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# The Clinical Applications of Fluorouracil in Ophthalmic Practice

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## Abstract

Fluorouracil (5-fluorouracil, 5-FU) is a pyrimidine analogue that was originally known for its widespread use as an anticancer drug. The ability of 5-FU to reduce fibroblastic proliferation and subsequent scarring has made it an important adjunct in ocular and periorbital surgeries. It is used in primary glaucoma filtering surgeries and in reviving failing filtering blebs, in dacryocystorhinostomy, pterygium surgery, and in vitreoretinal surgery to prevent proliferative vitreoretinopathy. In addition, 5-FU is also gaining recognition in the treatment and surgical management of ocular surface malignancies like ocular surface squamous neoplasia; however, the specific action of the drug on highly proliferating cells

limits its use in primary acquired melanosis of the conjunctiva. When applied topically, this drug has a low rate of sight-threatening adverse effects, is inexpensive, and is easy to administer, making it an important tool in enhancing the success rate in ophthalmic surgery and in reducing the recurrence of ocular surface neoplasia.

Fluorouracil (5-fluorouracil, 5-FU) is one of the most commonly used antimetabolites in ophthalmic practice. Both mitomycin (mitomycin-c) and 5-FU have anti-scarring properties that are utilised in ocular and adnexal surgeries, especially in patients in whom the natural healing process could result in an unfavourable surgical outcome. It is also used in treating various ocular surface neoplasias.

Here we review the various studies in the literature on the possible ophthalmic applications of 5-FU, the possible adverse effects and the potential future use. We conducted a MEDLINE search (January 1970 to August 2006) using the keyword '5 fluorouracil', and the combinations with the following keywords: 'chemotherapy', 'pharmacokinetics', 'eye', 'glaucoma', 'trabeculectomy', 'filtering surgery', 'filtering bleb', 'pterygium', 'dacryocystorhinostomy', 'lacrimal surgery', 'proliferative vitreoretinopathy',' vitrectomy', 'ocular surface neoplasia', 'primary acquired melanosis', 'conjunctival melanoma', 'strabismus', 'after cataract', 'intraocular tumours' and 'complications'. Manuscripts published in English in peer-reviewed journals were favoured. From these studies and their references, 670 abstracts were reviewed, and those relevant to our discussion were selected. Major ophthalmic and medical textbooks were also reviewed for content, as well as original references, and these were manually searched. Clinical studies were selected if they were randomised controlled trials, single- or double-blind, or interventions with 5-FU compared with placebo or other antifibrotic agents. Case series and single case reports were also included when reviewing experimental treatments. The commonly used terms employed in this review are defined in table I.

**Table I.** Definition of commonly used ophthalmological terms

| | |
|---|---|
| Bullous keratopathy | Corneal endothelial dysfunction causing bullous elevation of the corneal epithelium |
| DCR | Surgery for blockage of the lacrimal drainage system where a passage is created between the lacrimal sac and the nose |
| ECCE | Standard cataract surgery where lens nucleus is delivered through a 10mm incision |
| Endophthalmitis | Infection of ocular contents |
| Filamentary keratopathy | Formation of fine elongation of corneal epithelium in inflammation, oedema and degenerative states |
| Filtering bleb | The elevated area on the conjunctiva where the aqueous drains into after trabeculectomy |
| Hypotony | Very low intraocular pressure, which causes structural changes in the eye due to overfiltration or leakage |
| Intumescent cataract | Mature cataract, which is swollen because of increased fluid within the lens |
| Keratoconjunctivitis sicca | Severe dry eye |
| Overfiltration | Increased drainage of aqueous into the subconjunctival space as a result of reduced scarring |
| Pterygium | A wing shaped conjunctival overgrowth on to the cornea |
| Punctate keratopathy | Small, multiple epithelial erosions on the cornea |
| Retinal detachment | Detachment of the sensory retina from the retinal pigment epithelium, which can lead to loss of vision |
| Trabeculectomy | Surgery for glaucoma, which creates a fistula to facilitate drainage of aqueous humour from the anterior chamber to a subconjunctival space |
| Whorl-like keratopathy | Pigmented whorl shaped irregular corneal epithelium |
| YAG capsulotomy | Making a hole in the posterior capsule using YAG laser to improve vision after cataract surgery |

**DCR** = dacryocystorhinostomy; **ECCE** = extracapsular cataract extraction; **YAG** = yttrium-aluminium-garnet.

## 1. Pharmacology and Pharmacokinetics

### 1.1 Structure and Mechanism of Action

5-FU is a pyrimidine analogue with a chemical structure related to thymine and uracil. It was first synthesised in 1957 by Dushinski et al.[1] and was found to have significant activity against tumours of the gastrointestinal tract, head and neck, and breast.[2] It is metabolised by two routes after penetration into the cell: (i) the anabolic route which gives rise to active metabolites; and (ii) the catabolic route which results in drug elimination.[3,4] A summary of the metabolism of 5-FU is shown in figure 1.

5-FU has several cytotoxic effects that render it useful in ophthalmology.

1. Its active metabolite, 5-fluorodeoxyuridine 5′-monophosphate (FdUMP), inhibits thymidylate synthetase and the incorporation of thymidine into DNA. This mechanism is cell-cycle specific, affecting only those cells in the S (synthesis) stage, and is the principal antineoplastic mechanism.[5]

2. 5-FU is incorporated into RNA, and interferes with RNA and ribosomal RNA synthesis.[6]

3. 5-FU causes indirect disruption of the actin cytoskeleton in a dose-dependent manner.[7]

4. It promotes apoptosis in Tenon's capsule fibroblasts, a fact which is important in glaucoma surgery, where excessive conjunctival scarring is the commonest cause of surgical failure.[8]

5-FU induces apoptosis in cells in a time- and concentration-dependent manner.[9] Studies of the effect of 5-FU on homologous fibroblasts in rabbits have shown that it causes intracytoplasmic accumulation of vacuoles, morphological changes and inhibition of collagen deposition in the matrix.[10] It was also shown that a 5-minute exposure to 5-FU results in growth arrest of cultured Tenon's fibroblasts,[11] and that 5-FU interferes with qualitative fibroblast functions such as collagen lattice contraction.[12] Fibroblast apoptosis mediates the reduction in the number of fibroblasts that accompany resolution of the normal wound healing response. Unlike mitomycin, vascular endothelial toxicity has not been demonstrated with 5-FU.[13]

