Laser photocoagulation versus transscleral cryotherapy for threshold retinopathy of prematurity (Protocol)

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[Intervention Protocol]

Laser photocoagulation versus transscleral cryotherapy for threshold retinopathy of prematurity

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

Among infants with threshold retinopathy of prematurity, does treatment with laser photocoagulation, as compared to transscleral cyrotherapy, result in lower rates of visual impairment or initial morbidity?

BACKGROUND

As advances in neonatal medicine have allowed an increased survival of premature infants, retinopathy of prematurity (ROP), the leading cause of blindness among premature infants, has become more frequent (McNamara 1999). The incidence of acute ROP and its more severe stages varies inversely with gestational age and birth weight. Of infants born at less than 28 weeks gestation, 84% develop acute ROP, and 11% develop threshold ROP (Palmer 1991). Approximately 80% of infants with birth weight 750 - 999g develop acute ROP and 7% develop threshold ROP. In infants with birth weight less than 750g, the incidence of acute ROP increases to 90% with 15% developing threshold ROP (Palmer 1991). The incidence of all stages of ROP in a large cohort of extremely low birth weight (ELBW) infants (401-1000g) from the National Institute of Child Health and Human Development Neonatal Research Network, 1993 - 1994, was 70%, the smaller infants (501-600g) having higher incidence, 90%, compared to the larger infants (901-1000g), 50% (Vohr 2000). The Vermont-Oxford Network Database, an international neonatal intensive care unit (NICU) database, reports an incidence of ROP of 57.2% for the year 1997 (Blair 2001) in neonates with birth weight less than 1250g. The prospective, randomized, multicentre study of the effects of light reduction on infants with birth weights less than 1251g and gestational ages of less than 31 weeks showed an incidence of ROP of 54% and 58% in the experimental and control groups respectively, and an incidence of threshold ROP of 5% in both groups (LIGHT-ROP 1998).

Threshold ROP is defined as five contiguous or eight cumulative clock hours of stage 3 ROP located in zone I or II in conjunction with "plus disease" (ICROP 1984). Threshold ROP is the level of severity at which the risk of blindness without treatment approaches 50% (CRYO-ROP 1988). Peripheral retinal ablative therapy by laser photocoagulation or transscleral cryotherapy has been shown to improve visual outcomes in infants with threshold ROP (CRYO-ROP 1988; CRYO-ROP 1990a; CRYO-ROP 1990b; CRYO-ROP 1993; CRYO-ROP 1996; CRYO-ROP 2001; Andersen 2000; LaserROP 1994). Laser ablation or cryosurgery of the peripheral avascular retina destroys the cells that are the putative source of the growth factors that are believed to drive the new vessel growth characteristic of ROP, thus allowing regression of neovascularization (Pierce 1996; Aiello 1997).

The Cryotherapy for Retinopathy of Prematurity Trial (CRYO-ROP) showed that treatment results in a reduction from 51% to 31% in the occurrence of unfavourable structural outcomes including posterior retinal traction folds, retinal detachment and retrolental tissue or "mass" (CRYO-ROP 1990a). During the long term follow-up, favourable structural and functional outcomes continued to be observed in the cryotherapy treated group compared to the control group (CRYO-ROP 1990b; CRYO-ROP 1993; CRYO-ROP 1996, CRYO-ROP 2001). The study also prospectively recorded significant local perioperative (e.g. conjunctival hematoma, conjunctival laceration, retinal/preretinal/vitreous hemorrhage, transient closure of the central retinal artery) and systemic (e.g. bradycardia, cyanosis, seizure) adverse events related directly to the traumatic nature of the application of cryotherapy (CRYO-ROP 1988), although the ophthalmic complications of treatment were quite rare.

Laser therapy has gained widespread acceptance and has largely replaced cryotherapy in the treatment of ROP. Over the period 1994 to 1999, peripheral ablation using laser therapy was performed in 93% and cryotherapy in 7% of treated eyes in the multicentre randomized controlled trial comparing supplemental to conventional oxygen for prethreshold ROP (STOP-ROP 2000). Several prospective randomized trials have supported laser photocoagulation as being as effective in the management of threshold ROP (McNamara 1991; Iverson 1991; McNamara 1992; Hunter 1993), although none were on the scale of the CRYO-ROP multicentre trial. In the short term, laser therapy is better tolerated than cryotherapy with fewer ocular and systemic side effects (White 1997; Connolly 1998). Several authors have found better visual acuity outcomes and less myopia when comparing laser therapy with cryotherapy using historical controls (Algawi 1994; Laws 1997; Paysse 1999) with some studies reporting longer term outcomes at three, five and seven years of age (Knight-Nanan 1996; White 1997; Connolly 1998; O'Keefe 1998; Pearce 1998; Shalev 2001). There is also evidence that suggests that laser therapy may be more cost-effective than cryotherapy (Brown 1999). The main limitation of many studies comparing laser photocoagulation to cryotherapy is that they use historical or concurrent non-randomized cohorts rather than randomized controls (LaserROP 1994; Algawi 1994; Hammer 1995; Noonan 1996; Laws 1997; Yang 1997; McGregor 1998; O'Keefe 1998; Pearce 1998; Paysse 1999). The laser-treated eyes may have benefited from coincident advances in neonatology and ophthalmology, and better screening guidelines for ROP (Tasman 1988; RCO 1996; AAP 2001; CPS 1998; CAPO 2000).

