The efficacy of XEN gel stent implantation in glaucoma: a systematic review and meta-analysis

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Abstract

Background: XEN is a device for minimally invasive glaucoma surgery, and is used to treat POAG, pseudoexfoliative or pigmentary glaucoma, as well as refractory glaucoma. The efficacy of XEN in treating glaucoma remains to be confirmed and clarified. Hence, we conducted a systematic review and meta-analysis to examine the efficacy and associated complication of XEN implantations.

Methods: We conducted a literature search in PubMed, EMBASE, the Cochrane Library of Systematic Reviews, Web of Science, China National Knowledge Infrastructure, WanFang and SinoMed databases to identify studies, published before May 15, 2021, which evaluated XEN in glaucoma, and parameters for measurements included intra-ocular pressure (IOP), number of anti-glaucoma medications (NOAM), and bleb needling rate. We compared the measurements of XEN-only procedure between phaco-XEN and trabeculectomy, and we also did sub-analysis based on time points, glaucoma types, ethnics, etc. Sensitivity analyses and publication bias were conducted for evaluating bias. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA 2020) reporting guideline.

Results: We identified 78 eligible studies, analysis revealed obvious IOP reduction after XEN stent implantation (SMD: 1.69, 95% CI 1.52 to 1.86, p value < 0.001) and NOAM reduction (SMD: 2.11, 95% CI 1.84 to 2.38, p value < 0.001). Sub-analysis showed no significant difference with respect to time points, ethnicities, and economic status. No significant difference was found between XEN treatment effect on POAG and PEXG eyes and between pseudo-phakic and phakic eyes. Also no significant difference was found between XEN and phaco-XEN surgery in terms of IOP after surgery (SMD: -0.01, 95% CI -0.09 to 0.08, p value 0.894). However, NOAM (after publication bias correction) and bleb needling rate (RR: 1.45, 95% CI 1.06 to 1.99, p value 0.019) were lower in phaco-XEN group compared to XEN only group. Compared to trabeculectomy, XEN implantation had similar after-surgery IOP, however bleb needling rate (RR: 2.42, 95% CI 1.33 to 4.43, p value 0.004) was higher.

Conclusion: Our results confirmed that XEN is effective in lowering both IOP and NOAM till 48 months after surgery. It is noteworthy that XEN implantation leads to higher needling rate, compared to phaco-XEN or trabeculectomy. Further research, studying complications of XEN on non-European ethnicities, especially on Asian, are in urgent need before XEN is widely applied.

Keywords: Minimally invasive glaucoma surgery, XEN, Meta-analysis

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glaucoma (POAG) than people of European ancestry [2]. Intra-ocular pressure (IOP) lowering-la comoa treatments include anti-glaucoma medications, laser, surgery, and the combinations. Surgery is required when medications fail to control IOP or visual loss has reached a serious threshold.

Trabeculectomy and drainage device implantation are two methods widely adopted by clinicians. Trabeculectomy has become a standard surgical for glaucoma [3], it bypasses trabecular mesh and builds a drainage to help aqueous humor flow from anterior chamber to subconjunctival space. However, it can lead to high rates of complications including hypotony, anterior chamber hyphemia [4], etc. Minimally invasive glaucoma surgery (MIGS) has become surgical trend in recent years. As a type of MIGS, XEN Gel Stent (Allergan INC, Dublin, Ireland) implantations mimic the subconjunctival drainage of trabeculectomy, and are applied in real world since FDA approval in 2016. XEN implant is a 6-mm tube, made of porcine-gelatin cross-linked with glutaraldehyde, and has advantages of non-degrading and no tissue reaction [5] XEN45, the type of XEN that is now being merchandised, is designed to prevent hypotony and to maintain IOP around 6-8 mmHg with inner diameter of 45 μm [6]. XEN45 and XEN63, which is the new type of XEN, also have the indication of treating refractory POAG, and other types of OAG including pseudo-exfoliative glaucoma (PEXG). However, there are, currently, different opinions on the efficacy of XEN compared to traditional surgery in glaucoma according to previous studies [7–9], and its complications are also remain to be further investigated.

XEN is much easier to operate than trabeculectomy, thus it may help ophthalmologists, not specialists to treat glaucoma. Still, more evidence is required on the efficacy and complications of XEN before the device is widely applied. In this review, we did the most comprehensive meta-analysis on qualified clinical trials on this theme. With the data extracted, we did analysis to compare IOP-lowering and medication-lowering efficacy of XEN-only to XEN combined with phacoemulsification (phaco-XEN) and trabeculectomy surgeries respectively. Needling rate in different surgeries was also compared to study complications. Sub-analyses were carried out according to different study design, type of glaucoma, ethnicities, populations, economic status, and time points of follow-up to reduce confounding from those factors.

