COMPARISON OF THE EFFICACY OF HYDROXYPROPYL METHYLCELLULOSE/ DEXTRAN, SODIUM HYALURONATE AND POLYETHYLENE GLYCOL/PROPYLENE GLYCOL BASED COMMERCIAL ARTIFICIAL TEAR PRODUCTS USING THE NONINVASIVE TEAR FILM BREAKUP TIME

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ABSTRACT

Objective: To compare the efficacy of sodium hyaluronate, hydroxypropyl methylcellulose/dextran and polypropylene/polyethylene glycol based commercial artificial tear products using the noninvasive tear film breakup time.

Study Design: Quasi experimental Study.

Place and Duration of Study: Study was conducted at the Eye department of Combined Military Hospital Malir Cantt Karachi, from Sep 2017 to Nov 2017.

Methodology: Three different types of commercially available artificial tears were evaluated on 30 eyes of 30 patients, having all types of dry eyes diseases. The noninvasive tear film breakup time was measured before and then at 15, 30 and 45 mins after instillation of the artificial tear using keratometer. The active ingredients in these eye drops were sodium hyaluronate, polyethylene glycol/propylene glycol and hydroxypropyl methylcellulose/ dextran 70.

Results: Among the three artificial tears only Sodium hyaluronate eye drops caused a statistically significant increase in noninvasive tear film break up time at 45 mins post instillation. Polyethylene glycol/propylene eye drops extended tear film breakup time upto 30 mins. Comparison of the difference in extension of the breakup time was statistically insignificant between sodium hyaluronate and polyethylene glycol/polypropylene at 15 and 30 mins post instillation.

Conclusion: Sodium hyaluronate eye drops were effective in prolonging the noninvasive tear film breakup time upto 45 mins postinstillation while polypropylene/polyethylene glycol were effective upto 30 mins in all types of dry eye diseases.

Keywords: Dextrans, Hyaluronic acid, Hypromellose derivatives, Lubricant eye drops.

INTRODUCTION

Stability of the tear film is an important indicator for assessing the efficacy of an artificial tear which is measured by the tear film breakup time (TFBUT)[1]. Compared to other objective tests for evaluating the efficacy of artificial tears in dry eye disease there is evidence that repeatability of TFBUT is substantially more than the other tests[1]. Measurement of the TFBUT can be done either by calculating fluorescein breakup time (FBUT) or non-invasive breakup time (NIBUT)[1].

NIBUT technique has advantages over other methods as it allows the examiner to analyze the tear film in vivo and avoids instilling a substrate into the eye since the stability of the tear film is significantly shortened when fluorescein is instilled into the eye[1].

Localized inflammation of the ocular surface frequently exists in keratoconjunctivitis sicca [2] and artificial tears being the mainstay of therapy should ideally have a composition that is compatible with maintenance of a normal ocular surface epithelium[3]. In these circumstances sodium hyaluronate eye drops have been found to have a role in controlling the localized inflammation of dry eye syndrome for the reason that it is directly involved in stabilizing the ocular surface epithelial barrier [2] and on top of that it has viscoelastic properties[3].

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In moderate or severe dry eyes using artificial tears that are preserved with benzalkonium chloride can have a toxic effect on the eye, leading to poor tolerability and harm[4]. Therefore in patients with significant dry eye , a single dose of a nonpreserved tear preparation becomes the mainstay of therapy and bottled tear products are a reasonable alternative when preserved with relatively nontoxic compounds. These less toxic preservatives are poly quaternium-1, sodium chlorite and sodium perborate[4]. Among the commercially available artificial tear products these preservatives have been combined with the polypropylene/polyethylene glycol [5,6] and with hydroxypropyl methylcellulose (HPMC)/dextran 70 which are the active ingredients[6]. Polyquaternum-1 preservative is safe and has no effect on morphology and mitotic activity of cultured corneal epithelial cells[7]. Additionally polypropylene/polyethylene glycol eye drops increase the volume of tear film in damaged epithelial areas and prolong the retention of demulcents on the ocular surface[7].

Another important factor for patients is the cost comparison of artificial tears. Several factors are important when considering the economics of article tear substitutes which are drop size, number of drops per bottle, the volume of the bottle, and the cost of treatment per year. Since this information may not be easily available to patients, it is important that physicians educate their patients to make treatment of dry eye as affordable as possible[8]. Regarding affordability in Pakistan the most economical among these eye products is HPMC/dextran 70 and sodium hyaluronate while the polypropylene/polyethylene glycol product though highly priced yet the marketed bottle contains a substantial volume of artificial tear compared to sodium hyaluronate and HPMC/dextran 70[5,6].

