EFFICACY OF SODIUM CARBOXYMETHYLCELLULOSE IN THE TREATMENT OF DRY EYE SYNDROME

EFICACIA DE LA CARBOXIMETILCELULOSA SÓDICA PARA EL TRATAMIENTO DEL SÍNDROME DEL OJO SECO

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ABSTRACT

Aim: To assess the efficacy of sodium carboxymethylcellulose in the treatment of dry eye.
Material and methods: We carried out a prospective, randomized, masked-observer, control/problem group, single-center clinical assay during a period of 12 months in 19 patients that presented mild or moderate forms of dry eye. Patients were clinically evaluated each 3 months and treated with a 0.5% isotonic solution of sodium carboxymethylcellulose (CMC) or balanced salt solution. Subjective symptoms, functional tests and conjunctival impression cytology were performed according preexistent schedule study visits. To compare data between groups chi squared (χ^2) analysis was applied.
Results: We observed a significant ($p<0.05$) decrease in the frequency of subjective symptoms and a significant ($p<0.05$) improvement of tearfilm interface stability after CMC treatment. There was a tendency to improve the degree of corneal surface wettability and the tearfilm integrity with higher percentage improvements in the CMC group compared to controls. Improved baseline values in at least one of the objective functional tests carried out ($p<0.05$)

RESUMEN

Objetivo: Evaluar la eficacia de la carboximetilcelulosa sódica para el tratamiento del Síndrome de Ojo Seco (SOS).
Material y métodos: Se realizó un ensayo clínico prospectivo randomizado unicéntrico y enmascarado de tipo grupo problema/control con 19 pacientes que padecían un SOS leve o moderado, durante un período de 12 meses. Los pacientes fueron clínicamente evaluados cada 3 meses y tratados con una solución isotónica de carboximetilcelulosa sódica (CMC) al 0,5% o BSS. La toma de los síntomas subjetivos, las pruebas objetivas de funcionalidad clínica, y la citología de impresión conjuntival fueron realizadas según el protocolo preestablecido. Para la comparación de los datos entre los grupos se utilizó un análisis estadístico mediante prueba de chi cuadrado (χ^2).
Resultados: Se ha observado una disminución significativa ($p<0,05$) en la frecuencia de la sintomatología subjetiva asociada a una mejoría significativa ($p<0,05$) en la estabilidad de la interfase de la película lagrimal tras el tratamiento con CMC. Hubo una tendencia a la mejoría del grado de humecta-

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was also observed in an elevated percentage of patients in the CMC group (83.3%) compared with controls (34%). Furthermore, we observed a tendency to diminish the frequency of associated subjective symptoms after treatment. Conjunctival impression cytology did not provide significant differences related with therapeutic response.
Conclusions: The results show a significant beneficial effect of CMC to improve clinical parameters in mild and moderate forms of dry eye *(Arch Soc Esp Oftalmol 2006; 81: 85-92).*

Key words: Artificial tears, sodium carmellose, keratoconjunctivitis sicca, tear substitutes, Sjögren's syndrome.

ción de la superficie corneal y de la integridad de la película lagrimal, con un porcentaje superior de mejorías en el grupo problema. Se constató que un mayor porcentaje de pacientes en el grupo problema (83,3%) con relación al grupo control (34%), mejoraron por lo menos en una de las pruebas funcionales de evaluación ($p<0,05$). Asimismo, se observó una tendencia a la disminución de la frecuencia de síntomas subjetivos concomitantes tras el tratamiento con CMC. La citología de impresión (CI) no ha permitido establecer diferencias significativas con relación a la respuesta clínica al tratamiento.
Conclusiones: Se pudo constatar un efecto significativamente favorable de la CMC en la mejoría de los parámetros clínicos del SOS leve y moderado.

Palabras clave: lágrimas artificiales, carmelosa sódica, queratoconjuntivitis sicca, sustitutos de la lágrima, síndrome de Sjögren.

INTRODUCTION

The Dry Eye Syndrome (DES) is characterized by a set of alterations of the eye surface which could relate to tear quality, normal makeup of tearfilm and alterations in blinking or regular closing of eyelids (1,2), which entail a reduction of the stability of the tearfilm and the alteration of the eye surface (3,4).

In individuals over 45, about 20% of women and 15% of men present dry eye symptoms which clinically display various degrees of severity (1,5-7). Severe dry eye is the most infrequent and difficult to handle, while slight and moderate dry eye are frequently found in daily practice (1-4).

Recent studies (7-9) evidence the immunological alterations related to the pathogenesis of DES, not only in Sjögren's Syndrome but also in post-infection and aging alterations. However, at present there is a large enough basis to consider that a chronic irritation of the eye surface can lead to a predisposed eye surface due to hormonal or immunological factors (10).

