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Aqueous Chlorhexidine for Intravitreal Injection Antisepsis

A Case Series and Review of the Literature

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Purpose: To determine the incidence of endophthalmitis in a large clinical series using aqueous chlorhexidine for antisepsis before intravitreal injection and to review the ophthalmic literature regarding chlorhexidine efficacy and safety.

Design: Multicenter retrospective case series.

Participants: All patients receiving intravitreal injections from 7 retinal specialists.

Methods: An audit of intravitreal injections performed by retinal specialists who exclusively used aqueous chlorhexidine 0.05% or 0.1% for prophylaxis of infective endophthalmitis was undertaken. The incidence of endophthalmitis was determined from August 1, 2011, to February 28, 2015. A literature review was performed to critically appraise the ocular safety and efficacy of aqueous chlorhexidine.

Main Outcome Measures: Incidence of endophthalmitis after intravitreal injections.

Results: A total of 40 535 intravitreal injections were performed by 7 retinal specialists across 3 centers. Chlorhexidine was well tolerated, and only 1 patient with a suspected allergic reaction was noted. Three cases of endophthalmitis were identified with 1 culture-positive case. The 0.0074% (1 in 13 512) per-injection rate of endophthalmitis in this series compares favorably with previous series in which povidone-iodine has been used.

Conclusions: Aqueous chlorhexidine was associated with a low rate of postinjection endophthalmitis and was well tolerated by patients. *Ophthalmology 2016;■:1–7 © 2016 by the American Academy of Ophthalmology*

The most commonly used antiseptic for ophthalmic procedures is povidone-iodine (PI), and in a 2010 survey of retinal specialists, 758 of 761 respondents (99.6%) reported using PI before intravitreal injection.[1] Povidone-iodine has been long established as the gold standard for antiseptic prophylaxis for intraocular procedures, with Speaker and Menikoff[2] reporting a postoperative endophthalmitis rate of 0.06% using PI compared with 0.24% using silver protein solution, albeit in a nonrandomized study. Numerous studies have recommended the use of PI before intravitreal injection.[3–5] Chlorhexidine is an alternative antiseptic that was first used in ophthalmology as a disinfectant for soft contact lenses,[6,7] and it has been used for the treatment of acanthamoeba keratitis for more than 20 years.[8] In the United States, concerns regarding its ocular toxicity have limited the use of chlorhexidine.[5,9] Despite being well tolerated, the manufacturers explicitly warn against the use of aqueous chlorhexidine on the ocular surface (Figs 1 and 2).

Some patients experience iodine sensitivity or allergy, often after prolonged application of full-strength PI on the skin.[9,10] Although true immunoglobulin-E–mediated allergy is rare,[11] in 1 report 6.6% of patients developed mild to moderate eye irritation after the use of PI as antisepsis for intravitreal injections.[12] Povidone-iodine causes hyperemia and punctate epitheliopathy in a significant number of patients.[9,13] Before the study period, we observed that patients who reported iodine allergy or intolerance to PI seemed to experience less postinjection discomfort when chlorhexidine was used for antisepsis.

In a meta-analysis that included both retrospective and prospective studies, 197 cases of endophthalmitis of 350 535 (0.06%; 1/1779) intravitreal injections were identified.[14] In a more recent review including only large retrospective studies, 144 cases of endophthalmitis were identified of 510 396 (0.03%; 1/3544) intravitreal injections.[15] Povidone-iodine was used for antisepsis in all the included studies in both of these large reviews.

In other areas of medicine, chlorhexidine has gained favor over PI, although in many studies alcohol-based chlorhexidine has been used, rather than the aqueous form that we describe in the present series. Chlorhexidine has been shown to be more effective than PI in reducing postoperative surgical

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site infections.[16] Superiority also has been demonstrated in vaginal hysterectomy,[17] which is somewhat analogous to intravitreal injection, in that the procedure is performed on a mucosal surface where fluids can potentially affect the viability of biocides. In 2 nonophthalmic studies, synergy has been demonstrated when PI and chlorhexidine have been used sequentially on the skin.[18,19]

The aims of the present study were to determine the rate of endophthalmitis in a large series in which aqueous chlorhexidine was used for preinjection antisepsis and to review the ophthalmic literature regarding chlorhexidine efficacy and safety.

