Cost-Effectiveness of Treatment for Threshold Retinopathy of Prematurity

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ABSTRACT. Objective. Retinopathy of prematurity (ROP) is a leading cause of adverse visual outcomes in premature infants. Both laser photocoagulation and cryotherapy have been demonstrated in clinical trials to be efficacious in reducing the incidence of visual loss occurring secondary to threshold ROP. Visual data recently have become available concerning the long-term clinical efficacy of both treatments, as have data concerning the utility value of visual states in general. Accordingly, we undertook an analysis to ascertain the cost-effectiveness of laser photocoagulation and cryotherapy in the treatment of threshold ROP.

Design. A computer simulation economic model is presented to evaluate the cost-effectiveness of cryotherapy and laser photocoagulation therapy, compared with the natural course of the disease, for treating premature infants with threshold ROP. The model applies long-term visual data from previous clinical trials, utility analysis, decision analysis, and economic principles, such as present value analysis, to account for the time value of money to arrive at a cost per quality-adjusted life-year (QALY) gained.

Outcome Measures. Cost per QALY gained from laser therapy and cryotherapy.

Results. Laser photocoagulation therapy for threshold ROP costs $678 1998 US dollars (at a 3% discount rate to account for the time value of money) for each QALY gained from treatment. Cryotherapy for the same disease costs $1801 per QALY at a similar discount rate.

Conclusions. From the point of view of cost-effectiveness, laser therapy seems to have an advantage over cryotherapy for the treatment of threshold ROP. Pediatrics 1999;104(4). URL: http://www.pediatrics.org/cgi/content/full/104/4/e47; threshold retinopathy of prematurity, laser therapy, cryotherapy, cost-effectiveness.


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R etinopathy of prematurity (ROP) is the leading cause of blindness among premature infants.1 It occurs in some form in ~32% of infants with birth weights ≤1000 g.1 Among those infants with birth weights <1251 g, 7% to 8% will develop threshold ROP.2 Threshold ROP is defined as proliferative retinal vascular disease that is located in zone 1 or 2 in conjunction with plus disease and associated with 5 contiguous or 8 cumulative clock hours of extraretinal neovascularization.1 Of those who are treated for threshold disease, the long-term survival is ~88%.3

The Multicenter Trial of Cryotherapy for ROP initially demonstrated that retinal cryotherapy for threshold ROP decreased the incidence of an unfavorable anatomic outcome from 51% to 31%.2 Subsequently, the Laser ROP Study Group3 showed with a meta-analysis that the risk of an unfavorable outcome in eyes with threshold ROP was 19% with cryotherapy and 8% with laser therapy.

Now that children who were treated for threshold ROP are maturing, data concerning the long-term visual acuity results from prospective clinical trials are available.5–7 It seems that the mean visual acuity in eyes treated for threshold ROP may be better in those children treated with laser photocoagulation than in those treated with cryotherapy. Although systemic complications can be associated with cryotherapy5 and laser therapy,9 the incidence of such complications seems to be low.

Cost-effective analyses that involve utility theory are being reported with increasing frequency.10–13 Utility analysis incorporates patient-based preferences that allow the quality of life associated with a health (disease) state to be quantified. In view of recent data concerning utility values in patients with visual loss14 and new information on visual results after therapy for ROP,5–7 we undertook an analysis of the cost-effectiveness of laser photocoagulation and cryotherapy for the treatment of threshold ROP.

METHODS

Overview

Software produced by Treeage, Inc (Williamstown, MA)15 was used to perform decision analysis to simulate the clinical situation involving laser therapy, cryotherapy, and no therapy for patients with threshold ROP. This microcomputer model takes into account the mortality within this group of patients, as well as the treatment results expressed in utility form. The numbers of unilateral and bilateral cases also were factored into the analysis. Utility values were used at the terminal nodes at the right side of the decision tree to provide the most probable utility value outcomes given the different possible clinical scenarios. The utility
values were based on the visual acuity in the better seeing eye with lower levels of visual acuity yielding correspondingly lower utility values.14

The clinical data used for the analysis are described below. Additional clinical data and assumptions used in the analysis are shown in Table 1.

