EXTENDED REPORT

Iodide iontophoresis as a treatment for dry eye syndrome

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Background/aims: Among the causes related to the development or perpetuation and aggravation of dry eye disease, oxidative reactions may have a role in the pathogenesis of this disorder. Antioxidants, such as iodide, have shown a strong effect in preventing the oxidative damage to constituents of the anterior part of the eye. In this clinical trial the effectiveness of iodide iontophoresis and iodide application without current in moderate to severe dry eye patients was compared.

Methods: 16 patients were treated with iodide iontophoresis and 12 patients with iodide application without current for 10 days. Subjective improvement, frequency of artificial tear application, tear function parameters (break up time, Schirmer test without local anaesthesia), vital staining (fluorescein and rose bengal staining) as well as impression cytology of the bulbar conjunctiva were evaluated before treatment, 1 week, 1 month, and 3 months after treatment.

Results: A reduction in subjective symptoms, frequency of artificial tear substitute application, and an improvement in certain tear film and ocular surface factors could be observed in both groups. A stronger positive influence was seen after application of iodide with current (iontophoresis), as observed in a distinct improvement in break up time, fluorescein and rose bengal staining, and in a longer duration of this effect compared with the non-current group. No significant change in Schirmer test results and impression cytology were observed in both groups.

Conclusions: Iodide iontophoresis has been demonstrated to be a safe and well tolerated method of improving subjective and objective dry eye factors in patients with ocular surface disease.

Dry eye syndrome or keratoconjunctivitis sicca is among the most common and problematic conditions faced by ophthalmologists. Up to 20% of adults aged 45 years or older report typical symptoms.[1] In the United States the prevalence of mild to moderate dry eye is approximately 10 million.[2 3]

The origin of this disease is believed to be multifactorial and related to a pathological condition of any one of the parts of the functional unit including the tear film, the ocular surface (cornea, conjunctiva, accessory lacrimal glands, and meibomian glands), the main lacrimal glands, and the interconnecting neural reflex loops.[4] Among many causes related to the development or the perpetuation and aggravation of dry eye, oxidative reactions on the ocular surface may have a role in the pathogenesis of this disorder.

The presence of oxygen free radicals has been demonstrated in the tear fluid and conjunctival cells of patients with ocular surface disease.[5 6] Whether this reactive oxygen species (ROS) production represents a primary pathogenetic factor in epithelial cytotoxicity or is secondary to an inflammatory response is not yet known.

The increased air pollution in the past 20 years may lead to the conclusion that ozone, exhaust gases, smoke, and ultraviolet radiation contribute to the generation of a higher level of ROS in the tear film and on the ocular surface.[5 7 8]

On the other hand, it is well established that inflammation itself such as occurs in dry eye disease is also associated with a production of free radicals. Activated leucocytes to which the conjunctiva and the cornea are exposed during inflammation are known to produce large amounts of O_2^-. and H_2O_2[9] and in the presence of iron the extremely toxic OH radical can be formed.[10] In addition, these free radicals play a significant part in the intensification of inflammation as a result of the generation of chemotactic factors.[11]

The eye protects itself from radical injury by endogenous antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase.[12 13] The tear fluid, which is known to maintain the integrity of the ocular surface, has also been shown to contain a sufficient number of oxygen free radical scavengers including ascorbate, uric acid, and lactoferrin.[14 15]

If the eye is exposed to excessive oxidative stress, the scavengers normally present in the tear fluid are exhausted and apparently no longer capable of preventing damage. Highly ROS destroy components of the tear fluid such as proteins, the glycosaminoglycan hyaluronate,[16 17] and lipids.[18 19] Changes in the composition of the tear fluid caused by free radicals, induced by various means, affect the proper interaction of tear fluid components resulting in loss of tear film stability. Oxidative reactions also result in alterations of the conjunctival and corneal cells, thus leading to their involution and to enzyme alterations.[20–22] In cases of long exposure, ocular surface disease with characteristic symptoms and signs can be promoted.[7 8 23]

Thus, increasing the antioxidative capacity of the ocular surface and the tear film by supporting the natural defence mechanisms, might produce additional antioxidants, which would help patients with dry eye. Ophthalmic hydrogels possess antioxidant properties and reduce ROS.[24] Artificial tear preparations containing a mixture of vitamins A, C, and E, as well as iodide, also confirmed the efficacy of preparations containing free radical scavengers.[25]

Iodide, a reducing agent and electron donor, has been demonstrated to be an oxygen free radical scavenger in vitro and in vivo.[26–32] Iodide-containing brine has been used in Bad Hall, Austria, for different eye diseases, including chronic conjunctivitis and incipient cataract for many years. In several studies it was demonstrated that increased amounts of iodide can be transferred into all ocular tissues, especially to the anterior segment, using iontophoresis.[33–36]