Methods

Study Design

Seven retinal specialists from 3 Australian centers (centers 1, 2, and 3) were identified from members of the Australia New Zealand Society of Retinal Specialists who had *exclusively* used aqueous chlorhexidine antiseptic prophylaxis for intravitreal injection for a period of 1 year or more. An audit of billing and practice data of patients receiving intravitreal injections was performed. This retrospective study was approved by the Royal Australian and New Zealand College of Ophthalmologists Human Research Ethics Committee.

After a presentation detailing the safety, efficacy, and superior tolerability of aqueous chlorhexidine compared with PI for intravitreal injection (Dr. Alan Luckie, Oceania Retinal Association Meeting, August 2011, Queenstown, New Zealand), the ophthalmologists in the present study increasingly began using chlorhexidine rather than PI before intravitreal injection. The audit period commenced on the date each surgeon began exclusive use of chlorhexidine (between August 1, 2011, and January 1, 2013) through to February 28, 2015. Chlorhexidine gluconate 0.1% (Pfizer Australia, West Ryde NSW) was used in centers 1 and 3 (Fig 1), and chlorhexidine acetate 0.05% (Baxter Healthcare Pty Ltd, Old Toongabbie, NSW, Australia) was used in center 2 (Fig 2).

All cases of endophthalmitis were confirmed with a chart review. In each practice, protocols are in place to ensure that patients who fail to return for their scheduled visits are not lost to follow-up. Thus it is unlikely, but not impossible, that a patient could have developed endophthalmitis and been treated elsewhere without the knowledge of the practice and the treating ophthalmologist.

Ophthalmologists were also asked to report any patients who were found to be intolerant to chlorhexidine for any reason or requested to be switched back to PI. All intravitreal injections in the study period were considered for inclusion. Intravitreal injections of antibiotic or injections associated with another procedure (e.g., vitrectomy, cataract surgery) were excluded. "Endophthalmitis" was defined as any inflamed eye that was clinically suspected as having infective endophthalmitis and underwent an intravitreal antibiotic injection.

Intravitreal Injection Technique

All surgeons used their own technique for their intravitreal injections (summarized in Table 1). All surgeons flushed chlorhexidine across the conjunctiva, eyelids, and lashes. All surgeons in this study performed bilateral injections on the same day when required by the patient. Surgeon E used lidocaine gel for 2 months of the study period during which 1 case of endophthalmitis occurred. Surgeons E and G reapplied chlorhexidine after speculum insertion just before injection. Surgeons A and D did not use a speculum.

Literature Review Technique

A Medline search from 1946 to present was performed combining the term "chlorhexidine" AND "eye OR ocular OR ophthalmic OR ophthalmology." Further specific searches were done combining "chlorhexidine" with "toxicity," "safety," "allergy," "resistance," and "efficacy."

Results

A total of 40 535 consecutive intravitreal injections were performed. Three cases of endophthalmitis were identified (0.0074%, 1/13 512), of which only 1 was culture positive. The surgeon-specific data are summarized in Table 2.

One case of suspected allergy to chlorhexidine was documented. The patient developed itching with associated conjunctival hyperemia and eyelid swelling after 2 consecutive injections, and had a more severe reaction the second time. This occurred in center 1 where 9266 injections were performed for 931 patients. Apart from this case, no other patient requested to be switched back to PI. Although patients' pain scores were not formally assessed, the surgeons observed that patients who were switched over from PI to chlorhexidine frequently described less postinjection discomfort with chlorhexidine.

