Modified Technique of Ex-PRESS® Device Combined with a Scleral Pocket *Versus* Ahmed Glaucoma Valve for Hereditary Transthyretin Amyloidosis Glaucoma: A Comparative Study

Técnica Modificada com o Dispositivo Ex-PRESS® Combinada com um Bolso Escleral *Versus* Válvula de Ahmed no Glaucoma por Amiloidose Hereditária por Transtirretina: Um Estudo Comparativo

Rita Vieira [1], Ana Marta [1,2], André Ferreira [1,3], Ana Figueiredo [1], Rita Falcão Reis [1], Isabel Sampaio [1], Maria João Menéres [1,2]

[1] Ophthalmology Department, Centro Hospitalar Universitário do Porto (CHUPorto), Porto, Portugal
[2] Instituto de Ciências Biomédicas Abel Salazar (ICBAS), Porto, Portugal
[3] Faculdade de Medicina da Universidade do Porto (FMUP), Porto, Portugal

Recebido/Received: 2022-10-13 | **Aceite/Accepted:** 2024-07-22 | **Published online/Publicado online:** 2025-11-26 | **Published/Publicado:** 2025-12-26

DOI: https://doi.org/10.48560/rspo.28251

ABSTRACT

INTRODUCTION: Our purpose was to analyze and compare the efficacy and safety of two surgical procedures: an Ex-PRESS® modified technique *versus* Ahmed glaucoma valve (AGV) in the management of hereditary transthyretin amyloidosis (hTTRA) secondary open-angle glaucoma in our tertiary center.

METHODS: Retrospective, comparative study. The main outcomes were intraocular pressure (IOP) evaluation (baseline, 1st day, 1st week, 1, 3, 6 and 12 months) and number of hypotensive drugs (baseline, 6th and 12th months). As secondary outcomes, surgical complications, need for additional glaucoma surgery, optic disc retinal nerve fiber layer thickness (OD-RNFL), endothelial cell count (ECC) and LogMAR BCVA were evaluated. Complete surgical success was defined as unmedicated IOP ≤ 18 mmHg. The minimum follow-up was 12 months.

RESULTS: A total of 156 eyes were included: 32 eyes (20.5%) were submitted to the ExPRESS® modified technique (group 1) and 124 eyes (79.5%) were submitted to an AGV implant (group 2).

Intra-ocular pressure decreased significantly from baseline (group 1: 27.4±4.4 mmHg; group 2: 28.4±6.9 mmHg, p=0.411) until month 12 (group 1: 12.0±3.5 mmHg; group 2: 13.1±6.8 mmHg, p=0.013) in both groups, being statistically lower in eyes from group 1 (p=0.012).

There was also a significant reduction in the number of antiglaucoma medications from baseline (group 1: 3.8±0.6; group 2: 3.9±0.7, p=0.211) and 12th month (group 1: 0.4±0.8; group 2: 1.8±1.5, p<0.001), with group 1 exhibiting a significantly lower number of hypotensive drugs (p<0.001).

LogMAR BCVA remained stable from baseline (group 1: 0.25±0.26; group 2: 0.26±0.30, p=0.458), to 12th month (0.25±0.24; group 2: 0.23±0.29, p=0.874).

Transient hypotony was higher in group 1 (17 eyes, 53.1% *versus* 8 eyes from group 2, 6.5%), X^2=37.06, p<0.001.

Four eyes from group 1 (12.5%) and 7 eyes from group 2 (5.6%) needed an additional glaucoma surgery (X^2 Fisher exact test p=0.104). Complete surgical success was higher in eyes from group 1 (22 eyes- 68.8%, *versus* 29 eyes- 23.4%), p<0.001.

CONCLUSION: Although both procedures showed significant IOP reduction, ExPRESS® modified technique seems to be more effective when a lower IOP is needed. Also, with this novel technique a lower number of antiglaucomatous medications was necessary. On the other hand, hypotony was more frequent with the ExPRESS® modified technique.

KEYWORDS: Amyloidosis, Hereditary, Transthyretin-Related/surgery; Glaucoma Drainage Implants; Glaucoma/ surgery; Intraocular Pressure.

RESUMO

INTRODUÇÃO: O nosso objetivo foi analisar e comparar os resultados cirúrgicos de dois procedimentos: a técnica modificada Ex-PRESS® *versus* válvula de Ahmed (AGV) no tratamento do glaucoma secundário à amiloidose hereditária por transtirretina (hATTR) num centro terciário.

MÉTODOS: Estudo retrospetivo e comparativo. Os objetivos principais foram a avaliação da pressão intraocular (PIO) (no início, 1º dia, 1ª semana, 1º, 3º, 6º e 12º meses) e o número de medicamentos hipotensores (no início, 6º e 12º meses). Os objetivos secundários incluírama ocorrência de complicações cirúrgicas, necessidade de nova cirurgia de glaucoma, espessura da camada de fibras nervosas da retina (RNFL), contagem de células endoteliais (CCE) e melhor acuidade visual corrigida (MAVC) em LogMAR. O sucesso cirúrgico completo foi definido como PIO ≤ 18 mmHg sem medicação e sem necessidade de nova cirurgia. O seguimento mínimo foi de 12 meses.

RESULTADOS: Foram incluídos 156 olhos: 32 olhos (20,5%) foram submetidos à técnica modificada Ex-PRESS® (grupo 1) e 124 olhos (79,5%) à AGV (grupo 2).

A PIO diminuiu significativamente do início (grupo 1: 27,4±4,4 mmHg; grupo 2: 28,4±6,9 mmHg, p=0,411) até o 12º mês (grupo 1: 12,0±3,5 mmHg; grupo 2: 13,1±6,8 mmHg, p=0,013) em ambos os grupos, sendo significativamente menor no grupo 1 (p=0,012).

O número de fármacos hipotensores também diminuiu significativamente do início (grupo 1: 3,8±0,6; grupo 2: 3,9±0,7, p=0,211) até o 12º mês (grupo 1: 0,4±0,8; grupo 2: 1,8±1,5, p<0,001), sendo significativamente menor no grupo 1 (p<0,001).