The treatment of DES presents some difficulties because it is a chronic alteration which involves a long and strict therapy (2,11). Accordingly, an important fact for the therapeutic success of DES is the medical orientation and an understanding of the purpose of the therapeutic measures by the patient.

The objective of this work was to assess the efficacy of a sodium carboxymethylcellulose (CMC) solution as a tear substitute for treating DES. Likewise, the presence and severity of DES symptoms and signs was assessed by means of: a) subjective symptoms as a usefulness parameter for clinical diagnosis and follow-up of the therapeutic response, b) basic exploration by means of functionality tests for evaluating dry eye, and c) conjunctival impression cytology (CI) as criterion for clinical follow-up of the pathology and its response to the therapy.

SUBJECTS, MATERIAL AND METHODS

Design and population of the study

The study was designed as a single-center clinical trial, prospective, masked, limited in time and randomized with a problem/control group and a 12-month duration. The trial was carried out in accordance with ethical principles for research with human beings (12). Each patient was fully informed about the objective and purpose of the study and informed consent was obtained for his/her participation. All patients were initially assessed by a sin-

gle ophthalmologist and classified as per DES severity degrees: a) Slight, when fulfilling one or two criteria, b) moderate, when fulfilling 3 or 4 criteria, c) severe, when fulfilling over 4 criteria.

Patients with severe clinical symptoms were not included in the trial. We also excluded those with inflammatory pathologies of the eye surface or in the anterior segment, or who had been diagnosed glaucoma. The use of contact lenses and/or topical or systemic medication which could interfere in the production of tears (2) were also criteria for exclusion. In addition, patients who had eye surgery or eye trauma in the year prior to the beginning of the study were also excluded.

For selecting the treatment (CMC) and control (BSS) groups, a randomized inclusion protocol was utilized, in which patients involved in the trial were assigned in a ratio of 2:1 (treatment: control) by order of entry. Assignation in the problem group, therapeutic guidelines and clinical assessments up to the end of the study were determined and made by the ophthalmologists who participated in the research as per a previously established agenda and protocol (table I).

Clinical assessment criteria

The patients were assessed every 3 months for the first 6 months, with a final ophthalmological clinical assessment made after 12 months (table 1). The functional objective assessment tests for DES were made in the first (day 0) and last assessment (month 12) according to the described techniques and protocols (4). Said tests were applied in a recommended order (4) so as to reduce the interference of one test over another.

In addition, we utilized a simple-answer customized diagnostic questionnaire (13) which was given to the patients at the first and last clinical assessment of the trial.

Table I. Clinical evaluation protocol and trial follow-up scheme

Activity	Day 0	Month 3	Month 6	Month 12
Informed consent	*			
General ophthalmological evaluation	*	*	*	*
Medical & ophthalmological anamnesis	*			
Randomization	*			
Allocation of treatment	*			
Objective functional tests	*			*
Subjective symptoms	*	*	*	*
Customized symptoms questionnaire	*			*
Impression cytology	*			*
Treatment	*	*	*	*
Evaluation of efficacy	*	*	*	*
Evaluation of adverse effects		*	*	*

Material for the study

The problem group was given an isotonic 0.5% solution of sodium carboxymethylcellulose without preservatives found in the market (Cellufresh®, Allergan SA, Madrid), which was compared to the application of balanced saline solution (BSS) (manufactured by Alcon-Cusi SA, Barcelona) in the control group. Both products were supplied in their original presentation, and patients were recommended to apply 1-2 drops of product at least 3-4 times a day (or as needed) on the eye surface. They were not allowed to use any other type of topical eye medication during the trial.

Conjunctival Impression cytology

The Impression cytology (IC) was made in accordance with the above described techniques (14). Nelson's criterion was used (15) for interpretation and establishing the degree of conjunctival involvement. The cytologies were made before and after the treatment with a minimum period of 6 months and a maximum of 1 year between assessments. The preparation, tincture and interpretation of findings in the specimens were carried out by a single cytopathologist.

Statistical treatment

Collection and analysis of the data obtained from the results were recorded in a spreadsheet application (Microsoft Excel, Office Windows 2000). For comparison between the problem and control groups statistical analysis by means of chi square (χ^2) was used when allowed by data.

