

## A REVIEW OF THE CHOICE OF THERAPY IN PRIMARY OPEN ANGLE GLAUCOMA.

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### ABSTRACT

We are in the midst of a therapeutic revolution and the choice of therapy in the management of glaucoma can no longer be based on long-held beliefs. The choice between medical, surgical and argon laser trabeculoplasty as primary therapy for glaucoma has been a matter of debate and research for many years. Arguments are based mainly on 3 factors: efficacy, safety and cost. In Africa, other factors that must be considered include acceptability of surgery, compliance with medical therapy, scarcity and expense of modern drugs, absence of laser facilities among others. It is generally accepted that trabeculectomy surgery is the most acceptable form of therapy in Africans mainly because of its efficacy, late presentation and problems encountered during medical therapy. However many African patients are reluctant to have surgery for glaucoma mainly because of fear and the fact that there will be no visual improvement after the surgery. There are now several potent modern drugs, which though expensive have acceptable safety profile, and fewer problems with compliance.

The decision on the choice of therapy should be individualized and not be based on long-held beliefs.

**Key words:** therapy, glaucoma, choice.

### INTRODUCTION

If there is any controversial subject in medicine, it is GLAUCOMA. We can't define it; we can't cure it.<sup>1</sup> Most aspects of glaucoma remain a matter of debate and research. The definition, aetiology, diagnostic criteria and choice of therapy in primary open angle glaucoma are still debatable. This paper will concentrate on the choice of therapy. Many articles have been written on this subject giving foreign perspectives. This article will include the African perspective.

Primary open angle glaucoma is characterized by the most quantifiable parameters of any ophthalmic entity. These include the intraocular pressure, the aqueous outflow facility, and a variety of geometric measurements of the optic disc as well as a large number of ways to test and describe the visual defects. Despite this, we still lack a precise definition of primary open angle glaucoma.<sup>1</sup>

Primary open angle glaucoma is generally a bilateral, although not necessarily symmetrical disease characterized by the following:<sup>2</sup>

1. Glaucomatous optic nerve damage (cupping and atrophy).
2. Glaucomatous visual field loss and nerve fibre layer defects.
3. Repeated intraocular pressures greater than 21mmHg by applanation tonometry at some point in the disease was considered diagnostic.

However, about 20-30% of those with otherwise characteristic primary open-angle glaucoma will have intraocular pressures consistently less than 21mmHg.<sup>1</sup> This is referred to as normal tension glaucoma. Thus what we would call the CENTRAL DOGMA, which states that glaucoma is a disease caused by elevated intraocular pressure no longer holds sway.

4. Adult onset
5. Open and normal appearing angles
6. Absence of secondary causes of open angle glaucoma.

Glaucoma is a major cause of ocular morbidity. Estimates from the World

Health Organisation<sup>3</sup> show that 105million people globally are glaucoma suspects, about 13.5million people over the age of 40 years have primary open angle glaucoma (60% of the total burden of the disease), 6 million people have primary angle closure glaucoma (26.6%), 300,000 children (1.3%) have congenital glaucoma while 2.7 million (12.1%) have secondary glaucoma. Overall, approximately 70% of the world's cases of primary open-angle glaucoma are found in the developing countries. The World Health Organization also estimates that there are 5.2 million blind due to glaucoma comprising 3 million people blind from primary open-angle glaucoma, 2 million blind primary angle closure glaucoma and 200,000 blind from congenital glaucoma. Quigley<sup>4</sup> has stated that

glaucoma is the second leading cause of visual loss in the world after cataract, the number of people with primary glaucoma by the year 2000 being estimated at nearly 66.8 million with 6.7 million people suffering from bilateral blindness.

The various modalities for management of primary open angle glaucoma are medical, surgical or laser therapy.

### **SURGICAL THERAPY**

Trabeculectomy introduced by Cairns<sup>5</sup> in 1968 and later modified by Watson<sup>6</sup> and others has become the most popular procedure for surgical control of glaucoma. It lowers the intraocular pressure by the creation of a new channel ( fistula) for aqueous outflow between the anterior chamber and sub-Tenon's space.<sup>2</sup> The full thickness procedures which were in existence before the introduction of trabeculectomy were characterised by excessive aqueous drainage, flat or shallow anterior chambers, synechiae formation, endophthalmitis and formation of very thin filtering blebs which may rupture.<sup>7,8</sup> An attempt to minimize these complications has been to place a partial thickness scleral flap over the fistula as in trabeculectomy. Trabeculectomy has also been shown to increase the pulsatile ocular blood flow in the standing posture but has no effect in the lying measurements of pulsatile ocular blood flow<sup>9</sup>. If this reflects events in the optic nerve head, it may be an important factor in the success of trabeculectomy in reducing glaucomatous visual field damage.

