THE EFFECTIVENESS TEST OF EYEDROP LODOXAMIDE TROMETHAMINE 0.1 % AND SODIUM CROMOGLYCATE 2% IN VERNAL KERATOCONJUNCTIVITY IN DR. SOETOMO HOSPITAL, SURABAYA

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ABSTRACT

A study on the effectiveness of Lodoxamide Tromethamine 0.1% and Sodium Cromoglycate 2% has been conducted to 36 patients with vernal keratoconjunctivity in Ophthalmologic Outpatient Clinic, Dr Soetomo Hospital, Surabaya, from August 1999 to February 2000. The patients were divided into 2 groups, i.e., Lodoxamide and Cromoglycate groups. Observation was carried out at the first, second, third, and fourth weeks. From sample distribution, it was found that most of the patients (16 individuals) belonged to age group of 1 - 5 years (44.44%), followed 15 patients in age group of 6 - 10 years (41.67%). Male patients were 32 individuals or 88.89% of all patients, higher than female ones. Atopic history was 22% in children and 19.5% in family history. Regarding the type of vernal keratoconjunctivity, the combined type was found to be the most frequent compared to the others (96.11%). Most of the samples (52.78%) suffered from vernal keratoconjunctivity for less than 1 year. Results of observation revealed significant difference in therapy effectiveness between eyedrops Lodoxamide Tromethamine 0.1% and Sodium Cromoglycate 2% in subjective complaints/symptoms (such as itch, secrete, epiphora) and objective complaints/sign (hyperemia and conjunctival edema, corneal lesion), which was varied from the first to the third week, while at the fourth week the difference was not significant. There was no significant difference in therapy effectiveness between both eyedrops in the objective symptoms (trantas dots and laboratory test). Comparative analysis on the objective symptoms (papillary hypertrophy) between both groups could not be conducted. However, significant difference was found in group given with Lodoxamide Tromethamine 0.1% before and fourth week after treatment. In group given with Sodium Cromoglycate 2%, significant difference was not found until the study was over. Side effects of the treatment were not apparent during the study.

***Keywords**: lodoxamide tromethamine, sodium cromoglycate, vernal keratoconjunctivity*

INTRODUCTION

Vernal keratoconjunctivity is defined as asymmetric, bilateral conjunctival inflammation. It is possible to occur in cornea and most commonly found in young individual and has relapsing and long duration characteristics. A proportion of 60 - 70% is accompanied with another allergic history. Primary complaints are usually itch, elastic dirty yellow secrete, epiphore, uncomfortable sense, photophobia and even pseudoptosis if there are numerous conjunctival papillary hypertrophy of palpebra (Lousi, 1979; John et al., 1997-1998). Delmar RC (1994) and Smolin (1983) suggest that this disease occurs in individuals of 3-25 years old (it is rarely occurs in those below 3 years old or above 25 years old). Its incidence in male is twice higher compared to that in female at pre-pubertal age and the incidence is equal at puberty. The most common patients, according to Vaughn (1992) and Duke Elder (1965), are male and puberty individual aged 5-10 years. This is in line with result study by Ratna D. (1994). Laksmi T (1984), who found that vernal conjuctivity potential occurs anytime, and does not related with seasonal change.

Vernal keratoconjunctivity represents allergic reaction, belonged to type 1 hypersensitivity reaction. It occurs by antigen-immunoglobulin E binding on mast cell surface that trigger calcium transportation into mast cell membrane and change membrane permeability. This will induce anaphylaxis and manifest as allergic reaction (Smolin, 1981). As in other allergy, the basic management is to eliminate the allergen. However, this is often difficult due to difficulties in determining the exact allergen factor. Living in air-conditioned room or cold place can reduce complaints. In addition to this nonspecific treatment, including administration of aspirin, superficial surgical procedure, such as ceractomy, tarsectomy, and drugs, are also useful. Some drugs that can be used for therapy are antihistamine and vasoconstrictor, non-steroid anti inflammation, corticosteroid, acetylsistein, immunosuppressive and mast stabilizer. Corticosteroid is proved to be effective

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especially in emergency or severe cases. However, its long-term use can bring about cataract and glaucoma as complication, which, contrastingly, may reduce visual acuity.