**Search strategy**

Electronic databases, including PubMed, EMBASE, the Cochrane Library of Systematic Reviews, Web of Science, China National Knowledge Infrastructure, WanFang and SinoMed databases were searched up to May 2021 for all clinical studies assessing XEN implant in glaucoma. The search strategy included the Medical Subject Headings terms and/or text words. The following combined search term was used: (XEN implant, XEN Gel Stent, gelatin stent) and (Glaucoma) (for the full search strategy, see the Additional file 2: Appendix 2 in the Supplement). The studies were restricted to human, but not restricted by date, language, or publication status.

**Study selection**

Studies were selected by two independent reviewers (Xiang Yang and Yang Zhao using following criteria:

1) patients were clearly diagnosed with glaucoma (no matter for POAG or PEXG, etc.);
2) the study had a control design;
3) XEN stent (XEN-45 or XEN-63) was used;
4) sufficient information to calculate the effect size was available;
5) the manuscript was published in a peer-reviewed journal as a full paper.

And criteria for excluding studies were:

1) Animal studies;
2) No original studies (case report, letter and response, review and meta-analysis or meeting abstract)

In the first stage, the titles and abstracts of all retrieved articles were screened. Disagreements were referred to a third reviewer (Yu Zhong) to achieve a resolution. In the second stage, full texts of the potentially relevant studies were retrieved and reviewed using the same methods as in first stage.

**Data extraction and quality assessment**

The following information was independently extracted from the included studies by two investigators (Xiang Yang and Yang Zhao) and jointly verified for accuracy: author, year of publication, country of study, eyes included, female/male ratio, age, surgical implantation, follow-up period, etc. We contacted authors when there was unclear information. JADAD Scale [11] (for Randomized Controlled Trials) or Newcastle–Ottawa Scale [12] (for non-randomized Studies) were used for evidence quality assessment.
Outcome measures
The final included outcomes were: IOP before and after surgery; number of antiglaucoma medications (NOAM); bleb needling rate.

Statistical analysis
The pooled relative risk (RR) or standardized mean difference (SMD) in the meta-analysis were calculated by weighting individual risk ratio (RR)/SMD by the inverse of their variance. The RRs as well as 95% CIs were calculated using the random-effects model as it assumes that true effect might vary from study to study and thus, estimates the mean of a distribution of true effects, assigning a more balanced weight to each study. All tests were two-tailed with a $p$ value < 0.05 considered statistically significant. Analysis using the fixed-effects model was carried out in the absence of heterogeneity. The Cochran’s Q test was used to test for heterogeneity ($p$ value < 0.10 is indicative of heterogeneity). Given that the power of this statistical test is low when a meta-analysis includes a small number of studies, the Higgins test ($I^2$) was also used, that describes the percentage of total variation across studies due to heterogeneity rather than chance (low heterogeneity: < 25%, moderate heterogeneity: 25–75% and high heterogeneity: > 75%) [13]. Leave-one-out sensitivity as well as stratified analyses were conducted to assess statistical robustness and to detect the possible causes of heterogeneity between studies. The Begg rank correlation [14] and Egger regression asymmetry test [15] were used to examine publication bias ($P$ < 0.05 was considered statistically significant). If publication bias was confirmed, a trim-and-fill method developed by Duval and Tweedie was implemented to adjust the bias. Then, we replicated the funnel plot with their “missing” counterparts around the adjusted summary estimate. All those were conducted with the software Stata 15.0.

Results
Literature search
The search strategy for this meta-analysis yielded 725 publications, and 429 studies were excluded because of duplication. After reading the titles and abstracts, 57 studies were excluded. 239 possible full-text studies were carefully reviewed (Animal study [$n = 4$]; Case report [$n = 8$]; Review and meta-Analysis [$n = 64$]; Meeting abstract [$n = 25$]). Finally, 78 trials were included for quantitative analysis [5, 16–92] (Fig. 1). The characteristics of included lectures are summarized in Table 1.

Efficacy of XEN standalone surgery for the management of glaucoma
6554 eyes from 65 studies and 4385 eyes from 42 studies were included for IOP and NOAM analysis before and after XEN standalone procedure. There were no significant differences in IOP or NOAM between prospective and retrospective study (SFig1 and SFig2). Therefore, we combined them in the further analyses.

