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REVIEW

Long-term outcomes and risk factors for failure with the EX-press glaucoma drainage device

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Abstract

Purpose **To report on the long-term outcomes and risk factors for failure with the EX-PRESS shunt implanted under a scleral flap.**

Settings **Eye Department, University of Ancona, Ancona, Italy and the Oxford Eye Center, University of Witwatersrand, Johannesburg, South Africa.**

Methods **The medical records of glaucoma patients who underwent consecutive EX-PRESS implantations under a scleral flap between 2000 and 2009 were reviewed. The operations were performed by two experienced surgeons using an identical surgical technique. The potential risk factors for failure that were analysed included age, sex, race, glaucoma type, previous antiglaucoma medications, previous glaucoma surgeries, diabetes, and smoking. Complete success was defined as postoperative intraocular pressure (IOP) 5 mm Hg > IOP < 18 mm Hg without antiglaucoma medications. Qualified success was defined as 5 mm Hg > IOP < 18 mm Hg with or without antiglaucoma medications.**

Results **Two hundred and forty-eight eyes of 211 consecutive patients were included. The mean IOP was reduced from 27.63 ± 8.26 mm Hg preoperatively ($n = 248$) to 13.95 ± 2.70 mm Hg at 5 years ($n = 95$). The mean follow-up was 3.46 ± 1.76 years. Complete and qualified success rates decreased gradually from 83% and 85% at 1 year to 57% and 63% at 5 years follow-up, respectively. The risk factors for failure were diabetes, non-Caucasian race, and previous glaucoma surgery. Complete success rates of diabetic patients and non-Caucasian patients decreased from 63% and 75% at 1 year to 42% and 40% at 5 years follow-up, respectively.**

Conclusions **EX-PRESS success rates decrease over time but compare favourably with trabeculectomy literature data. The main identifiable risk factors for failure are diabetes, non-Caucasian race, and previous glaucoma surgery.**

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Keywords: glaucoma; risk factors; EX-PRESS; success rate

Introduction

During the past decade, the EX-PRESS glaucoma filtration device (Alcon Laboratories, Fort Worth, TX, USA) has gained increasing recognition as an alternative to trabeculectomy.[1–25] Although the standard trabeculectomy is still the most commonly used glaucoma operation worldwide, the EX-PRESS exhibits similar outcomes with fewer early postoperative complications.[1–25] The initial results following EX-PRESS implantations performed under conjunctival flaps during the late 1990s were disappointing because of early postoperative hypotony and late device erosions/extrusions. The switch to implanting the device under the scleral flap has yielded encouraging results that compare favourably with trabeculectomy.[1–25] As Dahan and Carmichael[1] published the first report on EX-PRESS implantation under a scleral flap in 2005, numerous publications followed and confirmed the safety and efficacy of the device.[1–25] Furthermore, retrospective non-randomized and prospective randomized studies compared it favourably with trabeculectomy.[4,8,9,12,19,20,23–25] The majority of these reports are short- to medium-term studies with relatively small cohorts of patients. To date, there are no long-term studies on larger groups of patients that include statistical analysis on the risk factors for failure with the

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EX-PRESS. Our study reports on the EX-PRESS long-term outcomes in 248 eyes of 211 patients operated between September 2000 and September 2009 at two different locations using an identical surgical technique. We also conducted statistical analysis to identify a number of risk factors for failure that include age, sex, race, glaucoma type, preoperative use of antiglaucoma drugs, previous glaucoma surgery, diabetes, and smoking.

