·Meta-Analysis·

Efficacy and economic analysis of Ex-PRESS implantation versus trabeculectomy in uncontrolled glaucoma: a systematic review and Meta-analysis

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Received: 2014-12-25 Accepted: 2015-05-14

Abstract

• AIM: To systematically review the current evidence based on the efficacy and cost of Ex-PRESS implantation and trabeculectomy (Trab) for uncontrolled glaucoma.

• METHODS: Clinical trials were identified by electronic databases (PubMed, EMBASE, ISI Web of science and Cochrane library), and data, such as intraocular pressure (IOP), the complete and qualified success rate, the postoperative complications and the cost, were exacted from these relevant studies. Weighted mean difference (WMD), odds ratio (OR) and 95% confidence intervals (CIs) were calculated and were pooled using a random-effects model.

• RESULTS: Eleven relevant publications and two abstracts met the inclusion criteria. The efficacy of Ex-PRESS was similar to that of Trab in the percentage of IOP reduction (IOPR %) at 1, 2y (WMD: -2.01; 95% CI: -7.92-3.90; *P*=0.50 and WMD: 2.89; 95% CI: -8.05-13.83; *P*=0.60, respectively). Ex-PRESS possessed a significant higher complete and qualified success rate (OR: 1.59; 95% CI: 1.07-2.35; *P*=0.02 and OR: 1.74; 95% CI: 1.06-2.86; *P*=0.03, respectively). Moreover, Ex-PRESS exerted a significantly lower frequency of hypotony and hyphema than Trab (OR: 0.39; 95% CI: 0.21-0.72; *P*=0.003 and OR: 0.27; 95% CI: 0.10-0.69; *P*=0.003, respectively). However, there was no consistent result on the cost between the two groups according to the previous three studies.

• CONCLUSION: Both Trab and Ex-PRESS have equivalent efficacy in lowering IOP, yet Ex-PRESS had a lower risk of hypotony and hyphema than Trab. Nevertheless, whether the cost of Ex-PRESS was less than that of Trab should be further investigated to ensure evidence-based conclusion in the long run.

• KEYWORDS: Ex-PRESS implantation; trabeculectomy; uncontrolled glaucoma; systematic review; Meta-analysis
DOI:10.18240/ijo.2016.01.21

Wang L, Sha F, Guo DD, Bi HS, Si JK, Du YX, Tang K. Efficacy and economic analysis of Ex-PRESS implantation versus trabeculectomy in uncontrolled glaucoma: a systematic review and Meta-analysis. *Int J Ophthalmol* 2016;9(1):124-131

INTRODUCTION

Glaucoma, a neurodegenerative disease characterized by progressive vision loss, is one of the leading causes of preventable blindness in the world. The worldwide prevalence of glaucoma is estimated to be about 1% in people aged 50y or older and will increase with age. It is predicted that more than 58 million people will be affected by open angle glaucoma (OAG) by the year 2020 [1]. Currently, the economic impact on health services is expected to be heavier due to increasing incidence, prevalence and cost of glaucoma. The direct cost of glaucoma treatment includes chronic use of medications, surgical procedures, medical visit and frequent exams, and handle of postoperative complications. The usual care of glaucoma is to initiate treatment with medication to reduce the intraocular pressure (IOP). It has been demonstrated that the vision loss from glaucoma could be delayed by lowering IOP. If patients with glaucoma are unable to achieve good control of IOP with maximal medical therapy or laser treatments or intolerant to topical preparations, it is necessary to perform surgeries to reduce IOP.

Traditionally, trabeculectomy (Trab) is considered the gold standard in the glaucoma surgery. However, there were some

postoperative complications including hypotony, choroidal detachment, bleb leak and encapsulated bleb, and more drugs or additional surgeries may be needed post operation, so it will further increase the total cost [2]. Consequently, it is essential to create a better and safer operation.

The Ex-PRESS glaucoma filtration implantation was developed as an alternative to Trab. It is a small, stainless and non-valved flow-restricting device. Implantation of the Ex-PRESS shunt under a scleral flap is similar to the traditional Trab, which can avoid the need for a peripheral iridectomy. Thus, implantation of the Ex-PRESS may reduce the likelihood of hyphema and result in less postoperative inflammation. Because of the fixed-diameter tube size and relative stable filtering volume of Ex-PRESS, the complications of hypotony caused by over-fluent filtering may be less. Therefore, the Ex-PRESS shunt may provide a more reliable filtering procedure for glaucoma surgeons, especially for those surgeons new to the procedure, such as ophthalmology residents. Consequently, the Ex-PRESS glaucoma filtration implantation has been used successfully in approximately 60 000 patients worldwide [3]. However, given the limited healthcare resources available, it is important to know whether the Ex-PRESS is highly cost-effective.

