

Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)

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Is mitomycin C better than 5-fluorouracil as antimetabolite in trabeculectomy for glaucoma?

Authors: Eduardo Pimentel[1,2], Jimena Schmidt[2,3]

Affiliation:

[1] Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

[2] Proyecto Epistemonikos, Santiago, Chile

[3] Departamento de Oftalmología, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

E-mail: jschmidt@uc.cl

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Abstract

INTRODUCTION

Trabeculectomy is considered the standard for glaucoma surgery. Postoperative scarring is one the factors associated with surgery failure. Different antimetabolites have been used in order to reduce this risk, particularly 5-fluorouracil and mitomycin C. Although both are considered effective, it is not clear if they are different in terms of success of trabeculectomy and adverse effects.

METHODS

To answer this question we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

RESULTS AND CONCLUSIONS

We identified four systematic reviews including 17 studies overall, of which 12 were randomized trials. We concluded mitomycin C might be more effective in reducing intraocular pressure and increasing qualified success compared to 5-fluorouracil. However, its use might be associated to a higher risk of complications.

Problem

According to the World Health Organization, glaucoma is the second cause of blindness worldwide. Among the known risk factors for the development of this disease, the intraocular pressure is the only one that can be modified. Trabeculectomy is the surgery of choice for patients with medically uncontrolled glaucoma.

Antimetabolites have been used as a strategy to improve the success of trabeculectomy, with the aim of reducing postsurgical scarring and thus favoring the aqueous humor outflow to the subconjunctival space. 5-fluorouracil and mitomycin C are considered effective, but it is not clear if there are differences in terms of success and risk of complications, such as bleb leak, cataract formation, ocular hypotonia and endophthalmitis.

Methods

To answer the question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages

- Mitomycin C might be more effective in reducing intraocular pressure and increasing qualified success rate compared to 5-fluorouracil.
- Mitomycin C might be associated with a higher incidence of complications than 5-fluorouracil (bleb leak, late hypotonia, narrow anterior chamber, endophthalmitis, cataract development).

About the body of evidence for this question

<p>What is the evidence. See evidence matrix in Epistemonikos later</p>	<p>We found four systematic reviews [1],[2],[3],[4] that included 17 primary studies reported in 19 references [5],[6],[7],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18],[19],[20],[21],[22],[23], of which, 12 correspond to randomized controlled trials, reported in 14 references [6],[8],[9],[10],[12],[13],[14],[15],[16],[17],[19],[21],[22],[23]. One of the trials [16], was conducted in patients with neovascular glaucoma, whose surgery of choice is not trabeculectomy, so it was excluded in the analysis of this article. This table and the summary in general are based on 11 randomized trials, since the observational studies did not increase the certainty of the evidence or provide additional relevant information.</p>
<p>What types of patients were included*</p>	<p>Regarding the type of glaucoma, five trials included patients with more than one type of glaucoma [6],[8],[15],[21],[22], four trials included patients with open-angle glaucoma [10],[13],[19],[23]. In two trials, the type of glaucoma was not reported [9],[12]. Regarding the risk of trabeculectomy failure, four trials included patients considered to be as high risk [6],[8],[9],[13], five included patient with a low risk of failure [10],[15],[19],[21],[23] and one trial included both high and low risk patients [22]. In one trial, the risk of trabeculectomy failure was not reported [12].</p>
<p>What types of interventions were included*</p>	<p>All trials compared mitomycin C against 5-fluorouracil [6],[8],[9],[10],[12],[13],[15],[19],[21],[22],[23]. The use of mitomycin was during the intraoperative period in all of the trials [6],[8],[9],[10],[12],[13],[15],[19],[21],[22],[23]. The dose used was a 0.2 mg/ml solution for 2 minutes in three trials [12],[19],[21], a 0.2 mg/ml solution for 5 minutes in two trials [22],[23], a 0.4 mg/ml solution for 2 minutes in one trial [15], a 0.4 mg/ml solution for 2.5 minutes in one trial [9], a 0.4 mg/ml solution for 5 minutes in one trial [8], a 0.5 mg/ml solution for 3.5 minutes in one trial [13], a 0.5 mg/ml solution for 5 minutes in one trial [6] and a dose of 0.02 mg in one trial [10]. The use of 5-fluorouracil was during the intraoperative period in six trials [10],[12],[13],[15],[19],[21], of which in five a solution of 50 mg/ml was administered for 5 minutes [12],[13],[15],[19],[21] and a dose of 5 mg was administered in one trial [10]. In the remaining five trials, 5-fluorouracil was used postoperatively [6],[8],[9],[22],[23]; in three trials 10 doses of 5 mg were administered [6],[8],[9], and in two 7 doses of 5 mg were administered [22],[23].</p>
<p>What types of outcomes were measured</p>	<p>The trials measured multiple outcomes, which were grouped by the systematic reviews as follows:</p> <ul style="list-style-type: none"> • Failure of trabeculectomy at one year. • Average intraocular pressure at the end of follow-up or at one year • Percentage decrease in postoperative intraocular pressure. • Absolute decrease in postoperative intraocular pressure. • Qualified success (objective intraocular pressure independent of the use of medical treatment) • Complete success (objective intraocular pressure without the need of medical treatment). • Complications (bleb leak, late hypotony, maculopathy, cataract, narrow anterior chamber, choroidal detachment, corneal epitheliopathy, tenon cyst, hyphema y endophthalmitis). • Number of drugs used during postoperative period. • Decrease in visual acuity. • Need for reoperation or post-surgical laser procedure • Absolute decrease in postoperative intraocular pressure in a low-risk group <p>The average follow-up of the trials was 21 months, with a range between 6 and 60 months.</p>