Patients and methods

Study design and surgical technique

The files of consecutive patients operated for uncontrolled glaucoma with the EX-PRESS under a scleral flap between September 2000 and September 2009 at the Oxford Eye Center, University of Witwatersrand in Johannesburg and at the Eye Clinic of the Polytechnic University of Marche-Ancona were reviewed. The protocol for this study was approved by the institutional review boards of both universities. The operations were performed by two experienced glaucoma surgeons who operated together on numerous occasions and agreed on an identical surgical technique, described in detail elsewhere.[1,5,24] Briefly, a fornix-based conjunctival flap with one radial relaxing incision was formed in an upper quadrant. A $5 \times 5\,mm^2$ limbal-based, 50% depth, scleral flap was raised into clear cornea. Mitomycin C (MMC) 0.05% solution was applied, for 1 min, onto the scleral bed only in the portion underlying the scleral flap. The conjunctival flap was not treated with MMC. The EX-PRESS implant was inserted into the anterior chamber under the scleral flap at the limbus. The scleral flap was securely sutured back with at least four 10/0 nylon sutures. The operations were always performed with an anterior chamber maintainer (ACM) connected to a bottle of balanced salt solution that was inserted in the anterior chamber (A/C) at the limbus in the lower temporal quadrant. The ACM allows intraoperative intraocular pressure (IOP) control and facilitates sutures adjustment of the scleral flap at the end of the procedure.

Preoperative data included patient age, sex, race, glaucoma type, previous surgery, glaucoma medications, IOP, cup disk ratio, and visual acuity. Postoperative data included IOP, visual acuity, complications, need for reinterventions, cup disk ratio, and need for antiglaucoma medications. Complete success was determined as $5\,mm\,Hg > IOP < 18\,mm\,Hg$ without antiglaucoma medications, without requiring further surgery or total loss of vision. Qualified success was determined by the same criteria with or without antiglaucoma medications. The patients were examined and followed up on day 1, day 7, month 1, month 3, month 6, and thereafter 6 monthly.

Statistical analysis

Survival Cox models analyses were carried out to identify risk factors associated with complete and qualified success. First, a bivariate analysis was performed to identify the risk factors for failure. A further multivariate analysis was performed, including all the variables identified as risk factors with a 0.1 *P*-value in the bivariate analysis. The preselected value for statistical significance was $P < 0.05$.

To take in account the correlation between an individual patient's eyes, a robust estimate of the variance was calculated using a Jackknife estimator, as recommended by Therneau.[26] The following potential risk factors for failure were analyzed: age, sex, race, glaucoma type, duration of antiglaucoma drugs preoperative use, previous glaucoma operations, diabetes, and smoking.

Bivariate analysis was performed for each analysis (the two survival analyses and the mixed-effect model). Multivariate analysis included all variables identified as risk factors with a 0.1 *P*-value in the bivariate analysis. The preselected value for statistical significance was $P < 0.05$. The R software was used for the statistical analysis.[27] The survival analysis was performed with the survival package.[26]

Results

Two hundred and forty-eight eyes of 211 patients with uncontrolled glaucoma underwent EX-PRESS implantation (with or without cataract extraction) between September 2000 and September 2009. Mean follow-up was 3.46 ± 1.76 years (range 0.5 to 7 years, median 3 years). The patients' demographic data, glaucoma types, and surgery types are summarized in Table 1. The great majority of the patients were Caucasian (82%) and the minority of the patients (18%) was from non-Caucasian races that included African Blacks, Indians, and patients of mixed African and Caucasian ancestry. For statistical analysis purposes, the non-Caucasian races were grouped together as one entity to be compared against the Caucasian group. Most of the patients (86.2%) suffered from open-angle glaucoma. All the 13 eyes (5.2%) that had narrow-angle glaucoma underwent a combined cataract extraction with EX-PRESS to maximize the IOP-lowering effect after operation by opening the angle. Eighteen eyes that were classified as 'other' had glaucoma secondary to uveitis or to retinal detachment surgery. None of the patients had neovascular or traumatic angle recession glaucoma.

One hundred and thirty-six eyes (55%) underwent EX-PRESS implantation alone and 112 eyes (45%) underwent a combined operation of cataract extraction with EX-PRESS implantation.