All 3 patients who developed endophthalmitis were undergoing treatment for neovascular age-related macular degeneration. They presented 3 to 4 days postinjection with visual acuity down to hand movements. Chlorhexidine 0.05% was used in 2 cases, and 0.1% was used in 1 case. A lid speculum was used in all 3 cases. A vitreous tap was performed in all cases followed by injection of vancomycin 1 mg in 0.1 ml and ceftazidime 2.25 mg in 0.1 ml. One patient subsequently underwent pars plana vitrectomy. Further details are summarized in Table 3.

Discussion

In the present series, 3 cases of endophthalmitis were identified of 40 535 intravitreal injections (0.0074%, 1/13 512) in which aqueous chlorhexidine 0.05% or 0.1% was used for preinjection antisepsis rather than PI. In a recent review of large retrospective series (>10 000 injections) in which PI was used for antisepsis, an endophthalmitis rate lower than 0.0074% was found in only 3 of 18 studies.[15]

Mechanism of Action

Chlorhexidine is a topical antiseptic that was first described in 1954.[20] It is a cationic biguanide that binds to and disrupts the bacterial cell wall followed by damage to the cytoplasm's semipermeable membrane leading to cytoplasmic damage and cell death.[21,22] Compared with PI, chlorhexidine exhibits more sustained antimicrobial activity and is not readily neutralized by organic matter.[21,22] Because PI is brown, it is easy to identify the area where it is been applied, unlike chlorhexidine, which is colorless when applied.

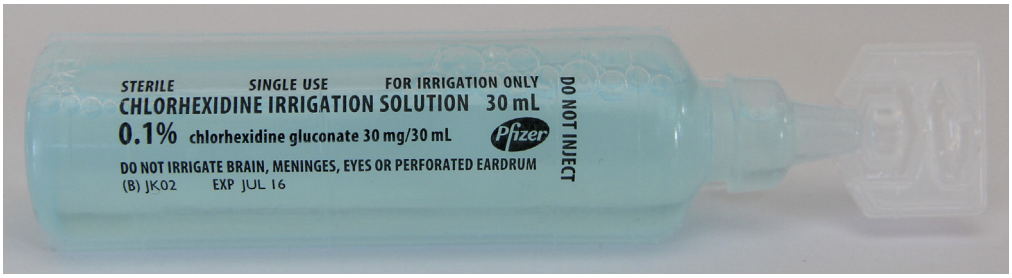

Figure 1. A 30-ml ampoule of chlorhexidine gluconate 0.1% (Pfizer Australia, West Ryde, NSW, Australia).

Spectrum

Chlorhexidine has broad-spectrum activity against gram-positive and gram-negative bacteria, yeasts, and some lipid-enveloped viruses, but it is not sporicidal.[21,22] Although bacterial susceptibilities to chlorhexidine have been studied in other clinical settings and in vitro, there have been few ophthalmic studies.[23] Chlorhexidine has been shown to be effective against *Staphylococcus epidermidis* on the rabbit eye.[24] Montan et al[25] found coagulase-negative Staphylococci in 70% of control eyes compared with 20% of eyes treated with chlorhexidine. However Propionibacteria were found in 15% of both treated and control eyes. Coagulase-negative staphylococci and Viridans group Streptococci are the 2 most commonly cultured organisms in post−intravitreal injection endophthalmitis,[14] and the susceptibility of these organisms to chlorhexidine on the conjunctival surface needs further study. There has been 1 reported case of gram-negative endophthalmitis after intravitreal ranibizumab injection in which chlorhexidine 0.05% was used for antisepsis.[26]

Efficacy

In a clinic-based study, conjunctival swabs were taken 3 minutes after instillation of PI 4%, chlorhexidine 0.05%, or ofloxacin 0.3% before corneal suture removal.[27] The mean percent reduction in colony-forming units by PI and chlorhexidine was 91% and 88% respectively, which was not statistically different. Sterile cultures were obtained in 52% of eyes with both PI and chlorhexidine.

Yokoyama et al[28] found a significantly higher positive culture rate from eyelid swabs in patients receiving 0.05% chlorhexidine compared with 10% PI. However, there was no difference in the culture rate from conjunctival swabs in patients receiving 0.05% chlorhexidine or 0.6% PI.

