EFFECTS OF COLLAGEN PUNCTAL PLUGS ON TEAR OSMOLARITY

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ABSTRACT

Background: Increased tear osmolarity has been identified as one of the markers of dry eye syndrome. Collagen punctal plugs are often used to aid in treatment of dry eye disease. This study looks at fluctuations in tear osmolarity in normal individuals who undergo punctal occlusion via collagen punctal plugs. If collagen punctal plugs lower tear osmolarity in normal individuals, this effect may be greater in people who have dry eye disease. Therefore, collagen punctal plugs could serve as an effective means of lowering tear osmolarity and treatment for dry eye disease. *Methods:* The following study used 30 participants' ages 20-46 years, 60 eyes total. Tear osmolarity was taken of each eye before punctal occlusion. In each participant the lower left puncta was fit with a collagen punctal plug. The right eye puncta remained open as a control group. After two days, tear osmolarity readings were taken. This concluded the study. R*esults:* Through chi-squared analysis ($p<0.05$), the results proved to be inconclusive neither proving nor disproving a relationship between punctal occlusion and changes in tear osmolarity in normal individuals who do not have hyperosmotic tears. *Conclusions:* More studies specifically involving dry eye patients need to be conducted to determine if there is potential to lower tear osmolarity through the use of collagen punctal plugs. This study may indicate that people without dry eye disease may possess an intact homeostatic mechanism that maintains tear osmolarity.

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CHAPTER 1

INTRODUCTION

Dry eye is said to occur in up to 20% of the population in North America, making it a disease commonly seen in clinical practice[1]. There are a wide range of clinical tests for detecting dry eye disease, but no current consensus as to which test is most accurate at detecting it[2]. According to the 2007 Dry Eye Workshop (DEWS) report, tear hyperosmolarity is indicative of dry eye disease and can be used as the "gold standard" for detecting dry eye disease[2]. The report established evidence that tear hyperosmolarity was the main source of ocular surface inflammation, damage and symptoms for dry eye disease[2]. The most accurate tests for measuring tear osmolarity aim to reduce reflex tearing by collecting nanoliter volumes of tears via non-invasive to minimally invasive means. The cut-off value for aiding in diagnosis of dry eye disease recommended by the DEWS report based off of collected data and other supportive research is 316 mOsm/L[2, 3].

Many different approaches exist in the treatment of dry eye disease based on severity and symptoms. One treatment form, punctal occlusion, works to prevent the drainage of tears from the ocular surface into the lacrimal sac by obstructing the lacrimal canaliculi. Temporary punctal occlusion is often trialed before permanently deciding to occlude the puncta[4,5]. Punctal occlusion reduces the need for ocular lubricants and improves symptoms of dry eye disease[6]. One concern for using this treatment form is

increasing sub-clinical ocular inflammation. However, studies have reported that temporary use of punctal plugs are an effective and safe form of treatment for patients who have keratoconjunctivitis sicca[4,7].

This study aims to evaluate the effects of collagen punctal plugs on tear osmolarity in normals whose tear osmolarity did not reach the cut-off value of 316 mOsm/L. With knowledge that hyperosmolarity of tears is indicative of dry eye disease, and punctal plugs increase tear volume in dry eye patients; it is postulated that punctal occlusion could lead to lower tear osmolarity. Studying the effect in normals may determine if there is an overall lowering of tear osmolarity that occurs as a general rule to punctal occlusion. If this proves true, punctal occlusion may be one of the most effective means of treating dry eye disease.

CHAPTER 2

METHODS

This study was conducted at the Michigan College of Optometry in Big Rapids, Michigan. The subjects ranged in age from 20 to 46 years old and were both male and female. Subjects were excluded from this study if they were experiencing any signs or symptoms of ocular inflammation, had systemic allergies which were causing ocular irritation, or any autoimmune disease. Furthermore, subjects were to remove contact lenses prior to this study for at least 2 hours and remain with them out for the duration of the study. The final subject count was 30 people, 60 eyes (n=60).

Tear samples were collected for evaluating tear osmolarity using the TearLab™ on both eyes of each subject. The microchip device collected roughly a 50 nanoliter (nL) sample of tears from the lateral canthus of each eye. Contact with the ocular surface was avoided to prevent reflex tearing.

Biomicroscopy of the anterior segment was performed to screen for signs of inflammation and to assess the integrity of the puncta. Once subjects were deemed as fit candidates, 0.50% proparacaine was used on the opening of the left lower puncta for anesthetic effect via a soaked cotton swab. A gauging probe was placed into the puncta to determine the size of collagen plug best suited for the participant's puncta.

