Mitomycin C versus 5-fluorouracil as an adjunctive treatment for trabeculectomy: a meta-analysis of randomized clinical trials

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CRD summary
The authors concluded that compared to trabeculectomy with 5-fluorouracil, trabeculectomy with mitomycin C was associated with higher rates of complete and qualified surgical success and was not associated with increased incidences of postoperative complications. Given the small evidence base and uncertainties regarding the robustness of the findings, the authors’ conclusions appear overly strong.

Authors' objectives
To compare the efficacy and safety of augmenting the surgical procedure trabeculectomy for treatment of glaucoma with mitomycin C or 5-fluorouracil (5-FU).

Searching
Seven databases including MEDLINE, CINAHL and ControlledTrials.com were searched to April 2011 for relevant articles. Search terms were reported. Reference lists of retrieved studies and reviews were scanned.

Study selection
Eligible were randomised controlled trials (RCTs) that compared 5-fluorouracil (5-FU) and mitomycin C as adjuvant therapy for trabeculectomy-related glaucoma treatment. Patients had to be adults aged 18 years or over with glaucomatous changes in the optic disc and intra-ocular pressure of at least 21mmHg. Trials had to include 12 months of postoperative follow-up. Treatment could consist of any dosage, time of application and duration of exposure. Trials were considered with or without needling, other glaucoma medications or suture removal. The primary outcome was mean intraocular pressure (mmHg) at follow-up end point (defined separately as intra-ocular pressure of ≤21 or ≤18mmHg). Secondary outcomes included complete surgical success and qualified surgical success (both at 12 months postoperatively), number of glaucoma medications and occurrence of severe complications. Conference abstracts were eligible if they provided sufficient information.

Studies were published between 1991 and 2002. Types of glaucoma included primary open-angle and primary angle closure, pigmentary, pseudoexfoliative, inflammatory, developmental and neovascular. Surgery included limbus-based conjunctival flap. Concentration dose and time of exposure varied between studies. 5-FU was administered intraoperatively or postoperatively.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Trial quality was assessed using the Cochrane risk of bias tool. The authors did not state how many reviewers assessed quality.

Data extraction
Data on relevant outcomes were extracted on an intention-to-treat basis and used to calculate mean differences, risk ratios or odds ratios and corresponding 95% confidence intervals.

The authors did not state how many reviewers extracted data.

Methods of synthesis
Pooled mean differences, risk ratios and odds ratios, each with 95% confidence intervals, were calculated using a fixed-effect model in the absence of statistical heterogeneity or a random-effects model where there was heterogeneity. Statistical heterogeneity was assessed using the I² statistic and Χ² test.

Subgroup analyses were conducted for mitomycin C low dose (≤0.2 mg/mL) versus 5-FU or mitomycin C high dose
(>0.2 mg/mL) versus 5-FU and mitomycin C versus intraoperative 5-FU or mitomycin C versus postoperative 5-FU.

**Results of the review**

Five RCTs (416 participants) were included. Mean follow-up time was 10.4 months. Three RCTs reported adequate sequence generation and allocation concealment. Blinding was reported in four RCTs and incomplete outcome data were adequately addressed in one RCT. No RCTs addressed selective outcome reporting. One RCT was reported to have other (undefined) sources of bias.

Adjuvant mitomycin C was associated with a statistically significantly lower mean intraocular pressure level following trabeculectomy than with 5-FU (MD -2.17mmHg, 95% CI -3.26 to -1.08; four RCTs). There were no significant differences between groups for the final number of glaucoma medications (two RCTs).

Qualified surgical success rates were higher for treatment with mitomycin C compared with 5-FU when intraocular pressure was up to 21mmHg (OR 2.19, 95% CI 1.18 to 4.08; two RCTs) and intraocular pressure up to 18mmHg (OR 1.82, 95% CI 1.01 to 3.28; three RCTs).

Complete success rates were also higher for treatment with mitomycin C compared to 5-FU with an intraocular pressure of up to 21mmHg (OR 1.67, 95% CI 1.04 to 2.69; four RCTs).

In subgroup analyses high dose mitomycin C was significantly associated with a higher rate of qualified success (intraocular pressure ≤21mmHg) than 5-FU; a higher proportion of eyes treated with mitomycin C achieved qualified success compared with those treated with intraoperative 5-FU. Other subgroup analyses did not report any statistically significant differences between groups.

There was a significantly lower incidence of postoperative corneal epithelial defects for mitomycin C compared to 5-FU (OR 0.25, 95% CI 0.08 to 0.79; three RCTs). There were no statistically significant differences for other adverse events.

Statistical heterogeneity, where reported, appeared to be low to moderate ($I^2=0\%$ to $I^2=56\%$).

**Authors’ conclusions**

Compared to trabeculectomy with 5-FU, trabeculectomy with mitomycin C was associated with higher rates of complete and qualified surgical success and was not associated with increased incidences of postoperative complications.

**CRD commentary**

The review question with clear with defined inclusion criteria. Several relevant sources were searched. Efforts were made to locate unpublished data. It is unclear whether language restrictions were applied. Trial quality was assessed and none of the studies met all the criteria, which suggested low to moderate quality. Appropriate methods to reduce reviewer error and bias were used for trial selection; it was unclear whether similar methods were used for assessing trial quality and for data extraction.

The methods of analysis appeared appropriate. The authors highlighted data limitations including variable definitions of surgical success, absence of patient stratification into different types of glaucoma and risk of surgical failure, limited analysis of complications and use of average quality data regarding follow-up period from trials of different durations. They also reported differences in surgical details reported and suggested caution in extrapolating the results to different surgical techniques. There were some minor discrepancies between tables and forest plots. The authors appeared to include trials with less than 12 months duration despite inclusion criteria that stipulated 12 months of follow-up. The small number of trials, small sample sizes and wide confidence intervals reduced the robustness of the findings.

Given the small evidence base and uncertainties regarding the robustness of the findings, the authors’ conclusions appear overly strong.

**Implications of the review for practice and research**

**Practice:** The authors stated that ophthalmologists should consider the use of mitomycin C over 5-FU as adjunctive therapy in trabeculectomy to achieve a better surgical outcome. No definitive recommendations could be made.
regarding choices between postoperative 5-FU and mitomycin C or with respect to different mitomycin C exposure times.

Research: The authors did not state any implications for research.

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