



Review Article

Review: Perspective on ocular toxicity of presurgical skin preparations utilizing Chlorhexidine Gluconate/Hibiclens/Chloraprep

Nancy E Epstein MD, FACS

Clinical Professor of Neurosurgery, School of Medicine, State University of New York at Stony Brook, NY and % Dr. Marc Agulnick, 1122 Franklin Avenue Suite 106, Garden City, NY 11530.

E-mail: *Nancy E Epstein - nancy.epsteinmd@gmail.com



***Corresponding author:**

Nancy E Epstein, MD, FACS,
Clinical Professor of
Neurosurgery, School of
Medicine, State University of
New York at Stony Brook, NY
and % Dr. Marc Agulnick, 1122
Franklin Avenue Suite 106,
Garden City, NY 11530.

nancy.epsteinmd@gmail.com

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ABSTRACT

Background: Chlorhexidine Gluconate (CHG), Hibiclens (4% CHG with 4% Isopropyl Alcohol Detergent), and Chloraprep (i.e. labeled CHG-based solutions), utilized as preoperative surgical preparatory solutions may all cause severe oculotoxicity and ototoxicity. Alternatively, 10% Povidone-Iodine (PI) solutions without detergent demonstrate minimal toxic effects on the eyes and ears.

Methods: Based on studies from 1984 to 2021, we compared the safety/efficacy of CHG-based versus PI-based solutions utilized for presurgical skin preparation near the cornea/eyes and ears (i.e., predominantly for cranial or cervical spine surgery).

Results: Some studies documented that even minimal exposure (i.e., “splash risk”) during face/neck skin preparation with CHG-based solutions could result in irreversible corneal injury and ototoxicity. Within minutes to hours, CHG-based non-detergent solutions posed the risks of; corneal epithelial edema, anterior stromal edema, conjunctival chemosis, bullous keratopathy, and de-epithelialization. Notably, even occlusive dressings like Tegaderm could not protect against CHG penetration. Alternatively, PI-based solutions posed no to minimal ocular and/or ototoxicity, while often demonstrating comparable protection against surgical site infections (SSI).

Conclusion: Chlorhexidine Gluconate (CHG), Hibiclens, and Chloraprep (i.e. CHG-based solutions) are often used as skin preparations near the face/eyes/spine (i.e., particularly anterior/posterior cervical procedures). However, if these solutions come in contact with the eyes, corneal irritation, abrasions, and even blindness may result. Alternatively, PI non-detergent solutions demonstrate safety/minimal oculotoxicity/ototoxicity, while frequently showing comparable efficacy against SSI.

Keywords: Chloraprep, Corneal toxicity, Hibiclens, Oculotoxicity, Ototoxicity, Povidone-iodine solution, Skin preparation

INTRODUCTION

Chlorhexidine gluconate (CHG), Hibiclens (4% CHG and 4% Isopropyl Alcohol), and Chloraprep (i.e. CHG-based solutions) presurgical skin preparations have well-documented oculotoxicity and ototoxicity. Therefore, great care must be utilized to avoid eye and ear contact when utilizing these presurgical preparation solutions when performing cranial and/or anterior or posterior cervical spine surgery, and occasionally, other procedures near the eyes/ears. Alternatively, Povidone-Iodine (PI) non-detergent solutions have demonstrated

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minimal eye/ear toxicity, while often showing comparable prophylaxis against surgical site infection (SSI). Here we reviewed the relative risks/benefits, and alternatives to CHG-based preoperative skin preparation solutions versus PI non-detergent solutions for patients undergoing procedures near the eyes/ears (i.e. cranial surgery, spinal surgery, and occasionally other procedures).

1984 RABBIT STUDY DOCUMENTED CORNEAL TOXICITY OF CHG/HIBICLENS

In 1984, Mac Rae *et al.* evaluated the corneal toxicity in rabbits of multiple skin preparations [Table 1].^[5] These included; tincture of iodine (2% iodine, 2.35% sodium iodine, 46% ethanol), Hibiclens (4% chlorhexidine; 4% isopropyl alcohol with detergent), PhisoHex (3% hexachlorophene/detergent),

Lavacol (70% ethanol), 7.5% povidone iodine scrub (PIS plus detergent), and 10% PI solutions (PI without detergent). At 3 h, all skin preparations resulted in marked de-epithelialization, conjunctival chemosis, and/or anterior stromal edema except the 10% PI solution without detergent and 0.9% Normal Saline. They concluded that only the 10% PI solution without detergent and NS showed no significant toxicity, while all other skin preparations were ototoxic or oculotoxic (i.e., to the cornea).