The plugs used in this study were Lacrimedics® sizes 0.3mm and 0.4mm. To insert the punctal plug, it was removed via jeweler's forceps from sterile packaging. The participant was placed behind a biomicroscope, and the plug was inserted into the lower puncta of the left eye. The subject's right eye puncta remained open as a control.

After receiving the punctal plug, participants were asked to return for a second tear osmolarity reading approximately 72 hours after wearing the plug. Tear samples were collected from each eye via the TearLab™, and readings were taken in mOsm/L. This concluded data collection.

CHAPTER 3

RESULTS

On day one the average tear osmolarity of the control eyes (n=30) was 290.3 mOsm/L (+/- 9.3 mOsm/L), and the test eyes (n=30) was 287.6 mOsm/L (+/-9.8 mOsm/L). Day two readings averaged 292.1 mOsm/L (+/-7.5 mOsm/L) in the control group and 288.4 mOsm/L (+/-6.3 mOsm/L) in the test group (Table 1). Overall, the average change in tear osmolarity for the control group was a 1.7 mOsm/L increase in tear osmolarity, and 0.8 mOsm/L increase in tear osmolarity in the test group. The control group changed by 0.7%, and the punctal plug group changed by 0.4%.

Table 1: Data Collection and Mean Results-Tear osmolarity readings (mOsm/L) collected from day one and day two

#	Tear Osmolarity--Baseline		Tear Osmolarity--Day 2		Change	Change
	OD	OS	OD	OS	in OD	in OS
1	289	281	295	297	6	16
2	290	286	289	290	-1	4
3	291	275	289	286	-2	11
4	290	282	301	295	11	13
5	283	290	302	294	19	4
6	290	290	284	288	-6	-2
7	285	285	285	281	0	-4
8	283	286	296	282	13	-4
9	288	280	290	282	2	2
10	275	278	288	305	13	27
11	280	282	286	280	6	-2
12	276	278	289	281	13	3
13	295	281	290	290	-5	9
14	286	285	284	285	-2	0
15	281	282	285	289	4	7
16	281	281	285	286	4	5
17	309	293	300	289	-9	-4
18	292	292	281	285	-11	-7
19	288	280	292	294	4	14
20	310	283	283	300	-27	17
21	311	313	303	294	-8	-19
22	294	309	291	293	-3	-16
23	294	287	301	284	7	-3
24	292	293	300	282	8	-11
25	289	305	303	293	14	-12
26	301	282	291	285	-10	3
27	285	282	291	279	6	-3
28	306	303	308	285	2	-18
29	289	280	298	288	9	8
30	287	303	282	289	-5	-14
Mean	290.3333333	287.5666667	292.0666667	288.3666667	1.733333333	0.8
Standard Deviation	9.300846581	9.849499666	7.464552246	6.266954016	9.401891063	10.86093919

To test the data we used the Chi-Squared Test of Independence (n=60, df=1) and calculated a Chi-Squared test statistic of 0.2715. The resulting P-value was 0.6023, meaning there was a 60.23% probability that the null hypothesis was true (Appendix B). This was not enough statistical evidence to reject the null hypothesis since the P-value was higher than our desired confidence level ($p<0.05$). This data does not conclusively show with statistical significance that the use of punctal plugs has any effect on tear osmolarity.

Further testing the data, we used the Paired t Test (N=30, df=29) and calculated a t- test statistic of -0.9928 to determine if variance in tear osmolarity readings were significant. The resulting P-value for the right eye was 0.8355, meaning there was a 83.55% probability that the null hypothesis was true given our data which stated that tear osmolarity remains the same before and after punctual occlusion. This is not enough statistical evidence to reject the null hypothesis since the resulting P-value was higher than the desired confidence level. Again, this data does not conclusively show with statistical significance that the use of punctal plugs has any effect on tear osmolarity.

To test the variance of tear osmolarity in the left eye we used the Paired t Test (N=30, df=29) and calculated a t- test statistic of -0.3967. The resulting P-value for the left eye was 0.6527, meaning there was a 65.27% probability that the null hypothesis was true. This is not enough statistical evidence to reject the null hypothesis and this data does not conclusively show with statistical significance that the use of punctal plugs has any effect on tear osmolarity.