Regarding the nature of vernal keratoconjunctivity that attacks young individuals, its relapsing and prolonged characteristiecs, as well as its occurrence that may come along with corneal lesion enabling to affect patient's visual acuity; it is essential to provide effective and safe drugs for long term use (MR. Alansmith, 1982; Lee & David, 1996).

Lodoxamide Tromethamine, as well as Sodium Cromogylate, is mast cell stabilizers or mast cell degranulating inhibitor. In hypersensitivity type I reaction, mast cell degranulates and releases vasoactive substance or allergic mediator such as histamine, heparin, protease, serotonin, prostaglandin and Platelet Activating Factor (PAF). Histamine triggers edema, itch and hyperemia. ECFA attracts eosinophil to target area; SRS-A/leukotrin causes edema and vascular permeability increase. Prostaglandin responsible to bronchoconstriction and increase of vascular permeability. It brings about vasodilatation, pain, fever and edema; while PAG attracts eosinophil more than ECFA, bronchoconstriction, vasodilatation, and vascular permeability increase.

Dalmar RC in his research (1992) reports that Lodoxamide Tromethamine and Sodium Cromogylate are safe for vernal keratoconjunctivity therapy. It was said that Lodoxamide Tromethamine is more effective considering its more considerable and rapid therapeutic response. Furthermore, Lodoxamide Tromethamine has advantage to prevent eosinophil migration, which secrete eosinophil activity-appropriate Eosinophil Cationic Protein (ECP) granule, Major Basic Protein (MBP) that may lead to corneal lesion, and Eosinophil Peroxidase (EOP) (Narsing, et. al., 1994; Clement W, 1996; Lee & David, 1996).

The author conducted effectiveness study of comparison between Lodoxamide Tromethamine and Sodium Cromoglycate on vernal keratoconjunctivity patient in Dr. Soetomo Hospital, Surabaya. This study was carried out to address the effectiveness differences between eyedrops Lodoxamide Tromethamine 0.1% and Sodium Cromoglycate 2% on vernal keratoconjunctivity patient in Dr. Soetomo Hospital. Considering the disease characteristics, i.e., occurring in young individuals, relapsing and protracted course; Lodoxamide Tromethamine has better effectiveness compared to Sodium Cromoglycate with respect to its action as mast cell stabilizer and eosinophil inhibitor whose secret may lead to corneal disparity. Hence, Lodoxamide Tromethamine can be alternatively used as therapeutic of choice for effective long-term treatment with minimum side effect.

METHOD

This study was double blind randomized clinical trial (Tjokroprawiro A, 1996), conducted in Ophthalmologic Outpatient Clinic, Dr Soetomo Hospital, Surabaya, from August 1999 to February 2000. Sample population were individual admitted to Ophthalmologic Outpatient Clinic, Dr Soetomo Hospital, Surabaya diagnosed with vernal keratoconjunctivity according to anamnesis, clinical examination and laboratory of conjunctival specimen. Sample size was taken using total sampling, comprising all patients with vernal keratoconjunctivity who came to Ophthalmologic Outpatient Clinic, Dr Soetomo Hospital, Surabaya, from August 1999 to February 2000.

Inclusion criteria for the samples (Mark BA, 1990) were vernal keratoconjunctivity patient not wearing contact lens, not using other drug that would affect the study, not having secondary infection eye disease, and willing to participate in the study. The drop out criteria (Mark BA, 1990; Ernest M., 1991) was related to particular condition i.e. when the patient did not return (loss to follow up), occurrence of another infection during the study and presence of drug hypersensitivity. The collected data were analyzed using Mann Whitney's test.

