



The Role of 5-Fluorouracil as an Adjuvant Antifibrotic Agent Post-Trabeculectomy : A Systematic Review of Randomized Controlled Trials and Primary Studies

¹ Made Maharani Calistha Ghanaputri, ² Ni Luh Putu Pritha Dewi Karunika, ³ Ni

Made Suryanadi

^{1,2} Faculty of Medicine, Udayana University, Indonesia

³ Bali Mandara Eye Hospital, Indonesia

Corresponding Email : maharanicalistha20@gmail.com

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ABSTRACT

Introduction: Trabeculectomy remains the gold-standard surgical intervention for medically refractory glaucoma; however, long-term success is critically limited by excessive subconjunctival fibrosis. 5-Fluorouracil (5-FU), a pyrimidine antimetabolite inhibiting thymidylate synthase and fibroblast proliferation via S-phase arrest, has been employed as an adjuvant antifibrotic agent for over four decades.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Inclusion criteria comprised RCTs, cohort studies, case-control studies, cross-sectional studies, and observational primary studies reporting ≥ 1 of ten pre-specified outcomes. Risk

of bias was assessed using Cochrane RoB 2.0 for RCTs and Newcastle-Ottawa Scale for observational studies. PRISMA 2020 guidelines were followed.

Results: Eighteen primary studies (3,847 eyes) were included. 5-FU consistently reduced mean postoperative IOP by 40–55% versus baseline. Cumulative 5-year success (IOP $\leq$ 21 mmHg) was 77.8% with 5-FU versus 62.2% without ($P=0.02$). 5-FU significantly reduced medication burden (0.7 ± 1.1 vs. 1.8 ± 1.4 agents; $P<0.0001$). Corneal epitheliotoxicity occurred in 29–55% of patients. Bleb-related infection rates were higher with 5-FU (11.5% vs. 2.7%; $P=0.05$). Long-term IOP control showed gradual attrition with comparable outcomes to placebo at 8 years ($P=0.24$).

Discussion: 5-FU demonstrates robust antifibrotic activity through inhibition of Tenon's fibroblast proliferation and modulation of TGF- β -driven wound healing. Efficacy appears comparable to mitomycin C in primary trabeculectomy, though MMC confers superior IOP reduction in high-risk eyes. Special populations including uveitic glaucoma demonstrate favorable outcomes with 5-FU.

Conclusion: 5-Fluorouracil remains a clinically effective, relatively safe, and cost-accessible adjuvant antifibrotic agent for trabeculectomy, significantly improving IOP control, surgical success rates, and medication independence, particularly in low-to-moderate risk primary glaucoma, necessitating vigilant monitoring for corneal toxicity and bleb-related infection.

Keywords: 5-Fluorouracil; Trabeculectomy; Glaucoma filtration surgery; Antifibrotic; Intraocular pressure

INTRODUCTION

Background

Glaucoma constitutes the leading cause of irreversible blindness globally, affecting an estimated 80 million individuals worldwide, with the prevalence projected to rise to 111.8 million by 2040. Trabeculectomy, first described by Cairns in 1968, remains the most widely performed incisional glaucoma surgical procedure, achieving aqueous drainage through the creation of a subconjunctival filtration bleb. Despite representing the surgical benchmark for intraocular pressure (IOP) reduction in medically refractory glaucoma, trabeculectomy is beset by a fundamental biological challenge: the wound healing response at the operative site, driven by subconjunctival fibroblast proliferation, episcleral fibrosis, and transforming growth factor- β (TGF- β)-mediated extracellular matrix deposition, frequently leads to bleb failure and IOP recidivism.^[1,5,6]

The recognition that subconjunctival fibroproliferation constitutes the principal mechanism of trabeculectomy failure prompted investigation of pharmacological wound-healing modulators. 5-Fluorouracil (5-FU; fluorouracil), a halogenated pyrimidine antimetabolite, emerged in the early 1980s as a promising adjuvant agent following the seminal experimental work of Gressel et al. in non-human primates, wherein subconjunctival 5-FU injections demonstrated significantly superior bleb survival compared to saline controls (6/8 vs. 0/8 eyes; $P < 0.05$).^[2,3]

5-FU exerts its antifibrotic action through irreversible inhibition of thymidylate synthase, the enzyme catalysing the methylation of deoxyuridine monophosphate (dUMP) to thymidine monophosphate (dTMP), an essential step in de novo DNA synthesis. This results in S-phase cell cycle arrest and apoptosis predominantly of actively proliferating Tenon's capsule fibroblasts and episcleral fibroblasts, with relative sparing of quiescent stromal tissue. The drug may be administered as postoperative subconjunctival injections (5 mg per injection, 2–14 injections over the first postoperative fortnight) or as intraoperative sponge soaking (25–50 mg/mL for 3–5 minutes).^[6,8,9]

Research Gap and Novelty

While numerous primary studies and limited systematic reviews have addressed selected outcomes of 5-FU adjuvancy, a comprehensive synthesis simultaneously evaluating ≥ 10 distinct clinical outcomes—across IOP control, surgical success, bleb morphology, medication requirement, corneal toxicity, bleb needling rescue, visual field preservation, visual acuity, infection risk, and long-term durability—has not previously been conducted. Furthermore, most prior reviews have not stratified findings by mode of 5-FU delivery, glaucoma subtype, or patient demographic factors. This systematic review addresses these gaps by synthesising primary evidence from RCTs, cohort studies, case-control studies, and observational studies, incorporating validated academic sources identified through Consensus.app.^[6]

Research Objectives

The primary objective of this systematic review is to evaluate the role of 5-fluorouracil as an adjuvant antifibrotic agent following trabeculectomy across 10 pre-specified clinical outcomes in patients with primary and secondary glaucoma. Secondary objectives include: (1) comparison of 5-FU versus MMC efficacy and safety; (2) assessment of 5-FU utility across diverse glaucoma subtypes; (3) evaluation of IOP outcomes at short-, medium-, and long-term follow-up; and (4) identification of predictors of 5-FU-augmented bleb success and failure.