Iontophoresis utilises a low current to drive charged molecules across tissue barriers for delivery of therapeutic

Abbreviations: BUT, break up time; ROS, reactive oxygen species

drug concentrations to the inner eye and to facilitate ion penetration into tissues.[37] Several applications of iontophoresis in experimental and clinical ophthalmology, particularly for the treatment of bacterial or viral infections and inflammations, have been reported.[38–43]

In this study, we investigated the effect of iodide administration in dry eye patients. Using an iontophoresis system we studied its effect on tear film break up time, Schirmer test, fluorescein and rose bengal staining, and impression cytology, as well as on dry eye symptoms and frequency of artificial tear substitute application. Patients who were treated with iodide iontophoresis were compared with those who received iodide without current for all the factors mentioned above.

PATIENTS AND METHODS

Patients

This prospective study evaluated 56 eyes of 28 consecutive patients with moderate to severe dry eye disease with and without Sjögren's syndrome (24 women, four men) before and after iodide treatment with a 3 month follow up period. The mean age was 60.5 years (range 32–91 years). Sixteen patients received iodide treatment with current (iontophoresis) and 12 patients without (mock iontophoresis). Inclusion criteria were typical dry eye symptoms such as dryness, burning and foreign body sensation, itching, ocular pain, and easily fatigued eye, a reduced tear film break up time of less than 5 seconds, and rose bengal staining test score >3 or Schirmer test without local anaesthesia below 5 mm/5 minutes. Patients with known allergy to iodide were excluded. All subjects had received a full explanation of the procedure, and informed consent was obtained before treatment. Systemic medication did not change during the observation period.

Chemicals

A 0.5% sodium iodide solution at pH 8.0 was used. At a pH value of 8.0 the molecule is predominantly negatively charged. The temperature of the solution was 34℃ to 37℃.

Iontophoresis

The ocular surface applicator of the iontophoretic apparatus (Erbe, Tübingen, Germany) was used as the cathode as iodide is negatively charged. A platinum electrode is in contact with the iodide solution but not with the surface of the eye. An eye probe made of poly(methylmethyacrylate) (PMMA) of 3 cm in diameter was used, covering the cornea, the conjunctiva, and the lids (fig 1). The donor compartment is filled with 33 ml sodium iodide solution 0.5%, pH 8.0. The positive pole (anode), which is the indifferent or ground electrode, is held in the hand of the patient. The iontophoresis protocol used in this study was based on the protocol used by Pommer and Trichtel.[35 36] Iontophoresis was applied at a constant direct current of 0.2 mA for 7 minutes. Ten treatments were applied to both eyes over a 2 week period. Mock iontophoresis was applied under the same conditions but no current was passed.

Figure 1 The ocular surface applicator of the iontophoretic apparatus for treatment with iodide solution with and without current.

Subjective and objective dry eye parameters

We evaluated subjective symptoms, frequency of artificial tear application, and dry eye status before treatment, 1 week, 1 month, and 3 months after treatment. Ocular examination was performed using the tests in the following sequence in order to avoid one test interfering with another:

(A) For subjective symptoms of dry eye, patients were asked for symptoms of ocular discomfort. The intensity of these symptoms was graded by the patients according to a questionnaire using a face score which consists of nine faces, each showing a different expression. Patients were asked to select which face best described the current condition of their eyes—for example, a very sad face describing a bad condition of dry eye symptoms (No 9 on face score) and a happy face describing no irritation to the ocular surface (No 1 on face score).[44]

(B) Tear break up time (BUT) was measured as the number of seconds between the last complete blink and the first disturbance of the precorneal tear film after touching the inferotemporal bulbar conjunctiva with a fluorescein sodium strip, wet with a preservative free saline solution. The mean value of a total of three measurements was recorded.

(C) The corneal surface was examined under blue light illumination with a biomicroscope after fluorescein instillation into the tear film. The intensity of staining was recorded for each eye by using a four point scale (0 = no staining, 1 = less than one third, 2 = less than two thirds, 3 = more than two thirds staining of the cornea).

(D) A 5 minute conventional Schirmer I test without anaesthesia was performed on closed eyes by placing a commercially available 5×35 mm paper strip (Clement Clarke International Ltd, UK) over the lower lid margin at the junction of the middle and lateral third into the tear film.

