Comparison between Ologen implant and Mitomycin C in trabeculectomy: A Systematic Review and Meta-Analysis

Xiaoyan Liu
Lanzhou University Second Hospital
Yali Du
The clinical medical department
Min Lei
Lanzhou University Second Hospital
Leyi Zhuang
Lanzhou University Second Hospital
Peng Lv (lvpeng201905@163.com)

Research article

Keywords: Trabeculectomy, glaucoma, Ologen, Mitomycin C, Meta-analysis.

Posted Date: June 26th, 2019

DOI: https://doi.org/10.21203/rs.2.10619/v1

Abstract

Objective To evaluate the effectiveness and safety of the biodegradable collagen matrix (Ologen) implant in trabeculectomy. Research design and methods We searched Pubmed, Cochrane library, Embase and Web of Science databases to find studies that met our pre-stated inclusion criteria. Reference lists of retrieved articles were also reviewed. The search was finished by February 2019. Study selection, data extraction, quality assessment, and data analyses were performed according to the Cochrane standards. Either a fixed or a random-effects model was used to calculate the overall combined risk estimates. The efficacy measures were the weighted mean differences (WMDs) for the intraocular pressure reduction (IOPR) and the glaucoma medications reduction, the odds ratio (OR) for the success rate and adverse events. Results Fifteen randomized controlled trials involved 682 eyes were included in the meta-analysis. There were no statistically differences between two groups in the IOPR at any time postoperatively. The MD of the IOPR was [MD= -0.45,95% Confidence Interval (CI), (-2.36,1.46), P=0.65] at one day, [MD= -0.82,95% CI, (-1.97, 0.33), P=0.16] at one week, [MD= -1.33, 95% CI,(-3.12, 0.47), P=0.15] at one month, [MD= 0.11,95% CI, (-1.87, 2.08), P=0.92] at three months, [MD= -0.60,95% CI, (-2.27, 1.06), P=0.48] at six months, [MD= -0.33,95% CI, (-1.99, 1.32), P=0.69] at one year, [MD= -0.13,95% CI, (-1.90, 1.65), P=0.89] at two years, [MD= 2.54,95% CI, (-2.83, 7.90), P=0.35] at three years, [MD= 3.04,95% CI, (-3.95, 10.03), P=0.39] at five years. There was no statistically significant difference between the Ologen groups and MMC groups concerned the complete success rate [OR=1.19, 95%CI, (0.83, 1.71), P=0.35]. With regard to the adverse events, no obvirously significance was observed. Seven studies reported the change of antiglaucoma medications. We found that the change of antiglaucoma medications is higher in MMC groups than that in Ologen groups [MD=-0.18, 95%CI, (-0.33, -0.03), P=0.02]. There is no significant difference in complications between the two groups. Conclusions From the current evidence, Ologen may be an alternative choice for trabeculectomy when considering the efficacy and safety. However, MMC might be the preferred choice concerned cost-effectiveness.

Background

Glaucoma is a group of diseases characterized by optic atrophy and visual field defects. It is the leading cause of irreversible blindness worldwide which can't be cure[1]. And the prevalence of glaucoma will be increasing to 79.6 million by 2020[2]. The main treatment for glaucoma is to reduce the intraocular pressure (IOP) in order to slow or prevent further vision loss through drugs, lasers and surgeries[3]. Trabeculectomy was first introduced by Cairns in 1968 and is still widely used [4-6]. The surgeons establish the aqueous drainage channel by excising part of the trabecular, draining the aqueous humor to the sclera and the conjunctiva, and then absorbing by the surrounding tissue. However, filtration obstruction caused by scar formation during tissue healing is the main cause of trabeculectomy failure[7]. In the past few years, the use of adjunctive antimetabolites has greatly improved the success rate of glaucoma surgery, such as the 5-flourouracil (5-FU) and Mitomycin C (MMC)[8-11]. However, the use of antimetabolites also brings a series of complications, such as shallow anterior chamber (AC), hypotony, bleb leakage, bleb infection, etc[12,13].

In recent years, some studies have attempted to use bevacizumab for trabeculectomy[14,15]. Vahedian Z and Kaushik J reported that adjunctive bevacizumab in trabeculectomy is effective and comparable to MMC[16,17]. In addition, results of a meta-analysis showed that the combination of bevacizumab with antimetabolites did not show any benefit or harm compared with antimetabolites alone[18]. Hence there is an urgently need for an adjunctive wound-modulating agent with properties that help achieve intraocular pressure control as well as low rates of complications[19]. Ologen, a biodegradable collagen-glycosaminoglycan copolymer matrix implant was introduced to reduce postoperative fibrosis and avoid complications related to the use of antifibroblastic agents[20]. It provides a scaffolding so as to guide the patterns of fibroblast migration and normalize secreted extracellular matrix deposition, preventing fibrosis and helping reorganize subconjunctival scarformation[21].

Whether the Ologen plant is an alternative device is unknown. Several randomized controlled trials (RCTs) to compare the outcomes of trabculectomy with Ologen implant versus MMC have been done. The benefit of the Ologen implant can be observed in some studies, they showed that the success rate using trabculectomy with the Ologen implant maybe higher than that achieved by trabculectomy with MMC[22-29], but not in the others[30,31]. These contradictory statements prevent us reaching a consensus. Thus, our objective is to compare the efficacy and safety of trabculectomy with Ologen implant versus MMC using a systematic review and Meta -analysis.

Methods

The systematic review and meta-analysis was performed according to the reporting guidelines implied by Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA statement[32,33].

Literature search (Search strategy)

We conducted PubMed, Embase, Web of science and Cochrane library database for articles published prior to February, 2019. We also searched Clinical Trials. The search terms were as follows:“trabeculectomy”, “Filtering Surgery”, “Trab”, “Biodegradable collagen matrix”, Ologen”, “Mitomycin”, and “MMC”. Retrieval strategies recommended by Cochrane Systematic Review Manual were followed, with the MeSH and freedom word combined and pre-retried. All abstracts, comparative studies, nonrandomized trials, and citations were searched comprehensively. A recursive manual search of cited references in published studies on the Internet websites was performed to identify other relevant studies. Further searches were done by reviewing abstract booklets and review articles. This study doesn’t have a limitation in the language and data of articles. Besides, we conducted a manual search using reference lists of included articles.