A MAVC (logMAR) permaneceu estável do início (grupo 1: 0,25±0,26; grupo 2: 0,26±0,30, p=0,458) até o 12º mês (grupo 1: 0,25±0,24; grupo 2: 0,23±0,29, p=0,874).

Como complicações cirúrgicas destaca-se a hipotonia transitória, que foi mais frequente no grupo 1 (17 olhos, 53,1%) do que no grupo 2 (8 olhos, 6,5%), X^2=37,06, p<0,001.

Quatro olhos no grupo 1 (12,5%) e 7 olhos no grupo 2 (5,6%) necessitaram de cirurgia adicional de glaucoma (Fisher X^2 p=0,104). O sucesso cirúrgico completo foi superior no grupo 1 (22 olhos, 68,8%, *versus* 29 olhos, 23,4%), p<0,001.

CONCLUSÃO: Ambos os procedimentos mostraram redução significativa da PIO, mas a técnica modificada Ex-PRESS® parece ser mais eficaz em atingir PIOs mais baixas e reduzir a necessidade de medicação tópica. No entanto, a hipotonia transitória foi mais frequente com a técnica modificada Ex-PRESS®. Outros resultados secundários não diferiram significativamente entre os grupos.

PALAVRAS-CHAVE: Amiloidose Hereditária Relacionada com Transtirretina/cirurgia; Glaucoma/cirurgia; Implantes de Drenagem para Glaucoma; Pressão Intraocular.

INTRODUCTION

Mutations in the gene encoding transthyretin (TTR), a protein mostly generated by the liver, cause the uncommon genetic condition known as familial amyloidotic polyneuropathy. This illness manifests as an adult-onset autosomal dominant disease with variable penetrance. The Val30Met mutation is the most prevalent TTR variation in Portugal and around the world. Along with Sweden and Japan, Portugal, the site of the disease's initial description, is one of the three main endemic clusters for hereditary transthyretin amyloidosis (hTTRA).[1,2] Nevertheless, since migration began, it has spread to every country. Once the disease is endemic in Portugal's northern coast, all those patients are

referred to the Centro Hospitalar Universitário do Porto (CHUPorto), a referral center for this condition, which explains our large experience with this type of glaucoma.

The disease is characterized by a multisystemic extracellular deposition of amyloid fibrils, leading to dysfunction of different organs and tissues, including the peripheral nerves, heart, kidney, ocular tissues, and others.[1–3] Regarding ocular involvement, patients with hTTRA may exhibit vitreous opacities, secondary open-angle glaucoma, abnormal conjunctival vessels, keratoconjunctivitis sicca, loss of corneal sensitivity, neurotrophic corneal ulcers, anterior capsule opacity of the lens, retinal vascular changes, pupillary light-near dissociation, irregular pupil, and optic neuropathy.[4-6]

There are currently a number of systemic therapies available for hTTRA, including liver transplantation, TTR stabilizing proteins (Vyndaqel,Tafamidis®), and gene therapy (RNA silencing—Patisiran, Onpattro® or Inotersen,Tegsedi®). All of them considerably increase the longevity and quality of life of these patients by reducing the systemic production of mutant TTR, but they do not affect ocular TTR production. The retinal pigment epithelium (RPE) and ciliary pigment epithelium produce TTR locally in the eye in addition to the liver, which explains why these patients have a greater prevalence of glaucoma.[4,7,8] This ongoing generation of mutant TTR may account for the difficulties in lowering intraocular pressure (IOP) and the faster progression of glaucoma in hTTRA patients, which frequently needs immediate surgical intervention.[7]

The hereditary transthyretin amyloidosis secondary open-angle glaucoma pathogenesis is still poorly understood. Some experts proposed mechanisms, including amyloid deposition in the intertrabecular space and Schlemm's canal or the deposition of perivascular amyloid in conjunctival and episcleral tissue, contributing to increased episcleral venous pressure and a rise in IOP.[9,10]

Aqueous humor drainage devices now play a significant role in treating certain kinds of refractory glaucoma, including hTTRA secondary glaucoma.[11] Marta *et al* showed excellent long-term results and low complication rates with Ahmed glaucoma valve (AGV) implantation in this type of glaucoma, in the biggest series published so far with hTTRA glaucoma patients.[12]

The Ex-PRESS® glaucoma filtration device consists of a modified trabeculectomy, once the communication to the anterior chamber (AC) is made with the device itself instead of a direct fistula. Ex-PRESS® implantation is technically easier compared with trabeculectomy, with fewer surgical steps and complications. Thereby, it was proven to be safe and effective in the surgical management of primary or secondary open-angle glaucoma.[13,14]

More recently, novel techniques of Ex-PRESS® implantation associated with deep sclerectomy have been described, with good rates of efficacy and safety.[15-17] Compared to Ex-PRESS® alone, this modification seems to be efficient, especially when very low postoperative IOP is needed.[17]

In recent years, we started to perform a modified technique of Ex-PRESS® implant in cases of severe open-angle glaucoma, particularly in hTTRA secondary glaucoma, once Ex-PRESS® alone did not seem to be effective in lowering IOP in these patients. The technique consists in the creation of a small scleral pocket, with 1.5x2 mm in the sclera, just behind the drainage hole of the Ex-PRESS® implant.

Hence, the purpose of this study was to analyze and compare the efficacy and safety of these two procedures, AGV and modified Ex-PRESS® technique, in patients with hTTRA secondary glaucoma, in our tertiary center.

MATERIAL AND METHODS

STUDY DESIGN

This is a retrospective, non-randomized, comparative analysis of patients with hTTRA secondary glaucoma who had AGV implantation or the Ex-PRESS® modified procedure at our Ophthalmology Department. This study was carried out in accordance with the principles of the Helsinki Declaration (1964) and its latest amendment (Brazil, 2013). The authors ensured that the patients' anonymity was carefully protected. All procedures were performed with informed consent, following the rules established by the institution. This study complies with the requirements of the institute's committee on human research ("Departamento de Ensino, Formação e Investigação") of Centro Hospitalar Universitário do Porto (CHUPorto).

INCLUSIONC RITERIA AND POPULATION DESCRIPTION

The inclusion criteria were: patients having a hTTRA diagnosis verified by laboratory tests with uncontrolled IOP under maximum topical medication or evidence of glaucoma progression noticed in functional or structural exams, namely visual fields or optic disc retinal nerve fiber layer thickness. Patients who had not at least one year of follow-up at the time of the documented review were excluded.