Three studies so far have compared the cost of Ex-PRESS with that of Trab[2,4-5]. One study[2] found that the two groups exhibited comparable efficacy and safety, while Ex-PRESS group cost more than Trab group. However, the other two studies[4-5] found that the Ex-PRESS could control IOP better than Trab, resulting in highly cost-effective when both postoperative IOP-lowering medications and additional eye surgeries were considered. These inconsistent results make it difficult to draw a conclusion that whether implantation of Ex-PRESS could be applied in clinical practice. Therefore, to evaluate whether Ex-PRESS offers any advantages for medically uncontrolled glaucoma in terms of efficacy and fewer postoperative complications with lower cost, we undertook a systematic review on economic analysis and Meta-analysis on efficacy and safety for Ex-PRESS and Trab.

SUBJECTS AND METHODS

The study was conducted according to the tenets of the Declaration of Helsinki. It was approved by the Review Board at the Affiliated Eye Hospital of Shandong University of Traditional Chinese Medicine.

Outcome Measures For efficacy, the primary outcome was the percentage reduction in preoperative to postoperative IOP. The secondary outcome measure was the complete success rate, which was defined as the proportion of patients with a target end-point IOP without antiglaucoma medication, and the qualified success rate, defined as target end-point IOP with or without antiglaucoma medications. Considering the safety of the Ex-PRESS, we mainly assessed the postoperative complications including hyphema, hypotony, choroidal detachment, flat anterior chamber, bleb leak, encapsulated bleb, maculopathy and endophthalmitis. The last outcome measure was the economic analysis, which was analyzed using both overall total cost and postoperative cost (including the cost of follow-up visits, medication required and additional surgery procedures).

Inclusion and Exclusion Criteria We included clinical trials (randomized and retrospective, prospective nonrandomized) that compared Ex-PRESS with Trab in patients with uncontrolled glaucoma and that reported efficacy outcomes (at least one of the outcomes of interest was included) or postoperative complications or cost (no matter how these had been specified). We excluded all publications that cannot obtain raw data that we require, the duplicate publications and letters, and reviews. In addition, some reports were combined as a single study when they were based on the same group of patients.

Search Strategy for Identification of Studies We made an electronic search in PubMed, EMBASE, ISI Web of science, and Cochrane library in English using key words including "glaucoma", "cost", "Ex-PRESS", "trabeculectomy" and equivalents. The titles and abstracts of original reports and review articles were independently scanned by two authors to determine whether they satisfied inclusion criteria. Retrieved articles were imported into EndNote X6 (Thomson Reuters, New York, NY, USA) where duplicate articles were manually removed. Moreover, the references of all retrieved articles were scanned artificially for additional relevant citations. There was no restriction on language or study design to avoid missing the literature having important influence on the results. We searched all databases from January 2002 to November 2014.

Data Extraction Two reviewers (Wang L and Sha F) extracted information from included studies independently in accordance with the unified standards. For some indirect raw data, we captured them in figures using GetData Graph Digitizer 2.25 (supplied by Fedorov S). Any disagreements about data extraction were discussed in common with two reviewers and resolved finally. The data extracted from each study contained: name of the first author, publication year, study design, country, numbers of subjects, preoperative and postoperative IOP, complete and qualified success rate, and costs of two groups. We also contacted authors by sending emails to request missing data to obtain the accurate outcomes.

Assessment of Literature Quality Both randomized-controlled trials (RCTs) and non-randomized-controlled trials (non-RCTs) were included in this current Meta-analysis. The qualities of the related studies were assessed using the Downs and Black quality assessment method [6] contains a list of 27 criteria evaluating the reporting, external validity, internal validity-bias, confounding (selection bias),

Table 1 Characteristics of included studies

Authors	Study design	Location	[1]No./ eyes	Age (a)	Follow-up (mo)	Downs and black scale					
						Reporting	External validity	Internal validity-bias	Internal validity confounding	Power	Total
Maris *et al*[15]	Retro	USA	50/50	66.4/66.5	10.8/11.2	10	2	5	3	3	23
Gallego-Pinazo *et al*[19]	Pro	Spain	20/20	75.0/76.4	9.7/10.3	7	2	4	3	1	17
Good and Kahook[16]	Retro	USA	35/35	68.9/69.3	28/28	8	2	4	2	2	18
Sugiyama *et al*[20]	Pro	Japan	10/11	64.2/71.3	12/12	10	3	5	3	0	21
de Jong *et al*[9]	RCT	Dutch	39/39	62.4/68.6	65.6/66.4	11	3	5	3	2	24
Marzette and Herndon[17]	Retro	USA	76/77	66.9/66.8	9.1/9.2	11	2	5	3	3	24
Dahan *et al*[13]	RCT	South Africa	15/15	65.4/65.4	23.6/23.6	11	2	5	5	1	24
Seider *et al*[18]	Retro	USA	36/57	71.0/70.8	12/12	11	2	4	3	3	23
Netland *et al*[14]	RCT	USA	59/61	69.4/67.8	24/24	11	3	5	3	3	25
Wagschal *et al*[10]	RCT	Canada	33/31	65.9/62.0	12/12	10	3	4	3	2	22

