Cost-effectiveness in the Treatment of Glaucoma

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Abstract

The cost-effectiveness of treating different types of glaucoma and 'pre-glaucoma status'—namely ocular hypertension, primary angle closure suspect, and primary angle closure—were investigated by numerous studies. Overtreatment could lead to undesirable opportunity cost and unnecessary exposure to adverse effects for the patients; under-treating moderate to advance glaucoma could lead to preventable blindness. Despite being a leading cause of blindness, the need for a comprehensive glaucoma screening program and early intervention of pre-glaucoma status is questionable. Numerous reports have investigated the cost-effectiveness of treating ocular hypertension, primary open angle glaucoma, and normal tension glaucoma. The cost-effectiveness of different treatment modalities and their application at different stages of glaucoma were also discussed. To date, there is no cost-effectiveness analysis for the treatment of primary angle closure glaucoma. Some early reports also suggested that prophylactic treatment for primary angle closure and primary angle closure suspect might not be the most effective modalities.

Keywords

Incremental cost-effectiveness ratios (ICER), quality-adjusted life year (QALY), intraocular pressure (IOP), ocular hypertension (OHT), primary angle closure suspect (PACS), primary angle closure (PAC) primary open angle glaucoma (POAG), normal tension glaucoma (NTG), chronic angle closure glaucoma (CACG)

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Lowering intraocular pressure (IOP) is the standard treatment of glaucoma. Its effectiveness in halting glaucomatous progression in primary open angle glaucoma (POAG),[1–3] ocular hypertension (OHT),[4] and normal tension glaucoma (NTG)[5,6] was confirmed by various randomized control trials (RTCs), whether by medication, laser treatment, or surgery. Management of primary angle closure glaucoma (PACG) is similar once the anterior chamber predisposition is reverted.[7] Prevalence of glaucoma is expected to rise with the aging population, hence the cost of treating glaucoma. The cost is already creating substantial burden to public health worldwide. A cost-of-illness study—a type of health economical study that measures all the costs of a particular disease—showed that the US spent more than US$2.5 billion annually for glaucoma, of which US$1.9 billion was spent on direct costs and US$0.6 billion as indirect costs.[8] Most cost-analysis studies concentrated on direct costs—medical consultations, diagnostic, follow-up investigations, and treatments. Since glaucoma is a disease of the elderly, the impact on productivity loss is relatively lower. Other indirect costs comprise time cost of care-givers, productivity loss from care-givers, and the societal costs of providing support to poorly sighted individuals. However, these are usually difficult to accurately quantify.

The cost of treating glaucoma increases with the severity of the disease. The annual cost of care per patient per year rose sharply from US$623 for early glaucoma to US$2,511 for advanced disease.[9] Similarly, the estimated average annual maintenance cost of late-stage glaucoma in Europe was €803.[10] For end-stage glaucoma, as much as 28 % of the total cost of care could be contributed to visual rehabilitation.[11] The total financial burden attributed to glaucoma was calculated to be US$2.9 billion per annum in the US if productivity cost was also considered.[12] Furthermore, the average healthcare cost per person in their first year of blindness was US$20,677 in the US.[13] This is important because glaucoma is a leading cause of blindness globally, accounting for 12.3 % of the 37 million people with bilateral visual loss around the world in 2002.[14] The World Health Organization (WHO) projected that the number of affected individuals would escalate to 80 million by 2020, 11.2 million of whom would suffer bilateral blindness attributable to the disease.[15]

Public healthcare systems have limited resources and could not provide exhaustive clinically beneficial interventions. In order to better allocate scarce health resources, calculating the cost for treatment of glaucoma is important. In health economic evaluation, all costs related to detection,

management, and outcomes of treatment of the disease should be taken into account,[16] since the 'cost' could represent an alternative benefit. There are several types of cost-analysis in healthcare. Cost minimization analysis is useful when the outcomes are expected to be the same across different options. In a cost-benefit analysis, both costs and benefits of the procedure under review are valued in monetary terms: the evaluation is thus based on the difference in inputs and outcomes in dollars. Another form of cost-benefit analysis is cost-consequence analysis, which acknowledges the presence of different types of benefit that cannot be measured by a single unit. Cost-effectiveness analysis compares various resource implications of different healthcare interventions, and expresses the outcomes in common natural units. For instance, dollar per mmHg for IOP control. In cost-utility analysis, weight is given to the patient's subjective level of well-being in different states of health. A quality-adjusted life year (QALY) is usually used in cost-utility analysis. This allows comparison of healthcare interventions across disease spectrums and healthcare specialties.