Treatment

Per the criteria of the Multicenter Trial of Cryotherapy for ROP,7 data were included in the present analysis only if the infant was involved with threshold ROP6 who were treated within 72 hours of the discovery of the threshold disease. Cryotherapy was performed by confluent freezing all avascular retina anterior to the mesenchymal ridge or extraretinal neovascularization in affected eyes.1,2 In a similar manner, only those eyes receiving laser in which all avascular anterior retina was treated with full scatter photoocoagulation14,16 were included.

Mortality and Morbidity

The Cryotherapy for ROP Cooperative Study Group followed a cohort of 291 infants with birth weights <1251 g who entered a prospective randomized clinical trial and were treated in one eye with cryotherapy for threshold ROP.2,3 Data obtained on the same cohort at 3 1/2 years after randomization revealed that there were 236 survivors among the original cohort of 291 infants.1 The average infant was examined and treated at 3 months of age. Thus, the mortality rate within 3% years after birth was 12% (35 deaths of 291 infants).

It was assumed that children who survived to this stage had a normal life expectancy, although confirmatory data are not available. Data on life expectancy were obtained using 1994 statistics obtained from the Centers for Disease Control and Prevention and the National Center for Health Statistics.17

The incidence of postoperative retinal detachment, cataract, or other ocular complications attributable to cryotherapy or laser therapy is unknown but is likely very low. The systemic morbidity associated with the treatments is low but present. Brown and associates8 found that cryotherapy induced cardiorespiratory arrest in 1 of 80 consecutive patients, and Vander and associates9 noted approximately the same results for laser therapy.

Bilaterality Versus Unilaterality of Threshold Disease

The Cryotherapy for ROP Cooperative Group found that 82.5% of the infants in the cohort of 291 infants developed bilateral threshold disease. For the purposes of our report, those patients with bilateral disease were assumed theoretically to have a similar visual result if they were to be treated with laser therapy in both eyes, have cryotherapy in both eyes, or have no treatment in both eyes. Because it is rare for ROP eyes to convert from a subthreshold-old state to threshold disease at 6 months after birth, which is when the data were reported, it was assumed that none of the unilateral cases would progress to bilateral threshold disease.

The patients with unilateral threshold ROP were presumed to have a normal eye with normal vision on the unaffected side. Thus, their vision was converted to a utility value by the method shown in the next two sections.

Visual Results

Visual results are emerging from clinical trials involving long-term follow-up of patients treated for threshold ROP.5,8 The most specific results for treated eyes come from the data of Connolly et al,6 who were able to quantify vision in Snellen form in threshold ROP eyes treated with laser therapy or cryotherapy and with a mean follow-up of 5.8 years. The most complete visual data on the natural course of untreated threshold ROP come from the Cryotherapy for ROP Cooperative Group7 that gathered data on survivors from a cohort of 291 patients with threshold ROP.

The assumption was made that once children were ≥5 years of age, the visual acuity would be stable in each eye. The incidence of long-term complications associated with ROP is unknown. It was assumed that the long-term complications (after 5 years of life) are equal in eyes that underwent laser therapy, cryotherapy, or no treatment.

The visual results for both treated eyes and untreated eyes were reported using the Snellen method, which is the most commonly used method for measuring visual acuity in clinical practice. For the purposes of this report, the Snellen visual acuity results in the eyes were converted to decimal form: 20/20 = 1; 20/25 = 0.8; 20/30 = 0.67; 20/40 = 0.5; 20/50 = 0.4; 20/60 = 0.66. The acuity at 20/70 = 0.29; 20/80 = 0.25; 20/100 = 0.2; 20/200 = 0.1; and 20/400 = 0.05. For a vision of counting fingers, a value of 0.025 was assigned, and for hand motions, a value of 0.0125 was assigned. No light perception was given a value of 0.0.

For the natural course of the disease,2 those eyes classified in the 20/40 or better range were assigned a mean acuity of 0.67 (20/30), those in the 20/40 to 20/60 range were assigned an acuity of 0.4 (20/50), those in the 20/60 to 20/200 range were given a mean acuity of 0.2 (20/100), those with 20/200 or worse were assigned an acuity of 0.05 (20/400), and those who had vision that was not quantifiable were given a mean acuity of 0.0125 (hand motions).

For those few patients with laser or cryotherapy treatment6 who did not have specific Snellen vision measurement, a value of 0.025 (counting fingers) was assigned to fix-and-follow or centered, steady, and maintained vision, whereas the one eye in the series with unsteady and unmaintained vision was assigned a value of 0.0125 (hand motions).