### 1.2 Ocular Pharmacokinetics

Tissue culture studies have shown that the concentration of 5-FU that is required to induce a 50% inhibition in rabbit conjunctival fibroblast prolifera-

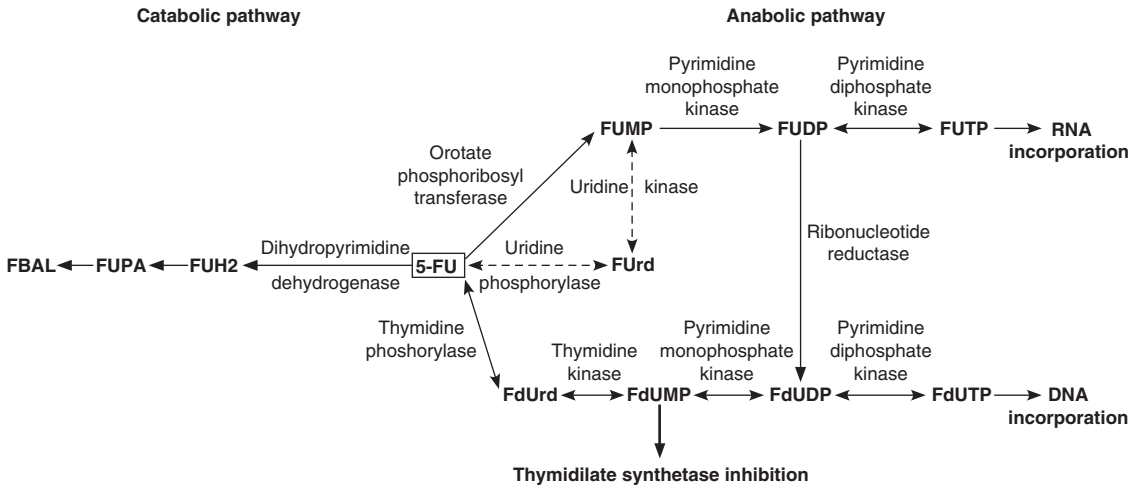


**Fig. 1.** Metabolism of fluorouracil (5-FU) after penetration into the cell. **FBAL** = α-fluoro-β-alanine; **FdUDP** = 5-fluoro-2′-deoxyuridine 5′-diphosphate; **FdUMP** = 5-fluoro-2′-deoxyuridine 5′-monophosphate; **FdUrd** = 5-Fluoro-2′-deoxyuridine; **FdUTP** = 5-fluoro-2′-deoxyuridine 5′-triphosphate; **$FUH_2$** = 5,6-dihydro-5-fluorouracil; **FUDP** = 5-fluorouridine-5′-diphosphate; **FUMP** = 5-fluorouridine-5′-monophosphate; **FUPA** = α-fluoro-β-ureidopropionic acids; **FUrd** = 5-fluorouridine; **FUTP** = 5-fluorouridine-5′-triphosphate.

tion is only 0.2 μg/mL.[14] Additional studies of 5-FU in rabbits showed a peak aqueous concentration of 69.5 μg/mL and a 12-hour concentration of 0.9 μg/mL, after a single subconjunctival injection.[15] The aqueous humour concentrations were greater with a topical application than with a subconjunctival injection.[16] It was also found in studies with rabbit eyes that after a single subconjunctival injection of 5-FU, using a liposomal delivery system, an aqueous concentration of 0.2 μg/mL was recorded for only 12 hours, whereas the same fibroblast inhibitory dose was found in the conjunctiva, cornea and sclera for 96 hours.[17] *In vitro* studies have also shown that there was no difference in the anti-proliferative effect of 5-FU on Tenon's capsule fibroblasts when 50 mg/mL was applied for 1 minute or 5 minutes.[18]

Intravitreal injections (1mg) in rabbit eyes result in a more sustained intraocular concentration of 5-FU than with a subconjunctival injection, which could justify its use in vitreoretinal surgery.[19] At these concentrations, the drug was non-toxic to the retina or the optic nerve.[19,20]

## 2. Ophthalmic Applications of Fluorouracil (5-FU)

In 1982, 5-FU was first used in ophthalmic practice by Blumenkranz et al.[20] They reported that intravitreal and subconjunctival injections of this drug were safely used and effective in experimental massive preretinal proliferation. This was the first report on the use of any antimetabolite as an anti-scarring agent. Since then, various studies were designed to evaluate the effect of 5-FU in different ophthalmic pathologies and surgeries.

### 2.1 Ocular Surgery

#### *2.1.1 Glaucoma Filtering Surgery*

Filtering surgery is usually reserved for glaucoma patients who are unresponsive to maximal medical and/or laser therapy, and fail to achieve the target intraocular pressure (IOP). Conjunctival wound healing and postoperative scarring are some of the crucial factors in determining the success of this operation and the final IOP.[21-23] Although the scarring response is unpredictable, it could be related to individual factors such as the patient's age and race, previous ocular surgery, postoperative inflammation and pre-existing neovascularisation. Antimetabolites play a very important role in the pharmacological modulation of wound healing, especially in patients with known risk factors. The main features that make 5-FU a useful adjunct in glaucoma filtering surgery are the localised and targeted effect on the exposed tissue, its short half-life and the ease of administration.[24]

One of the first clinical trials on the use of 5-FU in trabeculectomy was performed by Heuer et al.[25] in 1984. Since then, it has been used frequently as an intraoperative or postoperative adjunct, even in eyes with no obvious risk factors for surgical failure. As there are no specific guidelines regarding the optimal dose and mode of application, most surgeons use it on an empirical basis and according to their experience. The postoperative subconjunctival injections of 5-FU are sometimes used as a controlled mode to titrate the dose, based on the clinical response, thereby increasing the success rate and the chance of stabilising the patient's visual field.[26]

In addition to its adjunctive use in primary trabeculectomy, 5-FU has been used as adjunctive treatment in combined cataract and glaucoma surgeries, congenital glaucoma surgery, glaucoma drainage implants and needling revision of failed filtering blebs.