Table 1 Demographics, glaucoma types, and surgery types

	Eyes, N = *248* (%)	*Patients*, N = *211*
Age (years)		
Mean	63.9	62.0
SD	13.8	13.5
Median	66.0	66.0
Min	16	16
Max	89	89
Sex		
Males	154 (62%)	133
Females	94 (38%)	78
Race		
Caucasian	204 (82%)	179
Non-Caucasian	44 (18%)	32
Glaucoma types		
OAG	214 (86.2%)	
NAG (with planned cataract extraction)	13 (5.2%)	
PXFG	3 (1.2%)	
Other	18 (7.2%)	
Surgery types		
EX-PRESS alone	136 (55%)	
EX-PRESS combined with cataract extraction	112 (45%)	

Abbreviations: NAG, narrow-angle glaucoma; OAG, open-angle glaucoma; other, glaucoma related to uveitis or retinal detachment surgery; PXFG, pseudoexfoliation glaucoma.

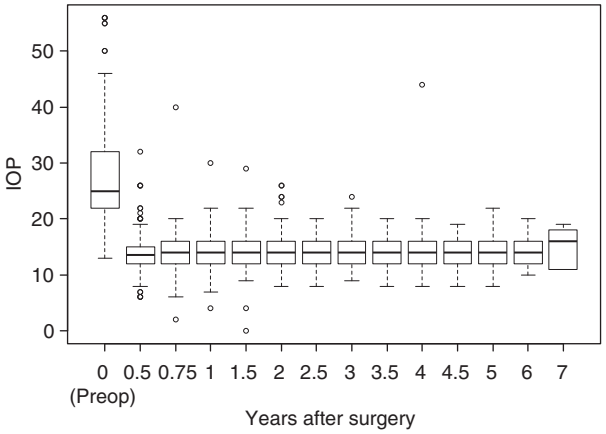

Figure 1 IOP progression as a function of time.

Table 2 Mean IOP and number of antiglaucoma medication at each year of follow-up

	Mean IOP ± SD			*Number of antiglaucoma medication used*			
	Mean IOP (mm Hg)	*± SD*	*Number of eyes*	*Mean*	*SD*	*Min*	*Max*
Preoperative	27.63	8.26	248	2.85	1.08	0	5
Year 1	13.80	2.83	238	0.03	0.17	0	1
Year 2	14.09	2.74	210	0.06	0.26	0	2
Year 3	14.04	2.73	165	0.11	0.33	0	2
Year 4	13.98	3.46	152	0.16	0.43	0	2
Year 5	13.95	2.70	95	0.10	0.34	0	2
Year 6	14.00	2.64	52	0.11	0.38	0	2
Year 7	14.17	2.65	6	0.20	0.45	0	1

The progression of mean IOP ± SD as a function of time with *n* values is shown in Figure 1.

The mean IOP ± SD at each year of follow-up and the number of antiglaucoma medications used are displayed in Figure 1 and Table 2. The mean preoperative IOP dropped from 27.63 ± 8.26 ($n = 248$) to 13.95 ± 2.70 mm Hg at 5 years ($n = 95$). The preoperative mean IOP dropped by nearly 50% during the first month postoperatively and stabilized thereafter around the 14 mm Hg mark. The number of preoperative antiglaucoma drugs in use was reduced from a mean of 2.85 ± 1.08 SD (range 0–5) to 0.03 ± 0.17 SD (range 0–2) at 1 year and 0.10 ± 0.17 SD (range 0–2) at 5 years postoperatively.

There were no intraoperative complications. Hyphema was found in four eyes (1.6%) in the first day postoperatively. Hypotony (IOP ≤ 6 mm Hg) was observed in 13 eyes (5.2%) during the first week after the surgery but required a postoperative intervention only in three cases. Two patients (0.8%) developed a bleb leak that required a bleb revision. The survival probability for complete and qualified success as a function of time during 5 years of follow-up is shown in Figure 2.

Both success rates diminished gradually over time from 83% and 85% at 1 year to 76% and 80% at 2 years, 66% and 73% at 3 years, 65% and 72% at 4 years, and 57% and 63% at 5 years of follow-up, respectively. The success rate gradually reduced in both the complete and qualified success groups from 83% at 1 year to around 60% at 5 years. The mean postoperative antiglaucoma medication number increased from 0.03 at 1 year to 0.10 at 5 years of follow-up.

