Scholars Journal of Applied Medical Sciences (SJAMS)
Abbreviated Key Title: Sch. J. App. Med. Sci.
ISSN 2320-6691 (Online)
ISSN 2347-954X (Print)

A Unit of Scholars Academic and Scientific Society, India
www.saspublishers.com

Ophthalmology

To Compare the Efficacy and Safety 2% Rebamipide, 0.18% Sodium Hyaluronate and 1% Carboxy Methyl Cellulose Eye Drops in Treatment of Mild to Moderate Dry Eye Disease

Dr. Snigdha Sen[1], Dr. Krishna Kuldeep[1*], Dr. Tirupati Nath[2], Dr. Maumita[3]
[1]Associate professor, department of Ophthalmology, S.N.M.C, Agra, Uttar Pradesh, India
[2]Assistant professor, department of Ophthalmology, S.N.M.C, Agra, Uttar Pradesh, India
[3]Junior resident, department of Ophthalmology, S.N.M.C, Agra, Uttar Pradesh, India

Original Research Article

***Corresponding author**
Dr. Krishna Kuldeep

Article History
Received: 16.02.2018
Accepted: 20.03.2018
Published: 27.03.2018

DOI:
10.36347/sjams.2018.v06i03.038

Abstract: The purpose of this study to compare the efficacy and safety 2% rebamipide, 0.18% sodium hyaluronate and 1% carboxy methyl cellulose eye drops in treatment of mild to moderate dry eye disease. Patients with mild to moderate dry eye were enrolled in this randomized prospective study. They were divided into 3 following groups, patients in rebamipide group treated with 2% rebamipide 4 times daily, in SH group treated with 0.18% sodium hyaluronate 6 times daily and CMC group treated with 1% carboxy methyl cellulose 6 times daily. Fluorescein corneal staining, tear film breakup time, schirmer's test, OSDI score and adverse reactions were assessed at baseline, 2weeks, 4weeks and 12 weeks after treatment initiation was done in this study. Sixty patients were allocated randomly in three groups, 20 patients in the rebamipide group, 20 patients in the CMC group, and 20 patients in the SH group. Three groups of drugs showed significant improvement in FCS, TBUT, schirmer's test and OSDI score at 2week, 4 week and 12 week of initiation of treatment. However, rebamipide group was showed statistically significant differences in the above indices than the CMC and SH groups. There were no significant adverse reactions observed during follow up. 2% rebamipide, 0.18% sodium hyaluronate, and 1% CMC were effective in the treatment of mild to moderate dry eye. But 2% rebamipide was more efficacious than 0.18% sodium hyaluronate and 1% carboxy methyl cellulose.
Keywords: dry eye disease, rebamipide, sodium hyaluronte, carboxy methyl cellulose.

INTRODUCTION

Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to ocular surface [1]. It diminishes quality of life, and is associated with limitations in several ordinary activities, including reading, driving, computer use, and professional work [2]. Dry eye is one of the most common ophthalmologic problems[3], and it is estimated that up to one-third population worldwide may be affected [3, 4].

The current managements of dry eye include tear supplementation, tear stimulation, anti-inflammatory agents, immunomodulatory agents, and environmental strategies [5]. Currently, the main therapy for dry eye is artificial tear, with anti-inflammatory therapy and punctual occlusion therapy as second and third line therapies [6]. The goal of topical therapy in the form of lubricating eye drops is to control the activity and progression of disease, to decrease signs and symptoms related to dry eye, and, as such, to contribute to prevent or delay health consequences [7]. Although there are many effective artificial tear formulations, carboxy methyl cellulose (CMC) and sodium hyaluronate are the two most commonly prescribed and used. CMC is an anionic cellulose polymer with a carboxy group substitution, and exhibits good bioadhesive characteristics. The anionic nature of CMC may be beneficial in increasing tear retention time. HA is a glycosaminoglycan disaccharide biopolymer composed of repeating alternating sequences of N- acetyl glucosamine and glucoronate in linear chains; importantly, HA formulations have the ability to bind water molecules and prevent dehydration.

Now, one new topical pharmacological agent has recently become commercially available for treating dry eye. 2% Rebamipide ophthalmic suspension is a

quinolone derivative which stimulates mucous secretion [8-10]. This new eye drop has enabled as to selectively treat the tear film layer and increase its stability.

The present work is, therefore, to study and compare the efficacy of 2% Rabemipide, 0.18% Sodium hyaluronate and 1% Carboxy methyl cellulose in treatment of mild to moderate dry eye.