##### Primary Trabeculectomy

In primary trabeculectomy, subconjunctival injections of 5-FU are given postoperatively, and the total dose is titrated based on the clinical response and toxicity. The site of injection and the distance from the original bleb varies from surgeon to surgeon. Several single- and multicentre studies have evaluated the role of postoperative 5-FU in improving the outcome of primary trabeculectomy. Some of these studies are summarised in table II.

The common dose of 5-FU per injection is 5mg in 0.1–0.5mL of saline (5%). The frequency of injections is variable, with an average of seven to eight postoperative injections over 2 weeks, depend-

**Table II.** Comparison of studies that used fluorouracil (5-FU) postoperatively in trabeculectomy

| Study (year) | No. of eyes | Study design | 5-FU schedule | Total dose (mg) | Outcome measures | Results (% success) | Follow-up period | Study limitations |
|---|---|---|---|---|---|---|---|---|
| Heuer et al.[27] (1986) | 27 | Pilot study | 3mg/5mg od over 2wk | 105 | IOP ≤21mm Hg | 5-FU: 69 | 6mo | Historical controls, complicated high risk glaucomas |
| Ruderman et al.[28] (1987) | 26 | p, r | 5mg od for 7d vs con | 35 | IOP <20mm Hg | 5-FU: 85<br>con: 25 | 12mo | Small sample size |
| Araie et al.[29] (1992) | 362 | p, nr | 5mg od | 35–50 | Kaplan Meir 5y probability of IOP <16mm Hg | 5-FU: 55.2<br>con: 0 | 5y | |
| Ophir and Ticho[30] (1992) | 41 | p, r | 5mg, 4–6 inj | 20–30 | IOP ≤20mm Hg | 5-FU: 96<br>con: 76 | 17.5mo | |
| Goldenfeld et al.[31] (1994) | 62 | p, r | 5mg, 5 inj | 25 | IOP ≤20mm Hg | 5-FU: 94<br>con: 73 | 12mo | |
| FFSS Group[32] (1996) | 213 | p, r | 5mg inj over 2wk | 105 | IOP ≤21mm Hg | 5-FU: 49<br>con: 26 | 5y | |
| Chaudry et al.[33] (2000) | 40 | p, r | 5mg, 3 inj over 11d vs con | 15 | IOP ≤21mm Hg<br><20% IOP reduction | No difference | 52wk | |
| Rothman et al.[34] (2000) | 52 5-FU<br>74 con | ret, c | 5mg in 0.3mL over 14d | 28.9 ± 10 | IOP ≤21mm Hg | 5-FU: 72<br>con: 51 | 58mo | |
| Akarsu et al.[35] (2003) | 36 | ret, c | MMC 0.04% vs 5-FU 5mg | 15–25 | IOP ≤21mm Hg with or without med | Success at 1y:<br>MMC: 82.3<br>5-FU: 73.6<br>Success at 4y:<br>MMC: 60.5<br>5-FU: 52.6 | 4y | Retrospective |

**c** = comparative; **con** = controls; **FFSS** = Fluorouracil Filtering Surgery Study; **inj** = injection; **IOP** = intraocular pressure; **med** = medication; **MMC** = mitomycin (mitomycin-C); **nr** = nonrandomised; **od** = once daily; **p** = prospective; **r** = randomised; **ret** = retrospective.

ing on the clinical response.[27-32] Some studies have shown success with an even smaller number of postoperative injections.[33-35]

The total dose of 5-FU used, the mean dose, site of injection, patient selection and study duration were significantly different between and within studies. Despite the perfect total dose remaining imprecise, the postoperative dose of 5-FU can be titrated depending on the clinical response and toxicity. Corneal epithelial toxicity is the most common adverse effect, and is reversible after stopping the injections.

Postoperative injections of 5-FU can be time consuming, as well as uncomfortable and inconvenient to both the patient and the surgeon. Therefore, investigators have considered alternative modes of delivery, including intraoperative topical application using sponges soaked in 25–50 mg/mL of 5-FU, applied between the sclera and conjunctiva for several minutes (table III).[36-42] This technique is a valuable adjunct in achieving successful bleb function and IOP control in low risk patients. This mode of administration is simpler, more comfortable to patients, limits the number of postoperative injections, and has fewer adverse effects without compromising success rates.

An overview of the published literature suggests that 5-FU (50 mg/mL) applied intraoperatively for 5 minutes increases the chances of successful filtration and reduction of IOP.

Interestingly, the long-term success rate with 5-FU seems to decrease at a rate similar to that seen in patients who were not treated with adjunctive antimetabolites.[43] This is probably related to continued uninhibited late fibrosis. In addition, this procedure carries a 5.7% risk of late (2 years) bleb-related endophthalmitis.[44] Nevertheless, 5-FU remains the antimetabolite of choice for many glaucoma surgeons, given the anti-scarring properties, ease of administration and the lack of major adverse effects.

### Combined Trabeculectomy and Cataract Surgery

Trabeculectomy is performed at the same time as cataract surgery in patients with significant cataract and glaucoma. Combined surgery is associated with a host of supplementary surgical variables that affect postoperative outcome compared with primary trabeculectomy. Cataract surgery is associated with disruption of the blood aqueous barrier, which increases the risk of fibrosis.[45,46] Although cataract surgery itself is known to reduce IOP, especially in eyes with occludable angles,[47] combined surgery offers unsatisfactory results. This has led to the use of antimetabolites to augment bleb survival in combined surgeries.

Hennis and Stewart[48] published one of the earlier reports on a group of glaucoma patients who underwent trabeculectomy combined with standard extracapsular cataract extraction (ECCE). They found no significant beneficial effect from using 5-FU. A possible explanation to their findings is the use of a suboptimal total dose of 5-FU that was probably not sufficient to overcome the fibroblastic response with ECCE. More recently, the potential benefit of adjunctive 5-FU was studied in combined surgeries using the more popular small incision cataract surgery (phacoemulsification).

