



Clinical Results After Sodium Treatment in Post-operative Corneal Oedema

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Abstract

Background: Evaluate the effectiveness of a hyperosmolar 5% sodium chloride treatment in corneal oedema.

Design: This prospective, randomized study was conducted in a university ophthalmology department setting.

Participants: 95 patients with post-operative corneal oedema were separated in 2 groups: 45 patients in group 1 treated with hypertonic eye drops; 50 patients in group 2 without anti-oedematous.

Methods: Patients in group 1 were treated with 5% sodium chloride hypertonic eye drops associated with 0.15% sodium hyaluronate in addition to the classical post-operative treatment for 1 month; and patients in group 2 were only treated with classical post-operative treatment (antibiotic, corticosteroids and artificial tears).

Main outcome measures: Visual acuity, pachymetry and density were measured at 1 day, 7 days, 1 month, 3 months and 6 months following surgery.

Results: Visual acuity was significantly better in group 1 than in group 2 at 7 days (0.85 ± 0.64 logMAR vs. 1.46 ± 0.8 logMAR, $p=0.024$) and one month (0.42 ± 0.35 logMAR vs. 1.03 ± 0.86 logMAR, $p=0.04$) but was no longer different at three and six months. Pachymetry decreased significantly in 7 days in group 1 (decrease of 17%, $p=0.04$), contrary to group 2 ($p=0.96$), but the difference between the 2 groups was not statistically significant ($p=0.15$). Corneal density was also not significantly different between the two groups.

Conclusion: 5% sodium chloride hypertonic eye drops reduces significantly post-operative corneal oedema treatment as shown by the improvement in visual acuity at one week and the downward trend in pachymetry.

Keywords: Corneal oedema; Hyperosmolar eye drops; Visual acuity; Pachymetry; Corneal density

Abbreviations: DCVA: Distance Corrected Visual Acuity; DSAEK: Descemet Stripping Automated Endothelial Keratoplasty; PK: Penetrating Keratoplasty; NS: Non-significant.

Introduction

Corneal oedema is a frequent clinical situation and multiples signs can be found, depending on oedema location and severity.

Main aetiologies can be divided in 4 classes:

- Mechanic causes such as traumatism, acute glaucoma, iatrogenic causes (cataract surgery, penetrating or lamellar keratoplasty)
- Corneal dystrophies such as Fuchs disease, posterior polymorphous corneal dystrophy
- Endothelial toxicity: benzalkonium chloride, silicon oil

- Inflammatory and infectious causes: Toxic Anterior Segment Syndrome (TASS), virus.

Corneal hydration depends on epithelial barrier integrity, tears evaporation, stromal imbibition pressure, pump and barrier function of the endothelium and intra-ocular pressure. Normal corneal hydration rate is about 78%. To maintain corneal transparency, stroma needs to be in a relative dehydration state.

Luxenberg [1], then Marisi [2] and Knezović [3] demonstrated hypertonic solution efficacy on corneal hydration by increasing water transfer from stroma to tears. Sodium chloride, by an osmotic effect, could regulate corneal hydration state in case of endothelial pump failure, to delay surgery.

The purpose of the present study was to evaluate clinical effectiveness of a 5% sodium chloride treatment associated with 0.15% sodium hyaluronate on visual acuity, pachymetry and corneal density in patients with corneal oedema.

Patients and Methods

This prospective randomized study was conducted in a university ophthalmology department setting, from April 2014 to April 2015. All patients were informed and gave their consent to the study in accordance to the Helsinki declaration and institutional review board was obtained.

