S1 (MH “Glaucoma+”)

Appendix 6. ZETOC search strategy

acupuncture and glaucoma

Appendix 7. AMED search strategy

1. glaucoma/
2. ocular hypertension/
3. ((increas$ or elevat$ or high$) adj3 ocular adj3 pressure).tw.
4. glaucoma$.tw.
5. or/1–4
6. acupuncture/
7. exp Traditional medicine chinese/
8. (acupuncture or acupressure).tw.
9. (((electro adj1 stimulat$) or electro) adj1 acupuncture).tw.
10. or/6–9
11. 5 and 10

Appendix 8. metaRegister of Controlled Trials search strategy

acupuncture and glaucoma

Appendix 9. ClinicalTrials. gov search strategy

acupuncture AND glaucoma

Appendix 10. ICTRP search strategy

Acupuncture AND Glaucoma

Appendix 11. National Center for Complementary and Alternative Medicine website search strategy

acupuncture and glaucoma

DATA AND ANALYSES

This review has no analyses.

Table 1

Characteristics of included studies *[ordered by study ID]*

Her 2010		
Methods	**Study design:** RCT. **Number randomized (total and per group):** 33 participants in total; 16 participants (28 glaucoma eyes) in the auricular acupressure group and 17 participants (32 glaucoma eyes) in the sham group **Number analyzed (total and per group):** 33 participants in total; 16 participants (28 glaucoma eyes) in the auricular acupressure group and 17 participants (32 glaucoma eyes) in the sham group **Exclusions and loss to follow-up:** 0. **Study follow-up:** 8 weeks.	
Participants	**Country:** Taiwan. **Age (mean ± SD, range), years:** 73.6 ± 9.1 in the acupressure group, 76.3 ± 10.5 in the sham group **Gender:** 3/16 in the acupressure group and 4/17 in the sham group are female **Inclusion criteria:** (1) age 30 years or older and (2) history of unilateral or bilateral glaucoma or ocular hypertension that has been treated for at least 1 year **Exclusion criteria:** (1) laser trabeculoplasty in the past; (2) filtering surgery for glaucoma in the past; (3) persistent ocular inflammation within the past 1 year; (4) start of or adjustment to the use of any systemic medication that affects the IOP within 3 months; (5) end-stage glaucoma with impending phthisis bulbi; (6) no detectable IOP because of poor psychological condition	
Interventions	**Treatment or intervention 1:** auricular acupressure. **Control or intervention 2:** sham group. **General procedures (e.g., pre-op or post-op tests, medications, procedures):** "Patients in the acupressure group received 'stimulator tapping' and massage of the auricular points (kidney, liver, and eye) over the right ear at our first course of outpatient clinic. Tapping stimulation was administered using a 1-mm alloy ball (Magrain; Sakamura, Kyoto, Japan) designed for acupressure, which was applied to the surface of the auricular acupoints. Subsequently, over a 4-week period, patients regularly massaged their ears using thumb and index finger (squeezing each side of the ear with inward pressure from opposing finger and thumb) twice per day for 9 minutes each time (3 minutes/each point). A regular follow-up was performed and the side for tapping, left ear or right ear, was alternated weekly. After 4 weeks of follow-up, tapping of the acupoints was discontinued and no further massages were given. The investigators re-evaluated IOP, uncorrected visual acuity, and best corrected visual acuity at the 8-week follow-up conducted at the clinic. Patients in the sham group received stimulator tapping but no massage at the sham auricular points (wrist, shoulder, and jaw). All other treatment modalities were the same as those for the acupressure group."	
Outcomes	**Primary outcome(s):** IOP and visual acuity with or without glasses were measured **Secondary outcome(s):** N/A. **Measurements taken, specify intervals at which outcomes assessed:** "IOP was measured with a Goldmann applanation tonometer (Haag-Streit AG, Koeniz, Switzerland). Visual acuity was examined with a 6-m visual acuity chart. The glaucomatous eyes were used for analysis of IOP, as were eyes with better than 0.01 (decimal) visual acuity. All visual acuity data were transformed to the LogMAR (MAR¼minimal angle resolution) form for analysis." **Unit of analysis (individual or eye):** eye or individual (1 eye per person was used for the analysis) **Other issues with outcome assessment (e.g., quality control for outcomes if any):** N/A.	
Notes	**Study dates:** N/A. **Funding source(s):** National Science Counsel of Taiwan (NSC 97-2320-B-039-022-MY3 and NSC 98-2815-C-039-097-B), Department of Health, Executive Yuan, Taiwan (DOH98-TD-F-113-098011), and China Medical University (CMU98-CT-10), Taichung, Taiwan, **Publication language:** English.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Method used to generate random sequence was not described in the article. After contacting the author, we received the following information: "We used computer to generate 40 (our original expected patient collection numbers) simple randomized allocation sequences. We then assigned patients to 'control' or 'trial' group according to their clinic visit order. So we knew the next patient would be assigned to which group, but we didn't know who would be the next one (patient's visit order was arranged by the clinic assistant, who didn't know the randomized allocation sequences). The patient him-/herself would not know which group he/she would be assigned."
Allocation concealment (selection bias)	Low risk	Method used to conceal allocation was not described in the article. We considered that allocation was adequately concealed after contacting the authors because "patient's visit order was arranged by the clinic assistant, who didn't know the randomized allocation sequences."

