Paediatric Aphakic Glaucoma

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Abstract

Aphakic glaucoma is the most common long-term complication seen following congenital cataract surgery. It has a reported incidence of between 15% and 45%. Many risk factors have been identified including microcornea, early surgery, persistent fetal vasculature, congenital rubella syndrome, Lowe syndrome, chronic inflammation and retained lens material. Diagnosis is often difficult as the classic signs of congenital glaucoma such as epiphora, blepharospasm and buphthalmos are usually absent. Additionally, it is also difficult to perform accurate ocular examinations on young children and examination under anaesthesia is usually required. Surgical intervention is often required with medical treatment providing adjunctive therapy. Surgical techniques performed include trabeculectomy with or without antifibrotic agents, glaucoma drainage devices (valved and non-valved), cyclodestructive procedures, goniotomy and trabeculotomy. Trabeculectomy with mitomycin C and glaucoma drainage devices are the two most commonly performed procedures. In spite of considerable advances having been made in the management of aphakic glaucoma, it still poses a significant management dilemma. Despite best standard of care two thirds of aphakic children end up with a mean visual acuity of ≤ 20/400.

Introduction

Aphakic glaucoma is a well recognised sight-threatening complication seen following uncomplicated paediatric cataract extraction. It is the most common long-term complication seen following congenital cataract surgery. The incidence has been reported in the literature to be between 15% and 45%, however, this may be dependent on the length of the post-operative follow-up period [1-5]. Despite the introduction of newer surgical techniques, the incidence remains high. Certain risk factors have been implicated including microcornea, early surgery, persistent fetal vasculature (PFV), congenital rubella syndrome, Lowe syndrome, chronic inflammation and retained lens material [2,3,6-10]. Aphakic glaucoma poses a significant clinical challenge, particularly with regards to diagnosis and treatment. These children are hard to diagnose as they can remain asymptomatic for a long period of time despite high intraocular pressures (IOP). The presentation is often delayed and hence, the signs of congenital glaucoma, namely, buphthalmos, corneal clouding and Haab's striae are not present. The treatment of aphakic glaucoma is often difficult and although medical management is the first line of treatment, surgical intervention is frequently required for adequate IOP control. Chen et al. [13] described glaucoma surgery being required in 57.1% of cases (170 eyes) of aphakic patients following congenital cataract surgery.

Aetiology

The pathophysiological mechanism of aphakic glaucoma remains unknown. Mills and Rob [11] noted that an angle-closure mechanism frequently occurred within the first few months after surgery and an open-angle glaucoma mechanism had a later onset with a mean of 7.4 years. This was also noted by Koc et al. [12] who found closed angles in 54% of eyes with early-onset glaucoma and 15% of eyes with delayed-onset glaucoma. Chen et al. [13] did not observe a similar pattern and found that glaucoma occurred in 20% of patients with the angle being open in 93% of cases. It is likely that the two mechanisms participate, with the early-onset form being caused by pupillary-block from active inflammation and retained lens material [11,12]. This incidence has largely been reduced by improved aspiration techniques combined with posterior capsulotomy and anterior vitrectomy, enabling the surgeon to remove the lens cortex and capsule more effectively [11,12,14,15].

Figure 1: Child with right congenital glaucoma and buphthalmos. This is in contrast to paediatric aphakic glaucoma which presents without any obvious clinical signs.

The mechanism and pathophysiology of glaucoma occurring in aphakes with open angles following congenital cataract surgery is largely not understood. It has been proposed that the defect responsible for producing the cataract may also affect aqueous outflow causing a form of goniodysgenesis [16]. It has also been suggested that 'barotrauma' to the immature angle may cause damage which would be supported by the high incidence of glaucoma in children who have surgery at a young age [17]. Stuctural changes to the angle drainage complex in the 'soft' paediatric eye have also been postulated, and this may possibly be supported by the possibly lower incidence of glaucoma in pseudophakic eyes [3,18-28]. The role of the vitreous in aphakic glaucoma is not fully

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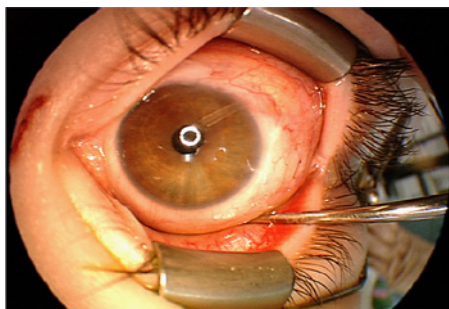
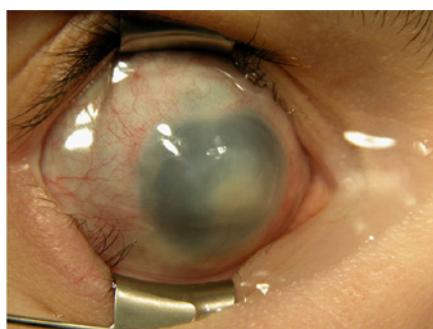**Figure 2:** Left aphakic glaucoma with an Ahmed valve.

