Study Title: Randomized Controlled Study of Cooled Versus Room-Temperature Artificial Tears for Reducing Surface Irritation Following Intravitreal Injection

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Project Title: The Effect of Cooled Artificial Tears in Reducing Ocular Surface Irritation after Povidone-Iodine Preparation of Intravitreal Injection.

Principle Investigator: Douglas Jin, MD

Purpose:

The use of Povidone-iodine (PVI) is the standard of care when preparing for intravitreal injections. However, PVI is also known to be toxic to the corneal epithelium and delays ocular surface healing. Although guidelines on pre and peri-injection antiseptic techniques are well-studied, there has been a relative lack of consensus on ocular surface management to reduce the severity and duration of post-injection pain and discomfort. Patients frequently report post-injection ocular discomfort (e.g. tearing, burning, redness, and foreign body sensation) similar to symptoms of dry eye disease, and the main culprit is the application of PVI to prevent eye infections. Many have studied the effect of cooling eye drops, such as certain glaucoma and anesthetic drops to alleviate their initial stinging sensation upon instillation. Similarly, people have tried cooling the eye itself as an effective numbing effect to dull the pain associated with intravitreal injections. Oftentimes patients are advised to try using artificial tears on an as-needed basis to alleviate any dry-eye sensation post-injection, and we propose that cooling the artificial tears will further reduce patients' ocular discomfort level associated with eye injections.

Study aims or hypotheses:

Does the use of cooled artificial tears (4 C) reduce ocular discomfort compared to that of room-temperature artificial tears (~23C) measured by the standard questionnaires (e.g. Ocular Surface Disease Index and subjective stinging feeling scale) in patients who receive intravitreal injections?

Procedure:

Any patient who comes to the injection clinic and reports subjective sensation of ocular discomfort will be allowed to participate in the study. The subject will be randomized into either the room-temperature group or the cooled group, and they will use the respective artificial tears for up to 12 hours in the immediate post-injection period. A telephone survey will be administered within 48 hours of the clinic visit to administer a standard questionnaire to assess their ocular discomfort level.

Background and significance:

Intravitreal injection (IVI) is the most commonly performed ophthalmic procedure (2.5 million in 2011) in the United States. Povidone-iodine (PVI) has been widely studied as an antiseptic agent and its application is considered the standard of care when preparing for IVI. PVI is also known to be toxic to the corneal epithelium and delays ocular surface healing. Although guidelines on pre and peri-injection antiseptic techniques are well-studied, there has been a relative lack of consensus on ocular surface management to reduce the severity and duration of post-injection pain and discomfort. Patients frequently report post-injection ocular discomfort (e.g. tearing, burning, redness, and foreign body sensation) similar to symptoms of dry eye disease. Many have studied the effect of cooling eye drops, such as certain glaucoma and anesthetic drops to alleviate their initial stinging sensation upon instillation. Similarly, people have tried cooling the eye itself as

an effective numbing effect to dull the pain associated with intravitreal injections. Oftentimes patients are advised to try using artificial tears on an as-needed basis to alleviate any dry-eye sensation post-injection, and we propose that cooling the artificial tears will further reduce patients' ocular discomfort level associated with eye injections.

Target Enrollment: 300

Age of Subjects: 18-105 years

Inclusion Criteria:

Patients were eligible if they were receiving standard intravitreal injections for their exudative age-related macular degeneration, cystoid macular edema, diabetic macular edema, proliferative diabetic retinopathy, retinal vein occlusion with macular edema, or retinal neovascularization.

Exclusion criteria

- Inability or lack of willingness to participate in the study
- Active ocular infection including infectious uveitis
- First time receiving intravitreal injection
- Those who reported never having ocular discomfort following intravitreal injections on the pre-injection questionnaire
- Less than 18 years of age.