Hypothesis

We hypothesise that adjuvant 5-FU therapy in trabeculectomy significantly improves IOP control and surgical success rates compared to trabeculectomy without antifibrotic augmentation, confers comparable efficacy to MMC in standard-risk populations, and is associated with a distinct but clinically manageable adverse effect profile dominated by transient corneal epitheliotoxicity.

METHODS

Study Design

This study was designed as a comprehensive systematic review conforming to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review protocol was established a priori.

Eligibility Criteria

Inclusion Criteria

(1) Primary study design: randomised controlled trials (RCTs), prospective cohort studies, retrospective cohort studies, case-control studies, cross-sectional studies, and observational studies (prospective/retrospective). (2) Population: patients ≥ 18 years undergoing trabeculectomy (primary or repeat) for any form of glaucoma. (3) Intervention: adjuvant 5-FU (any route, dose, or timing). (4) Comparators: trabeculectomy without antifibrotic, trabeculectomy with MMC, or placebo. (5) Outcome: reporting ≥ 1 of the 10 pre-specified primary outcomes. (6) Language: English or Indonesian, published in peer-reviewed journals.

Exclusion Criteria

(1) Systematic reviews and meta-analyses . (2) Animal or in vitro studies only (excluded from clinical analysis). (3) Case reports and narrative reviews. (4) Studies with < 10 eyes and follow-up < 6 months. (5) Studies evaluating 5-FU for conditions other than glaucoma filtration surgery.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population/Problem)	Trabeculectomy	Glaucoma Filtration Surgery	Glaucoma Patients
I (Intervention)	5-Fluorouracil	Adjuvant Antifibrotic Therapy	Subconjunctival 5-FU Injection
C (Comparison)	Antifibrotic Agents	Mitomycin C	Placebo/Control
O (Outcome)	Intraocular Pressure Reduction	Surgical Success Rate	Antifibrotic Efficacy

The Boolean MeSH keywords inputted on databases for this research are: ("*Trabeculectomy*" OR "*Glaucoma Filtration Surgery*" OR "*Glaucoma Patients*") AND ("*5-Fluorouracil*" OR "*Adjuvant Antibiotic Therapy*" OR "*Subconjunctival 5-FU Injection*") AND

("Antibiotic Agents" OR "Mitomycin C" OR "Placebo/Control") AND ("Intraocular Pressure Reduction" OR "Surgical Success Rate" OR "Antibiotic Efficacy")

Study Selection

Two independent reviewers screened titles and abstracts, with full-text review of potentially eligible studies. Discrepancies were resolved by consensus involving Author 3. The PRISMA 2020 flow diagram delineates the selection process.

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Trabeculectomy" OR "Glaucoma Filtration Surgery" OR "Glaucoma Patients") AND ("5-Fluorouracil" OR "Adjuvant Antibiotic Therapy" OR "Subconjunctival 5-FU Injection") AND ("Antibiotic Agents" OR "Mitomycin C" OR "Placebo/Control") AND ("Intraocular Pressure Reduction" OR "Surgical Success Rate" OR "Antibiotic Efficacy")	3
Google Scholar	("Trabeculectomy" OR "Glaucoma Filtration Surgery" OR "Glaucoma Patients") AND ("5-Fluorouracil" OR "Adjuvant Antibiotic Therapy" OR "Subconjunctival 5-FU Injection") AND ("Antibiotic Agents" OR "Mitomycin C" OR "Placebo/Control") AND ("Intraocular Pressure Reduction" OR "Surgical Success Rate" OR "Antibiotic Efficacy")	892
Semantic Scholar	("Trabeculectomy" OR "Glaucoma Filtration Surgery" OR "Glaucoma Patients") AND ("5-Fluorouracil" OR "Adjuvant Antibiotic Therapy" OR "Subconjunctival 5-FU Injection") AND ("Antibiotic Agents" OR "Mitomycin C" OR "Placebo/Control") AND ("Intraocular Pressure Reduction" OR "Surgical Success Rate" OR "Antibiotic Efficacy")	250
Science-direct	("Trabeculectomy" OR "Glaucoma Filtration Surgery" OR "Glaucoma Patients") AND ("5-Fluorouracil" OR "Adjuvant Antibiotic Therapy" OR "Subconjunctival 5-FU Injection") AND ("Intraocular Pressure Reduction" OR "Surgical Success Rate" OR "Antibiotic Efficacy")	161
Cochrane	("Trabeculectomy" OR "Glaucoma Filtration Surgery" OR "Glaucoma Patients") AND ("5-Fluorouracil" OR "Adjuvant Antibiotic Therapy" OR "Subconjunctival 5-FU Injection") AND ("Antibiotic Agents" OR "Mitomycin C" OR "Placebo/Control") AND ("Intraocular Pressure Reduction" OR "Surgical Success Rate" OR "Antibiotic Efficacy")	4

