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Dropfree Approaches for Cataract Surgery

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Summary:

Intraoperative injections offer the patient and surgeon assured drug delivery and hold promise to avoid the pitfalls of patient adherence, incorrect topical instillation and topical drop-associated corneal issues.

Keywords

intracameral antibiotic injection; dropfree; dropless; cataract surgery; subconjunctival triamcinolone acetate; cefuroxime; moxifloxacin; vancomycin

Introduction

The prior worldwide standard practice for prophylaxis against postoperative infections and inflammation following cataract surgery, and for iris dilation, has involved the application of perioperative eyedrops. Topical drop instillation may have inherent drawbacks including patient adherence, cost and negative impact on the environment from single use, plastic containers.

Early work on injectable drugs dates back to the late 1960's(1, 2) when the first steroids were injected for inflammation control following cataract surgery. In the decades that followed, the first antibiotics were injected or added to irrigating solutions to prevent endophthalmitis.(3, 4)

Barriers to the adoption of injection regimens have been a perceived lack of evidence of safety and effectiveness, absence of government approved, manufactured products, risk of contamination or dilution error from compounded products, and cost.(5) This review will consider replacement of eyedrops in favor of injectable drugs in the following three areas: pharmacologic iris dilation; endophthalmitis prophylaxis; and suppression of inflammation,

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Conflicts of Interest

The authors report no conflicts of interest

prevention of pain and postoperative cystoid macular edema (CME) following cataract surgery.

The Trouble with Drops

Incorrect technique of patient-administered eyedrops may be as high as 93%.(6) Table 1 lists potential risks of eyedrops. Corneal and conjunctival abrasions were observed in 68% of elderly study patients resulting from instillation of drops.(7) The potential for wound gape and efflux of fluid into the eye following pressure on the eye has been reported.(8) The result of these effects may be to increase the risk of endophthalmitis from the very treatment meant to diminish risk.

Iris Dilation

Dilation with topical cyclopentolate in the preoperative area of the surgical suite requires 90 minutes for maximal binding to receptors.(9) This may impact throughput efficiency. With the approval by the US FDA in 2007 of tamulosin, surgeons soon became aware of a trend of poor pharmacologic iris dilation and intraoperative lack of tone. Topical dilation drops were relatively ineffective for this “intraoperative floppy iris syndrome” or IFIS.(10)

Antibiotics

There are no studies to date showing level I evidence of the effectiveness of topical antibiotics in reducing endophthalmitis.(11) Intraocular penetration of drops is variable and poor, achieving only relatively low concentrations in the anterior chamber.(12) While a large retrospective study showed that topical fluoroquinolones and polymyxin/trimethoprim antibiotic drops reduce the risk of endophthalmitis(13), 5% of patients never filled their eyedrop prescription and were twice as likely to develop endophthalmitis.

Anti-inflammatories

Topical corticosteroids have been the mainstay of cataract surgeons for the prevention of postoperative inflammation and pain for decades. Prednisolone acetate is not as potent per weight of a corticosteroid as dexamethasone, but it has a longer duration of action due to its suspension preparation.(14) The literature is replete with comparison studies of corticosteroid and nonsteroidal anti-inflammatory agents (NSAID). There is general agreement that a combination of NSAID and steroid suppress inflammation in the early postoperative period better than steroid alone.(15, 16) Nevertheless, there have been no studies showing any benefit to visual acuity with the addition of NSAID at 3 months or more following surgery.(17) The number of cataract surgery patient eyes needed to treat with NSAID to prevent 1 case of cystoid macular edema has been calculated at between 238 and 320.(18, 19)

The costs of topical drops, which may be hundreds of dollars(20), should be weighed against the benefit of the treatment, particularly when injectable agents provide superiority of treatment, or at the very least, are in equipoise.

Dropfree Regimen

A dropfree prophylaxis strategy for cataract surgery includes techniques for the injection of drug for iris dilation, endophthalmitis prophylaxis and suppression of ocular inflammation.

Dilation

Intraoperative iris dilation was first studied by Behndig and associates in 2003.(21) They showed that intracameral injection with a mixture of lidocaine and epinephrine or phenylephrine provided faster, though less maximal, dilation compared to eye drops. This method is now accepted in Sweden as the method of choice.