RESULTS

Forty-five patients were examined, of which only 19 fulfilled the inclusion criteria and the assess-

ments established previously in the trial protocol. According to the clinical assessment criteria, 11% of patients (n = 5) exhibited severe dry eye syndrome and therefore received immediate treatment but were excluded from the study. Consequently, the problem group was made up by 13 patients and the control group by 6, all of them women. The average age of the problem group was 56.8 years (between 42 and 72) and 62 years for the control group (between 52 and 72). In the problem and control groups, 84.5% (n = 11) and 33.4% (n = 2) respectively exhibited moderate DES. The mean clinical follow-up period was of 9 and a half months, ranging between 6 and 12 months.

A high frequency of associated systemic pathologies was found in both groups. Sjögren's syndrome (33%-38%) and polyarthralgia (30%-33%) were the most frequently observed associations. Only 23% of the problem group patients and 33% of the control group did not exhibit pathologies associated to DES.

Subjective symptoms

In order to assess symptoms before and after treatment, a customized questionnaire was made up with 12 subjective symptoms, which was filled in by the patients at the initial visit and at the end of the study. A significant reduction ($p<0,05$) was observed in the frequency of some subjective symptoms after treatment with CMC. In the control group no variations were found in the frequency of symptoms.

So as to observe the concomitance of said symptoms, patients were classified according to the number of symptoms in the following groups:

a) up to 3 symptoms, b) up to 6 symptoms, c) up to 9 symptoms, d) over 9 symptoms, and e) all symptoms. It was seen that 61.5% of patients (n = 8) in the problem group exhibited between 7 and 9 concomitant symptoms prior to treatment, but this percentage went down to 46% (n = 6) after the treatment. In the same group, 23% of patients (n = 3) exhibited a maximum of 3 symptoms at the end of the study. Similarly, after the treatment with CMC we observed a shift in the number of patients toward groups exhibiting a lower number of concomitant symptoms (fig. 1). There were no variations in frequency in the control group treated with BSS.

During the trial we did not observe the appearance of adverse effects as a result of the utilization of the trial products. Both treatments were well tolerated without compromising the visual acuity of participants, with the exception of discrete visual blur immediately after application.

Objective functional tests

In order to assess clinical improvement, objective functional assessment tests were utilized for evaluating the DES (see Materials and Methods).

The basal Schirmer test, made after application of anesthetic eye drops, evidenced a tendency toward improvement in the humectation degree of problem group eyes. However, the differences were not statistically significant. Similarly, we recorded a higher percentage of eyes which improved their humectation degree in the problem group (34.8%) in relation to the control group (25%).

In addition, we observed a higher percentage of worsening of the humectation in control group eyes (25%) in relation to problem group eyes (8.7%).

The integrity of the cornea epithelium was studied by instilling 2% sodium fluorescein drops semi-quantified according to the degree of involvement between 0 and 3 crosses. Only 23% of patients (n= 3) of the problem group and 16.7% (n= 1) of the control group exhibited alterations of the cornea surface. After treatment with CMC all problem group patients experienced improvements in the degree of involvement of the cornea epithelium, while no improvement was observed in control group patients.

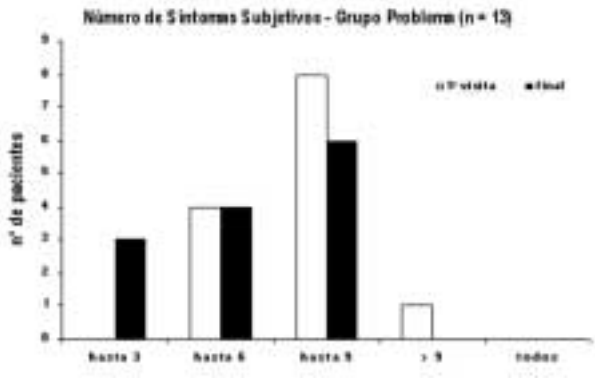

Fig. 1: Frequency of subjective symptoms before (white bars) and after (black bars) treatment with CMC in problem group patients (n=13). We observed a tendency toward the reduction of concomitant symptoms after treatment.

Tincture with Bengal Rose evidenced a tendency toward improvement of the integrity of the tearfilm in problem group patients. Likewise, we verified a higher percentage of eyes with improved integrity of the tearfilm in the problem group (50%) when compared to the control group (33.3%). However, said difference was not statistically meaningful.

Even though half of the assessed eyes of the problem group experienced improvements, 41.7% of the remaining eyes with positive tincture did not exhibit changes in the assessment. In the control group, four eyes (33.4%) exhibited negative tincture for the test.

The time of breakage of the tearfilm (BUT), assessed as a measure of stability of the interface between the tearfilm and the eye surface, exhibited a significant improvement ($p < 0.05$) in the problem group. We observed a higher percentage of eyes with improved BUT in the problem group (50%) in relation to the control group (16.6%). It must be emphasized that 21% of eyes in the problem group and 33% in the control group exhibited BUT compatible with normality prior to treatment (fig. 2).