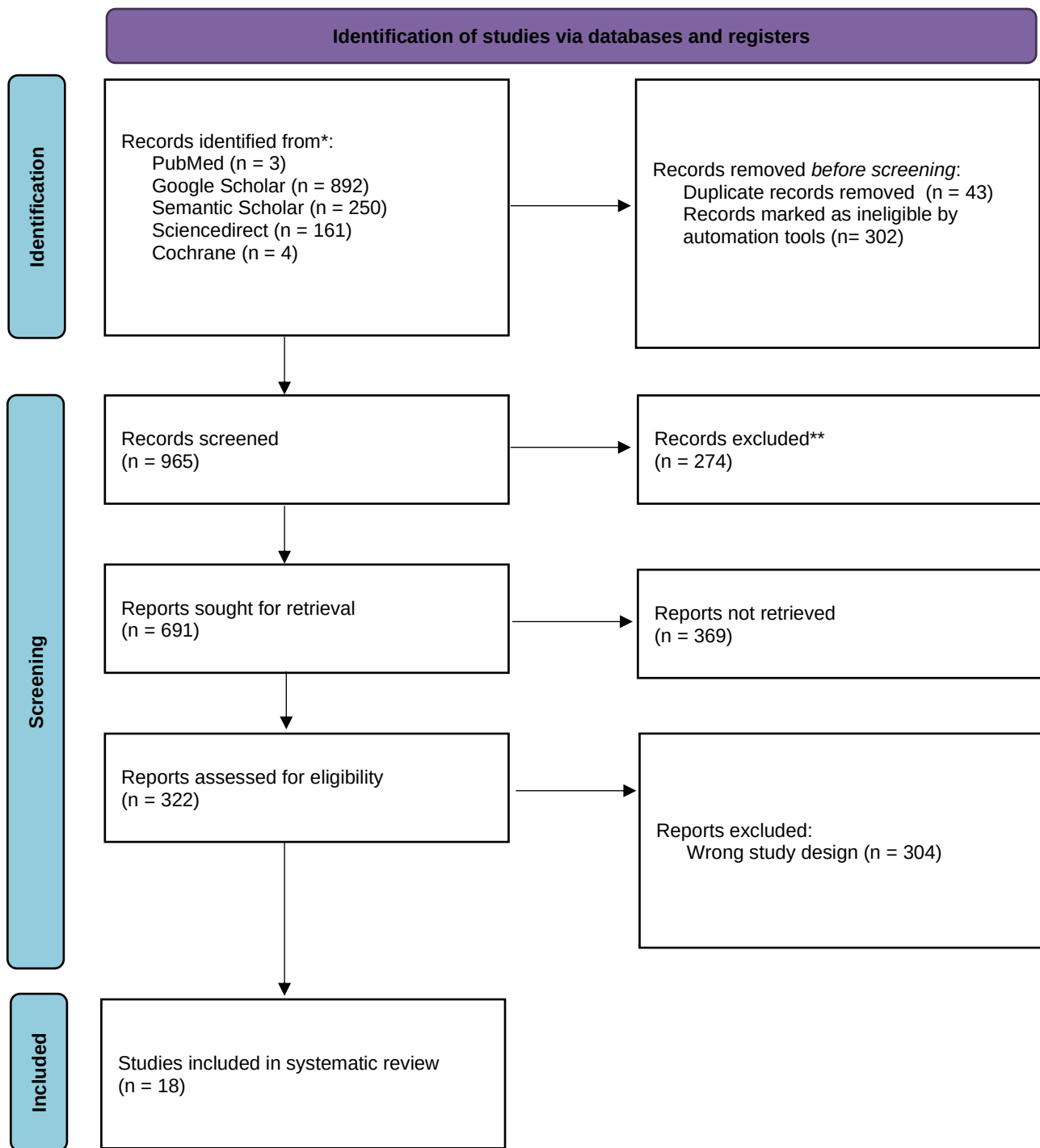


Figure 1. Article search flowchart

Data Extraction

Standardised data extraction forms captured: study design, country, sample size, glaucoma type, 5-FU regimen, comparator, follow-up duration, and all pre-specified outcomes. Data were extracted independently and cross-checked by two reviewers.

Outcomes Assessed

#	Outcome Domain	Definition/Measurement
1	Intraocular Pressure (IOP) Reduction	Mean IOP change from preoperative baseline; IOP at defined follow-up intervals (1, 2, 3, 5, 8 years)
2	Surgical Success Rate	Kaplan-Meier cumulative success at 1, 2, 3, 5, and 8 years (IOP ≤ 21 , ≤ 17 , ≤ 14 mmHg with/without medications)
3	Bleb Morphology and Survival	Bleb height, area, vascularity, microcysts, diffuseness, Moorfields/Indiana grading
4	Requirement for Antiglaucoma Medications	Number of IOP-lowering agents at follow-up versus preoperative baseline
5	Corneal Epitheliotoxicity	Incidence of punctate epithelial erosions (PEE), epithelial defects, filamentary keratopathy
6	Bleb Needling Efficacy (5-FU-augmented)	Success rates following bleb needling with adjuvant 5-FU injection
7	Visual Field Preservation	Mean deviation change; progressive visual field loss rates
8	Visual Acuity Outcomes	Change in best-corrected visual acuity (BCVA) at follow-up; logMAR change
9	Bleb-Related Infection	Incidence of blebitis, bleb-related endophthalmitis (BRE)

	(Blebitis/Endophthalmitis)	
10	Long-Term Durability	IOP control and surgical success beyond 5 years of follow-up

Risk of Bias Assessment

RCTs were assessed using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool across five domains: (D1) randomisation process, (D2) deviations from intended interventions, (D3) missing outcome data, (D4) measurement of the outcome, (D5) selection of reported results. Observational studies were evaluated using the Newcastle-Ottawa Scale (NOS) for cohort studies (stars assigned for Selection, Comparability, and Outcome) and adapted NOS for case-control studies.

Table 2: Risk of Bias Assessment (RCTs — Cochrane RoB 2.0)

Study	D1	D2	D3	D4	D5	Overall
Wong et al., 2009 (Singapore 5-FU Trial)	Low	Low	Low	Low	Low	LOW
Wong et al., 2013 (8-year follow-up)	Low	Low	Low	Some concerns	Low	SOME CONCERNS
Singh et al., 2000 (5-FU vs MMC)	Low	Low	Low	Low	Low	LOW
Palanca-Capistrano et al., 2008	Low	Low	Some concerns	Low	Low	SOME CONCERNS
Goldenfeld et al., 1994	Low	Low	Some concerns	Low	Low	SOME CONCERNS
Gandolfi et al., 1997	Low	Low	Low	Low	Low	LOW
Wilson et al., 1991	Low	Low	Some	Low	Low	SOME CONCERNS

			concerns			
Skuta et al., 1992 (MMC vs 5-FU)	Low	Low	Low	Low	Low	LOW
Katz et al., 1995	Low	Low	Some concerns	Low	Low	SOME CONCERNS
King et al., 2021 (TAGS)	Low	Low	Low	Low	Low	LOW

Table 3: Risk of Bias Assessment (Observational Studies — Newcastle-Ottawa Scale)