Conversion of Visual Acuity to Utility Values

It has been noted that the mean utility values of individuals with ocular disease diminish in proportion to the severity of visual loss in the better seeing eye.14 Recent data derived via multivariate regression analysis come from a large series of patients with visual loss from various ocular diseases.14 These data have allowed the conversion of Snellen visual acuity in the better eye to a mean utility value. The formula derived by this analysis is:

\[ Utility = 0.374x + 0.514. \]

Medical Costs

The costs obtained from this analysis were representative of those paid by the Health Care Financing Agency (HCFA) for provider services classified according to Current Procedural Terminology (CPT) data.10 The data utilized were from the state of Pennsylvania.19 The costs are summarized in Table 2.

The costs themselves included the payer's portion of the cost of treatment with laser photoocoagulation therapy (CPT code 67228) or cryotherapy (CPT code 67227) in both eyes for 82.5% of patients, and treatment with laser photoocoagulation therapy or cryotherapy in one eye in 17.5% of patients. These percentages directly reflect the percentages of premature infants in the Multicenter Trial of Cryotherapy for ROP Study with bilateral and unilateral threshold disease, respectively.2 The cost of an initial hospital consultation was taken from the same HCFA data using CPT code 99254. Because the laser therapy and cryotherapy codes most commonly have a 3-month postoperative period, no costs were attributed to

TABLE 1. Clinical Assumptions of the ROP Therapy Econometric Model of Cost-Effectiveness

<table>
<thead>
<tr>
<th>Assumption</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Additional cryotherapy is needed in 6.4% of cases and additional laser therapy is required in the same number. Nevertheless, because it is performed within a 30- to 90-day postoperative period (depending upon the insurer), there is no charge by the treating physician.2</td>
</tr>
<tr>
<td>2.</td>
<td>There is no mortality from either laser therapy or cryotherapy.14,16</td>
</tr>
<tr>
<td>3.</td>
<td>One of 80 patients who undergoes cryotherapy or laser therapy will experience a transient cardiorespiratory arrest59 that does not change the utility outcome in decision analysis; it only impacts upon costs.</td>
</tr>
<tr>
<td>4.</td>
<td>Those cases with bilateral threshold retinopathy of prematurity are considered to have a similar treatment result in each eye.</td>
</tr>
<tr>
<td>5.</td>
<td>Those with unilateral threshold ROP are presumed to have normal vision (20/20) in the opposite eye. In this instance, the utility is based upon the formula found for patients with normal vision in one eye and visual loss to at least 20/40 in the second eye.14</td>
</tr>
<tr>
<td>6.</td>
<td>Preservation of vision is assumed to be as valuable in children with neurologic deficits associated with prematurity as in those with normal psychomotor and social development parameters.</td>
</tr>
</tbody>
</table>
TABLE 2. Cost Data Associated with Treatment of Threshold ROP

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost per Patient</th>
<th>Noted</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser therapy for threshold ROP</td>
<td>$794</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryotherapy for threshold ROP</td>
<td>$908.85</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TABLE 3. Visual Outcome (in Snellen Decimal Equivalent) of an Eye with Threshold ROP

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Acuity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser therapy</td>
<td>0.49</td>
<td>6</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>0.23</td>
<td></td>
</tr>
</tbody>
</table>

RESULTS

Utilities

The mean visual results expressed in decimal equivalents using the Snellen system for acuity in premature infants with birth weights <1251 g who develop threshold ROP are shown in Table 3. The average eye with laser photoagulation therapy has a mean acuity of 0.49 at 5.8 years after treatment, whereas the average eye after cryotherapy has a mean acuity of 0.31 at a similar time after treatment. Untreated eyes with threshold ROP have a mean acuity of 0.23 at approximately the same time (5.5 years after treatment).

Decision Analysis

Three arms were used in the decision analysis tree for dealing with threshold ROP: 1) treatment with laser photoagulation; 2) treatment with cryotherapy; and 3) no therapy. The assumptions were made that the long-term survival in each of the arms was 88%, and that 82.5% of cases had bilateral threshold ROP.