To estimate the therapeutic effect on chronic diseases like glaucoma, long-term data are required because monies are spent in advance and health benefits occur in the future. A RCT can only demonstrate the clinical efficacy of an intervention and might not truly reflect the management in a practical setting because they were guided by strict protocols and have a limited follow-up period. Therefore, mathematical models are utilized to aid analysis and provide an advantage in that it allows combined analysis of data from different sources in a meaningful way (e.g. systematic reviews and meta-analyses). Also, different influential factors could be varied in order to investigate a range of management scenarios.

Most of the cost-effectiveness analyses concerning glaucoma treatment utilized Markov models. This is a useful tool when a decision problem involves recurrent events and continuous exposure to risk over time. A Markov model may comprise several mutually exclusive health statuses, for instance, OHT and early POAG. Specific costs are assigned to each health states. Knowing the annual probability of OH converting to POAG according to previous clinical studies,[4] members of the hypothetical population are allocated and subsequently reallocated into these health states at fixed time intervals. This 'event' or 'transition of status' is repeated and simulated over a desirable length of time. The distribution of the population over the health states in each cycle determines the amount of accumulative costs. Since the rate of conversion of the treated group differs from the untreated group, the defined health outcomes and the total expenditure over a specified period could be calculated and comparison of the incremental cost and effectiveness in terms of pre-specified unit, such as QALY, of the two strategies (i.e. 'treatment' versus 'observation only') could be made.

In this review, we address various aspects of cost-effectiveness for glaucoma management through (1) screening and treatment of 'pre-glaucoma status' and (2) treatment of POAG, NTG, and PACG.

Screening and Treatment of 'Pre-glaucomatous Status'

Screening and Treatment of Ocular Hypertension

Existing technologies allow early detection and effective interventions of glaucoma.[1,4] Logically, the cost of treatment would be lower if intervention is started at an early stage, since the cost increases with disease severity.[9] Screening could detect glaucoma at an asymptomatic stage, and glaucoma meets many of Wilson's criteria for screening.[17] However, this is not as straightforward as it seems. Critical parameters, such as IOP and visual field, are prone to variability.[18] Repeated testing at different visits would be required to make the measurement meaningful, which would not only increase the cost, but also occupied a significant portion for the total cost of glaucoma management,[19] rendering a public screening program impractical. Indeed, there is insufficient evidence to recommend for or against a screening program for glaucoma according to the US Preventive Service Task Force.[20,21] Furthermore, there is no common consensus as to how it should be performed.[22]

Opportunistic diagnosis of glaucoma during a routine ophthalmologic visit was suggested to be a cost-effective way of reducing visual loss and its associated morbidity in the setting of the US.[19] For the European region, a study that utilized a simulated model suggested that opportunistic screening of all patients in their initial visit is cost-effective to prevent blindness.[23] Others suggested that targeting towards the higher-risk group would be more cost-effective,[24] such as those with a family history of glaucoma[25] and of certain races (e.g. African descent).[26] Other risk factors identified by the Ocular Hypertension Treatment Study (OHTS)[27] and the European Glaucoma Prevention Study (EGPS)[28] include older age, a higher level of IOP, a thinner central corneal thickness (CCT), a larger vertical cup–disk ratio (vCDR), and a smaller pattern standard deviation (PSD) value on Humphrey automated perimetry.

However, none of these risk factors alone could provide an adequate sensitivity and specificity for screening purposes. For instance, IOP measurement above the usual cutoff point (>21 mmHg) have an estimated sensitivity of 47 % and specificity of 92 % for diagnosing POAG,[29] since 25 to 50 % of the subjects were NTG.[30] Indeed, the Baltimore Eye Survey indicated that only one-tenth or less individuals with an elevated IOP have glaucomatous field defect.[31] Despite the well-known beneficial effect of lowering IOP for OHT subjects according to the OHTS, the number needed to treat (NNT) in the study was 19.6.[4] Most patients with OHT do not develop POAG and there is no evidence to suggest any benefit of a systemic identification of OHT subjects in the population for early treatment. It is also not practical, given that the estimated prevalence of OHT ranges from 4.5 % to 9.4 % for individuals who are >40 years old.[32] Treatment of OHT before the onset of POAG is controversial.[33,34] The combined data of OHTS and EGPS has led to the development of the 5-year glaucoma conversion risk calculator.[35,36] This has the advantage of combining seemingly unrelated risk factors quantitatively into one single unit. This might at first sight seem to provide hope for a standardized treatment. However, there is so far no common consensus as to how best to utilize this risk calculator in clinical setting.