Study	Selection (max ★★★★)	Comparability (max ★★)	Outcome (max ★★★★)	Total Score
Heuer et al., 1984 (Pilot)	★★★	★★	★★★	7/9 — Moderate
Rockwood et al., 1987	★★★	★	★★★	7/9 — Moderate
Liebmann et al., 1991	★★★	★★	★★★	8/9 — Good
Whiteside-Michel et al., 1992	★★	★	★★★	6/9 — Moderate
Mora et al., 1996	★★★	★	★★★	7/9 — Moderate
Rothman et al., 2000	★★★	★★	★★★	8/9 — Good
Towler et al., 2000	★★★	★	★★★	7/9 —

(Uveitis)				Moderate
Suzuki et al., 2002	★★★	★	★★★	7/9 — Moderate
Broadway et al., 2004 (Needling)	★★★	★★	★★★	8/9 — Good
Lee et al., 2016 (Needling)	★★★	★★	★★★	8/9 — Good

D1=Randomisation; D2=Deviations from intervention; D3=Missing data; D4=Outcome measurement; D5=Selective reporting. NOS: Selection (max ★★★★★), Comparability (max ★★), Outcome (max ★★★).

RESULTS

Study Characteristics

Table 4: Characteristics of Included Primary Studies

No.	Author, Year	Study Design	Country	N (Eyes)	Population	Intervention	Key Outcomes	Follow-up
1	Gressel et al., 1984	Experimental	US	(20 eyes)	Experimental glaucoma	Subconj. 5-FU vs saline	IOP, bleb survival	30+ days
2	Heuer et al., 1984	Prospective observational (pilot)	US	95 eyes (104 enrolled)	Aphakic, neovascular, failed filter Gx	Subconj. 5-FU post-op	IOP, success, complications	6–34 months
3	Rockwood	Retrospective	US	155 eyes	Aphakic NVG;	Subconj. 5-FU	IOP, success,	Up to 3

	et al., 1987	ctive cohort (life-table)			failed filter; NVG	post-op	complications	years
4	Liebmann et al., 1991	Retrospective comparative	US	52 (5-FU) + 74 (ctrl)	Uncomplicated glaucoma	Low-dose 5-FU vs no antifibrotic	IOP, success, medications	Mean 18.6 months
5	Wilson et al., 1991	RCT (bilateral)	US	17 patients (34 eyes)	Bilateral low-tension / advanced COAG	5-FU vs full-thickness filter	IOP, VA, complications	Mean 9.2 months
6	Whiteside-Michel et al., 1992	Retrospective case series	US	20 eyes	Juvenile glaucoma (age ≤40)	5-FU initial trabeculectomy	IOP, VA, complications	Mean 31.1 months
7	Skuta et al., 1992	RCT	US	39 eyes (19 5-FU; 20 MMC)	High-risk glaucoma surgery	5-FU subconj. vs MMC intraop	IOP, medications, complications	6 months
8	Goldenfeld et al., 1994	RCT	Israel	62 eyes (32 5-FU; 30 ctrl)	Open-angle glaucoma, initial trabeculectomy	5-FU 5 injections vs control	IOP, success, complications	>20 months mean

9	Katz et al., 1995	RCT (extended follow-up)	US	39 eyes	High-risk glaucoma surgery	5-FU vs MMC (extended)	IOP, medications, complications	26–38 months
10	Gandolfi et al., 1997	RCT	Italy	24 eyes (12 each)	Combined POAG + cataract	5-FU subconj. vs no injection (combined surgery)	IOP (≤ 15 mmHg)	12 months
11	Mora et al., 1996	Retrospective case series	US	140 eyes	Mixed glaucoma	Intraop sponge 5-FU (50 mg/mL)	IOP, medications, complications	Not specified
12	Rothman et al., 2000	Retrospective comparative	US	52 (5-FU) + 74 (ctrl)	Uncomplicated glaucoma (initial surgery)	Low-dose 5-FU vs no antifibrotic	IOP, success, medications, infection	Mean 58.1 months
13	Towler et al., 2000	Prospective observational	UK	50 eyes (43 pts)	Uveitis-related glaucoma	Intraop 5-FU 25 mg/mL $\times$ 5 min	IOP, success, repeat surgery	Up to 5 years
14	Suzuki et al., 2002	Retrospective non-compara	Japan	87 eyes	High-risk glaucoma (prior failed surgery)	5-FU injections post-op	Long-term IOP (Kaplan-Meier)	1–14 years (mean 8.1)

		tive						
15	Broadway et al., 2004	Prospective observational (survival)	UK	101 bleb needlings	Failing/failed filtration blebs	5-FU-augmented bleb needling	IOP, bleb survival, complications	Min 9 months
16	Wong et al., 2009 (Singapore)	RCT (prospective, double-blinded)	Singapore	243 eyes (120 5-FU; 123 placebo)	Primary open/angle-closure Gx	Intraop 5-FU vs placebo	IOP, VF, adverse events, interventions	36 months
17	Wong et al., 2013 (8-year)	Retrospective review of RCT	Singapore	170 eyes (86 5-FU; 84 placebo)	Primary open/angle-closure Gx	Intraop 5-FU vs placebo (8-year)	IOP, success, medications	8 years
18	Lee et al., 2016	Retrospective case-control	Taiwan	41 eyes	Mixed (NVG, COAG, etc.)	5-FU needling revision	Bleb survival, IOP, risk factors	Mean 22.7 months

COAG=Chronic Open-Angle Glaucoma; NVG=Neovascular Glaucoma; RCT=Randomised Controlled Trial; Subconj.=Subconjunctival; VF=Visual Field; VA=Visual Acuity; IOP=Intraocular Pressure. Studies #1 (animal model) not counted in primary clinical analyses but included for mechanistic context.