The comparison between the different studies which used adjunctive 5-FU in combined surgery is presented in table IV.[49-54] The results of these studies were variable. The additional surgical factors associated with combined surgeries probably play a critical role in this non-convincing outcome.

### Congenital Glaucoma Surgery

Glaucoma filtering surgery in children is a challenging operation. The main factors known to reduce the success rate are an aggressive wound healing response, presence of a thick Tenon's capsule and low scleral rigidity. The anti-scarring effect of 5-FU and its low ocular toxicity make it an appealing adjunct in congenital glaucoma surgery. Zalish et al.[55] reported a small case series of two children (four eyes) who underwent trabeculectomy with postoperative 5-FU (5mg in 0.5mL). At a 16.5-month follow-up, functioning cystic filtering blebs were present in both patients, with significant reduction in IOP. Results from another study that compared the use of postoperative 5-FU versus intraoperative mitomycin followed by postoperative 5-FU, showed that in the 5-FU group all eyes had

**Table III.** Comparison of studies using 5-fluorouracil (5-FU) intraoperatively in trabeculectomy

| Study (year) | No. of eyes | Study design | Dose | Outcome measures | Results (%) | Follow-up (mo) | Study limitations |
|---|---|---|---|---|---|---|---|
| Mora et al.[39] (1996) | 140 | ret, LTA | 50 mg/mL; 5 min | 1) IOP <21mm Hg<br>2) IOP <21 and >30% reduction<br>3) IOP <15 and >30% reduction | 1) 79 without med; 92 with med<br>2) 69; 82<br>3) 59; 72 | 16 | Retrospective, no control group |
| Bell et al.[38] (1997) | 45 | ret | 25 mg/mL; 5 min | IOP reduction | Mean IOP reduction 42% | 24 | Retrospective, small sample, no controls |
| Anand et al.[36] (1998) | 76 | p, nr | 25 mg/mL; 5 min | IOP <21mm Hg | 6mo: 93<br>12mo: 81 | 6 | Short follow-up |
| Sidoti et al.[40] (1998) | 41 | p, LTA | 50 mg/mL; 5 min followed by postop 5-FU | IOP ≤21mm Hg and ≥5mm Hg | 6mo: 100<br>12mo: 97<br>15mo: 83 | 15 | Short follow-up |
| Singh et al.[42] (2000) | 113 | p, r | 5-FU: 50 mg/mL vs MMC: 0.04% | 1) Target IOP <21, 18, 15 and 12mm Hg<br>2) Visual acuity<br>3) Complications | No statistically significant difference between the two meds | 36 | |
| Wudunn et al.[41] (2002) | 115 | p, r, db | 5-FU 50 mg/mL; 5 min vs MMC 0.02%; 2 min | Target IOP ≤21, 18, 15, 12mm Hg at 12mo | At each target IOP, the success rates similar | 12 | Short follow-up |
| Mielke et al.[37] (2003) | 154 | ret, LTA | 5-FU 50 mg/mL; 5 min vs con | 1) Maintaining IOP ≤20mm Hg<br>2) Reduction of visual acuity ≤2 lines<br>3) Maintaining IOP ≤14mm Hg | 1) 5-FU 76; con 79<br>2) No difference<br>3) 5-FU 64; con 39 | 17 | Retrospective, short follow-up |

**con** = controls; **db** = double-blind; **IOP** = intraocular pressure; **LTA** = life table analysis; **med** = medication; **MMC** = mitomycin-C; **nr** = nonrandomised; **p** = prospective; **postop** = postoperative; **r** = randomised; **ret** = retrospective.

**Table IV.** Comparison of studies that used 5-fluorouracil (5-FU) in combined surgeries

| Study (year) | No. of eyes | Study design | 5-FU schedule | Type of surgery | Outcome measures | Results | Follow-up period | Study limitations |
|---|---|---|---|---|---|---|---|---|
| O'Grady et al.[49] (1993) | 74 | p, r | Postop 5-FU (5mg) × 5 ± 1.3 inj | Primary glaucoma triple procedure | IOP ≤20mm Hg on ≤1 glaucoma med | No difference between 5-FU and con | 13mo | Short follow-up |
| Gandolfi and Vecchi[50] (1997) | 24 | p, r | Postop 5-FU (5mg) × 5 inj | Clear corneal phaco with trab | IOP ≤15mm Hg | 1) 5-FU: 83%<br>2) con: 8% | 1y | Small sample size |
| Ren et al.[51] (1998) | 74 | p, r | Postop 5-FU (5mg) × 5 ± 1.3 inj | Primary glaucoma triple procedure | IOP ≤20mm Hg on ≤1 glaucoma med | No difference between 5-FU and con | 45mo | |
| Budenz et al.[52] (1999) | 78 | ret | 1) 5-FU: 50mg/mL; 5 min<br>2) MMC: 0.02–0.05%; 5 min<br>3) con | Phaco-trab | Failure:<br>1) Reoperation for glaucoma<br>2) IOP >15mm Hg with or with out med | No difference between groups | 17.6mo | Retrospective |
| Donoso and Rodriguez[53] (2000) | 40 | ret | Intraop 5-FU: 50 mg/mL | 1) Trab followed by cataract surgery<br>2) Combined phaco-trab | a) IOP ≤20mm Hg<br>b) IOP <15mm Hg | 1a) 100%<br>1b) 100%<br>2a) 88%<br>2b) 71% | 1. 21mo<br>2. 28mo | Retrospective |
| Singh et al.[54] (2001) | 186 | ret | Intraop 5-FU: 5%; 3 min<br>Postop 5-FU: 5%; variable no. of inj | 1) Trab with postop 5-FU<br>2) Phaco-trab with postop 5-FU<br>3) Trab with intraop and postop 5-FU | IOP <16mm Hg and >30% reduction at 2y follow-up | 1) 76% success<br>2) 55% success<br>3) 71% success<br>4) 29% | 2y | Retrospective |

**con** = controls; **inj** = injection; **intraop** = intraoperative; **IOP** = intraocular pressure; **med** = medication; **p** = prospective; **phaco** = phacoemulsification; **postop** = postoperative; **r** = randomised; **ret** = retrospective; **trab** = trabeculectomy.

surgical failure. In the mitomycin/5-FU group, surgical success was noted in seven of eight eyes.[56]

Postoperative injection of 5-FU is probably not a viable option in the paediatric age group because it requires multiple exposures to general anaesthetic. However, if children are given general anaesthetic for postoperative evaluation, including measurement of IOP, 5-FU injections given at that time is a sensible option. Implantation of a biodegradable drug delivery device with 5-FU at the time of filtering surgery – which would release small doses of antimetabolite without causing local and systemic toxicity – is probably an ideal option. Biodegradable devices with 5-FU for use in human eyes is not available now.

