Original Article

Tear and Ocular Surface Profile in Adult Anophthalmic Sockets

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ABSTRACT

Objective: To determine the tear and ocular surface profile of the anophthalmic socket in relation to the contralateral normal eye.

Methods: Twenty-five adult patients with unilateral anophthalmic sockets were included into the study. They were at least 2 months post-enucleation or post-evisceration and without any topical medications on the anophthalmic socket and control eye for at least 2 weeks. Assessment was performed using the following parameters: (1) meibomian gland evaluation, (2) ocular surface staining, (3) degree of conjunctival inflammation, (4) Schirmer I and II, and (5) conjunctival impression cytology.

Results: Mucoid discharge (52%) was the most common complaint in anophthalmic sockets, followed by itchiness (40%), tearing (36%), and dryness (4%). Compared to control eyes, the anophthalmic sockets had more pronounced and statistically significant lid wiper epitheliopathy, conjunctival staining, and bulbar inflammation. Meibomian gland dysfunction, Schirmer I and II, and conjunctival impression cytology showed no difference between the 2 groups. There was a correlation between the symptoms complained and the ocular staining patterns of the anophthalmic sockets.

Conclusion: Anophthalmia predisposes to various ocular surface problems, such as a change in the composition of tears, specifically an increase in the mucin component and a decrease in the aqueous and lipid components, resulting to increased tear viscosity.

Keywords: anophthalmic socket, lid wiper epitheliopathy, Schirmer test, conjunctival inflammation, conjunctival impression cytology

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Surgical anophthalmia results from the removal of the entire eye (enucleation) or of its contents (evisceration). Various symptoms ranging from increased mucoid discharge, tearing, discomfort, pruritus, and irritation have been reported in association with the anophthalmic socket. Most of these were attributed to the tear and ocular surface abnormalities that followed after the surgery.

Many studies[1-5] have been conducted to explain the etiology of mucoid discharge; by far, the most common and bothersome symptom related to the anophthalmic socket. There are two theories on the etiology of mucoid discharge; namely: 1) bacterial growth, typical of an infectious process; and 2) tear dysfunction.

The theory of bacterial growth states that there are pathogenic bacteria causing the mucoid discharge in anophthalmia. Therefore, there is a need to treat the mucoid discharge in anophthalmic sockets with antimicrobials. However, Vasquez and Lindberg disproved this theory of abnormal microbial causation in a bacteriologic study on symptomatic and asymptomatic anophthalmic sockets. They found no significant difference between the bacterial flora of anophthalmic sockets and that of the contralateral normal eye.[3] Similarly, a study (Silos SMJ, Pe-Yan MRL, Nievera LFC. Microbiologic study of anophthalmic sockets in Filipino patients; unpublished) done in 2001 at the Philippine General Hospital showed no difference in the bacterial flora between anophthalmic sockets and normal eyes.

The second theory of tear dysfunction is founded on the assumption that the normal anatomical architecture of the cornea and conjunctiva is disrupted after enucleation or evisceration. Available literature implicated a problem in either the aqueous or the mucin components of tears.[1,2,4-6]

In studies on the aqueous component, anophthalmic patients were presumed to have decreased aqueous production, consequently leading to accumulation of mucin and lipids and resulting in increase in mucus viscosity.[4] Allen and associates documented deficient aqueous production in anophthalmic sockets, with decrease in the mean scores for Schirmer I (total tears) and II (basic tears) tests.[1] Kim and colleagues had purported that the tear meniscus height and tear meniscus volume in artificial eyes measured by Fourier-domain optical coherence tomography was significantly lower than that of normal eyes, supporting aqueous tear deficiency as a cause of mucoid discharge.[2] However, this was not consistent with their results that showed no statistically significant difference in the Schirmer test scores between normal and artificial eyes.[2] Both studies have attributed decreased tear production to the abolished corneal reflex secondary to anophthalmia.[1,2] The aqueous component is important in the self-cleansing mechanism of the normal eye. In normal conjunctiva, mucus produced by goblet cells form networks of strands that are broken into coarser strands with each blink. Aqueous, together with the blink mechanism, removes the mucus strands from the corneal surface.[4] Decreased aqueous production, coupled with the relatively dry surface of the ocular prosthesis, abolishes the self-cleansing mechanism in anophthalmic socket leading to mucoid discharge.

