Cost-Effectiveness of Treating Normal Tension Glaucoma

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PURPOSE. To assess the long-term cost-effectiveness of treating normal tension glaucoma (NTG).

METHODS. A Markov decision-analytic health model was developed to determine the cost-effectiveness of treating NTG with IOP lowering therapy to prevent progressive visual field loss. Transitional probabilities were derived from the Collaborative Normal Tension Glaucoma Study and cost data obtained from the literature and the Medicare fee schedule. Incremental cost-effectiveness ratios (ICER) of treating all patients with NTG and treating selected individuals with risk factors for disease progression were determined using Monte Carlo simulation. Sensitivity analyses were performed by varying the cost of consultations, medications, laser/surgery, and adjusting utility loss from progressed states.

RESULTS. The ICER of treating all patients with NTG over a 10-year period was United States (US) $34,225 per quality-adjusted life year (QALY). The ICER would be reduced when treatment was offered selectively to those with risk factors for disease progression. The ICER for treating NTG patients with disc hemorrhage, migraine, and those who were female were US $24,350, US $25,533, and US $27,000 per QALY, respectively. The cost-effectiveness of treating all NTG patients in this model was sensitive to cost fluctuation of medications, choice of utility score associated with disease progression, and insensitive to cost of consultations and laser/surgery.

CONCLUSIONS. It is cost-effective, in the long-term, to offer IOP lowering therapy, aiming for a 30% reduction from the baseline, to all NTG patients. The incremental cost-effectiveness ratio of treating all patients with normal tension glaucoma over a 10-year period was $34,225 per quality-adjusted life year and should be offered to individuals in need.

Keywords: cost-effectiveness, normal tension glaucoma, Markov model

Normal tension glaucoma (NTG) is a clinical condition associated with a pathologically excavated optic disc, characteristic glaucomatous visual field loss, and an IOP that is consistently within the statistically normal range. The Collaborative Normal Tension Glaucoma Study (CNTG Study) was the first multicenter clinical trial to determine the role of IOP in disease progression. The methods and results of the CNTG Study were described in details in the series of publications by Anderson and his group.1–5 According to the intention-to-treat analysis, there was no significant difference in terms of visual field progression between the treated and untreated arms, yet this was thought to be due to a higher incidence of cataracts in the treated group.1 In a secondary analysis with data censored when cataracts affected visual acuity, 40% of the controls progressed at 3 years while only 20% in the treated arm showed a visual field progression. At 5 years, the proportion of the untreated group with disease progression increased to 60%, while that of the treated arm remained static.5 With such background, the current common practice is to offer IOP-lowering treatments to NTG patients with significant or progressive disease. The treatment target is to reduce the IOP by at least 30% from the baseline.6

Over the years, epidemiologic studies revealed that up to one third of patients with glaucoma could be classified as having NTG.7,8 On the other hand, cost-of-illness studies showed that more than $2.5 billion was spent annually in glaucoma care in the United States (US).9 While models have been derived to evaluate the cost-effectiveness of treating ocular hypertension and POAG with an elevated IOP,10–12 no research has tried to examine the cost-effectiveness of treating NTG, a prevalent subgroup of POAG. The purpose of this study was to assess the cost-effectiveness of treating NTG using a Markov decision-analytic health model and to compare the results with treatment strategies in ocular hypertension and POAG with elevated IOP.

MATERIALS AND METHODS

In this study, a Markov decision-analytic health model was developed to determine the long-term cost-effectiveness of treating NTG with IOP-lowering therapy to prevent progressive visual field loss. A Markov cycle tree analysis was built using the TreeAge Pro 2009 Healthcare software (TreeAge Software, Inc., Williamstown, MA).

In the Markov cycle, each member in the cohort was exposed to the costs, the risks, and the benefits associated with each treatment and progression of the disease as they transited through the associated health states. Using the Monte Carlo simulation, random sampling and trials at individual level were run, and cost and rewards were calculated for each patient as
they ran through the path. This was repeated for many random patients and the summary statistics converge on the true mean as more trials were run. In this study, 1,000,000 trials were performed for each path in the Markov cycle tree.

