



# The effect of tamarind seed polysaccharide-containing eye drop in dry eye syndrome: Results of an interventional, comparative, clinical study

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## ABSTRACT

**Background:** The mainstay of dry eye treatment is artificial tear solutions. Contralateral eye comparison of 2 types of artificial tears (Xiloial®; tamarind seed polysaccharide-containing lubricant eye drop versus Tearlose®) in managing dry eye disease was sought in this study.

**Methods:** This study was a prospective, interventional, contralateral eye comparison of 2 types of artificial tears used for managing dry eye disease. The study participants were categorized into mild (13–22 points), moderate (23–32 points), or severe (33–100 points) ocular surface disease according to the baseline ocular surface disease index (OSDI) questionnaire score. Schirmer I and tear film break-up time (TBUT) tests, as well as detailed slit-lamp examinations, were performed at baseline and at the end of the study. All participants received Xiloial® monodose eye drops for the right eye and Tearlose® eye drops for the left eye, administered as a single drop 4 times per day. Furthermore, they were instructed to perform lid hygiene every 12 h per day for both eyes.

**Results:** Thirty-five patients (70 eyes) with a mean  $\pm$  standard (SD) age of  $50.2 \pm 13.4$  years were included, and 14 (40%) were men. The mean  $\pm$  SD of the OSDI score was  $44.24 \pm 22.59$  at baseline. Of the 35 patients, 10 (28.6%), 5 (14.3%), and 20 (57.1%) had mild, moderate, and severe ocular surface disease, respectively, according to the baseline OSDI score. Compared to baseline, the mean values of both TBUT and Schirmer I tests improved significantly in both groups (both  $P < 0.001$ ). In comparing the final mean values between the 2 groups, this improvement was comparable for the Schirmer I test ( $P = 0.179$ ), but TBUT in Tearlose®-instilled eyes improved significantly more than in the fellow eyes ( $P < 0.001$ ).

**Conclusions:** Both Xiloial® and Tearlose® eye drops improved tear stability and tear production after a 2-week treatment period in eyes with dry eye disease. This improvement was comparable for tear production, but Tearlose®-instilled eyes showed significantly greater improvement in tear stability. Further studies with longer follow-up and larger sample sizes could provide more reliable results as a basis for the clinical use of this tamarind seed polysaccharide-containing lubricant eye drop solution in dry eye disease.

## KEY WORDS

dry eye disease, dysfunctional tear syndrome, OSDI, ocular surface disease index, treatment, artificial tear, Xiloial, Tearlose, TSP, tamarind seed polysaccharide

## INTRODUCTION

Dry eye disease, more recently referred to as dysfunctional tear syndrome, is a multifactorial disorder that causes eye discomfort, visual disturbance, and instability of the tear film, leading to the onset of either clinically apparent or obscure ocular surface inflammation [1, 2]. Dry eye also reduces the overall quality of life and

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deteriorates an individual's everyday activities [3]. Severe cases can lead to complications, such as severe corneal staining, erosions, and conjunctival scarring [1]. Dry eye is classified into aqueous-deficient and evaporative categories [1]. The mainstay of treatment is artificial tear solutions [4]. Based on age-specific data from large epidemiological studies, the prevalence of dry eye ranges from approximately 5% to over 35%, at different ages. This broad range of prevalence rates is due to the varying definitions used in these studies [5].

Tamarind seed polysaccharide (TSP) is a nonionic, neutral, branched carbohydrate derived from *Tamarindus indica* L. seeds. These natural polysaccharide compounds are similar to conjunctival and corneal mucosal transmembrane proteins. The composition of TSP gives the product mucomimetic, mucoadhesive, and pseudoplastic features, similar to the transmembrane glycoprotein layer of the cornea and conjunctiva, and provides it with optimal viscous properties [6-8]. Uncrosslinked hyaluronic acid plus TSP is an effective, safe, and well-tolerated therapy for dry eye symptoms [9]. Xiloial® (Xiloial® eyedrops; Farmigea, Pisa, Italy) is a new eye drop based on the unique synergistic activity of TSP and hyaluronic acid, created by biotechnological synthesis. In each vial, a Xiloial® monodose drop contains 0.2% sodium hyaluronate and 0.2% TSP, without preservatives [10]. Another artificial tear, with brand name Tearlose (Tearlose® eye drop, Sina Daru, Tehran, Iran), is composed of hydroxypropyl methylcellulose (HPMC) 0.3 gram, dextran 70 0.1 gram, and 0.01% benzalkonium chloride (BAK) as a preservative. The available form in the market is a 10-mL white plastic bottle with a nozzle dropper and pilferproof cap [11].