The total study sample included 3432 eyes before surgery and 3122 eyes after surgery. Overall analysis showed IOP had an obvious improvement after XEN stent implantation (SMD: 1.69, 95% CI 1.52 to 1.86, $p$ value < 0.001) (sFig3). Fewer NOAM was also achieved in glaucoma patients after XEN standalone procedure (SMD: 2.11, 95% CI 1.84 to 2.38, $p$ value < 0.001) (sFig4). Based on the follow-up duration, studies were divided into six categories: 6 m, 12 m, 18 m, 24 m, 36 m and 48 m. Considering IOP, no big difference was found at different time point (sFig5). As for NOAM, the difference became less and less with time, although significance was still not reached (sFig6). 6 studies addressing the IOP-lowering effect of XEN in Asian populations (168 eyes in before-surgery group and 160 eyes in after-surgery group), 8 studies addressing the treatment effect of XEN in North American populations (351 eyes in before surgery group and 284 eyes in after surgery group) and 45 studies addressing this association in European populations (2913 eyes in before surgery group and 2678 eyes in after surgery group), were included in the stratified analyses by ethnicity (SFig7). Subgroup was further done by developed vs. developing country (SFig8). No statistical difference was found in different gene background and medical care, the patients could get. NOAM reduction had no difference in developed vs developing country subgroup analysis (SFig9) or ethnicity subgroup analysis (SFig10). Heterogeneity was high in most of the stratified analyses.

Given that differences in the pseudo-exfoliation glaucoma (PEXG) and primary open angle glaucoma (POAG) could potentially bias the current meta-analysis, analyses by different glaucoma were also conducted. Three studies with 237 POAG eyes and 118 PEXG eyes were included. Interestingly, no different treatment effect was found in these analyses on IOP and Medication (SFig11-14). Furthermore, analysis was conducted in patients with or without prior interventional therapies and patients with pseudophakic and phakic eyes. IOP before and after XEN surgery, medication before and after procedure and bleb needling rate shown no difference in pseudophakic and phakic eyes (SFig15-19).
Efficacy and safety of XEN combined with cataract surgery for glaucoma patients