The aim of this review is to elucidate whether laser photocoagulation has advantages in safety and effectiveness over cryotherapy in improving visual outcomes in infants with threshold ROP.

OBJECTIVES

Among infants with threshold retinopathy of prematurity, does treatment with laser photocoagulation, as compared to transscleral cyrotherapy, result in lower rates of visual impairment or initial morbidity?

METHODS

Criteria for considering studies for this review

Types of studies

Randomized or quasi-randomized controlled trials evaluating the visual outcomes of laser photocoagulation versus transscleral cryotherapy in infants with eyes with threshold ROP, will be considered for inclusion. Information from reports with historical cohorts and concurrent non-randomized controls will also be examined, but not included in the primary analysis.

Types of participants

All studies of infants with threshold ROP will be considered for inclusion. Threshold ROP is defined according to the ICROP classification as five contiguous or eight cumulative clock hours of stage 3 ROP located in zone I or II in conjunction with "plus disease" (ICROP 1984). Studies describing 'stage 3 ROP' or 'stage 3 + ROP' will also be considered for evaluation.

Types of interventions

Studies will be considered for inclusion if eyes were randomized to ablation of the peripheral avascular retina either by laser photocoagulation (laser diode, laser argon, xenon arc photocoagulation) or by cryotherapy. Studies will be examined for whether the unit of randomization is eyes or infants. Studies in which the unit of randomization is eyes ensure a more rigorous comparison between laser therapy and cryotherapy especially in infants with symmetric disease when one eye is randomized to laser therapy and the other to cryotherapy. A subgroup analysis of infants with symmetric disease will be done. Studies in which the concurrent control group is 'no therapy' will not be considered for inclusion since the comparison of interest is laser therapy versus cryotherapy.

Types of outcome measures

Primary outcomes:

- Late visual impairment, assessed after three years of age, defined by a Snellen acuity equivalent of 20/60 or worse.

Secondary outcomes:

- Refractive outcome, particularly severe myopia assessed after three years of age, determined by retinoscopy and scored using refractive spherical equivalent (diopters)
- Unfavourable structural outcomes assessed early after therapy as defined by the CRYO-ROP Multicenter Trial (CRYO-ROP 1988): (1) retinal fold involving the macula; (2) retinal detachment involving zone 1 of the posterior pole; (3) retrolental tissue or "mass".
- Unfavourable eye structural outcomes occurring in early childhood, with assessments through at least 3 years of age: micro-ophthalmia, total retinal detachment, retrolental mass, vitrectomy, scleral buckle, glaucoma, cataracts, enucleation for ROP, etc
- Need for supplemental retreatment after initial cryotherapy for laser coagulation
- Acute systemic and/or ocular adverse effects related to either intervention. Local adverse events of retinal ablative therapy will include lid edema, conjunctival hyperemia, conjunctival laceration, central retinal artery occlusion, sceral rupture, etc. Systemic adverse events will include bradycardia or arrhythmia, significant apnea, cardiorespiratory arrest.

Search methods for identification of studies

The standard search strategy of the Cochrane Neonatal Review Group will be used. This includes a search of the Cochrane Neonatal Group Register of Clinical Trials and Cochrane Controlled Trials Register (CCTR) (Cochrane Library, Issue 2, 2002).
Relevant studies will be identified by searching the following: (1) computerized bibliographic databases: MEDLINE (1966-March 2002), EMBASE (1988-March 2002) and Web of Science (1975-August 2002); (2) citation searches; (3) reference lists of all selected articles as well as review articles; (4) the Oxford Database of Perinatal Trials. Unpublished, in press and in progress trials, abstracts from neonatal, pediatric and ophthalmologic meetings, and other pertinent research will be identified by contacting primary authors, researchers and other expert informants.
Search terms using MeSH headings and/or keywords will include: [retinopathy of prematurity (All fields) OR retrolental fibro$ (All fields) OR retrolenticular fibro$ (All fields) OR (retinopath$ adj5 prematur$) (All fields)] AND [exp laser surgery OR laser surg$ (All fields) OR laser coagulat$ (All fields) OR light coagulat$ (All fields) OR photocoaulat$ (All fields) OR endophoto$ (All fields) OR cryoablat$ (All fields) OR cryotherap$ (All fields) OR cryogenic$ (All fields) OR cryosurg (All fields)]. For the primary analysis, the search will be limited by publication type: [controlled clinical trial OR meta-analysis OR multicentre trial OR randomized clinical trial] OR by the following search terms: [random$ OR double blind$ or single blind$].
The search will not be limited by language or publication status.

