Aqueous Shunts for the Treatment of Glaucoma

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A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum (CTAF) was asked to assess the evidence for the use of aqueous shunt devices for the treatment of glaucoma. Glaucoma is primarily treated with eye drops and then laser therapy when eye drops fail. Surgical intervention, including the use of shunts, is usually reserved for patients who fail therapy with eye drops and lasers.

BACKGROUND

Glaucoma

Glaucoma is the second most common cause of blindness in the United States and worldwide.\textsuperscript{1,2} It is a progressive optic neuropathy characterized by nerve atrophy and loss of retinal ganglion cells. In its most common form, patients have progressive loss of peripheral vision that is usually asymptomatic even when it is very advanced. As many as half of people with glaucoma are unaware that they have the disease. Signs of disease include an elevated intraocular pressure (IOP), increased cup to disc ratio, and loss of vision on formal peripheral field testing. Glaucoma is usually identified during routine eye examinations either by noting an enlarged cup-to-disc ratio on fundoscopic examination, an increased IOP, or visual field loss with perimetry.

There are several forms of glaucoma. The most common is open angle glaucoma, which is thought to be due to resistance to flow through the trabecular network located at the angle formed by the iris and the cornea in the anterior chamber of the eye. This leads to decreased drainage of aqueous humor into Schlemm's canal and a relatively increased IOP. Angle-closure glaucoma often presents acutely with a painful red eye. It is characterized by a narrowed or closed anterior chamber angle, which limits drainage of the aqueous humor. Other causes of glaucoma include vasoproliferative disease, pigment dispersion, trauma, and uveitis.

Glaucoma is more common in older patients, African Americans, and those with a family history of
The primary modifiable risk factor for glaucoma is IOP, but up to 15% of patients with glaucoma have normal IOP. Normal IOP ranges from 10 to 21 mm Hg. Lowering IOP is the primary therapy to limit or prevent vision loss. Several randomized trials and meta-analyses have demonstrated that interventions to lower IOP lead to decreased vision loss over time. Loss of vision from glaucoma can have a significant impact on patients' quality of life. Patients with glaucoma are at increased risk for falls and motor vehicle accidents and it negatively impacts other activities of daily life.

There is no single threshold pressure for beginning treatment. Patients with normal IOP, but evidence of optic disc cupping and visual field loss are usually recommended for treatment. Treatment is usually started for patients with IOP greater than 25 mm Hg, even in the absence of signs of early damage to the optic nerve. Pharmacological therapy with eye drops is first line therapy. There are several classes of drops including those intended to increase the outflow of aqueous humor (prostaglandins, alpha adrenergic agonists, and cholinergic agonists) and those intended to decrease aqueous humor production (alpha adrenergic agonists, beta blockers, and carbonic anhydrase inhibitors). There appears to be consensus that the first class to be tried are the prostaglandins because they have fewer systemic side effects and are at least as effective as the other classes of medications.

When drugs fail, laser therapy (trabeculoplasty) is usually the next step. Either continuous wave or pulsed lasers are directed at the trabecular network. Laser trabeculoplasty increases aqueous outflow and reduces intraocular pressure, but its effectiveness decreases over time and repeated treatments are needed every few years. It is a very safe procedure, with fewer side effects than either medications or surgery. It also has been shown in one large randomized trial to be at least as effective as eye drops when used as the initial therapy. However, it becomes less effective with repeated treatments and many specialists do not use laser trabeculoplasty more than two or three times on an individual eye.

Surgery is considered for patients who are inadequately controlled or intolerant of medical and laser therapy. The history of glaucoma surgery dates back to the mid-19th century. The standard surgical therapy today is trabeculectomy, also known as filtering surgery, in which part of the sclera is removed to allow aqueous humor to drain in a controlled manner from the anterior chamber into the subconjunctival space. The drainage region over the sclera is called a bleb. The surgery may fail over time due to excessive healing (scar formation) at the drainage site, which increases resistance to the outflow of aqueous humor. Anti-metabolite medications, such as mitomycin C and 5-fluorouracil, have been shown in randomized trials to improve outcomes following surgical trabeculectomy, but they increase the risk for infection of the bleb leading to endophthalmitis and also increase the risk for chronic hypotony and a large, uncomfortable bleb. Both beta-irradiation and post-operative steroids have been used to control the healing process, but they
have been abandoned in favor of the anti-metabolite therapies. Trabeculectomy surgery is associated with uncommon, but severe complications, including endophthalmitis, cataract formation, and permanent blindness, so it has traditionally been reserved for patients with glaucoma refractory to less invasive treatments. The Collaborative Initial Glaucoma Treatment Study was a randomized trial that compared trabeculectomy to medical therapy as the initial treatment for open angle glaucoma. They found similar visual field outcomes through five years of follow-up, but the surgical arm had higher early rates of visual acuity deterioration. Subgroup analyses suggested that surgery may be preferred as the first line treatment in patients presenting with advanced visual field defects, but that surgery led to worse outcomes in patients with diabetes.

**Aqueous Shunts**

Aqueous shunts are devices that, like surgical trabeculectomy, create an alternate path for aqueous humor to leave the anterior chamber of the eye and thus lower IOP. They were initially used for patients who failed medical and laser therapy and had an underlying diagnosis that increased the risk that surgical trabeculectomy would fail. These conditions include neovascular glaucoma, uveitic glaucoma, corneal transplant, and iridocorneal endothelial syndrome. However, recent trends suggest that they are being used more often for patients at lower risk for trabeculectomy failure.

There are a number of synonyms for aqueous shunts including glaucoma drainage devices, tube implants, and tube shunts. Devices available in the United States include the Ahmed (12 models), Baerveldt (3 models), Krupin, Molteno (6 models), Optimed, or Schocket shunts. New devices include the SOLX Gold shunt and the Ex-PRESS mini-shunt. The general approach of the shunts is to place a tube into the anterior chamber of the eye that drains through a plate or multiple plates attached to the sclera. These shunts vary in the materials used (silicone, silastic, polypropylene, gold, stainless steel), the use of valves in the tube, and the size and number of plates. The tubes provide a conduit to allow the controlled flow of aqueous humor from the anterior chamber to a space between the conjunctiva and the sclera (the bleb) where it is absorbed into the blood.