Study selection

Two independent researchers reviewed all of the articles. Studies will be eligible only when they met with the following criteria: (1) clinical trails instead of animal experiments. (2) study design–randomized controlled clinical trials(RCTs). (3) comparison of the outcome between Ologen implant and MMC in primary trabeculectomy. (4) at least one of the outcomes reported: qualified success rate of operation, IOPR, postoperative complications, the use of glaucoma medications. (5) The follow-up period≥6 months. These studies will be excluded: (1) studies involving other types of glaucoma surgery such as non-penetrating glaucoma surgery. (2) observational studies or non-RCTs.

Data extraction and quality assessment (Data extraction)

Two independent researchers extracted the data from each RCT using a standardized data-collection form, if there were disagreements between them, the third reviewer would participate in the process. Information was recorded as follows:(1) the general characteristics: name of the first author, title, year of publication, countries, age, (2) study design: intervention arms, sample size, type of glaucoma (POAG, PEXG, PACG, Others), follow-up period, (3) outcome: preoperative and postoperative IOP, complete and qualified success rate, postoperative complications, postoperative adjunctive therapy medication. The Cochrane Risk of Bias Tool was used to assess the quality of included studies. This assessment included 6 parts: random sequence generation, allocation concealment, blinding (patient, personnel and assessor), incomplete outcome data, selective reporting and other bias. The risk of bias was determined according to the criteria described in the Cochrane Reviewer’s Handbook 5.2.0. Two reviewers used the “high risk”, “low risk” and “unclear” to evaluate the include literature. Any disagreements were resolved by discussion.

Statistical analysis

We used the RevMan software (Version 5.3, Cochrane Collaboration, Oxford, England) to conduct the Statistical analysis, a P value < 0.05 was considered significant, except where otherwise specified. Dichotomous data was presented as the relative ratio (OR) with a 95% CI. Weight Mean differences (WMD) with a 95% CI was calculated for continuous variables. The chi-square test was applied to analysis the statistical heterogeneity. The I^2 statistic, which is a quantitative measure of inconsistency across studies, was also calculated. If there was a significant heterogeneity, a random-effects statistical model was used to confirm the case results. A fixed-effect model for calculations of summary estimates and the 95% CIs were also applied, unless there was a significant heterogeneity.

Results

Literature search

The literature search yielded a total of 460 articles, 63 records from Embase, 50 from Web of science, 125 from Cochrane library and 222 from the PubMed database, screening out the reference lists of the included studies and 10 records were found. Most studies were excluded because they didn’t compare the effect of Ologen implant and MMC or they were not prospective studies. After assessing the full text of the potentially 30 relevant articles, 15 RCTs were enligible for our inclusion criteria and finally to be included in this meta-analysis[22,25-31,34-40]. The exclusion reasons were as follow: one was from the same patient group, and one compared the outcomes of trabeculectomy with or without an Ologen implant, seven were not comparative studies, five compared

phacotrabeculectomy with Ologen implant and MMC, one was about secondary glaucomas trabeculectomy with following failed trabeculectomy with MMC. A flow diagram showing the study selection process of the trials included in our meta-analysis is presented in Figure 1.

Characteristics of the trials

The studies eligible for analysis were published between 2010 and 2018, four randomized controlled trials were conducted in Egypt, two in Germany, China, one in Italy, USA, Iran, UK, India and Bangladesh. The characteristics of the qualified studies are presented in Table 1, a total of 682 eyes were entrolled (331 assigned to Ologen implant and 351 to MMC). The mean age of the patients ranged from 3.75-71.1years. Simple size in this study ranged from 14-107. The mean follow-up period ranged from 6 to 60 months. The baseline IOP ranged from 19.14-43.07 mmHg.

Quality assessment

Two reviewers independently evaluate the included studies using the risk of bias tools of Cochrane Handbook for Systematic Reviews of Interventions[32], if there were disagreements, the third researcher would take part in the discussion. The summary of the outcome was shown in Table 2. Of all the qualified studies, five of them described the sequence generation and allocation concealment process, the others didn't mention. As for the blinding of patient and personnel, thirteen studies didn't do it. The assessment bias were avoided. Six studies have incompleted data due to the loss to follow-up. Almost all the included RCTs avoided the bias of selective reporting.

Main anlalysis

Reduction in the IOP (IOPR)

We performed meta-analysis of the IOP at each time point, including one day, one week, one month, three months, six months, one year, two years, three years and five years after surgery. There were no heterogeneity among two groups at one week and two years postoperatively, the fix-effects models were used. While the others used the random-effects models. All study used same scales to report IOP, thus the MD was used. There was no statistically significant difference between the Ologen groups and MMC groups at each time after surgery (Table 3).

Complete success rate

Thirteen studies reported complete success rate. There was no significant heterogeneity between two groups (I^2=28%, p=0.16), and the fix-effects models were used. There was no statistically significant difference between the Ologen groups and MMC groups concerned the complete success rate [OR=1.19, 95%CI, (0.83, 1.71), P=0.35] (Figure 2).

Qualified success rate

Thirteen studies reported qualified success rate. There was no significant heterogeneity between each groups (I^2=11%, p=0.35), the fixed-effects models was used. The qualified success rate of the Ologen groups shows no significant difference with MMC groups [OR=1.59, 95%CI, (0.99, 2.55), P=0.05] (Figure 3).

Adverse events

We analyzed several adverse events, including shallow AC, hypotony, bleb leakage, hyphema, and choroidal detachment. The heterogeneity was not existed among each groups. In fixed-effects models, fortunately, there was no statistically significant difference between Ologen and MMC groups(Table 4).