Data collection and analysis

STUDY SELECTION
Relevance criteria will be assessed on characteristics of study design (randomized or quasi-randomized, controlled), study population (infants with threshold retinopathy of prematurity), study intervention (laser photocoagulation vs. cryotherapy) and outcome measures (visual impairment, myopia, etc). The selection of studies will involve two steps. First, the initial search of all the databases and reference lists will be screened independently by two investigators to identify trials with potential relevance. For this initial

search, the title and abstract, if available, will be assessed. Second, the full text of likely relevant articles will be obtained. Two reviewers will independently decide on trial inclusion using a standard form with pre-determined eligibility criteria. Disagreements will be resolved by consensus or by a third party when necessary.

If necessary, the reviewers will contact investigators for additional information or clarification of method of randomization, patient characteristics, details of interventions, definitions of events, additional relevant outcomes, and losses to follow up.

ASSESSMENT OF QUALITY

The Neonatal Review Group bases its quality assessments on systematic evaluation of the following biases as stated in the Cochrane Handbook: selection bias (masking of randomization), performance bias (masking of intervention), attrition bias (complete follow up) and detection bias (masking of outcome measurement). In the selected trials, all the biases will be evaluated as "Yes", or "Can't tell" or "No". Concealment of allocation will be assessed as adequate, inadequate or unclear (Schulz 1995). Two researchers will independently assess quality. Differences will be resolved by consensus or third party as necessary. Studies will also be assessed by whether an intention-to-treat analysis was used. Any funding source required by the study will be recorded. Language of publication, country of publication and dates over which the study was conducted will also be noted.

DATA EXTRACTION

Data will be extracted independently by two investigators. Unpublished data will be requested from authors as necessary for clarification of method of randomization, losses to follow up, patient characteristics, details of interventions, definitions of events, and additional outcomes.

A standard form will be used that will describe the following:

- Characteristics of the study (design; method of randomization; withdrawals/dropouts/losses to follow-up; eligible participants/eyes and actual participants/eyes completing the study)
- Study participants (eligibility and exclusion criteria; birth weight; gestational age; number of participants with symmetric disease)
- Intervention (type of laser used - argon, diode; need for supplemental treatment)
- Outcomes (average age of participants at follow-up assessment; visual acuity; myopia and degree of myopia; unfavourable retinal structural outcome; unfavourable eye structural outcome; local and systemic adverse effects).

Data will be entered into RevMan (Version 4.1) for data analysis.

DATA ANALYSIS

Data analysis will be conducted according to the methods of the Cochrane Neonatal Review Group.

Studies will be examined for whether the unit of randomization is eyes or infants. Data will be extracted for results in infants and in eyes, depending on the designs of the eligible trials. Analyses will be done separately on results in infants and in eyes. If more than one event in each category occurs in the infant/eye, then only one event will be counted: for instance, for unfavourable eye structural outcomes, if the retina was detached and required scleral buckling, then only one event will be recorded.

a) Categorical data

The proportion of randomized eyes which experience unfavourable outcomes (e.g. visual impairment, retinal detachment) in the laser therapy and cryotherapy groups will be extracted. The event rates will be unfavourable event rates and will be expressed as a relative risk (RR) with 95% confidence intervals, the relative risk being the ratio of unfavourable events in the laser and cryotherapy groups. A RR less than 1 will indicate a benefit in the laser therapy group compared to the cryotherapy group. The point estimate will be plotted to the left of a RR of 1, labelled 'Favours Laser Therapy' on the graph.

b) Continuous data

Continuous data (e.g. refractive error - mean spherical equivalents) will be reported as the mean and standard deviation in the laser and cryotherapy groups. Myopia is commonly associated with ROP and is reported in negative units. For refractive error, a mean difference (Laser therapy minus cryotherapy) and its 95% confidence interval will be plotted. When the mean difference is to the left of a mean difference = 0, this will indicate that the laser treated eyes/infants are more myopic than the cryotherapy treated eyes/infants. Thus a plot to the left of a mean difference = 0, may signify greater myopia following laser treatment.

c) Meta-analysis will be done, if appropriate, using the fixed effect model. For categorical outcomes, a summary relative risk and its 95% confidence interval will be calculated. For outcomes measured on a continuous scale, a weighted mean difference and 95% confidence interval will be calculated.

d) If the data are too sparse or too low quality, or too heterogeneous to proceed with statistical aggregation, a narrative, qualitative summary will be done, and a meta-analysis avoided.

e) Testing for heterogeneity will be done using degrees of freedom and Chi-square values (see Neonatal Review Group guidelines). Possible sources of heterogeneity will be assessed by subgroup and sensitivity analyses.

f) Testing for publication or other biases will be assessed using the funnel plot visually and quantitatively depending on the number of trials included in the review.

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* *Indicates the major publication for the study*

WHAT'S NEW

Last assessed as up-to-date: 27 May 2002.

Date	Event	Description
29 October 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 2002

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Department of Public Health Sciences, University of Alberta, Edmonton, Alberta, Canada.
- Department of Pediatrics, Division of Neonatology, University of Alberta, Edmonton, Alberta, Canada.
- Cochrane Neonatal Review Group, Canada.

External sources

- No sources of support supplied