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Title: Effectiveness of Non-Pharmacological Treatments for Acute Seasonal Allergic Conjunctivitis

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Abstract: Objective: To investigate whether artificial tears and cold compress alone or in combination provide a treatment benefit, whether they were as effective as, or could enhance topical anti-allergic medication.
Design: Randomized masked clinical trial.
Participants: Eighteen subjects (aged 29.5 ± 11.0 years) allergic to grass pollen
Intervention: Controlled exposure to grass pollen using an environmental chamber to stimulate an ocular allergic reaction followed by artificial tears (AT), 5 minutes of cold compress (CC), AT combined with CC, or no treatment applied at each separate visit in random order. A subset of 11 subjects also had epinastine (EH) applied alone and combined with CC in random order or instillation of a volume matched saline control.
Main Outcome Measures: bulbar conjunctival hyperemia, ocular surface temperature, ocular symptoms repeated before and every 10 minutes after treatment for 1 hour
Results: Bulbar conjunctival hyperemia and ocular symptoms decreased and temperature recovered to baseline faster with non-pharmaceutical treatments compared to no treatment ($p < 0.05$). AT combined with CC reduced hyperemia more than other treatments ($p < 0.05$). The treatment effect of EH was enhanced by combining it with a CC ($p < 0.001$). CC combined with AT or EH lowered the antigen-raised ocular surface temperature below the pre-exposure baseline. AT instillation alone or CC combined with AT or EH significantly reduced the temperature ($p < 0.05$). CC combined with AT or EH had a similar cooling effect ($p > 0.05$). At all measurement time intervals, symptoms were reduced for both EH and EH combined with CC than CC or AT alone or in combination ($p < 0.014$).
Conclusions: In a controlled exposure to grass pollen, cold compresses and artificial tears showed therapeutic effect on the signs and symptoms of allergic conjunctivitis. A cold compress enhanced the use of epinastine alone and was the only treatment to reduce symptoms to baseline within an hour of antigenic challenge. Signs of allergic conjunctivitis were generally reduced most by a combination of a cold compress in combination with artificial tears or epinastine.

Ref 2013-759R1
Effectiveness of Non-Pharmacological Treatments for Acute Seasonal Allergic Conjunctivitis

Dear Prof. Bartley,

RESPONSES IN CAPITALS

Thank you for submitting a revised version of the above-referenced manuscript. We would like to accept it for publication as soon as a few final issues have been satisfactorily addressed, as listed below:
WE ARE DELIGHTED
Thank you for revising your manuscript. In reviewing your revisions, I have only a couple of comments. First, as regards the suggestion of Reviewer 2:

P 7, LM 170 and multiple places elsewhere (including P 8, LM 193;
P 8, LM 201): When comparing 2 variables, use the term "between;" when comparing 3 or more variables, use the term "among."

I suspect that what the reviewer was trying to point out is that Strunk and White, in "The Elements of Style", recommend the following as regards the use of "among" and "between": "When more than two things or persons are involved, "among" is usually called for: "The money was divided among the four players." When, however, more than two are involved but each is considered individually, between is preferred: "an agreement between the six heirs."
I will leave the wording to your discretion.
MORE THAN TWO COMPARISONS ARE INVOLVED IN EACH CASE WE USE “BETWEEN” BUT EACH IS CONSIDERED INDIVIDUALLY, SO “BETWEEN” IS PREFERRED

However, as regards line 195, I agree with the reviewer and find the phrase, "diverging toward baseline" confusing. I don't understand how something can diverge back to its baseline. Converge? Perhaps. But diverge implies moving away. Again, please consider whether this is the clearest way to express what you intend. Thank you.
CHANGED TO “CONVERGING” AS SUGGESTED

Comments from the Editorial Office:

The "copyright" uploaded with your submission is not the correct form. The copyright form can be downloaded from the website. By the way, we no longer require the corresponding author declaration form.
CORRECT FORM UPLOADED

In the abstract, please change from:

Study Design: Randomised masked clinical trial.
to:
Design: Randomized masked clinical trial.
CHANGED AS SUGGESTED

In the text, change from:
Materials & Methods
to:
Materials and Methods
CHANGED AS SUGGESTED

The tables headers are long. Is it possible to move some of the text to the footers?
SHORTENED AS REQUESTED

Kind regards,

James Wolffsohn

Precis

Non-pharmaceutical treatments for acute presentation seasonal allergic conjunctivitis were found to be as efficacious in relieving the signs and symptoms of the ocular allergic response as a dual action antihistamine mast cell stabilizer.