RESULT

This was an experimental study with double blind randomized clinical trial in Ophthalmologic Outpatient Clinic, Dr Soetomo Hospital, Surabaya, from August 1999 to January 2000. Sample size was total sampling from all patients who met sample criteria during experiment period.

We obtained 36 individuals as samples that were divided into two groups, Lodoxamide Tromethamine and Sodium Cromoglyate group, each comprising 18 individuals. The collected data were analyzed by chi square or t test with significance level of 0.05 (5%) and was indicate significant if $p<0.05$ and insignificant if $p>0.05$

The study demonstrated that most of the patients (16 individuals) belonged to age group of 1 - 5 years (44.44%), followed by 15 patients in age group of 6 - 10 years (41.67%). Male patients were 32 individuals or 88.89% of all patients, higher than female, which are five patients (13.89%). Total atopic history in children

was found to be 22.2% and 19.5% in parents. The common type of vernal keratoconjunctivity was compound type (61.11%). Most of the samples (52.78%) suffered from vernal keratoconjunctivity for less than 1 year.

Table 1. Distribution of symptom (itch) on group Lodoxamide and Cromoglycate during the observation (before treatment and 1st, 2nd, 3rd, and 4th week after treatment)

	Treatment								N	p (S.NS)
	Lodoxamide Tromethamine				Sodium Cromoglycate					
Observation	0	1	2	3	0	1	2	3		
Before	-	10	8	-	-	10	8	-	36	1.000 (NS)
1st week	6	11	1	-	1	13	4	-	36	0.0216 (S)
P		0.0015 (S)				0.0431 (S)				
2nd week	14	4	-	-	4	14	-	-	36	0.0010 (S)
P		0.0002 (S)				0.0022 (S)				
3rd week	18	-	-	-	16	2	-	-	36	0.1513 (NS)
P		0.0002 (S)				0.0002 (S)				
4th week	18	-	-	-	18	-	-	-	36	1.000 (NS)
P		0.0002 (S)				0.0002 (S)				

Table 2. Distribution of symptom (secrete) on group Lodoxamide and Cromoglycate during the observation (before treatment and 1st, 2nd, 3rd, and 4th week after treatment)

	Treatment						n	p (S.NS)
	Lodoxamide Tromethamine			Sodium Cromoglycate				
Observation	0	1	2	0	1	2		
Before	1	16	1	-	10	8	36	0.3239 (NS)
1st week	12	6	-	5	13	-	36	0.0212 (S)
P		0.0022 (S)			0.0180 (S)			
2nd week	18	-	-	17	1	-	36	0.3173 (NS)
P		0.0003 (S)			0.0002 (S)			
3rd week	18	-	-	18	-	-	36	1.000 (NS)
P		0.0003 (S)			0.0002 (S)			
4th week	18	-	-	18	-	-	36	1.000 (NS)
P		0.0003 (S)			0.0002 (S)			

Table 3. Distribution of symptom (epiphora) on group Lodoxamide and Cromoglycate during the observation (before treatment and 1st, 2nd, 3rd, and 4th week after treatment)

	Treatment								N	p (S.NS)
	Lodoxamide Tromethamine				Sodium Cromoglycate					
Observation	0	1	2	3	0	1	2	3		
Before	-	15	3	-	-	15	3	-	36	1.000 (NS)
1st week	6	12	-	-	1	16	1	-	36	0.0256 (S)
P		0.0077 (S)				0.1088 (NS)				
2nd week	15	3	-	-	2	16	-	-	36	0.0000 (S)
P		0.0004 (S)				0.0431 (S)				
3rd week	18	-	-	-	13	5	-	-	36	0.0175 (S)
P		0.0002 (S)				0.0007 (S)				
4th week	18	-	-	-	18	-	-	-	36	1.000 (NS)
P		0.0002 (S)				0.0002 (S)				