MATERIALS AND METHODS

Patients with mild to moderate dry eye disease were enrolled in this study. Inclusion criteria were: (1) patients who had dry eye related symptoms (2) a no anesthesia schirmer's test value 6mm or more at 5 minutes (3) tear film breakup time(TBUT)<10seconds. (4) Fluorescein corneal staining score higher or equal to 3. Key exclusion criteria were: (1) anterior ocular disease (2) continued use of any eye drops (3) patients who underwent an operation to ocular surface disorder within 12 months or any intraocular surgery within 3 months before baseline examination. (4) Patients who had a punctual plug.

Study Design

This was a prospective randomized clinical study. Informed consents were obtained from all patients. Eligible patients were randomly allocated in 1:1:1 ratio and divided in 3 groups: rebamipide group, CMC group, and SH group. Patients in rebamipide group received 2% rebamipide ophthalmic suspension, 1 drop in each eye 4 times daily, Patients in CMC group received 1% carboxy methyl cellulose 1 drop in each eye 6 times daily and patients in SH group received 0.18% sodium hyaluronate 1 drop in each eye 6 times daily. Total treatment duration was 12 weeks. At baseline visit, patients were checked for whether they met the previously outlined inclusion and exclusion criteria and the following parameters were also assessed: fluorescein corneal staining, TBUT, schirmer's test, OSDI score and adverse reactions. All these parameters were evaluated at baseline, 2week, 4week, and 12 week.

Clinical assessment

Fluorescein corneal staining

5ul 2% fluorescein solution was instilled in the conjunctival sac as the patient blinked normally. Corneal staining was examined under standard illumination using a slit lamp microscope with a cobalt blue filter. According to the National Eye Institute report, the cornea was divided into 5 fractions [11], central, superior, temporal, nasal, and inferior. The degree of staining based on the following: grade 0 (normal): no staining; grade 1 (mild): superficial stippling micro punctate staining; grade 2 (moderate): macro punctate staining with some coalescent areas; grade 3 (severe): numerous coalescent macro punctate areas and/or patches. Each of the 5 regions was graded on a scale 0 to 3. The examiner circled the appropriate score for each region. The maximum score for each area was 3. The scores of the 5 areas were summed to obtain a total score for each eye. Therefore, the maximum score for each eye was 15.

TBUT

It was performed by moistening a fluorescein strip with sterile non preserved saline and applied it to the inferior tarsal conjunctiva. After several blinks, the tear film was examined by a broad beam of the slit-lamp microscope with a cobalt blue filter. The time lapse between the last blink and appearance of the first randomly distributed dark discontinuity in the fluorescein stained tear film was the tear break-up time. Break-up times less than 10 seconds were considered abnormal.

Schirmer's Test

This test was done without anaesthesia to measure tear volume as follows. The no. 41 Whatmann filter paper was folded 5 mm from one end and inserted at the junction of middle and outer third of lower lid without touching the cornea. The tear volume then was measured for 5 minute. The length in millimeters of tear fluid absorbed on the strip measured from the edge of the strip was recorded as tear volume.

OSDI score

Ocular surface disease index (OSDI) questionnaire contains 3 sections: section 1 is based on relative frequency of occurrence of each symptom (e.g., gritty feeling in eye, light sensitivity, and blurred vision), section 2 includes questions indicating limitations on certain activities (reading, driving at night, watching television), and section 3 is based on effect of environmental conditions (wind, low humidity, and air conditioning) on eyes. The OSDI score is based on a scale of 0-100, where 100 corresponds to complete disability (a response of "all of the time" to all questions answered) [12]. A negative change from baseline indicates improvement.

Safety Assessment

Adverse events were defined as any untoward medical occurrence in a participant. The participants were also encouraged to report any unfavorable or unintended symptoms or signs, such as itching sense, irrigation, and hyperemia.

Statistics

F-test (single factor ANOVA) was used for comparison of parameters in the 3 groups. A p-value <0.05 was considered to be statistically significant.

RESULTS

Patients

A total 60 patients were allocated randomly to receive 1 of the 3 treatment: 20 patients entered in the 2% rebamipide group, 20 patients entered in the 1% CMC group and 20 patients entered in the 0.18% sodium hyaluronate group. Of total 60 patients 18

patients (30%) were male and 42 patients (70%) were female.

Table-1: Age wise distribution

Age group	No.	%
20 to 30	6	10.00
31-40	8	13.33
41-50	10	16.67
51-60	14	23.33
>60	22	36.67
Total	60	100.00

Table-2: Sex wise distribution

Sex	No.	%
Male	18	30.00
Female	42	70.00
Total	60	100.00

Efficacy Results

Primary end point

FCS

FCS score was significantly decreased from baseline in each treatment group at each follow up visit. At all estimations (week 2, 4, 12), 2% rebamipide group showed statistically significant decrease in FCS score as compared with the SH group and CMC group.