Unlike other ophthalmic procedures, filtration surgery is aimed at interrupting the integrity of the globe and inducing prolonged hypotony. Thus the complex homeostasis of the eyeball is altered, sometimes indefinitely. The lens, cornea and other ocular structures are dependent on aqueous humour dynamics, intraocular pressure maintenance, and may be damaged by prolonged hypotony. Thus the risk of vision-threatening complications will always accompany filtering procedures<sup>10</sup>.

More recently, non-penetrating filtering surgeries have been introduced. The idea is to somehow enhance the natural aqueous outflow channels, rather than to create a new site. The avoidance of penetration into the anterior chamber should allow a more rapid recovery, with less risk of hypotony and its sequelae. One technique is known as deep sclerectomy, which was first described by Fyodorov<sup>11</sup> and Kozlov.<sup>12</sup> Here, the corneal stroma behind the anterior trabeculum and Descemet's membrane is removed. Another technique, first proposed by Zimmerman,<sup>13</sup> described as ab-externo trabeculectomy involves removal of the juxtacanalicular trabeculum and the inner wall of Schlemm's canal. In viscocanulostomy, described by Stegman et al,<sup>14</sup> the Schlemm's canal ostia are

surgically opened and dilated with a viscoelastic substance. However the technology and skill required for these techniques are not readily available in our environment.

### **COMPARATIVE STUDIES IN FAVOUR OF SURGERY.**

The first Moorfields prospective randomized surgical versus medical therapy trial in primary open-angle glaucoma between 1964 and 1982<sup>15</sup> appeared to favour the possibility that surgery was of some benefit in terms of visual field whereas medical therapy was probably better for visual acuity, but in neither case was convincing proof obtained. However, this study compared a modified Scheie's operation to medical therapy and Negro patients were excluded. The Glasgow study<sup>16</sup> was a randomized prospective multicentre trial of conventional management with initial medical therapy and surgery later when medical therapy fails on one hand, with trabeculectomy at diagnosis on the other hand. The patients were followed up for up to 5 years. Their result show that early surgery provided significantly better protection of visual field, and the extra loss of visual field with delayed operation occurred in the preoperative period. The second Moorfields study by Migdal et al<sup>17</sup> was a prospective randomized study designed to assess the relative efficacy of laser trabeculoplasty, medical therapy and trabeculectomy used as primary treatment in open-angle glaucoma. Follow-up was for a minimum of 5 years. Primary surgery resulted in the lowest mean intraocular pressures. The Friedman visual fields were shown to have deteriorated in patients in the medicine-treated group, but not in patients in the surgery treated group. The results from this study mirror the guidelines in the American Academy of Ophthalmology Preferred Practice Plan, which suggest that the chances of visual field progression are lessened if the target pressure for high tension glaucoma is in the mid or low teens.<sup>18</sup> However the patients studied in both the Glasgow and Moorfields studies were almost exclusively Caucasian and thus not representative of glaucoma patients in Africa or the United States. Furthermore, these studies did not have the benefit of the new more effective drugs currently available.

The next question is, does prior medical therapy affect the outcome of surgical therapy for glaucoma? Lavin et al<sup>19</sup> retrospectively reviewed the results of

surgery in 2 groups of patients. The first group underwent primary trabeculectomy having an average of 2 weeks of preoperative medical therapy, and the second group, which had received 1 year of topical antiglaucoma therapy prior to undergoing trabeculectomy (the multiple treatment group). The success rate (defined here as intraocular pressure less than 22mmHg) for the early trabeculectomy group was significantly higher than the multiple treatment group. Furthermore, all the failure occurred within the first 3 months, which corresponds, to the period of hypercellular response to wound healing. Studies on the conjunctival cell profile<sup>20</sup> showed that topical therapy affected the conjunctiva to different degrees with multiple drug regimen causing the most significant degree of subclinical inflammation than various single drug regimen. Biopsy showed an increase in pale cells, macrophages, mast cells and lymphocytes in the substantia propria following prolonged topical antiglaucoma drug administration. They further studied the effect of long-term topical antiglaucoma therapy on the result of glaucoma filtration surgery and related them to any differences in cell population profile of the conjunctiva.<sup>21</sup> Long term topical combination therapy and preoperative subclinical conjunctival inflammation induced by previous topical medication were identified as risk factors for failure of trabeculectomy. All these evidence lend support to the strategy of earlier trabeculectomy.