In some centers, cataract surgery was done at the same time when XEN stent was being implanted (phaco-XEN). In glaucoma patients IOP dropped significantly after phaco-XEN surgery irrespective of ethnicity (SFig20) or follow-up duration (SFig21). Medication needed for lowering IOP also had a clear reduction (SFig22). Further comparison was done between XEN standalone surgery and phaco-XEN surgery on IOP and medication. After procedure, there was no significant difference in IOP (SMD: \(-0.01, 95\%\) CI \(-0.09\) to \(0.08, p\) value 0.894) (SFig23) and NOAM (SMD: \(0.09, 95\%\) CI \(-0.04\) to \(0.23, p\) value 0.170) (Fig. 2) between two group. Stratified analysis was also done by ethnicity and follow-up duration for IOP. In Asian population a clear difference of after-surgery IOP was found between two procedures (SMD: \(0.57, 95\%\) CI \(0.23\) to \(0.91\)), which was absent in both European and North American patients (SFig24). On different follow-up time points, patients in different procedures shared a similar IOP (Fig. 3). Nevertheless, lower IOP before surgery was found in phaco-XEN group when baseline was analyzed (SMD: \(0.31, 95\%\) CI \(0.15\) to \(0.47, p\) value < \(0.001\)), especially in European population (SFig25). Patients whose IOP achieved < 18 mmHg, < 15 mmHg or had a reduction > 20% from baseline were counted and RR of success rate was obtained, which showed no difference in efficacy of treatment between XEN alone and phaco-XEN (data not shown). For considering complications, bleb
| First Author | Publish Year | Country | Study design | Eyes included | Male/Female | Age (Mean ± SD) | Surgical Implantation | Follow-up | JADA/NOS score |
|--------------|--------------|---------|--------------|---------------|-------------|----------------|----------------------|-----------|----------------|
| Sheybani, A | 2015         | US      | Prospective  | 37            | 14/23       | 69.6±7.7       | phaco-XEN            | 12 m      | 1              |
| Pérez-Torre-grosa, V. T | 2016        | Spain   | Prospective  | 30            | 5/13        | 76±5.85        | phaco-XEN            | 12 m      | 1              |
| Sheybani, A | 2016         | US      | Prospective  | 49            | 20/29       | 64.3           | XEN                  | 12 m      | 1              |
| Fea, A. M   | 2017         | Italy   | Prospective  | 12            | 5/6         | 71.3±10        | XEN                  | 12 m      | 1              |
| Galal, A.   | 2017         | Germany | Prospective  | 13            | 6/4         | 73.1±10        | phaco-XEN            | 12 m      | 1              |
| Grover, D   | 2017         | US      | Prospective  | 65            | 30/35       | 70±12.3        | XEN                  | 12 m      | 0              |
| Hengerer, F. H | 2017      | Germany | Retrospective | 242          | 100/142     | 67.6±13.6      | XEN; phaco-XEN       | 12 m      | 5              |
| Ilveskoski, L | 2017       | Finland | Retrospective | 10           | 4/6         | 77.4±5.7       | XEN                  | 6 m       | /              |
| Olate-Pérez, Á. | 2017    | Spain   | Prospective  | 30            | 5/13        | 76±5.85        | phaco-XEN            | 12 m      | 1              |
| Ozal, S.A   | 2017         | Turkey  | Retrospective | 15           | 10/5        | 63.6±13.3      | XEN; phaco-XEN       | 12 m      | /              |
| Schlenker, M. B | 2017   | Canada  | Retrospective | 354          | 176/178     | 66.4           | XEN; TB              | 36 m      | 7              |
| Arnjots, TS | 2018         | Sweden  | Retrospective | 19           | 7/12        | 74.2±8.4       | XEN; phaco-XEN       | 12 m      | /              |
| De Gregorio, A | 2018      | Italy   | Prospective  | 41            | 13/20       | 74±7.1         | phaco-XEN            | 12 m      | 0              |
| Hengerer, F. H | 2018     | Germany | Retrospective | 110          | 46/64       | 69.6±13.7      | XEN                  | 12 m      | 5              |
| Hohberger, B | 2018       | Germany | Retrospective | 111          | 64/47       | 68±14          | XEN                  | 6 m       | /              |
| Karimi, A   | 2018         | UK      | Retrospective | 17           | 9/8         | 76.1           | XEN                  | 12 m      | 1              |
| Karimi, A   | 2018         | UK      | Retrospective | 259          | 144/115     | 74.8           | XEN; phaco-XEN       | 18 m      |                |
| Mansouri, K | 2018         | Switzerland | Prospective  | 110          | 24/61       | 74.8±9.4       | XEN                  | 12 m      | 1              |
| Mansouri, K | 2018         | Switzerland | Prospective  | 149          | 32/81       | 74.4±9.4       | XEN; phaco-XEN       | 12 m      | 1              |
| Sng, C. C   | 2018         | UK      | Prospective  | 24            | 9/15        | 45.3±18.1      | XEN                  | 12 m      | 0              |
| Tan, S. Z   | 2018         | UK      | Retrospective | 43           | 18/21       | 70.1±13.8      | XEN                  | 12 m      |                |
| Widder, R. A | 2018      | Germany | Retrospective | 261          | 92/141      | 73±11          | XEN; phaco-XEN       | 18 m      |                |
| Arad, T     | 2019         | Germany | Retrospective | 10           | 4/6         | 64±4.7         | XEN                  | 24 m      |                |
| Gillmann, K | 2019         | Switzerland | Prospective  | 110          | 24/61       | 74.8±9.4       | XEN; phaco-XEN       | 24 m      | 1              |
| Heidinger, A | 2019       | Austria | Retrospective | 199          | 84/115      | 74.8±10.5      | XEN                  | 18 m      |                |
| Hengerer, F. H | 2019     | Germany | Retrospective | 148          | 89/59       | 68.4±13.9      | XEN                  | 12 m      |                |
| Ibáñez-Muñoz, A | 2019      | Spain   | Retrospective | 21           | 13/7        | 80.9±8.1       | XEN; phaco-XEN       | 12 m      |                |
| Kalina, AG  | 2019         | USA     | Prospective  | 47            | 14/28       | 78.15±8.55     | XEN; phaco-XEN       | 12 m      | 1              |
| Laroche, D  | 2019         | US      | Retrospective | 12           | -           | -              | XEN                  | 12 m      |                |
| Lenzhofer, M | 2019       | Austria | Retrospective | 64           | 35/29       | -              | XEN; phaco-XEN       | 48 m      | 1              |
| Lenzhofer, M | 2019       | Austria | Prospective  | 137          | 67/70       | 75.2±7.0       | XEN; phaco-XEN       | 24 m      | 1              |
| First Author          | Publish Year | Country   | Study design | Eyes included | Male/Female | Age (Mean ± SD) | Surgical Implantation | Follow-up | JADA/NOS score |
|----------------------|--------------|-----------|--------------|---------------|-------------|-----------------|-----------------------|-----------|----------------|
| Lenzhofer, M         | 2019         | Austria   | Prospective  | 66            | 28/38       | 72.2 ± 12.5     | XEN; phaco-XEN        | 12 m      | 0              |
| Mansouri, K          | 2019         | Switzerland | Prospective  | 149           | 32/81       | 74.4 ± 9.4      | XEN; phaco-XEN        | 24 m      | 1              |
| Marcos Parra, M.T    | 2019         | Spain     | Retrospective | 121           | 59/62       | 71.2 ± 11.7     | XEN; phaco-XEN, TB    | 12 m      |                |
| Marques, RE          | 2019         | Portugal  | Retrospective | 60            | 26/34       | 73              | XEN; phaco-XEN        | 6 m       |                |