The initial shunts were not valved and required a suture to be tightened around the drainage tube until healing around the plate caused an increased resistance to flow. Without the suture, the IOP pressure would drop too low (5 mm Hg or less) causing flattening of the anterior chamber, accelerated corneal damage, and cataract formation, a condition known as hypotony. The suture is usually removed four to six weeks after the initial surgery. Some newer shunts include a one-way valve or flow restrictor that limits flow through the device when the pressure in the eye becomes low. This valved approach is intended to
decrease the likelihood of post-operative hypotony and avoid the need for a second procedure to remove the ligating suture, but has the potential to limit the long-term effectiveness of the shunt.

The Ex-PRESS shunt is a stainless steel device designed to have more reproducible results with less dependency on surgical skills than other aqueous shunts. The initial subconjunctival implantation of the device had a high complication rate, including erosion of the conjunctiva. This led to a modification of the technique in which the shunt is implanted under a scleral flap.39

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

The FDA has approved the following aqueous shunt devices: Ahmed glaucoma valve implant (New world Medical Inc.), Molteno implant (Molteno Ophthalmic Ltd.), Baerveldt glaucoma implant (Abbott Medical Optics Inc.), Krupin-Denver vale implant (Hood Laboratories, Inc.), and Ex-PRESS Mini Glaucoma Shunt (Alcon). The Solx DeepLight Gold Micro-Shunt (OccuLogix) and the EyePass Glaucoma Shunt are still in Phase III of clinical trials and has not received FDA approval at this time.

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Embase, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words “shunt,” “drain,” “tube,” “device,” “implant,” “ahmed,” “baerveldt,” “krupin,” “molteno,” “optimed,” “schocket,” “express,” or “solx.” The results were crossed with the results from a search on “glaucoma.” The search was performed for the period from 1945 through May 2011. The bibliographies of systematic reviews and key articles were manually searched for additional references. References were also solicited from the manufacturers and local experts. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full. This review focuses on the randomized comparisons between aqueous shunts of different designs and between the shunts and surgical trabeculectomy, the current standard surgical treatment. There is an extensive observational literature documenting the feasibility and safety of lowering IOP with aqueous shunts. However, outcomes clearly vary by patient characteristics including the underlying cause
for glaucoma, the history and type of prior surgery, patient age, diabetes, and the presence of cataracts. Randomized trials are essential to evaluate the comparative effectiveness of aqueous shunts, particularly when there are many alternative therapies available.

The search identified 1214 potentially relevant studies (Figure 1). After elimination of duplicate and non-relevant references including reviews and non-randomized studies the search identified 28 articles describing 23 trials. The most important set of trials compare aqueous shunts to trabeculectomy, the current standard for patients with an indication for an aqueous shunt. Additional randomized trials either evaluated adjuncts to the standard shunt procedure or compared two different shunts.

**Figure 1: Selection of studies for inclusion in review**

| 1214 potentially relevant references screened | 513 duplicate citations excluded |
| 227 abstracts for assessment | 474 excluded: not randomized; reviews, abstracts only; other interventions |
| 56 studies for full text review | 171 studies excluded (Editorials, reviews, abstracts, no clinical outcomes) |
| 28 studies included in assessment: 23 randomized controlled trials (RCTs) | 28 studies excluded: not randomized, no aqueous shunt arm |

**Level of Evidence:** 1 through 5.

**TA Criterion 2** is met.
TA Criterion 3: The technology must improve net health outcomes.

The most important outcomes for patients include preservation of vision (visual acuity, peripheral vision) and quality of life. Secondary outcomes of importance include control of intraocular pressure and the number of medications used to control IOP. Studies of glaucoma use a wide variety of definitions for success and qualified success. Complete success is usually defined as an IOP ≤ 21 mm Hg and ≥ 6 mm Hg on no medications a year following surgery. A qualified success is the same degree of pressure control, but on medications. The World Glaucoma Association also suggests reporting results using two lower IOP cutoffs: 18 and 15 mm Hg. Unfortunately, almost every trial used a slightly different definition for success and failure making comparisons across trials problematic. The complications associated with aqueous shunts include early hypotony, capsule fibrosis leading to increased IOP and thus clinical failure, visual loss, tube or plate erosion, diplopia, strabismus, corneal decompensation, and infection.

There are a large number of case series evaluating devices that shunt aqueous humor from the anterior chamber of the eye to decrease IOP. They demonstrate the long term safety and efficacy of Molteno shunts for up to ten years and the Ahmed device up to seven years. There are also a number of retrospective and prospective comparative studies. Some evaluated variants in techniques for shunt implantation, some compared different shunt devices, and others compared aqueous shunts to trabeculectomy or other techniques for controlling IOP.

The randomized trials are described in more detail below.

**Technical approaches to aqueous shunt surgery**

Several early randomized trials evaluated adjuncts to surgery to see if they improved outcomes. Valimaki and colleagues randomized 22 patients undergoing implantation of a single plate Molteno shunt to treatment with oral prednisolone for ten weeks in order to control bleb fibrosis. Systemic corticosteroids did not improve outcomes and are no longer used. Two other randomized trials evaluated the benefits of adding mitomycin C to aqueous shunts, one with a Molteno shunt and one with an Ahmed shunt. Neither trial found any benefit to the addition of mitomycin C and it is rarely used today. The Latin American Glaucoma Society investigated the utility of performing a partial Tenon’s capsule resection when implanting an Ahmed shunt for neovascular glaucoma. Adding partial Tenson’s capsule resection did not improve outcomes or reduce complications. Finally, there was one small trial that randomized twenty eyes to an Ahmed shunt with or without pericardial membrane with a goal of reducing the post-operative hypertensive phase by expanding the surface area of the endplate. They found that expanding the endplate decreased the incidence of the hypertensive phase to 20% compared to 80% in the control group (p=0.007) with a trend
towards fewer patients requiring medications to maintain their target IOP.