The complete success survival probability curves of diabetic patients *vs* non-diabetics are displayed in Figure 3. Diabetic patients were at a higher risk for failure compared with non-diabetic patients. The complete success rates of diabetic patients dropped from 62.7% at 1 year to 41.8% at 2.5 years and stabilized at that level thereafter, whereas the non-diabetic patients' success rate at 1 year was 84.6% and decreased gradually to 58.5% at 5 years.

The qualified success survival probability curves of diabetic patients *vs* non-diabetics are displayed in Figure 3. The diabetic patient's qualified success rate was

only 62.7% at 1 year compared with 87.0% in non-diabetic patients. It dropped further to 41.8% at 2.5 years and stabilized at that level thereafter, whereas the non-diabetic patients' qualified success rate decreased gradually to 65.4% at 5 years. The complete success rate survival probability curves of Caucasians *vs* non-Caucasians are displayed in Figure 3. Non-Caucasian patients were at a higher risk for failure compared with Caucasian patients. Their initial complete success rate at 1 year was 74.8% compared with 84.3% in Caucasian patients. After 4 years of follow-up, the complete success rate in non-Caucasian patients was reduced to 40.0% and stabilized at that level thereafter, whereas the complete success rate of Caucasian patients decreased gradually to 61.2% at 5 years.

The qualified success survival probability curves of Caucasians *vs* non-Caucasians are displayed in Figure 3. Non-Caucasian patients were at a higher risk for failure compared with Caucasian patients. Their initial qualified success rate at 1 year was 76.0% compared with 86.9% in Caucasian patients. After 4 years of follow-up, the qualified success rate in non-Caucasian patients was reduced to 51.0% and stabilized at that l evel thereafter, whereas the qualified success rate of Caucasian patients reduced gradually to 66.9% at 5 years.

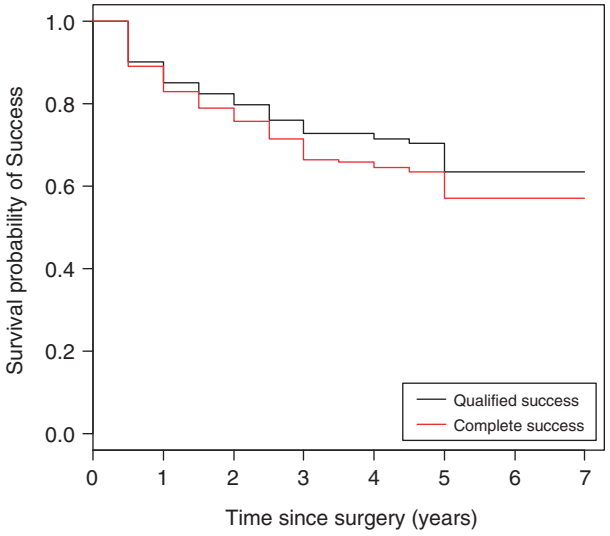

Figure 2 Complete and qualified survival probability curves as a function of time.