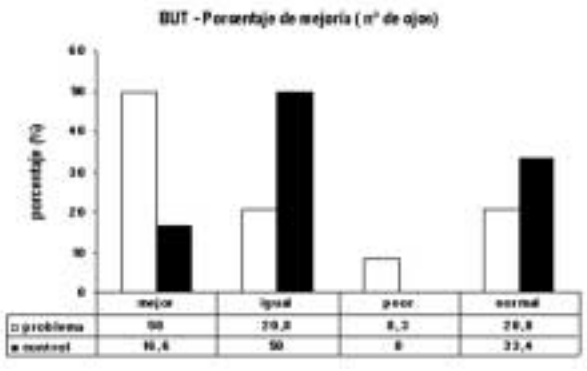

Fig. 2: Improvement in the breakage time of tearfilm (BUT) after treatment. A higher percentage of improvement (50%) was observed in the problem group (white bars) treated with CMC, in comparison to the control group (16.6%) (black bars) treated with saline solution. This difference was significant ($p<0.05$).

The assessment of the integrity of the lacrimal meniscus did not yield differences in response between the groups. All the control group eyes and 64% of the problem group assessed did not exhibit alterations in the integrity of the lacrimal meniscus prior to treatment.

Lastly, we attempted to establish a globalized functional assessment of the therapeutic response, taking into account the results observed in the most meaningful objective tests of this study: a) Schirmer test, b) tincture with sodium fluorescein, c) tincture with Bengal Rose, d) BUT. We established a score for quantifying an improvement (+ 2 points), no change (+ 1 point) and worsening (zero points) with regard to the test result. Thus, a score above or equal (≥) to 5 points represents an improvement of at least one of the objective assessment tests. With this criteria, we verified that 83.3% of patients (n = 10) of the problem group and 34% (n = 2) of the control group presented a ≥ score of 5 points when considering the results obtained in the objective functionality tests at the end of the study (fig. 3). This difference was meaningful ($p < 0.05$).

Conjunctival impression cytology

IC was made in 14 patients —24 eyes of the problem group and 4 of the control group— before and after treatment with the aim of verifying the therapeutic efficiency in the evolution of DES, as well as the applicability of the test for controlling clinical follow-up. Specimens were obtained preferably from the inferior bulbar conjunctiva. The cytopathological classification criteria were as described above (15).

Prior to treatment with CMC, the problem group eyes were distributed as follows: 70.8% (n= 17) in degree 1, 16.6% (n= 4) in degree 2, with 12.5% (n= 3) of normal results. After fulfilling the treatment we observed a slight reduction in the percentage of degree 1 eyes (62.5%, n= 15) with an ensuing increase in degree 2 eyes (25%, n = 6). This difference was not statistically meaningful. In the control group at the beginning of the study, 3 eyes were classified in degree 1 and an assessment gave normal results. At the end of the trial, all the control group eyes treated with saline solution were classified as degree 1.

No significant differences were observed in what concerns the degree of involvement of caliciform cells and metaplasic states of the conjunctiva between the trial groups before and after treatment. Likewise, the IC did not correlate with an improvement in the observed subjective symptoms or an improvement in some parameters of the functional objective assessment tests. However, we observed in the initial IC a higher prevalence (87.5%) of involvement of caliciform cells in problem group eyes.

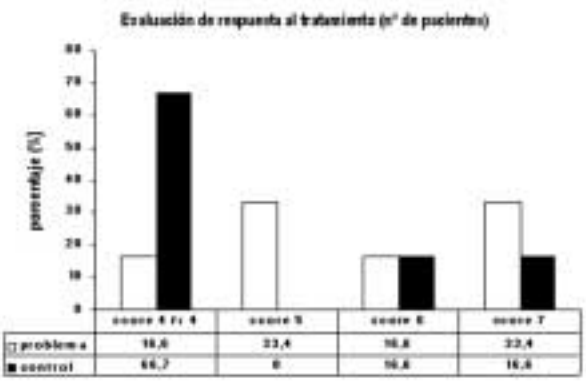

Fig. 3: Global functional assessment of the therapeutic response according to the scoring (improvement=2; no change=1; worsening=0) established for the objective assessment tests in the problem group (white bars), treated with CMC and the control group (black bars) treated with saline solution. The score 5 represents an improvement of at least one of the objective functional assessment tests after treatment. We observed a higher number of patients with scores =5 in the problem group (83.3%) in relation to the control group (34%). This difference was meaningful (p<0.05).