Table 4. Distribution of sign (papillary hypertrophy) on group Lodoxamide and Cromoglycate during the observation (before treatment and 1st, 2nd, 3rd, and 4th week after treatment)

	Treatment								N	p (S.NS)
	Lodoxamide Tromethamine				Sodium Cromoglycate					
Observation	0	1	2	3	0	1	2	3		
Before	1	13	3	1	4	14	-	-	36	0.0218 (S)
1st week	2	12	3	1	4	14	-	-	36	
P		0.3173 (NS)				0.3173 (NS)				
2nd week	2	12	3	1	4	14	-	-	36	
P		0.3173 (NS)				0.3173 (NS)				
3rd week	2	13	3	-	14	4	-	-	36	
P		0.1088 (NS)				0.3173 (NS)				
4th week	10	5	3	-	18	10	-	-	36	
P		0.0033 (S)				0.1422 (S)				

Table 5. Distribution of sign (conjunctival hyperemia and edema) on group Lodoxamide and Cromoglycate before and during the observation (before treatment and 1st, 2nd, 3rd, and 4th week after treatment)

	Treatment								N	p (S.NS)
	Lodoxamide Tromethamine				Sodium Cromoglycate					
Observation	0	1	2	3	0	1	2	3		
Before	2	10	6	-	1	14	3	-	36	0.4924 (NS)
1st week	5	13	-	-	2	16	-	-	36	0.0077
P		0.0077 (S)				0.1000 (NS)				(S)
2nd week	15	3	-	-	6	12	-	-	36	0.0027
P		0.3173 (NS)				0.0117 (S)				(S)
3rd week	18	-	-	-	14	4	-	-	36	0.0365
P		0.1088 (NS)				0.0007 (S)				(S)
4th week	18	-	-	-	18	-	-	-	36	1.000
P		0.0004 (S)				0.0003 (S)				(NS)

Table 6. Distribution of sign (trantas dot) on group Lodoxamide and Cromoglycate during the observation (before treatment and 1st, 2nd, 3rd, and 4th week after treatment)

	Treatment						n	p (S.NS)
	Lodoxamide Tromethamine			Sodium Cromoglycate				
Observation	0	1	2	0	1	2		
Before	4	13	1	8	9	1	36	0.2096 (NS)
1st week	4	13	1	8	9	1	36	0.0508
P		0.1797 (NS)			1.0000 (NS)			(NS)
2nd week	4	13	1	8	9	1	36	0.2096
P		1.0000 (S)			1.0000 (S)			(NS)
3rd week	12	6	-	9	9	-	36	0.3173
P		0.0003 (S)			0.0002 (S)			(NS)
4th week	17	1	-	17	4	-	36	0.1540
P		0.0003 (S)			0.0277 (S)			(NS)

Table 7. Distribution of sign (corneal lesion) on group Lodoxamide and Cromoglycate during the observation (before treatment and 1st, 2nd, 3rd, and 4th week after treatment)

	Treatment						n	p (S.NS)
	Lodoxamide Tromethamine			Sodium Cromoglycate				
Observation	0	1	2	0	1	2		
Before	-	14	4	-	16	2	36	0.3778 (NS)
1st week	8	10	-	2	16	-	36	0.0277
P		0.0022 (S)			0.0679 (NS)			(NS)
2nd week	16	2	-	7	11	-	36	0.0021
P		0.0003 (S)			0.0003 (S)			(NS)
3rd week	18	-	-	16	2	-	36	0.1513
P		0.0002 (S)			0.0003 (S)			(NS)
4th week	18	-	-	18	-	-	36	1.0000
P		0.0002 (S)			0.0002 (S)			(NS)

Table 8. Distribution of laboratory result on group Lodoxamide and Cromoglycate during the observation (before treatment and 1st, 2nd, 3rd, and 4th week after treatment)

