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REVIEW

Different strategies and cost-effectiveness in the treatment of primary open angle glaucoma

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Abstract: Glaucoma is the second highest cause of blindness worldwide with an estimated half of the glaucoma population unaware of their disease. To date, intraocular pressure is the most important modifiable risk factor and lowering it has been proven to reduce progression of visual field loss associated with glaucoma. Different strategies are available to lower intraocular pressure and include medical, laser, or surgical treatment in the form of topical or systemic medications, argon or selective laser trabeculoplasty, and glaucoma drainage surgery such as trabeculectomy, deep sclerectomy, or other drainage devices. The effectiveness of these treatments has been well documented however their cost-effectiveness between the developed world and third world remains unclear.

Keywords: intraocular pressure, sclerectomy, trabeculectomy, trabeculoplasty, open angle glaucoma

Introduction

Primary open-angle glaucoma (POAG) is defined as a chronic and progressive disease, characterized by acquired loss of optic fibers, glaucomatous disc progression, visual field changes, and open angles in the absence of known underlying cause. Rate of disease progression varies between patients. Majority of glaucomatous deterioration progresses over a period of years. Without treatment, mild glaucomatous visual field impairment would progress to at least unilateral blindness in 23 years.[1] Glaucoma prevalence is higher among the population over age 38 years. As the proportion of this age group increases, the proportional raise in glaucoma incidence will challenge our resources and ingenuity.[2]

As the second most common cause of blindness worldwide, Quigley and Broman estimate that by 2020, 79.6 million people will be inflicted with glaucoma worldwide, of which 11.2 million will be predicted to be blind bilaterally.[2] Epidemiological studies estimated half of the glaucoma population is unaware of their disease.[3] There is no cost-effective population-based screening program available at present for detection of glaucoma.[1,4] However, among patients with POAG, treatment maintaining good intraocular pressure (IOP) can prevent further visual field lost.[5]

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Current and emerging treatment options

Current treatment of POAG

IOP is an important modifiable risk factor for glaucoma.[6] It has been proven lowering IOP is beneficial in reducing progression of visual field loss in glaucoma.[5] Management of glaucoma requires a careful selection of one or more of the major treatment modalities – medications, laser therapy, and surgery.

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Medical

Medical treatment for glaucoma is divided into topical and systemic forms. Currently available medication acts by controlling IOP thereby reducing the risk of further visual field loss.[5] The five main classes of eye drops are: beta-blockers, cholinergic, carbonic anhydrase inhibitors, alpha-2 agonists, and prostaglandin analogs.

Meta-analysis of all trials comparing any topical drops versus placebo or untreated subjects, provided clear evidence of a positive treatment effect on visual field protection (odds ratio [OR] 0.62, 95% confidence interval [CI] 0.47 to 0.81).[7] Medical treatment is the first line treatment in the developed world.[8] With the increase of therapeutic options, surgical rates for glaucoma have reduced;[9] however, the cost of anti-glaucoma treatments has increased as a consequence. Long-term medication may be difficult to apply causing noncompliance in some patients. When more than two topical medications have failed to control IOP, laser, or surgical treatment is considered.[6]

Laser therapy

Trabeculoplasty is the shared term for the application of laser, in repetitive fashion, to the trabecular meshwork.[10] Different lasers used for trabeculoplasty vary in the degree of effect on trabecular meshwork.[10] Studies suggest that outcomes and safety of trabeculoplasty by argon laser and diode laser are similar.[11] Fifty percent of diode laser treatment eyes and 58% of argon laser treatment eyes were successful after 5 years.[12] Selective laser trabeculoplasty (SLT) is a frequency-doubled short-pulsed (Q-switched) neodymium: yttrium-aluminum-garnet laser.[10] SLT achieved a 2-year success rate (>20% reduction in IOP) in 38% of patients with POAG refractory to medical therapy.[13] Many studies show that if laser trabeculoplasty (LTP) was given as an initial treatment, up to half of the patients did not require medical treatment for 1–2 years post-treatment.[14,15] Therefore, fewer medications are needed if LTP is carried out. Many studies comparing LTP with medication are less relevant to current clinical practice as older generation pharmacological agents were trialed.[8] Studies comparing short-term (4–12 months) reduction in IOP SLT to Latanoprost have inconsistent findings.[16,17] Research to compare long-term treatment outcome would be useful to determine this.