In this interventional, prospective study, we compared 2 types of artificial tears (Xiloial® versus Tearlose®) for managing dry eye disease in contralateral eyes.

## METHODS

This prospective, contralateral eye comparison of the 2 types of artificial tears in managing dry eye disease, conducted at the ophthalmology clinic of Rudehen, Rudehen District, Damavand County, Tehran Province, Iran. The study protocol was approved by the ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran. This study adhered to the tenets of the Declaration of Helsinki. The purpose of the study was explained to all participants, and those who agreed to participate provided written informed consent.

The study participants were selected from cases referred to the ophthalmology clinic of Rudehen in 2018, who needed to use artificial tear solutions for treating dry eye disease. Inclusion criteria were individuals who had dry eye symptoms based on the ocular surface disease index (OSDI) questionnaire [12], with a score > 12, with no history of artificial tear use in the past 3 months. Dry eye disease was diagnosed using the OSDI questionnaire score, in addition to recording the patient's symptoms, Schirmer I test, and tear film break-up time (TBUT) results, and a detailed slit-lamp (Topcon slit-lamp, Topcon Corporation, Tokyo, Japan) examination conducted by an experienced ophthalmologist (S.R.). Exclusion criteria were a history of ocular surgery, such as refractive surgery; radiation therapy; use of systemic medications, ophthalmic eye drops, or therapeutic or cosmetic contact lenses; ocular surface infection or ocular allergy; and pregnancy or lactation. Thirty-five patients (70 eyes) were recruited using a non-probability convenience sampling technique. They were categorized into mild (13–22 points), moderate (23–32 points), or severe (33–100 points) [12] ocular surface disease, according to their baseline OSDI score.

Non-preserved saline was applied to moisten a sterile fluorescein strip (Indicator, Elham Teb Co., Tehran, Iran), and the strip was gently applied to the conjunctiva to avoid irritation of the eye and cause reflex tearing. The patient was instructed to keep their eyes open after a few blinks. The examiner recorded the time interval between the last blink and the first dry spot or black line appearance on the corneal surface in seconds [13]. A TBUT derived in this manner of less than 10 s was considered abnormal. The same procedure was repeated for the fellow eye, by the same examiner (N.N.).

To record basic and reflex tear secretion, the Schirmer I test was performed without local anesthesia. The eye was dried first, over closed lids. Then, a dry Schirmer strip (Opstrip Schirmer Tear Test Strips, Ophtech Unltd Co., New Delhi, India) was gently placed at the junction of the middle and lateral 1/3 of the lower eyelid. The patient was instructed to close their eyes. After 5 min, the strip was removed and the amount of wetting was recorded in mm [14, 15]. Wetting of less than 5 mm of the strip was considered abnormal. The same procedure was repeated for the fellow eye by the same examiner (N.N.).

All participants received 2 types of artificial tears, Xiloial® (Xiloial® eyedrops; Farmigea, Pisa, Italy) for the right eye and Tearlose (Tearlose® eye drop, Sina Daru, Tehran, Iran) for the left eye. They were instructed to instill only a single drop of each solution into the relevant eye, 4 times per day. Furthermore, they were instructed to apply warm compresses over closed lids for 10 min and to cleanse the eyelid with a baby shampoo solution (Firooz baby shampoo, Firooz Hygienic Group Co., Tehran, Iran) every 12 hours per day as a lid hygiene regimen. Participants returned after 2 weeks and underwent detailed slit-lamp examination by the same experienced ophthalmologist (S.R.), along with

repeated Schirmer I and TBUT tests for both eyes. All baseline and follow-up measurements were also performed between 09:00 AM and 12:00 PM in the same order, environment, and by the same person (N.N.).

The collected data were analyzed using IBM SPSS Statistics for Windows, version 23.00 (IBM Corp., Armonk, NY). Qualitative variables, such as gender and severity of dry eye, were presented as frequency and percentages, and quantitative variables were presented as mean and standard deviation (SD). Normality testing revealed a non-normal data distribution (Shapiro–Wilk test,  $P < 0.05$ ). Therefore, nonparametric statistics, including the Wilcoxon rank-sum test and the Mann–Whitney U test were applied to analyze changes between baseline and final values in each group, and to compare variables between the 2 groups, respectively. In all analyses, a  $P$ -value less than 0.05 was considered significant.

## RESULTS

Thirty-five patients (70 eyes) with a mean  $\pm$  SD age of  $50.2 \pm 13.4$  years (range, 18–75 years) were included in the study, of which 14 (40%) were men. The mean  $\pm$  SD OSDI score was  $44.24 \pm 22.59$  (range, 12.50– 87.50) at baseline. Of the 35 patients, 10 (28.6%), 5 (14.3%), and 20 (57.1%) had mild, moderate, and severe ocular surface disease, respectively, according to the baseline OSDI score.