	Treatment						n	p (S.NS)
	Lodoxamide Tromethamine			Sodium Cromoglycate				
Observation	0	1	2	0	1	2		
Before	1	12	5	1	13	4	36	0.7387 (NS)
1st week	11	7	-	9	9	-	36	0.5083
P		0.0010 (S)			0.0022 (S)			(NS)
2nd week	17	1	-	17	1	-	36	1.0000
P		0.0003 (S)			0.0003 (S)			(NS)
3rd week	18	-	-	18	-	-	36	1.0000
P		0.0003 (S)			0.0003 (S)			(NS)
4th week	18	-	-	18	-	-	36	1.0000
P		0.0003 (S)			0.0003 (S)			(NS)

DISCUSSION

This study was an experimental study using double blind randomized clinical trial to found the effectiveness of Lodoxamine Tromethamine 0.1% and Sodium Cromoglycate 2% eyedrops toward Vernal Conjunctivitis.

Variables measured were subjective complaint/symptom (itch, secret, and epiphora), objective complaint/sign (Papillary hypertrophy, conjunctival hyperemia and edema, trantas dot, and corneal lesion), and laboratory examination. Each was grouped with certain value. Observation was performed at first, second, third and fourth week after treatment. In each observation, we evaluated the progress of symptoms, signs and

laboratory examination. This study used biomicroscope slit lamp and laboratory examination.

Effectiveness analysis between the two groups before treatment and first, second, third and fourth week after the treatment was performed using Mann Whitney and Wilcoxon Rank Sum W test. While each groups' condition itself before and after the treatment was analyzed using Wilcoxon Matched Pairs Signed Rank test.

The study was carried out for 6 months, starting at August 1999 up to January 2000. The last patient was observed until February 2000. This study involved 36 patients, divided into Lodoxamide and Cromoglycate groups, each comprising equal number of patient. From t table, it is apparent that most of the patients were aged of 1-5, totally 16 individuals (44.44%), in which individual aged five took the highest proportion. It was followed with age group of 6-10 years, which were 15 patients (41.67%). Furthermore, male patients were 31 individuals (86.11%), higher than female, which were only five (13.89%). This was in line with the findings of Vaughn and Duke Elder that patients frequently suffered from this disease are pre-pubertal individuals aged 5-10 and male. The results also confirmed a study by Ratna D (1994), who found that age group 5-10 years (54%) and male (84%) as the most frequent patient, compared to female (16%) (Duke Elder, 1967; Ratna D, 1994; Vaughn D.G. et.al., 1992).

Youngest age obtained in this study was 3 years old while the oldest was 13 years old. Delmar RC (1994) and Smolin (1983) suggest that, regarding to age, the vernal conjunctivity patient below 3 years and above 25 years or puberty period are rare. Male incidence was twice than female in pre-pubertal period. However, it was equal in pubertal period. This is because pre-pubertal period is more sensitive to the allergen reaction, so that it has more possibility to experience allergic reaction. Any genetic and environmental factors may also play a role concerning the predominant prevalence of male patient (Delmar RC, 1994)

Atopic history of children themselves was 22.2% while that from parents was 19.5%. This percentage in children was lower than that resulted from the study of Ntim (1997), i.e. 35%. However, the percentage for parent was similar, i.e 20%. Louis (1979) suggested that 60-70% of vernal keratoconjunctivity patient was followed by another allergic history. The low percentage may result from the fact that data were only taken from anamnesis, without undertaking any particular allergy test. In this study, allergy manifested in asthma bronchial, dermatitis, and urticaria, which in line with the studies of 1CT Ntim and Ratna D.

It was disclosed that the majority type of vernal keratoconjunctivity was compounds between limbal and palpebra type with 61.11%. This corresponds suitably with the fact that the highest proportion of vernal keratoconjunctivity in Asia is compound type. Limbal type is common in Indians and Africans, in which the prognosis is better than compound type. Genetic factor seems to be responsible in the type of vernal keratoconjunctivity.