The patients included had a post-operative corneal oedema following cataract surgery, penetrating or lamellar keratoplasty (DSAEK (Descemet Stripping Automated Endothelial Keratoplasty)) and were divided in two groups:

- Patients in group 1 were treated with 5% sodium chloride hypertonic eye drops associated with 0.15% sodium hyaluronate in addition to the classical post-operative treatment for 1 month
- Patients in group 2 were only treated with classical post-operative treatment

The exclusion criteria were:

- Retinal disease such as maculopathy, age-related maculopathy, diabetic retinopathy
- Glaucoma
- Proven allergy to one of the hyperosmolar solution treatment excipients
- Per-or post-operative complications: posterior capsular rupture, surgically induced macular oedema (Irvine-Gass syndrome)

A complete ophthalmologic examination was performed pre-operatively, the first day of the treatment (D1), then 7 days after (D7), one month (M1), three (M3) and six months (M6); which included: distance corrected visual acuity (DCVA) (in logMAR units), slit-lamp biomicroscopy and Scheimpflug imaging (Pentacam®, Oculus Optikgeräte GmbH, Inc., Wetzlar, Germany).

The post-keratoplasty treatment included tobramycin and dexamethasone (Tobradex®, Alcon, Fort Worth, Texas, USA) QID for 6 months with decreasing doses and non-preserved artificial tears (Optive®, Allergan, Irvine, CA, USA). After cataract surgery, patients

were treated by topical antibiotics (ofloxacin (quinofree®, laboratoires Théa, Clermont-Ferrand, France)) TID for 7 days associated with corticosteroids (dexaméthasone, dexafree®, laboratoires Théa, Clermont-Ferrand, France) TID for 1 month. The hyperosmolar solution treatment was composed of 5% sodium chloride with 0.15% hyaluronate sodium (ODM5®, Horus Pharma, Saint-Laurent du Var, France) QID for 1 month.

A Pentacam® imaging was performed in all patients. This non-invasive system uses a rotating Scheimpflug camera, allowing anterior segment imaging from cornea to lens. A 475-nm wavelength LED is used. This system measures corneal topography, pachymetry and corneal density maps (CorneaDensito® software). Densitometry, intended as light-scattering, is calculated on the 12 corneal millimetres, on 4 concentric rings centred on the corneal apex. Zones range from apex to 2 mm, then 2 to 6 mm, 6 to 10 mm and finally from 10 to 12 mm. Cornea is divided in three layers: 120 anterior microns, central layer and 60 posterior microns. Total layer gives the average density over the complete thickness. Corneal density is expressed on a grey scale from 0 (maximal transparency, minimal light-scattering) to 100 (minimal transparency, maximum light-scattering) (Grey Scale Unit=GSU). Acceptable maps had at least 10.0 mm of corneal coverage with no extrapolated data in the central 9.0 mm zone.

Statistical analyses were performed using the XLstat-Pro 2015 software package (2015.1.02 Version, Addinsoft, Inc., Brooklyn, NY, USA). For quantitative values, mean comparisons were performed by a parametric paired Student t-test. For sub-group analysis, a non-parametric Mann-Whitney test was used. A p value<0.05 was considered statistically significant.

Results

95 patients were included: 45 in group 1 and 50 in group 2, with a mean age of 68.9 ± 13.9 (26; 93) years old at the time of the surgery, with a mean follow-up of 4.1 ± 2.3 (1; 6) months. Pre-operative features are summarized (Table 1).

	Group 1	Group 2	p
Patients (n)	45	50	NS
Age (years old)	65.8	70.5	0.19
Sex (male/female)	26/19	33/17	NS
Follow-up (months)	3.5 ± 2.3	4.4 ± 2.3	0.08
Initial DCVA (logMAR)	1.96	2.33	0.5
Pachymetry (µm)	765.6	724.4	0.63
Mean total densitometry	36.5	35.5	0.81
DSAEK	15	18	NS
PK	13	17	NS
Cataract surgery	17	15	NS

Table 1: Pre-operative characteristics of the population.

Visual acuity

Figure 1 illustrates DCVA in the 2 groups.

In group 1, a significant improve in visual acuity was observed at D7 by contrast to D1 with an average increase of 11 lines. Visual acuity improvement persisted after one month, 3 and 6 months of treatment.