Montan et al[25] found that positive cultures were obtained from the conjunctiva in 30% of eyes that were swabbed 5 minutes after irrigation with 10 ml of chlorhexidine 0.05%, compared with positive cultures in 80% of untreated control eyes. In their series, the endophthalmitis rate was 0.25% after phacoemulsification cataract surgery

Figure 2. A bottle of chlorhexidine acetate 0.05% (Baxter Healthcare Pty Ltd, Old Toongabbie, NSW, Australia) is safe to use for preinjection antisepsis, but it can easily be confused with chlorhexidine acetate 0.5%/0.1% cetrimide that is toxic to the cornea.

Table 1. Description of the Injection Techniques of All Surgeons

Surgeon	A	B	C	D	E	F	G
Hand antisepsis	ETOH	ETOH	ETOH	ETOH	S&W	ETOH	S&W
Gloves	Sterile	Sterile	Sterile	Sterile	Sterile	NS	NS
Mask	Yes	Yes	Yes	Yes	Yes	No	No
Chlorhexidine concentration	0.1%	0.05%	0.05%	0.05%	0.05%	0.1%	0.1%
Speculum	Nil	OW	OW	Nil	OW	OW	LS
Anesthetic	Alc	Bup	Bup	Alc + Tet	Bup	BNX	BNX
Reduction of vitreous efflux	None	None	None	CB	CB	None	None
Time from CHX application to injection	30 sec	30 sec	90 sec	60 sec	60 sec	30 sec	60 sec
Drapes	None	Paper	Paper	None	Paper	None	None
Injection site	Right eye ST, left eye SN	IN	IT	IT	IT	IT	IT

Note: Surgeon E also used lidocaine gel anesthesia for a 2-month period.
Alc = topical proxymetacaine (Alcaine; Alcon Laboratories, Inc, Fort Worth, TX); BNX = topical oxybuprocaine; Bup = topical bupivacaine; CB = cotton bud is placed over withdrawing needle; CHX = chlorhexidine; ETOH = 70% ethanol hand sanitizer; IN = inferonasal; IT = inferotemporal; LS = Lieberman speculum; NS = nonsterile gloves; OW = open wire speculum; SN = superonasal; ST = superotemporal; S&W = soap and water; Tet = tetracaine.

performed from 1994 to 1995 using preoperative chlorhexidine 0.05% and gentamicin 0.3% drops in combination. Their high rate of endophthalmitis could be attributed to the ineffectiveness of gentamicin on gram-positive bacteria, the lack of postoperative intracameral or subconjunctival antibiotics, or a high rate of posterior capsular tears during the early years of phacoemulsification cataract surgery.

Safety

Aqueous Chlorhexidine versus Formulations with Alcohol or Detergents. It is essential to use *aqueous* chlorhexidine gluconate rather than preparations containing alcohol or detergents as in chlorhexidine preparations for surgical scrubs. These have been shown to cause epithelial, stromal, and endothelial toxicity, with permanent stromal scarring or bullous keratopathy causing corneal opacification in the most severely affected cases.[29–31]

Epithelial Toxicity. The epithelial toxicity of chlorhexidine has been explored in several animal studies. Hamill et al[24] investigated the rate of healing of epithelial defects in rabbit eyes after instilling varying concentrations of aqueous chlorhexidine from 0.1% to 4%. The rate of healing compared with saline controls was not statistically different in the eyes that received concentrations of 1% or less. Conjunctival hyperemia was noted for concentrations of 1% to 4%, but not for 0.5% or less. Browne et al[32] found a concentration-dependent increase in mild circumcorneal injection and conjunctivitis as the concentration of chlorhexidine increased from 0.005% to 0.05% in rabbit eyes.

In the present clinical series, a concentration of 0.05% or 0.1% chlorhexidine was well tolerated by our patients, but in 4 prior series 0.05% has been used.[25,27,28,33] Chlorhexidine gluconate 0.2% as antisepsis for intravitreal injection has been described in a small series, with no postinjection pain or irritation reported in 5 patients (Velez G. Abstract: [*Invest Ophthalmol Vis Sci.* 2015;56:4179]).