| Midha, N             | 2019         | Switzerland | Prospective  | 149           | 63/70       | 74.4 ± 9.6      | XEN; phaco-XEN        | 24 m      | 1              |
| Qureshi, A           | 2019         | UK        | Retrospective | 37            | -           | 45.97 ± 15.24   | XEN                   | 12 m      |                |
| Reitsamer, H         | 2019         | Austria   | Prospective  | 161           | 90/95       | 71.8 ± 10.5     | XEN                   | 24 m      | 1              |
| Smith, M             | 2019         | UK        | Retrospective | 68            | 35/33       | 76 ± 10         | XEN                   | 12 m      |                |
| Teus, M. A           | 2019         | Spain     | Retrospective | 48            | 27/21       | 72.7 ± 12.51    | XEN                   | 48 m      |                |
| Barão, R.C           | 2020         | Portugal  | Retrospective | 42            | 12/30       | 71.7 ± 12       | XEN                   | 18 m      |                |
| Bager, E. F          | 2020         | Turkey    | Retrospective | 29            | 17/12       | 67.5 ± 10.3     | XEN                   | 24 m      |                |
| Bravetti, G.E        | 2020         | Switzerland | Retrospective | 60            | 32/28       | 64.7 ± 23.1     | XEN                   | 12 m      |                |
| Buffault, J          | 2020         | France    | Retrospective | 107           | 58/49       | 68.3 ± 10.8     | XEN; phaco-XEN        | 6 m       |                |
| Busch, T             | 2020         | Sweden    | Retrospective | 113           | 53/50       | 70.8 ± 11.8     | XEN                   | 12 m      |                |
| Cutolo, CA           | 2020         | Italy     | Prospective  | 123           | 58/65       | 74.5 (67.1–81.3)| XEN                   | 12 m      | 1              |
| Dar, N               | 2020         | Israel    | Retrospective | 46            | 22/24       | 74 ± 9.4        | XEN                   | 6 m       |                |
| Do, A                | 2020         | US        | Retrospective | 137           | 76/61       | 72 ± 13.2       | XEN                   | 12 m      |                |
| Fea, A. M            | 2020         | Italy     | Prospective  | 298           | 149/149     | 70.3 ± 11.8     | XEN                   | 12 m      | 1              |
| Fernández-García, A  | 2020         | Spain     | Retrospective | 40            | 17/23       | 77.31 ± 6.33    | XEN                   | 36 m      |                |
| Fernández-García, A  | 2020         | Spain     | Retrospective | 93            | 22/41       | 74 ± 8          | XEN                   | 36 m      |                |
| Gabbay, I. E         | 2020         | UK        | Retrospective | 151           | 82/69       | 74.3 ± 11.0     | XEN                   | 24 m      |                |
| Gillmann, K          | 2020         | Switzerland | Prospective  | 92            | 23/45       | 76.3 ± 9.1      | XEN                   | 36 m      | 1              |
| Gillmann, K          | 2020         | Switzerland | Prospective  | 37            | 10/27       | 77.7 ± 9.1      | XEN                   | 24 m      | 1              |
| Hong, K              | 2020         | US        | Prospective  | 28            | 11/17       | 66.6 ± 11       | XEN                   | 12 m      | 0              |
| Hu, J. Y             | 2020         | Singapore | Retrospective | 63            | 50/13       | 71.9 ± 7.1      | XEN                   | 6 m       |                |
| Ibáñez-Muñoz, A      | 2020         | Spain     | Retrospective | 73            | 39/34       | 79.7 ± 8.2      | XEN                   | 12 m      |                |
| Laborda-Guirao, T    | 2020         | Spain     | Retrospective | 80            | 42/38       | 74.0 ± 10.4     | XEN                   | 12 m      |                |
| Lavin-Dapena, C      | 2020         | Spain     | Prospective  | 11            | 2/9         | 78.8            | XEN                   | 18 m      | 0              |
| Linton, E            | 2020         | UK        | Retrospective | 151           | 38/113      | 71 ± 12.6       | XEN                   | 12 m      |                |
| Midha, N             | 2020         | Switzerland | Prospective  | 51            | 15/36       | 74.4 ± 9.4      | XEN                   | 24 m      | 0              |
| Olgun, A             | 2020         | Turkey    | Retrospective | 221           | 42/72       | 65.8 ± 10.6     | XEN                   | 24 m      |                |
| Olgun, A             | 2020         | Turkey    | Retrospective | 80            | 29/35       | 61.1 ± 12.1     | XEN                   | 3 m       |                |
| First Author | Publish Year | Country       | Study design | Eyes included | Male/Female | Age (Mean ± SD) | Surgical Implantation | Follow-up | JADA/NOS score |
|--------------|--------------|---------------|--------------|--------------|-------------|-----------------|-----------------------|-----------|----------------|
| Post, M [71] | 2020         | Poland        | Prospective  | 20           | 6/11        | 69.85 ± 4.69   | XEN                   | 12 m      | 1              |
| Rather, P.A. [73] | 2020       | US            | Retrospective| 92           | 31/35       | 75.3           | XEN, phaco-XEN       | 12 m      | 2              |
| Rauchegger, T [74] | 2020     | Austria       | Retrospective| 79           | 49/30       | -              | XEN, phaco-XEN       | 24 m      | 2              |
| Schargus, M. [77] | 2020      | Germany       | Retrospective| 113          | 73/80       | 70.2 ± 10.8    | XEN                   | 12 m      | 1              |
| Scheres, M. J [78] | 2020      | Netherlands   | Retrospective| 82           | 41/41       | 69 ± 8         | XEN                   | 24 m      | 1              |
| Sharpe, R [80] | 2020         | US            | Retrospective| 179          | 88/91       | 74.5 ± 7.6     | XEN, TB               | 6 m       | 1              |
| Teixeira, F.J [86] | 2020        | Portugal      | Prospective  | 12           | 6/6         | 59 ± 19        | XEN                   | 12 m      | 1              |
| Theillac, V [88] | 2020        | France        | Retrospective| 105          | 47/58       | 72.1 ± 8.7     | XEN                   | 6 m       | 2              |
| Walek, E [90] | 2020         | Poland        | Prospective  | 90           | -           | 72 ± 13        | XEN                   | 48 m      | 1              |
| Widdert, R A [92] | 2020      | Germany       | Retrospective| 90           | -           | 72 ± 13        | XEN                   | 48 m      | 1              |
| Chao, Y.J [23] | 2021         | China         | Retrospective| 37           | 24/14       | 53.4 ± 13.6    | XEN                   | 12 m      | 1              |
| Oddone, F [65] | 2021         | Italy         | Prospective  | 108          | 84/84       | 69.1 ± 12.9    | XEN                   | 6 m       | 0              |
| Reitsamer, H [76] | 2021        | Austria       | Retrospective| 212          | 83/94       | 76 ± 7.1       | XEN                   | 36 m      | 3              |
| Tan, N.E [84] | 2021         | US            | Retrospective| 50           | -           | 71.0 ± 13.4    | XEN                   | 12 m      | 1              |
| Urcola, A [89] | 2021         | Spain         | Retrospective| 20           | 3/7         | 76.1 ± 12      | XEN                   | 12 m      | 1              |