Attempts were made to make best use of the results from OHTS. The first was reported by the OHT group,[37] they modeled a hypothetic cohort of OHT individuals and evaluated the cost-effectiveness of offering treatment at various thresholds in a Markov decision-analytic model. Treatment thresholds were determined based on the annual risk for developing glaucoma. This study reported that the incremental cost-effectiveness ratios (ICERs) were US$3,670/QALY for treating people with OHT and a ≥5 % annual risk for developing POAG, and US$42,430/QALY for the treatment of those with a ≥2 % annual risk threshold. Sensitivity analyses

revealed that the decision was sensitive to the incidence of POAG without treatment, treatment efficacy, and the utility loss associated with different stages of POAG.

Later, Stewart et al.[38] reassessed the cost-effectiveness of treating OHT based on practice patterns derived from the OHTS and transition probabilities derived from the literature. ICERs were calculated adjusting for risk factors identified by multivariate analysis in the OHTS. The authors concluded that the ICER for treating all people with OHT to prevent one case from progressing to POAG was US$89,072/QALY. This did not seem cost-effective. Therefore, it was suggested that treatment should be offered selectively to those with specified risk factors, namely: age above 76, IOP above 29mmHg, CCT less than 533 µm, and CDR greater than 0.6.

On the contrary, it was argued that analyses based on the cohorts of OHTS represent a relatively low-risk population. With a patient-level simulation model, van Gestel et al.[39] suggested that an early treatment strategy is an advantage in a heterogeneous population of OHT patients. In addition, they also suggested that a 'watchful waiting' approach could be appropriate for the subgroup with a low conversion risk (10 % in 5 years), which agreed with the treatment strategy suggested by an expert panels (to treat a patient with >15 % conversion risk in 5 years).[40] Caution must be taken when applying these results; as aforementioned, some of these parameters, especially IOP, are prone to variability.[18] When IOP-lowering therapy is initiated, the target pressure should be achievable by monotherapy in 90 % of the cases.[41] A simulation model suggested that initial treatment with timolol or latanoprost created similar clinical effect in OHT patients. Furthermore, a meta-analysis that included nine OHT trials and one POAG trial quantified that the risk for conversion to glaucoma is reduced by approximately 14 % for each mmHg of extra IOP reduction and a greater reduction of IOP is associated with a greater reduction of this risk.[42]

Treatment of Primary Angle Closure Suspect and Primary Angle Closure

PACS and PAC are known to be at risk for the development of acute primary angle closure (APAC), or progression to PACG. Prophylactic laser peripheral iridotomy (LPI) may be considered for these conditions.[43] However, its effectiveness is controversial. The Vellore Eye Study demonstrated that only 22 % of PACS progressed to PAC.[44] None of these patients developed glaucoma or had an acute attack. The indication—hence the cost-effectiveness—of LPI for all patients with PACS or PAC is questionable. In their follow-up study, subjects that had originally been diagnosed as PAC were evaluated after 5 years; the rate of glaucoma progression and mean IOP seemed lower in patients who had prophylactic LPI. Assuming that LPI was 100 % effective, the NNT to prevent progression from PAC to PACG was four. However, there was no statistical significance between those who had undergone LPI and the untreated group in terms of progressing to PACG, which might be due to the relatively small sample size (28 eyes in total).[45] Further RCTs are required to investigate the effectiveness of prophylactic LPI before its cost-effectiveness could be accurately evaluated.

Treatment of Glaucoma

Primary Open Angle Glaucoma

Despite decades of offering medical treatment to POAG patients, it was not until recently that Rein et al.[19] proved in their study the cost-effectiveness of existing glaucoma care patterns in relation to the gain in quality of life (QoL). Using a computer simulation of 20 million people followed from age 50 to death or to age 100 years, it worked out that the ICERs of routine office-based identification and subsequent medical treatment of POAG were US$46,000/QALY and US$28,000/QALY, assuming conservative and optimistic treatment efficacies, respectively. Even after accounting for probabilistic uncertainty in the way individuals develop illness and the efficacy of treatment, routine assessment, and treatment were cost-effective approximately 100 % of the time at a willingness-to-pay (WTP) of US$64,000 or greater. If the cost of routine assessment were excluded and assuming a conservative efficacy, the cost-effectiveness was approximately 100 % of the time given a WTP of US$28,000 per QALY.