In studies on the mucus component, the conjunctival cytology study by Kim theorized that decreased goblet cell density and increased nucleus-to-cytoplasm ratio associated with squamous metaplasia led to decrease mucus production.[6] They attributed these cytology changes to constant irritation of prolonged prosthesis wear.[6] Their results, however, had been challenged by contrary results of other studies showing no significant changes in goblet cell density or epithelial cell morphology in anophthalmia.[5]

All previous studies have concluded that the etiology of increased mucus discharge was multifactorial. Therefore, the use of limited methods for evaluation could result to inconsistencies in explaining the etiology of increased mucus discharge in anophthalmia. Thus, our study investigated the role of tear dysfunction in the persistence of mucoid discharge. It utilized modified methods of assessing dry eye and inflammation, such as (1) meibomian gland evaluation, (2) conjunctival staining, (3) posterior lid margin staining, (4) conjunctival inflammation grading, (5) Schirmer testing, and (6) conjunctival impression cytology.

METHODOLOGY

Adult patients with unilateral anophthalmic sockets seen at the University of the Philippines - Philippine General Hospital (UP-PGH) were recruited into the study from May 2010 to July 2011.

They were at least 2 months post-enucleation or post-evisceration and at least 2 weeks without any topical medications on the anophthalmic socket. Cases were defined as the anophthalmic sockets without gross abnormalities with or without prosthetic conformers. Control eyes were defined as the contralateral eyes that had no gross abnormalities.

Patients were excluded if any of the following conditions existed: (1) use of topical antibiotics, steroids, artificial tears applied to anophthalmic socket and control eye within 14 days prior to examination; (2) gross abnormalities, such as lid lacerations, lid malposition, chalazion, hordeolum, conjunctivitis, or tearing due to nasolacrimal duct obstruction; (3) other recent ocular surgery (within the last 2 months); (4) implant extrusion or exposure; (5) contracted socket; and (6) shallow fornix in the involved socket.

Two weeks after discontinuation of topical medications, the patient underwent a series of tests conducted by a single investigator. An initial interview and screening was done to document the patient's demographic data (gender, age), type of surgery, laterality, time interval between surgery and screening, presence or absence of conformer, frequency of medications used, prosthesis care, and present complaints. The following tests were done: (1) meibomian gland evaluation, (2) conjunctival staining, (3) posterior lid margin staining, (4) conjunctival inflammation grading, (5) Schirmer I and II tests; and (6) modified conjunctival impression cytology, performed at least 1 week after the initial ocular examination and sent to the ocular pathology laboratory of the Institute of Ophthalmology.

Meibomian Gland Evaluation

A single slitlamp biomicroscope (Topcon SL D7, Tokyo Japan) was used to examine all patients. Both the upper and lower lids were examined at 16x magnification. The meibomian gland openings were identified and checked for inspissated orifices. Reference photos were used to determine inspissated meibomian glands (Figure 1).

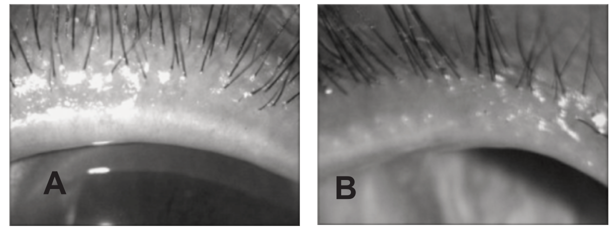


Figure 1. Meibomian gland evaluation showing no inspissated (A) and inspissated orifices (B).

Oxford Grading Scheme[7]

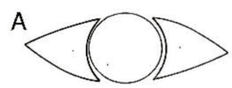
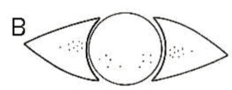
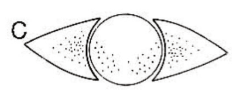
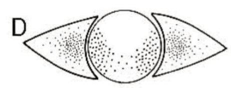
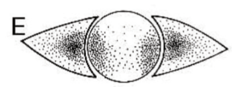
PANEL	GRADE	CRITERIA
	0	≤ panel A
	I	≤ panel B and > A
	II	≤ panel C and > B
	III	≤ panel D and > C
	IV	≤ panel E and > D
>E	V	> panel E

Figure 2. Modified Oxford Grading Scheme illustrating the different conjunctival staining patterns.