Baseline data included demographic characteristics [gender, age, systemic treatment (liver transplant, and Vyndaqel, Tafamidis® therapy)]; previous ocular surgeries (pars plana vitrectomy, phacoemulsification and glaucoma surgeries); type of surgery (1- ExPRESS® modified technique; 2- AGV); isolated or combined with cataract surgery.

SURGICAL TECHNIQUES

All surgical procedures were carried out by four experienced glaucoma surgeons (MJM, IS, RFR, AFig), under subtenonian anaesthesia with 2% lidocaine and sedation.

Modified ExPRESS® technique

The P50 ExPRESS® glaucoma filtration device (Alcon, Fort Worth, Texas, USA) was used. The surgery starts with the application of a corneal traction suture in order to expose the superior part of the globe. The technique comprises the following steps: limbal-based conjunctival incision

and dissection of conjunctiva and Tenon's capsule at 12 o'clock; cauterization of episcleral vessels; creation of the superficial scleral flap (4x4 mm, with 1/3 of depth); mitomycin 0.2 mg/mL application for 3 minutes; corneal paracentesis and viscoelastic introduction in the AC; scleral tunneling with a 27-gauge needle until AC; implant introduction at 12 o'clock; creation of small deeper flap (scleral pocket) in the posterior part of the scleral bed (just behind the drainage hole of the ExPRESS device), with 1.5x2 mm, and excision of this second flap; suture of the superficial scleral flap with 10-0 nylon sutures; closing the conjunctiva with a 10–0 nylon or 8–0 vicryl (at surgeon's discretion) and subconjunctival injection of cefazolin and dexamethasone. Figs. 1A-1D shows this surgical technique.

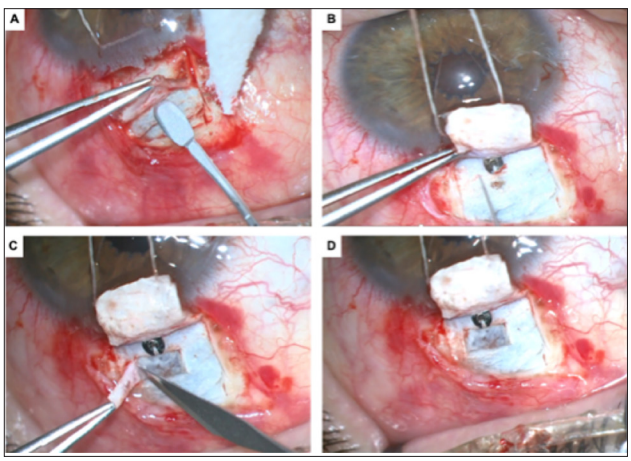

Figure 1. ExPRESS® modified technique. 1A: creation of the superficial scleral flap 4x4 mm; 1B: Insertion of implant into the AC after scleral tunelization with a 27G needle; 1C and 1D: creation of the deeper scleral flap 1.5x2 mm.

Ahmed Glaucoma Valve

The FP7 AGV model (New World Medical®, Rancho Cucamonga, CA, USA) was used. A limbal-based conjunctival incision is made to create a conjunctival flap between two rectus muscles in the supero-temporal quadrant, followed by: cauterization of episcleral vessels; priming of the AGV by introducing balanced salt solution in the tube; placement of the plate 8–10 mm posterior to the corneal limbus and sclera fixation with 8–0 nylon; scleral flap creation (two-thirds thickness); performing AC paracentesis and injection of viscoelastic substance; cutting the tube to a bevel-shaped angle of 30º; creating a route 1–3 mm posteriorly to the corneoscleral limbus, parallel to the iris with a 23-gauge needle; inserting the tube in AC or posterior chamber (PC); suture of the tube to the sclera with 8–0 nylon and covering with the scleral flap, that is sutured with 10–0 nylon; finally, the conjunctiva is closed with 10–0 nylon or 8–0 vicryl (by surgeon preference) and subconjunctival injection of cefazolin and dexamethasone are performed.

The tube was preferably placed in the PC if the patient was pseudophakic or had an indication of AGV implantation combined with cataract surgery by phacoemulsification. The tube was placed in the AC in phakic patients, if they had a good ECC and AC depth.

In the postoperative period, all patients were treated with topical antibiotics for 8 days, oral and topical steroids at weaning, and non-steroidal anti-inflammatory drops for 6 months. Antiglaucoma medication was added when IOP increased above 21 mmHg or when progression was verified.

OUTCOMES

The primary outcomes were intraocular pressure (IOP), which was measured at baseline, the first day, the first week, the first, third, sixth, and twelfth months; and the number of hypotensive eyedrops, which was measured at baseline, the sixth and twelfth months.

As secondary outcomes, the best corrected visual acuity (BCVA), endothelial cell count (ECC), and optical disc nerve fiber layer thickness (OD-NFL)]; early (within 1 month) and late (>1 month) surgical complications; and the need for further glaucoma surgery were assessed.

Snellen visual acuity was converted to logarithm of the minimum angle of resolution (logMAR) values to facilitate statistical analysis. Regarding surgical complications, hypotony was defined as having IOP <5 mmHg in 2 consecutive visits. Optic nerve RNFL thickness of 3.5 mm peripapillary ring was measured by optical coherence tomography with the Spectralis® (Heidelberg Engineering, Heidelberg, Germany); ECC count was measured with non-contact digital specular microscopy (EM-3000™ Tomey, Germany).

Surgical success was defined as IOP ≤ 18 mmHg (complete success if no medication was needed and qualified success if anti-glaucoma medication was needed). Surgical failure was defined as final IOP <5 mmHg or >21 mmHg with topical medication, need for other glaucoma surgery during follow-up or loss of light perception.

Statistical analysis was performed with SPSS version 27.0 for MacOS (SPSS Inc., IBM, Somers, NY). The normality of the variables was evaluated by the Kolmogorov-Smirnov test. The comparison between independent continuous variables was performed using the T Student test and Mann–Whitney test. The Fisher exact test was used for nominal scaled data. A p-value < 0.05 was considered statistically significant.