DOCUMENTATION OF CORNEAL TOXICITY FOR CHG-BASED SOLUTIONS

Multiple studies demonstrated significant corneal toxicity when using CHG-based preoperative skin preparation solutions for cranial, cataract, or spinal surgery [Table 1].^[6,9] Van Rij (1995) noted that mistakenly using CHG, Cetrimide

Table 1: Oculotoxicity of CHG-based versus PI-based solutions when used as a skin preparation. Near the eyes/ears (i.e., face) and cervical spine.

Author Ref# Year Journal	Study design	Data	Data	Data	Conclusion
Mac Rae <i>et al.</i> ^[5] 1984 Am J Ophthalmol	Corneal Tox Preop SP Rabbits Used BioM, Corneal Pachymetry Healing Studies EM	Groups NS TincI (2% I, 2.35% NAI/46%) Ethanol Hibiclens 4% CHG+4% Isopropyl Alcohol Det	Study Groups PhisoHex Lavachol (70% Ethanol) 7.5% PI Scrub/Det 10% PIS No Det	Findings 5 Min AA Moderate CEE Not Saline 3 Hrs Marked DE, CC, ASE All Not 10% PIS and 0.9% NS	1 Week; all Corneas Normal Conclude 10% PIS without Det Min Tox Other Preps Tox to Cornea
Van Rij <i>et al.</i> ^[9] 1995 Doc Ophthalmol	Tox Keratopathy Due to Accidental Use CHG, Cetrimide and Cialit Cataract Surgery	Use of Irrigation Solutions by OPH (Some Bottles Identical)	3 Years Chose Wrong Bottle 5x CHG, Cetrimide CHG/Cetrimide and Cialit	Result Acute CEE, BK 4 Pts Pen 1 Pt Cornea Covered Conjunctival Flap	Light EM CEE, LK Disrupted/ Loss ECL
Murthy <i>et al.</i> ^[6] 2002 Cornea	Prog UK Due to Topical CHG (0.02%)	Case 45 yo F Rx for UK with topical CHG 0.02% (+Propamidine 0.1%) Eye Drops	8 wk Drops Near Total Loss Corneal Epithelium Prog UK Required Pen Keratoplasty	Ulceration Loss of Bowman's Membrane LK Apoptosis LEC	Hibiclens=CHG 4% with +Det Culture No Organisms But Result Progressive UK
Darouiche <i>et al.</i> ^[3] 2010 NEJM	CHG (409) versus PI (440) for Prep Surgical Site	Hypothesis CHG Better Than PI Prep to Avoid SSI In 30 Days Postop	SSI Significantly Lower CHG versus PI <SSI Superficial and Deep	DATA 300-500,000 SSI/Yr/ USA CDC REC 2% CHG Inserted Catheters	Which to Use CHG versus PI to Avoid SSI in 27 Million Operations/yr/ USA
Bever <i>et al.</i> ^[1] 2016 World Neurosurg	CHG SP High Risks Eye Tox	2 Cases Corneal Damage -4% CHG SP Despite Tight OC Eye Dressing	Highly Tox CHG to Eye Recommend: 10% PIS SP Near Eyes	CHG Use Avoid Contact with Eyes	If use CHGHCG Add Protect AEP+ Tight OC

(Contd...)

Table 1: (Continued).

Author Ref# Year Journal	Study design	Data	Data	Data	Conclusion
Steinsapir and Woodward ^[8] 2017 Dermatol Surg	CHG for Ker Facial PS 11 Sentinel Cases Late 1980's	Toxic to Cornea Splash Risk Irreversible Damage Minimal Exposure	Research PubMed Embase LexisNexis Databases	CHG should NOT be Used on Face and Scalp Risk ME	PIS Safe Effective Choice
Brodie <i>et al.</i> ^[2] 2018 Curr Eye Res	BO Dressing Protect From PreSurg CHG SP 3 Arms to Experiment	CHG Excellent Antisepsis Standard Concentrate 2-4% Result Ocular Injury Even with BO Dressing- Tegaderm to Closed Eye	1 st Arm <i>in vitro</i> : CHG Pen Edge Tegaderm At 5 min Water No Pen Tegaderm 2 nd Arm Central Perm Tegaderm Impermeable to both CHG and Water at 90 min	3 rd Arm <i>in Vivo</i> CHG Pen 10 min Water Never Pen with Tegaderm Conclusion Tegaderm Perm Edges to CHG Not Water	Advise Avoid Tegaderm BO Dressing with CHGHCG Use PI Prep
Ghobrial <i>et al.</i> ^[4] 2018 J Neurosurg Spine	Preop SP CHG versus PI 6959 Consecutive Spinal Surgery Pt	Compare Efficacy SP ChlorPrep CHGHCG versus PI to Reduce SSI	2011-2015 SSI 2 (0.1%) MIS/885 Cases 1.1% Open 67 of 6074 Cases	SSI Pts DD 48/69 IF in 51/69 Index 1 st Surgery 38 RS	No Significant Differences in SSI PI 33 versus CHGHCG Chloraprep 36
Shive <i>et al.</i> ^[7] 2021 Dermatol Surg	Use of CHG SP Head/ Neck Review Tox Ears/Eyes	Review PubMed Web of Science	14 Cases Hearing Loss CHG/Ear 38 Cases Eye Tox-	38 Cases Eye Tox- 8 Direct Install 17 Periocular Surgical Prep (remaining prep less defined)	38 Cases Eye Tox- 7 Prep of Face 1 Scalp 2 Drips Distant Sites 3 Not specified