Ocular Surface Staining

A. Conjunctival Staining Patterns (CSP)

A standardized reporting of staining patterns, the Oxford Grading Scheme, had been modified for purposes of this study.[7] Each eye was assigned a grade from 0 to 5 based on the pattern of fluorescence noted on slitlamp biomicroscopy (Figure 2). A single drop of saline was placed on a 2% fluorescein-impregnated strip. The lower lid was pulled down and the strip tapped onto the lower tarsal conjunctiva. The conjunctival staining pattern was graded.

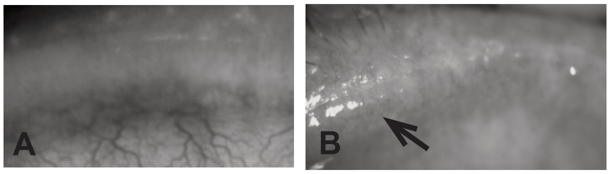


Figure 3. Posterior lid margin showing no staining (A) and PLM sign (B).

B. Posterior Lid Margin Staining (PLM)

A single drop of saline was placed on a lissamine-impregnated strip. The lower lid was pulled down and the strip tapped onto the lower tarsal conjunctiva. The upper posterior lid margin was checked for the presence or absence of staining (Figure 3).

Conjunctival Inflammation

The degree of bulbar conjunctival inflammation was assessed based on clinical findings of injection and edema.[8,9] A grade of 1 to 4 was given based on the appearance of the conjunctival vessels and the presence or absence of edema. Tarsal conjunctival inflammation was graded based on the criteria of Saini.[6,10] The slitlamp settings were standardized at 40X using the smallest spot size of 0.2 mm.

Schirmer Tests

Schirmer II without anesthesia, a measure of reflex tear production, was performed using a Schirmer strip placed at the lower cul de sac for 5 minutes. A normal Schirmer II was set at >15 mm in 5 minutes. Schirmer I, a measure of basal lacrimation, was done after topical proparacaine hydrochloride 0.5% (Alcaine, Alcon-Couvreur) was instilled. A normal basic secretion was set at >10 mm in 5 minutes.[11]

Conjunctival Impression Cytology

A cellulose acetate filter (Millipore PVT LTD), with pore size of 22 microns and cut into 7 by 7 sq mm, was used to impregnate against the conjunctival surface. The technique of impression cytology was adapted and modified from Tseng.[12]

All data were recorded and collated using Excel (Microsoft Corp., Redmond WA, USA). The study protocol was approved by the ethics review board of PGH.

RESULTS

A total of 25 patients with unilateral anophthalmic sockets were included in the study. Twenty-one (84%) were males and 4 females. Age ranged from 19-80 years old with median of 38 years. Seven underwent enucleation and 18 evisceration. Twelve had right and 13 left anophthalmic sockets. Mean interval between surgery and follow-up was 120 (±47) days.

At the time of initial evaluation, majority of the patients (92%) wore their conformers daily even during sleep and 8% had no conformers. Twenty-three (84%) patients applied some medications 3x daily as instructed by their doctors. Only 20% of patients cleaned the outer part of their conformers (daily or weekly) with soap and water while 80% wiped discharge from the lids and conformers as needed. Twenty-two (88%) patients had complaints regarding their anophthalmic sockets, such as early morning whitish, mucoid, discharge (52%), occasional itchiness (40%), tearing (36%), and dry sensation (4%).

Four (16%) anophthalmic sockets and 2 (8%) control eyes had inspissated meibomian glands indicating meibomian gland dysfunction (MGD). Using the McNemar's test, there was no significant difference ($p=0.32$) in the incidence of MGD between control and anophthalmic sockets.

Conjunctival staining with fluorescein was seen in 24 (96%) anophthalmic sockets: 12 had grade 1 (minimal) and another 12 had grade II (mild) staining. Grades III and IV were not observed in this group. In the control eyes, 5 had grade 1 staining while the rest exhibited no staining (grade 0). Using the Wilcoxon matched-pairs signed-rank test, there was a statistically significant difference in the conjunctival staining patterns of anophthalmic sockets and control eyes ($p<0.0001$).