Antiglaucoma medications

Only seven studies reported the change of antiglaucoma medications. Heterogeneity was not existed among each group (I^2=0%, P=0.53). In the fix-effects models, the change of antiglaucoma medications is higher in MMC groups than that in Ologen groups [MD=-0.18, 95%CI, (-0.33, -0.03), P=0.02](Figure 4).

Discussion

Trabeculectomy is commonly used in patients whose IOP can't be controlled by medicine or patients who unwilling to use drugs. Postoperative wound healing and cicatrization are the biggest challenge in trabeculectomy[41,42]. MMC and 5-FU act in the way by destroying the structure of DNA, which inhibits the replication of DNA in proliferative cells. Thus, the speed of proliferation of fibroblasts will be slowed down, reducing the scarring of the filtering bleb and the success rate will be improved eventually. However, this mediation would bring some complications, such as shallow AC and hypotony. An Ologen implant may be placed over the scleral flap during the operation, absorbing the aqueous humor and inducing a certain pressure on the scleral flap, which may reduce shallow AC and hypotony caused by excessive drainage. In the study of M Tanito, Ologen can be a useful therapeutic option for ocular hypotony after glaucoma filtration surgery[43]. The study of Dietlein TS showed that subconjunctival implantation of collagen matrix may present an additional surgical tool in the treatment of symptomatic ocular hypotony after filtering surgery[44]. However, the meta-analysis showed that Ologen didn't reduce shallow AC [OR=0.66, 95% CI, (0.33, 1.35), *P*=0.26] and hypotony [OR=0.60, 95% CI, (0.35, 1.04), *P*=0.07] significantly compared with MMC. Further research is needed to investigate the role of Ologen in reducing hypotony and shallow anterior chamber.

In the present study , there was no statistically significant difference between the two groups in reducing the IOP. In the included studies, the follow-up time ranged from 6 months to 60 months. Most of the studies were followed up within two years, and only two studies were followed for five years. One study showed no significant difference between the two groups at five years postoperatively[34], the other showed that Ologen was superior to MMC[22]. In this meta-analysis, the difference between the two groups was not statistically significant at 5 years. However, there were very few studies followed up to 5 years. Long follow-up RCTs were needed to compare the effects in reducing the IOP for long time between the two groups. And there was no statistically significant difference between Ologen group and MMC group both for complete and qualified success rate. Because the follow-up time varies from study to study, we need to dialectically look at this result. In terms of anti-glaucoma drugs, MMC is superior to Ologen. However, only seven studies have reported changes in anti-glaucoma drugs before and after surgery. More data was required to confirm the result.

For safety, results of adverse events were reported in most of the included studies. The adverse events included bleb leak, hyphema, Shallow AC, hypotony, Choroidal detachment and so on. Concerned overall adverse events, there was no statistically difference between the Ologen groups and control groups. And no one died patient was associated with Ologen and MMC in including studies.

In this meta-analysis, one study was about juvenile open-angle glaucoma (JOAG), the results showed that Ologen resulted in a lower long-term postoperative IOP, a better bleb morphology, and fewer complications[29]. Another was about congenital glaucoma showed that Ologen had equally effective results as MMC, and Ologen implantation is safe and has low incidences of complications[28]. The studies of Singab AAS and Elhefney EM showed that Ologen is a safe and effective adjuvant in combined trabeculotomy and trabeculectomy for treatment of Congenital glaucoma[24,45]. This may suggest that we should consider giving priority to Ologen in infants and adolescents, but more researches are needed to confirm our ideas.

Despite Ologen and MMC had similar efficacy in the IOP reduction, success rate and safety, Ologen was much more expensive than MMC, with approximately 5 times of MMC. Therefore, MMC might be the preferred choice concerned cost-effectiveness.

This meta-analysis of 15 random control trials involving 682 eyes. However, potential limitations of this study should be considered. First, the varying definitions of surgical success in the literature should be taken into consideration. Second, the data of success rate, adverse events and antiglaucoma medications came from the end-point owe to the lack of data reported in all phases of follow-up may bring some bias. In addition, the type of glaucoma included in each study is also different. Furthermore, the surgeries were performed by different surgeons would lead to an unavoidable potential bias. Finally, publication bias was inevitable.

Conclusions

From the current evidence, Ologen may be an alternative choice for trabeculectomy when considering the efficacy and safety. However, MMC might be the preferred choice concerned cost-effectiveness. Further intensive RCTs of high-quality, multiple centers and long term follow-up should be carried out to evaluate the effect of Ologen in reducing Shallow AC, hypotony and intraocular pressure reduction, and to assess whether Ologen has more advantages in juvenile open-angle glaucoma and congenital glaucoma patients.

Abbreviations

Ologen, biodegradable collagen matrix;

WMDS, weighted mean differences;

IOPR, intraocular pressure reduction;

OR, odds ratio;

CI, Confidence Interval;

MMC, Mitomycin C;

IOP, intraocular pressure;

5-FU, 5-flourouracil;

AC, anterior chamber;

RCTs, randomized controlled trials;

JOAG, juvenile open-angle glaucoma;

POAG, primary open-angle glaucoma;

PEXG, pseudoexfoliation glaucoma;

PACG, primary angle closure glaucoma;

MMC, Mitomycin C;

No.eyes, number of eyes;

NA, unclear.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent to publish: All authors are in agreement with the content of the paper.

Availability of data and materials : The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: Not applicable.

Authors' Contributions: Conceived and designed the experiments: XL YD ML PL. Performed the experiments: XL YD PL. Analyzed the data: XL YD ML ZL. Contributed reagents/materials/analysis tools: XL YD ML ZL. Wrote the paper: XL YD ML ZL.
Acknowledgements: Not applicable.

References

[1] Amoozgar B, Lin S C, Han Y, et al. A role for antimetabolites in glaucoma tube surgery[J]. Current Opinion in Ophthalmology, 2016, 27(2): 164-169.

[2] Quigley H A, Broman A T. The number of people with glaucoma worldwide in 2010 and 2020[J]. Br J Ophthalmol, 2006, 90(3): 262-7.