There might be no doubt about the need of treating POAG. The main concern is which strategy and modality is the most cost-effective? Medical treatment of POAG and OHT have long been the mainstay and most preferred modalities because it is comparatively less invasive. While a cost comparison was made between different classes of medication as first-line medication or monotherapy (e.g.β-blockers versus prostaglandin analogs [PGA]), comparisons were also made between monotherapy and dual therapy or mixed-combination formulae.[46–60] The common natural unit in most of these studies is cost per mmHg reduction in IOP, and they were supposed to aid decision-making for the choice of IOP-lowering agents in the clinical setting. However, some of these studies were driven by drug companies, and the costs of drugs could vary considerably across countries; hence, their results may not be uniformly applicable in all settings. It is also important to note that most of these studies did not consider the side-effect profile of individual class of IOP-lowering agents and their effects of the QoL. This is important, since a recent study utilizing three separate instruments to assess QoL found that the QoL and utility loss as a result of severe side effects from glaucoma medications is comparable to that resulting from a decrease of 10dB in mean deviation (MD).[61]

The emergence of new drugs and the chronic nature of glaucoma have caused a substantial rise of the therapeutic cost.[62–64] Laser trabeculoplasty (LTP) might provide an opportunity to reduce the long-term incremental cost of medication. The 9-year efficacy of argon laser trabeculoplasty (ALT) was demonstrated by the Glaucoma Laser Trial (GLT) during the 1980s. It demonstrated that ALT is as effective, if not more effective, than treatment with timolol.[65] This is in agreement with other studies that demonstrated the effectiveness of ALT at lowering IOP.[66–70] Therefore, LTP could be considered as a primary therapy for POAG. Using a Markov Model with a 25-year horizon, Stein et al.[71] demonstrated that PGAs and LTP are both cost-effective options for the management of newly diagnosed early POAG. The study showed that PGAs provide greater health-related QoL relative to LTP, with the assumption of optimal medication adherence. However, the problems with compliance of glaucoma medication and eye drop technique have been well documented.[72–74] and poor compliance is associated with worsening of the disease control.[72,74–76] Assuming more realistic level of medication adherence—which reduce the PGA's effectiveness by 25 % less than that documented in clinical trials—LPT may be more cost-effective than PGAs.

One must be cautious when interpreting the results of these well-designed studies. For instance, the study by Stein et al.[71] compared the cost-effectiveness of PGAs and LPT. If β-blocker was used instead of PGAs

as the first-line medication to make the comparison, the results could be totally different. LTP also has a higher upfront cost and has potential complications, such as formation of peripheral anterior synechiae, which could affect subsequent trabeculectomy should that be necessary for the patient in the future. Also, there is differential effectiveness of LTP in different ethnic groups, particularly in black African Americans[77,78] and African-Caribbean[79] people. The introduction of selective laser trabeculoplasty (SLT)[80] in 1995 has provided another alternative, with the advantage of avoiding thermal burn to the trabecular meshwork and potential repeatability. It is at least as effective as ALT and reduced the number of medication required.[81–84] However, the cost of SLT could be potentially higher, given its rather limited indications and usability in other eye disease conditions. To date, there is no cost-effectiveness analysis concerning the use of SLT.

Primary trabeculectomy for treating POAG has been a topic of debate.[85] Results of The Collaborative Initial Glaucoma Treatment Study (CGITS)[86] suggested that in moderate to severe glaucoma, primary surgery is more likely to achieve IOP lowering and preservation of visual field compared with primary medical treatment. On the contrary, for milder glaucoma, there is no substantial difference in progressive visual field loss, after adjustment between initiating medication (usually a β-blocker) or primary trabeculectomy. With the introduction of various IOP-lowering agents including PGAs, alpha-2 agonists, and carbonic anhydrate inhibitors since the mid-1990s, primary trabeculectomy for mild glaucoma is probably not justified, as this would unnecessarily exposed the patients to the risk for surgical complications. In the CGITS, the surgery group reported more local eye symptoms over the first few years[87] as well as a threefold increase risk for cataract over 5 years[86]—the latter would require subsequent removal and thus increment of cost.

There is limited trial comparing medical therapy to other surgical techniques, such as non-penetrating deep sclerectomy (NPDS), tube drainage devices, and cyclophotocoagulation. The last two are usually reserved for refractory POAG.[88] NPDS has a theoretical advantage over trabeculectomy in terms of early postoperative comfort and less complications,[89–95] such as hypotony.[96] Using a decision analysis model, Guedes et al. suggested that, for a 5-year period in the Brazilian Public National Health System, NPDS is less costly and more effective than medical therapy when three topical medications are required.[97] However, they have excluded the cost of transportation, medical visits, examinations, and indirect costs. They also showed that the cost increases with advanced glaucoma, thus advocated to perform NPDS in the earlier stage of glaucoma.[98] The results might not be applicable in other settings, since the procedure is surgeon-dependent, with a steep learning curve,[99] and the outcome of NPDS could be variable. Further study is required to verify its cost-effectiveness compared with other modalities.