RCT: Randomized controlled trials; Retro: Retrospective; Pro: Prospective non-randomized; Ex-PRESS: Ex-PRESS implantation; Trab: Trabeculectomy. [1]Ex-PRESS group/Trab group.

and power of included studies. Two reviewers (Wang L and Sha F) assessed the literature quality score according to the assessment method above and disagreements were resolved by the third reviewer (Guo DD).

Statistical Analysis When mean and standard deviation (SD) of IOP reduction (IOPR) were reported in the literature, they were used directly. If these data were not available, they were computed as follows: $IOPR=IOP_{baseline}-IOP_{endpoint}$, and $SD_{IOPR}= [SD^2_{baseline}+SD^2_{end\ point} - (2\times Corr\times SD_{baseline}\times SD_{end\ point})]^{1/2}$, where Corr was the correlation coefficient. In our present study, a Corr value was assumed as 0.5 since only partial information about the variance was provided from the clinical trials included in the paper [7]. The IOPR% and the SD of the IOPR% were then estimated as follows: $IOPR\%= IOPR/IOP_{baseline}$ and $SD_{IOPR\%}=SD_{IOPR}/IOP_{baseline}$, where IOPR% was the percentage of the IOPR. For continuous outcomes, weighted mean difference (WMD) was calculated. For dichotomous outcomes, odds ratio (OR) was estimated. The results were reported with 95% confidence intervals (CIs). We tested statistical heterogeneity across studies by using both the χ^2 and I^2 tests. I^2 was tentatively calculated and an I^2 of 25% to 50%, I^2 of 50% and I^2>75% were considered to have low, moderate and high heterogeneity, respectively [8]. Once I^2>50%, potential sources of heterogeneity were identified by sensitivity analysis, which was applied to evaluate the effect of methodological characteristics of all clinical trials on the results of this Meta-analysis. In terms of publication bias, we used funnel plot methods to assess the related outcomes.A P value <0.05 was considered statistically significant on the test for overall effect. Analyses were carried out using RevMan 5.2 software supplied by Cochrane Collaboration (Oxford, UK).

RESULTS

Identification and Selection of Studies Initially, 233 studies were identified, including 161 articles in English and 72 articles in Chinese. We excluded 218 articles due to duplicate publications or failure to satisfy the inclusion criteria formulated previously. Herein 13 relevant publications and 2 abstracts were selected through screening full-text or removing studies lack of needed data. Owing to 4 articles[9-12] from two identical clinical trials, we chose the latest publication for each clinical trial[9-10]. To achieve the complete data, we pooled the results from different articles that derived from an identical study, and we only pulled data from 2 articles, but did not include them in the present study[10-11]. Therefore, only 11 studies and 2 abstracts met the inclusion criteria in this paper review from 2007 to November 2014. Figure 1 provided the flow of search results.

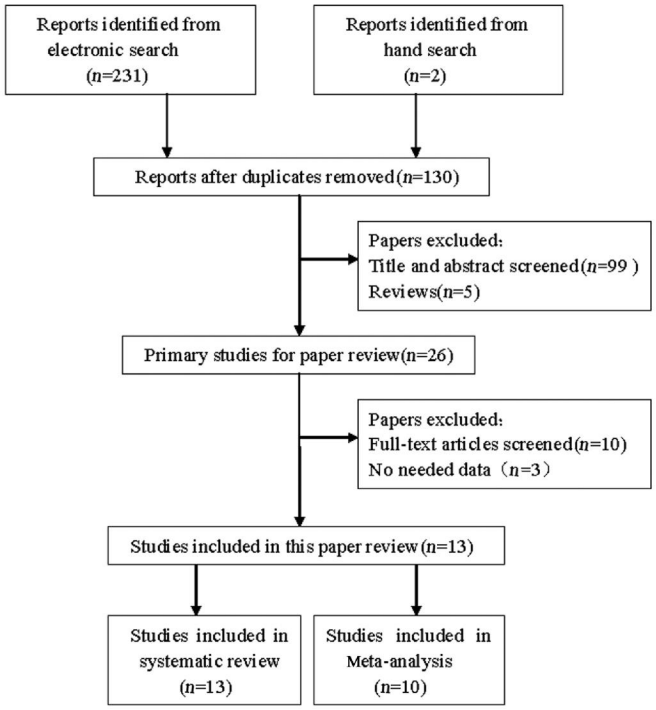

Figure 1 Flow diagram showing the process of study selection for this review.