Surgical

In developing countries, medical treatment is less readily available and may be too costly for long-term use. Surgery is hence the first line treatment in these countries.[18] Glaucoma surgical techniques have evolved from full thickness to guarded filtration procedure. The surgical procedure reduces the IOP by creating an alternative route for aqueous humor outflow. Trabeculectomy is the standard operation where a fistula is formed through the sclera to subconjunctival space to create a filtering bleb. However, scar formation underneath the conjunctiva can reduce the operation success rate. Failure rates with trabeculectomy in African patients varied widely between 5% and 72% before the use of adjunctive antifibrotics.[19] Using mitomycin, 5 fluorouracil and beta irradiation in conjunction with trabeculectomy could improve its success rate.[20–22] The use of these anti-scarring agents is generally accepted as improving trabeculectomy outcome with reported success rates from 73% to 93%.[20,21] However, antimetabolites may increase the incidence of complications, in particular corneal epithelial damage, wound leakage and shallow anterior chamber. Beta radiation reduces the risk of surgical failure from 30% to 5% after glaucoma surgery; however, it may increases the risk for cataract formation from 2.8% to 16.7%.[22]

On the other hand, glaucoma drainage devices are reserved for situations where trabeculectomy is unlikely to succeed.[23] Microsurgical procedures on the trabecular meshwork (trabecular aspiration, goniocurettage, laser trabecular ablation, angle shunting devices and trabeculotomy) and ciliary body (transscleral cyclophotocoagulation or cryoablation) have also been described.[23]

Emerging treatment options

Despite the available treatment options, glaucoma remains the second leading cause of irreversible blindness worldwide.[6] Even with good IOP control, optic nerve damage still continues to progress in many cases. This supports the fact that there is considerable space for improvement in current treatments. An ideal anti-glaucoma eye drop that is neuroprotective, or even stimulates neuro-regeneration, has yet to be successful in clinical trial. Most new drugs introduced are new formulations, combined preparation, and preservative free eye-drops.[6]

New formulations

The most common preservative used in eye drops, benzalkonium chloride (BAK), has been shown to be one of the main culprits in causing local side effects. It produces significant inflammatory and histopathological changes topically. Within the past decade, many anti-glaucoma drops have been reformulated to either preservative-free versions or modified

preservatives, ie, sodium chlorite based preservative or mixture of boric acid, propylene glycol, sorbital, and zinc chloride.[6]

BAK toxicity is dose-dependent. Long-acting combination preparations (ie, Timoptol®-LA [Merck and Co, Inc., Whitehouse Station, NJ, USA] and prostaglandins) given once a day will reduce amount of BAK exposure to 50% compared to twice daily version. There is no evidence of statistical difference in IOP reduction between BAK-containing and BAK-free eye drops.[6]

Neuroprotection

Mechanism of retinal ganglion cells death in glaucoma is poorly understood. Contributing factors proposed to date are neurotrophic growth factors deprivation, mechanical compression, optic nerve ischemia, reactive astrocytosis, excitotoxicity and oxidative stress.[6,24] Despite successful preclinical experiments, most Phase II and essentially all Phase III clinical trials of more than 100 potential neuroprotective drugs have failed to demonstrate efficacy, acceptable safety, or patient benefit. The largest randomized, progressive, Phase III clinical trial on neuroprotection looking at safety and efficacy of oral memantine (non-competitive antagonist of the NMDA-type glutamate receptors) in POAG has been completed, but failed to show benefit compared to the placebo group.[6,24] Further researchers will hopefully pursue the goal of neuroprotection in glaucoma patients.