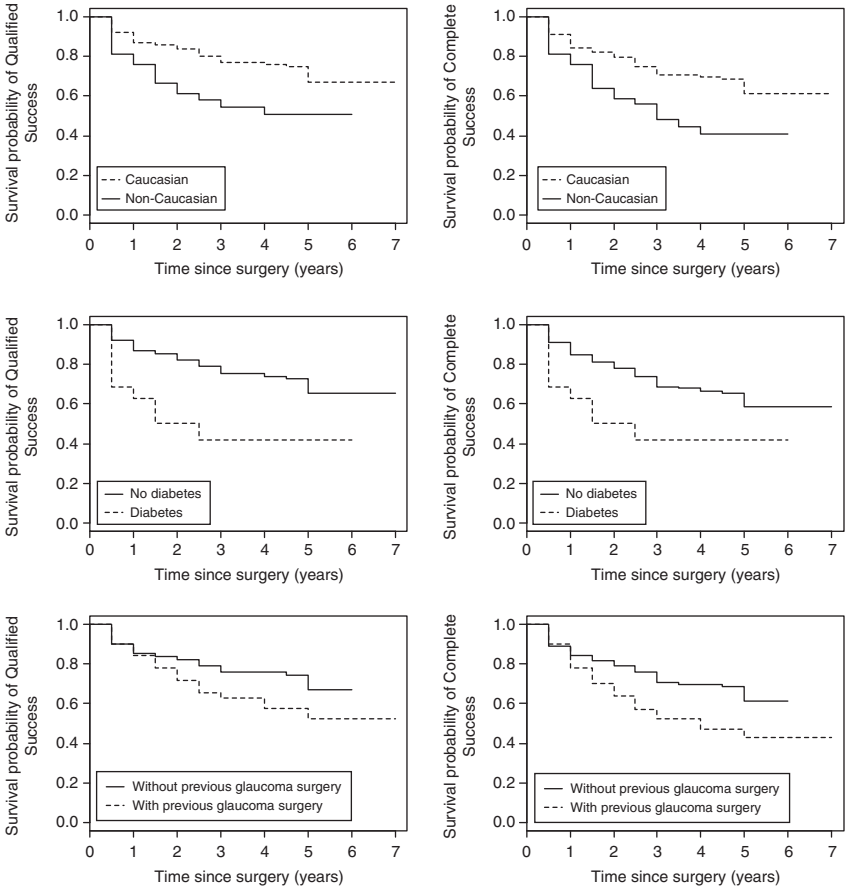

Figure 3 Survival probability curves associated with complete and qualified success in patients with and without risk factors for failure.

The complete success survival probability curves for patients with previous failed glaucoma surgery (PFGS) *vs* patients without PFGS are displayed in Figure 3. All previous surgeries were trabeculectomies. Patients with PFGS were at a higher risk for failure compared with patients without PFGS. The PFGS patients' complete success rate at 1 year was 82.0% compared with 85.2% in patients without PFGS. After 5 years of follow-up, the complete success rate in patients with PFGS was reduced to 50.6% compared with 66.2% in patients without PFGS.

The qualified success survival probability curves for patients with PFGS *vs* patients without PFGS are displayed in Figure 3. Patients with PFGS were at a higher risk for failure (qualified success) compared with patients without PFGS. The PFGS patients' qualified success rate at 1 year was 82.0% compared with 85.2% in patients without PFGS. After 5 years of follow-up, the qualified success rate in patients with PFGS was reduced to 50.6% compared with 66.2% in patients without PFGS.

The risk factors for failure (complete success) with their respective *P*-values are listed in Table 3. Race, diabetes, and previous glaucoma surgery were the most statistically significant risk factors for failure associated with complete success. The duration of preoperative use of antiglaucoma medications was nearly statistically significant ($P = 0.058$). Smoking, age, sex, and glaucoma type were not found to be risk factors for failure associated with complete success in our series.

The qualified success risk factors for failure with their respective *P*-value are listed in Table 3. Diabetes and non-Caucasian race were found to be statistically significant risk factors for failure associated with qualified success. Previous glaucoma surgery was found to be a nearly statistically significant risk factor for failure associated with qualified success ($P = 0.066$). Smoking, age, sex, and glaucoma type were not found to be risk factors for failure associated with qualified success in our series.

Discussion

Surgical procedures for medically uncontrolled glaucoma are mainly rated by their efficacy, safety, and feasibility. During the past decade, standard trabeculectomy, which is still recognized as the most commonly performed glaucoma operation worldwide, has increasingly been challenged with the introduction of the EX-PRESS glaucoma filtration device.[1–25] During the past 5 years, numerous studies comparing the EX-PRESS with trabeculectomy reported that the EX-PRESS offers similar IOP control, lower complications rate, and higher complete success rates.[4,8,9,12,19,20,23–25] These reports first included retrospective non-randomized studies,[4,13,19,23,25] and later on, prospective randomized studies.[9,12,20,24] Our study reports on 248 consecutive EX-PRESS implantations under a scleral flap over a period of 9 years with a maximum follow-up of 7 years. Our long-term outcomes are similar to the previous short- and mid-term results reported earlier.[1,3,4,8–13,16–20,23–25] The complete success rate in our study shows a decline from 83% at 1 year to 57% at 5 years. In a similar manner, de Jong *et al*[20] report on a complete success rate decline from 86.8% at 1 year to 59% at 5 years with the EX-PRESS. The tube *vs* trabeculectomy (TVT) study (5 years of follow-up) reports on a trabeculectomy success rate decline from 83% at 1 year to 46.4% at 5 years when using the same IOP upper limit (>17 mm Hg) as used in our study.[28] The 5-year TVT study does not specify if the reported success rate is complete or qualified, but it is reasonable to assume that the authors intended to report on the overall qualified success rate.