![Fig. 2](image_url) Meta-analysis of XEN-only surgery compared with phaco-XEN for NOAM after surgery. The total study sample included 618 eyes undergoing XEN only and 415 eyes undergoing phaco-XEN. Overall analysis of NOAM after surgery (SMD: 0.09, 95% CI -0.04 to 0.23, p value 0.170) had no difference between two groups.
Fig. 3  Meta-analysis of XEN-only surgery compared with phaco-XEN for IOP by follow-up duration after surgery. The total study sample included 1314 eyes undergoing XEN-only surgery and 1160 eyes undergoing phaco-XEN. Overall analysis of IOP after surgery (SMD: -0.01, 95% CI -0.08 to 0.07, p value 0.894) had no difference between two groups.
needling rate was compared. Although similar IOP reduction was found in XEN alone and phaco-XEN group, bleb needling rate was significantly high in XEN standalone group (RR: 1.45, 95% CI 1.06 to 1.99, \( p \) value 0.019) (Fig. 4).

**Efficacy and safety comparisons between XEN standalone and trabeculectomy procedure**

Besides comparing to phaco-XEN, XEN standalone procedure was also compared with trabeculectomy surgery. A preference of assigning patients of higher

| First author | XEN only n/N | phaco-XEN n/N | Bleb needling rate (95% CI) | Weight |
|--------------|--------------|---------------|-----------------------------|--------|
| Mansouri, K. (2018) | 18/30 | 37/109 | 1.77 (1.19, 2.62) | 22.50 |
| Mansouri, K. (2019) | 16/33 | 42/99 | 1.14 (0.75, 1.74) | 21.40 |
| Midha, N. (2019) | 18/30 | 27/109 | 2.42 (1.56, 3.76) | 20.67 |
| Midha, N. (2020) | 5/13 | 15/38 | 0.97 (0.44, 2.15) | 10.79 |
| Reitsamer, H. (2019) | 50/114 | 33/88 | 1.17 (0.83, 1.64) | 24.65 |
| Overall, DL | 107/220 | 154/443 | 1.46 (1.06, 1.99) | 100.00 |