New agents

Several drugs are under investigation that might be used in the future as glaucoma therapy. A new class of glaucoma drug that may be coming to the market is a Rho kinase inhibitor (RKI), which inhibits the Rho-associated protein kinase (ROCK)-signaling pathway.[6] The ROCK-signaling pathway promotes cellular contraction and transdifferentiation fibroblast into myofibroblast. ROCK inhibitors hence relax the trabecular meshwork and subsequently increase outflow facility leading to reduced IOP. RKIs, in early clinical trials, have been shown to be highly effective in lowering IOP and may also slow progression of glaucomatous optic neuropathy by working directly on the optic disc blood vessels. It may also improve filtering surgery success rates by inhibiting myofibroblast formation.[25]

Review of the cost-effectiveness and pharmacoeconomic studies

Methods

A search of the literature was performed in PubMed using the terms "cost + effectiveness + glaucoma". The search was limited only to articles published in English. From the 206 titles returned, the authors included the titles comparing cost-effectiveness of surgical or laser treatment versus conventional medical treatment. Abstracts of these topics were evaluated; three papers were identified in this process. The aim of this section is to understand further factors underlying cost-effectiveness through published literature. With this in mind, the remaining articles were evaluated with systematic quality criteria tools. This method has been used in the past to look at cost-effectiveness.[26]

Results

Findings from previous studies about cost-effectiveness are inconclusive. Studies comparing cost-effectiveness of surgical or laser intervention with medical treatment is lacking in the scientific literature. Glasgow trial 1988, which compared initial medical therapy versus initial trabeculectomy surgery, found that the total estimated prospective cost per patient over an 8-year period was higher in the initial medical group than the trabeculectomy group.[23,27] On the other hand, the Guedes et al study[28] comparing non-penetrating deep sclerectomy and maximum tolerated medical therapy within Brazilian institutions showed that surgical management is less costly and more effective than medical therapy. However, this study's direct cost calculation excluded the cost of medical visits and exams. Stein et al[29] compared the cost-effectiveness of treating newly diagnosed mild open angle glaucoma with prostaglandin analogs, LTP and observation only, using the Markov model with a 25-year horizon.[29] With optimal medical adherence, medical treatment is presumed to be superior to laser treatment; however a more realistic level of adherence may prove the other way round.

Developing nations

Burden of disease

Globally, 90% blindness is concentrated in the poorest part of the developing world.[30] Not only are citizens burdened with increased risk of blindness: loss in productivity and increased health care demand further exhaust the already sparse resources. Glaucoma-attributable visual impairment resulted in the loss, in Ghana, of over 8,400 disability-adjusted life years (DALYs) and US$21 million in productivity. Despite open-angle glaucoma (OAG) being more prevalent in the developing world, information on the cost-effectiveness of glaucoma treatment is very limited.[31]

Surgery, despite being the preferred treatment, is still experiencing a low uptake rate in developing countries.[31] Glaucoma is often asymptomatic when treatment is proposed and

therefore patients will not perceive any visible improvement postoperatively. On top of that, glaucoma surgery could even potentially turn an asymptomatic condition into symptomatic complications, or permanent visual impairment. Hence, it is not surprising that acceptance for trabeculectomy is poor in the developing world. Poor follow up in glaucoma patients has also been reported in studies from Nigeria.[32] There is a need to improve understanding of the disease to create awareness of the importance to prevent progression.

Cost analysis

Direct and indirect costs

When comparing the cost of therapy from the patient's perspective (out of pocket payments), the annual direct cost (based on 3 years average) in Nigeria for medical versus surgical treatment was US$273±$174 and US$283±$202, respectively.[33] Based on this information, a one-off surgical fee appeared to be a cheaper option than medical therapy. However, we all should be aware that many glaucoma patients undergoing trabeculectomy may still require continuous medical therapy and potential resurgery (trabeculectomy, premature cataract extraction, and other complications). Successful trabeculectomy, not requiring additional medication, has the lowest cost of treatment, whereas advanced glaucoma and failed trabeculectomy are associated with higher cost of treatment.[33] Non-drug costs (direct non-medical and indirect cost) accounted for 54%–66% of the overall treatment cost.[34–36] Direct non-medical costs include costs not directly related to medical treatment, such as transportation. The average transportation fee per clinic visit is US$16.7.[37] The number of work hours lost due to a follow-up visit is 3–8 hours, ie, US$30 lost per visit to hospital. The cost is higher if the person accompanying the patient has also taken time off work.[37]