Markov Model: Medical Aspect

The model was created with the cycle stage set at 1 year. Patients in the model were placed into either treatment or observation health states. The probability of progression over 10 years was projected from the CNTG study results. It was assumed that patients in both groups remained stable for the first 2 years, as NTG is known to be a slowly progressing disease and no data reporting progression in the first 2 years was available from the CNTG study. In the third year of the model, progression was presumed to occur by the proportion observed in the CNTG study (i.e., 20% in the treatment arm and 40% in the observation arm according to the “four-of-five” criteria). The percentages of progression at 5 years were 20% in the treated arm and 60% in the observation arm. Since the proportion of patients showing progression despite treatment was the same at the third and fifth year, it was assumed that those who progress despite treatment would demonstrate progression by the third year and those who do not would remain stable with treatment. For the purpose of modeling, it was assumed that patients in the treatment arm who did not progress at the third year would remain static in the rest of the model, while for those in the observation arm, 20% of those who survived the cycle would progress in the next cycle. The time horizon set for modeling was 10 years.

For both groups, the baseline assessment would include a comprehensive visit for new patients, a gonioscopy, a central corneal thickness measurement, a visual field test, optical coherence tomography, and disc photography. The frequency of subsequent follow-up visits and clinical tests were derived as recommended by the American Academy of Ophthalmology Preferred Practice Pattern.

 Patients who were placed in the treatment arm needed to achieve consistent IOP reduction by 30% from their baseline. According to Lee et al., the surgical rates in POAG ranged from 28.4% to 34.9%. It was, therefore, assumed in this analysis that 70% of the patients could achieve IOP control via medical therapy and 30% would require laser or surgery to attain the treatment goal. From the meta-analysis by Cheng et al., it was reported that timolol and latanoprost were the two most effective IOP-lowering agents in patients with NTG. In Cheng’s study, the relative IOP reductions were 15% to 18% for timolol and 20% to 24% for latanoprost. Since none of them could achieve an IOP reduction of 50%, it was assumed that all patients would need dual therapy with some requiring triple therapy to achieve target IOP. Patients were assumed to populate in a 3:1 ratio to approximate the ratio of patients who were prescribed two vs. three or more medications as in the Ocular Hypertension Treatment Study. Among those who required surgical intervention, it was assumed that half would undergo laser trabecuoplasty and half would receive trabeculectomy. Supplementary medical treatment would be offered to those who demonstrate persistent disease progression after trabecuoplasty or trabeculectomy. Again, this was assumed to be in a 3:1 ratio in terms of dual and triple therapy.

Quality-adjusted life years (QALY) gained through halting disease progression in NTG were calculated based on utility scores. Utility is a preference-based measure of patient-perceived quality of life associated with a particular health state. Kobelt et al., using the EQ-5D as a descriptive instrument, reported a utility score of 0.84 for POAG patients with Hodapp-Anderson-Parrish (HAP) Stage 1, 0.80 for patients with HAP Stage 2 to 4, and 0.72 for those with HAP Stage 5. In this model, Kobelt’s estimates for patient with HAP Stage 1, defined as Humphrey mean deviation (MD) –0.01 to –6 dB, were used for NTG patients at the beginning of the model. Since in the CNTG cohort, the baseline MD score was approximately –8 dB, and the mean MD slope of progression was –0.9 dB/yr, it was presumed that NTG patients in this cohort would not progress beyond HAP Stage 4 of POAG (defined by a MD score of –20.01 or worse) over a 10-year horizon. Therefore, a utility score of 0.80 was adopted for NTG patients with disease progression in this model.

Markov Model: Economic Aspect

In this study, only direct costs from the payer’s perspectives were considered. The items included were consultations, diagnostic tests, medication, and procedures, namely laser trabecuoplasty and trabeculectomy. Cost data on consultations, diagnostic tests, and procedures were derived from the Medicare fee schedule using the standard Current Procedural Terminology code. Medicare is the social insurance program mandated by the US government to provide health insurance coverage to US residents aged 65 and older. Current Procedural Terminology code is a standard coding system of health care interventions developed by the American Medical Association. Medical, surgical, and diagnostic services are described in details and designated specific codes to facilitate uniform communication on medical procedures amongst clinicians, patients, institutes, and payers for administrative, financial, and analytical purposes. On the other hand, costs of medications were adopted from a cost analysis by Rylander and Void published in 2008, in which yearly cost of topical glaucoma medications were determined from evaluation of volume of commercially available packages, number of drops per milliliter, and common dosing patterns and the average wholesale price of each medication. All the costs were nominal costs as in 2008 in US dollars. All costs were discounted at 3% per annum.