Posterior lid margin staining with lissamine green showed 25 (100%) anophthalmic sockets with posterior lid margin staining or lid wiper epitheliopathy (LWE), compared to only 8 (32%) of control eyes. Using McNemar's test, there was a statistically significant difference in the incidence of LWE in anophthalmic sockets compared to control eyes ($p<0.0001$). Of the 8 patients with bilateral LWE, 3 (38%) had abnormal Schirmer I results.

Bulbar conjunctival inflammation was noted in all 25 (100%) anophthalmic sockets, with 9 (36%) having grade 2 and 16 (64%) grade 3 scores. Among control eyes, 24 (96%) had grade 1 and 1 (4%) grade 3 scores. Using Wilcoxon matched-pairs signed-rank test, there was a statistically significant difference in the incidence of bulbar conjunctival inflammation in anophthalmic sockets compared to control eyes ($\rho<0.001$).

Tarsal conjunctival inflammation was noted in all the anophthalmic sockets: 11 (44%) had grade 1 and 14 (56%) grade 2 scores. Among control eyes, 13 (52%) had grade 1 and 12 (48%) grade 2 scores. Using Wilcoxon matched-pairs signed-rank test, there was no statistically significant difference in the incidence of tarsal conjunctival inflammation in anophthalmic sockets compared to control eyes ($\rho=0.57$).

In Schirmer II test, a mean of 14.93 (±8.43) mm was seen in 23 anophthalmic sockets wearing conformers, mean of 26 mm in 2 anophthalmic sockets not wearing conformers, and mean of 17.40 (±9.22) mm in 23 control eyes. Using paired t-test, there was no statistically significant difference in the incidence of dry eye using Schirmer II test between the anophthalmic sockets wearing conformers and the control eyes ($p=0.54$).

The repeat Schirmer II test done on 23 anophthalmic sockets with conformers showed a mean of 18.36 (±8.31) mm after the conformers were taken off. Using paired t-test, there was a statistically significant difference in the Schirmer II test results in anophthalmic sockets with conformers and after they were taken off ($p=0.05$).

In Schirmer I test with topical anesthetic, a mean of 13.28 (±6.33) mm was seen in the 25 anophthalmic sockets without conformers and a mean of 14.18 (±8.32) mm in the 25 control eyes. Using paired t-test, there was no statistically significant difference ($p=0.54$) between the 2 groups.

One (5%) specimen was excluded from cytology examination because it was deemed unfit for evaluation. All 24 remaining impressions from anophthalmic sockets were stage 0. Five impressions from the control group were graded as stage 1. Using Wilcoxon matched-pairs signed-rank test, there was no statistically significant difference ($p=1.0$) between the 2 groups.

DISCUSSION

The most common symptoms in the anophthalmic socket were the presence of mucoid discharge (52%), itchiness (40%), and tearing (36%) which were similar to the findings of other studies.[1] Dryness (16%) was present and confirmed by the conjunctival staining patterns, the posterior lid margin signs, and the bulbar conjunctival inflammation. The conjunctival staining and LWE in anophthalmic sockets could be attributed to the constant friction between the conjunctival epithelium of the upper lid and the conformer.[13] Three patients with bilateral LWE and abnormal Schirmer I results also showed the presence of preexisting dry eye prior to surgery. The important structural relationship between the conjunctiva of the upper lid and surface of the cornea needed for tear film physiology is obviously absent in anophthalmic sockets.

Bulbar conjunctival inflammation was more pronounced among anophthalmic sockets, similar to other studies. This could be due to constant mechanical irritation of the overlying conformer or irritation from stasis of tears behind the prosthesis, leading to chronic mucoid discharge.