Taking into account the value of cost effectiveness against the additional benefits that these artificial tears offer our objective was to compare the efficacy of sodium hyaluronate, hydroxypropyl methylcellulose/dextran and polypropylene/polyethylene glycol based commercial artificial tear products using the noninvasive tear film breakup time.

METHODOLOGY

This quasi experimental study was conducted at the Eye department of Combined Military Hospital Malir Karachi. Three types of commercially available artificial tears were tested on same subjects with dry eyes. They were Tears Naturale II TM eye drops (Active ingredients: DUASORBTM dextran 70 (0.1%), hypromellose, Alcon-Couvreur, Puurs, Belgium), Hyalosan TM eye drops (Active ingredient: Sodium Hyaluronate 0.18%, Sante pvt, ltd. Karachi Pakistan) and Systane TM eye drops (Active ingredient: Polyethylene glycol 400 (0.4%), propylene glycol 0.3% Alcon Laboratories, Inc. Fort Worth, TX, USA). A sample size of 30 patients for analyzing each type of artificial tear was calculated to detect a difference of ≥10 secs in mean NIBUT before and after instillation of an artificial tear with 95% power, assuming a two sided α of 0.05, using a reference value of mean NIBUT of 22.63 secs and a SD of 10.92 secs of normal eyes [10] that was recorded with the same instrument as used in our study and with the help of WHO calculator and formula $n=\sigma 2\ (z1-\alpha/2 + z1-\beta)\ 2/(\mu o-\mu a)$. The study was approved from ethical review committee of hospital. The study was carried out in 03 months from September 2017 to November 2017. A total of 30 patients (30 eyes) participated in this study. Patients aged 18 years and above were selected consecutively from among all those patients who attended the outpatient section of the eye department for various symptoms. Before further evaluation those patients were excluded from the study who were known cases of dry eye syndrome and using artificial tears. Additionally patients with acute infectious conjunctivitis, allergic conjunctivitis, contact lens wearers, autoimmune conjunctivitis, corneal scarring, ocular or intraocular surgery, concomitant topical and systemic medications that may cause dry eyes were also excluded. Mc Monnies dry eye history questionaire was used to screen patients for dry eyes at a cutoff point of 14.5. Respondents having a score greater than

14.5 were then subjected to fluorescein tear film break up time (FTBUT) in both eyes. Patients having a FTBUT of less than 10 secs were finally selected to participate in the study and the eye with a shorter FTBUT was chosen for further testing. A written informed consent was taken from the participants.

The efficacy of artificial tears was measured by recording the NIBUT in seconds before and after instillation of an artificial tear. A baseline NIBUT was recorded for each patient and then a single drop of artificial tears was instilled and NIBUT was remeasured at 15 mins, 30 mins and 45 mins. Each patient was tested thrice for each type of artificial tear. There was an interval of at least 24 hours between each type of artificial tear.

A slitlamp examination was performed and relevant findings were recorded. NIBUT was measured by Topcon Ophthalmometer OM-4 (Topcon Corp, Tokyo, Japan) using reflection of the keratometric mires from corneal surface. The subject was instructed to blink several times and then hold his eyes open and refrain from blinking. Using a stopwatch the time taken from last blink to the first significant appearance of distortion or disruption of keratometric mires was recorded. NIBUT was recorded as the average of three consecutive readings. A black patch was placed over the eye not being tested. Room temperature and humidity were kept constant during examination and air currents were not allowed in examination room. The instrument illumination setting was kept at normal and a dark room was maintained.

Artificial tear eye drop bottles were kept at room temperature. Once opened it was not used for more than 28 days. Each bottle was not used for more than one patient. Before instillation the procedure was explained. During instillation ,care was taken not to instill more than one drop and it was ensured that the dropper tip did not touch any ocular structure. The drop was instilled in the lower fornix. After which patient was instructed to blink normally. NIBUT was recorded by one observer only for all patients.

Statistical analysis was performed using SPSS version 20.0. Descriptive statistics and normality test were computed for each variable. Frequency and percentages were calculated to describe the cause of dry eyes in the study subjects. Wilcoxon signed ranks test was selected as data was nonparametric to compare the efficacy of each artificial tear by analyzing baseline value of NIBUT of each patient with the value of NIBUT recorded at 15 mins, 30 mins and 45 mins after instillation of that artificial tear. The difference between the baseline NIBUT and NIBUT at 15 mins, 30 mins and 45 mins was also calculated for each patient according to the type of artificial tear used. For comparing the efficacy between artificial tears, Wilcoxon signed ranks test was employed to detect whether there was a significant difference in the NIBUT between the artificial tears when both the artificial tears had shown a statistically significant improvement in NIBUT at 15 mins, 30 mins and 45 mins. The tests were 2-tailed and a p-value ≤0.05 was considered to be statistically significant.