CHAPTER 4

DISCUSSION

This study provided no evidence that there is a change in tear osmolarity in subjects who undergo short term punctal occlusion. There are limited studies on the changes in tear osmolarity with the use of punctal plugs. One 1989 and a more recent 2013 study states that punctal occlusion significantly decrease tear osmolarity in dry eye patients[8,9]. However, normal subjects were not evaluated during these studies[8,9]. An additional study evaluating the volume of tears after punctal occlusion in normals versus dry eye patients determined that volume is increased in those who have dry eye disease and remained the same in the control group[10]. Based on this information it can be hypothesized that patients with dry eye would have a lowered tear osmolarity, and normals would not exhibit any change in osmolarity. This research may point to evidence that those who do not have dry eye disease may have an intact homeostatic mechanism to maintain tear osmolarity.

Although the results of the Paired t Test proved to be statistically inconclusive, there was a difference in the calculated P-value between the right and left eye tear osmolarity variances. The right eye P-value of 0.8355, strongly points to evidence that the variance in tear osmolarity from measurement one to measurement two was minimal. We would expect this result because this was the control group with no punctal

occlusion. The P-value of the left eye, 0.6527 was also statistically inconclusive but was much lower than the right eye value. This may suggest that with more data we could prove that there is a relationship between the variance in tear osmolarity with the use of punctal plugs.

There were several limitations to this study. There was a small sample size, and participants were not specifically screened for dry eye disease via different testing mechanisms or symptom surveys. In future studies, specifically obtaining dry eye patients can aid in determining if punctal occlusion is the most effective mean for lowering tear osmolarity. Furthermore, collecting serial tear osmolarity readings may produce different results. The two day interval was chosen for this experiment due to the manufacturer stating the collagen plugs dissolve after 4-7 days. Other studies which observed dry eye patients over longer period of time proved to produce significant results that pointed towards evidence that punctal plugs are an effective way to decrease tear osmolarity[8,9]. Overall, there are very few studies analyzing tear osmolarity with the use of punctal plugs in both dry eye and normal individuals.

CHAPTER 5

CONCLUSION

Further research in this area may help provide better understanding of the effects of punctal occlusion on tear osmolarity in normal and dry eye patients. There is evidence supported by other studies to suggest that punctal plugs lower tear osmolarity[8,9]. Tear osmolarity still proves to be the best diagnostic number for diagnosis of dry eye syndrome. Future research should aim to look into what dry eye treatment method most effectively lowers tear osmolarity. Futhermore, if a homeostatic mechanism exists to maintain tear osmolarity discovering its properties and what causes disruption in dry eye patients will aid in creating new treatment modalities for those with dry eye syndrome.

REFERENCES

1. Tomlinson A. Epidemiology of dry eye disease. In: Asbell P, Lemp MA, eds. Dry Eye Disease: The Clinician's Guide to Diagnosis and Treatment. New York: Thieme, 2006:1–15.

2. International Dry Eye Workshop. Methodologies to diagnose and monitor dry eye disease. In: 2007 Report of the International Dry Eye Workshop (DEWS). Ocul Surf 2007;5(2): 108 –123.

3. Tomlinson A, Khanal S, Ramaesh K, et al. Tear Osmolarity: Determination of a referent value for dry eye diagnosis. Invest. Ophthalmol. Vis. Sci. 2006;47:4309-15

4. Sabti S, Halter JP, Braun Frankl BC, et al.. Punctal occlusion is safe and efficient for the treatment of keratoconjunctivitis sicca in patients with ocular GvHD. Bone Marrow Transplant. 2012;47:981–984.

5. Chen F, Wang J, Chen W, et al.. Upper punctal occlusion versus lower punctal occlusion in dry eye. Invest Ophthalmol Vis Sci. 2010;51:5571–5577.

6. Nava-Castaneda A, Tovilla-Canales JL, Rodriguez L, Tovilla Y, Pomar JL, Jones CE. Effects of lacrimal occlusion with collagen and silicone plugs on patients with conjunctivitis associated with dry eye. Cornea. 2003;22(1):10–4.

7. Mansour, Khaled, Leonhardt, Carolien J, Kalk, Wouter W, et. al.. Lacrimal Punctum Occlusion in the Treatment of Severe Keratoconjunctivitis Sicca Caused by Sjogren Syndrome: A Uniocular Evaluation. Cornea. 2007;26(2):147-150

8. Gilbard J, Rossi S, Azar , Heyda K. Effect of Punctal Occlusion by Freeman Silicone Plug Insertion on Tear Osmolarity in Dry Eye Disorders. CLAO Journal. 1989;15(3):216-218

9. David Eldridge, Michael Berg, Benjamin Sullivan, and William Townsend The Influence of Punctal Occlusion on Osmolarity in Dry Eye Subjects Invest. Ophthalmol. Vis. Sci. 54: E-Abstract 6048.