#### ACCEPTABILITY OF PRIMARY SURGERY

Trabeculectomy is regarded as the standard form of treatment for patients with primary open angle glaucoma in developing countries including Nigeria and it is now gaining acceptance worldwide.<sup>22</sup> Despite this, many of our patients are reluctant to have surgery as primary treatment option for glaucoma.

Osazuwa<sup>23</sup> compared patients in University of Benin Teaching Hospital, Benin City with patients at Bristol Eye Hospital, England between 1983 and 1984. He noted that operation is dreaded by our largely illiterate patients who believe that any disease that requires surgery is a hopeless one. Bekibele and Oluleye<sup>24</sup> reported the findings of 22 new patients seen at the University College Hospital Ibadan. Only 18 % of patients preferred surgery to medical therapy. In Benin, Omoti et al<sup>25</sup> reported that only 32.5% of 154 patients accepted surgery as the initial treatment option. The main reasons for refusal were knowledge that there might be no improvement, fear of surgery and high cost of surgery.

#### MEDICAL THERAPY

The field of ocular therapeutics is dynamic and there has been an ever increasing range of topical and systemic drugs available for glaucoma. Until 1995,

only 3 large groups of topical glaucoma medications were available, namely cholinergic drugs, sympathomimetic drugs and  $\beta$ -blockers. The  $\alpha_2$ -agonists such as clonidine were available in a few countries. With the advent of topical carbonic anhydrase inhibitors, soon followed by brimonidine, another  $\alpha_2$ -agonist, a new class of drugs, the prostaglandin analogues, heralded by latanoprost are now available.<sup>26</sup> Others include travoprost, bimatoprost and unoprostone. These newer drugs are more potent, have fewer side effects and can be applied once daily thereby improving compliance. However they are not readily available in our environment and are very expensive.

#### IS MEDICAL THERAPY BETTER THAN SURGERY?

Those who favour initial medical therapy base their argument on safety, cost and to some extent, efficacy. Sharir and Zimmerman<sup>27</sup> discuss the numerous sight threatening and less commonly, life threatening complications, which may follow trabeculectomy. These are unlikely with medical therapy. They also face the risk of devastating endophthalmitis for life. This risk, though small could result in an epidemic if all patients with glaucoma worldwide were to undergo primary trabeculectomy.

Diggory and Franks<sup>28</sup> have stated that the risk of topical medical therapy to general health, particularly that of elderly people, have been underestimated and that surgery is likely to be both a safer and a more effective option. They stress the risk of respiratory obstruction, reduced exercise tolerance and falls in the elderly due to impaired cardiovascular responses (with bradycardia, hypotension and impaired heart rate response) found with topical beta antagonists. Although nasolacrimal occlusion has been shown to improve the therapeutic index and decrease systemic absorption and side effects<sup>29</sup>, Diggory et al<sup>30</sup> have demonstrated poor compliance with this procedure and a lack of statistically significant difference in systemic side effects between those who claimed to comply and those who did not. It must be noted that when severe and potentially life threatening systemic complication occur, they present to other physicians and the contribution of eye drops is commonly overlooked or underestimated. Deaths from aplastic anaemia, thrombocytopenia and agranulocytosis have been reported resulting from therapy with carbonic anhydrase inhibitors.<sup>31</sup> Sharir and Zimmerman<sup>27</sup> also argued that it is wrong to believe that one-step surgery will save money. Their 1991 estimates show that the cost of bilateral uncomplicated glaucoma surgeries roughly equals 8 years of medical treatment. Since about a third of patients may need additional medical therapy or re-operations for failed surgery, premature cataract extraction and other

complications, the final cost of surgery may be more. The collaborative initial glaucoma treatment study<sup>32</sup> (CIGTS) also compared medication with filtering surgery in newly diagnosed early open-angle glaucoma. They showed that visual field and visual acuity losses were greater in the surgery group for the first 3 years, but these differences were not seen at 5 years. Thus, this study showed the equivalent ability of medicine and surgery to maintain a good visual field, although surgery reduced intraocular pressure more.