#### Glaucoma Drainage Devices

Glaucoma drainage devices (GDDs) are used to reduce IOP in refractory glaucoma by providing controlled outflow of aqueous humour into a subconjunctival space created by the plate of the device. The filtration occurs through the fibrous capsule that surrounds the plate.[57] The natural wound healing response may reduce the fluid outflow by thickening the walls of the capsule; therefore, these drainage devices are rarely functional for more than 5 years.

5-FU was used as adjunct in filtering surgery using the non-valved Baerveldt implant.[58] In this retrospective series, which included 51 eyes that underwent non-valved Baerveldt implant for refractory glaucoma, 3 groups of 17 patients received either no antimetabolite, 5-FU (50 mg/mL for 3 minutes), or mitomycin (0.04% for 3 minutes). The use of antimetabolites did not appear to influence early postoperative pressure control or development of complications. It is possible that the presence of a foreign body, a constant stimulus for fibroblast proliferation, may later overcome the antiproliferative effects of antimetabolites. However, the reason for the lack of difference in IOP in the immediate postoperative period remains uncertain and could probably be related to the short exposure time (3 minutes).

Jacob et al.[59] used collagen plugs containing 1.125mg of 5-FU in the silicone tube of the Baerveldt implant to determine whether the wound healing response could be reduced by a controlled release of an antimetabolite. This experimental study on rabbit eyes has shown that these biodegradable plugs placed within the silicone tubes of the GDD can safely deliver 5-FU to filtering blebs over time. This prolongs the functional life of the bleb by decreasing the thickness of the anterior fibrous capsule, increasing sufficient aqueous outflow and, thereby, reducing IOP to physiological levels.

Although studies do not support the use of 5-FU as an intraoperative adjunct in GDD surgeries, animal studies using collagen plugs containing 5-FU have shown promising results. The early postoperative IOP remains low after surgery with GDD insertion, even without antimetabolite and, therefore, long-term follow-up is essential to evaluate the possible contribution of these adjunctive agents.

#### Revision of Failed Filtering Blebs

Needling of the filtering bleb is a promising alternative to repeat trabeculectomy in patients with encapsulated bleb (Tenon's cyst) and scarred blebs that lead to bleb failure and subsequent increase in IOP. Needling is done as an outpatient procedure under topical anaesthesia with only minimal discomfort to the patient. Repeat trabeculectomy is a potential risk factor for failure, as with any surgical manipulation of the bleb, and therefore, the use of antimetabolites during needling is a practical option to reduce the fibroblastic response. Several studies have evaluated bleb needling using adjunctive 5-FU in doses of 1–5mg.[60-62]

Ophir and Porges[63] have shown that needling with intrableb injection of 5-FU (1mg) and transconjunctival anterior chamber paracentesis through the bleb was well tolerated and efficacious in severe intractable neovascular glaucoma. Although these studies had no control arm, if the outcome is compared with the same eye prior to treatment or to the expected natural course in failed trabeculectomies, the findings support the use of 5-FU in this procedure.

### *2.1.2 Pterygium Surgery*

Chronic irritation and cosmetic appearance are probably the most common indications for pterygium excision. Decrease in visual acuity due to in-

duced astigmatism or extension into the pupillary zone are rarer indications. Recurrence is the most undesirable outcome of pterygium surgery, with rates as high as 90% with the bare sclera (no grafting) technique.[64] By adding conjunctival grafts over the exposed sclera, the recurrence rate is reported to be much lower (5–39%).[65,66]

Different modalities were designed to control postoperative fibroblast proliferation and migration, which are considered the main causes for recurrence. β-Irradiation was previously used, but this modality is limited by its high cost, the need for special equipment and higher user expertise.[67] Mitomycin was found to reduce the incidence of recurrent pterygia, however the possible complications – ranging from mild ocular discomfort to scleral perforation – limit its use.[68-70] Unlike mitomycin, which is toxic to both proliferating and quiescent cells, 5-FU is toxic only to proliferating cells, thereby reducing the potential adverse effects.[13,21]

5-FU has been used as an intraoperative topical adjunct during pterygium surgery and by postoperative injections. The use of topical 5-FU did not show convincing results: the recurrence rates were as high as 25% and were even higher than with β-irradiation.[71,72] On the other hand, postoperative subconjunctival injections (10 mg/mL) with a total dose of 1–3mg of 5-FU titrated according to the response showed more encouraging results in halting the appearance of recurrent pterygia after excision.[73] In a prospective study, Akarsu et al.[74] evaluated the efficacy of intraoperative 5-FU (25 mg/mL for 3 minutes) in primary pterygium and the effect of postoperative subconjunctival 5-FU injections (weekly for 2–4 weeks) on recurrent pterygium. 28 eyes with primary pterygium underwent excision with intraoperative 5-FU and 25% had recurrence at 12 months. However, the size of the recurrent pterygia was smaller in patients who were treated with additional postoperative injections.

In a recent prospective, randomised, controlled clinical trial, Prabhasawat et al.[75] compared the efficacy of subconjunctival 5-FU and triamcinolone in halting the progression of impending recurrent pterygium. 109 eyes with impending recurrent pterygia were randomised into three groups; one group served as control, the second group received intralesional 5-FU (5mg weekly for 2 weeks) and the third had one intralesional injection of triamcinolone 20mg. 5-FU and triamcinolone were both effective in preventing progression of recurrent pterygium compared with controls. 5-FU prevented recurrence in 87% of eyes, with no major adverse effects.