We found that most of the patients suffered from vernal keratoconjunctivity for less than a year with percentage 52.78% and those suffering for more than 2 years were 8.33%. Smolin (1981) suggest that this disease occurs in a long period and relapses until 4-10 years. Considering the course of the disease that most commonly less than a year, it is necessary to provide explanation regarding to the disease itself and suggestion on safe long-term treatment. A study from Ntim (1997) found that the attack onset was before 4 years of age, meaning that the duration was 4 years.

From table 1, analysis of itch symptom using Wilcoxon Matched Pairs Signed Rank test found significance difference before treatment and from first to fourth week after treatment. This shows that both drugs are able to reduce the symptom (itch). However, the reduction on group Lodoxamide occurred earlier and more considerable than Cromoglycate. This is in accordance with study of Delmar R (1992) and supported by Andrea Leonardi (1997) and Lee & David (1996) who suggested that Lodoxamide reduced the itch symptom more rapidly than Cromoglycate.

Lodoxamide group had higher proportion of itch-reduced patient compared to Cromoglycate, especially at the first and second weeks of observation. In third week, patient with such complaint were not found anymore in Lodoxamide group, and at fourth week we found no more such complaint in both groups.

Itch is the main symptom complained by vernal keratoconjunctivity patient as a result of histamine release, one of allergic mediator, attributable to mast cell degranulating. Lodoxamine prevents eosinophil migration into tears and conjunctiva, thus eosinophil not migrating (in blood) through inhibition pathway releases histaminase that inactivated histamine. Thereby, Lodoxamine is more effective than Cromoglycate in overcoming the main complaint (itch) in the patients. This is very beneficial for the patient as the complaint can be rapidly overcome, despite the fact that at the end of observation, which was fourth week after treatment, both drugs demonstrated the same result (Smolin, 1981).

Analysis of table 2 on secrete symptom, using Wilcoxon Matched Pairs Signed-Rank test. we found significant difference before and after treatment, from the first week until fourth week, both in Loxamide and Cromoglycate group. Analysis of secrete symptom by Mann Whitney U Wilcoxon Rank Sum W test reveals significant difference between Lodoxamide and Cromoglycate only at the first week.

On the first week we found significant decrease of secrete symptom on Lodoxamide group compared to Cromoglycate, albeit the decrease was no longer significant at the next week.

In vernal keratoconjunctivity, eosinophil in blood vessel releases aryl sulfatase and together with MBP, they inactivate SRSA. SRSA and prostaglandin are responsible for conjunctival secretion. Since SRSA has been inactivated then it is apparent that therapy with Lodoxamide is more rapid in reducing secrete (Smolin, 1981).

Table 3, which represents epiphora symptom, one of corneal lesion triad, was analyzed using Wilcoxon Matched Pairs Signed Rank test. The table shows significant difference before and after treatment, since first week until fourth week of observation, in Lodoxamide group. In Cromoglycate group, significant difference was found from the second week. This finding correlates well to the study of Delmar (1992). It reveals higher proportion of epiphora-reduced patient on Lodoxamide group especially at first and second week. Mann Whitney U Wilcoxon Rank Sum W test found significant difference between Lodoxamide and Cromoglycate on first, second, and third weeks after treatment. However, it became insignificant at fourth week.

Vernal keratoconjunctivity occurred as there are specific and non-specific allergens causing mast cell degranulating and likely, lymphocyte response. Eosinophil plays a role with respect to tissue destruction on allergic reaction. One of eosinophil granule, MBP, has known to be inducer of mast cell degranulation, toxic has ability to prevent eosinophil migration into tears and conjunctiva, thus allergic reaction especially further cornea lesion can be prevented. Since epiphora is one of clinical symptom triad of cornea lesion, it is reasonable then that analysis of corneal lesion sign is almost similar to epiphora (Lee & David, 1996: Delmar, 1992; Andrea Leonardi, 1997).