10. Chen F, Shen S, Chen W, Wang J, et al.. Tear Meniscus Volume in Dry Eye after Punctal Occlusion. Invest Ophthalmol Vis Sci. 2010;51(4):1965-1969.

APPENDIX A

IRB APPROVAL FORM

Ferris State University

Institutional Review Board (FSU - IRB)
Office of Academic Research
Ferris State University
1201 S. State Street-CSS 310 H
Big Rapids, MI 49307
(231) 591-2553
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To: Dr. Brian McDowell, Chelsie Rupp and Emily Emerson
From: Dr. Stephanie Thomson, IRB Chair
Re: IRB Application #140303 (Title: *Changes in Tear Osmolarity with the use of Collagen Punctal Plugs)*
Date: April 9, 2014

The Ferris State University Institutional Review Board (IRB) has reviewed your application for using human subjects in the study, "*Changes in Tear Osmolarity with the use of Collagen Punctal Plugs*" (#140303) and approved it as *expedited –category 2D* from full committee review. This approval has an expiration date of one year from the date of this letter. **As such, you may collect data according to procedures in your application until April 9, 2015**. It is your obligation to inform the IRB of any changes in your research protocol that would substantially alter the methods and procedures reviewed and approved by the IRB in this application. Your application has been assigned a project number (#140303) which you should refer to in future communications involving the same research procedure.

We also wish to inform researchers that the IRB requires follow-up reports for all research protocols as mandated by Title 45 Code of Federal Regulations, Part 46 (45 CFR 46) for using human subjects in research. We will send a one-year reminder to complete the final report or note the continuation of this study. The final-report form is available on the IRB homepage. Thank you for your compliance with these guidelines and best wishes for a successful research endeavor. Please let us know if the IRB can be of any future assistance.

Regards,

Ferris State University Institutional Review Board
Office of Academic Research, Academic Affairs

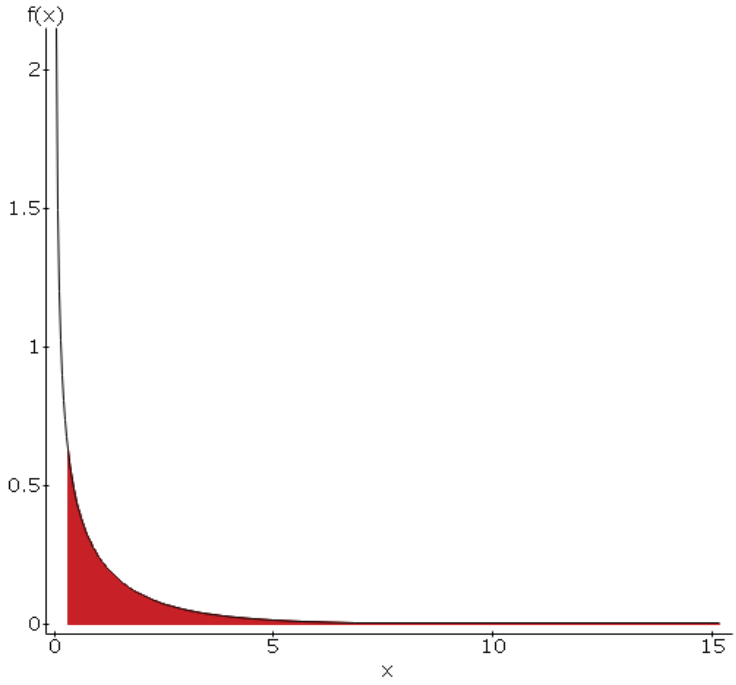
APPENDIX B

CHI SQUARED ANALYISIS

Experimental Results			
	Increase/No Change	Decrease	Total
OD	18	12	30
OS	16	14	30
Total	34	26	60

Expected Theoretical Results			
	Increase/No Change	Decrease	**Total**
OD	17.000	13.000	**30**
OS	17.000	13.000	**30**
Total	**34**	**26**	**60**

Chi-Squared Test Statistic:	**0.271493213**
Degrees of Freedom:	1
P-Value:	0.602



DF: 1

P(X ≥ 0.2714932) = 0.60233188