RESULTS

BASELINE DATA

A total of 156 eyes were included: 32 eyes (20.5%) were submitted to the ExPRESS® modified technique (group 1) and 124 eyes (79.5%) were submitted to an AGV implant (group 2). Mean age at surgery was 52.1±8.7 and 51.3±6.8 years old in group 1 and 2, respectively (p=0.629). Seventy-eight (50%) eyes were from female subjects and 78 (50%) from male subjects, without differences between groups (X^2 Fisher exact test, p=1.00). Systemic symptoms of hTTRA started at the average age of 30.4±9.3 years with no differences between groups (p=0.355).

A total of 137 eyes (87.8%) belonged to patients who had a previous liver transplant: 25 from group 1 (78.1%) and 112 from group 2 (90.3%), X^2 Fisher exact test p=0.072. Patients who did not undergo a liver transplant were under Tafamidis®. The mean age of liver transplant was 37.2±8.0 years, with no differences between groups (p=0.399).

Sixteen eyes (10.3%) had previous glaucoma surgeries: 2 eyes from group 1 (6.2%) and 14 eyes from group 2 (11.3%), X^2 Fisher exact test, p=0.402. Concerning previous glaucoma surgeries, trabeculectomy was performed in 10 eyes, cyclophotocoagulation in 1 eye, EX-PRESS® implant in 1 eye (from group 2), Ahmed valve implant in 2 eyes (from group 1), trabeculectomy and cyclophotocoagulation in 1 eye, and trabeculectomy, nonpenetrating deep sclerectomy, and cyclophotocoagulation in 1 eye.

Seventy-eight eyes (50%) underwent pars plana vitrectomy for vitreous amyloid, 15 eyes from group 1 (46.9%) and 63 from group 2 (53.1%), with no differences between groups (X^2 Fisher exact test, p=0.842).

One hundred and ten eyes were phakic (70.5%) and 46 eyes were pseudophakic (29.4%), with no differences between groups (X^2 Fisher exact test, p=0.663). Baseline data is presented in Table 1.

OUTCOMES

Post-operative follow-up was higher in eyes submitted to AGV implantation (3 years [1-7], *versus* 2 [1-3] years), p=0.033.

IOP decreased significantly in both groups from baseline (group 1: 27.4±4.4 mmHg; group 2: 28.4±6.9 mmHg, p=0.411) to 1st day (group 1: 5.00±2.9 mmHg; group 2: 8.6±6.6 mmHg, p=0.003), to 1st week (group 1: 6.9±4.1 mmHg; group 2: 10.0±6.9, p=0.016), to 1st month (group 1: 11.7±7.8 mmHg; group 2: 17.0±6.4 mmHg, p<0.001), to 3rd month (group 1: 11.6±6.1 mmHg; group 2: 16.4±3.9 mmHg, p<0.001), to 6th month (group 1: 13.1±6.8 mmHg; group 2: 15.4±4.5 mmHg, p=0.029), and 12th month (group 1:12.0±3.5 mmHg; group 2: 13.8±3.9 mmHg, p=0.013). This IOP reduction was statistically significant in both groups, but eyes submitted to ExPRESS® modified technique exhibited significantly lower IOP over time (p=0.012), until the last follow-up records. IOP values are represented in Fig. 2.

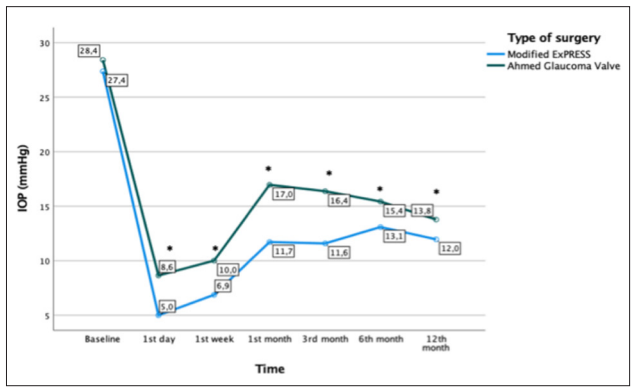

Figure 2. IOP evolution during follow-up. (*) means statistically significant values between groups.

There was also a significant reduction in the number of antiglaucoma medications from baseline (group 1: 3.7±0.6; group 2: 3.9±0.7, p=0.211) to 6th month (group 1: 0.6±1.0; group 2: 1.4±1.3, p<0.001) and 12th month (group 1: 0.4±0.8; group 2: 1.8±1.5, p<0.001). The final number of antiglaucoma medications was significantly lower in eyes submitted to the ExPRESS® modified technique (p<0.001). Fig. 3 shows the number of antiglaucoma medications in both groups.

Table 1. Baseline data.

Variable	Total	ExPRESS mod (group 1)	AGV (group 2)	*p*-value
Number of eyes	156	32 (20.5%)	124 (79.5%)	
Gender	78 female (50%) 78 male (50%)	16 female (50%) 16 male (50%)	62 female (50%) 62 male (50%)	p=1.00
Age at surgery	51.5±6.5 y.o.		51.3±6.8 y.o	p=0.629
Age systemic symptoms	30.4±9.3 y.o	26 (41.9)	30.9±10.5 y.o	p=0.355
Liver transplant	137 (87.8%)	8 (12.9)	112 (90.3%)	p=0.072
Age at liver transplant	37.2±8.0 y.o.	42 (67.7)	37.2±8.0 y.o.	p=0.399
Previous glaucoma surgeries	16 (10.3%)	2 (6.2%) 1 AGV 1 Trab	14 (11.3%) 9 Trab 1 TSCPC 1 Trab+TSCPC 1 ExPRESS 1 Trab+NPDS+TSCPC	p=0.402
Previous PPV	78 eyes (50%)	15 (46.9%)	63 (53.1%)	p=0.842
Previous cataract surgery	46 eyes (29.4%)	11 (34.4%)	35 (28.2%)	p=0.663
Follow-up		2.4±2.9 years	3.4±2.2 years	p=0.033

y.o. (years-old); Trab: trabeculectomy; TSCPC: transscleral cyclophotocoagulation; NPDS: non-penetrating deep sclerectomy

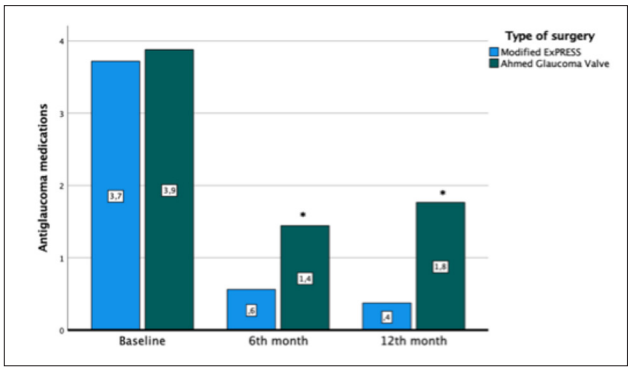

Figure 3. Number of antiglaucoma medications. Number within bars correspond to the mean value. (*) means statistically significant values between groups.