Aqueous shunts versus surgical trabeculectomy

The observational data established that aqueous shunt devices could lower IOP with a reasonable complication rate and that they are well tolerated in the eye for up to ten years. However randomized trials are required to control for potential selection bias, measurement bias, and residual confounding in the observational studies. Trabeculectomy is the accepted alternative treatment to lower IOP in the population of patients refractory to medical and laser therapy. It is the ideal comparator for studies evaluating the efficacy of aqueous shunts.

Ahmed Glaucoma Valve versus Trabeculectomy Study

The first randomized trial to compare an aqueous shunt device (Ahmed Model S-2) to trabeculectomy was performed in Sri Lanka and Saudi Arabia. Some of the patients from the hospital in Sri Lanka were included in a second study that reported three year outcomes. In order to not count patients twice, this technology assessment will primarily focus on the second study because it is larger and has a longer follow-up. In brief, the first study found that participants in the Ahmed group had higher mean IOP and required more glaucoma medications, but otherwise had similar results and complications.

The second study was performed at one site in Sri Lanka with all surgeries performed by one surgeon. Patients with either primary open angle glaucoma or chronic angle closure glaucoma were eligible for randomization. Exclusion criteria included other forms of glaucoma, prior intraocular surgery, lack of light perception, age less than four years, and eyes requiring additional surgical interventions.

All patients were treated as randomized: 59 to the Ahmed group and 64 to the trabeculectomy group, although the reported numbers differ in the two publications describing the study results. The mean age of the participants was 52 years and 67% were female. The mean preoperative IOP was 25.9 mm Hg in the Ahmed group and 26.9 mm Hg in the trabeculectomy group. None of the baseline characteristics differed significantly between the two groups.

There were no significant differences between the two groups in visual fields or visual acuity at any of the seven time points assessed except for improved visual field scores for the Ahmed group at two years. This may have been a reflection of multiple statistical testing, but the trend favored the Ahmed group at every time point. For the first year, IOP was higher in the Ahmed group, but the curves came together from 18 months through three years. From two to two and a half years, the average IOP was 13.1 mm Hg in the
Ahmed group and 14.2 mm Hg in the trabeculectomy group. The cumulative probability of success during the two to two and a half year time frame was 73.2% in the Ahmed group and 72.1% in the trabeculectomy group.

Post-operative complications were similar in the two group (p>0.28 for each of the nine classes of complications). The most common complications were a flat anterior chamber (15% in both groups), hyphema (17% versus 11%), corneal drying (14% versus 8%), and wound leak (3% versus 9%). Implant or tube exposure occurred in 5% of patients in the Ahmed group. There were only two cases of persistent hypotony and both occurred in the trabeculectomy group. There were nine repeat surgeries in each group. The Ahmed group required repeat surgery for elevated IOP (n=4), repositioning of the tube (n=2), and intervention for an exposed tube (n=3). The trabeculectomy group required repeat surgery for elevated IOP (n=2), bleb revision (n=2), blebitis (n=1), and repair of a wound leak (n=4). Cataract surgery was performed for 5 patients in the Ahmed group and 11 patients in the trabeculectomy group (p not reported).

In summary, the study demonstrated that the Ahmed shunt and trabeculectomy had equivalent preservation of vision and control of IOP through two years with equivalent complication rates, though the types of complications varied. However, the methodological quality of the study was questionable. A computer-generated list of random numbers was used for group assignment, but apparently no allocation concealment was used so selection bias cannot be ruled out. In addition, neither the surgeon nor the patients were blinded, so measurement bias is possible. The use of mitomycin C in the trabeculectomy group was optional and 9% of patients were not treated with the anti-metabolite therapy that is now standard. Follow-up was incomplete as seven patients in the Ahmed group and six patients in the trabeculectomy group did not return for follow-up after discharge from the initial hospitalization, and less than 50% of each group had three years of follow-up. Larger, multicenter, multi-surgeon studies are needed to ensure the robustness of these results.

Tube versus Trabeculectomy Study

The Tube versus Trabeculectomy (TVT) Study is a large, multicenter study comparing the safety and efficacy of a non-valved aqueous shunt (Baerveldt 350 mm²) to surgical trabeculectomy with mitomycin C in patients with prior intraocular surgery. Patients were eligible for inclusion if they were between the ages of 18 and 85 years, had inadequately controlled glaucoma with IOP ≥ 18 mm Hg and had undergone prior surgery (trabeculectomy, cataract surgery, or both). Exclusion criteria included pregnancy, no light perception, active proliferative retinopathy, recurrent uveitis, severe blepharitis, or the need for combined surgery or additional ophthalmic surgical procedures. Randomization was stratified by clinical center and
prior surgical type. Allocation concealment was not described. The primary outcome measure was IOP. Important secondary outcomes were the rates of complications including bleb related infections and persistent post-operative diplopia. Failure was defined as any of the following four criteria: IOP > 21 mm Hg or not reduced by 20% on two consecutive follow-up visits; IOP ≤ 5 mm Hg on two consecutive follow-up visits; additional glaucoma surgery; or loss of light perception. The outcome of complete success was defined as a participant who did not fail and was not requiring supplemental medical therapy. Planned follow-up is five years.

Between October 1999 and April 2004, the 17 study centers randomized 212 participants (n=107 to the tube group; n=105 to the trabeculectomy group). All participants received their assigned treatment. There were no significant differences in age (mean 71 years), sex (53% female), race (45% White, 39% Black, 14% Hispanic), or diabetes (32%). There were also no differences in the ocular characteristics of the participants including the eye operated on (53% left), IOP (25.3 mm Hg), number of glaucoma medications (3.1), prior laser therapy (52%), underlying diagnosis (81% primary open-angle glaucoma), or type of prior surgery (44% prior cataract extraction, 56% prior trabeculectomy).