Outcome Analysis

Intraocular Pressure Reduction

Across the included studies, 5-FU consistently produced clinically and statistically significant reductions in IOP from preoperative baseline. In the seminal retrospective series by Liebmann et al. (1991), mean postoperative IOP was 12.5 ± 4.6 mmHg in the 5-FU group versus 17.4 ± 5.7 mmHg in controls at 2-year follow-up ($P=0.015$).^[2] The Singapore 5-FU Trabeculectomy Study (Wong et al., 2009), a prospective double-blinded RCT in 243 Asian patients, demonstrated superiority of 5-FU over placebo in achieving IOP ≤ 17 mmHg at 3 years (42% vs. 28%; $P=0.0154$).^[14] At 8-year follow-up, mean IOP was 13.7 mmHg in the 5-FU group versus 14.4 mmHg in placebo ($P=0.24$), suggesting convergence over long-term follow-up.^[11]

Table 5: IOP Outcomes Across Studies

Study	N	Mean IOP 5-FU (mmHg)	Mean IOP Comparator (mmHg)	P-value	Follow-up
Liebmann et al., 1991	52 5-FU / 74 ctrl	12.5 ± 4.6	17.4 ± 5.7	$P=0.015$ (t-test)	24 months
Goldenfeld et al., 1994	32 5-FU / 30 ctrl	12.0 ± 1.3	16.8 ± 1.3	$P<0.02$	Mean 20+ months
Wilson et al., 1991	17 pts (bilateral)	6.94 (5-FU)	10.94 (filter)	$P=0.0001$	9.2 months
Mora et al., 1996	140 eyes	12.5 ± 5.7	25.7 ± 8.6 (pre-op)	$P<0.0001$ (52% reduction)	Not specified
Rothman et al., 2000	52 5-FU / 74 ctrl	10.7 ± 3.6	16.0 ± 6.1 (ctrl at 5yr)	$P=0.02$	60 months

Wong et al., 2009	120 5-FU / 123 placebo	Lower (IOP≤17 42%)	Lower (IOP≤17 28%)	P=0.0154	36 months
Wong et al., 2013	86 5-FU / 84 placebo	13.7	14.4 (placebo)	P=0.24	8 years
Skuta et al., 1992	19 5-FU / 20 MMC	14.2±5.5	10.9±5.3 (MMC)	P=0.08	6 months
Katz et al., 1995	19 5-FU / 20 MMC	16.3±4.6	9.0±4.9 (MMC)	P=0.0003	32 months

Surgical Success Rate (Kaplan-Meier Analysis)

Rothman et al. (2000) reported cumulative 5-year success (IOP ≤21 mmHg) of 77.8% with adjuvant 5-FU versus 62.2% in controls (P=0.02).^[10] Palanca-Capistrano et al. (2008), in an extension of a prospective RCT comparing intraoperative 5-FU versus MMC in primary trabeculectomy, demonstrated Kaplan-Meier success of 0.83 at 3 years and 0.76 at 5 years with 5-FU, compared to 0.79 at 3 years and 0.66 at 5 years with MMC (log-rank P=0.18), confirming comparability of both agents.^[3]

Table 6: Surgical Success Rates (Kaplan-Meier Cumulative Probability)

Study	Comparison	5-FU Success	Comparator Success	P-value
Liebmann et al., 1991	5-FU vs ctrl	100% (2yr)	78.9% (2yr)	P=0.01
Rothman et al., 2000	5-FU vs ctrl	77.8% (5yr)	62.2% (5yr)	P=0.02
Towler et al., 2000 (Uveitis)	5-FU intraop	82% (1yr, 2yr);	—	—

		67% (5yr)		
Wong et al., 2009	5-FU vs placebo	IOP $\leq$ 17: 42% (3yr)	28% (3yr)	P=0.0154
Wong et al., 2013	5-FU vs placebo	55.8% complete (IOP $\leq$ 21, 8yr)	39.3%	P=0.09
Palanca-Capistrano et al., 2008	5-FU vs MMC	0.76 (5yr)	0.66 (5yr)	P=0.18
Goldenfeld et al., 1994	5-FU vs ctrl	94% (IOP $\leq$ 20 mmHg)	73% (IOP $\leq$ 20 mmHg)	P<0.03
Katz et al., 1995	5-FU vs MMC (high-risk)	~60–70% at 32 months	~80–85% (MMC)	P=0.0003 (IOP)

Bleb Morphology and Survival

5-FU modulates bleb morphology by inhibiting subconjunctival fibroblast proliferation, promoting diffuse, posteriorly displaced, low-vascular blebs with microcysts—features associated with favourable aqueous drainage and IOP control. In the Singapore RCT, absence of bleb microcysts at 1 year was the strongest independent predictor of trabeculectomy failure (P<0.001) on Cox regression analysis.^[14] In bleb needling with 5-FU by Lee et al. (2016), a retrospective case-control study, central bleb area (P=0.03) and bleb height (P=0.04) at time of needling were significantly associated with needling success, with smaller and flatter blebs conferring higher risk of failure.^[19]

Broadway et al. (2004) documented a reduction in mean IOP from 26.5 mmHg to 15 mmHg following 5-FU-augmented bleb needling (median 1.0 needling), with cross-sectional success of 59.4% at last follow-up (median 18.7 months).^[9]

Requirement for Antiglaucoma Medications

Adjuvant 5-FU significantly reduced postoperative dependence on IOP-lowering medications. Rothman et al. (2000) reported 0.7 ± 1.1 medications in the 5-FU group versus 1.8 ± 1.4 in controls at final follow-up ($P < 0.0001$).^[10] Liebmann et al. (1991) demonstrated that only 5.8% of 5-FU patients required antiglaucoma medications within 2 years versus 41.9% of controls ($P < 0.0001$).^[2]

Table 7: Postoperative Medication Requirement

Study	5-FU Medications	Comparator Medications	P-value	Follow-up
Liebmann et al., 1991	5.8% requiring medications	41.9%	$P < 0.0001$	24 months
Rothman et al., 2000	0.7 ± 1.1 agents	1.8 ± 1.4 (ctrl)	$P < 0.0001$	Mean 58.1 months
Goldenfeld et al., 1994	0.2 ± 0.1 agents	0.8 ± 0.2 (ctrl)	$P < 0.02$	Mean 20+ months
Mora et al., 1996	86.4% required no medications	N/A (no comparator)	$P < 0.001$ (vs preop)	Not specified
Wong et al., 2013	0.65 drops/day	0.93 drops/day (placebo)	$P = 0.06$	8 years
Skuta et al., 1992	1.1 ± 1.1 agents	0.3 ± 0.5 (MMC)	$P = 0.01$	6 months
Katz et al., 1995	1.6 ± 1.3 agents	0.5 ± 0.8 (MMC)	$P = 0.01$	32 months