Figure 3: Right end-stage aphakic glaucoma.

understood. It is possible that even a short-term exposure of the angle to vitreous may cause an alteration to the aqueous outflow system.

A genetic predisposition to the development of glaucoma has also been proposed. This is supported by occasional clustering of glaucoma in families with congenital cataract and by the frequent bilateral nature of the disease. Kirwan et al. [29] reported eight out of 12 aphakic patients with a family history of congenital cataract to develop aphakic glaucoma. This included three siblings from one family and two sibling pairs from two additional families. The role of genetics in the development of aphakic glaucoma, however, still remains poorly understood. Known important risk factors for the development of glaucoma include young age at the time of surgery [3,6,11,12,26,30], microcornea [11,12,31,32], microphthalmia [12] and PFV [11,33]. Parks et al. [31] found an incidence of 33% of glaucoma in eyes with a corneal diameter of less than 10mm. Wallace et al. [32] reported the prevalence of microcornea to be as high as 94% in aphakic glaucoma patients. This study also suggested that nuclear sclerosis imposed increased risk of developing glaucoma. Chak et al. [34], however, did not find any significant association between microophthalmia and glaucoma and felt that the age at detection and microophthalmia may be relevant as the presence of the latter may lead to earlier detection and, hence, earlier surgery with better outcomes.

Diagnosis

Diagnosis of glaucoma following congenital cataract surgery is often difficult as they generally lack the classical signs of congenital glaucoma such as epiphora, blepharospasm and buphthalmos. It is also difficult to measure the IOP with the child awake and examination under anaesthesia is usually required in young children. Many general anaesthetics lower the IOP but reliable readings can be achieved during spontaneous breathing prior to tracheal intubation [35]. Diagnosis cannot be based on IOP alone as central corneal thickness (CCT) can be significantly thickened in aphakic glaucoma [9,36,37]. Diagnosis criteria should, therefore, include corneal diameter, gonioscopy, cycloplegic refraction, optic nerve head evaluation and visual fields where possible. It is not usually possible to assess visual fields in children under 6 years old.

The frequency of follow-up examinations is very much dependent on the individual case. Asrani and Wilensky [38] proposed examinations every three months for the first year postoperatively, twice yearly for the next 10 years and annually thereafter.

Critical period of visual development and timing of surgery

The development of the visual pathway is significantly affected by visual deprivation. Dubowitz et al. [39] proposed that a 'latent' phase exists during the early neonatal period whereby the immature visual system is not dependent on the cortex but is mediated through sub-cortical pathways. It appears that during this 'latent' period visual deprivation does not have a significant impact on prospective visual outcome. This 'critical period' is thought to be 6 weeks following birth for unilateral deprivation and may be up to ten weeks for bilateral deprivation [40,41]. The literature to date regarding age at cataract surgery in the first year of life is unclear and is largely retrospective. In many cases confounding factors such a PFV and microcornea were not excluded. Khan et al. [2] found the highest incidence of glaucoma occurred when surgery was performed before one month of life and at five to six months of age. Interestingly they found a nadir of aphakic glaucoma risk for surgery at 3-4 months of age which they were unable to explain. They excluded microcornea and PFV, both significant confounding factors. Chen et al. [13] found no particular age in the first year associated with a greater risk of aphakic glaucoma. Lundvall et al. [42] found that aphakic glaucoma occurred in infants undergoing surgery in the first week of life. Michaelides et al. [6] described surgery occurring during the first month as life as posing the greatest risk. Vishwanath et al. [30] concurred with this. In contrast, Watts et al. [43] proposed that surgery during the first two weeks of life has the most favourable outcome regarding incidence of aphakic glaucoma as compared with surgery occurring between 13.5 days to 43 days of life. This study only had an average follow-up period of 2.85 ± 1.9 years (mean ± standard deviation, SD). Several population studies from Denmark, Sweden and the United Kingdom have looked at timing of cataract surgery. Haargaard et al. [44] found the highest risk for glaucoma was before 9 months of age while Magnusson et al. [45] concluded that there is a relationship between surgery in the first ten days of life and glaucoma risk. Chak et al. [34] found earlier detection of cataract to be the only significant risk factor to be associated with aphakic glaucoma.