Study Characteristics and Quality The basic characteristics of the included studies were described in Table 1. Ten studies were used to analyze the efficacy and safety for Ex-PRESS and Trab. Therefore, a total of 769 eyes

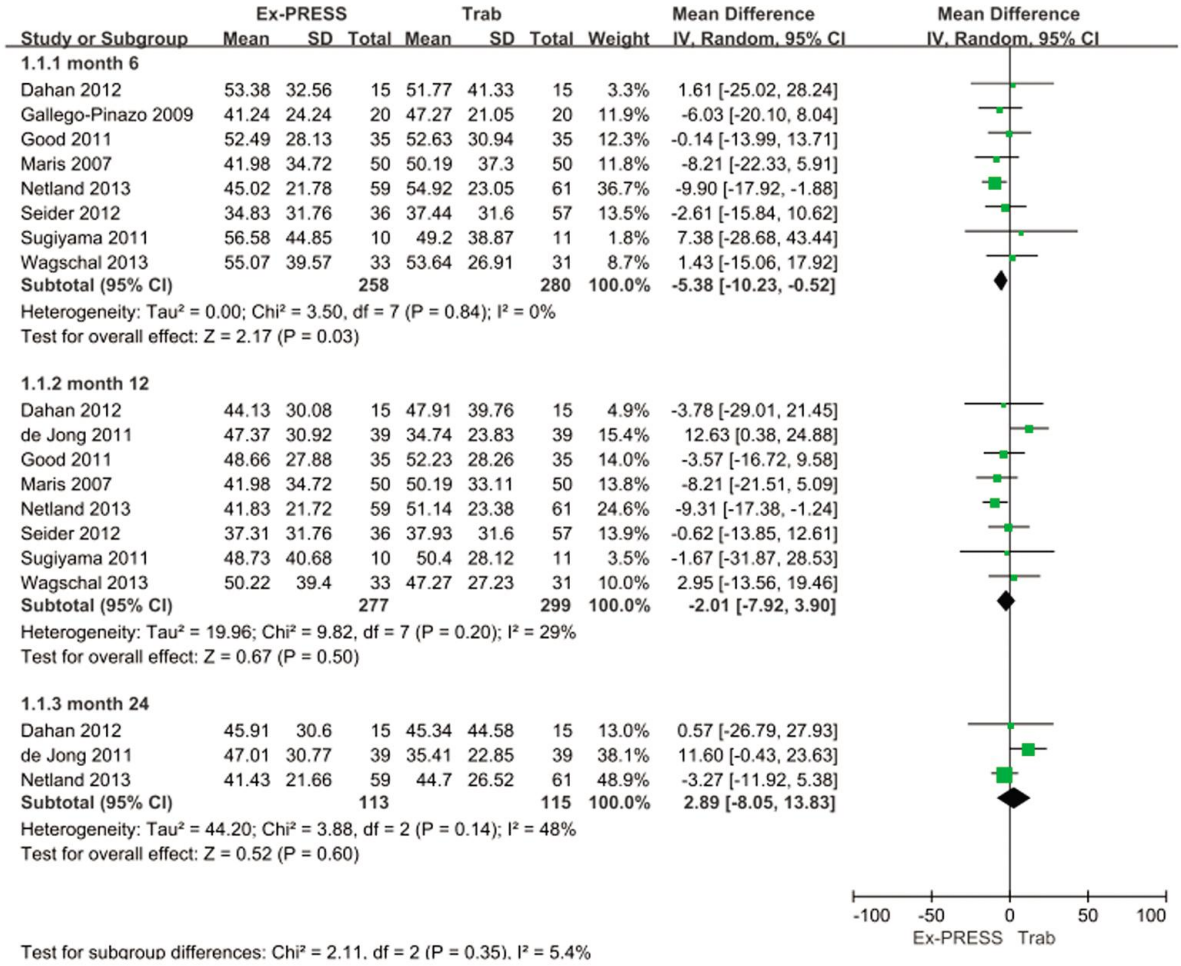

Figure 2 A forest plot of the subgroup analyses of studies included comparing Ex-PRESS group with Trab group for change in various follow-up time Mean differences (green squares) and 95% CIs (bars) are given for each study. Also shown are the shaded diamonds of the summary MDs based on the Inverse Variance random-effects model.

from 739 patients were included in the present Meta-analysis. Meanwhile, we further estimated the cost difference between two operations using a systematic review, which involved in 1 article[2] and 2 abstracts[4-5].