Ker: Keratitis, Presurg: Presurgical, CI: Corneal injury, SP: Skin preparation, SC: Skin cleanser, CHG: ChlorHexidine gluconate, Sig: Significant, CD: Corneal damage, ME: Middle ear, BO: Bio-occlusive, Perm: Permeability, Pen: Penetrability, Min: Minutes, Preop: Preoperative, EM: Electron microscopy, NS: Sodium chloride, hr(s): Hours, Tox: Toxicity, Det: Detergent, AA: After applications, CEE: Corneal epithelial edema, DE: De-epithelialization, CC: Conjunctival chemosis, ASE: Anterior stromal edema, PIS: Povidone iodine solution, Protect: Protection (i.e., Measures), AEP: Absorbent eye pads, OC: Occlusive dressing, Min: Minimal, I: Iodine, NI: Sodium Iodine, TinctI: Tincture of iodine, Install: Installation, OPH: Ophthalmologists, BK: Bullous keratopathy, K: Keratoplasty, LK: Loss of keratocyte, ECL: Endothelial cell layer, UK: Ulcerative keratitis, wk: Weeks, LEC: Loss of endothelial cells, AK: Acanthamoeba keratitis, Rx: Treated, Pt(s): Patient(s), SSI: Surgical site infections, DD: Degenerative disease, IF: Instrumented fusions, Rev: Revision surgery, MIS: Minimally invasive surgery, REC: Recommendation, Sig: Significant, BioM: Biomicroscopy, Prog: Progressive, PI: Povidone-Iodine, CDC: Centers for Disease Control

or Cialit solutions for irrigation during cataract surgery resulted in acute corneal changes that included; epithelial edema, bullous keratopathy, loss of keratocytes, and loss of the endothelial cell layer.^[9] In Murthy *et al.* (2002) case study, eye drops containing Topical CHG (0.0.2%) were utilized in a 45-year-old patient (2002).^[6] Within 8 weeks, they encountered near complete loss of the corneal endothelium/epithelial cells resulting in ulcerative keratitis (i.e., later warranting a penetrating keratoplasty), and ulceration involving Bowman's membrane.

STUDIES DOCUMENTING COMPARABLE OR SUPERIOR PREVENTION OF SSI UTILIZING CHG-BASED SOLUTIONS VERSUS PI SOLUTIONS FOR SURGICAL SKIN PREPARATIONS

Several studies documented that CHG-based versus PI-based skin preparation solutions provided comparable or superior prevention of SSI [Table 1].^[3,4] In 2010, Darouiche *et al.*, in a study specifically designed to address the insertion of percutaneous catheters, found that CHG (409 patients) significantly reduced

the risk of postoperative superficial and deep SSI at 30 postoperative days versus those receiving PI (440 patients).^[3] Note, however, that the Centers for Disease Control did not issue a specific recommendation favoring CHG-based solutions over PI solutions to address other surgical procedures including spine operations (i.e., also approximately 27 million total operations performed/year in the US). In 2018, Ghobrial *et al.* compared the efficacy of the preoperative skin preparation with CHG versus PI solutions in 6959 consecutive patients undergoing a variety of spinal procedures (2011–2015); the infection rates were comparable for both types of skin preparations (i.e., 2 (0.1%) infections for minimally invasive surgical cases (total 885) and 1.1% for open procedures (67 of 6074 cases)) 6074 [Table 1].^[4]