Taking into account the above variables with the utility values described in the previous section applied to the terminal nodes of the decision analysis tree, the mean decision analysis utility value for a patient with threshold ROP treated with laser therapy was 0.65. The mean utility value for a patient treated with cryotherapy was 0.59, and the mean utility value for patients in the group without treatment was 0.57.

QALYs

The number of QALYs is calculated by multiplying the improvement in utility conferred by a treatment modality by the number of expected years the modality will be in effect. For the 88% of children who survived to the 3½-year level, the mean total life expectancy was 76.4 years. Because treatment was administered at 3 months of life, and because stabi-
therapy over no treatment was 6.08 (0.07 corresponding gain in nondiscounted QALYs for this mental effect (0.65–0.57) over no treatment. Thus, the therapy showed a gain of 0.79 QALY.

Laser therapy conferred a gain of 0.20 QALY, and laser therapy showed a gain of 0.79 QALY.

Sensitivity analysis of the values using varying discount rates revealed that with a 1% discount rate over the 76-year period of life expectancy of the average surviving infant, the $/QALY for cryotherapy is $1801 and for laser therapy is $678 (Table 4).

Sensitivity analysis for $/QALY at a discount rate of 1% per year yields a $/QALY for cryotherapy of $1003 and for laser therapy of $377. With a discount rate of 5% per year, the $/QALY for cryotherapy is $2658 and for laser therapy is $1017. With a large discount rate of 10% per year, the corresponding figures are $5315 for cryotherapy and $2030 for laser therapy.

**DISCUSSION**

The results of this study suggest that both cryotherapy and laser therapy are exceedingly cost-effective treatments for threshold ROP. Both treatments result in a substantial improvement in mean quality of life that lasts over the lifetime of the average patient with threshold ROP. Although this study noted that the actual patient treatment costs associated with cryotherapy ($1063) are less than those associated with laser therapy ($1607), evidence from a randomized clinical trial has shown that eyes treated with laser therapy have better long-term visual results than those treated with cryotherapy. These recent results were not completely unexpected by those well versed in treating threshold ROP. Results from the Laser ROP Study Group previously suggested the increased clinical efficacy of laser therapy over cryotherapy from the anatomic point of view.

Overall, using a 3% discount rate over the 76-year period of life expectancy of a patient with threshold ROP, the cost for laser therapy is $678/QALY and the cost for cryotherapy is $1801/QALY. The greater long-term clinical efficacy of laser therapy and the subsequent increased improvement of quality of life conferred by the better visual results suggest that it should be considered to be the preferred treatment if a clinician must choose between laser therapy and cryotherapy. Nevertheless, in instances with cloudy media (such as from vitreous hemorrhage or a marked tunica vasculosa lentis), laser therapy may not be possible, and cryotherapy may be the only option.

When comparing the cost-effectiveness of one medical interventional treatment with another, care must be taken to minimize the number of confounding factors. If possible, utility valuation should be undertaken with the same investigational methodology (using the time trade-off method, the standard gamble method, or another method), because the
results of these different methods can differ substantially.\textsuperscript{28,29} Utility values obtained from different populations (eg, patients, physicians, administrators, and the general public) also can differ substantially for the same disease state.\textsuperscript{27,30} We believe, as do others,\textsuperscript{31-33} that, when possible, preferences obtained from patients should be used, because those who have experienced diseases firsthand are best able to assess the degree to which the disease impairs quality of life. The utility values used in the present study were derived solely from patient preferences.\textsuperscript{14} Similar discounting methods and rates also should be used to account for differences in the time value of money caused by inflation, opportunity costs, or currency exchange differences. The sensitivity analysis in the present study demonstrates the vast differences in results that can occur from altering the discount rate alone, particularly when the treatment benefit effect occurs over many years and/or in the distant future. These substantial differences reflect the effect of compounding that occurs when calculating discount rates. Finally, comparing medical costs should reflect a uniform scale, such as the scale used by the HCFA.\textsuperscript{19} Comparing cost-efficiency from one country to another is particularly difficult because of the lack of standard costs and the effect of currency exchange fluctuations.\textsuperscript{34}