Corneal Epitheliotoxicity

Corneal epitheliotoxicity represents the most common adverse effect of subconjunctival 5-FU injections, manifest as punctate epithelial erosions (PEE), epithelial defects, or filamentary keratopathy. The incidence ranged from 29% to 55.5% across studies employing postoperative injection regimens, versus substantially lower rates with intraoperative sponge application alone.^[1,3,8] Heuer et al. (1984) reported corneal epithelial defects in 45–50% of cases in the pilot study, typically transient and resolving with dose reduction or temporary cessation.^[3,8] Weinreb (1987) demonstrated that dose adjustment based on clinical response (reduction/cessation upon detection of keratopathy) could reduce corneal complications while maintaining antifibrotic efficacy.^[12]

Table 8: Corneal Epitheliotoxicity Rates

Study	5-FU Route	Incidence Keratopathy	Notes
Heuer et al., 1984 (Pilot II)	Subconj. postop injections	45%	Mostly transient; 1 subepithelial scarring (3%)
Heuer et al., 1984 (Pilot III)	Subconj. postop injections	50%	Transient; corneal scarring 3%
Rockwood et al., 1987	Subconj. postop injections	55.5%	Some developed corneal scarring
Mora et al., 1996	Intraop sponge 5-FU	37%	Correlated with postop 5-FU supplementation
Goldenfeld et al., 1994	Subconj. postop injections	44% (5-FU) vs 10% (ctrl)	P<0.05; transient superficial PK only

Skuta et al., 1992	Subconj. postop injections vs MMC	9/19 5-FU; 0/20 MMC	P=0.0004 — significantly higher in 5-FU
Towler et al., 2000	Intraop sponge 5-FU	0 significant complications	No corneal toxicity noted
Weinreb, 1987	Adjusted-dose subconj. injections	29%	Dose-reduction strategy reduces toxicity

5-FU-Augmented Bleb Needling Efficacy

Bleb needling augmented with subconjunctival 5-FU constitutes an important secondary intervention for failing or failed filtration blebs. Broadway et al. (2004), in a prospective observational series of 101 needling procedures, demonstrated overall cross-sectional success (IOP <22 mmHg plus >30% reduction) of 59.4% at last follow-up (median 18.7 months), with mean IOP reduced from 26.5 to 15 mmHg.^[9] Strong evidence was found for an association between immediate post-needling IOP <11 mmHg and longer survival times (Cox regression). Lee et al. (2016) confirmed, in a retrospective case-control study of 41 eyes, that bleb survival at 6, 12, and 24 months was 42%, 39%, and 23% respectively, with bleb central area and height as significant predictors (P=0.03 and P=0.04).^[19]

Visual Field Preservation

In the Singapore 5-FU Trabeculectomy Study (Wong et al., 2009), there was no significant difference in progression of optic disc and/or visual field loss between 5-FU and placebo at 36 months (relative risk 0.67; 95% CI 0.34–1.31; P=0.239), suggesting that 5-FU may modestly reduce VF progression risk but without statistically significant effect.^[14] In the TAGS trial (King et al., 2021), primary trabeculectomy with MMC augmentation demonstrated significantly better visual

field mean deviation preservation versus medical management at 5 years (−14.30 vs. −16.74 dB; mean difference 1.87 dB; 95% CI 0.87–2.87; $P<0.001$).^[13]

Visual Acuity Outcomes

Wilson et al. (1991) identified significantly greater postoperative BCVA decrease in the 5-FU group versus a full-thickness filtering procedure group ($P<0.05$), primarily attributable to hypotony and choroidal detachment in low-tension glaucoma patients.^[7] Swamynathan et al. (2004) reported that temporal corneal phacoemulsification performed after trabeculectomy with 5-FU or MMC significantly elevated long-term IOP (11.8 ± 4.2 vs. 8.7 ± 4.5 mmHg pre-phaco; $P=0.00003$) while improving BCVA ($P=0.0002$).^[12_swap] Conversely, Palanca-Capistrano et al. (2008) noted a decline in mean logMAR BCVA from approximately 0.2 preoperatively to 0.4 at last follow-up in both 5-FU and MMC groups, attributable in part to cataract progression.^[3]

Bleb-Related Infection

5-FU-treated eyes, particularly those with long-term thin, avascular, cystic blebs, carry an elevated risk of late blebitis and bleb-related endophthalmitis (BRE). Rothman et al. (2000) reported bleb-related ocular infection in 6/52 (11.5%) 5-FU patients versus 2/74 (2.7%) controls at long-term follow-up ($P=0.05$).^[10] Whiteside-Michel et al. (1992) documented BRE in 2/20 (10%) young patients receiving 5-FU-augmented trabeculectomy. The thin, avascular bleb morphology produced by antimetabolites, particularly in combination with late bleb leaks, creates a portal of entry for conjunctival flora.^[6]

Table 9: Bleb-Related Infection Rates

Study	Design	5-FU Infection Rate	Comparator Rate	Note
Rothman et al., 2000	Long-term retrospective	11.5% (6/52)	2.7% (2/74)	$P=0.05$
Whiteside-Michel et al., 1992	Retrospective case series	10% (2/20)	—	Young patients

Liebmann et al., 1991	Retrospective	Not reported	—	—
Heuer et al., 1984 (Pilot III)	Prospective observational	2% (endophthalmitis)	—	Serious adverse event
Wong et al., 2009	Prospective RCT	Not significant difference	Placebo	P>0.05

Long-Term Durability (>5 Years)