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Summary of Findings

The information on the effects of mitomycin C compared to 5-fluorouracil for trabeculectomy is based on 11 randomized trials involving 770 eyes.

Seven trials reported mean intraocular pressure at the end of follow-up or at one year (386 eyes) [6],[8],[9],[10],[13],[21],[23], 10 trials evaluated qualified success (594 eyes) [6],[8],[9],[10],[13],[15],[19],[21],[22],[23], eight trials evaluated bleb leak (545 eyes) [6],[8],[9],[13],[15],[21],[22],[23], four trials evaluated late hypotony (211 eyes) [10],[13],[22],[23], three trials evaluated development of cataract (235 eyes) [6],[13],[21], five trials evaluated narrow anterior chamber (311 eyes) [8],[13],[15],[22],[23] and four trials evaluated endophthalmitis (315 eyes) [6],[9],[13],[21].

The summary of findings is as follows:

- Mitomycin C might be more effective in reducing intraocular pressure than 5-fluorouracil, but the certainty of the evidence is low.
- Mitomycin C might increase qualified success rate compared to 5-fluorouracil, but the certainty of the evidence is low.
- Mitomycin C might be associated to a higher incidence of bleb leak, but the certainty of the evidence is low.
- Mitomycin C might be associated to a higher incidence of late hypotony, but the certainty of the evidence is low.
- Mitomycin C might be associated to a higher incidence of cataract development, but the certainty of the evidence is low.
- Mitomycin C might be associated to a higher incidence of narrow anterior chamber, but the certainty of the evidence is low.
- Mitomycin C might be associated to a higher incidence of endophthalmitis, but the certainty of the evidence is low.

Mitomycin C versus 5-fluorouracil in the surgical treatment of glaucoma				
Patients	Patients with glaucoma with indication of surgical treatment			
Intervention	Intraoperative mitomycin C			
Comparison	Intra or postoperative 5-fluorouracil			
Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	WITHOUT 5-fluorouracil	WITH mitomycin C		
	Difference: patients per 1000			
Intraocular pressure (mmHg)	12.8 mmHg	10.1 mmHg	--	⊕⊕○○ ^{1,2} Low
	MD: 2.71 mmHg less (Margin of error: 1.68 to 3.75 less)			
Qualified success	865 per 1000	940 per 1000	RR 1.09 (1.03 to 1.15)	⊕⊕○○ ^{1,2} Low
	Difference: 75 more (Margin of error: 26 a 130 more)			
Bleb leak	48 per 1000	59 per 1000	RR 1.23 (0.62 to 2.45)	⊕⊕○○ ^{1,3} Low
	Difference: 11 more (Margin of error: 18 less to 69 more)			
Late hypotony	37 per 1000	54 per 1000	RR 1.47 (0.50 to 4.36)	⊕⊕○○ ^{1,3} Low
	Difference: 17 more (Margin of error: 18 less to 123 more)			
Cataract	79 per 1000	147 per 1000	RR 2.01 (0.89 to 4.0)	⊕⊕○○ ^{2,3} Low
	Difference: 68 more (Margin of error: 9 less to 237 more)			
Narrow anterior chamber	90 per 1000	112 per 1000	RR 1.25 (0.68 to 2.29)	⊕⊕○○ ^{1,3} Low
	Difference: 22 more (Margin of error: 29 less to 116 more)			
Endophthalmitis	5 per 1000	19 per 1000	RR 3.96 (0.45 to 34.87)	⊕⊕○○ ^{1,3} Low
	Difference: 14 more (Margin of error: 3 less to 162 more)			

Margin of error: 95% confidence interval (CI).
RR: Risk ratio.
MD: Mean difference.
GRADE: Evidence grades of the GRADE Working Group (see later).

*The risk **WITH 5-fluorouracil** is based on the risk in the control group of the trials. The risk **WITH mitomycin C** (and its margin of error) is calculated from relative effect (and its margin of error).

¹ One level of certainty of the evidence was decreased due to a moderate risk of bias in the included trials.
² One level of certainty of evidence was decreased due to inconsistency of the results.
³ One level of certainty of evidence was decreased due to imprecision of results.