All the costs of treatment in the management of NTG are listed in Table 1. Major input parameters in the current Markov Model of treating NTG are summarized in Table 2.

Markov Model: Sensitivity Analysis

For sensitivity testing, one-way deterministic analyses were performed by varying the cost for the following items: follow-up visits, medications used over 10 years, and procedural intervention (i.e., laser trabecuoplasty/trabecelectomy). Results were also tested by replacing the utility value for HAP Stage 5 (i.e., 0.72 for NTG patients who have shown disease progression in the model). Sensitivity analysis was also performed by substituting the United States cost data with Hong Kong cost data. Probabilistic sensitivity analysis was not performed as relevant data on parameterized distribution were not available.

RESULTS

Cost-Effectiveness Analysis

The Markov cycle tree for treating NTG over a 10-year time horizon, together with probabilities of transition through various health states (Markov states) were presented in the Figure. The incremental cost was the difference between the averaged costs spent on the treated cohort, including the cost for baseline assessment, medications/laser/surgery and follow-up evaluation, and the averaged cost required for those stayed in observation group, mainly the cost for baseline assessment and subsequent regular follow-ups. The incremental effectiveness was the averaged QALY gained in the treated group over
the observation group. In the current model, the ICER of treating all patients over a 10-year period was $34,225 per QALY.

According to the multivariate analysis performed in the CNTG Study, NTG patients with concurrent disc hemorrhage or migraine, or who were female, were at increased risk of progressive visual field loss if left untreated, the risk ratios were 2.72, 2.58, and 1.85, respectively. The ICERs for treating this group of patients were calculated by adjusting the transition probabilities accordingly. The ICERs were $24,350, $25,535, and $27,000 per QALY for patients with disc hemorrhage, migraine, or who were female, respectively (Table 3).

Sensitivity Analysis
Sensitivity analyses were performed by varying the cost of consultations, medications, and laser/surgery, and by adjusting utility loss from progressed states. The results are shown in Table 4. Overall, the ICER of treating all NTG patients in this model was considered sensitive to cost fluctuation of medications and choice of utility score associated with disease progression; insensitive to cost of consultations and cost of laser/surgery.

For the sensitivity analysis substituting the cost information with Hong Kong data, it was revealed that there was a major discrepancy in ICERs between the US (ICER = US $34,225/QALY) and Hong Kong (ICER = US $14,481/QALY) settings. This could be attributed to the significantly lower cost of medications in Hong Kong, despite a higher surgical cost.

DISCUSSION
NTG, as a prevalent subgroup of POAG, is an important disease entity that affects millions of individuals worldwide. While controlling the IOP remains the mainstay of management in NTG, no research has tried to examine its cost-effectiveness. This study showed that, compared with observation, the ICER was US $34,225 per QALY gained for treating all NTG patients with IOP reduction interventions. The cost per QALY gained drops to US $27,000 or below when only those with risk factors for progression were treated. The World Health Organization (WHO) defines a health care intervention as highly cost-effective when the cost per disability-adjusted life year is less than the country’s gross national product (GNP) per capita. It should be understood that QALY is not the same as disability-adjusted life year and should not be used interchangeably; however, it is worthwhile to draw reference using this WHO benchmark. Assuming equivalent thresholds can be applied to QALY, the QALY-based cost-effectiveness of treating all NTG patients was 0.72 times the US 2008 GNP per capita of