Table-3: Comparison of fluorescein corneal staining sum score

Drugs	Baseline Mean(SD)	2nd week Mean(SD)	4th week Mean(SD)	12th week Mean(SD)
Rebamipide	3.00(1.94)	2.02(1.28)	1.29(1.20)	0.75(0.55)
CMC	3.10(1.86)	2.41(1.73)	1.85(1.39)	1.10(1.00)
SH	3.15(1.64)	2.50(1.24)	1.95(1.53)	1.15(0.86)
p-value	0.761	0.045	0.003	0.0001
CD at 5%		0.26	0.24	0.104

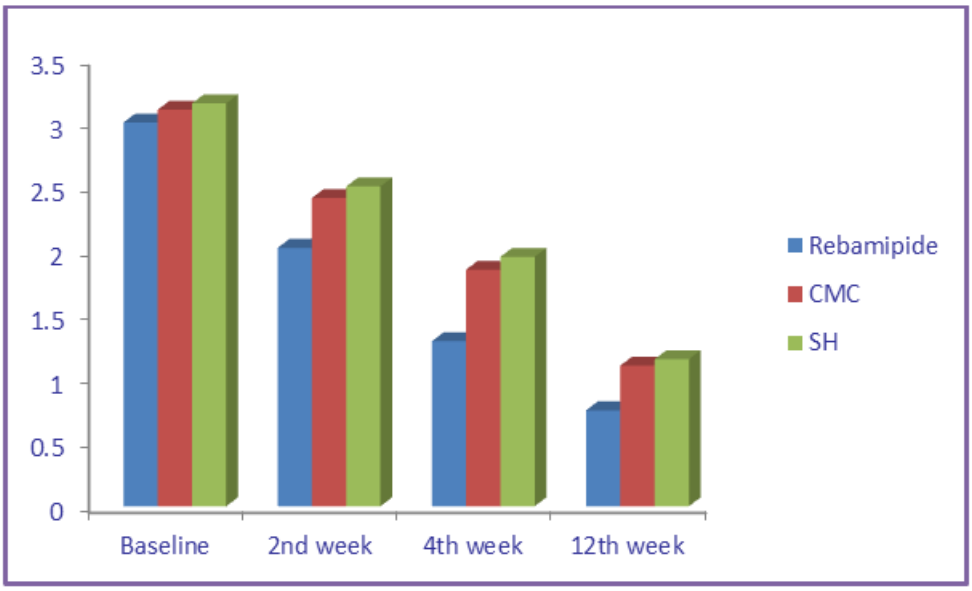

Fig-1: Comparison of FCS Score

Secondary end points

TBUT

Improvement in TBUT from baseline was observed in each group at each follow up visit. Rebamipide group showed statistically significant difference in improvement of TBUT score than CMC and SH group at all follow up visit.

Table-4: Comparison of TBUT

Drugs	Baseline Mean(SD)	2nd week Mean(SD)	4th week Mean(SD)	12th week Mean(SD)
Rebamipide	7.90(1.86)	9.15(2.08)	11.95(2.04)	13.10(0.81)
CMC	7.70(2.28)	8.15(1.59)	10.07(2.35)	12.05(1.49)
SH	7.84(1.97)	8.30(1.66)	10.42(1.74)	11.95(2.28)
p-value	0.096	0.030	0.0001	0.003
CD at 5%		0.32	0.372	0.30