Normal Tension Glaucoma

The long-term cost-effectiveness of treating NTG has recently been investigated by Li et al.[100] Utilizing a Markov decision-analytic health model and the results of Collaborative Normal Tension Glaucoma Treatment study (CNTG),[5,101] the study calculated that the ICER of treating all patients with NTG over a 10-year period was US$34,225/QALY. The authors adopted the cost of medication from the study by Rylander and Void in 2008,[102] since medication constitutes the major expenditure in NTG treatment.[8] The ICER for offering treatment selectively to those with any risk factor for disease progression—disk hemorrhage, migraine, and female gender[103]—range from US$24,350 to US$27,000 per QALY. It was concluded that it is cost-effective to offer a 30 % reduction of IOP-lowering therapy for all NTG patients. The cost-effectiveness is sensitive to cost fluctuation of medications and choice of utility score associated with disease progression, but insensitive to cost of consultations and laser/surgery. It is important to note that, like many other cost-effective analyses, the calculation was performed according to RCTs that were performed in the era when only less-potent IOP-lowering agents were available. Therefore, the cost-effectiveness could be affected by the emergence of new medications. Furthermore, updated research on glaucoma-specific utility values is recommended, as the disease severity in glaucoma is difficult to quantify, unlike conditions such as cataract or macular disease in which disease severity highly correlate with visual acuity.[100]

Primary Angle Closure Glaucoma

LPI is the recommended initial therapy as this could eliminate pupil block.[43] This is supplemented by topical IOP-lowering agent if IOP control is unsatisfactory, followed by trabeculectomy and/or cataract extraction. Tham et al. have published a series of prospective clinical trials concerning different modalities of treatments for PACG. For medically controlled PACG with cataract, both phacoemulsification and combined phacotrabeculectomy are effective in IOP reduction, the latter being more effective, hence less medication is required at the end of the study, but associated with more complications.[104] For medically uncontrolled PACG with or without cataract, phacoemulsification, trabeculectomy,[105] and combined phacotrabeculectomy[106] are all effective in IOP reduction, the latter two being more effective in reducing IOP, hence reduction of the use of medication, but again associated with more complications.[104,105] Despite the prevalence of PACG in East Asians[107,108] and Chinese,[109] there is no cost-effective analysis for these surgical procedures in treating PACG. It was shown that combined phacotrabeculectomy resulted in more surgical complications than phacoemulsification alone in eyes with coexisting PACG and cataract, although the two treatment groups had comparable visual acuity or disease progression up to 2 years after surgery.[110] The benefit of a particular intervention in reducing long-term drug costs may be offset by extra cost introduced by the management of surgically related complications. Similarly, there is a lack of cost-effectiveness analysis for APAC, although direct cost of treatment has been reported in Singapore.[111]

Conclusions

Cost-effectiveness analyses for the treatment of glaucoma are based on the results of RCTs and mathematical modeling. They provide good references for clinicians in terms of clinical decision-making. It is important to note that they apply only if the conditions fulfill certain assumptions. Therefore, one should apply the results from these studies in the context of the specific community in which the study was conducted, as well as taking into consideration the unique situations of each patient. Life expectancy,[112,113] racial differences,[77–79] and differences between healthcare systems and gross national product (GNP) influence the cost-effectiveness of a particular treatment. GNP is important because, according to the WHO, a healthcare intervention is considered highly cost-effective when the cost per disability-adjusted life year is less than the country's GNP per capita. Treatment is moderately effective if the cost is between one to three times of GNP per capita. QALY was considered in

most of the cost-effectiveness analyses for glaucoma treatment, although it is not entirely the same as disability-adjusted life year, it is worthwhile to draw reference from this WHO benchmark.

The cost-effectiveness of treating all 'pre-glaucoma' conditions—OHT, PACS, and PAC—is relatively low. Decision of treatment should be based on specific individual circumstances. Medical treatment or LPT might be cost-effective for treatment of early glaucoma. For moderate to severe glaucoma, surgery is more likely to yield satisfactory clinical results. However, with the introduction of newer medications and surgical techniques, further studies are required in order to make an up-to-date conclusion on cost-effectiveness. ■

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