Among the 10 included studies, there were 4 randomized-controlled trial (RCT) studies [9-10, 13-14], 4 retrospective studies [15-18], and 2 prospective studies [19-20]. For geographic distribution, 5 studies were carried out in America, 1 in Spain, 1 in Dutch, 1 in Japan, 1 in South American, and 1 in Canada. We used the Downs and Black Scale method to evaluate the methodological qualities of the included studies in the current Meta-analysis. The Downs and Black quality assessment scores for all studies included were over 16 (50% of total score) (mean: 22.10; SD: 2.69).

Efficacy Analysis All the 10 studies on IOPR % calculated by the formula stated were analyzed through the Review Manager. We used the random effect model for Meta-analysis regardless of heterogeneity test with or without statistical significance. The aggregated results of these studies suggest that Ex-PRESS reduced IOP with a numerically greater change from baseline. However, the difference was not statistically significant compared to Trab (WMD: 2.39; 95% CI: -1.80-6.58; P=0.26). In addition, no heterogeneity was observed among studies (χ^2=4.24, P for heterogeneity=0.89, I^2=0.00%). Given various follow-up times, we performed subgroup analyses, which were based on different durations. In this review, there were 8 studies[10,13-16,18-20], 8 studies[9-10,13-16,18,20] and 3 studies[9,13-14] to evaluate the effect of two surgical procedures on IOP-lowering at 6, 12 and 24mo postoperative by subgroup analysis, respectively. We found that there was a similar result in comparison with Ex-PRESS and Trab regarding IOPR% at 1, 2y after surgery (P=0.50, 0.60, respectively). Nevertheless, statistical difference was found at 6mo (P=0.03), which showed that Ex-PRESS had a lower IOPR% compared with Trab (detailed data were presented in Figure 2).

Moreover, we performed sensitivity analysis on the basis of different study designs, which included RCTs, retrospective and prospective non-randomized controlled trials (Retro and Pro). For the subgroup analysis according to the design above-mentioned, Ex-PRESS did not significantly reduce IOP (RCTs: WMD: 0.62; 95% CI: -5.65-6.88; P=0.85; P for heterogeneity=0.96; I^2=0.00%; Retro: WMD: 4.32; 95% CI: -2.02-10.66; P=0.18; P for heterogeneity=0.83; I^2=0.00%;

Table 2 Sensitivity analysis to assess the effect of included studies on percentage IOP reduction

Studies	*n*	WMD (random) (95%)	Heterogeneity			Overall effect	
			Q	*P*	I^2 (%)	*Z*	*P*
All trials	10	2.39 (-1.80, 6.58)	4.24	0.89	0.00	1.12	0.26
RCT	4	0.62 (-5.65, 6.88)	0.33	0.96	0.00	0.19	0.85
Pro	2	7.59 (-4.78, 19.95)	0.43	0.51	0.00	1.20	0.23
Retro	4	4.32 (-2.02, 10.66)	0.89	0.83	0.00	1.34	0.18

Table 3 Complete success and qualified success from Ex-PRESS implantation and Trab

Success	Studies (*n*)	Event rate, *n*/N		OR (95%CI)	Heterogeneity			Overall effect	
		Ex-PRESS	Trab		*Q*	*P*	I^2 (%)	*Z*	*P*
Complete success									
All trials	6	164/234	150/254	1.59 (1.07, 2.35)	2.89	0.72	0.00	2.30	0.02
Only RCT	3	55/87	40/85	1.94 (1.05, 3.59)	1.11	0.57	0.00	2.11	0.03
Qualified success									
All trials	10	345/373	349/398	1.74 (1.06, 2.86)	6.31	0.61	0.00	2.19	0.03
Only RCT	4	134/146	124/148	2.25 (1.07, 4.73)	3.11	0.38	4.00	2.13	0.03

RCT: Randomized controlled trials; CI: Confidence interval; OR: Odds ratio; Ex-PRESS: Ex-PRESS implantation; Trab: Trabeculectomy.

Table 4 Postoperative complications from Ex-PRESS implantation and Trab

Complications	No. events (*n*)	Event rate, *n*/N		OR (95%CI)	Heterogeneity			Overall effect	
		Ex-PRESS	Trab		*Q*	*P*	I^2 (%)	*Z*	*P*
Flat anterior chamber	6	24/249	16/269	1.60 (0.85, 3.26)	2.94	0.71	0.00	1.49	0.14
Maculopathy	2	4/126	7/127	0.56 (0.16, 1.97)	0.05	0.83	0.00	0.90	0.37
Encapsulated bleb	5	8/183	15/204	0.60 (0.26, 1.40)	1.06	0.90	0.00	1.18	0.24
Bleb leak	8	36/318	28/335	1.34 (0.79, 2.27)	4.14	0.76	0.00	1.09	0.28
Choroidal detachment	8	28/324	54/347	0.58 (0.26, 1.28)	12.44	0.09	44.00	1.35	0.18
Endophthalmitis	3	1/119	2/111	1.02 (0.14, 7.35)	0.90	0.34	0.00	0.02	0.99

CI: Confidence interval; OR: Odds ratio; Ex-PRESS: Ex-PRESS implantation; Trab: Trabeculectomy.