Table 1 shows the mean values for the TBUT and Schirmer I test at baseline and final assessment, in the Xiloial®- versus Tearlose®-instilled eyes. As shown in Table 1, the mean values for TBUT and Schirmer I test at baseline were comparable between the 2 groups ( $P = 0.771$  and  $0.658$ , respectively). Compared to baseline, the mean values of both TBUT and Schirmer I tests improved significantly in both groups (all  $P < 0.001$ ) (Table 1).

Table 1. Baseline and final TBUT and Schirmer I tests results in study participants (intra- and inter-group comparisons)

Variable	Time of assessment	Xiloial® Group	Tearlose® Group	P-value*
TBUT (s), Mean $\pm$ SD (Range)	Baseline	4.83 $\pm$ 2.54 (2 to 10)	4.94 $\pm$ 2.48 (2 to 11)	0.771
	Final	6.60 $\pm$ 3.11 (3 to 16)	9.09 $\pm$ 3.54 (3 to 18)	<b>&lt; 0.001</b>
	P-value**	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>	
Schirmer I test (mm), Mean $\pm$ SD (Range)	Baseline	6.23 $\pm$ 6.14 (0 to 27)	6.37 $\pm$ 5.05 (0 to 20)	0.658
	Final	11.6 $\pm$ 9.09 (2 to 35)	10.26 $\pm$ 6.24 (2 to 25)	0.176
	P-value**	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>	

Abbreviations: TBUT, tear break-up time; s, seconds; SD, standard deviation; mm, millimeter. Note: The right eye received Xiloial® eye drops, and the left eye received Tearlose® eye drops. Xiloial® monodose (Xiloial® eyedrops; Farmigea, Pisa, Italy) contains 0.2% sodium hyaluronate and 0.2% TSP, without preservative. Tearlose (Tearlose® eye drop, Sina Daru, Tehran, Iran) contains hydroxypropyl methylcellulose 0.3 gram, dextran 70 0.1 gram, and 0.01% benzalkonium chloride as a preservative. P-values  $< 0.05$  are shown in bold. P-value\*, based on the Mann–Whitney U test; P-value\*\*, based on the Wilcoxon rank-sum test.

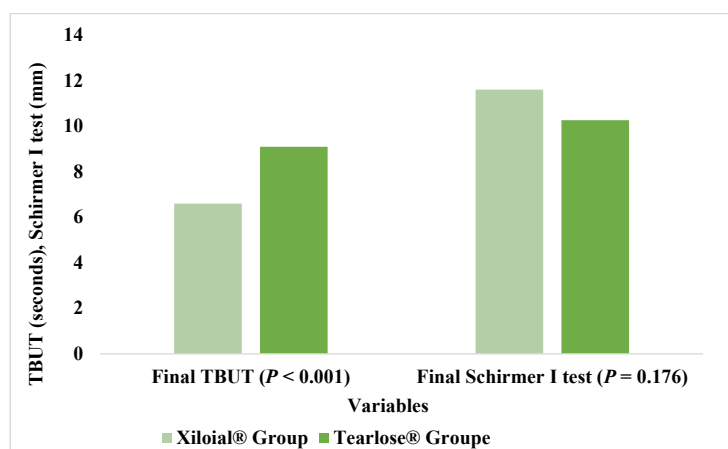


Figure 1. Comparison of tear stability (TBUT) and tear production (Schirmer I test) results between Xiloial® monodose-treated eyes versus Tearlose®-treated eyes at the end of study. Abbreviations: TBUT, tear break up time; mm, millimeter. Note: The right eye received Xiloial® eye drops, and the left eye Tearlose®. Xiloial® monodose (Xiloial® eyedrops; Farmigea, Pisa, Italy) contains 0.2% sodium hyaluronate, 0.2% TSP, without preservative. Tearlose (Tearlose® eye drop, Sina Daru, Tehran, Iran) contains hydroxypropyl methylcellulose 0.3 gram, Dextran 70 0.1 gram, and 0.01% benzalkonium chloride as a preservative. P-value, based on the Mann–Whitney U test.

The improvement from baseline to final value was comparable for the Schirmer I test ( $P = 0.179$ ), but the TBUT in the Tearlose®-instilled eyes improved significantly more than in the fellow eyes that received Xiloial® eye drops ( $P < 0.001$ ) (Table 1 and Figure 1). Despite the absence of a statistically significant difference in the final mean Schirmer I test values, Xiloial®-instilled eyes had a higher mean value than the fellow eyes.