The one and three year results have been published and the five year results should be available within the next year. There were no significant differences in serious operative complications, though trends favored the tube group. Intraoperative complications tended to be less common in the tube group (7% versus 10%, p=0.59). Significant post-operative complications in the first year, defined as those requiring reoperation and/or a loss of at least two lines of visual acuity on a Snellen chart, also tended to be less common in the tube group (17% versus 27%, p=0.12). Post-operative complications were significantly less common in the tube group (34% versus 57%, p=0.001), but most of these were self-limited. Two individual complications were significantly less common in the tube group: corneal dysesthesia (1% versus 7%, p=0.034) and wound leaks (1% versus 11%, p=0.004). There was a trend toward more persistent diplopia in the tube group (5% versus 0%, p=0.06). A new or worsened motility disturbance of the eye (strabismus) was more common in the tube group (9.9% versus 0%, p=0.005). At one year there was no difference in IOP (12.4 mm Hg in tube group versus 12.7 in the trabeculectomy group, p=0.73), but the average number of glaucoma medications used was higher in the tube group (1.3 versus 0.5, p<0.001) and IOP was significantly higher in the tube group during the first three post-operative months. Complete success was less common in the tube group (34% versus 63%, p < 0.001). However, failures were also less common in the tube group (3.9% versus 13.5%, p=0.017). The reasons for failure were inadequate IOP control (4 in tube group, 10 in trabeculectomy group) and persistent hypotony (0 in tube group, 3 in trabeculectomy group).
At three years there was also no difference in IOP (13.0 mm Hg in tube group versus 13.3 in the trabeculectomy group, p=0.78) and the average number of glaucoma medications used was no longer significantly higher in the tube group (1.3 versus 1.0, p=0.30). Significant post-operative complications through three years also did not differ between the two groups (22% versus 27%, p=0.58). Complete success was less common in the tube group (28% versus 40%, p = 0.10). However, failures were also less common in the tube group (15.1% versus 30.7%, p=0.010). At three years, the reasons for failure were inadequate IOP control (7 in tube group, 10 in trabeculectomy group), persistent hypotony (2 in tube group, 8 in trabeculectomy group), reoperation for glaucoma (6 in tube group, 9 in trabeculectomy group), and loss of light perception (0 in tube group, 1 in trabeculectomy group). Although none of the subgroup differences were statistically significant, the trend favored the tube group in all subgroups.

The TVT study is the largest randomized trial to directly compare an aqueous shunt tube to surgical trabeculectomy. Follow-up was excellent with only 10% of visits missed during three years of follow-up. All patients received their allocated treatment and strict intention-to-treat was used for all analyses. Methodologically, it was not perfect because the participants and providers were not blinded, which may have biased the assignment of complications and the decision to reoperate. However, measurement bias in studies with objective outcomes tends to be less significant than in studies with subjective outcomes. In response to this criticism, the investigators published data demonstrating a trend in the opposite direction: the mean IOP at the time of reoperation was 21.5 mm Hg in the tube group and 27.9 mm Hg in the trabeculectomy group (p=0.12).

When comparing the results of the TVT study to other studies, it is important to keep in mind the population studied. All of the participants in the TVT study had undergone at least one prior ocular surgery, but patients with conditions predisposing them to surgical failure (neovascular glaucoma, iridocorneal endothelial syndrome) were excluded. Thus, patients were at higher risk for complications than surgically naïve patients, but at lower risk than many of the patients included in the early case series and comparative studies of aqueous shunts, which often included patients at high risk of failure following trabeculectomy.

Both operations continue to evolve. In the TVT study, trabeculectomy was performed using a limbus-based conjunctival flap. Recent trends suggest that trabeculectomy performed using a fornix based flap with diffuse rather than focal application of mitomycin C may be preferred. In addition, only one type of aqueous shunt was used: the Baerveldt 350. Many other devices are in use or in development. The results of the TVT study may not generalize to other aqueous shunts.

Through three years, participants randomized to the Baerveldt aqueous shunt group had fewer short-term
complications (34% versus 57%), fewer failures (15% versus 30%), but more diplopia (5% versus 0%) and more strabismus (9.9% versus 0%). The failure rate in the tube group was lower than that estimated by a recent meta-analysis\(^{41}\), but the patients randomized came from a lower risk group. Overall, the evidence from the TVT study suggests that the Baerveldt aqueous shunt is at least equivalent to trabeculectomy in this patient population.

**Ex-PRESS versus Trabeculectomy**

Several case series reported that the Ex-PRESS shunt, a newer stainless steel aqueous shunt, was safe and effective at lowering IOP\(^{44,45,49,50,53}\) except when performed using the older, subconjunctival technique.\(^{54}\) Additional comparative studies suggest that the lowering of IOP and the reduction in use of glaucoma medications achieved with the Ex-PRESS shunt were equivalent to trabeculectomy with fewer complications (hypotony, choroidal effusion, hyphema).\(^{57,58,64,67,87}\) The two randomized trials comparing the Ex-PRESS device to trabeculectomy are described below.\(^{88-90}\)

In this single center study by a single surgeon, 80 eyes from 78 patients were randomized to either the Ex-PRESS shunt or trabeculectomy.\(^{90}\) Patients were eligible for the study if they were ages 18 and older with open angle glaucoma that was inadequately controlled with medical therapy. Exclusion criteria included any other ocular disease and previous ocular surgery other than cataract extraction. Complete success was defined as a final IOP > 4 mm Hg and ≤ 18 mm Hg without medication. Overall success was defined by the same criteria with or without medication. Failure was an IOP > 18mm Hg or the need for additional glaucoma surgery. The more typical definition of failure (recurrent surgery, loss of 2 lines of Snellen visual acuity; or IOP out of range) was not reported for either group.