Evaluation of symptoms (itch, secrete and epiphora) was based on auto anamnesis (the patient him/herself) or hetero anamnesis (patient's mother). The youngest patient was 3 years old while the oldest was 13 years old. Most of the patient can report any progress except secrete symptom. Some of them with minimum or without secrete have blurred and confused the term.

In Table 4, from analysis of papillary hypertrophy sign using Mann Whitney Wilcoxon Rank Sum W test, we found significant difference of papillary hypertrophy distribution between Lodoxamine and Cromoglycate group before treatment. Hence, subsequent analysis could not be done. On group Lodoxamine, papillary hypertrophy was found from first to third grade (superior palpebral papillary hypertrophy to cobble stone that covering tarsus), while on Cromoglycate group we only found first grade (superior palpebral papillary hypertrophy).

From sign (papillary hypertrophy) analysis using Wilcoxon Mathced Pairs Signed Rank test on Cromoglycate group, there were no significant difference until the last observation, while on Lodoxamine's the significant difference appear at fourth week of observation.

Histologically, papillary hypertrophy consists of dead epithelial cell, MN, PMN, eosinophil and eosinophil granules. Lodoxamine prevents eosinophil migration into tears. The progress of papillary hypertrophy from mild grade to nothing, or size changing to become smaller papillary hypertrophy (for cobble stone), may require a longer time.

Although allergic process as a background of vernal keratoconjunctivity can be treated completely with drugs, but in some cases inflammation debris still existed, in which possible to delay healing process, such as cobblestone that completely fill tarsus. Albeit its surface is flat, it can lead to upper corneal irritation and potential to inhibit further ulcer epithelialisation when corneal ulcus occur. Therefore, it is useful to perform cryotherapy or tarsectomy on cobblestone permanent papillary hypertrophy (Lee & David, 1996)

From table 5, analysis of sign (hyperemia and edema of conjunctiva) with Wilcoxon Matched Pairs Signed Rank test on Lodoxamide group found significant difference before and after treatment, from first to fourth weeks of observation. While on Cromoglycate group, it was found significant difference before and second week after treatment. We found higher proportion of patient with reduced conjunctival hyperemia and edema in Lodoxamide group, either in first and second week after treatment. From analysis of sign (conjunctival hyperemia and edema) using Mann Whitney U Wilcoxon Rank Sum W test, we found significant difference on first week until third week after treatment.

In type 1 hypersensitivity reaction from vernal keratoconjunctivity, mast cell releases anaphylactic mediator, such as histamine, SRSA, and prostaglandin which all of these three mediators caused hyperemia and edema on conjunctiva. One of inhibition mechanism of type I hypersensitivity reaction is through cAMP value. cAMP increase causes mast cell to be unstable or easy to be degranulated. Histamine interacts with receptors causing an increase of cAMP. Eosinophil Derived Inhibitor (EDI) activates adenylcyclase and increases cAMP. Another mechanism is that first, eosinophil adenilsiklase increases of cAMP. Second, eosinophil releases arul sulphatase and, together with MBP, inactivate SRSA.

Lodoxamide prevents eosinophil migration from blood vessel, and this eosinophil in blood vessel release EDI and aryl sulphatase that plays role in inhibition mechanism. Consequently, therapeutic response of Loxamide toward conjunctiva hyperemia and edema is more rapid (Smolin, 1981; Lee & David, 1996)

From table 6, analysis of sign trantas dot using Wilcoxon Matched Pairs Rank Test on Lodoxamide group revealed significant difference before and third week to fourth after treatment, while on Cromoglycate it was at fourth week after treatment. The number of patient with negative trantas dot on Lodoxamide was 17 individuals (97.44%). In Cromoglycate group trantas dot consisted of eosinophil and desquamated cell. Lodoxamide has affect/inhibit eosinophil migration into tears and conjunctiva, thus prevent further eosinophil accumulation. From analysis of trantas dot sign using Mann Whitney U Wilcoxon Rank Sum W test, it showed no significant difference between the two groups until the end of the observation. This was likely due to limited number of sample and the remaining desquamated cell.