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Masking of participants and personnel was not described in the article. After contacting the author, we received the information that “patients were blinded of their treatment group whereas the outcome assessors were not blinded.”
Blinding of outcome assessment (detection bias) All outcomes	High risk	See above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up was reported.
Selective reporting (reporting bias)	Unclear risk	Original protocol was not available.
Other bias	Low risk	No other bias was identified.

Table 2

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Jiang 1996	Not a randomized controlled trial.
Kumar 1994	Nonrandomized comparative study; acupuncture as defined in this review was not used
Nesterov 1997	Nonrandomized comparative study; acupuncture as defined in this review was not used
Xu 2012	Not a randomized controlled trial.

Table 3

Characteristics of studies awaiting assessment *[ordered by study ID]*

Hu 1995	
Methods	Fifty Chinese patients (61 eyes) were included. Twenty-five patients (32 eyes) were assigned to acupuncture plus "Western medicine," and 25 patients (29 eyes) were assigned to "Western medicine" only
Participants	Patients with acute angle-closure glaucoma.
Interventions	Group 1: acupuncture (acupuncture 30 minutes once daily for 5–7 days) plus "Western medicine" (did not specify the drug name or the usage) Group 2: pilocarpine 1% eye drop plus carbonic anhydrase inhibitor (did not specify the usage)
Outcomes	Intraocular pressure (IOP) (time points measured were not reported in the article)
Notes	
Huo 2009	
Methods	Ninety-six Chinese patients (166 eyes) were included. Forty-four patients (77 eyes) were assigned to pricking blood treatment, and 52 patients (89 eyes) were assigned to timolol
Participants	Patients with primary open-angle glaucoma.
Interventions	Group 1: pricking blood at Neiyingxiang (EX-HN9). Group 2: timolol maleate 0.5% eye drop (did not specify the usage)
Outcomes	Intraocular pressure (IOP) (time points measured were not reported in the article)
Notes	
Wu 2010	
Methods	Sixty Chinese patients (120 eyes) were included. Thirty patients (60 eyes) were assigned to acupuncture and 30 patients (60 eyes) were assigned to timolol
Participants	Patients with primary open-angle glaucoma.
Interventions	Group 1: acupuncture for 20 minutes. Group 2: timolol eye drop twice daily (did not report the concentration of timolol or the duration of use)
Outcomes	Intraocular pressure (IOP), visual acuity, visual field loss, and cup/disc ratio (time points measured were not reported in the article)
Notes	
Zhang 1995	
Methods	One hundred forty-eight Chinese patients (246 eyes) were included. Ninety-six patients (166 eyes) were assigned to pricking blood therapy, and 52 patients (80 eyes) were assigned to pilocarpine
Participants	Patients with chronic primary glaucoma and chronic angle-closure glaucoma
Interventions	Group 1: pricking blood at Erjianxue. Group 2: pilocarpine 1% eye drop once (did not specify the duration of therapy)
Outcomes	Intraocular pressure (IOP) (time points measured were not reported in the article)
Notes	
Zhang 2003	
Methods	One hundred ninety-eight Chinese patients (204 eyes) were included. One hundred eight patients (111 eyes) were assigned to acupuncture with manipulation, and 90 patients (93 eyes) were assigned to acupuncture without manipulation
Participants	Patients with acute angle-closure glaucoma.
Interventions	Group 1: acupuncture with manipulation. Group 2: acupuncture without manipulation.
Outcomes	Aqueous flow (F value at 3, 6, and 12 months).
Notes	
Zhang 2009	

Methods	Forty-nine Chinese patients (86 eyes) were included. Forty-three eyes were assigned to acupuncture, and 43 eyes were assigned to timolol
Participants	Patients with primary open-angle glaucoma.
Interventions	Group 1: acupuncture. Group 2: timolol 0.5% eye drop twice daily.
Outcomes	Intraocular pressure (IOP) at 6 months.
Notes	
Zhou 2007	
Methods	Forty-four Chinese patients (60 eyes) were included. Twenty-two patients (30 eyes) were assigned to acupuncture, and 22 patients (30 eyes) were assigned to no treatment
Participants	Patients had undergone glaucoma surgery.
Interventions	Group 1: acupuncture. Group 2: no treatment.
Outcomes	Visual acuity, visual field (time points measured were not reported in the article)
Notes	

Table 4

Characteristics of ongoing studies *[ordered by study ID]*

JPRN 2009	
Trial name or title	Acupuncture for Glaucoma.
Methods	This is an interventional, parallel, randomized study.
Participants	Inclusion criteria: patients with glaucoma treated for at least one year with ocular hypotensive medication Exclusion criteria: laser trabeculoplasty, any ocular surgery; inflammation within one year; other abnormal ocular condition; or starting or adjusting the use of any systemic medication affecting intraocular pressure (IOP) within three months
Interventions	Patients will be randomly assigned to either standard treatment or standard treatment plus acupuncture
Outcomes	1. IOP. 2. Blood flow volume of eyeball.
Starting date	27/10/2009.
Contact information	t-seki@m.tains.tohoku.ac.jp
Notes	Recruitment status: not yet recruiting.