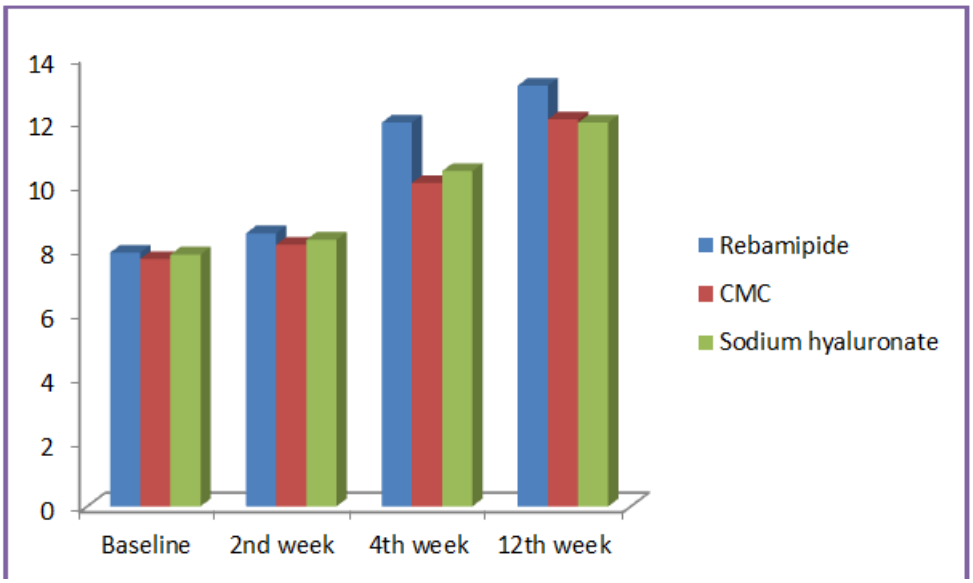

Fig-2: Comparison of TBUT

Schirmer's test

Schirmer's test value was significantly increased from baseline in each treatment group at each follow up visit. There was significant difference present in rebamipide group as compared with CMC and SH group in change from baseline tear production.

Table-5: Comparison of schirmer's test value

Drugs	Baseline Mean(SD)	2nd week Mean(SD)	4th week Mean(SD)	12th week Mean (SD)
Rebamipide	8.60(2.28)	9.20(2.81)	15.05(3.83)	25.55(2.65)
CMC	8.10(2.20)	8.25(3.34)	13.75(3.53)	23.35(5.57)
SH	8.55(2.26)	8.60(2.26)	13.30(2.81)	23.60(3.93)
p-value	0.470	0.004	0.001	0.0471
CD at 5%		0.461	0.62	0.78

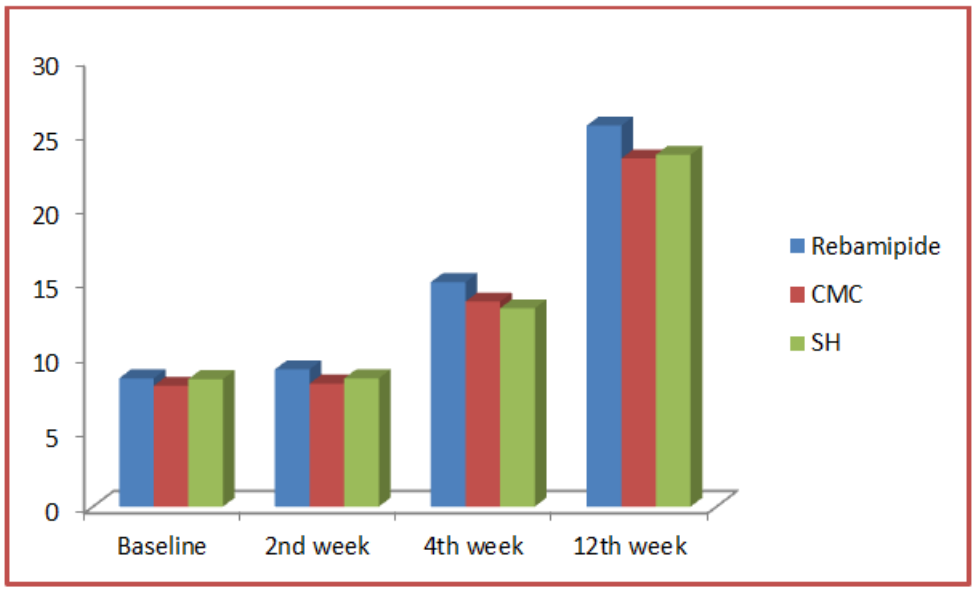

Fig-3: Comparison of Schirmer Test Value

OSDI score

OSDI score improved significantly from baseline in each treatment group. There were statistically significant difference seen in rebamipide group than CMC and SH group in mean OSDI score change from baseline at 4 and 12 weeks. Between SH and CMC group, SH group was significantly different from CMC group.