Willingness to pay per disability – adjusted life year (WTP/QALY ratio)

As there is a lack of consensus guidelines on maximum willingness to pay for each DALY (WTP/DALY) gained, the WHO Commission on Macroeconomics and Health and the WHO CHOICE have developed guidelines that specify the use of a nation's per capita gross domestic product (GDP) to set cost-effective thresholds.[38] Interventions that cost less than three times per capita GDP per DALY are possibly cost-effective; interventions that cost less than per capita GDP per each DALY gained are highly cost-effective.[30] The per capita GDP is US$2,240 in Ghana (2005).[39] A Ghana study that assessed the cost-effectiveness of hypothetical case-finding and treatment scenarios, including US guideline-level care and one-time laser surgery, showed one-time laser surgery interventions following self-referral are highly cost-effective and guideline care after syndromic referral may be cost-effective.[30] Screening interventions in both treatment options are not cost-effective as willingness to pay is less than 4.4 and six times per capita GDP. When productivity gains are considered, this exceeded medical costs only for laser surgery following self-referral (Table 1).[30]

Additional options

Africa has a higher failure rate to conventional trabeculectomy, which is likely to be due to racial differences in the wound-healing response that predispose patients to scar formation at surgical site.[40] Studies reported greater success in IOP reduction by adding antimetabolites to surgery, with 89% patients achieving >25% reduction in IOP at 3 years.[41] Another trial conducted in South Africa has also proved augmenting trabeculectomy with B-radiation is beneficial.[21] However, there is higher risk of complications in these groups (cataract formation, leaking blebs, late endophthalmitis, and hypotony). Patients would therefore need regular long-term follow-up care to evaluate these potential problems. Despite proven success, this also implies a higher cost and burden to health care resources, ie, preventable vision loss (more cataract surgeries to counter any complication arising from the primary surgery), regular follow-up (outpatients, transportation, time off work etc).[40] Patients are less likely to perceive this as a beneficial procedure and it would potentially further reduce surgery uptake in the long-run. QALY to assess cost-effectiveness would be helpful to assess the practicality of implementing augmenting antimetabolites and B-radiation in treatment in the developing world.[41]

Table 1 Cost per DALY, WTP and cost-effectiveness of different interventions and treatment strategies for Ghana

	Cost per DALY (US$)	WTP (× per capita GDP)	Cost effectiveness
Diagnosis upon incidence			
Guidelines care	6,896	3.07	No
Laser	1,771	0.52	Highly
Syndromic			
Guidelines care	3,947	1.76	Likely
Laser	1,771	0.79	Highly
Screening			
Guidelines care	13,504	6	No
Laser	9,808	4.47	No

Note: Data from Wittenborn et al.[30]
Abbreviations: DALY, disability-adjusted life years; GDP, gross domestic product; WTP, willingness to pay.

Developed nations

Unlike developing nations that have limited data on how and when to treat glaucoma, glaucoma management is better researched in developed nations. The focus in developed nations has evolved from determining whether something works, to evaluating which works better, and whether it is worth the expenditure. Many studies have evaluated the cost of glaucoma medications alone – one of the many components of glaucoma management cost. Differences in research methods, the way each study determined treatment costs and the outcome measured, makes it difficult to compare the cost of glaucoma and the costs or cost-effectiveness between studies.[30]

Factors affecting pharmacoeconomic evaluations of glaucoma medication

Treatment costs

A Glasgow study analyzed lifetime health care-related direct cost in ocular hypertension, normal tension glaucoma and POAG, based on drug (19 different medications) and non-drug (inpatient/outpatient, surgical or medical procedures, and diagnostic testing) costs. The average yearly and lifetime cost of glaucoma treatment per patient was GBP475 and GBP3,001, respectively.[3] These figures are comparable with the cost of early surgical treatment which is an average cost of GBP2,560 over an 8-year period.[35] Medical treatments are not inferior. Drug costs vary over time; unlike the normal inflationary pattern, drug costs typically remain stable or decline over time.[34] As the prostaglandin analogues become generic, their unit costs will be cheaper, hence making medical treatment even more favorable.