Studies show that a single intraoperative application of 5-FU offers no advantage in terms of preventing recurrence. Intralesional injection gives a higher concentration of the drug for a longer time, directly into the fibrovascular area. This causes a better inhibitory effect and decreases the recurrence. Although there is no clear guidance to the optimal dose, frequency or duration of treatment, postoperative injections of 5-FU (5mg) seem to be the only safely used and effective adjunct for the treatment of early recurrent pterygia.

#### *2.1.3 Lacrimal Surgery*

Standard external dacryocystorhinostomy (DCR) is a highly successful surgical technique in primary acquired nasolacrimal duct obstruction.[76] This surgery, which has been the procedure of choice since 1904, has a very low failure rate (1–20%).[77,78] The endonasal laser DCR technique failed to show a better outcome than external DCR;[79-82] however, the endoscopic technique is gradually gaining popularity and results in comparable outcomes to the external technique in some of the more recent studies.

The development of obstruction at the rhinostomy (ostium) site is the main cause of surgical failure.[83] Making a larger ostium may possibly reduce the risk of recurrence; however, the fibroblastic response and scarring are the main factors that need to be controlled.[84]

Only a small number of studies evaluated the effect of 5-FU on the outcome of DCR surgery. Although some studies show that 5-FU may delay or prevent ostium obstruction,[85] others did not show a better outcome in terms of recurrence.[77,86]

Many issues regarding the use of antimetabolites in DCR surgery remain unsolved. The lack of large randomised controlled studies with long follow-up

periods prevents definite conclusions about the success rate with this drug, the optimal dose and application time, and the subgroups of patients that need this therapy (should 5-FU be used in all cases or in repeat surgery alone, or in patients with risk factors for failure such as previous failure in the contralateral side?).

#### *2.1.4 Vitrectomy for Proliferative Vitreoretinopathy*

Proliferative vitreoretinopathy (PVR) is the migration and proliferation of cells on the retinal surface, as well as into the vitreous and the subretinal space. This leads to collagen production and subsequent scarring and contraction, which leads to retinal detachment and visual loss.[87] Successful management of PVR plays a very important role in the anatomical reattachment of the retina after surgery. Recurrence of PVR is the leading cause of failure of retinal reattachment surgery.[88]

To stabilise the anatomical attachment of the retina after surgery, a number of pharmacological adjuncts have been used experimentally to reduce fibrous tissue proliferation.[89,90] 5-FU has been shown to reduce the rate of PVR in animal models.[20,91,92] Toxicity studies have shown that single short-term exposure (5–30 minutes) of 5-FU (0.25 mg/mL) is effective in inhibiting proliferation of retinal pigment epithelial cells and contraction of collagen lattices without killing the cells.[91] 5-FU could thus be used during vitrectomy, giving a single short-term exposure, while reducing toxicity to surrounding photoreceptors. In a case series on 22 patients, Blumenkranz et al.[93] have shown that a combination of periocular and intraocular 5-FU improves the long-term prognosis of retinal reattachment surgery. Single case reports in human eyes have also shown favourable results.[94]

Asaria et al.[95] published a large prospective randomised trial that showed a significant reduction in postoperative PVR when 5-FU (200 µg/mL) and low molecular weight heparin (LMWH, 5 IU/mL) are added to the intraocular infusion set for 1 hour during retinal detachment surgery. LMWH and 5-FU are believed to have a synergistic effect. However, a recent similar study by Charteris et al.[96] did not find any benefit with this combination.

There are several studies in the literature which have shown that 5-FU is a potential adjunct in retinal reattachment surgery alone or in combination with corticosteroids and anti-inflammatory drugs.[91,97] However, most of the studies are experimental or based on a small number of patients. Larger clinical studies are required to confirm the potential benefits. Given that there are very few options available to reduce the risk of PVR in retinal detachment surgery, the use of 5-FU may be justified.

### 2.2 Ocular Malignancy

Ocular surface neoplasia can be either benign or malignant, and is subdivided into squamous and melanocytic lesions, based on the cell of origin. The malignant squamous neoplasia, or ocular surface squamous neoplasia (OSSN), is classified into intraepithelial neoplasia and invasive squamous cell carcinoma. Melanocytic neoplasms include the premalignant primary acquired melanosis with atypia (PAM) and malignant melanoma.[98,99]

Surgical excision with adequate tumour-free margins is the definitive treatment for malignancies, irrespective of the location. In diffuse ocular surface tumours, this requires removal of a large area of ocular tissue with resultant disturbances in ocular motility, astigmatism and possible corneal opacity. The high recurrence rates of 33–56% have made alternative therapies very popular.[100]

5-FU acts on rapidly proliferating epithelial cells with limited adverse effects on normal epithelium, and was therefore used as a topical treatment for preinvasive OSSN as early as 1986.[101] Few published reports confirm the efficacy of topical 5-FU drops in the treatment of OSSN, as shown in table V.[102-106] The usual dose is 1% over 2–4 weeks. In a series of eight patients with recurrent and incompletely excised conjunctival squamous cell carcinoma, Midena et al.[104] used similar doses of 5-FU drops, four times daily for 4 weeks. At a mean follow-up of 27 months, all patients showed clinical regression of their tumours. One patient, who had recurrence, needed an additional course of 5-FU after which he remained disease free. Acute tran-

**Table V.** Comparison of studies using 5-fluorouracil (5-FU) in ocular surface squamous neoplasia

| Study (year) | Diagnosis | No. of eyes | Type of study | 5-FU dose (%) | Duration | Follow-up period (mo) | Study outcome | Study limitations |
|---|---|---|---|---|---|---|---|---|
| Yeatts et al.[102] (1995) | Intraepithelial neoplasia | 6 | Case series | 1 | qid for 14–21d; repeated 3 times<br>3 patients with surgery; 3: 5-FU alone | 3–30 | 4/6 success<br>1/6 had deep invasion | |
| Midena et al.[103] (1997) | Squamous cell carcinoma | 1 | Case report | 1 | qid for 4wk | 7 | No rec | Single case |
| Yeatts et al.[105] (2000) | Intraepithelial neoplasia | 7 | Case series | | qid for 2–4d; repeated 2–6 times | 7–36 | 4/7: no rec<br>2/7: re-tt 5-FU<br>1/7: re-tt MMC | |
| Midena et al.[104] (2000) | Squamous cell carcinoma | 8 | Case series | 1 | qid for 4wk | 27 | 7/8: one course<br>1/8: two courses | |
| Yamamoto et al.[106] (2002) | Intraepithelial neoplasia refractive to MMC | 1 | Case report | | qid for 2wk | 30 | 1/1 | Single case |

**MMC** = mitomycin-C; **qid** = four times daily: **rec** = recurrence; **re-tt** = re-treatment.

sient keratoconjunctivitis responsive to artificial tears and antibacterials was the only adverse effect.