Following the link to access the interactive version of this table ([Interactive Summary of Findings-iSoF](#))

About the certainty of the evidence (GRADE)*
<p>⊕⊕⊕⊕</p> <p>High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.</p>
<p>⊕⊕⊕○</p> <p>Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate</p>
<p>⊕⊕○○</p> <p>Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.</p>
<p>⊕○○○</p> <p>Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.</p>
<p>*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.</p> <p>† Substantially different = a large enough difference that it might affect a decision.</p>

Other considerations for decision-making

To whom this evidence does and does not apply

- The evidence presented in this summary applies to glaucoma patients with surgical treatment indication in patients with and without high risk of trabeculectomy failure.
 - Most patients included in the trials were adults. So, this evidence should not be extrapolated to pediatric patients.
-

About the outcomes included in this summary

- The outcomes intraocular pressure and qualified success were chosen because they are crucial for the success of the procedure. In addition, complications of surgery were chosen as safety parameters. This selection is based on the opinion of the authors of the summary, but generally agree with the outcomes reported in the systematic reviews.
-

Balance between benefits and risks, and certainty of the evidence

- Mitomycin C could increase qualified success and be more effective in reducing mean intraocular pressure than 5-fluorouracil. However, it might be associated to more complications. Also, it is important to keep in mind the limitations of the existing evidence.
-

Resource considerations

- Only one systematic review [1] looked for economic outcomes. However, no data was found in the trials. So, it is not clear whether the cost/benefit would be favorable for the use of mitomycin C considering the increase in the efficacy of trabeculectomy, but also the increase in the complication rate compared to 5-fluorouracil.
-

What would patients and their doctors think about this intervention

- The evidence presented in this summary would probably lead to variable decisions depending on whether clinicians place more value on efficacy or safety.
 - The limited certainty of the existing evidence can also be a factor that leads to variations in decision-making.
-

Differences between this summary and other sources

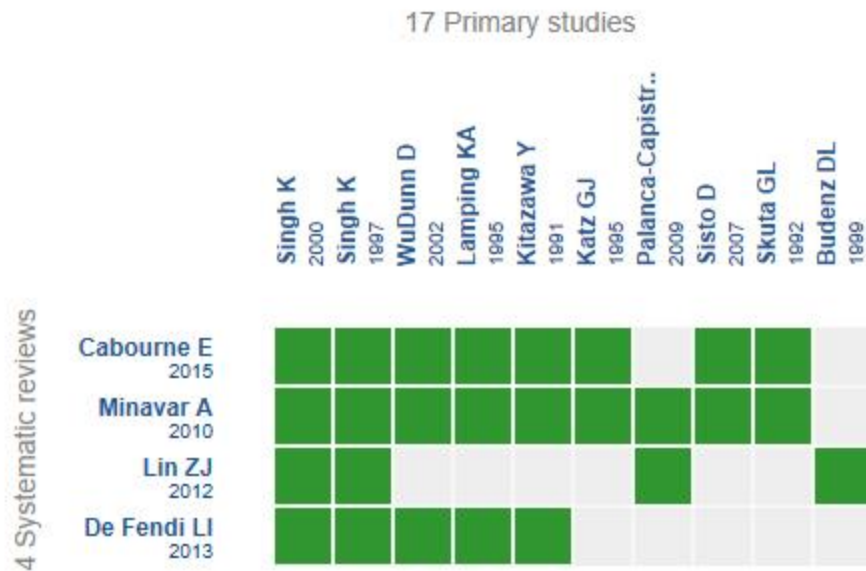
- The conclusions of this summary agree with the most complete systematic review identified [1], being cautious about the results due to the limitations of the evidence and the risk of bias of the primary studies.
 - The conclusions of this summary coincide with the main guidelines which recommend the use of antimetabolites taking into account their risks and benefits [24],[25].
-

Could this evidence change in the future?

- The probability that future research changes the conclusions of this summary is high, due to the uncertainty on the existing evidence.
 - There are at least two ongoing trials in the International Clinical Trials Registry Platform of the World Health Organization evaluating this question [26],[27]. On the other hand, there are trials comparing the mitomycin C against new adjuvant agents (e.g. bevacizumab) [28],[29].
 - No systematic reviews were found in the International prospective register of systematic reviews (PROSPERO) of the National Institute for Health Research.
-

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



An evidence matrix is a table that compares systematic reviews that answer the same question.

Rows represent systematic reviews, and columns show primary studies.

The boxes in green correspond to studies included in the respective revisions.

The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version**: [5-fluorouracil compared with mitomycin C in glaucoma](#)

Notes

The upper portion of the matrix of evidence will display a warning of “new evidence” if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE

(Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here

(<http://dx.doi.org/10.5867/medwave.2014.06.5997>)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

Potential conflicts of interest

The authors do not have relevant interests to declare.

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Author address:

[1] Centro Evidencia UC
Pontificia Universidad Católica de Chile
Centro de Innovación UC Anacleto Angelini
Avda. Vicuña Mackenna 4860
Macul
Santiago
Chile



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