Disease progression

Progressive or unstable glaucoma would require more follow-up visits, diagnostic tests and time off work to attend clinics (direct non-drug and indirect costs). Additional eye drops prescribed to control IOP would increase direct drug costs further. A study across Europe estimated US$613 (Euro 455) per person per year for stage 0 and peaked at stage 4 with US$1,335 (Euro 969), and then slightly decreased for stage 5 at US$1,221 (Euro 886). This implies a 30%–50% cost saving by preventing glaucoma progression from stage 0/1 to stage 4/5.[43] Patients who are non-compliant to treatment are more likely to incur higher costs, as their condition is more likely to be progressive.[43]

Adherence

Noncompliance with a prescribed drug regime can decrease the efficacy of the therapy and hence increase treatment costs.[44] The Markov model quantifies cost and health consequences with disease stages over time. By using this model, Stein et al[29] simulated 25 years prediction of cost-effectiveness of treating newly diagnosed OAG with prostaglandin analogs (PGAs), LTP and non-treatment. This comprehensive study considered the impact of medication adherence in its analysis, however has not included indirect costs such as productivity. For the 25 years base model, the predicted cost of untreated glaucoma, LTP and PGAs are US$2700, US$13,788, and US$18,101 respectively.[29] Quality-adjusted life years (QALYs) for these groups are 16.06, 16.71, and 17.14, respectively.[29] The incremental cost-effectiveness of PGA and LTP versus no treatment is therefore US$14,179 and US$16,824 per QALY. PGA therefore provide greater health related quality of life (QoL) relative to LTP, based on this model. However, when adherence to medication is taken into account, ie, if PGAs were 25% less effective than reflected in this study, LTP would be the preferred option.[29] The Glaucoma Laser Trial,[15] also supports LTP as treatment option as 2%–25% of the medication group versus 2%–6% of the LTP group would require laser and surgical treatment each year, respectively.[38] However, the IOP lowering effect of LTP reduces with time and 80% of patients would eventually require medical treatment after 7 years.[13]

Cost of failure

Glaucoma medications are the first line treatment for POAG in the developed world. Medications are normally well tolerated and have minimal side effects. However, the main drawback is the cost, as patients would normally need to be on life-long treatment. The optimal strategy is to start long-term medical management with minimal therapy switches. The increased cost in direct drug treatment may be counterbalanced by a reduction in outpatient visits, surgery, and low vision support. Overall medical therapies accounted for around 8%–42% of the total cost of glaucoma.[42,44]

A study[45] comparing hospital-based and community-based (high street optometrist) glaucoma clinics showed that the latter is at least twice as costly (GBP63.91 versus GBP145.62). The main reason for non-cost-effectiveness in this case is due to the higher overhead costs in the community-based clinic, which could only approximate costs of a hospital-based review by increasing the number of patients seen in the community-based clinic to 25 patients per day.[45] The Bristol shared care glaucoma study[47] suggested the non-cost-effectiveness of this

model was due to re-referrals back to the hospital from the community-based clinics and closer follow-up intervals in community-based clinics.[46]

Glaucoma and QoL

Glaucoma reduces QoL. QoL is a subjective assessment and hence it impacts each individual patient differently. The relationship between disease progression and QoL are inversely proportional.[46] Despite many reported methods to measure QoL, there is no one gold standard. QoL is recognized as an important outcome in understanding disease progression and evaluating the effectiveness of health care interventions.