Similarly, other reports on trabeculectomy augmented by fluorouracil or MMC report on a 50% or less success rate for trabeculectomy at 5 years of follow-up.[29,30] Therefore, the EX-PRESS long-term success rates of de Jong and of our study compare favorably with those of trabeculectomy.[20,28–33]

Table 3 Risk factors for failure associated with complete and qualified success

	Risk factors for failure associated with complete success					*Risk factors for failure associated with qualified success*				
	P *(bivariate comparison)*	*Multivariate model*				P *(bivariate comparison)*	*Multivariate model*			
		HR	*HR 95% CI*		P-*value*		*HR*	*HR 95% CI*		P-*value*
			Inf	*Sup*				*Inf*	*Sup*	
Diabetes (diabetic/non-diabetic patients)	**0.012**	**2.55**	**1.02**	**6.04**	**0.046**	**0.002**	**2.89**	**1.50**	**5.54**	**0.001**
Race (Caucasians/non-Caucasians	**0.007**	**0.41**	**0.22**	**0.78**	**0.007**	**0.009**	**0.50**	**0.27**	**0.95**	**0.03**
Previous glaucoma surgery (yes/no)	**0.02**	**1.54**	**1.07**	**2.21**	**0.02**	0.066	1.56	0.88	2.75	0.12
Duration of preop medication (HR for every additional year)	0.058	0.97	0.95	1.007	0.14	0.11				
Smoking (yes/no)	0.37					0.14				
Age (HR for every additional 10 years)	0.39					0.4				
Glaucoma type	0.75					0.7				
Sex	0.66					0.7				

Bold data are statistically significant.

The risk factors for failure in trabeculectomy mentioned in the literature are age, race, previous glaucoma surgery, diabetes, glaucoma type, and previous use of antiglaucoma medications.[30–33] In our study, the most statistically significant risk factors for failure with the EX-PRESS were found to be, in order of importance, diabetes ($P = 0.001$), non-Caucasian race ($P = 0.007$), and previous failed glaucoma surgery ($P = 0.02$). The duration of preoperative use of antiglaucoma medications was found to be nearly statistically significant ($P = 0.058$) as a risk factor for failure with the EX-PRESS. All these risk factors for failure with the EX-PRESS are also mentioned as being statistically significant to various degrees in the reports on trabeculectomy.[30–33]

The complete and qualified success rates in diabetic patients were significantly lower than in non-diabetic patients during the whole duration of our study. Diabetic patients have an altered postoperative healing process because of their high transforming growth factors (TGFs) aqueous concentration.[34–37] The TGFs have a major role in scar tissue formation in the eye and induce the synthesis of growth factors that control cell migration, proliferation, enzyme production, and matrix deposition. Excessive scar formation after glaucoma surgery can lead to surgery failure.[36]

African and African-American race has been reported as a higher risk for failure because of presumed excessive scar formation with consequent filtration surgery failure.[38–40] Broadway *et al*[41] compared the conjunctiva of 'black' and 'white' patients undergoing trabeculectomy with respect to the results of surgery and differences in conjunctival cell profile. They reported that trabeculectomy was less successful in black patients (67% compared with 80%). There was a tendency for the conjunctiva from black patients to contain more fibroblasts. Conjunctiva obtained from the patients whose filtration surgery subsequently failed was found to contain more fibroblasts, macrophages, and basal epithelial pale cells. A greater number of conjunctival macrophages and possibly fibroblasts in black patients may partially explain the tendency for a lower success rate of filtration surgery in this group.[41]