Chlorhexidine 0.02% to 0.2% is used as a therapy for acanthamoeba keratitis.[34] It has also been described as a treatment for bacterial keratitis[35] and fungal keratitis[36] using concentrations of up to 0.2% without patient intolerance, allergy, or toxicity.

Table 2. Summary of Intravitreal Injections and Endophthalmitis by Center and Surgeon

Center	Study Period	Surgeon	No. of Injections			Allergy	Endophthalmitis
			In Office	*In OR*	*Total*		
1 Newcastle	February 1, 2012, to February 28, 2015	A	4080	5186	9266	1	0
2 Adelaide	January 1, 2013, to February 28, 2015	B	1980	6156	8136	0	0
		C	865	1999	2864	0	0
		D	472	1251	1723	0	0
		E	1175	3691	4866	0	2
3 Brisbane	August 1, 2011, to February 28, 2015	F	?	?	8919	0	1
	March 5, 2012, to February 28, 2015	G	?	?	4761	0	0
Total					40 535	1	3 (0.0074%)

OR = operating room; ? = data not available.

Table 3. Details of the Endophthalmitis Cases

Case	Date	Sex	Age, yrs	Center	Agent	Location	Chlorhexidine Concentration	Vitrectomy	Culture Result	VA before Endophthalmitis	Final VA
1	May 24, 2013	M	86	2	Aflibercept	OR	0.05%	No	No growth	6/15	6/75
2	July 25, 2013	F	86	3	Aflibercept	Office	0.1%	Yes	No growth	6/6	6/12
3	August 23, 2013	M	88	2	Ranibizumab	OR	0.05%	No	Coagulase-negative *Staphylococcus aureus*	6/15	6/60

OR = operating room; VA = visual acuity.

A series describing toxicity in 26 eyes of 22 patients was reported in whom 0.5% chlorhexidine acetate/0.1% cetrimide (Baxter Healthcare Pty Ltd, Old Toongabbie, NSW, Australia) was inadvertently used instead of 0.05% chlorhexidine acetate before intravitreal injection (Fig 2). Severe pain was experienced in 12 eyes for several days. In 2 eyes, there was marked epithelial and stromal edema without frank ulceration that took 3 days to recover (personal communication, Dr. Peter Jeffries. Presented at the "Complications Forum" of the Australian and New Zealand Society of Retinal Specialists Annual Retina Symposium, June 15, 2014, Sydney, Australia).

Endothelial Toxicity. Green et al[37] demonstrated in vitro toxicity to the corneal endothelium with swelling and a dose-dependent sloughing of cells and loss of microvilli when rabbit corneas were bathed in chlorhexidine at various concentrations above 20 μg per ml (0.002%). When the endothelium was protected and only the epithelium exposed, there was no toxic effect.

The inadvertent use of chlorhexidine for intraocular irrigation during cataract surgery, instead of balanced salt solution, has been in reported in 5 patients with resultant endothelial loss.[38,39] Penetrating keratoplasty was required in 3 of the cases, and a Gundersen flap was required in 1 case.

Retinal Toxicity. Animal studies have shown that intravitreal injection of a small volume of low-concentration PI is well tolerated.[40] Although similar studies for chlorhexidine are lacking, it is unlikely that the corneal endothelium or retina would be exposed to a toxic concentration of chlorhexidine after an intravitreal injection of a therapeutic substance given that the tiny volume of chlorhexidine entering the posterior segment would be diluted by the vitreous and aqueous humor, and passage to the endothelium would be impeded by the posterior capsule and zonules in most cases.

Ototoxicity. Chlorhexidine can cause sensineural deafness if it enters the middle ear through a perforated tympanic membrane.[30] Although chlorhexidine may be used to copiously flush the ocular surface, care should be taken to ensure that it does not inadvertently enter the patient's ear.