Our results showed no significant difference in Schirmer I and II between anophthalmic sockets and their contralateral eyes, suggesting that tear production in the anophthalmic socket was comparable with the control, similar to the study of Kim.[2] Other studies, however, showed the presence of severe tear deficiency (Schirmer <5 mm) in up to 50% of patients with anophthalmic sockets.[1]

After removal of the conformers in anophthalmic sockets, Schirmer II showed higher values, suggesting that the basal and reflex tear production were still sufficient and that the absence of the corneal reflex, initially believed to cause tear dysfunction, had no or minimal effect on the incidence of tear dysfunction. The relatively lower values of Schirmer II prior to conformer removal may be explained by the mechanical pooling of tears behind the ocular prosthesis as theorized by Kim and associates.[2]

All the impressions from the anophthalmic sockets exhibited normal goblet cell density and morphology. Among the control group, 5 demonstrated early loss of goblet cells. Altogether, there was no significant difference in the conjunctival impression between the anophthalmic socket and its contralateral eye in this study. The short duration of the anophthalmic condition (average 4 months) likely would not show any definite changes. In contrast, long-term ocular prosthesis wear with average of 10 years showed squamous metaplasia and diminution of the goblet cell population.[6]

In correlating the symptoms elicited in anophthalmic sockets and the results obtained with the different examinations, only lid wiper epitheliopathy and conjunctival staining were present in all (100%) anophthalmic sockets. Majority of them experienced increased mucoid discharge.

Anophthalmia, in itself, predisposes to various ocular surface problems and complaints, such as increased mucoid discharge, which was the most common in this study. Anatomical disruption due to enucleation or evisceration did not immediately lead to decreased tear production nor translate to conjunctival cytologic changes in the early postoperative period. However, there appeared to be a change in the composition of tears, specifically an increase in the amount of mucin secondary to ocular inflammation and a decrease in the amount of aqueous brought about by the presence of the conformer. These led to increase in tear viscosity and the problem of increased mucoid discharge early in the condition.

A larger sample size and longer follow-up will be needed to determine the long-term changes associated with the anophthalmic socket.