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transition probabilities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of progression in observation group at 3 years</td>
<td>0.4</td>
<td>2</td>
</tr>
<tr>
<td>Risk of subsequent progression in observation group who are stable at 3 years</td>
<td>0.2</td>
<td>2</td>
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<tr>
<td>Risk of progression in treatment group at 3 years</td>
<td>0.2</td>
<td>2</td>
</tr>
<tr>
<td>Utility scores</td>
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</tr>
<tr>
<td>HAP Stage 1 of POAG</td>
<td>0.84</td>
<td>16</td>
</tr>
<tr>
<td>HAP Stages 2–4 of POAG</td>
<td>0.80</td>
<td>16</td>
</tr>
<tr>
<td>HAP Stage 5 of POAG</td>
<td>0.72</td>
<td>16</td>
</tr>
<tr>
<td>Cost</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline assessment cost for both observation and treatment group (comprehensive visit for new patient, gonioscopy, pachymetry, VF, OCT, and DP)</td>
<td>$344</td>
<td>13, 18, 19</td>
</tr>
<tr>
<td>Annual cost for patient in first 2 years of observation (3 follow-up visits, annual VF, OCT, and DP)</td>
<td>$441</td>
<td>13, 18, 19</td>
</tr>
<tr>
<td>Annual cost for patient in observation group with no progression (2 follow-up visits, annual VF, OCT, and DP)</td>
<td>$354</td>
<td>13, 18, 19</td>
</tr>
<tr>
<td>Annual cost for patient in observation group with progression (3 follow-up visits, annual VF, OCT, and DP)</td>
<td>$441</td>
<td>13, 18, 19</td>
</tr>
<tr>
<td>Averaged cost for patient in first year of treatment (3 follow-up visits, annual VF, OCT, DP, and cost of medications/laser trabeculoplasty/surgery)</td>
<td>$1128</td>
<td>13, 18, 19</td>
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<td>Averaged cost for patient in second year of treatment (3 follow-up visits, annual VF, OCT, DP, and cost of medications)</td>
<td>$941</td>
<td>13, 18, 19</td>
</tr>
<tr>
<td>Annual cost for patient in treatment group with no progression (2 follow-up visits, annual VF, OCT, DP, and cost of medications)</td>
<td>$854</td>
<td>13, 18, 19</td>
</tr>
<tr>
<td>Annual cost for patient in treatment group with progression (3 follow-up visits, annual VF, OCT, DP, and cost of medications)</td>
<td>$1335</td>
<td>13, 18, 19</td>
</tr>
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All cost values are in US currency.
US $47,580. The year 2008 was chosen to match the data on costs of medications adopted from the cost analysis by Rylander and Void published in 2008, as medications constitute the major expenditure in treatment of NTG. Apart from the WHO standards, the National Institute for Health and Clinical Excellence (NICE) under the National Health Service (NHS) of the United Kingdom, in its website stated that ‘‘if a treatment costs more than £20,000 to 30,000 per QALY, then it would not be considered cost effective.’’ This converts to US $29,805 to $44,707 per QALY (Conversion rate 1 US Dollar [USD] = 0.67 British Pound Sterling [GBP]). Since the ICER for treating all NTG patients was US $34,225 per QALY gained, it is considered to be cost-effective.

According to the Ocular Hypertension Study Group,10 the ICERs were US $3670/QALY and US $42,430/QALY for treating ocular hypertension subjects with a greater than or equal to 5% and greater than or equal to 2% annual risk of developing POAG, respectively. In Stewart’s model,11 the ICER for treating all people with ocular hypertension to prevent one case from progressing to POAG was US $89,072/QALY and was not considered cost-effective. The author suggested that treatment might be offered selectively to those with risk factors, namely age above 76, IOP above 29 mm Hg, central corneal thickness less than 533 μm, or cup-to-disc ratio wider than 0.6, where ICER values ranged from US $35,633 to $45,155 per QALY gained. Similarly, Rein et al.,12 using a computer simulation of 20 million people followed from age 50 to death or to age 100, reported that the ICER values of routine office-based management of POAG ranged from US $28,000 to $46,000 per QALY, depending on treatment efficacy. The ICER of treating all NTG patients as revealed in the current Markov model, thus, compares favorably with the cost-effectiveness of treating POAG and ocular hypertension. In both cases of NTG and ocular hypertension, the cost-effectiveness of treatment improves when treatment is offered selectively to individuals at higher risk of progression.