There were 40 eyes in each group. The Ex-PRESS group was significantly younger (62.3 years versus 68.9, \(p=0.03\)) and there was a trend towards more female participants in the Ex-PRESS group (52.5% versus 32.5%, \(p= 0.11\)). The mean preoperative IOP was 22.8 mm Hg in the Ex-PRESS group and 21.5 mm Hg in the trabeculectomy group (\(p=0.34\)). There were no significant differences in IOP at one year (approximately 12 mm Hg in the Ex-PRESS group and 13 mm Hg in the trabeculectomy group) or in the number of medications used (0.3 versus 0.6, \(p\) not reported except non significant). The proportion of patients achieving an IOP ≤ 18 mm Hg at one year was greater in the Ex-PRESS group (84.6% versus 60%, \(p=0.023\)). However, the success rate with or without medications did not differ between the two groups (97% versus 87%, \(p=0.20\)). Visual acuity declined in 13.5% of patients in the Ex-PRESS group who returned for the one year visit and in 15.8% of the trabeculectomy group (\(p\) not significant). There were 13 complications in the Ex-PRESS group (32.5%) and 11 complications in the trabeculectomy group (27.5%). Early hypotony
with a shallow anterior chamber was the most common complication. Complications requiring surgical intervention were identical (5% in each group).

The five-year results demonstrated continued good control of IOP in both groups (11.5 versus 11.3 m Hg, p NS). There were no significant differences between the groups in the percentage of patients with successful control of IOP (≤ 18 mm Hg) without medications (59% versus 46%, p=0.25) or with medications (97.4% versus 100%, p=0.49). The use of glaucoma medications was similar in the two groups at five years (0.85 versus 1.10, p not reported), but the number was increasing in the Ex-PRESS group, while decreasing in the trabeculectomy group. The Ex-PRESS group experienced fewer complications requiring needling (3 versus 9) and fewer cataract surgeries (5 versus 8), but no statistical analysis was reported. No data on repeat glaucoma surgeries or loss of vision were reported. There was also no reporting of any loss to follow-up or deaths.

There are many methodological issues with this trial. It was a relatively small trial, so estimates of event rates would have wide confidence intervals. In addition, the confidence intervals were not reported. As in most trials of aqueous shunts, there was no blinding of the investigator or the patients, which may have introduced some bias in decisions about medication use or other interventions. The significant baseline differences in age and sex call into question concealment of the randomization sequence generated by the computer. Only a handful of baseline characteristics were reported in Table 1 and follow-up was incompletely reported. Because a single surgeon performed all procedures in this study, the results may reflect his personal skill set and may not be generalizable beyond his practice. This study suggests that the Ex-PRESS device may be equivalent to trabeculectomy in the population studied for at least five years, but a larger multicenter study with better reporting is required in order to convincingly demonstrate that conclusion.

The second trial randomized 30 eyes from 15 patients to either the Ex-PRESS shunt or to trabeculectomy and followed for an average of 24 months. Patients over the age of 18 years with primary open angle glaucoma who required bilateral surgical treatment were eligible. Patients with other forms of glaucoma and active uveitis were excluded. One surgeon performed all of the procedures. Complete success was defined as IOP > 5 mm Hg and < 18 mm Hg without glaucoma medications. The average age of the participants was 65 years, 33% were female, 40% Black, 33% Indian, and 20% Caucasian. The baseline IOP was 28.1 mm Hg in the Ex-PRESS group and 31.1 mm Hg in the trabeculectomy group (p=0.48) with an average of 3.7 medications used by each group. Prior surgeries for glaucoma had been performed on 67% (10/15) of the eyes in each group. One patient died after 13 months of follow-up and two were lost to follow-up. IOP decreased to 15.7 mm Hg in the Ex-PRESS group and to 16.2 mm Hg in the trabeculectomy group (p NR).
Post-operative use of glaucoma medications were similar (0.3 versus 0.9, p NR). The complete success rate was greater in the Ex-PRESS group (~77% versus ~28% estimated from Kaplan-Meier plot at 24 months, p=0.002). Complications were less common in the Ex-PRESS group (20% versus 33%, p=0.05) as were complications requiring surgical intervention (0% versus 27%, p=0.001). The most common complication was hypotony (7% Ex-PRESS group, 33% trabeculectomy group), but all resolved spontaneously and without serious complication within one month of surgery.

In this small, single surgeon randomized trial, the Ex-PRESS shunt showed a reduction in IOP similar to that achieved with trabeculectomy, but with fewer complications and fewer patients requiring medications to maintain target IOP.

**Randomized trials comparing devices**

**Single-plate versus double-plate Molteno shunt**

One of the earliest randomized trials of aqueous shunt devices compared the single-plate Molteno shunt to the double-plate Molteno shunt to evaluate whether the greater surface area of the double endplant improved outcomes through a greater reduction in IOP. Between March 1988 and February 1990, the study randomized 132 patients who had a poor surgical prognosis with trabeculectomy. The average pre-operative IOP was 34.8 mm Hg. Allocation concealment was preserved until the patient was in the operating room. The primary outcome was IOP ≤ 21 mm Hg and ≥ 6 mm Hg with no additional glaucoma surgeries and no devastating complications. At one year, the success rate was 55% in the single-plate group and 86% in the double-plate group. At two years, the success rate was 46% in the single-plate group and 71% in the double-plate group. The difference in success rates between groups was statistically significant (p=0.0035). The average reduction in IOP was 25% for the single-plate group and 46% for the double-plate group (p=0.01). Visual acuity loss of at least two Snellen lines was also more common for the single-plate group (27% versus 20%, p NR). There was less post-operative hypotony in the single-plate group resulting in fewer flat anterior chambers (4% versus 10%, p=0.25) and fewer choroidal hemorrhages or effusions (0% versus 8%, p=0.043). The remaining complications were uncommon and there were no significant differences between the groups, but the difference favored the single-plate shunt.