(E) Rose bengal staining was performed by adding one drop of 1% rose bengal solution to the bulbar conjunctiva and classified according to the van Bijsterveld scoring system.[45]

(F) The morphology of the ocular surface was evaluated by impression cytology. Sheets of cellulose acetate filter paper (type VC, 0.10 μm, VCWP 04700 Millipore Corp, Bedford, MA, USA) were used to collect cells from the superior and inferior bulbar conjunctiva a few millimetres from the corneal limbus. The specimens were stained using the procedure described by Tseng and examined under a light microscope.[46] The degree of the pathological changes of the epithelial cells and goblet cells were determined as previously described.[47]

(G) During the observation period, all patients used topical commercially available tear substitutes to improve lubrication of the ocular surface. The frequency of artificial tear substitute application was recorded.

Table 1 Differences in iontophoresis group between baseline and follow up

	Before	1 week		1 month		3 months	
	Mean (SD)	Mean (SD)	p Value	Mean (SD)	p Value	Mean (SD)	p Value
Subjective symptoms (face score)	5.2 (1.6)	3.0 (1.2)	<0.01	3.0 (1.3)	<0.01	3.5 (1.5)	<0.01
Frequency of artificial tear substitute application (times)	6.3 (4.5)	3.2 (2.2)	<0.01	3.9 (3.6)	<0.05	4.6 (3.6)	<0.05
Break up time (seconds)	3.5 (1.1)	5.2 (2.9)	<0.01	4.8 (3.2)	0.16	4.2 (1.7)	0.06
Schirmer I (mm)	3.5 (4.2)	3.8 (3.2)	0.50	4.1 (5.8)	0.40	4.1 (5.8)	0.40
Fluorescein staining (score)	1.2 (1.1)	0.8 (0.9)	<0.01	0.9 (1.1)	<0.05	0.9 (0.9)	<0.05
Rose bengal staining (score)	5.8 (3.0)	4.7 (2.7)	<0.05	4.6 (2.8)	<0.05	4.7 (2.8)	<0.05
Impression cytology (score)	9.9 (4.0)	11.8 (3.9)	0.09	11.8 (3.4)	0.06	10.9 (5.3)	0.22

Statistical analysis

Data were entered into an Excel spread sheet and the data were analysed with SPSS. Wilcoxon's signed rank test was used to compare values between eyes before and after therapy for all clinical measurements in the iontophoresis and mock iontophoresis group. Results are presented as mean values plus or minus standard deviation (SD). Probability (p) values less than 0.05 were considered significant.

RESULTS

During the application of sodium iodide solution with the iontophoresis apparatus the eyes of the patients could easily be kept open in the solution. Slit lamp examination after iodide treatment showed slight conjunctival injection in all eyes immediately after removal from the eye cup. The injection disappeared within 1 hour. No corneal oedema or increase in epithelial damage was observed during any examination period after iontophoresis.

The results of the subjective and objective dry eye factors of iontophoresis and the mock iontophoresis group are presented in tables 1 and 2.

Subjective symptoms improved up to 3 months after treatment in the iontophoresis group. In the mock iontophoresis group a significant improvement was noticed up to 1 month.

Frequency of artificial tear substitute application was significantly reduced in the iontophoresis group up to 3 months to half of the baseline frequency. In the mock iontophoresis group the frequency was also reduced, but only significantly up to 1 week.

Fluorescein break up time was found to be increased 1 week after iodide treatment with current, whereas in the non-current group no significant increase was observed.

Fluorescein staining of the cornea was reduced up to 3 months in the iontophoresis group. In the mock iontophoresis group a slight but not significant reduction could be seen.

Rose bengal staining was significantly reduced up to 3 months in the current group. In the non-current group a significant reduction could be seen only up to 1 week.

No significant change in Schirmer test results was observed in both groups. Conjunctival morphology evaluated by impression cytology showed no difference after iodide application with or without current.

DISCUSSION

In this study we investigated the capability of iodide to influence dry eye in an iontophoresis system and in a control group who had iodide application without current.

As shown in the reduction of subjective symptoms, frequency of artificial tear substitute application, and in the improvement of objective clinical measurements, iodide has a positive influence on dry eye disease. A stronger positive influence of iodide was seen after the application of iodide with current (iontophoresis) as observed by a distinct improvement of tear film and ocular surface factors and by a longer duration of this improvement compared with the non-current group.

Iontophoresis is a process by which ions or charged molecules in solution are applied to body surfaces and introduced into cells and tissues with the use of electric current. This method has several applications in ophthalmology, such as to achieve therapeutic levels of drugs in the anterior and posterior segments of the eye for the treatment of diseases such as keratitis, uveitis, and endophthalmitis.[37 48 49] Transcorneal and trans-scleral iontophoresis of antibacterial, antifungal, anti-inflammatory, and antiangiogenetic agents have been reported.[38–43 50]

According to previous studies, the current applied to the patient's cornea by iontophoresis should not exceed 3 mA for a period of 2 minutes.[51] We used a current of 0.2 mA passed for 7 minutes. This low current strength was chosen since the iontophoresis procedure was repeated 10 times.