The current consensus is that cataract surgery can be delayed until 4 weeks and possibly up to 6 weeks without significantly affecting visual potential. A large prospective multicentre study is necessary to establish optimum timing of surgery and it relationship to visual rehabilitation and risk of aphakic glaucoma.

Intraocular lens implantation

In recent years primary intraocular lens (IOL) implantation has become increasingly popular. Advantages include better amblyopia management compared to aphakic glasses and contact lenses and the lower rate of glaucoma in pseudophakic eyes reported in the literature [3,18-28]. Kirwan et al. [29] retrospectively reviewed 338 eyes. The incidence of glaucoma was found to be 33% (15 eyes) in the aphakic

Author	Aphakic glaucoma eyes (numbers)	Procedure	Anti-metabolite dose and duration	Success criteria	Success rate
Pakravan (2007)	15	Trabeculectomy + MMC	0.2 mg/ml for 2 minutes	IOP 5- 21 mmHg with or without medication	33 % (without medication) 40 % (with ≤ 2 medications)
Chen et al (2004)	61	Trabeculectomy + MMC or 5-FU (1 without anti-metabolite)	Not specified	IOP ≤ 21 mmHg with or without medication	24.6%
Mandal et al (2002)	21 aphakic 2 pseudophakic	Trabeculectomy + MMC	0.4 mg/ml for 2-3 minutes	IOP 6-21 mmHg with or without medication	36.8% (without medication) 21.1% (one medication)
Sidoti et al (2000)	3	Trabeculectomy + MMC	0.4 mg/ml for 1.5-8 minutes	IOP 5-21 mmHg with medication	66.6%
Azuora-Blanco et al (1999)	8	Trabeculectomy + MMC	0.4 mg/ml for 1-5 minutes	IOP < 21 mmHg without medication	0%
Wallace et al (1998)	13	Trabeculectomy + MMC	0.2 or 0.4 mg/ml for 4 minutes	IOP < 26 mmHg or < 21 mmHg with medication	62%
Beck et al (1998)	9	Trabeculectomy + MMC	0.25 or 0.5 mg/ml for 5 minutes	IOP < 22 mmHg with or without medication	78%
Asrani and Wilensky (1995)	12	Trabeculectomy + MMC (5 eyes without anti-metabolite)	Not specified	IOP < 22 mmHg	85%

SD, standard deviation; MMC, mitomycin C; 5-FU, 5-fluorouracil

Table 1: Relevant studies involving trabeculectomy (± mitomycin C or 5-fluorouracil) in paediatric aphakic glaucoma.

Author	Aphakic glaucoma eyes (numbers)	Procedure	Success criteria	Success rate	Complication/failure rate
Al-Mobarak et al (2009)	5	5 eyes; Ahmed valve ± MMC	IOP ≤ 22 mmHg with or without medication	63.3% survival at 2 years(for all 42 eyes in study)	Severe complications: 7.1% Additional surgical procedures: 26.2 %
Pakravan et al (2007)	15	15 eyes: Ahmed valve + MMC	IOP 5- 21 mmHg with or without medication	20 % (no medication) 66.7 % (with ≤ 2 medications)	13.3 % failure rate
Chen et al (2004)	34	32 eyes: Ahmed valve 2 eyes: Molteno valve	IOP ≤ 21 mmHg with or without medication	44.1%	Not specified
Kirwan et al (2005)	19	19 eyes: Ahmed valve (10 eyes with MMC)	IOP ≤ 15 mm Hg with or without medication	6 eyes (without medication) 12 eyes (with medication)	One eye defined as failure
Beck et al (2004)	10 (congenital cataract or PHPV)	32 eyes: Ahmed valve 8 eyes: Baerveldt valve	IOP < 23 mmHg with medication	71.7 % (for all 46 eyes in study)	Severe complications: 1% Additional surgical procedures: 45.7%
Morad et al (2003)	3	60 eyes: Ahmed valve	IOP 5-21 mmHg with or without medication	77 % (for all 60 eyes in study)	50 % complication rate