The use of antimetabolite agents during glaucoma filtration surgery has been reported to improve surgical outcomes in African and African-American patients.[42–44] The success rates of our non-Caucasian patients that included Africans, Indians, and patients of mixed race origin were 50% lower on average compared with the Caucasian patients. Salim *et al*[45] reported on nearly equal success rates with the EX-PRESS in black and white Americans. The difference between their results and ours is most probably owing to the fact that our study has a longer follow-up and that our patients included Africans, Indians, and patients of mixed ancestry, whereas their study included African-Americans only.

Although previous glaucoma surgery was reported to be a risk factor for failure in filtration surgery, there are no exact numerical figures to quantify it in the literature.[30–33] Our study reports on a 30% lower success rate on average, in patients who underwent previous glaucoma surgery compared with patients who did not. The presumed reason for the lower success rate is the increased earlier conjunctival scarring near the area of the second filtration surgery.

Prior prolonged use of topical antiglaucoma medications has been reported to reduce the success rate of filtration surgery in the past.[46–48] Our study found nearly statistical significance for this risk factor for failure. The literature on the adverse effects of topical antiglaucoma medication on the outcome of filtration surgery dates from the era before the routine intraoperative use of antimetabolites. Wound healing modulation by antimetabolites has increased glaucoma surgery success rates and has lessened the adverse effects of topical antiglaucoma medications by allowing bleb formation.[29,30,32,42–44] As MMC was used intraoperatively in 100% of our patients, the adverse effects of prior topical medications were lessened. Furthermore, EX-PRESS implantation induces less inflammation than standard trabeculectomy because it does not involve tissue removal such as sclerectomy and iridectomy, thus reducing failure rate.[4,8,9,12,19,20,23–25]

Similarly, age and glaucoma type were not found to be statistically significant risk factors for failure in our study most probably because of the lesser inflammation induced by EX-PRESS implantation compared with standard trabeculectomy.

The main limitation of this study is its retrospective design with the potential for investigator bias in selection of cases and loss to follow-up. However, we identified all the patients who had an EX-PRESS implantation during the study period through the surgical logbooks in the two study centres ensuring a complete cohort. The losses to follow-up were realistic and were taken into account by the statistical analysis. Because this was a large consecutive case series with a long follow-up, the risk factors for failure were detected more accurately than in smaller series with shorter follow-up.

In summary, our study confirms previous short- and mid-term reports on the EX-PRESS but has a longer average follow-up of 3.46 ± 1.76 years (range 0.5–7 years). The complete and qualified success rates ($5\,\text{mm Hg} < \text{IOP} < 18\,\text{mm Hg}$) decline on average 5% per year of follow-up from 83% and 85% at 1 year to 57% and 63% at 5 years, respectively. Our outcomes are similar to or better than previously published standard trabeculectomy long-term outcomes. The risk factors for

failure with the EX-PRESS are comparable to those reported on for trabeculectomy and include, in order of importance, diabetes, non-Caucasian race, and previous glaucoma surgery. Unlike intrabeculectomy, age and glaucoma type were not found to be a statistically significant risk factor for failure when using the EX-PRESS.

Summary

What was known before

- EX-PRESS provides similar IOP control to trabeculectomy in the short and medium term.
- EX-PRESS has less postoperative complications, needs less postoperative interventions, and has higher complete success rates than trabeculectomy.

What this study adds

- EX-PRESS provides better long-term outcomes compared with those reported in the current literature for trabeculectomy.
- Similarly to trabeculectomy, the main risk factors for failure when using the EX-PRESS are diabetes, non-Caucasian race, and previous glaucoma surgery.
- Unlike in trabeculectomy, age and glaucoma type were not found to be a statistically significant risk factor for failure when using the EX-PRESS.

Conflict of interest

ED: consultant for Alcon Laboratories; ED is a paid consultant to Alcon Laboratories. SB is used by CEMKAEVAL, a company that provides services in statistical analyses and epidemiology. All the other authors declare no conflict of interest.

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