LogMAR BCVA remained stable from baseline (group 1: 0.25±0.26; group 2: 0.26±0.30, *p*=0.458), to 1st month (group 1:0.32±0.25; group 2: 0.28±0.30, *p*=0.674) and 12th month (0.25±0.24; group 2: 0.23±0.29, *p*=0.874), with no differences between groups. Fig. 4 shows logMAR BCVA values.

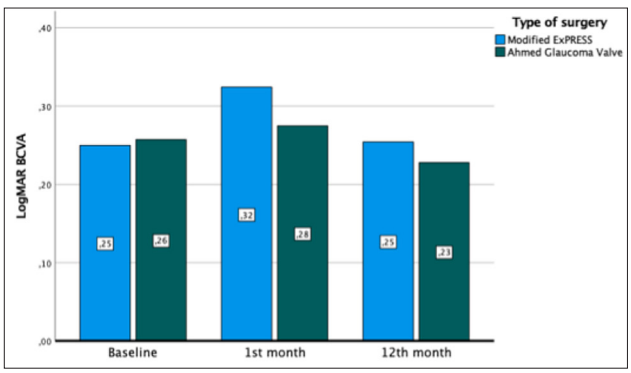

Figure 4. LogMAR BCVA during follow-up. Number within the bars correspond to the mean value.

Eighty-seven eyes (55.8%) were submitted to surgery combined with phacoemulsification, namely 2 eyes from group 1 (6.2%) and 85 eyes from group 2 (68.5%), X^2=40.02, *p*<0.001. The association of phacoemulsification to glaucoma surgery did not influence final IOP in both groups (13.0±4.0 with phaco; 12.3±3.1 without phaco, *p*=0.213).

Eyes submitted to ExPRESS® modified procedure showed more immediate post-surgical complications compared to eyes submitted to AGV implantation (13 eyes-40.6%; *versus* 19 eyes-15.3%, *p*=0.007).

Transient hypotony, defined as IOP <5 mmHg, was significantly higher in eyes submitted to the ExPRESS® modified technique (17 eyes, 53.1% *versus* 8 eyes from group 2, 6.5%), X^2=37.06, *p*<0.001. From group 1, eleven eyes with transient hypotony had a shallow anterior chamber (34.4%), and 6 eyes (18.8%) showed a transient choroidal detachment. From group 2, four eyes (3.2%) that exhibited hypotony presented AC shallowing and one eye (0.8%) presented a choroidal detachment.

Other early surgical complications were: In group 1, one eye presented with total hyphema (3.1%) and one eye with a vitreous hemorrhage (3.1%), which happened in a hypocoagulated patient. In the AGV group, three eyes exhibited hyphema (2.4%), three eyes had vitreous hemorrhage (2.4%), two eyes had a corneal ulcer (1.6%), tube obstruction occurred in two eyes (1.6%) and one eye had a choroidal haemorrhage (0.8%), which needed a pars plana vitrectomy.

Late complications were more frequent in group 2 (9 eyes-8.1%- *versus* 2 eyes-7.4% in group 1), but this difference was not statistically significant (*p*=0.688). Corneal decompensation was the most frequent complication (1 eye from group 1 (3.1%) - and 4 eyes from group 2-3.2%). In eyes with AGV, the tube was repositioned to the PC and one of them needed Descemet stripping endothelial keratoplasty after 1 year. Bleb encapsulation happened in one eye from group 1. This patient was submitted to a needling

Table 2. Early and late surgical complications.

	Total	ExPRESS modified	AGV	*p*-value
Early complications	32 eyes (20.5%)	13 eyes (40.6%)	19 eyes (15.3%)	*p*=0.007
Transient uncomplicated hypotony	25 eyes (16.0%)	17 eyes (53.1%)	8 eyes (6.5%)	*p*=0.007
Hypotony with shallow AC	15 eyes (60% of total hypotony)	11 eyes (64.7%)	4 eyes (50%)	*p*<0.001
Choroidal detachment	7 eyes (28% of total eyes with hypotony)	6 eyes (3.5%)	1 eye (12.5%)	*p*<0.001
Hyphema	4 eyes (2.6%)	1 eye (3.1%)	3 eyes (2.4%)	*p*<0.001
Vitreous hemorrhage	4 eyes (2.6%)	1 eye (3.1%)	3 eyes (2.4%)	
Corneal ulcer	2 eyes (1.3%)	---	2 eyes (1.6%)	
Tube obstruction	2 eyes (1.3%)	---	2 eyes (1.6%)	
Choroidal hemorrhage	1 eye (0.6%)	---	1 eye (0.9%)	
Late complications	10 eyes (7.2%)	2 eye (7.4%)	9 eyes (8.1%)	*p*=0.688
Corneal decompensation	5 eyes (3.6%)	1 eye (3.7%)	4 eyes (3.6%)	
Tube exposure	2 eyes	---	2 eyes (1.8%)	
IOL subluxation	2 eyes	---	2 eyes (1.8%)	
Bleb encapsulation	1 eye	1 eye (3.7%)	1 eye (0.9%)	

and bleb revision 3 months after surgery, with subsequent controlled IOP without medication until the last follow-up. The other long-term complications in group 2 were tube exposure (2 eyes, 1.6%), IOL subluxation (2 eyes, 1.6%) and bleb encapsulation in 1 eye (0.8%). All these complications were successfully managed surgically.

Table 2 shows all surgical complications.