Table-6: Comparison of OSDI score

Drugs	Baseline Mean(SD)	4th week Mean(SD)	12th week Mean(SD)
Rebamipide	28.50(5.05)	16.5(2.88)	6.50(0.42)
CMC	28.00(4.30)	20.1(3.57)	14(1.20)
SH	28.70(4.80)	19.7(2.42)	10.70(0.85)
p-value	0.094	0.0001	<0.0001
CD at 5%		0.541	0.16

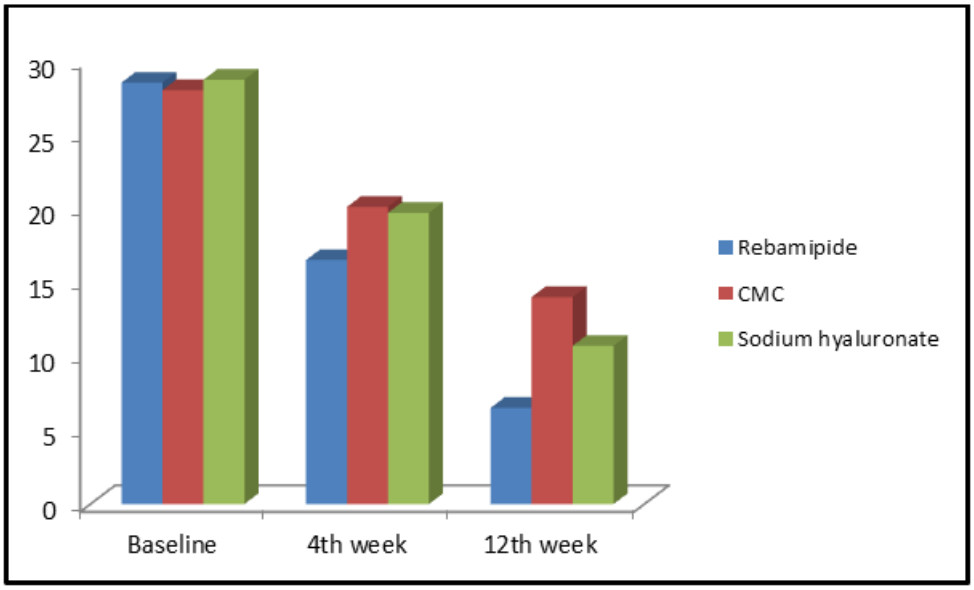

Fig-4: Comparison of OSDI Score

Safety Evaluation

Adverse events were observed in 8 patients (20%) in the 2% rebamipide group and in 4 patients (10%) in the 0.18% sodium hyaluronate group and no adverse event seen in CMC group. The most frequently observed adverse event was dysgeusia (bitter taste), which was observed in 2% rebamipide group. All cases of dysgeusia reported in this study were judged to be treatment related. Dysgeusia and all eye disorders were mild in severity and resolved either with appropriate treatment or with no treatment. No deaths and no serious or severe adverse events were observed in this study.

Table-7: Adverse effect

Drugs	No. of patients	Adverse effect	
		No.	%
Rebamipide	20	8	20.00
CMC	20	0	0.00
Sodium hyaluronate	20	4	10.00

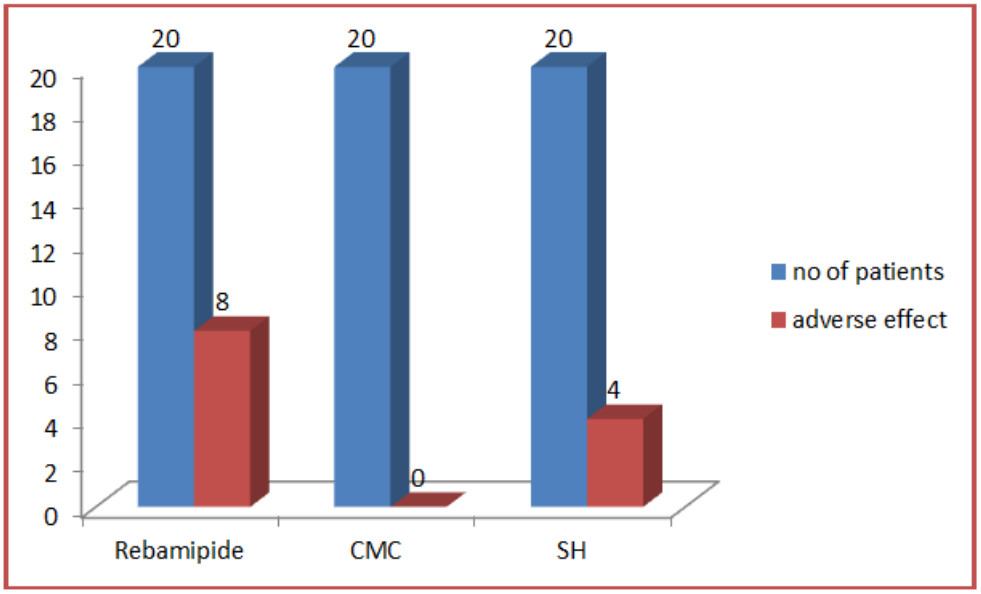

Fig-5: Compare the adverse effect

DISCUSSION

Our study results suggested that the 3 group of drugs 2% rebamipide, 0.18% sodium hyaluronate and 1% CMC improved the objective signs and subjective symptoms of mild to moderate dry eye but it was observed that 2% rebamipide has greater efficacy than other two groups.