[3] Wang X, Khan R, Coleman A. Device-modified trabeculectomy for glaucoma. The Cochrane database of systematic reviews. 2015: CD010472.

[4] Perez C I, Mellado F, Jones A, et al. Trabeculectomy Combined With Collagen Matrix Implant (Ologen)[J]. J Glaucoma, 2017, 26(1): 54-58.

[5] Cairns J E. Trabeculectomy. Preliminary report of a new method[J]. American journal of ophthalmology, 1968, 66(4): 673-679.

[6] Watson P G, Barnett F. Effectiveness of trabeculectomy in glaucoma[J]. American journal of ophthalmology, 1975, 79(5): 831-845.

[7] Jampel H D, Mcguigan L J, Dunkelberger G R, et al. Cellular proliferation after experimental glaucoma filtration surgery[J]. Archives of ophthalmology (Chicago, Ill. : 1960), 1988, 106(1): 89-94.

[8] Fontana H, Nouri-Mahdavi K, Lumba J, et al. Trabeculectomy with Mitomycin C: outcomes and risk factors for failure in phakic open-angle glaucoma[J]. Ophthalmology, 2006, 113(6): 930-936.

[9] Bindlish R, Condon G P, Schlosser J D, et al. Efficacy and safety of Mitomycin-C in primary trabeculectomy: five-year follow-up[J]. Ophthalmology, 2002, 109(7): 1336-41; discussion 1341-2.

[10] Cillino S, Zeppa L, Di Pace F, et al. E-PTFE (Gore-Tex) implant with or without low-dosage Mitomycin-C as an adjuvant in penetrating glaucoma surgery: 2 year randomized clinical trial[J]. Acta Ophthalmol, 2008, 86(3): 314-21.

[11] Allen L E, Manuchehri K, Corridan P G. The treatment of encapsulated trabeculectomy blebs in an out-patient setting using a needling technique and subconjunctival 5-fluorouracil injection[J]. Eye (London, England), 1998, 12 (Pt 1): 119-123.

[12] Spaeth G L, Mutlukan E. The use of antimetabolites with trabeculectomy: a critical appraisal[J]. Journal of glaucoma, 2001, 10(3): 145-151.

[13] Hsu W-C, Ritch R. Biodegradable collagen matrix implant for trabeculectomy AU - Zelefsky, Joseph R[J]. Expert Review of Ophthalmology, 2008, 3(6): 613-617.

[14] Biteli L G, Prata T S. Subconjunctival bevacizumab as an adjuvant in first-time filtration surgery for patients with primary glaucomas[J]. International ophthalmology, 2013, 33(6): 741-746.

[15] Simsek T, Cankaya A B, Elgin U. Comparison of needle revision with subconjunctival bevacizumab and 5-fluorouracil injection of failed trabeculectomy blebs[J]. Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics, 2012, 28(5): 542-546.

[16] Vahedian Z, Mafi M, Fakhraie G, et al. Short-term Results of Trabeculectomy Using Adjunctive Intracameral Bevacizumab Versus Mitomycin C: A Randomized Controlled Trial[J]. Journal of glaucoma, 2017, 26(9): 829-834.

[17] Kaushik J, Parihar J K, Jain V K, et al. Efficacy of Bevacizumab Compared to Mitomycin C Modulated Trabeculectomy in Primary Open Angle Glaucoma: A One-Year Prospective Randomized Controlled Study[J]. Curr Eye Res, 2017, 42(2): 217-224.

[18] Chen H-J, Lin C, Lee C-H, et al. Efficacy and Safety of Bevacizumab Combined with Mitomycin C or 5-Fluorouracil in Primary Trabeculectomy: A Meta-Analysis of Randomized Clinical Trials[J]. Ophthalmic research, 2018, 59(3): 155-163.

[19] Narayanaswamy A, Perera S A, Htoon H M, et al. Efficacy and safety of collagen matrix implants in phacotrabeculectomy and comparison with Mitomycin C augmented phacotrabeculectomy at 1 year[J]. Clin Exp Ophthalmol, 2013, 41(6): 552-60.

[20] Papaconstantinou D, Georgalas I, Karmiris E, et al. Trabeculectomy with Ologen versus trabeculectomy for the treatment of glaucoma: a pilot study[J]. Acta Ophthalmologica, 2010, 88(1): 80-85.

[21] Hsu W-C, Ritch R, Krupin T, et al. Tissue bioengineering for surgical bleb defects: an animal study[J]. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie, 2008, 246(5): 709-717.

[22] Yuan F, Li L, Chen X, et al. Biodegradable 3D-Porous Collagen Matrix (Ologen) Compared with Mitomycin C for Treatment of Primary Open-Angle Glaucoma: Results at 5 Years[J]. J Ophthalmol, 2015, 2015: 637537.

[23] Cillino S, Di Pace F, Cillino G, et al. Biodegradable collagen matrix implant vs Mitomycin-C as an adjuvant in trabeculectomy: a 24-month, randomized clinical trial[J]. Eye (Lond), 2011, 25(12): 1598-606.

[24] Singab A a S, Mohammed O A, Saleem M I H, et al. A Comparative Study: The Use of Collagen Implant versus Mitomycin-C in Combined Trabeculotomy and Trabeculectomy for Treatment of Primary Congenital Glaucoma[J]. J Ophthalmol, 2017, 2017: 9241459.

[25] Eldaly Z, Maasoud A, Saad M, et al. Comparison between Ologen implant and different concentrations of Mitomycin C as an adjuvant to trabeculectomy surgery[J]. Oman Journal of Ophthalmology, 2017, 10(3): 184.

[26] Sarker B K D, Abdullahi S M, Hassan Z, et al. Outcome of trabeculectomy with Ologen versus Mitomycin C: A comparative prospective study in Bangladesh[J]. European Journal of Ophthalmology, 2018: 112067211877184.

[27] Marey H M, Mandour S S, Ellakwa A F. Subscleral trabeculectomy with Mitomycin-C versus Ologen for treatment of glaucoma[J]. Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics, 2013, 29(3): 330-334.