In Table 7, corneal lesion sign analysis by Wilcoxon Matched Pairs Signed test on Lodoxamide group disclosed significant difference from the first week observation after treatment, while it was found from the second week after treatment on Cromoglycate group. From the same sign analysis using Mann Whitney U Wilcoxon Rank Sum Test, we found significant difference between Lodoxamide and Cromoglycate group at the first and second week after observation.

One of eosinophil granule, MBP, known to be toxic to corneal epithelia, prevents reepithelization and stimulates mast cell degranulation. MBP accumulation was found on the base of ulcus, in which prevent further reepithelization. For this reason, superficial keratectomy is considered necessary to be performed. Lodoxamide prevents eosinophil migration to tear and conjunctiva. Consequently, it prevents MBP granule to cause further corneal lesion and make the therapeutic response to cornea lesion is better than Cromoglycate. This is in line with study performing by Dalmar in 1992 (Delmar, 1994; Lee & David, 1996).

In this study, corneal lesion was most commonly at first grade (pungtat cornea lesion on superior limbus) and a small number of it was in second grade (corneal lesion at nearly the entire of cornea). They were divided equally on Lodoxamide and Cromoglycate group. Therapy using those two mast cell stabilizers was able to restore corneal lesion in both groups at the end period of the observation. Although progression/therapy response of Lodoxamide was more rapid especially at the first and second week, in cornea ulcus where there is MBP accumulation on the base of ulcus, supratarsal steroidal injection therapy is necessary in order to obtain more rapid response toward the symptom. To prevent further accumulation, it can be combined with Lodoxamide as maintaining therapy.

From Table 8, analysis of laboratory examination result of eosinophil from conjunctival specimen using Wilcoxon Matched Pairs Signed Rank test revealed significant difference on both Lodoxamide and Cromoglycate group from the first week after treatment until the end of observation. However, graph 8 shows fairly lower proportion of patient with positive eosinophil laboratory result at the first week from Lodoxamide group. The presence of one or more eosinophil on conjunctival specimen per field represent any allergic reaction happen to eye, whereas numerous eosinophil represent mediator responsible for type I Hypersensitivity on vernal keratoconjunctivity, such as histamine, SRS-A, PAF, prostaglandin, heparin, ECF-A, protease and serotonin. Eosinophil also responsible for inhibition mechanism of allergic reaction on vernal keratoconjunctivity, in other words this material is very much responsible to hypersensitivity reaction on vernal keratoconjunctivity. This study found no significant difference in laboratory examination result between Lodoxamide and Cromoglycate group. This may due to limited number of sample and possible observation error when perform examination to conjunctival specimen (Smolin, 1981 and Lee & David, 1996). It was found no either ocular or systemic side effect as listed in side effect list both in Lodoxamide and Cromoglycate group during the research.

CONCLUSION AND SUGGESTION

Conclusion

This study reveals more rapid response of Lodoxamide Tromethamine 0.1% therapy regarding to symptoms

(itch, secrete, epiphora) and signs (conjunctival hyperemia and edema, corneal lesion), compared to Sodium Cromoglycate. Moreover, with the same drug we obtain better restoration of papillary hypertrophy with Lodoxamide Tromethamine 0.1% therapy at the fourth week after treatment. The same result at the fourth week was attained with administration of Lodoxamide Tromethamine 0.1%. There were no side effects complained after administration of the two eyedrops.

Suggestion

According to this study, we can consider Lodoxamide Tromethamine 0.1% eyedrops as an alternative drug of choice for the vernal keratoconjunctivity patients. Study should be performed with appropriate number of sample, thus we can generalize the result.

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