### **PROBLEMS WITH MEDICAL THERAPY IN OUR ENVIRONMENT**

The problems encountered with medical therapy in our environment include the following: The limited range of antiglaucoma drugs available. The cost of these drugs is very high since they are manufactured outside the country usually in nations that have better economic conditions and much stronger currencies. Poor accessibility- the drugs are not usually available in the locality of most of the patients who live in rural areas. There is an ever increasing menace of fake, adulterated and expired drugs. Poor compliance- this is particularly so because the patients have to continue these drugs for life even though they do not experience any improvement in vision.<sup>33</sup> The non-compliance rate in Benin city, Nigeria has been found to be as high as 63.2%.<sup>33</sup> Late presentation, poor follow-up clinic attendance because of long distances, high cost of transportation and other factors.<sup>22</sup> Side effects of the drugs. Poor awareness of the concept of control: People want a cure, not control. The concept of daily long-term or life-long application of medications to the eyes is so strange as to result in non-compliance. Drug instability:

Nigeria is in the tropical region with plenty of sunshine nearly all year round. This may affect the shelf life of antiglaucoma drugs due to the temperatures attained. Epinephrine eyedrops rapidly change colour when exposed to light resulting in photooxidation products which are toxic to the retina.<sup>23</sup> Culture and beliefs: Some of our patients are very superstitious and ascribe their disease to the influence of an evil one. Such patients do not believe in treatment by mere instillation of eye drops.<sup>23</sup> The commonly seen patients are ready to get along with one good eye, attributing visual loss in the other eye to an act of God, till the vision in the good eye starts to deteriorate at which time treatment options become limited. Difficulty instilling eyedrops.<sup>33</sup> Some patients may experience difficulty instilling topical drops into the eye because of old age, very poor vision or inconvenience such as while working or traveling. Multiple drug therapy: Many of the patients have other co-existing chronic diseases such as hypertension, diabetes, cardiac and pulmonary

disorders which also require medication. This may result in confusion, drug interactions, increase in the total cost of the medication and ultimately poor compliance.

### **NON-INTRAOCULARPRESSURE LOWERING MEDICATION**

The exact mechanism of optic nerve head damage is still poorly understood. This has led to the search for drugs that address the other non-intraocular pressure risk factors. This has led to the concepts of vasoprotection and neuroprotection. Direct neuroprotection usually refers to interfering with a cascade of programmed cell death or apoptosis. Several intraocular pressure lowering drugs are known to have vasoprotective and neuroprotective effects.<sup>34</sup> Latanoprost, dorzolamide, betaxolol and unoprostone have vasoprotective effects. Betaxolol and brimonidine have neuroprotective effects. This explains the observed superiority of betaxolol over timolol in visual field preservation in glaucoma.<sup>35</sup> Briefly, other neuroprotective medication include:<sup>34</sup> A brain-derived neurotrophic factor which promotes ganglion cell survival; free radical scavengers like ginkgo biloba extract and vitamin E; glutamate receptor blocker like memantine; nitric oxide scavengers like melatonin and ginkgo biloba; as well as several other chemicals. Some of these drugs are already available in some multivitamin preparations. However, they are usually expensive and not readily available in our environment.

### **LASERS**

There are also those who favour initial argon laser trabeculoplasty. Jampel<sup>36</sup> states that laser trabeculoplasty is the best initial treatment for patients with chronic open-angle glaucoma. He based his argument on the favourable safety profile of argon laser trabeculoplasty, the absence of the compliance issue and the results from the glaucoma laser trial follow-up study.<sup>37</sup> It prospectively compared initial laser trabeculoplasty to medical therapy and found that during the course of up to 9 years, the eyes that received laser trabeculoplasty first, had intraocular pressures averaging 1.2mmHg lower and slightly better visual fields than eyes that received medications first. Other advantages of argon laser trabeculoplasty are that it is extremely time and cost effective. However it is not readily available in our environment and earlier studies showed that it was less effective in blacks.<sup>38</sup> Later studies, like the Advanced Glaucoma Intervention Study (AGIS) showed that argon laser trabeculoplasty was effective in black patients.<sup>39</sup>

Other forms of laser therapy include:<sup>40</sup> selective laser trabeculoplasty (SLT) which uses a Q-switched 532-nm Nd:YAG laser and acts by a process known

as selective photothermolysis. The laser energy can also be delivered externally to produce a direct opening into the anterior chamber through limbal tissue to achieve filtration (holmium ab externo sclerostomy). It can also be applied internally through a fiberoptic probe via a transcameral approach (ab interno Nd:YAG laser sclerostomy). These techniques are however not readily available in our environment.

## CONCLUSION

Glaucoma therapy is undergoing a rapid revolution and the choice of therapy can no longer be based on long-held beliefs. Primary surgery may remain the most rational choice for treatment of primary open-angle glaucoma among the poor majority in our environment for whom compliance with medical therapy, high cost of modern drugs and poor accessibility may be a problem. For the elite and rich patients, it may be worthwhile to give them the benefit of the new array of drugs currently available rather than expose them to the risks of surgery at the outset. There is also the problem of poor acceptability of surgery. Thus the choice of therapy must be individualized.

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