Allergy. Allergy to chlorhexidine is well described, with complications ranging from mild irritant contact dermatitis to life-threatening anaphylaxis.[41,42] Only 1 case of a suspected allergic reaction was documented during the study period.

Optimal Concentration

The optimal concentration of aqueous chlorhexidine on the ocular surface has not been established. As described earlier, concentrations of 0.05% to 0.2% have been used safely, but the bactericidal effects of these various concentrations on the ocular surface have not been compared. Although 5% PI is the most commonly used concentration on the ocular surface, the optimal concentration of PI is debatable, and efficacy has been described for concentrations as low as 0.25%.[15]

Optimal Contact Time

It has been suggested that the onset of action of chlorhexidine is less immediate compared with PI.[22,43,44] In 1 in vitro study, a 30-second contact time of 2% chlorhexidine produced negative cultures against all 7 micro organisms tested, including *Staphylococcus aureus*.[45] Clinical studies to establish the minimum contact time for chlorhexidine 0.05% to 0.2% on the ocular surface are needed. The ideal contact time for PI is debatable, with a range of 30 seconds to 2 minutes having been described.[15]

Method of Instillation

Irrigation of the conjunctival surface and fornices with 10 ml of PI has been shown to reduce conjunctival bacterial colonization before intravitreal injection, compared with instilling just 1 to 2 drops of PI onto the bulbar conjunctival surface.[46] Studies comparing different methods of applying chlorhexidine have not been performed.

Resistance

There is no consensus on the definition of "resistance" to biocides such as PI and chlorhexidine, and no standardized method for testing it exists.[47] There have been numerous reports that methicillin-resistant *S. aureus* is less susceptible to chlorhexidine compared with methicillin-sensitive *S. aureus*, and efflux-medicated chlorhexidine resistance genes in Staphylococci have been identified.[47] Kunisada et al[48] demonstrated in vitro that bacteria acquire resistance to various antiseptics including chlorhexidine, but not to PI. Hsu et al[49] recently reported that the use of PI without topical antibiotics after serial intravitreal injections does not promote bacterial resistance or change the conjunctival flora. Similar studies for chlorhexidine have not been performed.

Conclusions

In the present series, we found that aqueous chlorhexidine 0.05% or 0.1% used for the prophylaxis of endophthalmitis after intravitreal injection was well tolerated and associated with an endophthalmitis rate lower than many previous series in which PI has been used. Our results should be interpreted with caution given that this was a retrospective study. Recall bias may have affected the number of cases identified with endophthalmitis or chlorhexidine allergy, although cases of endophthalmitis are not easily forgotten. More important, it is possible that patients could have developed endophthalmitis and sought treatment elsewhere. The application of chlorhexidine was not standardized, and it is possible that the treating ophthalmologists used a greater volume of chlorhexidine or a longer contact time compared with when they used PI.

We have also highlighted several areas for further research. In particular, the ideal concentration and contact time that afford maximal reduction in conjunctival bacterial counts with minimal toxicity need to be established. Comparison with PI and the possibility of synergy deserve further study, as does the question of bacterial resistance after repeated application. Future prospective studies will also compare patients' pain scores postinjection after using chlorhexidine compared with PI. Although such studies are feasible, huge numbers of patients would need to be enrolled to determine whether 1 antiseptic agent is superior to the other, given that endophthalmitis is an uncommon event after intravitreal injection.

Safety concerns have limited the use of chlorhexidine in ophthalmology to date, particularly in the United States. There have been several reports of severe corneal toxicity occurring with nonaqueous preparations, and it is paramount to use aqueous chlorhexidine rather than preparations containing alcohol or detergents. In our experience, aqueous chlorhexidine 0.05% to 0.1% for preinjection antisepsis is safe, and others suggest that up to 0.2% may be well tolerated. Care must be taken to ensure that concentrations above this are not inadvertently used, as highlighted in Figure 2. With further validation, aqueous chlorhexidine may be considered a worthy alternative to PI, and warnings against use on the ocular surface may become a thing of the past.

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