DISCUSSION

This study verified that frequent, continued and long term instillation of a CMC isotonic solution has a beneficial effect for slight and moderate DES in comparison with the control use of saline solution. We have observed a significant improvement of the subjective symptoms associated to the pathology, in addition to an increase of the base values observed in some objective functional tests carried out for assessing the involvement of the eye surface. Said results are compatible and confirm previous research on the efficacy and tolerance of tear substitutes which contain CMC in solution (16-18).

DES is a frequent pathology in daily clinical practice, and most therapeutic approaches essentially have in common the utilization of tear substitutes without preservatives (2,7,10). It is assumed that an ideal tear substitute for treating DES should have some essential characteristics such as absence of toxicity, adequate viscosity, no interference in visual acuity and capacity, no alteration in the production of mucin, having humidifying function in addition to aiding the stabilization of the tearfilm and exhibiting a prolonged time of presence on the eye surface (2,11).

Tear hyper-osmolarity has been considered to be one of the primary mechanisms which gives rise to the subjective symptom of discomfort and the associated inflammatory process which is observed on the eye surface (19). In addition, research of the tearfilm physiology proved that the presence of some elements such as bicarbonate and potassium in the tear are important not only for electrolytic balance but also for the integrity of the eye surface (2,20,21). The CMC solution utilized in this study has an electrolytic composition similar to that of the human tear and, since it is isotonic, it can surely contribute to correct osmolarity and pH distortions generally observed in DES. We believe that all this could explain the meaningful reduction seen in the frequency of the subjective symptoms in the problem group. In addition, we can associate said improvement to the increase humectation of the cornea surface as identified in the values obtained with the Schirmer test.

The caliciform solutions placed on the eye surface (22) produce the mucin layer, which is essential for the stability of the tearfilm (2). Previous research (21) suggest that the CMC solution has the capacity to restore the function of the caliciform cells and improve the previous metaplasic states of epithelial cells of the conjunctiva observed through IC (16).

Unfortunately, in our study IC was unable to demonstrate differences vis-à-vis the degree of involvement of the caliciform cells in both groups before and after treatment. However, we did notice a significant improvement of the stability of the interphase between the tearfilm and the eye surface in the problem group, through the assessment of BUT and the Bengal Rose test.

The properties of CMC include viscoelasticity (11) which contributes to the lubrication of the eye surface. This increases the stability of the pre-corneal tearfilm which, in turn, protects the eye surface against environmental aggressions (8). Similarly, due to its molecular characteristics as a polysaccharide (11), CMC exhibits retensive properties which enhances the permanence of the compound and increases the moistening of the eye surface (23). Accordingly, this could explain the higher percentage of patients (83.3%) in the problem group who exhibited significant improvements in at least one of the objective evaluation tests at the end of the

study in relation to the control group (34%) which was given BSS.

On the other hand, it is known that the absence of preservatives in tear substitutes is essential to avoid toxic effects on the corneal epithelium and avoid worsening the inflammatory process associated to DES (2,7,10,11).

In our study it is important to emphasize the high frequency of systemic pathologies associated to DES. Sjögren's syndrome and polyarthralgiae were most frequent. It is known that many vascular diseases which involve collagen, among which we find a number of self-immune pathologies, usually appear associated with DES in varying degrees of severity (10). It is considered that the reduction of tear secretion, which is present in said pathologies, is a consequence of the infiltration of inflammatory cells in the tear glands which may also affect the conjunctiva (9,24).

In this study, as a consequence of the randomization utilized for choosing the treatment, there is a greater frequency of patients with a moderate involvement in the problem group (84.5%) in relation to the control group (33.4%). Even though the isolated use of topical treatment with drops signified an improvement of the presentation in a significant proportion of patients, it is highly probable that a possible supplementary therapeutic association would raise the percentage of observed benefits. It must be recalled that in severe cases where conjunctival keratinization is observed, as well as corneal damage in varying degrees, presence of filaments and serious epithelial defects, other coadjuvant therapeutic strategies are recommended (2,7,10,11).

Finally, the safety and efficiency of CMC were assessed according to tolerance, appearance of possible adverse effects and measures recorded in the objective tests for assessing the state of the eye surface. The absence of adverse symptoms and the results observed in relation to tolerance, allow us to conclude that the frequent application of a 5% isotonic solution of CMC without preservatives on the eye surface is safe, well tolerated and capable of contributing to an alleviation of subjective symptoms in slight and moderate DES. In our view, the fact that the chosen tear substitute exhibited a positive response to the subjective symptoms is one of the important parameters and surely one which will contribute to improved long-term compliance with the treatment, regardless of other considerations.

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