Keeping the above inexactitudes in mind, for comparison we have calculated that a single vessel coronary artery bypass procedure for left main coronary artery disease is associated with an incremental, 1998 US dollar cost-effectiveness of $6880/QALY\textsuperscript{35} and that a liver transplant is associated with an incremental cost-effectiveness of $327 500/QALY.\textsuperscript{36} To our knowledge, data concerning the incremental cost-effectiveness of most interventional procedures associated with the sequelae of prematurity are not presently available. Although there are no absolute standards for cost-effectiveness, it has been suggested arbitrarily that interventional therapies costing $\geq$100 000/QALY are not particularly cost-effective, whereas those costing $<20 000/QALY are cost-effective.\textsuperscript{35,36}

Thus, both laser therapy and cryotherapy for ROP seem to be excellent values. The permanent improvement in vision that translates to improved quality of life from these treatments, which are of moderate cost, explains why they are especially cost-effective. In essence, laser therapy and cryotherapy are clinically efficacious treatments with long-standing beneficial effects that are not prohibitively expensive by modern health care standards.

Previous authors have studied the cost-effectiveness of screening and cryotherapy for threshold ROP. Javitt and associates\textsuperscript{37} wrote an excellent treatise on the subject in 1993 and noted that appropriate ophthalmic screening of premature infants and subsequent cryotherapy treatment for threshold disease produce a substantial overall saving for the United States at a cost of $2488 to $6045/QALY, depending on the screening strategy. There are several important differences between that paper and the present study. Javitt and associates\textsuperscript{37} took into account general ROP-screening costs in addition to those of cryotherapy, whereas the present study concentrated basically on interventional treatment for threshold disease. Neither the Javitt paper nor this paper took into account the long-term follow-up costs associated with ROP over a lifetime. More importantly, however, was the fact that long-term visual acuity data after cryotherapy and laser treatment for threshold ROP were not available for Javitt and colleagues.\textsuperscript{37} They assumed that good and bad anatomic fundus results correlated with either excellent vision or blindness, respectively, which is not the case.\textsuperscript{7} Thus, the utility assumptions were substantially different in that paper, compared with the present paper. Despite the differences, both the Javitt paper and the present study demonstrate the substantial cost-effectiveness of treatment for ROP.

The present study has theoretical drawbacks that should be noted. The study by Connolly et al,\textsuperscript{6} on which the follow-up visual acuities were based, had a relatively small cohort of patients, and the follow-up period was only 5.8 years; the visual sequelae of laser therapy and/or cryotherapy after 5.8 years are not known. Additionally, the utility values that we used were calculated from a formula derived by multivariate analysis from a large sample of adults with visual loss.\textsuperscript{14} It can be argued that, because visual loss from ROP typically occurs earlier in life, these patients might adapt better and have a higher utility score associated with visual loss than do adults who lose vision later in life. Nonetheless, it has been demonstrated in a large study that there is not a correlation between the length of time of visual loss and utility values.\textsuperscript{14}

Although an overestimation utility impairment in ROP patients may bias the results toward decreased cost-effectiveness, the visual data used in our study may actually underestimate the cost-effectiveness of treatment for threshold disease. The mean age of patients from whom the visual data were obtained was <6 years. The difficulty in coaxing children of that age with perfect eyes to read beyond the 20/30 or 20/25 line is well appreciated by ophthalmologists. Therefore, it is likely that if the visual results were measured 5 years later, the mean vision would be improved at the upper end of the scale.

It should be noted that premature children who develop neurologic impairment were included in the economic analysis in the present study. It has been estimated that ~22% of infants with a birth weight <1250 g have a major handicap with neurologic involvement.\textsuperscript{38} Other authors\textsuperscript{37} have excluded this group in cost-effectiveness analysis for ROP, but we believe that vision is just as valuable to those with neurologic impairment, and perhaps even more so, as to those without neurologic impairment.

Also of note is the fact that our analysis did not include Markov modeling in the decision analysis aspect. Markov modeling is a useful tool when a decision analysis involves risk that is continuous over time.\textsuperscript{39} Although the software program that we used has substantial Markov process capability,\textsuperscript{15} the incidence of long-term complications associated with ROP are unknown. Because assumptions are often the most important part of economic modeling, we
chose to ignore this issue rather than use subjective and potentially misleading information. Nonetheless, we believe that the incidence of serious ocular complications (eg, retinal detachment, cataract, and glaucoma) after 5/4 years of age is relatively low1 and that the difference in the late ocular complication rates between those who are treated for ROP and those who are not is likely to be minimal.

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