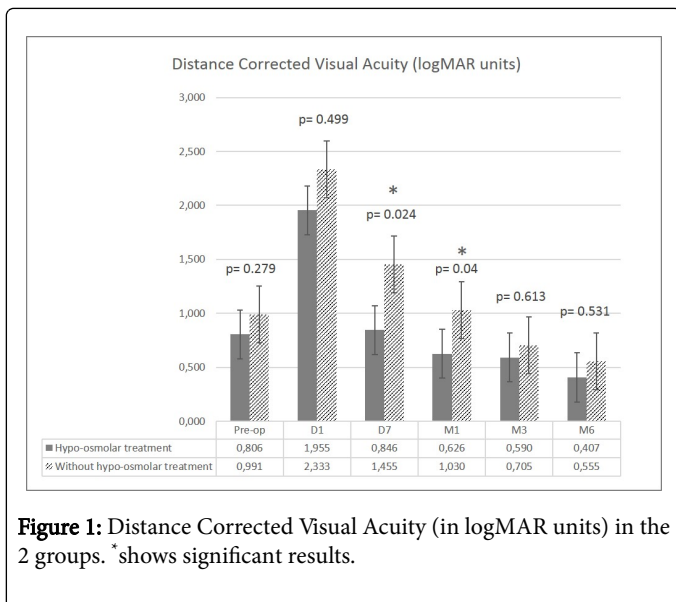


Figure 1: Distance Corrected Visual Acuity (in logMAR units) in the 2 groups. *shows significant results.

In group 2, DCVA was not significantly improved at 7 days postoperatively ($p=0.09$). By contrast, visual acuity significantly improved at one month postoperatively against D1 ($p=0.008$) and continued to improve at 3 months ($p=0.003$) and 6 months ($p<0.0001$) postoperatively.

At D7, DCVA was significantly higher in group 1 treated by 5% sodium chloride (0.85 ± 0.64 logMAR (0.09; 2) vs. 1.46 ± 0.8 logMAR (0.2; 3), $p=0.024$) such as one month (0.63 ± 0.65 logMAR (0; 3) vs. 1.03 ± 0.86 (0; 3), $p=0.04$).

In sub-group analysis, at D7, DCVA was significantly higher in patients who undergone cataract surgery in group 1 than in group 2 (0.6 ± 0.2 logMAR (0.1; 2) vs. 1.16 ± 0.6 logMAR (0.6; 2), $p=0.04$). Results were not significantly different in penetrating or endothelial keratoplasty group at D1, one month, 3 and 6 months.

Pachymetry

Figure 2 represents mean pachymetry in the 2 groups.

In group 1, at D7 the mean pachymetry was 635.5 ± 93.8 μm (447; 893), which represented a decrease of 17% by contrast to D1 corneal pachymetry (765.6 ± 274.2 μm (486; 1824), $p=0.04$), but was still higher than pre-operative pachymetry ($p=0.03$). At one month, the mean pachymetry was 594.7 ± 116 μm (285; 862) and was no longer statistically different from pre-operative pachymetry ($p=0.52$) and remain stable at three and six months.

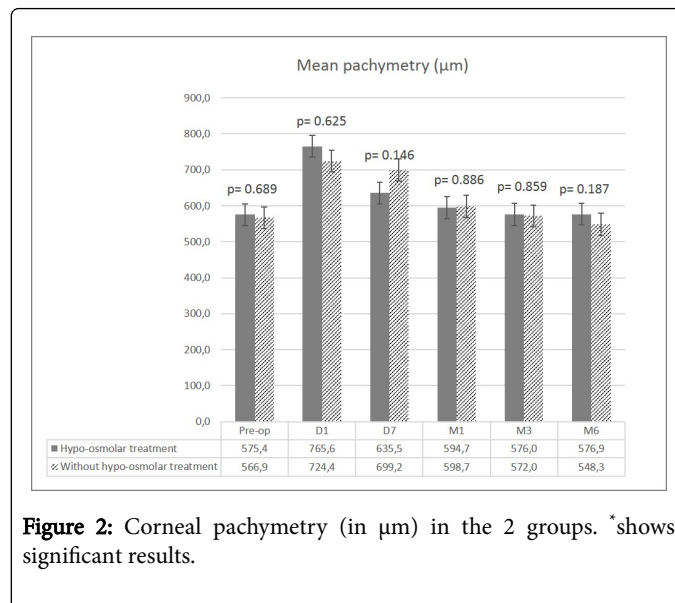


Figure 2: Corneal pachymetry (in μm) in the 2 groups. *shows significant results.