REFERENCES

1. Allen L, Kolder HE, Bulgarelli EM, Bulgarelli DM. Artificial eye and tear measurements. *Ophthalmology* 1980;87:155-157.
2. Kim SE, Yoon JS, Lee SY. Tear measurement in prosthetic eye users with fourier-domain optical coherence tomography. *Am J Ophthalmol* 2010;149:602-607.
3. Vasquez RJ, Linberg JV. The anophthalmic socket and the prosthetic eye: A clinical and bacteriologic study. *Ophthal Plast Reconstr Surg* 1989;5:277-80.
4. Adams A. The morphology of human conjunctival mucus. *Arch Ophthalmol* 1979;97:730-734.
5. Chang WJ, Tse DT, Rosa RH, et al. Conjunctival cytologic features of giant papillary conjunctivitis associated with ocular prosthesis. *Ophthal Plast Reconstr Surg* 2005;21:39-45.
6. Kim JH, Lee MJ, Choung H-K, et al. Conjunctival cytologic features in anophthalmic patients wearing an ocular prosthesis. *Ophthal Plast Reconstr Surg* 2008;24:290-295.
7. Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. *Cornea* 2003;22:640-50.
8. Miyazaki D, Tominaga T, Yakura K, et al. Conjunctival mast cell as a mediator of eosinophilic response in ocular allergy. *Molecular Vision* 2008;14:1525-1532.
9. Riley HD. Slit lamp illumination types associated ocular conditions and slit lamp examination procedures. *Indiana University School of Optometry Lecture Notes*. January 2007: http://www.opt.indiana.edu/riley/HomePage/1lecturenotes.html> (cited April 9, 2010).
10. Saini JS, Rajwanshi A, Dhar S. Clinico-pathological correlation of hard contact lens related changes in tarsal conjunctiva by impression cytology. *Acta Ophthalmol* 1990;68:65-70.
11. Skuta GL, Cantor LB, Weiss JS. Diagnostic approach to ocular surface disease. *External Disease and Cornea*. American Academy of Ophthalmology, 2008-2009:62-63.
12. Tseng SCG. Staging of conjunctival squamous metaplasia by impression cytology. *Ophthalmology* 1985; 92:728-33.
13. Korb DR, Herman JP, Greiner JV, et al. Lid wiper epitheliopathy and dry eye symptoms. *Eye and Contact Lens* 2005;31:2-8.
14. Gillan WDH. Conjunctival impression cytology: a review. *S Afr Optom* 2008;67:136-141.
15. Singh R, Joseph A, Umapathy T, et al. Impression cytology of the ocular surface. *Br J Ophthalmol* 2005;89:1655-1659.
16. Allansmith MR, Ostler HB, Butterworth M. Concomitance of bacteria in various areas of the eye. *Arch Ophthalmol* 1969;82:37-42.
17. Bang BG, Bang FB. Responses of upper respiratory mucosae to dehydration and infection. *Ann NY Acad Sci* 1963;106:625-640.
18. Clodius L, Schozel E, Martin O. Artificial eyes: surface changes following use as observed by the scanning electron microscope. *Chirurgia Plastica* 1981;6:17-23.
19. Dahl A. Dry eye syndrome overview. December 5, 2007: http://www.emedicinehealth.com/dry_eye_syndrome/article_em.htm (accessed February, 13 2010).
20. Egbert PR, Lauber S, Maurice DM. A simple conjunctival biopsy. *Am J Ophthalmol* 1977;84:798-801.
21. Glasgow B. Conjunctiva. Medrounds Publications. October 12, 2005: www.medrounds.org/ocular-pathology-study-guide (accessed February, 13, 2010).
22. Goto E, Koji E, Atsushi S, et al. Tear evaporation dynamics in normal subjects and subjects with obstructive meibomian gland dysfunction. *Invest Ophthalmol Vis Sci* 2003;44:553-9.
23. Hughes MO. A pictorial anatomy of the human eye/anophthalmic socket: a review for ocularists. *J Ophthalmic Prosthetics* 2007;12:51-63.
24. Jordan A, Baum J. Basic tear flow. Does it exist? *Ophthalmology* 1980;87:920-30.
25. Knop E, Brewitt H. Conjunctival cytology in asymptomatic wearers of soft contact lenses. *Graefes Arch Clin Exp Ophthalmol* 1992;230:340-7.
26. Miller SD, Smith RE, Dippe DW, et al. Bacteriology of the socket in patients with prostheses. *Can J Ophthalmol* 1976; 11:126-129.
27. Murchison AP, Bernardino CR. Evaluation of the anophthalmic socket. *Rev Ophthalmol* 2006;13:76-80.
28. Nyboe JC, Fahmy JA. The bacterial flora of the conjunctival anophthalmic socket in glass-prosthetic carriers. *Acta Ophthalmol* 1974;52:801-809.
29. Paranhos RMZF, Batalhao CH, Semprini M, et al. Evaluation of ocular prosthesis biofilm and anophthalmic cavity contamination after use of three cleansing solutions. *J Appl Oral Sci* 2007;15:33-38.
30. Prydal JI, Campbell F. Study of precorneal tear film thickness and structure by interferometry and confocal microscopy. *Invest Ophthalmol Vis Sci* 1992;33:1996-2205.
31. Reddy M, Reddy PR, Reddy SC. Conjunctival impression cytology in dry eye states. *Indian J Ophthalmol* 1991;39:22-24.
32. Saedon H, Cheung D. Occult traumatic nasolacrimal duct obstruction causing anophthalmic socket contraction presenting 20 years later: a case report. *Cutan Ocul Toxicol* 2008;27:87-89.
33. Sangwan VS, Tseng SCG. New perspectives in ocular surface disorders. An integrated approach for diagnosis and management. *Indian J Ophthalmol* 2001;49:153-168.
34. Schiffman RM, Christianson MD, Jacobsen G, et al. Reliability and validity of the ocular surface disease index. *Arch Ophthal-*

mol 2000;118:615-621.

35. Song JS, Oh J, Baek SH. A survey of satisfaction in anophthalmic patients wearing ocular prosthesis. *Graefe' Arch Clin Exp Ophthalmol* 2006;244:330-335.
36. Tseng SCG, Hatchell D, Tierney N, Huang AJW, Sun TT. Expression of specific keratin markers by rabbit corneal, conjunctival, and esophageal epithelia during vitamin A deficiency. *J Cell Biol* 1984;99:2279-86.
37. Tseng SH, Chen YT, Cheng HC, et al. Impression cytology study of conjunctival epithelial phenotypes on the healing ocular surface after pterygium excision. *Cornea* 2001;20:244-50.
38. Vardizer Y. Favorable effects of lacrimal plugs in patients with an anophthalmic socket. *Orbit* 2007;26:263-266.