The 2% rebamipide was effective at improving both the objective sign and subjective symptoms of dry eye at 2 week, 4 week and 12 week of follow up. Rebamipide demonstrated a marked improvement in FCS score. Such improvements in staining scores are important because they indicate an improvement in the ocular surface [13], FCS reflecting corneal epithelial integrity. Staining with FCS is the standard method used to demonstrate the ocular surface damage [13, 14].

Rebamipide also improved the secondary end point objective value of TBUT and schirmer's test. Rebamipide has been shown to increase the number of periodic acid-Schiff-positive cells (goblet cells) in the conjunctiva [15] and mucin level in cornea and conjunctiva [15, 16]. Because decreased mucin levels on the surface of the cornea and a decreased density of goblet cells have been observed in patients with dry eye [17], the method of action of rebamipide is expected to be beneficial for this disease. With this mechanism, rebamipide also is expected to be effective in patients with dry eye resulting from short TBUT, because disturbance of ocular surface mucin is thought to be one of the main cause of tear film instability and accompanying shorter TBUT [1], Ueda et al. study results showed that there was significant improvement in the fluorescein ocular surface staining score, schirmers and TBUT [18]. We postulated that 2% rebamipide improve tear production and quality as seen with schirmer and TBUT value.

In addition to its benefits on objective measures, 2% rebamipide was more effective than 0.18% sodium hyaluronate and 1% CMC on OSDI scoring, showing greater improvement in symptoms. Koh *et al*., [19] studied the role of rebamipide in the quality of vision in patients with dry eye who have mucin deficiency. The authors reported an improvement

in the optical quality due to stabilization of the tear film by mucin production by rebamipide. In our result, it was seen that rebamipide improved the FCS score, TBUT, Schirmers value and OSDI score which is supported by above study.

Rebamipide ophthalmic suspension does not contain preservatives that can be detrimental to eye health. One of the most commonly used preservatives in ocular product is benzalkonium chloride, which destabilizes the tear film, disrupts the corneal epithelium, decrease the density of goblet cells, and causes conjunctival squamous metaplasia and apoptosis damage to deeper ocular tissue [20, 21]. Thus, rebamipide may be expected less harmful even if it is used in the long-term

This study also showed that other two drugs SH and CMC significantly improved the objective signs and subjective symptoms of dry eye at all-time points. There were no statistically significant difference between the SH and CMC group in FCS scoring, TBUT and schirmer's test except in OSDI scoring, in which SH group showed better improvement of OSDI score than that of CMC group. SH is a glycosaminoglycan disaccharide biopolymer and consists of repeating alternating sequences of N-acetyl-glucosamine and glucuronate in linear chains [22]. It has a huge capacity to bind water, the affinity is 1000-fold of its own weight, and it resists dehydration [23]. Moreover, previous reports shows that hyaluronate effectively improve ocular surface damage [24], promotes epithelial cell proliferation [25] and migration [26], and stimulates epithelial wound healing [27].

CMC is an anionic cellulose polymer with a carboxylic group. CMC exhibits excellent bioadhesive characterestics [28, 29], and its anionic characterestics may be beneficial in increasing the tear retention time [30]. SH has a stabilizing effect on the tear film [31], which protects the ocular surface from irritations. The high water retention capacity of SH also contributes to a favorable microenvironment during the ocular surface repair process [32]. It is well established that, compared with CMC, hyaluronan has better pseudo plastic and elastic properties, similar to those of natural tears, which helps to maintain a stable tear film between as well as during blinks [33]. As a result patient treated with SH experienced significantly better comfort, while almost 60% patients treated with CMC reported blurred vision. Brignole *et al*., [34] compared the efficacy of SH and CMC and reported that there were no statistically significant differences between the 2 eye drops, assessed by flow cytometry, objective clinical parameters (corneal staining and TBUT), and final improvement of subjective symptoms. In our study results showed that there was no statistical significant difference in SH and CMC group except OSDI scoring which was better in SH group.

In our study it was shown that rebamipide was more efficacious than sodium hyaluronate and CMC. This result is supported by Kinoshita *et al*., study, a comparison of 2% rebamipide ophthalmic suspension with 0.1% sodium hyaluronate in a Randomized multicenter phase 3 studies showed marked improvement in signs and symptoms of dry eye disease as compared to sodium hyaluronate [35]. In our study we included the Carboxy methyl cellulose eye drop in a separate group of patients and results showed that CMC had lower efficacy than rebamipide. In between CMC and SH group there was no significant difference between in two group except in OSDI scoring which was better in SH group of drugs. The efficacy of rebamipide group was better than rest of two groups.