RESULTS

Median age of the patients were 38 years. Male to female ratio was 5:1. Out of the total 30 patients 14 (47%) had meibomian gland dysfunction, 11 (37%) patients were suffering from anterior blepharitis. There were 3 (10%) patients diagnosed with trachoma and 2 (7%) patients had secondary sjogren syndrome.

The median (Q3-Q1) baseline value of NIBUT was 10.5 (9) secs. At 15 mins HPMC/ dextran eye drops did not demonstrate a significant extension in NIBUT (table-I). Polyethylene glycol/ propylene glycol and sodium hyaluronate eye drops produced a statistically significant improvement in NIBUT at the same point in time when compared with the pre-instillation NIBUT (table-I). The median(Q3-Q1) improvement in the NIBUT for polyethylene glycol/propylene glycol and sodium hyaluronate eye drops were 8.5 (25) secs and 9.0 (29) secs respectively. Comparison of the difference in the improvement of NIBUT at 15 mins between polyethylene glycol/propylene

glycol and sodium hyaluronate eye drops revealed that the difference between them was statistically insignificant (p=0.97).

At 30 mins HPMC/dextran eye drops did not extend the NIBUT (table-I). Polyethylene glycol/propylene glycol and sodium hyaluronate eye drops caused the NIBUT to extend significantly from the baseline NIBUT (table-I). The median (Q3-Q1) extension in NIBUT at 30 mins was 17.5 (36) secs and 20.0 (36) secs for polyethylene glycol/propylene glycol eye drops and sodium hyaluronate eye drops respectively. On comparing polyethylene glycol/ propylene glycol eye drops and sodium hyaluronate eye drops the extension in the NIBUT was statistically insignificant at 30 mins (p=0.51).

At 45 mins only sodium hyaluronate eye drops produced a significant improvement in the NIBUT (table-II). The median (Q3-Q1) improvement in NIBUT was 9.5 (29) secs. Both polyethylene glycol/propylene glycol and HPMC/dextran eye drops failed to produce a statistically significant improvement in NIBUT (table-II).

Table-I: Comparison of pre- and post-instillation noninvasive breakup time at 15 and 30mins (n=30).

Non Invasive Breakup Time (secs)			
Artificial tear	**Baseline Median (Q3-Q1)**	**15 mins, Median (Q3-Q1) *p*-value**	**30 mins, Median (Q3-Q1) *p*-value**
HPMC/dextran	10.5 (16.2-7.0)	15.5 (32.0-9.7) 0.068	12.5 (26.25-7.75) 0.08
Polyethylene glycol/ Propylene glycol propy	10.5 (16.2-7.0)	20.5 (42.25-10.75) 0.01	29.0 (46.25-13.0) <0.001
Sodium Hyaluronate	10.5 (16.2-7.0)	23.5 (45.0-15.75) <0.001	28.5 (51.0-14.75) <0.001

Table-II: Comparison of pre- and post instillation noninvasive breakup time at 45 mins (n=30).

Noninvasive Breakup Time (secs)			
Artificial tear	**Baseline Median (Q3-Q1)**	**45 mins Median (Q3-Q1)**	***p*-value**
HPMC/Dextran	10.5 (16.2-7.0)	13.0 (32.0-9.0)	0.06
Polyethylene glycol/ propylene glycol	10.5 (16.2-7.0)	15.0 (17.0-11.5)	0.23
Sodium Hyaluronate	10.5 (16.2-7.0)	27.5 (49.25-11.0)	<0.001

DISCUSSION

Tear substitutes are most frequently employed as first line therapy to meet the aim of treatment in dry eye, which is to enhance the stability of the precorneal tear film[10]. Commercially available tear substitutes provide benefit through a variety of mechanisms which is different for each product however these mechanisms are partially understood[11]. Stabilizing the precorneal tear film, replenishing the tear volume, preserving a smooth refracting surface, reducing tear osmolarity and reducing friction between lid and cornea are the modes by which the benefits of these tear substitutes is related to[11].

The artificial tear products vary in their composition, viscosity, duration of action, presence and type of preservative, osmolarity /osmolality and pH[12]. The main ingredient in all these artificial tears are hydrogel polymers[13]. Hydrogels used in artificial tears include carboxymethyl cellulose, hydroxypropyl methylcellulose, dextran, polyvinylpyrrilodine, polyethylene glycol, polyvinyl alcohol, carbomer, polyacrylic acid and hyaluronic acid[13]. In our study the Hydrogel polymers that we selected were HPMC/dextran 70, sodium hyaluronate and polyethylene glycol/ propylene glycol and we studied one of their mode of action which was to stabilize the precorneal tear film. To achieve this purpose we measured the prolongation effect of these compounds on the NIBUT.