There was a significant decrease in optic disc RNFL thickness of the 3.5 mm peripapillary ring (OD-RNFL) from baseline (88.6±21.2 and 82.1±18.7 μm in groups 1 and 2, respectively, p=0.121) and 12th month follow-up (73.6±23.0 and 63.0±23.3 μm in groups 1 and 2, respectively- p<0.001). At month 12, OD-RNFL was significantly lower in group 2 (p=0.026).

ECC decreased in both groups from baseline (group 1: 2217±669; group 2: 2533±543 cells/mm^2, p=0.102), and 12th month (group 1:1964±602; group 2: 2004±571 cells/mm^2- p<0.001), but this decrease was more significant in eyes submitted to AGV implant (p=0.011). Final ECC was similar among patients whose tube was inserted in the AC (2007±592 cells/mm^2) or the PC (1991±506 cells/mm^2), p=0.914.

Complete surgical success was achieved in 22 eyes from group 1 (68.8%) and 29 eyes from group 2 (23.4%), p<0.001; Qualified success in 6 eyes from group 1 (18.8%) and 88 eyes from group 2 (71.0%), p<0.001. Surgical failure, defined by the need for further glaucoma surgeries, happened in 4 eyes from group 1 (12.5%) and 7 eyes from group 2 (5.6%), (X^2 Fisher, p=0.104).

Among eyes that needed an additional glaucoma surgery, 4 eyes from group 1 were submitted to AGV implantation; the 7 eyes from group 2 were submitted to transscleral cyclophotocoagulation in a median of 11 months after surgery [9;12].

Overall, eyes that underwent a previous PPV did not show a difference in complete surgical success (X^2 Fisher exact test, p=0.733), qualified surgical success (X^2 Fisher exact test, p=1.00) or surgical failure (X^2 Fisher exact test, p=0.453).

DISCUSSION

Among all ophthalmic manifestations, glaucoma is the major cause of vision loss in patients with hTTRA disease.[1-3] Since life expectancy is increasing due to the development of effective systemic treatment options, there is a tendency to an increase of eye disease, including glaucoma, since eye TTR production does not stop. We also know, from our experience and from published literature that this type of glaucoma has an early onset, is rapidly progressive and the majority of patients will need surgical treatment promptly.[1-3]

There are limited studies in the literature regarding surgical procedures in hTTRA secondary glaucoma. The first published studies were related to trabeculectomy.[9,18] Based on their earlier short-term results, Kimura *et al*[9] revealed that trabeculectomy with mitomycin C (MMC) looked to be the most promising therapy. However, Kawaji *et al*[18] with their longer follow-up study found that trabeculectomy with MMC had limited success in hTTRA glaucoma. In addition, Latasiewicz *et al* reported the results of non-penetrating deep sclerectomy, revealing that NPDS was an effective treatment of FAP glaucoma.[19]

In hTTRA disease, the amyloid fibrils may also be deposited in the conjunctiva. These patients also have a higher incidence of dry eye disease and usually a long used of antiglaucoma medications. Hence, it is unclear if bleb-dependent procedures, such as trabeculectomy and NPDS, would be a good option for those patients. Thus, a few studies were carried out regarding glaucoma drainage devices.

From our glaucoma department experience, the results we had with trabeculectomy, before 2010, were uninspiring. Hence, from then, aqueous humor drainage devices, namely the Ahmed glaucoma valve implant, became the gold standard to treat these patients in our department. AGV was the election tube because we had a higher experience with this device in refractory glaucomas. Nevertheless, other tubes like the Baerveldt glaucoma implant may be equally effective, as suggested by Kakihara *et al*[20] in their case series of hTTRA secondary glaucoma with long-term follow-up. A recent work, published by our glaucoma department, showed good long-term results of AGV implantation in hTTRA secondary glaucoma. To date, that is the largest series with the longest follow-up in the literature reporting a success rate of a surgical technique in this type of glaucoma. Marta *et al*[12] showed a cumulative probability of success (with or without medications) of 0.98 at 1 year and 0.72 at 6 years of follow-up, without a significant rate of surgical complications.

Since the last 3 years, a modified technique using the P50 ExPRESS® device was developed and introduced in our practice. Although this is a bleb-dependent procedure, such as trabeculectomy and NPDS, this modified technique with a posterior scleral pocket seems to be much more effective than ExPRESS® alone, which was tried as an option in the past, but with unsatisfactory results.

Bissig A. and Sylvain R *et al*,[21] from the Mermoud group, in 2010, first described a novel technique of a modified non-penetrating deep sclerectomy (NPDS) associated with Ex-PRESS X-200 implant for open-angle glaucoma. Their technique consisted of the creation of a limbus-based superficial scleral flap of 5x5 mm and 300 μm thickness, followed by a deeper flap in the posterior part of the scleral bed, with 3x4.5 mm, without opening Schlemm's canal, and excision of the second flap. Then, a paracentesis with a 21 G needle anterior to the deep sclerectomy and the insertion of the Ex-PRESS X-200 implant through the 21 G paracentesis into the anterior chamber were performed. After 18 months of follow-up, a cumulative success of 69% and 85%, with or without medication, respectively, was found, whereas surgical failure occurred in just one patient. Antiglaucoma medications also suffered a reduction of 79%. Regarding surgical complications, they reported 15% of transient hypotony and 8% of shallow AC, which are lower values compared to our results. On the other hand, 58% required subconjunctival MMC injections to treat bleb encapsulation, which only happened in 1 eye in our study. This could be explained by the shorter period of MMC application in their technique (30-60 seconds *versus* 3 minutes in our study).

In a posterior work from Mermaud group, Gindroz F and Sylvain R *et al*[15] reported their results with the same technique of a modified NPDS associated with the use of ExPRESS model LR-50 (Optonol Ltd., Neve Ilan, Israel) and phacoemulsification. They reported low complication rates (4 eyes with hypotony with shallow AC and choroidal effusion), a cumulative complete success of 45.6% and a qualified success rate of 85.2% at 48 months. This technique is similar to ours, despite that we perform a smaller deep flap, with 1.5x2 mm, and the device used is the P50 model instead of the X-200, meaning that ours has a smaller inner lumen (50 μm *versus* 200 μm). Although our reported rates of hypotony were higher, in theory, the creation of a smaller deep flap and the use of a device with a smaller inner lumen would prevent hypotony. Nevertheless, our hypotony cases were addressed cautiously, using cycloplegic eyedrops and AC viscoelastic injection under the slit lamp, and solved without affecting final visual acuity or IOP results.