In an effort to reduce ocular toxicity, Yeatts et al.[105] have described a pulse dose administration regimen of 1% 5-FU drops, four times daily for 4 days, repeated every month for 4–6 cycles, which was better tolerated with minimum adverse effects. Yamamoto et al.[106] have successfully used topical 5-FU (1%) in the treatment of one patient with OSSN who did not respond to treatment with mitomycin.

There has been only one case report on the use of 5-FU in the treatment of PAM with atypia.[107] 5-FU was used as adjunctive therapy to surgical excision followed by amniotic membrane transplantation. Topical 5-FU was instilled four times a day for the first 4 days of the month for 3 months. There was no recurrence noted at 3-month follow-up.

In a recent survey on the treatment practice in OSSN, Stone et al.[108] found that most surgeons prefer the use of antimetabolites as adjuncts to surgical therapy. Antimetabolites were used as primary therapy only in situations where surgery was declined by the patient or deferred due to medical risk. Among the antimetabolites, 5-FU was the least preferred.

Though few, evidence suggests that 5-FU is effective in the treatment of preinvasive OSSN. In invasive OSSN, it could be used as an adjunct to surgical excision; however, larger scale studies with long follow-up periods are required to establish the efficacy of treatment. Given that 5-FU affects rapidly proliferating cells; its use in PAM is limited.

## 3. Ocular Complications Associated with Topical 5-FU

### 3.1 Ocular Surgeries

Because 5-FU is more toxic to actively replicating cells, its effect on the corneal epithelium is very pronounced.[21] This is dose dependent and is more common with total doses of more than 100mg.[109] The manifestations include punctate keratopathy, filamentary keratopathy, epithelial defects and whorl-like keratopathy (table VI). These changes are reversible and have no long-term effect on visual acuity. However, in some patients, severe secondary complications like bacterial ulceration, corneal melting and perforation can occur.[110] These complications are usually more common in patients with underlying ocular surface disorders, such as keratoconjunctivitis sicca, bullous keratopathy and exposure keratopathy, and patients treated with topical corticosteroids. Injection of 5-FU using a no-reflux technique was reported to significantly re-

**Table VI.** Complications associated with the use of fluorouracil in ocular surgery

| Glaucoma surgery | Other surgeries |
|---|---|
| Punctate keratopathy | Punctate epithelial erosions |
| Filamentary keratopathy | Keratoconjunctivitis |
| Whorl-like keratopathy | |
| Transconjunctival oozing | |
| Conjunctival leaks | |
| Shallow anterior chamber | |
| Hypotony | |
| Hypotonic maculopathy | |
| Endophthalmitis | |
| Hyphaema | |
| Choroidal effusion | |

duce corneal complications.[111] In this technique, subconjunctival 5-FU is given using a 30-G needle inserted right up to the hub. After the injection, the entry point is pressed with a cotton-tipped applicator to prevent reflux of the drug into the tear film and the ocular surface. Preoperative risk assessment and adjusting the dose of 5-FU postoperatively according to the clinical response and complications can also reduce toxicity without compromising success rate. These complications are not common with intraoperative topical use.[21]

Endophthalmitis is one of the most serious adverse effects that can occur after filtration surgery, and can result in blindness.[112] The use of antimetabolites can lead to thin-walled and avascular blebs which, although better in controlling the IOP, can be associated with increased aqueous leaks and subsequent development of endophthalmitis.[113] This complication was reported to occur as late as 56 months after surgery.[114] The most common causative agents are *Streptococcus* and *Staphylococcus* species.[115] Furthermore, the thin-walled blebs lead to low outflow resistance and subsequent overfiltration. Overfiltration can lead to hypotony and result in visual loss from corneal, retinal and macular complications.[116] Although there seems to be a difference in the rate of complications, depending on the type of conjunctival flap (limbus-based versus fornix-based) used in mitomycin-augmented trabeculectomy,[117] there are no such reports to date in trabeculectomies with adjunctive 5-FU. Although these complications are rare, it is important to monitor patients closely who have undergone trabeculectomy with antimetabolites for any of the possible complications. These patients should be instructed to seek immediate medical attention whenever signs or symptoms of bleb-related infection or overfiltration arise.

### 3.2 Ocular Malignancies

Unlike with its use as adjuncts in glaucoma surgery, the reported complications associated with the use of 5-FU in ocular malignancies are very mild and transient.[102-106]

## 4. 5-FU versus Mitomycin

The use of antimetabolites in ophthalmic practice has improved the management of complicated and difficult surgeries and potentially lethal ocular malignancies.[118] However, ophthalmologists have not reached a general consensus as to which of these two commonly used drugs, mitomycin and 5-FU, is preferred. Several clinical trials have aimed to compare the toxicity and clinical effect of these agents. Smith et al.[13] compared the toxicity of mitomycin and 5-FU *in vitro* against cultured fibroblasts and capillary endothelial cells. 5-FU was found to be toxic to fibroblasts but spared endothelial cells, whereas mitomycin was equally toxic to both cell types.