CORNEAL DAMAGE DESPITE UTILIZATION OF TIGHT AND/OR BIO OCCLUSIVE OCULAR DRESSINGS

Even tight or bio occlusive dressings (i.e. Tegaderm) did not adequately protect the eyes from dripping skin CHG-based preparations or “splashes” [Table 1].^[1,2,7,8] In 2016, Bever *et al.* noted that CHG (4%) skin preparations resulted in 2 cases of significant ocular toxicity even when a tight protective Tegaderm dressing was placed to protect the eyes during surgery.^[1] They recommended using PI solutions as a safe/effective alternative. If CHG-based solutions had to be used, “tightly occlusive dressings” including “eye pads should be added to avoid eye exposure, but would/could not guarantee adequate eye protection.” Brodie *et al.*, (2018) similarly found that although CHG-based solutions provided excellent protection against infection (2–4%), using Tegaderm as a bio occlusive dressing did not adequately protect the closed eyes from injury.^[2] In their 3 pronged study, the first *in vitro* prong involved a 5 min application of CHG versus water; the CHG-based solution penetrated the edges of the Tegaderm dressing while simple water did not. In the second arm, central penetration of a Tegaderm dressing at 90 min was tested with a CHG-based solution versus water; the Tegaderm was impermeable to both. However, in the third *in vivo* arm, CHG-based solutions penetrated the Tegaderm edges within 10 min while water did not. They concluded that Tegaderm did not provide a sufficient bio occlusive dressing against CHG-based solutions, and that PI solutions should be used instead. In 2017, Steinsapir and Woodward noted 11 sentinel cases of corneal toxicity due to CHG for presurgical skin preparation on the face.^[8] CHG-based solutions, even including minimal “splashes”, were toxic to the cornea. PI-based solutions, therefore, provided a safer and more effective alternative. In Shive *et al.* (2021), CHG-based solutions were used in head and neck surgery.^[7] They resulted in 14 cases of ototoxicity and 38 cases of ocular toxicity; 8 from direct contact, 17 from periocular skin preparation, 7 preparations to the face and 1 to the scalp, 2 drips/distant sites, and 3 that were not specified.^[7]

CONCLUSION

Multiple studies have documented the safety/efficacy of PI-based solution skin preparations when used near the eyes, ears, face, and neck (i.e., cranial, cervical spine, cataract/ surgery, other). Alternatively, CHG-based solutions (i.e., including Hibiclens and Chloraprep) have proven both oculotoxic and ototoxic. As both products have shown nearly comparable SSI prevention, careful attention must be given when using CHG over PI solutions near the eyes or ears.

Declaration of patient consent

Patient’s consent not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Bever GJ, Brodie FL, Hwang DG. Corneal injury from presurgical chlorhexidine skin preparation. *World Neurosurg* 2016;96:610.e1-4.
2. Brodie F, Bever G, Hwang DG. Performance of bio-occlusive dressing as barrier protection from presurgical chlorhexidine skin preparation. *Curr Eye Res* 2018;5:576-9.
3. Darouiche RO, Wall MJ, Itani KM, Otterson MF, Webb AL, Carrick MM, et al. Chlorhexidine-Alcohol versus Povidone-Iodine for Surgical-Site Antisepsis. *N Engl J Med* 2010;362:18-26.
4. Ghobrial G, Wang MY, Green BA, Leyene HB, Manzano G, Vanni S, et al. Preoperative skin antisepsis with chlorhexidine gluconate versus povidone-iodine: A prospective analysis of 6959 consecutive spinal surgery patients. *J Neurosurg Spine* 2018;28:209-14.
5. Mac Rae SM, Brown B, Edelhauser HF. The corneal toxicity of presurgical skin antiseptics. *Am J Ophthalmol* 1984;97:221-32.
6. Murthy S, Hawksworth NR, Cree I. Progressive ulcerative keratitis related to the use of topical chlorhexidine gluconate (0.02%). *Cornea* 2002;21:237-9.
7. Shive M, Hou Z, Zachary C, Cohen J, Rivers JK. The use of chlorhexidine as a skin preparation on the head and neck: A systematic review of ocular and ototoxicity. *Dermatol Surg* 2021;47:34-7.
8. Steinsapir KD, Woodward JA. Chlorhexidine keratitis: Safety of chlorhexidine as a facial antiseptic. *Dermatol Surg* 2017;43:1-6.
9. van Rij G, Beekhuis WH, Eggink CA, Geerards AJ, Remeijer L, Peis EL. Toxic keratopathy due to the accidental use of chlorhexidine, cetrimide and cialit. *Doc Ophthalmol* 1995;90:7-14.

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