Shugar in 2006 reported on the benefit of lidocaine-epinephrine in cases of IFIS.(22) Intraoperative phenylephrine injection was also shown to effectively dilate and stabilize iris tone in IFIS.(23, 24) Although epinephrine is slightly more effective for intraoperative pupil dilation, it is unstable at neutral pH, which prevents this agent from being a ready-to-use commercial product. Phenylephrine, however, can be formulated and shipped by compounders due to its longer shelf-life. Depending on the agent, intraoperative dilation may have a longer onset than drops.(25, 26)

Preservatives such as benzalkonium chloride, chlorobutanol and methylparabens should be avoided.(27, 28) Epinephrine containing a bisulfite concentration of 1:16,000 was found to be safe to the corneal endothelium.(29)

Mydrane® (Théa Pharmaceuticals, Keele, UK), a combination of tropicamide, phenylephrine and lidocaine, is available commercially in Europe. This agent achieved 95% maximal pupil dilation within a mean of 28.6 seconds and remained more stable than the comparison topical group.(30, 31)

Omidria® (Omeros, Seattle, USA), a combination of phenylephrine and ketorolac, is FDA-approved for intraoperative dilation and control of postoperative pain. This combination agent appears to be superior to a single bolus of intracameral epinephrine for reducing intraoperative and postoperative complications, surgical time and the need for pupillary expansion devices.(32, 33)

Endophthalmitis prophylaxis

The choice of antibiotic agent for intracameral injection must consider both effectiveness of infection prevention and safety to the corneal endothelium and retina.

Effectiveness

The primary advantage of intracameral antibiotic injection is the delivery of a very high concentration of drug directly into the operative, anatomical space at most risk of initial infection. The first large study showing benefit of an injected antibiotic at the time of surgery, was by Montan and associates in Sweden, using cefuroxime.(34) Within 5 years, Peter Barry and colleagues in the European Society of Cataract and Refractive Surgeons completed a randomized controlled trial showing the benefit of intracameral cefuroxime

injection in reducing the incidence of endophthalmitis.(35) The study remains the only level I evidence to date showing the prophylactic benefit of any topical or injected antibiotic. There was some criticism of the study in the years following its publication, citing a higher than expected background infection rate, potential bias from stopping the study prior to full enrollment(36) (because the safety committee found a clear benefit to the injection) and a potentially better prophylaxis antibiotic in the form of moxifloxacin.(37)

Subsequent observational studies supported the effectiveness of both cefuroxime and moxifloxacin injection in reducing postop endophthalmitis.(13, 38, 39**) Rates of endophthalmitis in Sweden, India and the US, in centers where antibiotic injection are widely adopted, now typically number 1 infection in 5,000 cases or less(39**, 40), a remarkable improvement from the peak rates of 0.25% (1 in 400) in the early aughts, when clear cornea incisions were first adopted.(41) These very low rates of infection following conversion to intracameral injection were achieved in centers with an already low baseline infection rate, which speaks to the potential broad benefit of this modality irrespective of preadoption endophthalmitis rates.

Choice of drug

For surgeons and surgery centers in Europe, where an approved cefuroxime product is available, and in India, where moxifloxacin is commercially available, the conversion to intracameral antibiotic injection is straightforward. In the US, where no FDA-approved, commercial product is available, antibiotic must be compounded. The most reliable sources for these agents are large compounding pharmacies, termed by the government as *outsourcing facilities*, that follow section 503B of the Federal Food, Drug and Cosmetic Act of 2013. These pharmacies are inspected by the FDA and must provide a strict sterile environment and perform validating testing following good manufacturing practices.(42)

The choice of antibiotic should follow an analysis of the types of endophthalmitis-causing organisms prevalent in the region where the surgery center is located and where the patient lives. European cataract centers have had substantial and successful experience with cefuroxime. The overall endophthalmitis rate has significantly dropped, albeit with a slight proportional uptick in resistant *Enterococcus* associated cases.(43*) In India, where Gram negative organisms cause a proportionally higher number of postoperative infections, cefuroxime does not appear to be as effective as moxifloxacin.(39**, 44)