Kozobolis V *et al*[16] described their results with a different technique of a modified NPDS associated with the ExPRESS P-50 implant. Their technique comprises a 4x4 deeper flap fashioned to create a trabeculodescemetic membrane and excision of this deeper flap, followed by ExPRESS mini-shunt insertion into the AC through the trabeculodescemet membrane. They compared this technique with trabeculectomy in severe cases of primary open-angle glaucoma, reporting a higher decrease in IOP, a lower number of antiglaucoma medications and higher absolute success at 12 months with de modified NPDS associated with ExPRESS. Although the surgical technique itself is very different from ours, they do not report surgical complications, which would be important to evaluate surgical safety.

In the same way, Marietta Fraczkiewicz-Skok *et al*[17] reported their outcomes using a similar technique to Kozobolis.15 In their prospective, randomized control study with a 24-month follow-up, they reported a higher reduction in IOP and a lower number of hypotensive eyedrops, compared to the ExPRESS implant alone.

Few studies are comparing ExPRESS and AGV implants. Zhang M *et al*[22] reported a better IOP control and fewer antiglaucoma medications with ExPRESS in their sample of Asian patients, with no differences regarding surgical complications. Waisbourd M *et al*,[23] also compared Ex-PRESS implant and AGV in severe cases of open-angle glaucoma. They reported comparable failure rates, but more postoperative complications in the AGV group. AGV is a valved device that provides a complex mechanism to control aqueous humor outflow, decreasing the risk of postoperative hypotony-related complications.[24] In fact, in our series hypotony was significantly higher with the modified ExPRESS technique, which can be explained by the fact that this is a non-valved device. It is important to notice that transient hypotony without AC shallowing is expected in the immediate post-op of a filtering surgery such as our technique, so any additional treatment was carried out beyond rest. Eyes that showed a shallow AC with or without choroidal detachment were managed using cycloplegic drops, and viscoelastic injection at the slit-lamp was performed as needed.

Corneal decompensation was our most common late complication, happening in 5 eyes (3.6%), which is lower than some reports in the literature, estimated to be 9%–27% on long-term follow-up.[24-26] Four of these were eyes submitted to AGV with the tube placed in the AC, which were posteriorly submitted to cataract surgery with tube replacement to the PC, and only 1 eye had to be submitted to an endothelial keratoplasty. The other eye from the modified ExPRESS technique that exhibited an endothelial decompensation had previous Fuchs endothelial dystrophy. Once a sectorial corneal oedema remains, the patient is waiting for a posterior lamellar keratoplasty. We hypothesize that AGV may produce a higher rate of endothelial cell loss due to the length and width of the tube, compared to the ExPRESS device.

One limitation of this study is the difference in follow-up between the two groups, which explains why we cannot compare results between groups over a longer follow-up time. This can be explained by the fact that the modified ExPRESS technique was introduced in our practice in the last 3 years, while AGV has been performed since 2010 as the gold-standard treatment in hTTRA glaucoma. This can also explain the difference in sample size. Although a good sample size is presented, in the future, we would have more eyes submitted to this novel technique and a longer follow-up that can strengthen our results.

This is the first research that has successfully compared two different glaucoma device implants in a large sample of hTTRA secondary glaucoma. We believe that this can help guide the treatment in centers where this diagnosis is less common.

In conclusion, although both procedures demonstrated significant IOP reduction, ExPRESS® modified technique seems to be more effective when a lower IOP is needed. Also, with this novel technique, a lower number of antiglaucoma medications was necessary. Hence, the absolute surgical success was superior with the ExPRESS®. Although hypotony was more frequent with the ExPRESS modified technique, it had no injury regarding final visual acuity and IOP. Late surgical complications were uncommon in both procedures, highlighting the safety of both procedures.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

BC: Responsible for gathering the data, presenting the results, and creating the manuscript.

PG: Responsible for the statistical analysis and the manuscript revision.

NRA: Contributed for the data collection.

AM: Supervised this project and contributed with her expertise to its conclusion.

All the authors read and approved the final manuscript. All the authors had full access to all the data and take full responsibility for the integrity of the data and the accuracy of the data analysis; all were responsible for conceiving this research.

BC: Responsável pela recolha dos dados, apresentação dos resultados e elaboração do manuscrito.

PG: Responsável pela análise estatística e pela revisão do manuscrito.

NRA: Contribuiu para a recolha de dados.

AM: Orientou este projeto e contribuiu com a sua experiência para a sua conclusão.

Todos os autores leram e aprovaram o manuscrito final. Todos os autores tiveram acesso total a todos os dados e assumem total responsabilidade pela integridade dos dados e pela exatidão da análise dos mesmos; todos foram responsáveis pela conceção desta investigação.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2024 e da Associação Médica Mundial.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

ETHICAL DISCLOSURES

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2024).

Provenance and Peer Review: Not commissioned; externally peer-reviewed.