Table VII summarises various studies which compared the use of 5-FU and mitomycin in glaucoma surgeries.[35,41,42,52,56,119-123] Most of these studies were designed in a prospective and randomised fashion and included eyes at high risk for failure. In most studies no difference was found between mitomycin and 5-FU in terms of outcome and complications.[41,42,121,122] In a prospective randomised trial on 80 pseudophakic eyes that subsequently underwent trabeculectomy, Lamping and Belkin[119] compared the use of intraoperative mitomycin (0.04% for 2.5 minutes) and postoperative 5-FU (5mg in 0.5mL) which was injected 180° from the surgical site once daily for 10 days. The mitomycin group had better IOP control and required a smaller number of postoperative antiglaucoma

**Table VII.** Studies comparing 5-fluorouracil (5-FU) with mitomycin (MMC) in ocular surgeries

| Study (year) | Type of surgery | Study design | No. of eyes | MMC % | 5-FU | Follow-up (months) | Outcome | Complications |
|---|---|---|---|---|---|---|---|---|
| Lamping and Belkin[119] (1995) | Trab in pseudophakic patients | p, r | 80 | 0.04, 2.5 min | 5mg/0.5mL, s/c od × 10d | 32 | Lower IOP and less no. of postop med with MMC | More with MMC |
| Katz et al.[123] (1995) | Trab, high risk | p, r | 39 | 0.05, 5 min | 5mg s/c × 10 inj | 12 | Lower IOP and less no. of postop med with MMC | No significant difference. More Tenon's cyst with MMC |
| Singh et al.[120] (1997) | Trab, Black African | p, r | 81 | 0.05, 3.5 min | 50 mg/mL, 5 min intraop | 10 | Lower IOP with MMC | Similar complication rates |
| Smith et al.[122] (1997) | Trab | ret | 73 | 0.02, 3–5 min | 50 mg/mL, 5 min intraop | 20.9 | No difference in IOP | Similar complication rates |
| Budenz et al.[52] (1999) | Phaco-trab | ret | 78 | 0.02–0.05, 5 min | 50 mg/mL, 5 min | 17.6 | No difference in IOP | Transient hypotony with MMC |
| Vijaya et al.[121] (2000) | Trab, Indian eyes | p, nr | 32 | 0.02–0.04, 1 min | 50 mg/mL, 1 min intraop | MMC: 16<br>5-FU<br>13 | No difference in IOP | Ischaemic blebs with MMC |
| Singh et al.[42] (2000) | Trab, low risk | p, r | 108 | 0.04, 2 min | 50 mg/mL, 5 min intraop | MMC 28; 5-FU 26 | No difference in IOP | Low complication rate |
| Snir et al.[56] (2000) | Paediatric trab | p, r | 12 | 0.02–0.04, 3 min, then 5mg 5-FU s/c intraop | 5–7.5mg, s/c intraop | 5-FU 23; MMC 27 | Increased success rate with MMC/5-FU group | No significant complications |
| Membrey et al.[124] (2000) | Trab in NTG | ret | 86 | 0.01, 3–5 min | 25 mg/mL, 5 min | 5-FU 45; MMC 18 | No significant difference in IOP and postop meds | Increased incidence of complications with MMC |
| Wudunn et al.[41] (2002) | Trab | p, r, db | 115 | 0.02, 2 min | 50 mg/mL, 5 min | 12 | At each target IOP, the success rates similar | Low complication rate |
| Akarsu et al.[35] (2003) | Trab, high risk | ret | 36 | 0.04, 3 min | 5mg, s/c od × 5 inj | 5-FU 40; MMC 35 | Lower IOP with MMC at 24mo | Similar complication rates |

**db** = double-blind; **inj** = injection; **IOP** = intraocular pressure; **intraop** = intraoperative; **IOP** = intraocular pressure; **meds** = medications; **NTG** = normal tension glaucoma; **nr** = nonrandomised; **od** = once daily; **p** = prospective; **phaco** = phacoemulsification; **postop** = postoperative; **r** = randomised; **ret** = retrospective; **s/c** = subconjunctival; **trab** = trabeculectomy.

medications at 32-month follow-up at the expense of increased complications.

The treatment of normal tension glaucoma (NTG) presents a therapeutic challenge, with evidence that reduction of IOP slows disease progression. Antimetabolites are used as adjuncts when trabeculectomy is performed for NTG to achieve very low target IOP. As the target IOP is very low, NTG patients are at a much higher risk of hypotony and associated complications. Membrey et al.[124] have shown that 5-FU is better than mitomycin in maintaining lower target IOP without sight-threatening complications in these patients.

On the basis of the data available in the literature, it is difficult to conclude which of the antimetabolites is superior in ocular surgery or in treating ocular neoplasia. It seems that both 5-FU and mitomycin are useful adjuncts, and when used judiciously can improve the outcome of treating various ocular pathologies.

## 5. Future and Experimental Ocular Treatment Options

### 5.1 Strabismus Surgery

Increased postoperative fibrosis is an important factor that can result in restriction of ocular movements and failure of strabismus surgery. A 5-minute application of a sponge soaked in 5-FU 50 mg/mL was found to be effective in reducing postoperative scarring following strabismus surgery in rabbits.[125,126] In combination with the use of barriers like polytetrafluoroethylene or Interceed™ [1] between the sclera and muscle, 5-FU has also proven to be beneficial in delayed adjustment of sutures after strabismus surgery.[127,128]

### 5.2 Posterior Capsular Opacification

The most common postoperative complication of extracapsular cataract surgery is opacification of the posterior capsule (PCO). This is usually treated with capsulotomy using a neodymium-doped yttrium-aluminium-garnet (Nd: YAG) laser. The laser treatment is usually simple and straightforward; however, rare retinal complications can occur. Various drugs, as well as 5-FU, have shown favourable results in preventing or reducing the formation of PCO after cataract surgery in rabbit eyes.[129,130]

## 6. Conclusion

5-FU has been shown to be very effective as adjunct therapy in primary trabeculectomy and needling revision of failed trabeculectomy. However, its use in combined surgery, congenital glaucoma surgery and GDD has not been successful because of various confounding factors. 5-FU has also shown promising results in the treatment of ocular surface squamous malignancies. The localised and targeted effect on the exposed tissue, its short half-life, low cost, ease of administration and infrequency of vision-threatening adverse effects make 5-FU a very popular drug in ophthalmic practice.

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**1** The use of trade names is for product identification purposes only and does not imply endorsement.

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