\( (I^2 = 59.9\%, \ p = 0.041) \)

**Fig. 4** Meta-analysis of XEN-only surgery compared with phaco-XEN for bleb needling rate. The total study sample included 220 eyes undergoing XEN-only surgery and 443 eyes undergoing phaco-XEN surgery. Overall bleb needling rate was significantly high in XEN-only group (RR: 1.45, 95% CI 1.06 to 1.99, \( p \) value 0.019)

| First author | XEN only | Trabeculectomy | IOP Before surgery (95% CI) | Weight |
|--------------|----------|----------------|----------------------------|--------|
| Marcos Parra (2019) | 17 | 22.20 (6.80) | 30 | 21.30 (5.80) | 0.15 (-0.45, 0.74) | 7.30 |
| Olgun, A. (2020) | 51 | 24.40 (4.30) | 60 | 25.80 (6.10) | -0.26 (-0.64, 0.11) | 18.44 |
| Olgun, A. (2020) | 31 | 23.70 (4.00) | 49 | 29.10 (9.30) | -0.70 (-1.16, -0.24) | 12.09 |
| M. A. Teus (2019) | 10 | 19.00 (4.60) | 15 | 19.50 (6.40) | -0.09 (-0.89, 0.71) | 4.04 |
| Wagner, F. M. (2020) | 82 | 19.00 (5.30) | 89 | 21.00 (6.20) | -0.35 (-0.65, -0.04) | 28.37 |
| Sharpe, R. (2020) | 90 | 17.80 (6.00) | 89 | 20.40 (9.00) | -0.34 (-0.64, -0.05) | 29.76 |
| Overall, IV | 281 | 332 | -0.33 (-0.49, -0.16) | 100.00 |

\( (I^2 = 7.5\%, \ p = 0.368) \)

**Fig. 5** Meta-analysis of XEN surgery compared with trabeculectomy procedure for IOP before surgery. The total study sample included 281 eyes undergoing XEN-only surgery and 332 eyes undergoing trabeculectomy procedure. Overall analysis of IOP before surgery (SMD: -0.33, 95% CI -0.49 to -0.16, \( p \) value < 0.001) was lower in trabeculectomy procedure group.
IOP to trabeculectomy group was found when checking baseline (SMD: -0.33, 95% CI -0.49 to -0.16, p value < 0.001) (Fig. 5). After surgery, IOP showed no difference between two groups (Fig. 6), while patients underwent trabeculectomy had lower bleb needling rate (RR: 2.42, 95% CI 1.33 to 4.43, p value 0.004) (Fig. 7).

Sensitivity analyses and publication bias
When leave-one-out sensitivity analyses were conducted, all the results remained statistically robust (Table 2, SFig26-33). Egger and Begg test was applied to test publication bias. Publication bias was found in IOP and medication comparison before and after phaco-XEN surgery. Publication bias was also found in after-surgery
medication comparison of XEN standalone vs. phaco-XEN groups (Table 2). By trim and fill method, both the results of fixed and random effects model are the same with original result (Additional file 3: Appendix 3, SFig34-36), except for after-surgery medication comparison of XEN standalone vs. phaco-XEN groups.

### Discussion

By screening through 725 research records and finally going into details of 78 clinical trials concerning XEN gel stent implantation in glaucoma, we conducted the most comprehensive meta-analysis ever since, in our knowledge. In this study, quantitative analyses were done to generate consolidated results, however, with no randomized clinical trial (RCT) available, elaborately designed RCTs should be carried out in the future for more convincing conclusions.

In this study, we were able to statistically evaluate the efficacy of XEN implantation in glaucoma in terms of IOP and NOAM. Both the measurements were effectively controlled within six months of XEN surgery and according to Lenzhofer. et al. [54] and Teus. et al. [87], IOP was maintained at a level of 13.40 ± 3.10 mmHg and 10.20 ± 5.20 mmHg 48 months after surgery. NOAM seems to increase with longer time points, follow-up period over 48 months is required to find out whether this is significant. Although there is genetic heterogeneity among different ethnicities concerning glaucoma morbidity, we did not find any difference when evaluating IOP or NOAM reduction efficacy of XEN surgery among African, European, North American, Oceanian, or Asian. Currently, most trials are on European and more clinical studies are in urgent need in other areas, especially for China mainland.