[28] Mohamed T H, Salman A G, Elshinawy R F. Trabeculectomy with Ologen implant versus Mitomycin C in congenital glaucoma secondary to Sturge Weber Syndrome. International journal of ophthalmology. 2018: 251-255.

[29] El-Sayyad F, El-Saied H M A, Abdelhakim M. Trabeculectomy with Ologen versus Mitomycin C in Juvenile Open-Angle Glaucoma: A 1-Year Study[J]. Ophthalmic Res, 2017, 57(4): 230-238.

[30] Rosentreter A, Schild A M, Jordan J F, et al. A prospective randomised trial of trabeculectomy using Mitomycin C vs an Ologen implant in open angle glaucoma[J]. Eye (Lond), 2010, 24(9): 1449-57.

[31] Rosentreter A, Gaki S, Cursiefen C, et al. Trabeculectomy Using Mitomycin C versus an Atelocollagen Implant: Clinical Results of a Randomized Trial and Histopathologic Findings[J]. Ophthalmologica, 2014, 231(3): 133-140.

[32] Higgins J, Green S P, Cochrane C. Cochrane handbook for systematic reviews of interventions[M]. John Wiley & Sons, 2008: xxi, 649 p.

[33] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement[J]. Bmj, 2009, 339(jul21 1): b2535-b2535.

[34] Cillino S, Casuccio A, Di Pace F, et al. Biodegradable collagen matrix implant versus Mitomycin-C in trabeculectomy: five-year follow-up[J]. BMC Ophthalmol, 2016, 16: 24.

[35] Yu L, Qin H. Collagen matrix compared with Mitomycin C for treatment of primary open-angle glaucoma with trabeculectomy performed[M]. 17. 2017: 1712-1715.

[36] Tanna A P, Rademaker A W, De Moraes C G, et al. Collagen matrix vs Mitomycin-C in trabeculectomy and combined phacoemulsification and trabeculectomy: a randomized controlled trial[J]. BMC Ophthalmol, 2016, 16(1): 217.

[37] Maheshwari D, Ramakrishnan, Gupta A. Comparative study of MMC augmented trabeculectomy vs an Ologen implant in open angle glaucoma[J]. Glaucoma Free Papers, 2012.

[38] Senthil S, Rao H L, Babu J G, et al. Comparison of outcomes of trabeculectomy with Mitomycin C vs. Ologen implant in primary glaucoma[J]. Indian J Ophthalmol, 2013, 61(7): 338-42.

[39] Nilforushan N, Yadegari M, Hodjat P. Comparison of the Success Rate of Trabeculectomy with OculusGen versus Trabeculectomy with Mitomycin C[J]. IRJO, 2011, 23(4): 3-12.

[40] Mitra A, R R K, Pmt M a K, et al. To Compare the Outcome, Complications and Management of Complications of Trabeculectomy with Ologen Implant Versus Trabeculectomy with MMC[J]. Glaucoma Free Papers, 2012.

[41] Addicks E M, Quigley H A, Green W R, et al. Histologic characteristics of filtering blebs in glaucomatous eyes[J]. Archives of ophthalmology (Chicago, Ill. : 1960), 1983, 101(5): 795-798.

[42] Hitchings R A, Grierson I. Clinico pathological correlation in eyes with failed fistulizing surgery[J]. Transactions of the ophthalmological societies of the United Kingdom, 1983, 103 (Pt 1): 84-88.

[43] Tanito M, Okada A, Mori Y, et al. Subconjunctival implantation of Ologen Collagen Matrix to treat ocular hypotony after filtration glaucoma surgery[J]. Eye (Lond), 2017, 31(10): 1475-1479.

[44] Dietlein T S, Lappas A, Rosentreter A. Secondary subconjunctival implantation of a biodegradable collagen-glycosaminoglycan matrix to treat ocular hypotony following trabeculectomy with Mitomycin C[J]. The British journal of ophthalmology, 2013, 97(8): 985-988.

[45] Elhefney E M, Al-Sharkawy H T, Kishk H M, et al. Safety and efficacy of collagen matrix implantation in infantile glaucoma[J]. European journal of ophthalmology, 2017, 27(3): 289-294.