Title Page

Full Title: Effectiveness of Non-Pharmacological Treatments for Acute Seasonal Allergic Conjunctivitis

Condensed Title: Seasonal Allergic Conjunctivitis Non-Pharmacological Treatments

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Abstract

Objective: To investigate whether artificial tears and cold compress alone or in combination provide a treatment benefit, whether they were as effective as, or could enhance topical anti-allergic medication.

~~Study~~ Design: Randomi~~z~~zed masked clinical trial.

Participants: Eighteen subjects (aged 29.5 ± 11.0 years) allergic to grass pollen

Intervention: Controlled exposure to grass pollen using an environmental chamber to stimulate an ocular allergic reaction followed by artificial tears (AT), 5 minutes of cold compress (CC), AT combined with CC, or no treatment applied at each separate visit in random order. A subset of 11 subjects also had epinastine (EH) applied alone and combined with CC in random order or instillation of a volume matched saline control.

Main Outcome Measures: bulbar conjunctival hyperemia, ocular surface temperature, ocular symptoms repeated before and every 10 minutes after treatment for 1 hour

Results: Bulbar conjunctival hyperemia and ocular symptoms decreased and temperature recovered to baseline faster with non-pharmaceutical treatments compared to no treatment ($p < 0.05$). AT combined with CC reduced hyperemia more than other treatments ($p < 0.05$). The treatment effect of EH was enhanced by combining it with a CC ($p < 0.001$). CC combined with AT or EH lowered the antigen-raised ocular surface temperature below the pre-exposure baseline. AT instillation alone or CC combined with AT or EH significantly reduced the temperature ($p < 0.05$). CC combined with AT or EH had a similar cooling effect ($p > 0.05$). At all measurement time intervals, symptoms were reduced for both EH and EH combined with CC than CC or AT alone or in combination ($p < 0.014$).

Conclusions: In a controlled exposure to grass pollen, cold compresses and artificial tears showed therapeutic effect on the signs and symptoms of allergic conjunctivitis. A cold compress enhanced the use of epinastine alone and was the only treatment to reduce symptoms to baseline within an hour of antigenic challenge. Signs of allergic conjunctivitis were generally reduced most by a combination of a cold compress in combination with artificial tears or epinastine.

Ocular allergy represents a group of hypersensitivity disorders that primarily affects the conjunctiva. The most common form of ocular allergy is seasonal allergic conjunctivitis (SAC), accounting for 90% of cases [1, 2]. The most prevalent allergens in SAC are grass, tree, and weed pollen and outdoor moulds [2]. In the United Kingdom (UK), the prevalence of ocular allergy to grass pollen in patients attending optometric practice is estimated to be 8% [3]. Although the signs and symptoms of SAC are usually mild, it may hinder school performance, work productivity and everyday tasks such as driving [4, 5, 6].

The primary treatment strategy for SAC involves avoidance of the offending allergen to prevent the initiation of the allergic response. However, complete avoidance is not often possible and use of topical anti-allergic medications is required when signs and symptoms occur [7, 8, 9]. It has been suggested that non-pharmacological treatments such as artificial tears and cold compresses may be used in conjunction with allergen avoidance strategies and anti-allergic medications to help bring about symptomatic relief [9, 10, 11, 12]. However, there appears to be no evidence in the scientific literature which demonstrates the efficacy of using artificial tears or cold compresses for treating SAC. Therefore the aim of this study was to investigate the efficacy of instillation of artificial tear substitutes (AT) and application of cold compresses (CC) alone and in combination in patients with confirmed ocular allergic sensitivity to a controlled exposure of grass pollen using an environmental chamber model. In addition, the effectiveness of these treatments compared to a topical dual action antihistamine-mast cell stabilizer licensed for the treatment of SAC alone and in combination with CC was investigated.

Materials and& Methods

The study received ethical approval from the Aston University Research Ethics Committee and was registered as a clinical trial (NCT01569191 ClinicalTrials.gov). The research was conducted in accordance this the principles expressed in the Declaration of Helsinki.

Subjects

All participants were ≥18 years old volunteers from a University population with no history of asthma, any active eye pathology and were not using ocular or systemic medications known to affect the eye. None of the participants experienced any form of allergic conjunctivitis at least 1 month before the study took place or used anti-allergic medication over the 14 days prior to testing.