Concerning HPMC/dextran we found that it failed to show a significant prolongation in NIBUT. We selected HPMC combination with dextran on the basis that HPMC is a viscosity

imparting agent and forms a thin precorneal tear film while dextran provides mechanical strength to this film[14]. Contrary to our results a study by Prabhaswat showed a significant improvement in NIBUT at 15, 30 and 60 mins from the baseline values[15]. The probable reason is that Prabhaswat purely studied patients with lipid tear deficiency (LTD) while our cohort was more diverse in that it consisted of not only LTD patients but also included patients with other causes of evaporative dry eye including mucin deficiency and on top of that also included patients with aqueous tear deficiency (ATD). In ATD the tear volume is reduced due to failure of lacrimal tear secretion [16] whereas it is normal in LTD eyes and hence HPMC/dextran might have failed in prolonging TBUT in eyes with ATD in our patients as the TBUT is lower in ATD than in patients with meibomian gland dysfunction[17]. We did not measure the NIBUT at 5 and 10 mins postinstillation but we believe that HPMC/ dextran might have shown prolongation of NIBUT.

Polyethylene glycol/propylene eye drops extended the NIBUT significantly at 15 mins and 30 mins postinstillation in our cohort. The TFBUT increases because polyethylene glycol/propylene are combined with hydroxypropyl guar (HP-guar) and exist in a borate containing solution in the dispensing bottle[18,19]. Which after contact with the patient's tear, which is at a different *p*H, causes the HP-guar to cross-link with borate to create a more viscous and elastic matrix which binds with the hydrophobic exposed areas of epithelial cells [20] and additionally prolongs the retention of active ingredients[18,19,20,21]. Our results are in agreement with a study by Ousler *et al*. Who also reported significant improvement in TFBUT with identical eye drops at 15 and 30 mins[22]. However at 45 mins polyethylene glycol/ propylene could not extend the NIBUT. In contrast Ousler *et al*. Study demonstrated that polyethylene glycol/propylene eye drops not only extended TBUT at 45 mins but also its effect on extending the TBUT significantly lasted upto 60 mins[22]. Our results differ presumably for the reason that we studied a smaller cohort of 30 patients and on the contrary Ousler had a larger sample size of 50 dry eye patients[22].

Compared to polyethylene glycol/propylene eye drops, the sodium hyaluronate eye drops significantly extended the NIBUT at 45 mins from the preinstillation value. Previous studies have demonstrated that the 0.10% conc. Of hyaluronic acid significantly extended the NIBUT at 40 mins post instillation[23]. Similarly using a hypotonic preparation of 0.18% hyaluronic acid Prabhaswat *et al*. showed that in dry eye patients suffering from LTD hyaluronic acid eye drops not only significantly improved the NIBUT at 60 mins but were able to prolong the NIBUT at 90 mins as well[15]. Although we did not measure the NIBUT at 60 and 90 mins but in contrast to Prabhaswat our study patients were suffering from all types of dry eye syndromes and we found hyaluronan to significantly prolong NIBUT in various types of dry eye disease upto 45 mins postinstillation using the commercially available isotonic hyaluronic acid solution rather than hypotonic one. Moreover Mengher demonstrated that 0.1% HA prolonged the NIBUT even for a few hours after instillation in moderate dry eye patients[24]. In Pakistan Cheema *et al* also showed that sodium hyaluronate eye drops had a significantly prolonged effect on the TBUT at 4 weeks postinstillation in all types of dry eye patients[25].

At 45 mins post instillation sodium hyaluronate performed better than polyethylene glycol/propylene eye drops. A number of factors could explain this reason. Sodium hyaluronate has 02 distinct roles while the eye is open and during blinking. When the eye is open being more viscous it coats the surface of the eye and does not drain thus prolonging the TBUT and during the blink its viscosity reduces and it spreads across the eye[23]. Besides viscosity the residence time of sodium hyaluronate on the ocular surface is significantly more prolonged than HPMC and polyvinyl alcohol which is believed to be due to adherence of its molecules on the ocular surface. The prolonged retention time of sodium hyaluronate in terms of few hours on the ocular surface and its ability to retain tear

fluid on the ocular surface may be another explanation for outperforming the polyethylene/ propylene glycol preparation in terms of the NIBUT at 45 mins postinstillation.

CONCLUSION

To conclude sodium hyaluronate eye drops were effective in prolonging the noninvasive tear film breakup time upto 45 mins postinstillation while polypropylene/polyethylene glycol are effective upto 30 mins in all types of dry eye diseases.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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