Tables

Table 1 Baseline characteristics of qualified randomized controlled trials

Trial(year)	Country	Group	No.eyes	Mean age(y)	Follow-up(m)	IOP(mmHg)	Glaucoma type				glaucoma medications
							POAG	PACG	PEXG	Others	
Rosentreter (2010)	Germany	Ologen	10	62.8±9.5	12	27.2±10.5	na	na	na	na	2.5± 1.4
		MMC	10			22.4±6.6	na	na	na	na	2.3± 1.4
Andre (2013)	Germany	Ologen	15	67.9±10.2	12	28.0 ± 9.4	9	0	3	3	3.4 ± 1.6
		MMC	15	65.0±10.5		23.9 ± 5.0	11	0	3	`1	3.6 ± 1.5
Fei (2015)	China	Ologen	31	55.73±9.074	60	43.07±6.23	31	0	0	0	
		MMC	32	54.94±10.525		41.41±5.11	32	0	0	0	
Salvatore (2016)	Italy	Ologen	20	65.8±6.4	60	27.3±6.0	13	0	7	0	2.6± 0.2
		MMC	20	63.2±7.2		26.7±5.2	12	0	8	0	2.5±0.3
Angelo(2016)	USA	Ologen	45	69.4 ±10.7	24	21.2± 6.1	38	2	1	4	3.07 ±1.00
		MMC	48	71.1± 10.0		20.4 ±6.0	43	3	1	1	3.21 ±1.13
Lei(2017)	China	Ologen	14	40. 5±9. 26	6	37. 1±5. 41	14	0	0	0	
		MMC	18	41. 2±8. 54		36. 8±4. 35	18	0	0	0	
Zeiad (2017)	Egypt	Ologen	10	54.7±6.36	6	27.43±2.97	3	0	1	6	2.8±0.63
		MMC	10	51.9±10.04		27.56 ± 2.69	4	0	1	5	2.9±0.57
Fathi (2017)	Egypt	Ologen	20	23.3± 4.3	12	34.7±5.1	0	0	0	20	
		MMC	20			35.5±5.0	0	0	0	20	
Bipul (2018)	Bangladesh	Ologen	52	42.9 ±8.9	12	23.5± 6.5	27	15	0	10	
		MMC	55	43.4 ±8.4		23.6± 5.9	28	15	0	12	
Thanaa(2018**)**	Egypt	Ologen	10	3.93±1.07	12	29.8±3.08	0	0	0	10	
		MMC	10	3.75±0.75		29±3.16	0	0	0	10	
Naveed(2011**)**	Iran	Ologen	7	59±12.6	6	19.14±3.8	7	0	0	0	3.14±0.37
		MMC	7	59±12.6		21.71±4.1	7	0	0	0	2.86±0.89
Maheshwari(2012)	Indian	Ologen	20	NA	12	26.7±7.9	20	0	0	0	
		MMC	20	NA		26.7±7.9	20	0	0	0	
Arijit(2012**)**	UK	Ologen	28	61.22±12.24	6	28.2±9.66	19	0	6	3	3.2 ± 0.3
		MMC	36	62.43±14.43		32.4±10.6	21	0	12	3	3.4 ± 0.6
Sirisha(2013)	India	Ologen	19	48 ± 10	24	26.4 ± 11.3	8	11	0	0	3.2 ± 0.9
		MMC	20	45 ± 12		26.3 ± 15.7	12	8	0	0	3.2 ± 0.9
Hatem(2013**)**	Egypt	Ologen	30	50.2±10.2	12	29.87±3.44	18	4	2	6	
		MMC	30	49.07±5.8		31.47 ±3.8	13	5	4	8	

IOP, intraocular pressure; POAG, primary open-angle glaucoma; PEXG, pseudoexfoliation glaucoma; PACG, primary angle closure glaucoma; MMC, Mitomycin C; No.eyes, number of eyes; NA, unclear.

Table 2 Evaluation of the risk of bias of qualified RCTs in the meta-analysis

Trial(year)	sequence generation	Allocation concealment	Blinding			Incomplete outcome data	Selective reporting	Other bias
			patient	personnel	assessor			
Rosentreter(2010)	unclear	yes	no	no	yes	yes	no	unclear
Andre (2013)	yes	yes	no	no	yes	no	no	unclear
Fei (2015)	yes	yes	no	no	yes	no	no	unclear
Salvatore (2016)	yes	yes	no	no	yes	no	no	unclear
Angelo(2016)	yes	yes	unclear	unclear	yes	yes	no	unclear
Lei (2017)	unclear	unclear	no	no	yes	no	no	unclear
Zeiad (2017)	unclear	unclear	no	no	yes	yes	no	unclear
Fathi (2017)	unclear	unclear	no	no	yes	yes	no	unclear
Bipul (2018)	no	no	no	no	yes	yes	yes	unclear
Thanaa (2018)	unclear	unclear	no	no	yes	no	no	unclear
Naveed (2011)	yes	unclear	no	no	yes	no	no	unclear
Maheshwari(2012)	unclear	unclear	unclear	unclear	yes	unclear	unclear	unclear
Arijit (2012)	unclear	unclear	no	no	yes	no	no	unclear
Sirisha (2013)	yes	yes	no	no	yes	yes	no	unclear
Hatem (2013)	unclear	unclear	no	no	yes	no	no	unclear

Table 3 The reduction in intraocular pressure from baseline for Ologen implant versus MMC

Time	Ref.	No.	MD	95%CI	*P*-value	Model	I^2	*P*-value
1d postoperatively	[22,25,29-31,34,35,37-39]	10	-0.45	[-2.36,1.46]	0.65	R	60%	0.007
7d postoperatively	[22,27,28,30,31,35,38-40]	9	-0.82	[-1.97,0.33]	0.16	F	46%	0.06
1m postoperatively	[22,27-31,35,38-40]	10	-1.33	[-3.12,0.47]	0.15	R	62%	0.005
3m postoperatively	[22,27-31,34,35,38-40]	11	0.11	[-1.87,2.08]	0.92	R	73%	<0.0001
6m postoperatively	[22,25,27-31,34,35,38-40]	12	-0.60	[-2.27,1.06]	0.48	R	67%	0.0005
1y postoperatively	[22,26-31,34,37-39]	11	-0.33	[-1.99,1.32]	0.69	R	65%	0.002
2y postoperatively	[34,36,38]	3	-0.13	[-1.90,1.65]	0.89	F	0%	0.73
3y postoperatively	[22,34]	2	2.54	[-2.83,7.90]	0.35	R	86%	0.008
5y postoperatively	[22,34]	2	3.04	[-3.95,10.03]	0.39	R	91%	0.0006

Ref. , references; No. , number of studies.

Table 4 Adverse events comparing Ologen group with MMC group

Complications	Ref.	No.	OR	95%CI	*P*-value	Model	I^2	*P*-value
Shallow AC	[25-31,38,40]	9	0.66	[0.33,1.35]	0.26	F	0%	0.87
Hyphema	[22,25-27,30,31,34-36,38]	10	1.44	[0.72,2.88]	0.30	F	3%	0.41
Bleb leakage	[22,25,26,30,31,34-36,38,40]	10	0.56	[0.26,1.20]	0.14	F	0%	0.62
Hypotony	[22,25,29-31,34-36,38,40]	10	0.60	[0.35,1.04]	0.07	F	0%	0.55
Choroidal detachment	[22,30,31,34,36,38]	6	0.93	[0.39,2.22]	0.88	F	0%	0.69

Ref. , references; No. , number of studies.