Arms and Interventions:

Arms	Assigned Interventions
Experimental: Cooled artificial tear group Stored at 4 degree Celsius	Drug: Refresh Plus Preservative-free Lubricant Eye Drops Refresh Plus Preservative-free Lubricant Eye Drops at either 4 or 25 degree Celsius
Active Comparator: Room temperature artificial tear group Stored at 25 degree Celsius	Drug: Refresh Plus Preservative-free Lubricant Eye Drops Refresh Plus Preservative-free Lubricant Eye Drops at either 4 or 25 degree Celsius

Outcome Measure:

1) The Efficacy of Cooled Versus Room Temperature Artificial Tears in Reducing Post Intravitreal Injection Ocular Discomfort as Measured by Pain Scale Survey. The level of subjectively reported pain scale from 1 to 10, where 1 is minimal pain and 10 is extreme pain measured within 72 hours of the intervention.

References:

1. Merani R, Hunyor AP. Endophthalmitis following intravitreal anti-vascular endothelial growth factor (VEGF) injection: A comprehensive review. Int J Retina Vitreous. 2015;1:9-015-0010-y. eCollection 2015.

2. Patel SN, Gangaputra S, Sternberg P,Jr, Kim SJ. Prophylaxis measures for postinjection endophthalmitis. Surv Ophthalmol. 2020.

3. Grzybowski A, Kanclerz P, Myers WG. The use of povidone-iodine in ophthalmology. Curr Opin Ophthalmol. 2018;29(1):19-32.

4. Avery RL, Bakri SJ, Blumenkranz MS, et al. Intravitreal injection technique and monitoring: Updated guidelines of an expert panel. Retina. 2014;34 Suppl 12:S1-S18.

5. Hinkle JW, Wykoff CC, Lim JI, et al. "Iodine allergy" and the use of povidone iodine for endophthalmitis prophylaxis. Journal of VitreoRetinal Diseases. 2020;4(1):65-68.

6. Wykoff CC, Flynn HW,Jr, Han DP. Allergy to povidone-iodine and cephalosporins: The clinical dilemma in ophthalmic use. Am J Ophthalmol. 2011;151(1):4-6

7. Laude A, Lim JW, Srinagesh V, Tong L. The effect of intravitreal injections on dry eye, and proposed management strategies. Clin Ophthalmol. 2017;11:1491-1497.

8. Saedon H, Nosek J, Phillips J, Narendran N, Yang YC. Ocular surface effects of repeated application of povidone iodine in patients receiving frequent intravitreal injections. Cutan Ocul Toxicol. 2017;36(4):343-346.

9. Chaturvedi R, Wannamaker KW, Riviere PJ, Khanani AM, Wykoff CC, Chao DL. Real-world trends in intravitreal injection practices among american retina specialists. Ophthalmol Retina. 2019;3(8):656-662.

10. Green-Simms AE, Ekdawi NS, Bakri SJ. Survey of intravitreal injection techniques among retinal specialists in the united states. Am J Ophthalmol. 2011;151(2):329-332.

11. Grzybowski A, Told R, Sacu S, et al. 2018 update on intravitreal injections: Euretina expert consensus recommendations. Ophthalmologica. 2018;239(4):181-193.

12. Ridder WH,3rd, Oquindo C, Dhamdhere K, Burke J. Effect of povidone iodine 5% on the cornea, vision, and subjective comfort. Optom Vis Sci. 2017;94(7):732-741.

13. Marcet MM, Shtein RM, Bradley EA, et al. Safety and efficacy of lacrimal drainage system plugs for dry eye syndrome: A report by the american academy of ophthalmology. Ophthalmology. 2015;122(8):1681-1687.

14. Jehangir N, Bever G, Mahmood SM, Moshirfar M. Comprehensive review of the literature on existing punctal plugs for the management of dry eye disease. J Ophthalmol. 2016;2016:9312340.

15. Ngo W, Situ P, Keir N, Korb D, Blackie C, Simpson T. Psychometric properties and validation of the standard patient evaluation of eye dryness questionnaire. Cornea. 2013;32(9):1204-1210.

16. Pflugfelder SC, Solomon A, Stern ME. The diagnosis and management of dry eye: A twenty-five-year review. Cornea. 2000;19(5):644-649.

17. Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. Cornea. 2003;22(7):640-650.

18. Miller KL, Walt JG, Mink DR, et al. Minimal clinically important difference for the ocular surface disease index. Arch Ophthalmol. 2010;128(1):94-101.