## DISCUSSION

The current study was a contralateral eye comparison of the performance of 2 types of artificial tears in the management of dry eye disease, namely Xiloial® and Tearlose®. Despite significant improvements in TBUT and Schirmer I tests in both eyes, TBUT as an indicator of tear film stability was significantly enhanced in Tearlose® instilled eyes compared to Xiloial®-instilled fellow eyes. Despite no significant difference in the final mean Schirmer I test values, Xiloial®-instilled eyes had a higher mean value than the fellow eyes. No serious adverse effects were observed in either eye.

A randomized, single-center clinical study by Rolando et al. [7] compared the tolerability and performance of TSP with that of 0.2% hyaluronic acid in the treatment of dry eye. Thirty patients randomly received 3 or more drops per day of either 0.5% TSP, 1% TSP, or 2% hyaluronic acid for 90 days. The primary objective was to assess the tolerability of TSP drops using a visual analog scale tolerability questionnaire and an adverse event rate. The secondary objective was to improve tear film stability, which was assessed based on changes in subjective symptoms and ocular surface staining. TSP, similar to 2% hyaluronic acid, was effective in improving TBUT and corneal and conjunctival staining. However, TSP had significant inter-visit differences as compared to 2% hyaluronic acid in improving blinking, reducing subjective symptoms, foreign body sensation, and ocular pain [7]. In the current study, we assessed Xiloial® eye drops containing 0.2% TSP plus 0.2% sodium hyaluronate versus Tearlose® (composed of 3% HPMC) in the contralateral eye. Similar to Rolando et al. [7], we found that both eye drops improved the stability of the precorneal tear film and tear secretion, as evidenced by a significant increase in TBUT and Schirmer strip wetting, with a more significant increase in TBUT in Tearlose®-treated eyes. In contrast to Rolando et al. [7], we could not evaluate subjective symptoms in the studied eyes because this was a contralateral eye comparison, and it was difficult for patients to differentiate symptomatic improvement between the 2 eyes clearly. Furthermore, we did not record details of the adverse events; however, no serious complications were noted in the 2-week follow-up examination in any of the participants.

Versura et al. [10] examined the effect of a 2-month treatment with Xiloial® to relieve symptoms of discomfort with disposable soft contact lens use. They included 12 females and 3 middle-aged men with an OSDI questionnaire score  $> 12$ , TBUT  $< 10$  seconds, and Schirmer I test  $> 10$  mm after 5 minutes, mild punctate keratopathy, and conjunctival staining in Oxford grade  $\leq 4$ . Xiloial® was administered at a single dose 3 times daily for 2 months. Patients were evaluated at the time of enrollment, after 3 days of washout, and after 1 and 2 months of treatment, by means of the OSDI score, TBUT test, Schirmer I test, ferning test, ocular surface damage using the Oxford grading system, and detection of serum albumin in tears. At the endpoint, the mean  $\pm$  SD of all variables improved significantly. Tolerance was high, with no side effects. Two months of Xiloial® eye drop use reduced redness and damage to the ocular surface and symptoms of lens-induced discomfort [10]. We included 35 cases: 10 (28.6%), 5 (14.3%), and 20 (57.1%) cases that had mild, moderate, and severe ocular surface disease, respectively, according to their baseline OSDI score. We observed a significant improvement in objective measurements, including the TBUT test and Schirmer I test, in eyes that received Xiloial® monodose eye drops. Furthermore, no serious adverse events were noted during the final examination. A short follow-up time, failure to employ further objective measures, such as the ferning test, ocular surface damage using the Oxford grading system, and detection of serum albumin in tears are among the limitations of our study as compared with Versura et al.'s study [10].

Jacobi et al. [15] conducted a prospective, randomized clinical trial to compare the safety and efficacy of 2 lubricant drops, namely preservative-free hydroxypropyl (HP)-Guar (SYSTANE UD®) versus preservative-free TSP 1% (VISINE INTENSIV 1% EDO®) eye drops. Sixty-five eyes of 28 patients with moderate dry eye disease were examined. Eye drops were administered 5 times a day in both groups for 3 months. Patients in both groups showed subjective improvement in symptoms of dry eye disease, as determined by the final OSDI score. Both eye drops improved TBUT, as a tear film stability measure, which was statistically significant in the HP-Guar group. Both eye drops increased the mean values of the Schirmer I test at the final assessment, but this was not statistically significant. Both artificial tear formulas improved tear film stability and increased patients' quality of life. HP-Guar was slightly more effective in protecting the ocular surface by reducing the evaporation of the tear film [15]. In the current study, Xiloial® (preservative-free TSP 0.2%) and Tearlose® were administered to the right and left eye of each participant, respectively. Similar to Jacobi et al. [15], we found increased TBUT in both groups. This change was statistically significant compared to baseline values and was more marked in Tearlose®-

instilled eyes. The mean values of the Schirmer I test increased in both groups, similar to the findings of Jacobi et al [15]. However, our results were statistically significant and comparable for both eye drops. In our study, this significance was achieved despite the shorter follow-up at the final assessment compared to that in the Jacobi et al. study. A possible explanation could be the nonhomogeneous nature of our study population, in which the severity of dry eye ranged from mild to severe, whereas their study included only moderate cases.