Screening Protocol

Subjects underwent skin prick (SPT) and bilateral conjunctival challenge tests (CCT) to confirm systemic and ocular allergic sensitivity to grass pollen [13, 14, 15] . SPT was performed on the forearm using grass pollen solution (10 HEP, Soluprick SQ, ALK-ABELLO, Denmark) and positive (histamine solution) and negative (saline) controls. After 20 minutes, the size of the wheal response was measured and a positive result was recorded for diameters ≥3mm. CCT was performed by applying 20µL of grass pollen (Soluprick SQ, ALK-ABELLO, Denmark) solution in two-fold increasing concentrations from 3IR/mL to 100IR/mL to one eye (selected at random to be the experimental eye) and saline solution to the contralateral (control) eye every 10 minutes until a composite score of ≥5 using a standardized scoring method was reached [13, 14, 16]. Eligible subjects who had a positive SPT and CCT proved sensitivity to grass pollen were enrolled into the study with written informed consent.

Eighteen subjects (one third male) took part in the study with a mean age of 29.5±11.0 (age range 20-65). At each visit subjects underwent slit lamp bio-microscopy to ensure signs and symptoms of SAC were not present prior to testing. This was followed by a series of measurements on both eyes including slit lamp examination and grading of nasal and temporal bulbar conjunctival hyperemia using a grading scale (Jenvis Research, Germany), and ocular surface temperature of the cornea and temporal and nasal bulbar conjunctiva (5mm^2 area, 2 seconds post-blink) using an infra-red camera (Thermo Tracer TH7102, NEC, Japan) where a series of digital markers were used to ensure the temperature was measured at the same location for each subject[17]. Ocular allergy symptomology was also measured using the eye symptom section from the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) on a 0 to 6 scale, with the summed score for itching, watering, swelling and soreness resulting in a score between 0 and 24 [18].

Subjects were exposed to between 251 and 500 grains/m^3 of Timothy grass pollen (*phleum pratense*; equivalent to a “very high” pollen count classification; concentration monitored using a Burkard continuous air sampler) in a computer controlled environmental chamber (Design Environmental, 32 Rassau Industrial Estate, Ebbw Vale, Gwent) at a temperature of 20°C and 70% ambient humidity (average local conditions in June in the UK) on separate visits with the concentration established that caused ocular itching graded ≥3 (RQLQ grade) and a ≥0.5 unit change (Jenvis scale) in nasal and temporal bulbar conjunctival hyperemia occurred in both eyes after 5 minutes of exposure.

Once the concentration of pollen for each individual had been established, on separate occasions separated by at least one week, out of the allergy season, the subjects had baseline measurements taken and were then exposed to pollen at this concentration for 5 minutes and 5 minutes post exposure the same measurements were repeated. This was

followed by application bilaterally of either an AT applied to the temporal conjunctiva (Blink Refreshing Eye Drops 0.5ml single use vial, Abbot Medical Optics, USA), CC applied to the closed eye lid for 5 minutes (frozen gel-pack: Boots Pharmaceuticals, Nottingham, UK), AT combined with CC (for 5 minutes, 5 minutes after AT instillation) or no treatment (NT) to the eyes in random order (computer generated) at each visit (examiner masked). The same measures were then repeated every 10 minutes for 1 hour at each visit.

A subgroup of 11 randomly selected subjects (mean age of 29.1±12.9 years, range 20-65) attended for three further identical visits receiving 1 drop of Epinastine Hydrochloride (EH, Relestat 0.5mg/ml, Allergan, USA), 1 drop of EH combined with CC (for 5 minutes, 5 minutes after instillation of EH), or a single drop of saline (termed vehicle, equivalent to the same volume as the drug but without the active ingredients to determine how much of the effect was lubrication compared to pharmaceutical) in random order to assess the efficacy of non-pharmaceutical agents, against a dual action antihistamine/mast cell stabilizer licensed for seasonal allergic conjunctivitis.