Pro: WMD: 7.59; 95% CI: -4.78-19.95; P =0.23; P for heterogeneity=0.51; I^2=0.00%, respectively) (Table 2).

Six studies [9-10,13,16-18] reported the relevant data for complete success rate, which was defined that IOP was controlled ≥5 mm Hg and ≤21 mm Hg or ≥5 mm Hg and ≤18 mm Hg without medications. Analysis of those data showed that the complete success rate was statistically significantly higher in Ex-PRESS group than that in Trab group (OR: 1.59; 95% CI: 1.07-2.35; P=0.02). A sensitivity analysis was performed to evaluate the effect of excluding the non-randomized studies [16-18], and the statistical results did not change (OR: 1.94; 95% CI: 1.05-3.59; P=0.03) (Table 3).

All studies [9-10,13-20] have reported the qualified success rate which was defined the IOP was well controlled ≥5 mm Hg and ≤21 mm Hg or ≥5 mm Hg and ≤18 mm Hg with or without medications. These data demonstrated that the qualified success rate showed statistically significant difference between Ex-PRESS and Trab groups (OR: 1.74; 95% CI: 1.06-2.86; P =0.03). A sensitivity analysis was performed to examine the effect of excluding the non-randomized studies[15-20], whereby the statistical results did not change (OR: 2.25; 95% CI: 1.07-4.73; P=0.03) (Table 3).

Safety Analysis All complications were analyzed through the Review Manager method. We found that compared with Trab, the Ex-PRESS was associated with a significantly lower frequency of hypotony and hyphema, with the pooled ORs of 0.39 (0.21, 0.72) and 0.26 (0.10, 0.64), respectively (Figure 3). Although hypotony is closely associated with flat anterior chamber, maculopathy and choroidal detachment, no significant difference was found in these adverse events associated with the pooled ORs of 1.60 (0.85, 3.26), 0.56 (0.16, 1.97), and 0.58 (0.26, 1.28), respectively (Table 4). Meanwhile, there were no apparent differences for bleb leak, encapsulated bleb and endophthalmitis associated with the pooled ORs of 1.34 (0.79, 2.27), 0.60 (0.26, 1.40), and 1.02 (0.14, 7.35), respectively (Table 4).

Cost and Cost –effectiveness Based on the results of previous studies on economic analysis, we found that in the short term (postoperative 1-year), Ex-PRESS possessed greater overall total cost and similar postoperative cost compared with Trab. However, in the long term (postoperative 5-year), postoperative cost with EX-PRESS was less than that of Trab because of better-controlled IOP and less need for surgeries, which contribute to offsetting the cost of the Ex-PRESS device to some degree. Patel *et al* [2] performed an economic analysis of 1-year postoperative cost and overall total cost difference of the Ex-PRESS device compared with Trab. The result showed no significant

