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Letter to the Editor: Effect of Povidone Iodine 5% on the Cornea, Vision, and Subjective Comfort

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We read with interest the recent study by Ridder et. al[1] published in the July 2017 issue of *Optometry and Vision Science,* which reported that application of 5% povidone-iodine ophthalmic solution (PVP-I, Betadine) in 10 normal subjects caused discomfort, increased corneal epithelial fluorescein staining, and transient changes in visual function (acuity and contrast sensitivity). Previous large-scale studies have reported that ophthalmic PVP-I has good patient tolerability and an excellent safety profile.[2–4] It has been widely utilized in clinics around the globe for decades to disinfect the eye prior to surgery[5] and intravitreal injections,[6] and more recently by some eye-care practitioners for the treatment of adenoviral conjunctivitis.[7] While the results of Ridder and colleagues[1] indicate that PVP-I alters vision and damages the corneal epithelium to a greater extent than previously recognized, we would like to point out a couple of potential limitations in their study design.

First, in this study,[1] PVP-I was placed on the eye for 2 to 3 minutes and then “washed out” with a single drop of proparacaine hydrochloride. The drug product label provided with Betadine 5% ophthalmic solution (Alcon, Fort Worth TX), states that after this solution “has been left in contact for two minutes, sterile saline solution in a bulb syringe should be used to flush the residual prep solution from the cornea, conjunctiva, and the palpebral fornices”. It is not clear from Ridder and colleagues’ report[1] why a single anesthetic drop was used post-Betadine exposure, as opposed to full saline irrigation. Nor are we aware of this approach being typically used in clinical practice. The lack of a thorough saline flush potentially affects the standardization of exposure time, as the single wash-out drop may have resulted in diluted PVP-I remaining in the eye for an unknown prolonged period. Furthermore, dilution of PVP-I up to 1000 fold can have the paradoxical effect of increasing the concentration of free iodine present due to the complex interactions between iodine, the carrier polymer, the polymer-triiodide complex, and its environment.[8–10] The possible extended contact time of the eye to free iodine may explain why this study reported that the

effect on visual acuity was delayed, with a significant decrease occurring at 30 minutes, but not 5 minutes, post-Betadine exposure.[1]

Second, the order of administration of Betadine and saline was not randomized (all subjects were exposed to Betadine first) and masking of the subjects and clinicians to treatment type was not attempted.[1] The authors state that randomization and masking were not possible due to the expected discomfort and discoloration effects associated with Betadine application. However, other groups have found ophthalmic PVP-I is tolerated with minimal discomfort,[3, 4] and ocular staining could be minimized by employing post-treatment irrigation. Therefore, these reasons are not necessarily valid *a priori* assumptions. A more rigorous design would have been to randomize the treatment order and have the ocular examination and visual assessments performed by a masked clinician. This would eliminate, or at least minimize, the potential for conscious or unconscious bias.

We commend the authors for their work in this field and agree with their premise that an ideal antiseptic ophthalmic solution should have broad spectrum antimicrobial activity while causing negligible effects on corneal epithelial integrity. For clinicians that routinely use Betadine 5% ophthalmic solution, it is encouraging that its effects on patient discomfort, visual function, and corneal fluorescein staining observed in this study[1] were relatively transient. However, the reported effects may still have been more pronounced than what occurs with standard clinical use due to the insufficient rinse employed. Any influence of potential bias can be better addressed in future studies that employ double-masked study designs and randomized treatment order. Betadine has accumulated an impressive safety record over its decades of use, and we feel that the authors' conclusion in their abstract[1] that Betadine 5% "significantly decreases epithelial integrity of the cornea, decreases functional vision, and increases subjective complaints" needed to be clarified in light of these caveats. We appreciate the value of continued investigations regarding Betadine's safety and tolerability going forward.

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