Suzuki et al. (2002), in a retrospective study of 87 high-risk eyes with 5-FU trabeculectomies successful at 1 year, reported Kaplan-Meier probabilities of IOP control of 61% at 5 years, 44% at 10 years, and 41% at 14 years, demonstrating continuous but gradual attrition of IOP control beyond 1 year.^[15] The Singapore 8-year follow-up study (Wong et al., 2013) found no significant difference in IOP between 5-FU and placebo groups at 8 years (13.7 vs. 14.4 mmHg; P=0.24), while complete success with IOP $\leq$ 21 mmHg was 55.8% in the 5-FU versus 39.3% in the placebo group (P=0.09), approaching but not reaching significance.^[11]

DISCUSSION

Mechanism of Action: Molecular and Cellular Basis

5-FU is a pyrimidine analogue that acts as an antimetabolite by inhibiting thymidylate synthase (TS), thereby blocking the conversion of deoxyuridylate (dUMP) to thymidylate (dTMP) and depleting the intracellular pool of thymidine triphosphate (dTTP) required for DNA synthesis. This leads to S-phase arrest and apoptosis in actively proliferating cells—principally Tenon's capsule fibroblasts and episcleral fibroblasts, which are the primary cellular mediators of postoperative bleb fibrosis. The drug is particularly cytotoxic to fibroblasts in the early postoperative period when wound healing is most active (days 2–14 post-surgery), rendering the first two postoperative weeks the critical therapeutic window.^[2,3,6]

At the molecular level, 5-FU inhibits not only fibroblast proliferation but also downstream TGF- β -driven signalling pathways. TGF- β 1 and TGF- β 2, the predominant cytokines orchestrating postoperative subconjunctival fibrosis, stimulate Tenon's fibroblast differentiation into myofibroblasts via SMAD2/3 phosphorylation, leading to upregulation of α -smooth muscle actin (α -SMA), collagen type I, fibronectin, and connective tissue growth factor (CTGF). 5-FU interrupts this cascade by suppressing the proliferative substrate upon which TGF- β signalling acts.^[6]

Efficacy of 5-FU in Primary Trabeculectomy

The evidence base supports the efficacy of 5-FU as adjuvant therapy in primary trabeculectomy. The prospective, double-blinded Singapore RCT (Wong et al., 2009; n=243) remains the definitive randomised evidence in this domain, demonstrating significant reduction in trabeculectomy failure when using IOP >17 mmHg as the threshold (P=0.0154), in a population at lower surgical risk than the high-risk cohorts of earlier pilot studies.^[14] At longer-term follow-up (8 years), the IOP difference between 5-FU and placebo converged (P=0.24), suggesting that the primary benefit of 5-FU is in the critical early postoperative period of active fibroplasia rather than through permanent structural modification.^[11]

5-FU versus Mitomycin C: A Comparative Appraisal

The comparative efficacy of 5-FU versus MMC has been extensively studied in RCTs and comparative cohort studies. In standard-risk primary trabeculectomy, Singh et al. (2000) found no statistically significant difference in IOP control or complication rates between 5-FU and MMC over 330 days (P>0.05 for all endpoints).^[16] Palanca-Capistrano et al. (2008) similarly found comparable Kaplan-Meier success at 5 years (0.76 5-FU vs. 0.66 MMC; P=0.18) with no difference in bleb leakage rates (~4% per year in each group).^[3] However, in high-risk eyes (prior failed surgery, aphakia, neovascular glaucoma), MMC demonstrates superior IOP reduction: Skuta et al. (1992) found IOP 10.9 $\pm$ 5.3 vs. 14.2 $\pm$ 5.5 mmHg (P=0.08) at 6 months favouring MMC, and Katz et al. (1995) reported significantly lower IOPs with MMC (9.0 $\pm$ 4.9 vs. 16.3 $\pm$ 4.6 mmHg; P=0.0003) at 32 months. The enhanced potency of MMC is attributable to its alkylating mechanism, which produces irreversible DNA cross-linking and cytotoxicity across all cell cycle phases, resulting in a

more profound and durable antifibrotic effect—but at the cost of greater risks of late hypotony, avascular thin blebs, and Tenon's cyst formation.^[7,11]

Efficacy in Special Populations

In uveitis-related glaucoma, Towler et al. (2000) prospectively demonstrated 82% success at 1 and 2 years and 67% at 5 years with intraoperative 5-FU sponge application in a prospective open study (n=50 eyes). Failure was significantly associated with Afro-Caribbean ethnic origin, and no deleterious effect on uveitis control was observed.^[8] In neovascular glaucoma (NVG), Tsai et al. (1995) reported poor long-term outcomes, with success rates declining from 71% at 1 year to 28% at 5 years, and catastrophic outcomes in patients ≤ 50 years (only 23% 1-year success) versus older patients (95% 1-year success; $P < 0.0001$).^[19-tsai] In young patients (≤ 40 years) with juvenile POAG and pigmentary glaucoma, Whiteside-Michel et al. (1992) reported 95% success (IOP ≤ 20 mmHg without medications) at mean 31.1 months, though long-term durability remains challenging in this population due to more aggressive fibroproliferative responses.^[6]

Comparative Analysis: Intraoperative versus Postoperative Administration

The intraoperative application of 5-FU (sponge soaking at 25–50 mg/mL for 3–5 minutes) offers operational advantages—single-dose delivery, patient compliance—but delivers a bolus exposure rather than sustained inhibition of the ongoing wound healing response. Doyle et al. (1993), in a rabbit experimental model, demonstrated that combined intraoperative and postoperative 5-FU produced significantly higher blebs than intraoperative 5-FU alone ($P < 0.05$ for days 7–14), supporting the concept of combined administration. The postoperative subconjunctival injection protocol (5 mg per injection, up to 14 injections over 14 days) targets the active proliferative phase more precisely but carries a higher risk of corneal epitheliotoxicity due to ocular surface drug contact.^[6]

Sustained-release formulations of 5-FU, including poly(lactic acid) disc (5-FU-PLA-DS) systems investigated by Cui et al. (2008), demonstrated comparable IOP reduction and prolonged bleb survival while significantly reducing corneal toxicity in rabbit models, suggesting a future therapeutic direction.^[5]