Figures

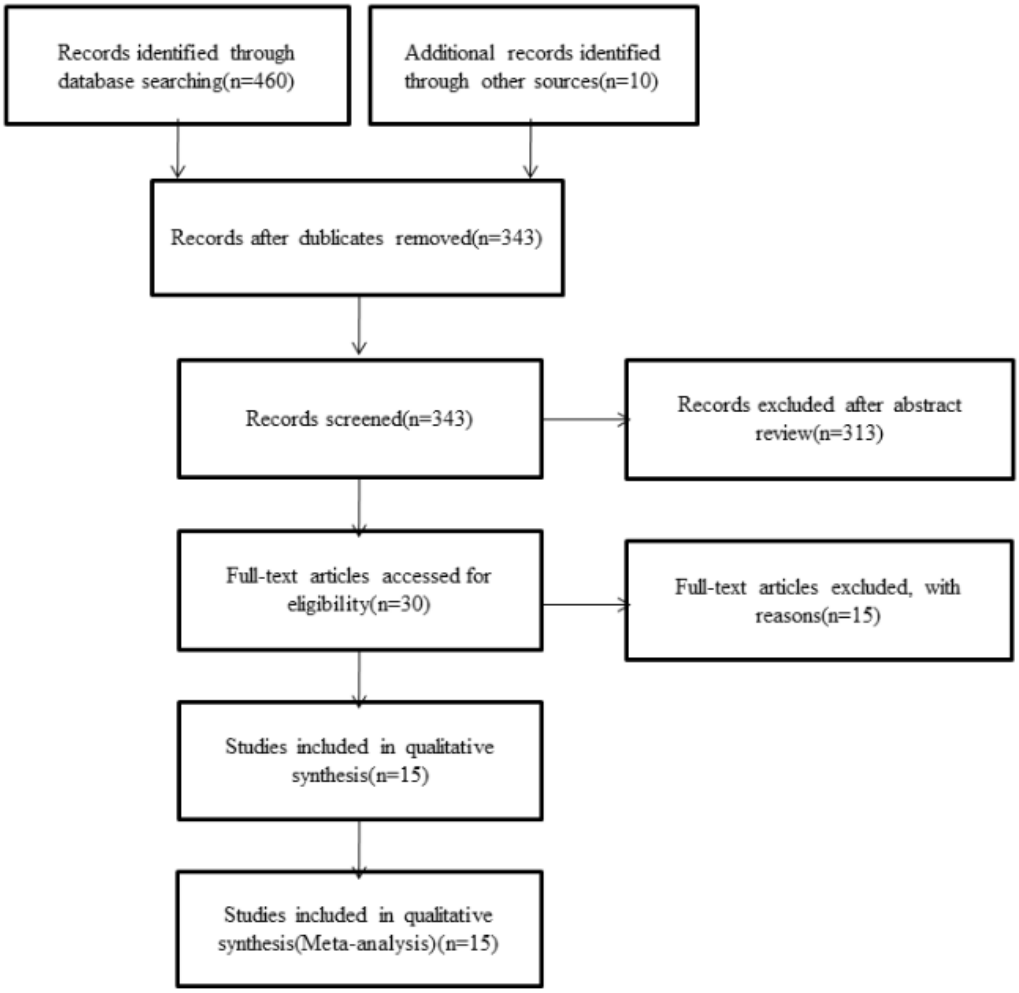

Figure 1

Flow chart of randomized controlled trials included in the meta-analysis

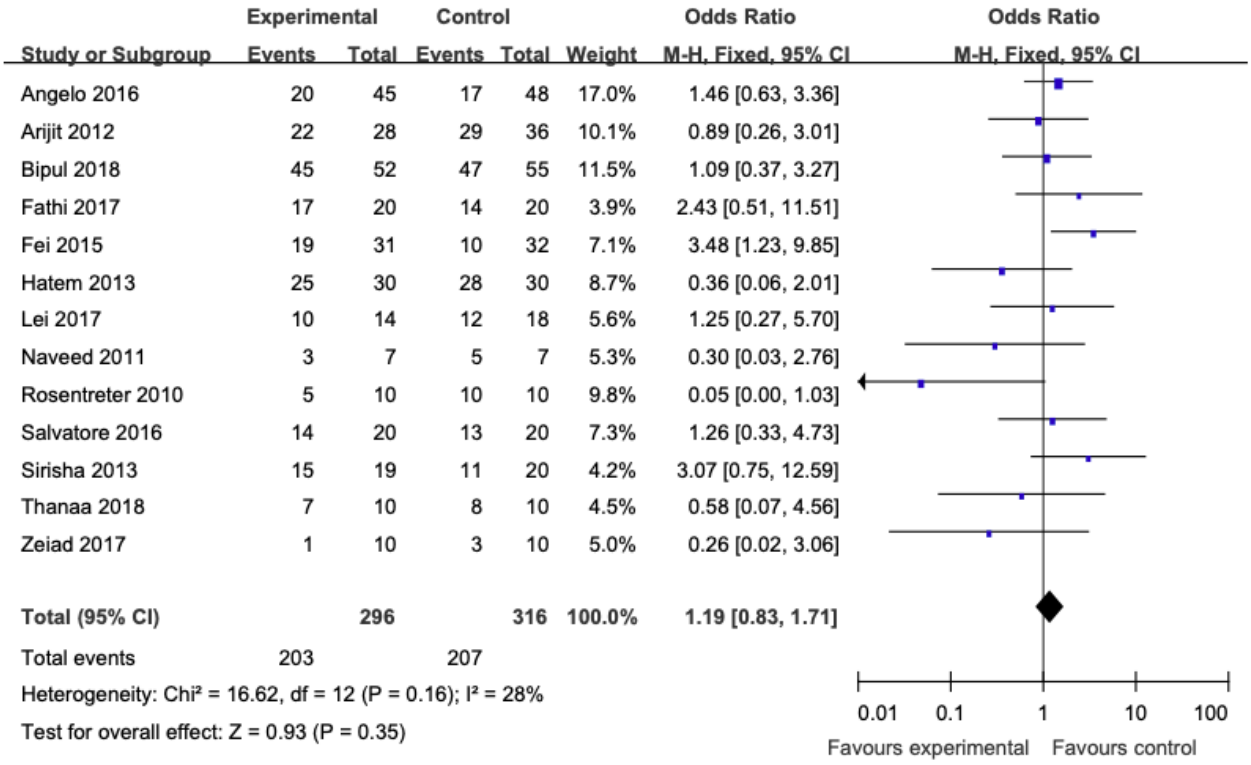

Figure 2

The compete success rate comparing Ologen implant and MMC

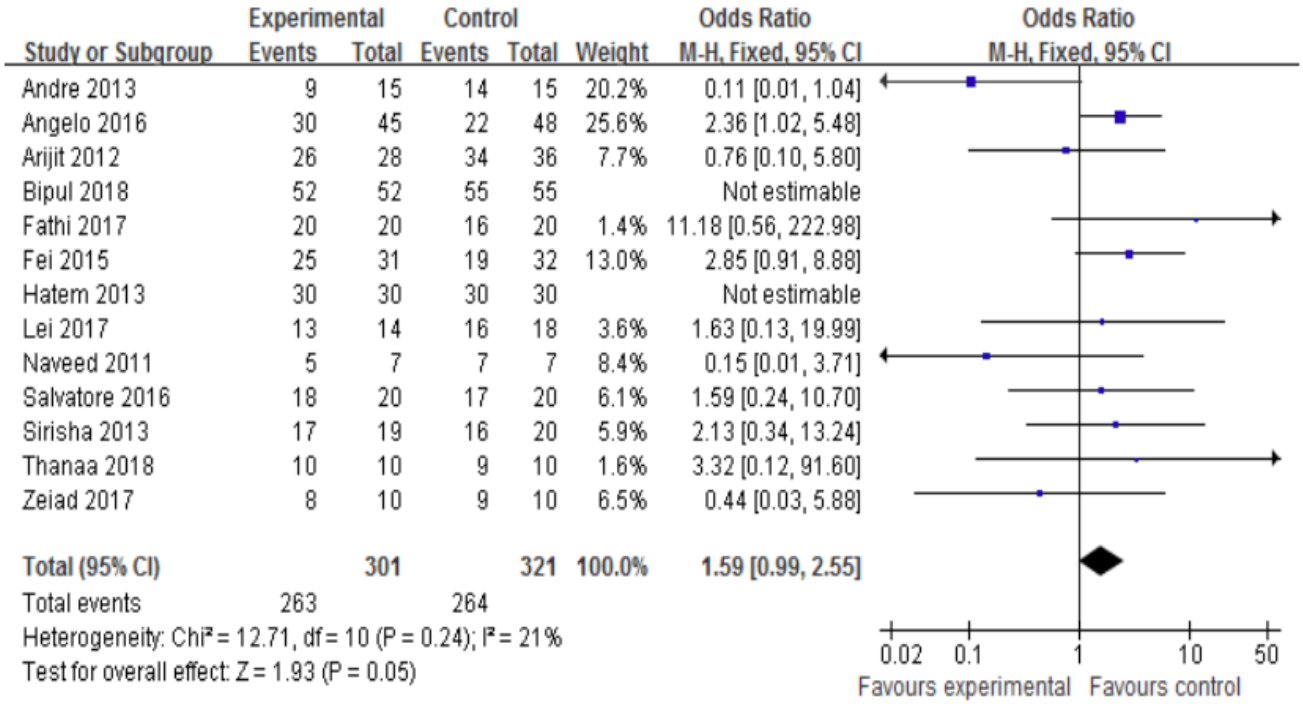