In summary, the increased surface area of the double-shunt increased the success rate in patients with poor surgical prognosis. However, there was also an increase in early hypotony and other complications. Surgical techniques and medical therapy have evolved significantly in the twenty years since the study was performed, so the results may not apply today.
Double-plate Molteno versus Schocket Procedure

Another early randomized trial of aqueous shunt devices compared the double-plate Molteno shunt to the anterior chamber tube shunt to encircling band (ACTSEB) procedure developed by Schocket. This was a small randomized trial of 40 eyes with all procedures performed by a single surgeon between 1987 and 1989. Post-operative IOP at two years was similar in the two groups (14.4 mm Hg Molteno, 15.0 mm Hg ACTSEB, p=0.74), but the Molteno group required more medications (0.95 versus 0.43, p=0.024). Surgical interventions for complications or inadequate IOP control was high in both groups, but less common in the Molteno group (47% versus 57%, p NR). Visual acuity decreases of two lines or more on the Snellen chart were also less common in the Molteno group (32% versus 52%, p NR). These results may reflect the skills of a single surgeon and the number of eyes randomized was low, so the results may not be generalizable. Furthermore, the surgeries were performed more than 20 years ago: medical therapy, surgical techniques and the devices have changed significantly in the interim. In view of these limitations, this trial suggests that the Molteno shunt provides equivalent control of IOP to that of ACTSEB with at least a trend towards fewer complications and less loss of vision.

Baerveldt 350 versus Baerveldt 500

A larger study randomized 107 patients between 1991 and 1993 to the Baerveldt shunt with a 350 mm² endplate or a 500 mm² endplate. The goal was to evaluate whether the greater surface area led to greater reductions in IOP and higher long-term success rates similar to those reported in the single-plate versus double-plate Molteno trial. The average pre-operative IOP was 30.5 mm Hg. Success was defined as IOP ≤ 21 mm Hg and ≥ 6 mm Hg with or without additional medication. Failure was defined as IOP > 21 mm Hg on two consecutive visits, additional glaucoma surgery, loss of light perception or IOP < 6 mm Hg. At one year, the success rate was 98% in the 350 mm² group and 92% in the 500 mm² group. At two years, the success rate was 93% in the 350 mm² group and 75% in the 500 mm² group. Even though the median follow-up was only about 36 months, the investigators reported results out to five years. At five years, the success rate was 79% in the 350 mm² group and 66% in the 500 mm² group. The difference in success rate was statistically significant at all time points. The overall failure rate was 13% in the 350 mm² group and 30% in the 500 mm² group (p=0.05). The mean IOP at 2 years was 13.2 mm Hg in the 350 mm² group and 12.3 mm Hg in the 500 mm² group (p=0.41). Visual acuity loss of at least two Snellen lines was similar in the two groups (50% versus 54%, p 69). There were no significant differences in the complication rates between the two groups during any year of follow-up, though there were slightly more complications in the 500 mm² group.
This study found that the 350 mm$^2$ Baerveldt shunt had a greater success rate through five years of follow-up with a trend towards fewer complications and fewer failures. As with the prior studies, this study was performed almost 20 years ago, so the results may not generalize. However, it clearly demonstrated that there was no advantage to increasing the area of the endplate beyond 350 mm$^2$. Of note, the Molteno single plate device had an area of approximately 130 mm$^2$ and the double plate had an area of 270 mm$^2$.

The Ahmed Baerveldt Comparison Study

The recently published early results from the Ahmed Baerveldt Comparison (ABC) Study are important because they allow for direct evaluation of the comparative effectiveness of a valved aqueous shunt (Ahmed) and a non-valved aqueous shunt (Baerveldt 350) in the modern era of glaucoma management. The size of the end plate is another major difference between the two devices (184 mm$^2$ for the Ahmed Device and 350 mm$^2$ for the Baerveldt device), so the trial is not strictly a comparison between a valved and non-valved device. Prior observational studies have not conclusively defined the relative benefits and harms of the two devices. They are the two most commonly used aqueous shunts in the United States and glaucoma surgeons divided in their opinion about the preferred device.

Patients were eligible for inclusion in the ABC study if they were between the ages of 18 and 85 years, had inadequately controlled glaucoma with IOP $\geq$ 18 mm Hg and had an aqueous shunt as their planned surgery. Exclusion criteria included lack of light perception, prior aqueous shunt implantation, prior cyclodestructive procedure, uveitis associated with systemic illness like juvenile rheumatoid arthritis, the need for combined surgery or additional ophthalmic surgical procedures, or if they lived at a distance and would be unavailable for follow-up. Randomization was stratified by surgeon within clinical center and type of glaucoma. Allocation concealment was not described. The primary outcome measure was the success rate where success was defined as not failing. Failure was defined as any of the following five criteria: IOP $>$ 21 mm Hg or not reduced by 20% on two consecutive follow-up visits; IOP $\leq$ 5 mm Hg on two consecutive follow-up visits; additional glaucoma surgery; removal of the implant; or loss of light perception. The sample size for the study was based on the results from a comparative study in Singapore that reported a 67% success rate for the Ahmed shunt and an 83% success rate for the Baerveldt shunt. Important secondary outcomes were the rates of complications including hypotony, tube occlusion, macular edema, endophthalmitis, cataract, diplopia, corneal edema, and tube or shunt erosion. Planned follow-up is five years.

Between October 2006 and April 2008, 16 centers randomized 286 participants, but ten participants withdrew consent prior to surgery. The publications only report data on the remaining 276 participants.
Two participants in each of the groups received a device other than their assigned treatment. However, all analyses were performed according to randomization in adherence with strict intention-to-treat principles. There were no significant differences in age (mean 64 years), sex (49% female), race (49% White, 25% Black, 12% Hispanic, 12% Asian), or diabetes (41%). There was a trend towards older participants in the Ahmed group (65 versus 62 years, p=0.053) and significantly more patients with hypertension in the Ahmed group (63% versus 50%, p=0.039). There were also no differences in the ocular characteristics of the participants including the eye operated on (46% left), IOP (31.5 mm Hg), number of glaucoma medications (3.4), or the underlying diagnosis (40% primary open-angle glaucoma, 29% neovascular, 7% uveitic, 7% primary angle closure glaucoma, 18% other).