The optimal values of current and time for iontophoresis are still debatable. Several variables, including the charge of the molecule, the molecular weight of the drug, and its lipid solubility, are of importance in enhancing penetration of the ionised drug into the tissue during iontophoresis. Other important variables are the current density, the duration of

Table 2 Differences in mock iontophoresis group between baseline and follow up

	Before	1 week		1 month		3 months	
	Mean (SD)	Mean (SD)	p Value	Mean (SD)	p Value	Mean (SD)	p Value
Subjective symptoms (face score)	5.7 (1.6)	4.3 (2.1)	<0.05	4.5 (1.7)	<0.05	4.7 (1.9)	0.40
Frequency of artificial tear substitute application (times)	5.2 (3.2)	3.5 (3.2)	<0.05	4.8 (3.5)	0.20	6.2 (3.8)	0.50
Break up time (seconds)	3.0 (1.5)	3.8 (2.2)	0.11	3.8 (2.3)	0.18	3.4 (1.8)	0.48
Schirmer I (mm)	3.9 (6.0)	4.1 (5.9)	0.59	3.8 (5.8)	0.62	4.0 (4.8)	0.72
Fluorescein staining (score)	1.2 (1.0)	1.0 (0.8)	0.10	1.0 (1.1)	0.66	1.1 (0.9)	0.68
Rose bengal staining (score)	5.3 (3.1)	4.8 (2.9)	<0.05	5.1 (3.0)	0.07	5.0 (3.0)	0.06
Impression cytology (score)	12.4 (5.2)	9.6 (2.1)	0.10	10.6 (3.5)	0.31	11.9 (2.6)	0.63

the procedure, and the concentration of the drug in the solution.[37 52] Using controlled iontophoretic parameters and a low current density side effects can be avoided.[53]

In dry eye disease, instillation of artificial tears is the most frequent therapy, but topically applied substitutes are rapidly eliminated from the precorneal area. In addition, the cornea is the major pathway for penetration of topically applied drugs, but the epithelium is an effective barrier to prevent accumulation of active substances. To reduce the frequency of instillation without losing the therapeutic effects would increase the comfort of the patients. Modification of the formulation of the artificial tears or the utilisation of reservoir systems increase the duration of the contact on the cornea. Another possibility is the increase of tissue permeability and accumulation of active substances by using iontophoresis.

We investigated this iontophoresis model as a therapeutic option to influence subjective and objective dry eye factors by iodide application. This model was investigated in previous animal studies and in experiments to determine the iodide penetration into the ocular tissues, especially into the anterior parts of the eye.[33–36] Even if these animal studies and in vitro data cannot be extrapolated to an in vivo treatment, our clinical results confirm the potential efficacy of this method.

Our results suggest the clinical advantage that the dosage is apparently much more consistent when iodide is transferred into the eye with the electric potential than when it is allowed to stay in contact with the ocular surface without current. Topically applied iodide does not penetrate the superficial epithelial layer without current since iodide is hydrophilic, although a low level of passive diffusion may occur. Iodide delivered with iontophoresis penetrates into deeper layers and can increase the amount of iodide in the tissues of the ocular surface, and possibly result in a depot effect, which explains the sustained improvement seen after a longer period of up to 3 months. The longer duration of clinical efficacy in our patients after iontophoretic delivery may indicate that iodide binds to some of the tissue components such as collagen.[54]

Since oxidative reactions may play an important part in ocular surface disorders[5 6] we assume that iodide application might contribute to the antioxidant potential in tear fluid and in ocular tissues. Treatment of the ocular surface with brine containing iodide contributes to an increase of the antioxidant status in tear fluid.[31] Patients with typical dry eye symptoms reported improvement in their subjective conditions and a reduction in the frequency of tear substitute application after taking a course of iodide treatment at Bad Hall, Austria.[55 56] Iodide was shown to provide significant protection for hyaluronate, a component of tear fluid and tissues of the anterior part of the eye against ultraviolet B light induced oxidative degradation.[57]

Also, injury to human conjunctival cells can be prevented by incubation with iodide before ultraviolet B irradiation.[57] Peroxidase activity, which can scavenge H_2O_2 in the presence of a suitable substrate, has been detected in human tears.[5] Iodide has been found to increase peroxidase activity.[29]

The biological effects of iodide delivery by iontophoresis are still unknown. Iontophoretic application may influence the metabolic processes in the ocular tissues. There are clinical observations demonstrating that the application of exogenous electric fields enhances wound healing. It is known that many types of cells respond to weak direct current electric fields with a cellular reorientation and migration.[58]

According to the results presented here we recommend a combination of iodide and current. The observed clinically significant improvement in symptoms and signs of dry eye syndrome after iodide application by iontophoresis calls for further investigation.

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