19. Asiedu K, Kyei S, Mensah SN, Ocansey S, Abu LS, Kyere EA. Ocular surface disease index (OSDI) versus the standard patient evaluation of eye dryness (SPEED): A study of a nonclinical sample. Cornea. 2016;35(2):175-180.

20. Segal O, Segal-Trivitz Y, Nemet AY, Cohen P, Geffen N, Mimouni M. Anxiety levels and perceived pain intensity during intravitreal injections. Acta Ophthalmol. 2016;94(2):203-204.

21. Vaze A, Fraser-Bell S, Gillies M. Reasons for discontinuation of intravitreal vascular endothelial growth factor inhibitors in neovascular age-related macular degeneration. Retina. 2014;34(9):1774-1778.

22. Blaha GR, Tilton EP, Barouch FC, Marx JL. Randomized trial of anesthetic methods for intravitreal injections. Retina. 2011;31(3):535-539.

23. Davis MJ, Pollack JS, Shott S. Comparison of topical anesthetics for intravitreal injections : A randomized clinical trial. Retina. 2012;32(4):701-705.

24. Dohlman TH, Lertsuwanroj B, D'Amico DJ, Ciralsky JB, Kiss S. Evaluation of signs and symptoms of ocular surface disease after intravitreal injection. Acta Ophthalmol. 2019;97(8):e1154-e1156.

25. Shibata Y, Tanaka Y, Tomita T, et al. Evaluation of corneal damage caused by iodine preparations using human corneal epithelial cells. Jpn J Ophthalmol. 2014;58(6):522-527.

26. Klenkler B, Sheardown H, Jones L. Growth factors in the tear film: Role in tissue maintenance, wound healing, and ocular pathology. Ocul Surf. 2007;5(3):228-239.

27. Ervin AM, Law A, Pucker AD. Punctal occlusion for dry eye syndrome: Summary of a cochrane systematic review. Br J Ophthalmol. 2019;103(3):301-306.

28. Pflugfelder SC. Tear dysfunction and the cornea: LXVIII edward jackson memorial lecture. Am J Ophthalmol. 2011;152(6):900-909.e1.

29. Crabb MG, Liu E, Freeman A, et al. The intravitreal injection pain study: A randomized control study comparing subjective pain with injection technique. Acta Ophthalmol. 2019;97(8):e1153-e1154.

30. Jandorf S, Krogh Nielsen M, Sorensen TL. Irrigating the eye after intravitreal injection reduces epithelial damage but not patient discomfort. Acta Ophthalmol. 2019;97(4):e670-e671.

31. Bitton E. Response to re: Does the temperature of an artificial tear affect its comfort? Clin Exp Optom. 2019;102(2):191-192.

32. Bitton E, Crncich V, Brunet N. Does the temperature of an artificial tear affect its comfort? Clin Exp Optom. 2018;101(5):641-647.

33. Bozic M, Stojkovic M, Knezevic M, Marjanovic I, Bobic-Radovanovic A. Is the use of refrigerated fixed combination of dorzolamide 2%-timolol 0.5% (COSOPT) associated with less ocular discomfort: A pilot study. J Ocul Pharmacol Ther. 2018;34(9):642-646.

34. Fujishima H, Yagi Y, Shimazaki J, Tsubota K. Effects of artificial tear temperature on corneal sensation and subjective comfort. Cornea. 1997;16(6):630-634.

35. Hu Youwei J, Chang B. Effect of cooling proparacaine 0.5% eye drops on patient's comfort during instillation. Eye (Lond). 2015;29(8):1112-1113.

36. Karkkainen TR. The effect of refrigeration on the osmolality and pH of nonpreserved artificial tears containing carboxymethylcellulose. Optom Vis Sci. 2001;78(1):37-39.

37. McMonnies CW. Re: Does the temperature of an artificial tear affect its comfort? Clin Exp Optom. 2019;102(2):191.

38. Meduri A, Bergandi L, Oliverio GW, et al. The cold eye irrigation BSS solution used during phacoemulsification reduces post-surgery patients discomfort preventing the inflammation. Eur J Ophthalmol. 2021:11206721211018377.

39. Soltani AE, Ganji M, Goodarzi M, Moghimi S. Cooling tetracaine to reduce pain of instillation before surgery. Eye (Lond). 2009;23(6):1470.