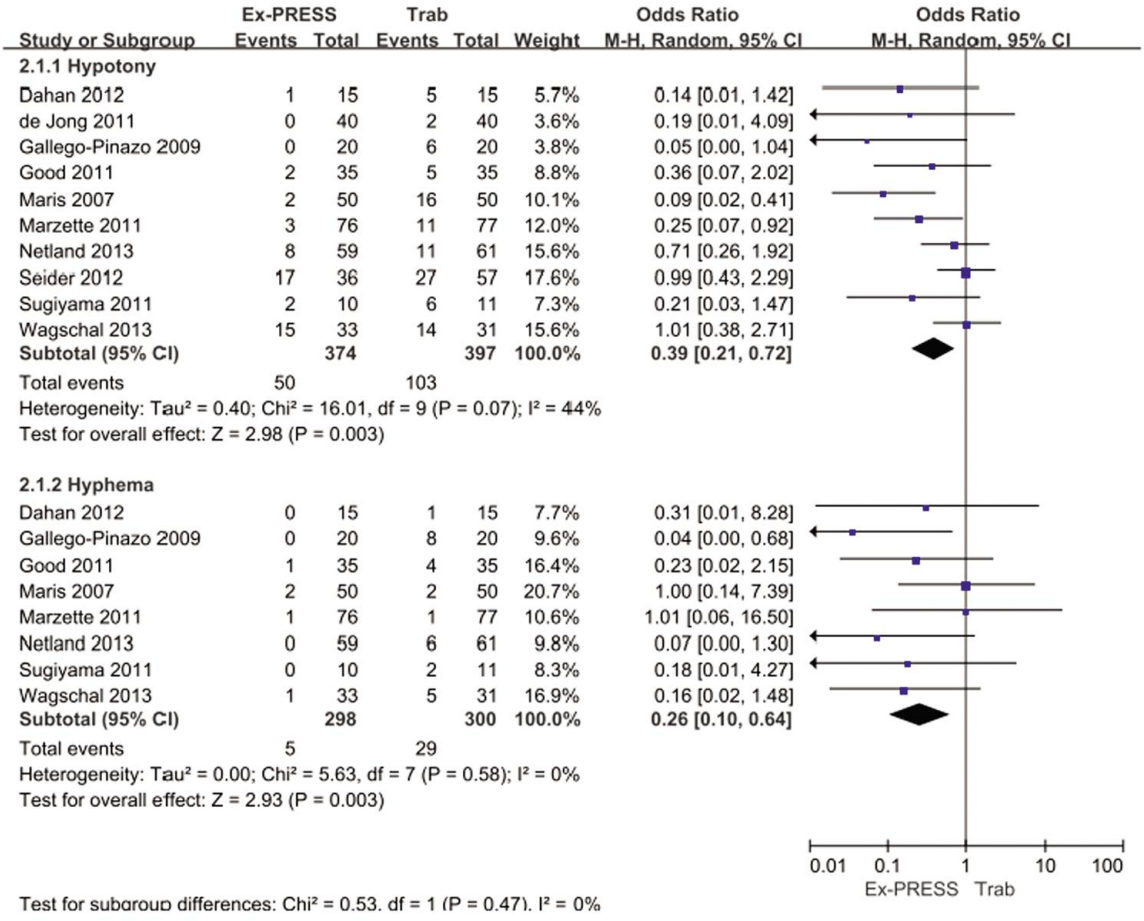

Figure 3 Postoperative complications for Ex-PRESS versus Trab Odds ratios (blue squares) and 95% CIs (bars) are given for each study. Also shown are the shaded diamonds of the summary ORs based on the Mantel-Haenszel random-effects model.

difference between two operations. The cost of Ex-PRESS device itself ($900 per case) was the leading cause of higher cost in Ex-PRESS group than that in Trab group. de Jong *et al* [4-5] reported the cost of the two operations at 5y after surgery in Netherlands and France that Ex-PRESS could control IOP better than Trab, generating postoperative savings in both IOP-lowering medications and eye surgeries.

DISCUSSION

As a new promising glaucoma surgery, the Ex-PRESS has gained interest with a possible trend. The primary purpose of this study was to update and critically evaluate the efficacy and cost of Ex-PRESS in glaucoma. Though many literatures about Ex-PRESS have been published in the world, there was a paucity of high-quality studies comparing Ex-PRESS with Trab for success rate, complications and cost. Our investigation included 10 studies related to efficacy comparing Ex-PRESS with Trab according to inclusion criteria. However, only three studies [2,4-5] associated with the cost for Ex-PRESS versus Trab were reported in developed countries. We herein performed a systematic review to compare the cost difference between the two operations.

Recently, guidelines published by the World Glaucoma Association on the design and reporting of glaucoma surgical trials have highlighted the importance of economic evaluation that plays a role in the assessment of new interventions[21]. The significant economic implications of the insertion of an Ex-PRESS device need to be considered if this procedure is to supersede Trab as the standard of practice. In fact, the cost associated with the two operations includes surgery itself and the relevant postoperative cost, and the latter is calculated based on the pooled cost of follow-up visits, additional procedures, and medication required [2], which is associated with the efficacy and safety. Thus, the efficacy and safety are both taken into consideration sufficiently to well analyze the cost for two operations.

In the present systematic review, we also found that the Ex-PRESS could achieve higher success rate than Trab, including both complete and qualified success rate, though they achieved similar results in lowing IOP comparable to those of Trab in different durations. A published Meta-analysis[22] showed that the success rate was similar for Ex-PRESS and Trab, which differed from our conclusion. The reason for the conflicting results may be because more RCTs were included in our study, which can provide more sufficient and competent evidence. Meanwhile, with the increased application of Ex-PRESS and rich experience in surgeons, the success rate will be increased. Consequently,

high qualified success rate means drug savings and less postoperative cost for glaucoma patients.