No significant adverse event seen in 3 groups of drugs. In rebamipide group most frequently observed adverse event was bitter test. This was observed 8 patients out of 20 patients (20%).In phase 2 and phase 3 trial showed 9.7% and 15.7% patient had bitter test which was lower than our study. In SH group 4 patients out of 20 were observed adverse effect (10%). No adverse event seen in CMC group.

The limitations of our study are small sample size, not use lissamine green solution for conjunctival staining. For dry eye disease long term treatment would be required because it is often seen as a chronic disease. Further studies may be required for further enhancement whether the improvements reported with rebamipide are maintained in the longer time.

CONCLUSION

Patients were treated with 3 commercially available eye drops containing 2% rebamipide, 0.18% sodium hyaluronate, and 1% CMC and these drugs were effective in the treatment of mild to moderate dry eye. Three groups of drugs significantly improved the condition of the corneal surface, lengthened the TBUT and schirmer's test value and reduced the OSDI score. But the results of our study showed that 2% rebamipide was well tolerated and provide better efficacy than 0.18% sodium hyaluronate and 1% CMC. So, 2% rebamipide could therefore be prescribed advantageously from early stage of dry eye. In comparison to sodium hyaluronate and CMC group there were no statistically significant difference found in between two groups except OSDI scoring which was better in sodium hyaluronate group. No significant adverse events were seen in three groups of drugs during the study period.

REFERENCES

1. Definition DE. Classification. The definition and classification of dry eye disease: Report of the definition and classification Subcommittee of the international dry eye workshop (2007). The Ocular Surface. 2007 Apr;5(2):76.