In another study, Barabino et al. [16] tested the effect of Xiloial® monodose versus Optive monodose (Carmellose sodium) for 3 months, both administered 4 times daily, on moderate dry eye disease in a multicenter, randomized, double-masked trial. Forty-nine patients with moderate dry eye disease, with an OSDI questionnaire score between 10 and 25, a TBUT < 10 seconds, or a 5.5-mm Schirmer 1 test result after 5 min, and a green lissamine staining score < 2 (based on the National Eye Institute score system) were included. Their study found statistically significant improvements in dry eye signs and symptoms in both groups, but the mean decrease in OSDI value was almost twice in the Xiloial® group compared with the Optive group at the end. Moreover, compared to baseline, the response to treatment was significantly greater in the Xiloial® monodose treatment group than in the control group. Both treatments significantly increased the TBUT [16]. The current study, despite having a shorter follow-up period and a more diverse population in terms of severity of dry eye disease than Barabino et al.'s study [16], also found an increase in tear film stability associated with a significant increase in TBUT. In addition, compared to baseline values, we found a significant increase in tear film production assessed by the Schirmer I test in both Xiloial® and Tearlose® instilled eyes.

Hyaluronic acid, which has viscous lubricating properties, has been used as a supplement for ocular mucin [17] and is included in the Xiloial® eye drop formulation. The combination of hyaluronic acid with TSP enhanced the residence time of the solution [17]. These 2 polysaccharides are compatible in solutions [17], and a synergistic interaction has been demonstrated between them [18]. The current clinical study found increased tear stability and production 2 weeks after Xiloial® eye drop instillation. These observed clinical improvements could be attributed to the properties of the 2 polysaccharides, which are the main ingredients of Xiloial® eye drops.

This prospective study revealed the short-term efficacy of Xiloial® monodose eye drops containing 0.2% TSP plus 0.2% sodium hyaluronate in enhancing tear film stability (increased TBUT) [19] and tear secretion (increased Schirmer I test values) [20] in treating dry eye disease, with no serious adverse effects. The results were similar to those of Tearlose® (composed of 3% HPMC) in the contralateral eye comparison. However, as this was a contralateral eye comparison, evaluating symptomatic relief of dry eye was not feasible, as patients could not differentiate between symptomatic improvement between the 2 eyes. We did not record details of mild or moderate adverse events, but noted no serious complications. More objective measures, such as ocular surface staining and detection of serum albumin in tears, could overcome the lack of symptomatic assessment, which we did not perform in this study. Furthermore, since Tearlose® is a BAK-preserved artificial tear, BAK could interrupt the validity of results, due to a detrimental impact on the ocular surface, and consequent measurements of quality of life [21]. Further comparisons with a preservative-free equivalent may provide more reliable and realistic results when compared with the clinical efficacy of Xiloial® monodose eye drops in the long term. The nonhomogeneous nature of our study population, in which the severity of dry eye ranged from mild to severe, is another limitation. Future randomized studies should use a larger sample size and longer follow-up period, and should investigate specific severity levels of dry eye disease, to provide more reliable results concerning the efficacy, tolerability, and safety of this TSP-containing lubricant eye drop.

## CONCLUSIONS

Both Xiloial® and Tearlose® eye drops improved tear film stability and production during a 2-week treatment period in eyes with dry eye disease. This improvement was statistically comparable in terms of tear production, but the mean Schirmer I test value in the Xiloial® group was slightly higher than that in the fellow eyes. Tearlose®-instilled eyes showed a significantly greater improvement in tear film stability. Further studies addressing our limitations may provide more reliable results as a basis for the clinical use of this TSP-containing lubricant eye drop solution in the management of dry eye disease.

## ETHICAL DECLARATIONS

**Ethical approval:** The study protocol was approved by the ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran. This study adhered to the tenets of the Declaration of Helsinki. The purpose of the study was explained to all participants, and those who agreed to participate provided written informed consent.

**Conflict of interests:** None

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