PHPV, persistent hyperplastic primary vitreous; MMC, mitomycin C

Table 2: Relevant studies involving glaucoma drainage devices in paediatric aphakic glaucoma.

group and 13% (7 eyes) in the pseudophakic group. Duration of follow-up was significantly longer (113 ± 69 months and 56 ± 44 months in the aphakic and pseudophakic groups, respectively) and age of surgery was significantly lower in the aphakic group. Asrani et al. [18] looked at 501 eyes and reported a 0.27% (1/377) incidence of pseudophakic glaucoma as compared with an 11.3% (14/124) incidence of glaucoma in the aphakic group. Again, there was a longer duration of follow-up (7.24 ± 3.98 years as compared with 3.91 ± 2.74 in the pseudophakic group) and age of surgery was significantly lower in the aphakic group (2.73 ± 2.65 years as compared with 5.06 ± 4.7 years in the pseudophakic group). Asrani et al. [18]proposed both a chemical and mechanical theory as to how an IOL may be protective. The chemical theory suggests that the IOL provided a barrier from the toxic material of the vitreous and the mechanical theory speculates that the IOL provides support to the angle, thus preventing collapse of the trabecular meshwork [18]. Selection criteria play a key role and many surgeons do not implant IOLs in eyes deemed at higher risk of glaucoma. Therefore the lower incidence of aphakic glaucoma in pseudophakic eyes may be a product of selection bias for lens insertion. Disadvantages of implanting an IOL include the frequent necessity for additional surgical procedures. This is largely due to the fact that these eyes are more susceptible to intense posterior capsular opacification and excessive uveal inflammation.

Corneal thickness

CCT has been established as an important predictive factor in glaucoma development. It is known that a thicker cornea overestimates IOP and a thinner cornea underestimates IOP [46-49]. CCT has been shown to be higher in aphakic and pseudophakic eyes of children as compared with normal eyes with this higher CCT value being more pronounced in those with glaucoma. It has been suggested in the literature that this higher CCT in children following cataract surgery in an acquired phenomenon, however, this is mainly speculative [9,37]. Lim et al. [36] carried out a longitudinal study in 2011 looking at CCT in children before and after congenital cataract extraction. Those with unilateral cataract extraction demonstrated a significant difference of 29.7 ± 43.1 μm between the affected and fellow eye from baseline pre-

operatively. In bilateral cases they showed a statistical increase in CCT of 27.4 ± 39.4 μm. Baseline CCT readings were similar pre-operatively in both eyes and were comparable to values in normal paediatric eyes in the two groups. They also looked at a group of patients who were aphakic or pseudophakic but without any pre-operative CCT measurements. They found CCT to be higher in those with glaucoma but found no statistical significant change in CCT over the 28 month study interval. They proposed that the eyes in children following cataract removal may actually have altered properties that render the IOP even lower than the actual 'true' IOP. They advise not to adjust the CCT on the basis of the higher CCT readings. This highlights the need to take into account other indices in addition to IOP, which may suggest glaucoma development and progression, in order to ensure accurate diagnosis and monitoring.

Medical management

Management of aphakic glaucoma is challenging. Medical management is often the first line of treatment. Beta-blockers, carbonic anhydrase inhibitors and pilocarpine are well established medical treatment options. Unlike primary congenital glaucoma, aphakic glaucoma patients can respond well to medical treatment and some patients may achieve sufficient IOP control with this treatment alone. Asrani et al demonstrated satisfactory IOP control in 63.6% of patients (21 of 33 eyes) with medical treatment alone [38]. In clinical practice, however, this is less often the case with medical therapy often not being sufficient to control the progression of glaucoma and, hence, is often an adjunctive treatment in addition to surgical intervention.

The two most commonly used beta-blockers are timolol and betaxolol. Plasma levels of timolol greatly exceed those seen in adults following use of timolol 0.25% [50]. It is, therefore, likely that this higher plasma level seen following timolol use would be associated with increased systemic side-effects. Serious adverse effects such as apnoeic episodes have been reported in the literature [51].

Acetazolamide is a carbonic anhydrase inhibitor and is most effective as an oral preparation in children. This is not ideal for long-term use as this medication can be associated with significant renal and hepatic side-effects and growth suppression [52]. Pilocarpine works by facilitating the outflow of aqueous in aphakic glaucoma. The use of pilocarpine in the treatment of aphakic glaucoma is limited but it may offer some benefit as an adjunctive treatment in certain cases. Newer medications such as latanoprost, brimonidine and dorzolamide are used less frequently in children as compared with adults. Latanoprost is a prostaglandin analogue that works by increasing uveoscleral outflow, however, the majority of children do not respond well to this drug. Brimonidine is a selective alpha-adrenergic receptor agonist that works by reducing aqueous production and by increasing uveoscleral outflow. This drug, however, is associated with extreme fatigue and somnolence. Enyedi et al. reported two children to be transiently unrousable following administration of this drug [53].