Besides POAG, XEN implantation is indicated to treat refractory POAG when previous treatments failed, and also for special types of OAG including PEXG, pigmentary glaucoma, juvenile glaucoma, and uveitic glaucoma. Studies stated that XEN is effective in treating both refractory glaucoma [93] and uveitic glaucoma [94], with bleb fibrosis, being the most common complications, which requires bleb needling. We did analysis on the four trials comparing XEN efficacy in POAG and PEXG and the results further confirmed that XEN implantation can reduce IOP and NOAM in PEXG as powerful as POAG.

Phacoemulsification is often combined with traditional filtering surgery such as TB, and phaco-XEN is possibly considered by clinicians while deciding the surgery. Whether phaco-XEN is superior to XEN-only or not has drawn attentions from a lot of studies. Thirty studies with totally over 1,000 eyes in each group were included in our analysis and we found no significant difference in IOP-lowering effect between XEN-only and phaco-XEN groups at the last follow-up. When we go into sub-analysis of various time points, XEN-only reveals lower after-surgery IOP than phaco-XEN in the short time points of 6 months and 12 months, the gap narrows with time, although this trend is of no significance. Lim. et al. [8] and Bo. et al. [9] did meta-analysis for closer time points of 1 day, 1 week, 1 month, 3 months, and 6 months, they showed that XEN-only has significant lower IOP than the combined group. Considering the time point of 6 months, our results are consistent with the above two meta-analysis that XEN-only has significant lower IOP than the combined group. We also found that NOAM and bleb needling rate was significantly lower in phaco-XEN than XEN-only, which indicates fewer fibrosis in combined group and phaco-XEN can be adopted with patients in high-risk of fibrosis. Traditional TB also showed lower bleb needling rate than XEN implantation, thus in our opinion, this new type of MIGS leads to worse bleb fibrosis although the gel is compatible in human

### Table 2  Sensitivity Analysis and Publication bias

|                          | SMD Fluctuation | 95% CI Fluctuation | Publication bias (P value) |
|--------------------------|-----------------|--------------------|---------------------------|
| **Before and after XEN surgery** |                 |                    |                           |
| IOP                      | 1.65 ~ 1.71     | 1.49 ~ 1.88        | 0.298                     |
| Medication               | 2.06 ~ 2.14     | 1.80 ~ 2.41        | 0.597                     |
| **Before and after phaco-XEN surgery** |                 |                    |                           |
| IOP                      | 1.60 ~ 1.72     | 1.37 ~ 1.99        | 0.007                     |
| Medication               | 2.13 ~ 2.28     | 1.78 ~ 2.65        | 0.048                     |
| **XEN vs. phaco-XEN surgery** |                 |                    |                           |
| IOP before surgery       | 0.25 ~ 0.33     | 0.11 ~ 0.50        | 0.162                     |
| IOP after surgery        | -0.21 ~ 0.02    | -0.13 ~ 0.13       | 0.405                     |
| Medication before surgery| 0.28 ~ 0.35     | 0.11 ~ 0.54        | 0.970                     |
| Medication after surgery | 0.82 ~ 0.14     | -0.07 ~ 0.28       | 0.014                     |
Conclusion

In this meta-analysis including 78 trials with thousands of eyes, we did the most comprehensive exploration ever on the efficacy of XEN implantation in treating glaucoma. To conclude, XEN is effective in both lowering IOP and NOAM till 48 months after surgery. It is also as effective in patients of PEXG as those of POAG, in terms of IOP, NOAM, and needling rate. Phaco-XEN may require fewer medications for patients after surgery, however the final IOP is similar to XEN-only surgery. It is noteworthy that XEN implantation leads to higher bleb fibrosis and needling rate, and phaco-XEN or TB may be a better choice to prevent filtering failure. Further studies on vision-threatening complications such as hypotony, choroidal leakage, and bleb infection comparing to other surgeries are in urgent need for evaluating safety of XEN implantation. Also, clinical trials on Asians are quite limited which restricts the application of XEN to a wider part of the world.

Supplementary Information

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Precis

Our study revealed that XEN-only implantation procedure is as effective as phaco-XEN and trabeculectomy in lowering IOP in glaucoma. However, XEN procedure leads to higher bleb needling rate than trabeculectomy.

Data and materials availability

All data needed to evaluate the conclusions in the paper are present in the paper or the Supplementary Materials.

Authors’ contributions

Xiang Yang composed the manuscript and did the literature searching and screening. Yang Zhao did the literature searching, screening, and data extraction. Zhong Yu was in charge of checking the involved publications and data. Xuanchu Duan came up with the idea and supervised the whole process. The author(s) read and approved the final manuscript.

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