In the US, moxifloxacin is the most popular antibiotic injection choice.(5) This may relate to the theoretic advantage of Gram negative coverage, though the preponderance of endophthalmitis organisms in the US are Gram positive.(45, 46) Moxifloxacin is also notable for the simplicity of injecting an aliquot of full-strength brand name topical solution. (47) A caveat to this approach, however, is the current labelling of the product as “not for intraocular use”. Herrinton et al could not detect a statistical difference between infection rates in eyes injected with 1 mg cefuroxime and those injected with 0.1%/0.1 mL moxifloxacin.(13)

Vancomycin, which has exquisite action against Gram positive organisms, has generally fallen out of favor among surgeons due to a retinal vasculitis which has been associated with

injections of this agent.(48) The US FDA and the American Society of Cataract and Refractive Surgery have issued advisories against routine intracameral injection of vancomycin.

Safety

Between the two commonly injected intracameral agents, cefuroxime is relatively safe for the cornea endothelium at a dosage of 1 mg.(49) A 9 mg dose was reported to cause temporary macular edema(50) while injections exceeding 50 mg have resulted in permanent corneal and retinal damage.(51) Injections of the correct dosage of cefuroxime have also been reported to result in macular changes on ocular coherence tomography(52, 53) however the agents used do not appear to be approved, manufactured products and may have been contaminated or incorrectly compounded.

There is no established dose or injection method for moxifloxacin at this time. Injection volumes between 0.03 mL (166 µg)(54) and 0.1 mL (500 µg)(47) of “full strength” moxifloxacin (0.5%) have been reported. This is compared to the standard dose of 1,000 µg of cefuroxime. “Undiluted” or “full strength” moxifloxacin refer to a concentration of 0.5%, corresponding to the topical brand Vigamox® (Alcon, Irvine, CA, USA) which was used as a source of moxifloxacin in earlier studies. Moxifloxacin may have a narrower therapeutic index than cefuroxime due to reports of toxicity to the cornea endothelium in the lab in concentrations as low as 500 µg/mL.(49, 55) To address this, larger volume injections of 0.4 mL have been recently proposed of diluted solution.(56, 57) Larger injection volumes of more dilute solutions may have the advantage of producing a more consistent final concentration of drug in the AC irrespective of a patient’s pseudophakic volume.(58)

Elimination of topical antibiotic

Following the report of initial success of injected cefuroxime in Sweden, follow-up studies were notable in that a low rate of endophthalmitis was achieved with antibiotic injection alone, without prescribing perioperative antibiotic drops.(59, 60) In addition, two large studies showed no statistical difference in infection rates in eyes treated with intracameral antibiotics plus topical drops versus eyes receiving injection alone.(13, 38)

Inflammation suppression

Table 2 lists the studies comparing triamcinolone acetonide injection to topical agents and the effects on anterior chamber inflammation and macular thickness. (18, 61–65) While the location and dosages of injection varied, the triamcinolone groups were either equivalent or better than the comparison topical group for the primary outcome variable. One study demonstrated a higher IOP in the injection group than in the topical group.(63**) This is not surprising since injections of higher doses of steroid, closer to the limbus, are more likely to produce a rise in IOP.(66*, 67) A balance of dose and injection site, that is anterior enough to suppress cell and flare and yet not so anterior to cause an IOP increase, is needed.

Dropfree strategies

The simplest approach combines intracameral antibiotic injection with subconjunctival injection of triamcinolone acetonide, both of which have supporting evidence in the literature. Newer technologies, recently approved and on the horizon, are also described below.

Intracameral antibiotic + subconjunctival steroid

Combining intracameral antibiotic injection with subconjunctival injection of 4 mg triamcinolone had similar infection and inflammation rates in one prospective study compared to drops.(64*) A second prospective study showed less macular thickening on OCT with triamcinolone 20 mg injection and similar visual acuity compared to drops.(65*)

Intravitreal injection

Another option for injection of antibiotic and anti-inflammatory drug is via a transzonular or pars plana approach.(68*) Concerns with this approach include the lack of comparative studies showing safety and effectiveness and an unknown long term risk of damage to the zonular matrix or the retina. There is also a lack of data describing the pharmacokinetics of either antibiotic or corticosteroid in the vitreous space for the *prevention* of endophthalmitis. A recent report of 4 endophthalmitis cases with this approach may support additional concern for this modality.(69*)