Surgical management

Surgical intervention is very often necessary when medical treatment is not adequate to control the condition. The poor success rates and potential complications with many surgical procedures may result in delay in treatment and allow the glaucoma to rapidly progress. Surgical techniques performed include trabeculectomy with or without antifibrotic agents, glaucoma drainage devices (valved and non-valved), cyclodestructive procedures, goniotomy and trabeculotomy. There is no consensus as to the optimal surgical procedure or combination,

however, trabeculectomy with mitomycin C and glaucoma drainage devices are emerging as two of the most commonly performed procedures.

Trabeculectomy was first described in 1967 [54] and has had several modifications to date including the addition of antifibrotic agents. Previous studies reporting the outcome of filtering surgery in paediatric glaucoma without the use of adjunctive antifibrotic agents have demonstrated disappointing results [11]. Mitomycin C has emerged as the most commonly used and most effective antimetabolite used during trabeculectomy. It is an antibiotic isolated from *Streptomyces caespitosum* which has the ability to inhibit fibroblastic proliferation by inhibiting DNA-dependent RNA synthesis. The literature to date has demonstrated very mixed results regarding trabeculectomy with mitomycin C following congenital cataract extraction. The reported success rates varied from 0% to 85%. [38,55-62]. Asrani and Wilensky [38] described their success rate, defined as IOP < 22 mmHg, in 12 aphakic eyes with or without medication as 85%, while in stark contrast, Azoura-Blanco et al. [55] found their success rates (defined as IOP < 21 mmHg) to be 0% in eight aphakic eyes without any medication after one year. Chen et al. [13] reported success rates of 24.6% for IOP ≤ 21 mmHg with or without glaucoma medication, with no need for further surgery.

The use of adjunctive chemotherapy may increase trabeculectomy success; however, it is also associated with increased risk of serious complications such as bleb-related infection and endophthalmitis. Wallace et al. [61] reported one case of bleb-related infection in 16 eyes (6%) while Mandal et al. [58] reported two eyes (22.2%) of one patient to develop bleb-related infection on two different occasions which ultimately resulted in hypotony refractory to treatment and poor visual outcome. Sidoti et al. [60] noted five patients (17%) to experience bleb-related complications and of these, two (7%) developed endophthalmitis at a mean follow-up of 27.9 months post-operatively. Beck et al. [56] reported late-onset endophthalmitis in five patients (8%) at 18-48 months post-operatively. Mandal et al. [58] proposed that the high rate of intraocular infection seen in these children is largely contributed to by their long-life expectancy, the presence of a large thin-walled avascular bleb and the difficulty in maintaining strict hygiene in this group of young patients. It has been suggested in the literature that using a lower dose of mitomycin C may reduce complications. Agarwal et al. [63] used a lower dose in high risk cases of congenital glaucoma and found that 0.2 mg/ml of mitomycin for four minutes to be as effective as the higher 0.4 mg / ml concentration but with lower incidence of complications and thin-walled blebs.

A less potent anti-metabolite such as 5- fluorouracil can also be used in paediatric glaucoma management. It is a pyrimidine analogue that works by inhibiting DNA and RNA synthesis and is also an inhibitor of fibroblast formation. It can be used at the time of surgery, injected sub-conjunctival around the bleb site or more commonly given as a subconjunctival injection after surgery [64]. The primary disadvantage of 5-fluorouracil treatment is the frequent postoperative visits required. Toxicity is low but delayed healing and persistent epithelial defects may occur.