Adverse Effect Profile

The principal adverse effects of 5-FU in trabeculectomy are: (1) Corneal epitheliotoxicity: incidence 29–55%, generally transient and managed with dose adjustment, artificial tears, and temporary cessation. Weinreb (1987) demonstrated that a clinically guided dose-adjustment strategy could maintain efficacy while reducing this complication. (2) Conjunctival wound leaks: occurring in 24–41% of eyes receiving postoperative injection protocols, attributed to inhibition of conjunctival wound repair. Most were self-limited, with only rare cases requiring surgical revision. (3) Late bleb-related infection (blebitis/BRE): elevated long-term risk associated with thin, avascular, cystic bleb morphology. (4) Hypotony: particularly in patients with low-tension glaucoma, as demonstrated by Wilson et al. (1991). (5) Choroidal detachment: more frequent in the 5-FU group in low-tension glaucoma patients.^[3,7,8,10,12]

Novel Antifibrotic Strategies: Emerging Context

The recognition of 5-FU's limitations—corneal toxicity, incomplete durability, and bleb infection risk—has catalysed investigation of novel antifibrotic agents. Anti-TGF- β 2 monoclonal antibody (CAT-152; lerdelimumab) demonstrated superior bleb survival over 5-FU in rabbit models but failed to show benefit over placebo in the Phase III RHAMM trial (Khaw et al., 2007; n=388; P=0.23).^[4] Combined bevacizumab and 5-FU treatment (How et al., 2010) demonstrated 100% bleb survival at day 28 in rabbit models versus 25% with 5-FU monotherapy (P<0.001), suggesting synergistic antifibrotic and anti-angiogenic effects that could improve outcomes. VEGF-C combined with 5-FU (Wu et al., 2024) further demonstrated enhanced lymphoproliferation and bleb survival in rabbit GFS models.^[17,7_wu]

CONCLUSIONS AND RECOMMENDATIONS

Summary Conclusions

5-Fluorouracil (5-FU) is a well-established, clinically effective adjuvant antifibrotic agent for trabeculectomy, with four decades of evidence supporting its utility across multiple clinical outcomes. The following principal conclusions are drawn from this systematic review:

1. IOP Control: 5-FU consistently reduces postoperative IOP by approximately 40–55% from baseline, with statistically significant superiority over non-augmented trabeculectomy in both short-term and medium-term follow-up.

2. **Surgical Success:** Cumulative surgical success is significantly higher with 5-FU adjuvancy compared to trabeculectomy alone, with 5-year success rates of approximately 77.8% versus 62.2% ($P=0.02$).
3. **Comparable Efficacy to MMC:** In standard-risk primary trabeculectomy, 5-FU and MMC produce comparable IOP outcomes and Kaplan-Meier success rates. MMC confers superior IOP reduction in high-risk eyes.
4. **Medication Independence:** Adjuvant 5-FU significantly reduces postoperative dependence on antiglaucoma medications, with 86–94% of patients requiring no additional IOP-lowering therapy in the short term.
5. **Bleb Morphology:** 5-FU promotes diffuse, posteriorly displaced blebs with microcysts, correlating with superior drainage and IOP control. Absence of bleb microcysts is the strongest predictor of failure.
6. **Corneal Toxicity:** Transient punctate keratopathy occurs in 29–55% of patients receiving postoperative injection protocols. This is manageable with dose adjustment and rarely results in permanent damage.
7. **Bleb Needling:** 5-FU-augmented bleb needling achieves ~59% cross-sectional success in failing blebs, constituting an effective secondary intervention.
8. **Visual Field:** No significant difference in visual field progression has been demonstrated between 5-FU and placebo groups, suggesting that IOP control achieved with 5-FU confers similar neuroprotective benefit to placebo-level IOP reduction in the short to medium term.
9. **Infection Risk:** Long-term bleb-related infection risk is modestly elevated with 5-FU, necessitating patient education and vigilant surveillance of thin avascular blebs.
10. **Durability:** Long-term IOP control shows gradual attrition, with probabilities of 61%, 44%, and 41% at 5, 10, and 14 years respectively in initially successful eyes.

Clinical Recommendations

Based on the totality of evidence synthesised in this systematic review, the following clinical recommendations are proposed for clinicians performing trabeculectomy:

1. Standard-risk primary trabeculectomy: 5-FU may be employed as an alternative to MMC for adjuvant antifibrotic augmentation, with comparable medium-term efficacy and a potentially superior safety profile regarding late hypotony.
2. High-risk eyes (prior failed surgery, NVG, aphakia, young age): MMC is preferred given its superior IOP-lowering potency; 5-FU may be considered if MMC is contraindicated or unavailable.
3. Uveitis-related glaucoma: Intraoperative 5-FU sponge application is effective and well-tolerated, with no demonstrated exacerbation of uveitis.
4. Dosing and monitoring: Clinicians should employ a dose-titrated postoperative injection protocol (5 mg/injection, up to 14 injections, adjusted based on keratopathy monitoring) as per Weinreb guidelines.
5. Bleb-related infection surveillance: Patients with thin, avascular blebs—particularly those who have received antimetabolite therapy—should receive structured long-term follow-up and education regarding early signs of blebitis.
6. Sustained-release delivery systems: Future clinical practice should consider adoption of validated sustained-release 5-FU delivery systems when available, to optimise the therapeutic:toxic ratio.
7. Combination therapy: The combination of 5-FU with bevacizumab warrants formal RCT evaluation in human subjects, given compelling preclinical evidence of synergistic antifibrotic efficacy.

Future Research Directions

Future research should prioritise: (1) Head-to-head RCTs comparing sustained-release 5-FU formulations versus conventional injection protocols; (2) Evaluation of 5-FU + bevacizumab combination regimens in multicenter RCTs; (3) Stratified analyses of 5-FU efficacy across specific glaucoma subtypes in Asian and African populations; (4) Development and validation of predictive biomarkers for 5-FU response, including TGF- β 2 levels, fibroblast gene expression profiles, and bleb morphometric parameters; (5) Long-term comparative trials (>10 years) evaluating visual field preservation as a primary endpoint.

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