In group 2, D7 mean pachymetry was not significantly different from D1 ($p=0.8$). At one month, pachymetry was 598.7 ± 87 μm (466; 835), still different from preoperatively ($p=0.02$), but was reduced by 16% in comparison to D1 ($p=0.013$). At 3 and 6 months, mean pachymetry was no longer different from pre-operative ($p=0.43$ and $p=0.45$ respectively).

No statistical difference was found between the 2 groups with a clear downward trend in group 1 treated with hyperosmolar solution.

In sub-group analysis, a statistical difference between the 2 groups at D7 was found for DSAEK sub-group (632.35 ± 93.6 μm (447.33) in group 1 vs. 847.9 ± 132.3 (709; 1025) in group 2, $p=0.003$) was found. Results were not statistically significant for other surgeries.

Corneal densitometry

Figure 3 shows mean total corneal densitometry in the 2 groups.

In the 2 groups, mean total corneal densitometry do not decrease at D7 or M1 by contrast to D1. At M3 and M6, mean total corneal densitometry was significantly different from D1 ($p=0.049$ and $p=0.04$ in group 1; $p=0.04$ and $p=0.003$ in group 2, respectively).

Total average corneal densitometry was not significantly different between the 2 groups, as in the sub-group analysis.

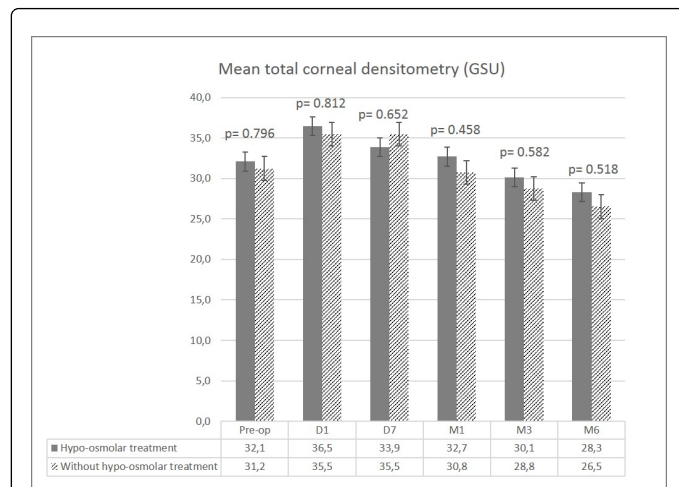


Figure 3: Mean total corneal densitometry (GSU=Grey Scale Unit) in the 2 groups. *shows significant results.

If we consider the different corneal layers (anterior 120 µm, posterior 60 µm and central layer), no statistical difference was observed; and the same results were found considering the different annuli (0 to 2 mm, 2 to 6 mm, 6 to 10 mm or 10 to 12 mm zones).

Figure 4 illustrates corneal pachymetric and densitometric maps in a patient treated by 5% hyperosmolar sodium chloride. A decrease in pachymetry and densitometry is observed from D1 to D7.