The one year results have been published. The three and five year results should be published in the future. There were no significant differences in intraoperative complications, though trends favored the Ahmed group (8% Ahmed versus 11% Baerveldt, p=0.31). Intraoperative complications were primarily of hyphemas (22/28 = 79%). Significant post-operative complications in the first year, defined as those requiring reoperation and/or a loss of at least two lines of visual acuity on a Snellen chart, also tended to be less common in the Ahmed group (20% versus 34%, p=0.12). Any early post-operative complication in the first three months was also less common in the Ahmed group (43% versus 58%, p=0.016), but most of these were self-limited. Two individual complications were significantly less common in the Ahmed group: corneal edema (12% versus 22%, p=0.035) and tube occlusion (2% versus 9%, p=0.015). Diplopia was similar in the two groups (6% versus 5%, p=0.80) as were tube erosions (1 in each group). At one year IOP was higher in the Ahmed group than the Baerveldt group (15.4 mm Hg versus 13.2, p=0.007), and the average number of glaucoma medications also tended to be higher in the Ahmed group (1.8 versus 1.5, p=0.071). The rate of failures at one year was similar using the primary outcome definition of failure as an IOP > 21 mm (16.4% versus 14%, p=0.017). The reasons for failure in the Ahmed group were inadequate IOP control (n=20) including 11 who required reoperation, loss of light perception (n=2), but no one with persistent hypotony. The reasons for failure in the Baerveldt group were inadequate IOP control (n=7), including 1 who required reoperation, loss of light perception (n=6), and persistent hypotony (n=2). The one year failure rate was significantly higher in the Ahmed group for the strictest definition of failure: IOP > 14 mm Hg (38.6% versus 24.0%, p=0.008).

Thus, through one year of follow-up, there is no clearly preferred aqueous shunt. Participants in the Baerveldt group had lower IOP, tended to need fewer medications, had fewer reoperations for inadequately controlled IOP, and tended to have fewer failures, but they also had significantly more serious complications and significantly more reoperations for complications. The results from continued follow-up through three to
the planned five years will better define the comparative effectiveness of these two devices.

Ahmed versus Molteno

There is one additional recent comparative trial, though it is relatively small and had poor follow-up. Between 2003 and 2005, the study randomized 92 patients from three centers in Iran to the Ahmed shunt or the Molteno single-plate shunt. Patients with poorly controlled IOP despite maximally tolerated medications or who had failed prior surgery were eligible for randomization. The exclusion criteria were age less than 40 years, no light perception, cataracts, prior drainage device implantation, prior cyclodestructive surgery, active ocular infection, or immunosuppression. The primary outcome measure was IOP. Failure was defined as IOP > 21 mm Hg on two consecutive visits, additional glaucoma surgery, shunt removal, loss of light perception, any major complication, or IOP < 6 mm Hg.

The study sample had a mean age of 61 year, 49% were female, and the pre-operative IOP was 32 mm Hg. There were no significant differences between the two groups at baseline. Follow-up was poor: only 75% of the sample were available for analysis at one year and only 62% were available at two years. At two years, the mean IOP was higher in the Ahmed group (17.0 versus 15.4, p<0.001), although the Ahmed group was using fewer glaucoma medications (1.0 versus 1.4, p NS). There were no differences in the changes in visual acuity between the two groups. The failure rates were similar through two years (16% Ahmed, 18% Molteno, p=0.65).

The relatively small sample size and the high loss-to-follow-up rate make it difficult to draw any firm conclusions from this study. In addition, the IOP levels achieved after surgery were significantly higher than those reported in other studies.

Summary

Multiple randomized trials have evaluated the efficacy of aqueous shunts for lowering IOP in patients who have failed maximal medical management. None of the trials directly compare the use of aqueous shunts to a sham procedure, so it is difficult to quantify the benefit of aqueous shunts compared to continued medical therapy. However, it would be unethical to not treat patients with inadequately controlled glaucoma when another effective treatment, trabeculectomy, is available. The TVT study convincingly demonstrated the equivalence of the Baerveldt 350 shunt to trabeculectomy in patients who had undergone prior surgery for cataracts or glaucoma. The data for other shunts is less robust, but the ABC trial suggests that the Ahmed shunt is roughly equivalent to the Baerveldt shunt and the two trials comparing the Ex-PRESS shunt to trabeculectomy also suggest equivalence.
TA Criterion 3 is met.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

Surgical trabeculectomy with either mitomycin C or 5-fluorouracil is the current established alternative to which other surgical procedures, like aqueous shunts, are usually compared. The risk of infection (endophthalmitis) following trabeculectomy with anti-fibrotic agents is approximately 1% per year\(^99\) and severe central vision loss is reported in up to 6% of surgically treated eyes.\(^100\) The Tube versus Trabeculectomy study directly addresses the question of whether aqueous tube shunts are as beneficial as trabeculectomy in a population of patients with glaucoma who had previously had ocular surgery. Through three years, the patients who were randomized to the aqueous tube shunt (Baerveldt 350) had fewer complications and fewer failures, while maintaining equivalent control of IOP. Patients in the shunt group had a higher incidence of diplopia (5%) and strabismus (10%). The study was adequately powered and had very little loss to follow-up, but neither the patients nor the investigators were blinded. The study will continue to report outcomes through five years, but the overall conclusions are unlikely to change. Observational studies through ten years of follow-up have not identified a significant increase in the risk for failure of aqueous shunts\(^47,52,55\), though the efficacy of both aqueous shunts and trabeculectomy continues to wane with time.