REFERENCES

1. Beirão M, Matos E, Reis R, Beirão I, Costa PP, Torres P. Spatial visual contrast sensitivity in liver transplanted Portuguese familial amyloidotic polyneuropathy (ATTR V30M) patients. Amyloid.2012;19:152–5.
2. Planté-Bordeneuve V, Kerschen P. Transthyretin familial amyloid polyneuropathy. Handb Clin Neurol. 2013;115:643 58.
3. Beirão JM, Moreira LM, Oliveira JC, Menéres MJ, Pessoa BB, Matos ME, et al. Aqueous humor erythropoietin levels in open angle glaucoma patients with and without TTR V30M familial amyloid polyneuropathy. Mol Vis. 2014;20:970–6.
4. Martins AC, Rosa AM, Costa E, Tavares C, Quadrado MJ, Murta JN. Ocular manifestations and therapeutic options in patients with familial amyloid polyneuropathy: a systematic review. Biomed Res Int. 2015;2015:282405. doi: 10.1155/2015/282405.
5. Beirão M, Matos E, Beirão I, Pinho-Costa P, Torres P. No ocular involvement in familial amyloidotic polyneuropathy ATTR V30M domino liver recipientes. Transpl Int. 2012;25:646–51.
6. Conceição I, Carvalho M. Clinical variability in type I familial amyloid polyneuropathy (Val30Met): comparison between late- and early-onset cases in Portugal. Muscle Nerve. 2007;35:116–8.
7. Kawaji T, Ando Y, Nakamura M, Yamamoto K, Ando E, Takano A, et al. Transthyretin synthesis in rabbit ciliary pigment epithelium. Exp Eye Res. 2005;81:306–12. doi: 10.1016/j.exer.2005.02.003.
8. Beirão JM, Malheiro J, Lemos C, Beirão I, Costa P, Torres P. Ophthalmological manifestations in hereditary transthyretin (ATTR V30M) carriers: a review of 513 cases. Amyloid. 2015;22:117-22. doi: 10.3109/13506129.2015.1015678.
9. Kimura A, Ando E, Fukushima M, Koga T, Hirata A, Arimura K, et al. Secondary glaucoma in patients with familial amyloidotic polyneuropathy. Arch Ophthalmol. 2003;121:351–6.
10. Beirão NM, Matos ME, Meneres MJ, Beirão IM, Costa PP, Torres PA. Vitreous surgery impact in glaucoma development in liver transplanted familial amyloidosis ATTR V30M Portuguese patients. Amyloid .2012;19:146–51.
11. Lee CK, Ma KT, Hong YJ, Kim CY. Long-term clinical outcomes of Ahmed valve implantation in patients with refractory glaucoma. PLoS One. 2017;12:e0187533.
12. Marta A, Vieira R, Figueiredo A, Reis R, Sampaio I, Beirão JM, Menéres MJ. Ahmed valve for secondary glaucoma in patients with hereditary transthyretin amyloidosis. Eye. 2022;36:111-8. doi: 10.1038/s41433-021-01443-y.
13. Chan JE, Netland PA. EX-PRESS Glaucoma Filtration Device: efficacy, safety, and predictability. Med Devices. 2015;8:381-8. doi: 10.2147/MDER.S63350..
14. Shaarawy T, Goldberg I, Fechtner R. EX-PRESS glaucoma filtration device: Review of clinical experience and comparison with trabeculectomy. Surv Ophthalmol. 2015;60:327-45. doi: 10.1016/j.survophthal.2015.01.001Erratum in: Surv Ophthalmol. 2015;60:508.
15. Gindroz F, Roy S, Mermoud A, Schnyder CC. Combined Ex-PRESS LR-50/IOL implantation in modified deep sclerectomy plus phacoemulsification for glaucoma associated with cataract. Eur J Ophthalmol. 2011;21:12-9. doi: 10.5301/ejo.2010.541.
16. Kozobolis V, Panos GD, Konstantinidis A, Teus M, Labiris G. Modified deep sclerectomy combined with Ex-PRESS filtration device versus trabeculectomy for primary open angle glaucoma. Int J Ophthalmol. 2017;10:728-32. doi: 10.18240/ijo.2017.05.11.
17. Frączkiewicz-Skok M, Konopińska J, Mariak Z, Rękas M. Comparison of ExPress Implantation and Partial Deep Sclerectomy Combined with ExPress Implantation and Simultaneous Phacoemulsification. J Ophthalmol. 2019;2019:7424376. doi: 10.1155/2019/7424376..
18. Kawaji T, Inoue T, Hara R, Eiki D, Ando Y, Tanihara H. Longterm outcomes and complications of trabeculectomy for secondary glaucoma in patients with familial amyloidotic

polyneuropathy PLoS One. 2014;9:e96324.
19. Latasiewicz M, Millá E, Giralt J, Molina JJ, Matas J. Nonpenetrating deep sclerectomy as an effective treatment of glaucoma related to familial amyloid polyneuropathy. J Glaucoma. 2015;24:e80-3. doi: 10.1097/IJG.0000000000000126. PMID: 25264993.
20. Kakihara S, Hirano T, Imai A, Miyahara T, Murata T. Baerveldt glaucoma drainage implant surgery for secondary glaucoma in patients with transthyretin-related familial amyloid polyneuropathy.Jpn J Ophthalmol. 2020;64:533–8.
21. Bissig A, Feusier M, Mermoud A, Roy S. Deep sclerectomy with the Ex-PRESS X-200 implant for the surgical treatment of glaucoma. Int Ophthalmol. 2010;30:661-8. doi: 10.1007/s10792-010-9382-z.
22. Zhang M, Li B, Sun Y. EX-PRESS and ahmed glaucoma valve in treatment of refractory glaucoma. Acta Ophthalmol. 2016;94:e382-3. doi: 10.1111/aos.12898.
23. Waisbourd M, Fischer N, Shalev H, Spierer O, Ben Artsi E, Rachmiel R, Shemesh G, Kurtz S. Trabeculectomy with Ex-PRESS implant versus Ahmed glaucoma valve implantation-a comparative study. Int J Ophthalmol. 2016 Oct 18;9(10):1415-1420. doi: 10.18240/ijo.2016.10.08. PMID: 27803857; PMCID: PMC5075655.
24. Riva I, Roberti G, Oddone F, Konstas AG, Quaranta L. Ahmed glaucoma valve implant: surgical technique and complications. Clin Ophthalmol. 2017;11:357-67. doi: 10.2147/OPTH.S104220.
25. Wilson MR, Mendis U, Paliwal A, Haynatzka V. Long-term follow-up of primary glaucoma surgery with Ahmed glaucomavalve implant versus trabeculectomy. Am J Ophthalmol. 2003;136: 464–70.
26. Kook MS, Yoon J, Kim J, Lee MS. Clinical results of Ahmed glaucoma valve implantation in refractory glaucoma with adjunctive mitomycin C. Ophthalmic Surg Lasers. 2000;31: 100–6.

Corresponding Author/
Autor Correspondente:

Rita Vieira
Ophthalmology Department, Centro Hospitalar Universitário do Porto;
Largo do Prof. Abel Salazar,
4099-001 Porto, Portugal
E-mail: anarita.vieira1693@gmail.com

ORCID: 0000-0002-5309-6347