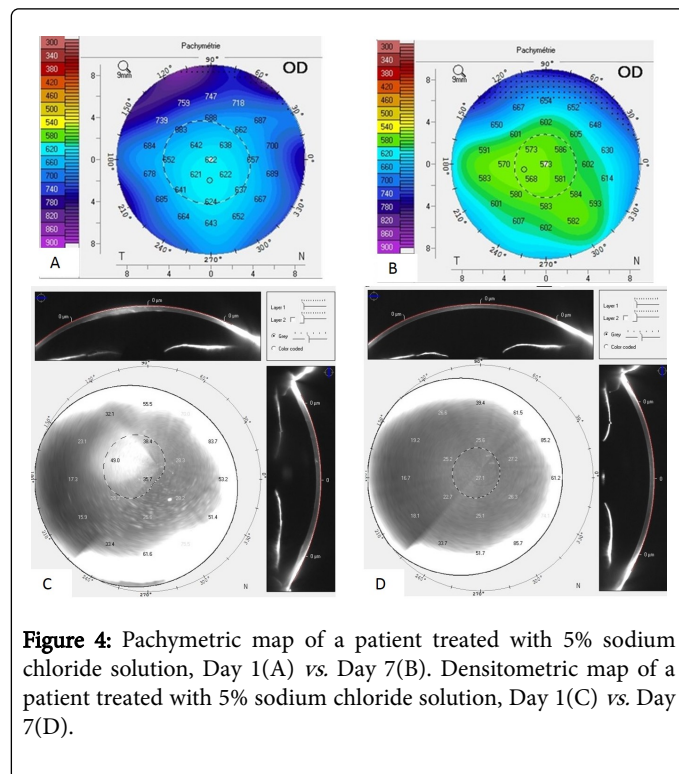


Figure 4: Pachymetric map of a patient treated with 5% sodium chloride solution, Day 1(A) vs. Day 7(B). Densitometric map of a patient treated with 5% sodium chloride solution, Day 1(C) vs. Day 7(D).

Side effects

The hyperosmolar treatment was stopped in 4 patients before one month of treatment, due to stinging eyes. No other side effect was recorded.

Discussion

Corneal oedema is due to an increase of normal stroma hydration, directly correlated to corneal thickness. A few treatment exists [4]. When oedema became irreversible, surgery is unavoidable, waiting for new promising treatments such as Rho-Associated Kinase Inhibitor Eye Drop [5].

Previously, Green's pre-clinical study [6] on rabbits showed a 20 to 25% decrease of the pachymetry 30 min to 4 h after a 5% sodium chloride instillation. Luxemberg [1], in the 70's reported efficacy of hypertonic solutions on 7 patients with a decrease of pachymetry until 20% with 5% sodium chloride ointment. In 1975, Marisi and Aquavella [2] reported visual effects on 89 eyes of 75 patients with a symptomatic corneal oedema, treated with 5% hyperosmolar saline solution 4 to 8 times a day for 18 months. A visual acuity improvement was noted in 61% with a good local tolerance. Knezović's study [3] on corneal oedema due to bullous keratopathy, reported a significant increase in visual acuity with a significant decrease in pachymetry at D7, ongoing for one month in initial stage (limited to stromal oedema) after 5% saline solution treatment 2 eye drops QID. In patients with advanced bullous keratopathy, no visual acuity improvement was found but a central thickness improve at D7 was observed.

In our study, we used a 5% hyperosmolar sodium chloride solution with 0.15% sodium hyaluronate. Sodium chloride, thanks to its osmotic power, allows water transfer from stroma to tears, and improve transiently corneal hydration state. Sodium hyaluronate has a protective and healing effect on corneal epithelium and allows a better local tolerance of the treatment [7,8].

We observed a significant increase in visual acuity at D7 and M1 in patients treated with hyperosmolar solution, also found in cataract sub-group in which the healthy endothelium helps with oedema resorption. A decrease of pachymetry was only found in endothelial keratoplasty sub-group. The decrease in pachymetry in DSAEK sub-group is not necessarily correlated to a visual acuity improvement, because the hyperosmolar solution effectiveness is located on the epithelium and anterior stroma layers. Sodium hyaluronate, by stabilizing the tear film can participate to visual acuity improvement.

Herein, we report the first study on hyperosmolar sodium chloride solution effect on corneal density measured with Pentacam®. This Scheimpflug rotating camera corneal density, expressed in grey scale unit from 0 (minimal light-scattering) to 100 (maximal light-scattering). This density is an indirect indicator of corneal transparency [9,10] and will increase with corneal oedema. However, in our study, we didn't notice a significant decrease in corneal density with hyperosmolar solution treatment. The effect on corneal density can be delayed.

Hyperosmolar solution is a logical and interesting treatment with its efficacy in low to moderate corneal oedema. In case of an advanced corneal oedema or associated with fibrosis, keratoplasty is currently the only remaining treatment.

Acknowledgements:

None

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