2. Miljanovic B, Dana R, Sullivan DA. Impact of dry eye syndrome on vision-related quality of life. Am J Ophthalmol; 2007; 143(3):409-415.
3. Pinho Tavares FD, Fernandes RS, Bernardes TF, Bonfioli AA, Carneiro Soares EJ. Dry eye disease. InSeminars in ophthalmology 2010 May 1 (Vol. 25, No. 3, pp. 84-93). Taylor & Francis.
4. Gayton JL. Etiology, prevalence, and treatment of dry eye disease. Clinical ophthalmology (Auckland, NZ). 2009;3:405.
5. Pflugfelder SC, Geerling G, Kinoshita S, Lemp MA, McCulley J, Nelson D, Novack GN, Shimazaki J, Wilson C. Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop (2007). Ocular Surface. 2007 Apr 1;5(2):163-78.
6. Stanković-Babić G, Zlatanović G, Đorđević-Jocić J, Cekić S, Vujanović M. Therapeutical approach to dry eye syndrome. Medicinski pregled. 2010;63(11-12):793-800.
7. Pflugfelder SC, Geerling G, Kinoshita S, Lemp MA, McCulley J, Nelson D, Novack GN, Shimazaki J, Wilson C. Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop (2007). Ocular Surface. 2007 Apr 1;5(2):163-78.
8. Iijima K, Ichikawa T, Okada S, Ogawa M, Koike T, Ohara S, Shimosegawa T. Rebamipide, a cytoprotective drug, increases gastric mucus secretion in human: evaluations with endoscopic gastrin test. Digestive diseases and sciences. 2009 Jul 1;54(7):1500-7.
9. Naito Y, Yoshikawa T. Rebamipide: a gastrointestinal protective drug with pleiotropic activities. *Expert Rev Gastroenterol Hepatol* 2010; 4:261-70.
10. Yamasaki K, Kanbe T, Chijiwa T. Gastric mucosal protection by OPC-12759, a novel antiulcer compound, in the rat. *Eur J Pharmacol* 1987; 142:23-9.
11. De Paiva CS, Pflugfelder SC. Corneal epitheliopathy of dry eye induces hyperesthesia to mechanical air jet stimulation. *Am J Ophthalmol.* 2004; 137 (1):109-115.
12. Schiffman RM, Christianson MD, Jacobsen G. Reliability and validity of the ocular surface disease index. *Arch Ophthalmol.* 2000; 118(5):615-621.
13. de Pinho Tavares F, Fernandes RS, Bernardes TF. Dry eye disease. *Semin Ophthalmol* 2010; 25:84-93.
14. Hamrah P, Alipour F, Jiang S. Optimizing evaluation of lissamine green parameters for ocular surface staining. *Eye (Lond)* 2011; 25:1429-34.
15. Urashima H, Takeji Y, Okamoto T. Rebamipide increase the mucin-like substance contents and periodic acid Schiff reagent-positive cells density in normal rabbits. *J Ocul Pharmacol Ther* 2012; 28:264-70.
16. Takeji Y, Urashima H, Aoki A, Shinohara H. Rebamipide increase mucin-like glycoprotein production in corneal epithelial cells. *J Ocul Pharmacol Ther* 2012; 28:259-63.
17. Rivas L, Oroza MA, Perez-Esteban A, Murube-del-Castillo J. Morphological changes in ocular surface in dry eyes and other disorders by impression cytology. Graefe's archive for clinical and experimental ophthalmology. 1992 Jul 1;230(4):329-34.
18. Ueda K, Matsumiya W, Otsuka K, Maeda Y, Nagai T, Nakamura M. Effectiveness and relevant factors of 2% rebamipide ophthalmic suspension treatment in dry eye. BMC ophthalmology. 2015 Dec;15(1):58.
19. Koh S, Inoue Y, Sugmimoto T. Effect of rebamipide ophthalmic suspension on optical quality in the short break-up time type of dry eye. *Cornea.* 2013; 32(9):1219–1223.
20. Burstein NL. The effects of topical drugs and preservatives on the tears and corneal epithelium in dry eye. *Trans Ophthalmol Soc U K* 1985; 104:402-9.
21. Baudouin C, Labbe A, Liang H. preservatives in eyedrops: the good, the bad, and the ugly. *Prog Retin Eye Res* 2010; 29:312-34.
22. Meyer K. chemical structure of hyaluronic acid. *Fed Proc*. 1958; 17:1075-1077.
23. Nakamura M, Hikida M, Nakano T. characterization of water retentive properties of hyaluronan. *Cornea* 1993; 12:433-436.
24. Aragona P, Papa V, Micali A. Long term treatment with sodium hyaluronate-containing artificial tears reduces ocular surface damage in patients with dry eye. *BR J Ophthalmol*. 2002; 86:181-184.
25. Inoue M, Katakami C. The effect of hyaluronic acid in corneal epithelial cell proliferation. *Invest Ophthalmol Vis Sci*. 1993; 34:13-15.
26. Gomes JA, Amankwah R, Powell-Richards A. Sodium hyaluronate(hyaluronic acid) promotes the migration of human corneal epithelial cells in vitro. *Br J Ophthalmol*. 2004; 88:821-825.
27. Giovanni C, Claudio B, Settimio R. Hyaluronan-induced stimulation of corneal wound healing is pure pharmacological effect. *J Ocul Pharmacol Ther*. 2004; 20:548-543.
28. Peppas NA, Buri PA. Surface, interfacial and molecular aspects of polymer bioadhesion of soft tissues. *J control Release*. 1985; 2:257-275.
29. Hunt G, Kearney P, Kellaway IW. *Mucoadhesive Polymers in Drug Delivery Systems Fundamentals and Techniques*. Weinheim, Germany: VCH; 1987:180-199.
30. Holly FJ. Aqueous tear substitutes. In: Lamberts DW, Poster DE, eds. *Clinical Ophthalmic Pharmacology*. Boston, MA: Little Brown; 1987:497-518.

31. Papa V, Aragona P, Russo S. Comparison of hypotonic and isotonic solutions containing sodium hyaluronate on the symptomatic treatment of dry eye patients. *Ophthalmologica*. 2001; 215:124-127.
32. Aragona P, Papa V, Micali A. Long term treatment with sodium hyaluronate-containing artificial tears reduces ocular surface damage in patients with dry eye. *Br J Ophthalmol*. 2002; 86:181-184.
33. Tiffany JM. Viscoelastic properties of human tears and polymer solutions. InLacrimal Gland, Tear Film, and Dry Eye Syndromes 1994 (pp. 267-270). Springer, Boston, MA.
34. Brignole F, Pisella PJ, Dupas B. Efficacy and safety of 0.18% sodium hyaluronate in patient with moderate dry eye syndrome and superficial keratitis. *Graefes Arch Clin Exp Ophthalmol* 2005; 243:531-538.
35. Kinoshita S, Oshiden K, Awamura S. Rebamipide Ophthalmic Suspension Phase 3 Study Group A randomized, multicenter phase 3 study comparing 2% rebamipide (OPC-12759) with 0.1% sodium hyaluronate in the treatment of dry eye. *Ophthalmology*. 2013; 120(6):1158–1165.