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Standardized clinical evaluation of dry anophthalmic socket syndrome in a real-world approach

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ABSTRACT

Purpose: To assess which signs and eye prosthesis care habits are related to subjective discomfort in patients with dry anophthalmic socket syndrome (DASS), using standardized tools from daily practice.
Methods: 62 anophthalmic sockets were compared with their healthy fellow eye using the Standard Patient Evaluation of Eye Dryness (SPEED) score. The correlations between SPEED questionnaire and the prosthesis care, discharge characteristics score, conjunctival inflammation score, meibomian gland dysfunction (MGD) scores and Schirmer I test were studied.
Result: The anophthalmic sockets group achieved a higher SPEED test score ($p < 0.01$), discharge score ($p < 0.01$), conjunctival inflammation score ($p < 0.01$), MGD scores ($p < 0.01$) and lower Schirmer I test ($p < 0.01$) compared with their fellow, healthy eye. Patients with a prosthesis replacement of one year or less, those with a current fit time of one year or less and those with a cleaning frequency above one month reported better SPEED, ($p < 0.01$), conjunctiva inflammation ($p < 0.01$) and MGD scores ($p < 0.01$).
Conclusion: Most anophthalmic patients suffer mild to severe DASS, which seems related to discharge, conjunctival inflammation and MGD. Moreover, certain practices related to the care of the prosthesis such as replacing with a frequency lower than yearly, current fitting time inferior to one year and a removing and cleaning regime above one month, were related to a lower discomfort sensation, conjunctival inflammation and MGD. Clinicians should consider the DASS when facing patients with anophthalmic socket and discomfort symptoms.

1. Introduction

The loss of an eye is an event of great impact in the life of a patient that entails important changes in their daily routine, such as being involved in the maintenance of the ocular prosthesis and the anophthalmic cavity [1]. When writing about evisceration and enucleation procedures, most scientific literature is focused on surgical techniques, implants, or even complications, however, the way that the cavity changes over time, and how patients and clinicians may adapt to these changes, is becoming an issue of increasing interest [1–8]. Pine

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et al. [1] described how the concerns of patients with ocular prostheses change over time. It has been described that the main concern for these patients is the health of the remaining eye, however, other issues are also present and must be considered. During the first period after losing an eye, patients are more concerned about the loss of stereopsis and peripheral vision, but other issues more related to discomfort, such as discharge and dryness, increase in importance over time [1].

Increasing attention has been placed on the dry anophthalmic socket syndrome (DASS) recently [9,10]. This syndrome has been proposed to be caused by multiple reasons such as reduced tear production due to the disturbance in tear reflex, meibomian gland dysfunction (MGD) caused by lid margin abnormalities, loss of globet cells, eyelid laxity, and lagophthalmos [2,5,9–11]. These factors contribute to a loss of tear film homeostasis and conjunctival inflammation that generate chronic discomfort and ocular surface dysfunction [10].

The purpose of this study is to evaluate which signs and care routine of the ocular prosthesis are associated with subjective discomfort in patients with anophthalmic sockets, using standardized real-world measurements.

2. Materials and methods

2.1. Design

This was a cross-sectional, observational, and non-interventional study. Sixty-two patients were enrolled. For each patient, data were collected from the anophthalmic socket and the remaining eye, (one hundred twenty-four *eyes* – note that the term "eye" will refer to both the anophthalmic sockets and the remaining eyes to facilitate the reading of the paper). The study was conducted in two tertiary hospitals, in adherence to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee for Biomedical Research of the Province of Granada (*0218-N-23*). Informed consent was obtained from all the patients after an explanation of the study. Inclusion criteria were (1) patient with anophthalmic socket and eye prosthesis for at least 6 months and (2) age $\geq$ 18 years. Exclusion criteria included (1) patients who used anti-inflammatory or antibiotic medication in either eye during the last week, (2) patients with complications of the anophthalmic socket that can be related to discomfort symptoms such as conjunctival cyst, implant exposure, or chronic conjunctivitis, (3) patients with an active infection in either *eye*, (4) patients with eyelid malposition and (5) patients wearing bilateral, defective, or poor fitting prosthetic eyes.