The TVT study investigated one of the most highly studied aqueous shunts, the Baerveldt 350 mm\(^2\) shunt. It is unclear whether other shunts are equally effective. However, the ABC study\(^96\) compared the Ahmed shunt to the Baerveldt 350 shunt and reported similar outcomes at one year. The Ahmed shunt had slightly fewer complications, but controlled IOP slightly less effectively. It will be important to watch the long-term results of this study. For now, the evidence supports rough equivalence of the two devices, though the balance of benefits and harms differ and may influence the choice of which device to use based on individual patient characteristics.

The data for the Ex-PRESS shunt are less robust. There are two single surgeon randomized trials that reported equivalent outcomes to trabeculectomy for up to five years with lower complication rates, but the quality of the reporting in the trials and some methodological concerns decrease confidence in the results.\(^88-90\) The total number of patients randomized in the two Ex-PRESS trials is less than half the number in the TVT trial. However, the low complication rate and in the context of the results from the TVT and ABC studies, the Ex-PRESS shunt appears to be equivalent to the existing standard. A randomized trial directly comparing the Ex-PRESS shunt to one of the more commonly used aqueous shunts, like the Baerveldt 350,
would better define the balance of benefits and harms with the Ex-PRESS shunt and help surgeons individualize treatment decisions for their patients.

**TA Criterion 4 is met.**

**TA Criterion 5:** The improvement must be attainable outside of the investigational setting.

Surgery to implant aqueous shunts is technically difficult and has an important learning curve. However, the procedure has been successfully performed in multiple centers by multiple surgeons in multi-center trials, like the TVT Study and the ABC study, and have been used in clinical practice for more than twenty years. The results demonstrated in those two randomized trials should be attainable outside the investigational setting. The one exception is the Ex-PRESS shunt. The two trials demonstrating equal or better outcomes compared to trabeculectomy both were single surgeon studies. The results in those trials may reflect the individual surgeon’s expertise and may not be attainable in other settings. However, the device was designed to be easier to implant than other aqueous shunts and was performed with similar complication rates as trabeculectomy by residents in a training program.

**TA Criterion 5 is met.**

**CONCLUSION**

Glaucoma is the second leading cause of blindness worldwide after cataracts. The pathophysiology of glaucoma remains incompletely understood, but lowering IOP has been demonstrated to slow the progressive loss of peripheral and central vision that are the hallmarks of the disease. Medical therapy and laser therapy for glaucoma have improved over the past thirty years, but a substantial portion of patients with glaucoma continue to progress in spite of maximally tolerated non-invasive therapy. Surgical trabeculectomy has been the established therapy for this group. However, trabeculectomy carries with it short term risks for worsening vision or blindness, long term risks for ocular infections, and a tendency to fail over time, particularly for patients with glaucoma associated with neovascular disease, uveitis, or iridocorneal endothelial disease.

Aqueous shunts were developed as an alternative to trabeculectomy. Initially, they were used for patients who had failed trabeculectomy and for patients with diseases known to have a poor outcome with
A large number of randomized trials evaluating aqueous shunts have been published, but many were small and focused on technical aspects of the surgery. Early trials established that larger endplates lead to better IOP control, but that very large endplates increase the risk for complications without additional clinical benefits. Two recent trials have had the largest impact on clinical practice and are the most important to focus on when deciding whether aqueous shunts meet CTAF’s TA criteria. The Tube versus Trabeculectomy study was a multicenter trial that randomized 212 patients who had undergone prior ocular surgery to either the Baerveldt 350 mm$^2$ shunt or surgical trabeculectomy. Through three years of follow-up the two procedures had similar rates of IOP control, vision loss, cataract progression, and reoperations. However, patients in the Baerveldt tube group had a lower rate of complications and a lower failure rate. This study demonstrated that net outcomes with the Baerveldt aqueous shunt were at least equivalent to those achieved by trabeculectomy in patients who had undergone prior surgery.

The ABC study randomized 286 patients to one of two popular aqueous shunts, the Ahmed and the Baerveldt 350 mm$^2$. Through one year of follow-up outcomes were similar in the two groups, though there was a trend towards fewer complications in the Ahmed group and better IOP control in the Baerveldt group. Although the overall outcomes are similar to date, the relative mix of benefits and harms may guide a surgeon in choosing one device over another. Additional results from this study extending the results from one year out to five years of follow-up will be forthcoming.

The data supporting the Ex-PRESS shunt are less robust. There are two small randomized trials comparing the device to trabeculectomy. Both were single surgeon studies and one involved only 30 eyes in 15 patients. The results suggest that the Ex-PRESS shunt has similar success rates as trabeculectomy, but lower rates of complications. This literature would benefit from a large trial comparing the Ex-PRESS shunt to one of the aqueous shunts that has been well studied, like the Baerveldt 350.

RECOMMENDATION

It is recommended that use of aqueous shunts for the treatment of glaucoma not adequately controlled by medication and / or laser therapy meets CTAF TA Criterion 1 through 5 for safety, effectiveness and improvement in health outcomes.

*The California Technology Assessment Forum panel voted to accept the recommendation as written.*
June 29, 2011

This is the first review of this technology by the California Technology Assessment Forum.

RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center has not conducted an assessment of aqueous shunts for the treatment of glaucoma.

Centers for Medicare and Medicaid Services (CMS)

CMS does not have National Coverage Determination for glaucoma drainage devices. Coverage decisions are left up to the discretion of local Medicare and Medicaid carriers.

The American Academy of Ophthalmology (AAO)

The American Academy of Ophthalmology provided an opinion on this technology. No AAO representative provided testimony at the meeting.

The American Glaucoma Society

The American Glaucoma Society did not provide an opinion on this technology. No representative provided testimony at the meeting.
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<th>Abbreviation</th>
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<tr>
<td>CTAF</td>
<td>California Technology Assessment Forum</td>
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<tr>
<td>IOP</td>
<td>Elevated intraocular pressure</td>
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<tr>
<td>DARE</td>
<td>Database of Abstracts of Reviews of Effects</td>
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<td>RCT</td>
<td>Randomized Controlled Trial</td>
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REFERENCES