Traditionally, clinical indicators (IOP, visual field, visual acuity, and side effects of anti-glaucoma medications) were used to monitor glaucoma medication efficacy.[47] Glaucoma affects vision related quality of life (VRQoL) by reducing peripheral visual field and visual acuity. The Random Forest method uses these data to predict VRQoL, which enables clinicians to understand patients' VRQoL based on standard clinical measurements.[48]

Glaucoma and ocular surface disease

Ocular surface disease (OSD) symptoms can be debilitating and if severe can affect a patient's quality of life and ability to function. A high prevalence of symptoms and signs of OSD were found in a population of patients with glaucoma or ocular hypertension.[49] Pisella et al's prospective epidemiological survey[50] on 4,107 patients showed 57% of patients reported at least one symptom at some time after eye drop instillation. Discomfort on instillation (38%) was the most commonly reported symptom followed by symptoms between instillations – burning and stinging (37%), foreign body sensation (28%), dry eye sensation (22%), tearing (20%), and eyelid itching (17%). Comparison at the first visit showed OSD is more prevalent in glaucoma patients using preservative-containing eye drops compared with patients using preservative-free eye drops. The frequency of signs and symptoms is correlated with the number of preserved eye drops used.[52] This is consistent with Leung et al's[51] findings that coexistence of OSD and the use of BAK-containing medications may impact the VRQoL.[52] A change from a preservative-containing to a preservative-free glaucoma eye drop, or even a reduction in the number of preservative-containing eye drops used, is associated with a significant decrease in the frequency of signs and symptoms of ocular irritation.[51] Recently it has been reported that preservative-free prostaglandin analogues may improve QoL as compared to medications containing preservatives.[51]

Glaucoma and mental burden

QoL can be affected in many ways. The diagnosis of glaucoma leads to increased mental burden upon patients. Eighty percent of patients experience negative emotion despite being free of symptoms.[53] Mental burden increases with disease progression, decrease in vision, fear of blindness, social withdrawal and depression. Life-long follow-up visits and examinations are inconvenient; this decreases QoL more than visual dysfunction.[54]

Glaucoma treatment and follow-up

Glaucoma patients require long-term medications. Medical treatment is effective only if the patient is compliant to their treatment. A meta-analysis found that noncompliance occurs in 5% to 80% of glaucoma patients.[55] There are many factors contributing to poor compliance: side-effects associated with topical glaucoma treatments can limit compliance and reduce QoL; elderly patients often find eye drops difficult to administer. The inconvenience of using topical medication and side-effects from medication further decreases QoL. Primary surgery has been associated with more eye discomfort than medications.[23] Life-long follow-up visits are, in practice, inconvenient.

Glaucoma and compliance

Patients' compliance in using glaucoma medication prevents visual impairment; however, adherence is difficult to measure as patients routinely overestimate their level of compliance. Mansberger et al[56] developed a Glaucoma Treatment Compliance assessment tool, which has high repeatability, content, construct, and predictive validity. Factors associated with glaucoma patient adherence are fear of blindness, forgetfulness, health literacy, difficulty with drop application, and age.[56] The patient's compliance increased if they received personalized information and guidance. Surgery is the treatment of choice in the developing world as poor compliance makes medical treatment an ineffective option.

Visual dysfunction and psychological burden (awareness of diagnosis, knowledge of potential blinding states, inconvenience of eye drops, side effects of treatments, and aggravated economic burden) of glaucoma lead to reduced QoL. Information regarding these is useful when planning for therapeutic choices and adaptation for the patient in their home environment.

Conclusion

The social and economic burden of glaucoma is higher in developed nations due to increased life expectancy, older population age and higher per capita GDP. This increases the relative cost-effectiveness of treatment interventions to mitigate glaucoma burden.[30] Many studies are conflicting in their findings making it impossible to reach a consensus. This is partly because there is no universal standard to measure effectiveness outcomes.[57] Each study provides only a few components of the extensive real world costs with little information on differential effectiveness in achieving target IOP or costs associated with rectifying adverse effects. Many cost-effectiveness studies based on data from developed nations are irrelevant for developing nations. In the developing nation, individual patient availability and affordability to treatment may vary the treatment choice. Therefore, the choice of treatment, whether surgical or medical, needs to be individualized and validated by local retrospective and prospective observational studies.[37] There is a strong need to increase the quantity and quality of local study looking at the cost-effectiveness of interventions and disease burden. Treatment resources should be allocated to those patients at highest risk of developing functional impairment from the disease and the therapy of choice should take into account efficacy, adherence to treatment and potential side effects.[58]

Disclosure

The authors report no conflicts of interest in this work.

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