Firstly, patients completed a face-to-face interview using a three-section questionnaire:

Section 1 included demographic data and information about cavity and prosthetic care habits. Data were gathered on gender, age, anophthalmic side, time since surgery in years, prosthesis replacement frequency in years, current prosthesis fitted time in years, last prosthesis professional polishing in months, prosthesis professional polishing frequency in months, prosthesis cleaning frequency, and prosthesis cleaning frequency reason.

Section 2 included a standardized dry eye questionnaire. Patients filled in the Spanish version of Standard Patient Evaluation of Eye Dryness (SPEED) [12], separately for the anophthalmic socket and for the healthy fellow eye, always beginning with the right side.

Section 3 evaluated the anophthalmic socket discharge characteristics using the visual analogue scale proposed by Pine et al., [6] which is based on four different categories: frequency, colour, volume and viscosity.

Following the survey, the palpebral conjunctival inflammation was graded from 0 to 4 using the same scale described by Pine et al. [6]. In addition, MGD was assessed using the following maneuvers, performing the most invasive test last [12]. First of all, the eyelid margin inflammation was assessed with the standardized classification of Foulks-Bron [13]. The sum of these three parameters gives a measure of meibomian gland inflammation (from 0 to 9). In a second step, meibomian glands expression was assessed as follows: ten central glands of the lower eyelid were compressed digitally, and discharge was evaluated using three criteria, quality, volume and compressibility. The quality was scored on a scale from 0 to 3 (0 clear and liquid discharge, 1 thicker, 2 granular, 3 solid). The volume was also evaluated on a scale from 0 to 3, where 3 reflects that there is no discharge. The compressibility of the gland was determined according to the amount of force that is necessary to squeeze the glands and was evaluated on a scale from 0 to 3 according to the pressure needed (0 minimal, 1 light, 2 moderate, 3 heavy). The sum of these three parameters forms the measure of the secretory component of the meibomian glands on a scale from 0 to 9 [12].

Finally, Schirmer I test was performed in the anophthalmic socket and the fellow eye using prepackaged, standardized, sterile 35 mm $\times$ 5 mm filter paper strips (I-DEW Tearstrip, Mitron). Strips were placed over the lateral third of the lower lid and results were determined after five minutes by evaluating the amount of wetting measured in millimeters.

2.2. Statistical analysis

Statistical analysis was performed with SPSS statistical software (version 26.0, IBM Corp, Armonk, New York, USA). Descriptive statistics were median and interquartile range as the distribution of all variables, as assessed with the Kolmogorov-Smirnov test, was found to be non-normal. Differences in qualitative variables were assessed with the Chi-square test. The differences between the anophthalmic socket and the healthy eyes group and the comparisons of the two groups were evaluated with the U of Mann Whitney for all variables. Additional two group comparisons were made for prosthesis replacement (cut off in one year), actual prosthesis time (cut off one year) and cleaning frequency (cut off one month), all with the U of Mann Whitney. The correlation analysis was conducted with the Spearman Rho test. For all tests, the level of significance was established at 95 % (P value $<$ 0.05). The sample size was evaluated with the GRANMO® calculator (Institut Municipal d'Investigació Mèdica, Barcelona, Spain. Version 7.12). The two-sided test was used. The risk of alpha and beta was set at 5 % and 20 %, respectively. The estimated standard deviation (SD) of the differences was set at 0.10, the expected minimum SPEED difference was set in 0.06 and finally the loss to follow-up rate was set in 0.10. This achieved a recommended sample size of 49 anophthalmic sockets and 49 healthy eyes.

3. Results

Sixty-two anophthalmic sockets and sixty-two healthy eyes from sixty-two patients were included in this study. All demographic data are presented in Table 1, including anophthalmic side, time from surgery, prosthesis replacement, current prosthesis mean fitted time, frequency and time of last professional polishing, and prosthesis cleaning frequency and reason for that. The comparison between anophthalmic socket and healthy eyes within the SPEED test, discharge score, conjunctival inflammation grade, eyelid morphology score, meibomian gland expression, and Schirmer I test are presented in Table 2.