Figure 3

The qualified success rate comparing Ologen implant and MMC

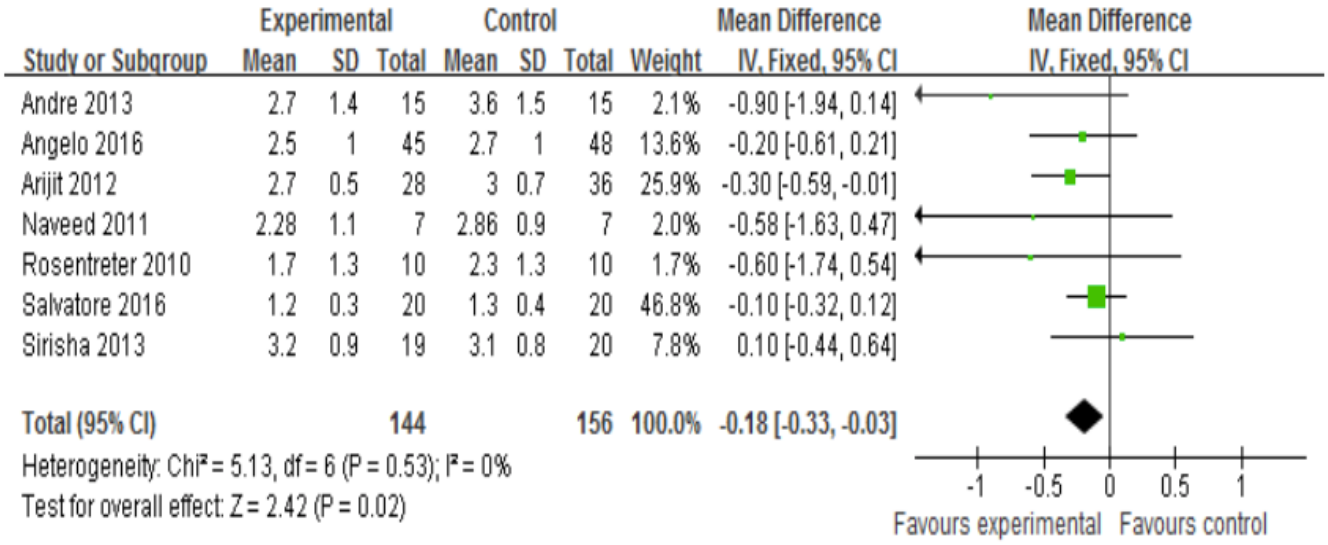

Figure 4

The antiglaucoma medications comparing Ologen implant and MMC

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMAchecklist.doc