In assessing the complication, it was noted that Ex-PRESS had a significantly lower frequency of hypotony and hyphema than traditional Trab. In the meantime, patients with the Ex-PRESS in place were less likely to experience hypotony, which may be due to inherent flow regulations of the P-50 model's 50 μm internal lumen diameter [9,13,16,23]. Hypotony that may lead to vision loss needs extra handle and thus results in more postoperative cost. Whereas the Ex-PRESS procedure did not require the creation of a peripheral iridectomy conducted in Trab, which may contribute to less likelihood of hyphema. Ex-PRESS had fewer rates of complications (including maculopathy, encapsulated bleb, and choroidal detachment) than Trab, but no significant difference was found.

Regarding the cost-effectiveness, the present study deduces that the postoperative cost might be gradually reduced with higher success rate, savings in IOP-lowering medications and eye surgeries in Ex-PRESS group. Guidelines for the adoption and appropriate utilization of new technologies have previously been published by Laupacis *et al* [24]. The decision on whether to implement a new therapy depends on not only the levels of evidence (the quality of the study), but also the likelihood of the magnitude of the incremental costs required to achieve each additional unit of benefit. The suggested grades of recommendation classify therapies on the basis of the magnitude of their incremental net benefits of a technology. Moreover, based on the findings we obtained, the Ex-PRESS is more effective than Trab because of a higher success rate and less complications. So the Ex-PRESS device would be classified as grade B or C or D - more effective and more costly than Trab[24].

Nevertheless, there were several limitations in this review. First, the studies included in the present study were mostly performed in developed countries. The reason may be that the studies involved in Ex-PRESS did not be carried out or published in developing countries where the cost effective surgery is urgently needed. Importantly, the major global burden of glaucoma still remains in developing countries[1]. Therefore, relevant studies should be done in developing countries. Second, we cannot fully exclude publication bias because we did not gain access to unpublished results and more details of the abstract. Third, there was a large disparity in study quality because all studies included were too varied in the types of clinical studies, surgeon types, different generations of the Ex-PRESS devices used, types of surgery performed, resulting in the conclusions from this Meta-analysis were not robust. Fourth, despite an extensive systematic search of the literature, only 3 studies assessed the cost of Ex-PRESS versus Trab, the 3 studies were performed at different times, different locations and different medical equipment prices, which could reduce the confidence level of the outcomes. Last, data from trials included in this Meta-analysis were compared at different durations, and we had no choice but to select the follow-up end-point to analyze major outcomes.

To our knowledge, the long-term results are still lacking in the present Meta-analysis paper. The two studies performed by de Jong *et al* [4-5], which have a mean follow-up period of 5y, showed that the postoperative costs for Ex-PRESS was less than Trab. With the increase in availability of more studies about the cost of the Ex-PRESS, it can potentially improve our study. Leaving the limitations aside, our findings implied that the Ex-PRESS could achieve higher success rate and less complication than Trab in the relative short-term based on the results of related studies with pooled samples, though it might cost much more than Trab because of surgery device. In the long run, the cost-effectiveness of the Ex-PRESS will decrease due to savings in eye surgeries (*e.g.* needling and cataract surgery) and eye drop medications during the follow-up[4].

In conclusion, our study indicates that the Ex-PRESS could achieve higher success rate and fewer complications (*i.e.* hypotony and hyphema) compared with Trab in the short-term. Meanwhile, it is confirmed that Ex-PRESS had a lower postoperative cost than Trab at 5-year when referred to cost-effectiveness. Nevertheless, the results should be considered with cautions because of the limitation (*e.g.* language limitation, publication bias, difference in study quality and different durations). Despite the limitations, we believe that the results of the current Meta-analysis study are clinically useful for glaucoma treatment. To draw an accurate conclusion, more RCTs with larger sample sizes or systematic studies are urgently needed to better evaluate the long-term benefits and cost-effectiveness both for Ex-PRESS and Trab. Although the Ex-PRESS shunt is gaining popularity, there was no complete consistence with the type of glaucoma for the use of the Ex-PRESS implantation, and reports concerning the relative efficacy and safety of Ex-PRESS and Trab are controversial. The implantation of Ex-PRESS shunt possesses a markedly higher cost and might be a major limitation in its adoption into clinical practice, especially in developing countries. In view of this point, it is necessary to inform the glaucoma patients about the cost-effectiveness and voluntary choice of the Ex-PRESS. Nevertheless, further studies should be done to evaluate cost-effectiveness to allow optimal choice of glaucoma surgery.

ACKNOWLEDGEMENTS

Foundation: Supported by the National Natural Science Foundation of China (No.81373826).

Conflicts of Interest: Wang L, None; **Sha F,** None; **Guo DD,** None; **Bi HS,** None; **Si JK,** None; **Du YX,** None; **Tang K,** None.

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