Regarding the qualitative analysis of dry eye syndrome (DES), 20 out of the 62 anophthalmic sockets (32.2 %) were classified as without or mild DES, 7 anophthalmic sockets (11.2 %) with moderate DES, and 35 anophthalmic sockets (56.5 %) with severe DES compared to the healthy fellow eye. In this later group, 49 eyes (79 %) reported without or mild DES, 9 eyes (14.5 %) with moderate DES and 4 eyes (6.4 %) with severe DES.

According to studies published by Pine et al. [7] and Bonaque-González et al. [14], the longevity of an ocular prosthesis ranges between 2 and 6 years in adults; however, this could be supported by professional re-polishing annually to assess the prosthesis for damage, to re-assess fit and to assess the socket. Additionally, they described that the prosthesis should not be removed and cleaned more frequently than monthly as mechanical irritation caused by removing the prosthesis and

Table 1
Demographics of anophthalmic patients.

Gender	
Male, *n* (%)	60 (48.4 %)
Female, *n* (%)	64 (51.6 %)
Age (years)	63(25)
Anophthalmic Side	
Right, *n* (%)	33 (53.2 %)
Left *n* (%)	29 (46.7 %)
Surgery Time (years)	22(40.5)
Prosthesis Replacement (years)	3(2)
Never Replace, *6* (9.67 %)	
Current Prosthesis Mean Fitted Time (years)	2(1.9)
Last Prosthesis Professional Polishing (months)	12(21)
Never Polished, *37* (59.67 %)	
Prosthesis Professional Polishing Frequency (months)	12(19)
Never Polished, *37* (59.67 %)	
Prosthesis Cleaning Frequency	
Diary, *n* (%)	24 (38.7 %)
Weekly, *n* (%)	18 (29.0 %)
Monthly, *n* (%)	12 (19.4 %)
Bimonthly, *n* (%)	6 (9.7 %)
Semiannual, *n* (%)	2 (3.2 %)
Prosthesis Cleaning Frequency Reason	
Secretions, *n* (%)	34 (54.8 %)
Inconvenience, *n* (%)	10 (16.1 %)
Ocularist Guideline, *n* (%)	16 (25.8 %)
Personal Custom, *n* (%)	2 (3.2 %)
Quantitative variables were presented within mean ± standard deviation (minimum to maximum range)	

Table 2
SPEED test, conjunctival inflammation, anterior blepharitis, eyelid morphology, secretions, gland expression, Schirmer test between anophthalmic and healthy eye.

Characteristics	Anophthalmic Eye	Healthy Eye	*P value U of Mann Whitney*
SPEED Test[1] *(Score Points)*	8.0(8.0)	2.0(4.0)	*<0.01 U = 725.0*
Conjunctival Inflammation *(Grade 0 to 4)*	1.0(1.0)	1.0(1.0)	*<0.01 U = 1056.0*
Anterior Blepharitis *(Score Points 0 to 9)*	4.0(2.2)	2.0(3.0)	*<0.01 U = 1014.0*
Eyelid Morphology *(Score Points 0 to 9)*	3.0(3.0)	1.0(3.0)	*<0.01 U = 1144.0*
Secretions (Score Points 4 to 40)	10.5(10.5)	4.0(0.0)	*<0.01 U = 471.5*
Gland Expression *(Score Points 0 to 9)*	3.0(2.0)	3.0(3.0)	*<0.01 U = 1278.0*
Schirmer Test[1] *(millimeters)*	9.0(7.5)	15.0 (10.0)	*<0.01 U = 2700.0*

the introduction of foreign materials and bacteria into the socket occurs with cleaning and should be minimized. Despite these recommendations, there are no studies that evaluate its effectiveness for post-adaptation care of an ocular prosthesis.

For the analysis of the anophthalmic sockets, regarding the frequency of the prosthesis replacement, the sample was split into 2 groups: short-term replacement (data of one year) and long-term replacement (data combination of 2, 3, and 4 years). For the analysis of the professional polishing, the sample was split into two groups: short-term (data combination of 3, 6 and 12 months) and long-term (data combination of 18 and 24 months). And for the cleaning frequency, the sample was split into high cleaning frequency (data combination of dairy, weekly, and monthly) and low cleaning frequency (data combination of bi-monthly and semiannual). To combine data across different time frames within these groups, the mean for all cases was calculated, ensuring a uniform approach to assessing the impact of replacement frequency on patient outcomes.