Developing Technologies

A suspension of dexamethasone (Dexycu®, Eyepoint Pharmaceuticals, Watertown, USA) for intracameral injection posterior to the iris was cleared for FDA approval in 2018. The new agent was shown to be better than placebo for clearance of anterior chamber cell and flare.(70*) The injectable suspension was comparable to prednisolone drops in anterior chamber clearing and with a slightly higher proportion of eyes with corneal edema and increased IOP.(71*)

A dexamethasone impregnated canalicular plug (Dextenza®, Ocular Therapeutix, Bedford, USA) was also approved in 2018. Phase 3 data showed superiority over placebo for pain and postop inflammation.(72*)

Technologies currently in development include IOL presoaking in antibiotic and NSAID. (73, 74) Adding an intracameral antibiotic injection at the conclusion of surgery to placement of a presoaked lens may provide a high initial concentration of drug from the injection along with a sustained level of drug in the days following surgery.(75*)

Conclusions

Intraoperative injections offer the patient and surgeon assured drug delivery and hold promise to avoid the pitfalls of patient adherence, incorrect topical instillation and topical drop-associated corneal issues. The authors currently inject a lidocaine-phenylephrine combination at the beginning of surgery for iris dilation. One of the authors (NS) prescribes patients cyclopentolate drops to instill at least 1 hour before arriving to the surgery center.

In the penultimate step, moxifloxacin 0.1% or 0.15% is injected for stromal hydrated and then to flush and replace the aqueous contents. Finally, 0.4 mL of triamcinolone acetate 10 mg/mL (4 mg) is injected in the subconjunctival space at least 5-6 mm posterior to the limbus. Tunneling the needle for 1-2 mm and injecting slowly avoids reflux of drug, while avoiding conjunctival vessels avoids subconjunctival hemorrhage.

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Purpose of Review:

Routine prophylaxis for adverse events following cataract surgery are evolving. Prior reliance on topical eyedrop instillation by patients is giving way to surgeon directed injections at the time of cataract surgery. The benefit of this new approach is assured delivery of drugs in standardized doses which should optimize the healing process and prevent untoward events with higher confidence.

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Recent Findings:

Adoption rates of intracameral antibiotic injection amongst European and American cataract surgeons is increasing. Techniques to inject periocular corticosteroid for routine inflammation prophylaxis are also in development. In combination with intraoperative pharmacologic dilation, a dropfree modality can be achieved.

Key Points

- Topical eyedrops have inherent risks including nonadherence, errors in instillation technique and even potential injury to the eye
- Intracameral antibiotic injection is most a likely sufficient chemoprophylaxis strategy to prevent endophthalmitis, without the need for topical antibiotic eyedrops
- Subconjunctival corticosteroid injection is at least equivalent to topical corticosteroid drops and may be sufficient for long-term visual outcome irrespective of topical nonsteroidal anti-inflammatory agents.

Table 1

Potential Eye Drop Risks

Drug exposure failure	Prescribing error
	Prescription not filled by patient
	Failure to instill the drops
	Stopping prematurely
Contamination	Eyelid/lash touch to dropper tip
	Poor hand hygiene
Microtrauma to eye	Corneal abrasion
	Conjunctival abrasion

Table 2

Studies of triamcinolone acetonide injection at the conclusion of cataract surgery

Author	Dose (mg)	Location	Topical Comparison	Inflammation in Injection Group	IOP in Injection Group
Paganelli (2004)[61]	40	PST	PA	Same	Lower
Negi (2006)[62]	20-30	PST	BM	Same	Same
Shorstein (2015)[18]	2	Subconjunctival	PA	Same	Same
PREMED (2018)[63]	40	Subconjunctival	DX + BF	Lower CST	Higher
Rattan (2018)[64]	4	Subconjunctival	DX	Same	Lower
Lindholm (2019)[65]	20	Subconjunctival	DX	Lower CST	Same

PST – posterior sub-Tenon's; PA – prednisolone acetate; BM – betamethasone; DX – dexamethasone; BF – bromfenac; CST – central subfield macular thickness on optical coherence tomography