In the models for ocular hypertension, the cost-effectiveness decision was sensitive to the incidence of POAG without treatment, treatment efficacy, cost of medications, and utility loss from POAG. Likewise, the cost-effectiveness of treating NTG in the current model was sensitive to changes in the cost of medications and estimated utility loss from progressed states. These consistent findings could be explained by the fact that treatments of ocular hypertension and NTG, both known to have slow progression, largely rely on medical therapies. Medications incur recurrent costs that constitute the main bulk of the total cost of the intervention as time goes by.

Despite an earnest effort to stimulate the real life situation, there are several limitations to this current model. Firstly, only
effectiveness of the treatment. Fourthly, the cost of this study, in the direction of increasing the cost of their license protection, generic substitutes of a much lower cost might be available in the market, thus, altering the results of the study. The effectiveness of the treatment is a result of the prevention of utility loss from degeneration, amblyopia and occipital blindness, and so on, leading to poor baseline utility, the results from this model would not apply. Lastly, the findings of this study, like many other cost-effectiveness analyses, were calculated from a model of hypothetical cohort created based on clinical data drawn from multiple studies from the literature. Assumptions were made when essential information was not directly available. Such assumptions may limit the accuracy of the results from the model. For example, the assumption that half of the patients intended for surgical intervention would have undergone laser trabeculoplasty might not be entirely true as the choice of intervention as well as the treatment efficacy is related to the baseline IOP. In reviewing the treatment and associated cost of US and European POAG patients, Lee reported a laser trabeculoplasty rate of 54% to 58% among all patients who have received surgery. However, in the treatment of NTG where the baseline IOP is consistently lower than that in POAG, the rate might differ. Furthermore, apart from supplementary medication, second surgery or refinement surgery might be required when laser trabeculoplasty fails, thus, affecting the overall surgical costs. We attempted to assess the impact of such related cost by increasing the cost for surgery by 50% in the sensitivity analysis and found that it would only change the ICER by 2%. This might be explained by the fact that compared with the recurrent cost incurred by medical therapy, the costs of surgery constitute a relatively minor portion in the overall treatment cost, which included all the expenses from follow-up consultations and investigations.

It might be noted that despite there was a substantial increase in the incidence of cataracts in the treated group observed in the CNTG Study, the loss of utility from cataract and the cost of cataract surgery was not included in the current Markov model. It is because it was commented by the CNTG Study Group that “the rate of development of cataracts in the untreated control subjects was significantly lower than in the surgically treated subgroup but not statistically different from...
the rate in the medically treated subgroup.”\(^1,2\) Nowadays, given the availability of potent IOP-lowering agents such as topical beta-blockers and prostaglandin analogues, we would expect fewer patients requiring surgical intervention to achieve IOP control than in the CNTG Study where treatment modality was restricted by the study design, thus, less filtration surgery related cataract. Moreover, the development of visually impairing cataract and the threshold for cataract surgery is known to be variable, depending on one’s lifestyle, visual demand and general condition. Therefore, it would be very difficult to define which part of the cost of cataract surgery should be attributed to the treatment for NTG. Again, a crude reference could be drawn from the sensitivity analysis. When the cost of surgery was increased by 50%, which should be able to cover the further expenses arise from extraction of filtration surgery related cataract, the resultant ICER would change from US $34,225 per QALY to US $35,000 per QALY.

It is apparent that results of cost-effectiveness analyses are highly sensitive to the utility value of various disease states quoted. However, utility loss secondary to glaucoma has not been investigated widely. Unlike other ophthalmic conditions, like cataract and macular disease where disease severity is almost proportionately reflected in the level of visual acuity, glaucoma causes mainly a constricted visual field, and central visual acuity may remain unchanged even in advanced disease. Therefore, further research on glaucoma-specific utility values would be very helpful in defining the true effectiveness of existing treatment strategies and new interventions to be offered.

This economic evaluation of NTG treatment aims to provide reference materials in addition to clinical evidence. In any case, modeled data should not supersede clinical judgment. It is recommended that the ultimate decision on management should balance the benefits and risks of treatment, and take into account the perceived life span of the patient. Open discussion with the patient is highly recommended.

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**References**