According to the results, short term replacement reported better SPEED, discharge score, conjunctival inflammation, eyelid morphology and Schirmer I test (Table 3). The last professional polishing did not achieve statistically significant differences within any variables when the comparison was done between two groups. However, when the variables were compared by high cleaning frequency and low cleaning frequency statistically significant differences were found in favor of low frequency (Table 3).

Using the Spearman rank order correlation, significant associations were found between the SPEED score and the discharge score ($\rho = 0.459$, $p < 0.01$), conjunctival inflammation ($\rho = 0.432$, $p < 0.01$), meibomian gland expression score ($\rho = 0.27$, $p < 0.01$) and finally inverse correlation within age ($\rho = -0.315$, $p = 0.01$). The time from the last prosthesis replacement was also correlated with the SPEED test ($\rho = 0.320$, $p = 0.01$), conjunctival inflammation score ($\rho = 0.373$, $p < 0.01$), meibomian gland expression score ($\rho = 0.335$, $p < 0.01$), and inversely correlated within the Schirmer I test ($\rho = -0.291$, $p = 0.02$). No other statistically significant differences were found.

4. Discussion

The results of the higher SPEED test score in the anophthalmic site

Table 3
Variables comparison by prosthesis maintenance.

Prosthesis Replacement			
Characteristics	Short-term (1 year)	Long-term(2, 3 and 4 years)	*P value U of Mann Whitney*
SPEED Test *(Score Points)*	3.0(4.0)	9.0(8.0)	*<0.01 U = 282.0*
Conjunctival Inflammation *(Grade 0 to 4)*	1.0(1.0)	1.0(1.0)	*0.02 U = 259.5*
Anterior Blepharitis *(Score Points 0 to 9)*	1.0(4.0)	4.0(2.0)	*<0.01 U = 276.0*
Eyelid Morphology *(Score Points 0 to 9)*	1.0(3.0)	3.0(2.0)	*0.02 U = 261.0*
Secretions (Score Points 4 to 40)	4.0(4.0)	13.0(9.5)	*<0.01 U = 297.5*
Schirmer Test *(millimeters)*	17.0(3.0)	9.0(6.0)	*<0.01 U = 35.5*
Actual Prosthesis Polishing Time			
Characteristics	Short-term (3, 6, and 12 months)	Long-term (18 and 24 months)	*P value U of Mann Whitney*
SPEED Test *(Score Points)*	7.0(9.5)	9.0(5.5)	*0.01 U = 519.5*
Conjunctival Inflammation *(Grade 0 to 4)*	1.0(1.0)	2.0(1.5)	*0.02 U = 539.5*
Gland Expression *(Score Points 0 to 9)*	3.0(2.0)	4.0(2.5)	*0.04 U = 490.5*
Cleaning Frequency			
Characteristics	High frequency (daily, weekly and monthly)	Low frequency (bi-monthly and semiannual)	*P value U of Mann Whitney*
SPEED Test *(Score Points)*	8.5(8.0)	4.0(8.2)	*0.14 U = 146.5*
Conjunctival Inflammation *(Grade 0 to 4)*	1.0(1.0)	1.0(0.7)	*0.02 U = 120.5*
Anterior Blepharitis *(Score Points 0 to 9)*	4.0(2.0)	3.0(3.2)	*0.04 U = 126.0*
Eyelid Morphology *(Score Points 0 to 9)*	3.0(2.2)	1.5(2.7)	*0.04 U = 123.5*

compared to the healthy fellow eye, and the fact that 42 patients (67.7 %) had mild or severe DES are consistent with other studies previously reported and suggest that most anophthalmic patients suffer from DASS [9]. The SPEED test was also correlated with other parameters, such as discharge score, conjunctival inflammation, meibomian gland compression, current prosthesis mean fitting time, and inverse correlation with age. These findings suggest that the SPEED test could be a tool for evaluating the symptoms of patients with anophthalmic socket. Although there is no questionnaire specifically designed for these patients, this test may have advantages compared to others previously used to assess DASS, such as the Ocular Surface Disease Index (OSDI) and the Symptom Assessment iN Dry Eye (SANDE), because it is not complicated by presenting items intended to assess visual quality and acuity [9,12,15–17].