The first drainage implant was introduced in 1968 by Molteno (Molteno Ophthalmic Ltd, Dunedin, New Zealand) to treat refractory glaucoma [65]. Following on from this, multiple implants have emerged over the past few decades, namely valved devices such as Krupin (Hood Laboratories, Pembroke, MA, USA), Ahmed (New World Medical Inc, Rancho Cucamonda, CA, USA) OptiMed (Kowa Optimed, Torrance, CA, USA) and non-valved devices such as Baerveldt (1990;

Advanced Medical Optics, Inc., Santa Ana, CA, USA) and Schocket (Hood Laboratories, Pembroke, MA, USA). Success rates of both valved and non-valved glaucoma drainage devices in children have been promising. The literature demonstrates results superior to that of trabeculectomy with mitomycin C. Al-Mobarak et al. [66] reported success rates with the Ahmed valve, defined by IOP ≤ 22 mmHg with or without medication, of 63.3% at 24 months in a study of 42 eyes. This study, however, included multiple glaucoma pathologies with only 11.9% (5 eyes) having a diagnosis of aphakic glaucoma. Pakravan et al. [59] reported success rates (defined by IOP ≤ 21 mmHg with or without medication) with the Ahmed valve in treating aphakic glaucoma as 86.7%. This compared with success rates of 73.3% in the trabeculectomy with mitomycin group. In contrast, Chen et al. [13] described success rates of only 44.1%, however, this still compared favourably against the trabeculectomy group who success outcome was only 24.6%. Success was defined in this study as IOP ≤ 21 mmHg with or without medication with no need for further surgery. Kirwan et al. [67] reported 12 out of 18 eyes achieving an IOP of 15 mmHg or less with an Ahmed valve alone or additional medication in the treatment of aphakic glaucoma. They also made a very important observation that there was good IOP control in three eyes after six years follow-up.

Recognised complications associated with valve implantation include hypotony, choroidal effusion and localised infection and more rarely tube exposure, ocular motility issues and endophthalmitis [59,67]. Complication rates of Ahmed valve use have been previously reported as 26.7% [59] which is comparable to Kirwan et al. [67] who described complications occurring in six out of 19 eyes. Morad et al. [68] reported complications occurring in 50% (30 out of 60 eyes) which was comparable to the 46% described by Beck et al. [69]. The most common complication was tube-cornea touch (35%) followed by cataract (11%) and corneal decompensation (9%). Mobarak et al. [66] looked at Ahmed valve insertion in 42 eyes in the first two years of life and found the most common complications to be tube malpostitioning, retinal detachment and endophthalmitis. Postoperative hypotony is an important complication that occurs less frequently with Ahmed valve due to the unidirectional function of aqueous. However this can also cause a hypertensive effect that is usually around one month. This occurs due to fibrosis occurring around the valve site [64,70]. Kirwan et al described the beneficial effects of needling over the valve plate with 5-fluorouracil in both early and late post-operative phase. They described a useful indicator of success as an immediate drop in IOP following a needling procedure.

Cycloablative procedures such as diode laser cyclophotocoagulation and cyclocryotherapy have been applied in the setting of refractory paediatric glaucoma [71,72]. More recently endocyclophotocoagulation has emerged as an additional treatment modality with promising results and possibly less risk of postoperative hypotony [73]. Kirwan et al. [71] looked at 77 eyes who underwent transscleral diode cyclophotocoagulation, of which 34 eyes had a diagnosis of aphakic glaucoma. They described 62% having a successful outcome, defined as IOP < 22 mmHg or 30% reduction in IOP following one treatment. Interestingly, they also found that the IOP lowering effect seen in aphakic eyes was sustained for a longer duration that that of phakic eyes. Similarly, this sustained IOP lowering effect was also observed by Autrata and Rechurek [74]. Carter et al. [73] looked at the use of endocyclophotocoagulation in 24 eyes, of which 32 were aphakic. They described success rates of 38% (13 of the 34 eyes) following one treatment, after a minimum of 12 months. The cumulative success rates increase to 53% when multiple treatments were included.

Despite the very promising results, these procedures are associated with significant sight-threatening complications such as retinal detachment [71,73,74].

Additional surgical interventions include angle surgery, such as trabeculotomy and goniotomy. Chen et al. [13] reported a success rate of only 16% in 24 eyes, however in stark contrast to this Bothun et al. [75] reported treatment success in 57.1% in 14 eyes following these procedures.

Conclusion

Despite considerable advances, the diagnosis and management of aphakic glaucoma still poses a significant dilemma. Up to 45% of all aphakic patients may go on to develop glaucoma which may not occur for years following surgery, hence, lifelong surveillance is crucial. Medical therapy may be sufficient to control glaucoma progression in certain patients; however, the greater majority will go on to require surgical intervention. Even with best standard of care, many aphakic patients have poor vision which may ultimately lead to blindness. The poor visual outcome results from many factors including amblyopia, late diagnosis, potential poor compliance with medications, delayed surgery and surgical complications.

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