Our findings indicate that patients have significantly higher discharge scores in the anophthalmic socket compared to the healthy eye; which is in line with the work of Pine et al. [3,6–8]. They reported that increasing discharge may be related to a longer external prosthesis life and a more frequent cleaning régimen [3,6–8]. In addition, the hydrophobic nature of PMMA prostheses makes it difficult to sustain an even tear film. Similarly, the study indicates higher conjunctival inflammation of the anophthalmic socket compared to the fellow eye, which appears related to prosthesis replacement times over one year and cleaning frequency under one month. These findings could highlight the need for treatments with proven efficacy for MGD in anophthalmic socket patients with discomfort symptoms [12,15–23].

Another well-studied parameter in this group of patients is tear production [2,5,9,24]. It is generally accepted that enucleated/eviscerated patients have reduced tear production in the anophthalmic socket due to the absent corneal réflex [5,24]. Dryness and discomfort are also more significant if decreased eyelid blinking, eyelid malposition, or incomplete eyelid closure are present. That was the reason why patients with eyelid malposition were excluded and reflex tear production was assessed in isolation during the study [5,24]. The low tear production in anophthalmic sockets has recently been described using Fourier-Domain Optical Coherence Tomography (FD OCT), which allowed the reduction in tear meniscus height to be measured [24]. Following the principle of using daily-practice procedures and examinations, this study assessed reflex tear production with the Schirmer I test, obtaining a significantly lower score in anophthalmic socket compared with the fellow eye. These results are consistent with previously published studies and would point to the importance of artificial tears supplementation in the sockets of patients with discomfort [18].

It was observed that those patients who replace the prothesis with a frequency greater than once yearly reported worse SPEED test, discharge score, conjunctival inflammation, eyelid morphology, and Schirmer I test compared with those who replace them yearly or more frequently. Moreover, when the prosthesis fitting time extended beyond 12 months, worsening in SPEED test, conjunctival inflammation, and meibomian gland expression were observed. Furthermore, those patients with a cleaning frequency of less than one month also reported worse SPEED test scores, conjunctival inflammation, and eyelid morphology alterations.

The purpose of this research is to provide guidance on how real-world standardized tools can be used for a comprehensive evaluation of patients with anophthalmic sockets suffering from discomfort. The examination protocol should include an assessment of symptoms, discharge characteristics, slit lamp examination with special emphasis on conjunctival inflammation and MGD signs, and a Schirmer I test to evaluate the reflex tearing component. Due to interobserver variability, results will vary between clinicians and must be acknowledged as one of the main limitations of the study since two different observers were employed across sites.. Another limitation is evaluating the SPEED test for each eye separately to contrast the patient's symptoms between the anophthalmic socket and the healthy eye. This may be difficult to differentiate for some patients. There was also a lack of standardization [25] when carrying out the Schirmer I test regarding the light and temperature condition due to the multicentric locations of the study. However, it was considered that this would reflect the lack of regulation usually employed in similar studies and be close to procedures in daily clinical practice.

In summary, most anophthalmic patients suffer heightened discomfort that seems to be related to discharge, conjunctival inflammation, and MGD. Certain prosthesis care routines such as replacement with a frequency greater than one year and a removal and cleaning regime less often than once per month were related to a greater discomfort sensation, conjunctival inflammation and MGD. Eye care practitioners should be aware of the presence of DASS when assessing a patient with anophthalmic socket and consider the employment of artificial tears and treatments for MGD in those with discomfort symptoms. Future studies should delve deeper into the diagnosis of this syndrome and develop specific therapeutic protocols to improve the quality of life of these patients.

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Statement of consent

A statement of consent to publish this case was gathered from all patients.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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