Statistics

The randomization code was held by a non-masked researcher and the code broken after data entry by the statistician. Statistical analysis was performed using SPSS for Microsoft Windows. As ocular surface temperature and conjunctival hyperemia were found to be normally distributed (Kolmogorov-Smirnov Test > 0.05), their changes over time were evaluated by repeated measures Analysis of Variance (ANOVA), and where statistical significance was identified, post-hoc analysis was performed using paired t-tests. This approach limited the number of statistical comparisons to minimize the chance of Type I statistical errors. Changes in ocular symptomology were evaluated by the Friedman test and post-hoc analysis where statistical significance was identified was performed using Wilcoxon signed-rank tests. Statistical significance was taken as $p < 0.05$. Sample size, even of the

pharmaceutical comparison subgroup, met the requirements for sufficient replicates for a repeated measures design.[19]

Results

Non-Pharmaceutical Treatment Efficacy versus No Treatment

Ocular Symptomology

Although the symptoms differed in overall magnitude, with itching rated as the severest symptom and swelling the least, the profile with time after treatment and recovery was similar for each of the symptoms so they were averaged for analysis. The global ocular symptom scores were similar at baseline at each visit ($X=6.091$, $p=0.107$) as was the post exposure effect ($X=2.729$, $p=0.435$). They decreased with time after treatment (CC: $X=88.489$, $p<0.001$; AT: $X=88.258$, $p<0.001$; AT+CC: $X=87.639$, $p<0.001$; Figure 1), with all treatments reducing symptoms more than no treatment ($p < 0.001$), but none of the treatments returned global ocular symptom scores to baseline levels within 1 hour after antigen exposure (no treatment 58.6% relative return to baseline, CC 71.6%, AT 84.8%, AT+CC 86.9%; $p<0.001$).

Bulbar Conjunctival Hyperemia

Hyperemia was similar at baseline at each visit ($F=0.955$, $p=0.438$) as was the post exposure effect ($F=0.267$, $p=0.898$). There was no difference in conjunctival hyperemia between the eyes ($F=0.112$, $p=0.742$), however, the nasal conjunctiva was more red than the temporal conjunctiva over the measurement period (1.71±0.62 versus 1.47±0.56 Jenvis units; $F=33.711$, $p<0.001$). There was a significant difference in conjunctival hyperemia following each of the treatments ($F=68.211$, $p<0.001$; Figure 2), with a reduction in redness with time ($F=302.764$, $p<0.001$), although this recovery differed with treatment ($F=9.469$, $p<0.001$) and none of the treatments achieved complete recovery to baseline within 60 minutes (no treatment 16.5% relative return to baseline, CC 57.9%, AT 73.3%, AT+CC 76.5%; $p<0.001$). However, all treatments produced a significant improvement in hyperemia over time compared to no treatment both nasally and temporally ($p<0.05$).

Ocular Surface Temperature

Ocular surface temperature was similar at baseline at each visit (F=0.685, p=0.605) as was the post exposure effect (F=0.636, p=0.639). There was no difference in temperature between the eyes (F=0.017, p=0.897), however there were significant differences in temperature between corneal, nasal and temporal locations (F=97.899, p<0.001). There was a significant difference in temperature following each of the treatments (F=19.684, p<0.001; Figure 3), with the temperature ~~di~~converging toward baseline over time (F=32.955, p<0.001), although this recovery differed with treatment (F=122.796, p<0.001). Temporal bulbar conjunctival and corneal temperatures returned to baseline levels (was no longer significantly different; p>0.05) with the application of cold compress (within 50 minutes), artificial tears (within 40 minutes) and artificial tears combined with cold compress (within 40 minutes), whereas for the nasal bulbar conjunctiva the return to baseline temperature was generally faster (40, 30 and 40 minutes respectively). Ocular surface temperature did not return to baseline levels without treatment at any location (relative return to baseline 57.0%; p<0.05).

Relative Efficacy of Non-Pharmaceuticals versus a Dual Action Pharmaceutical

Ocular Symptomology

All ocular symptom changes with time were similar so they have been averaged for presentation and analysis. At all measurement time intervals, symptoms were reduced for both EH and EH in combination with a CC compared to a CC or AT alone or in combination (p < 0.01; Figure 4). Only EH alone and in combination with a CC reduced global ocular symptom scores to baseline levels within the post-antigen exposure hour over which subjects were monitored (after 60 minutes: p=0.414, p=0.705). A CC enhanced the pharmaceutical benefit of EH alone up to 20 minutes (p<0.05), where thereafter they were similarly efficacious (p>0.05). A CC also further reduced symptoms when combined with AT

compared to AT use alone up to 20 minutes ($p < 0.05$). The drug effect was from the active ingredients rather than the saline vehicle control ($p < 0.001$).

Bulbar Conjunctival Hyperemia

There was a significant difference in conjunctival hyperemia between each of the treatments ($F=11.728$, $p<0.001$; Table 1), with a reduction in redness with time ($F=581.320$, $p<0.001$), although this recovery differed with treatment ($F=9.463$, $p<0.001$). AT combined with CC outperformed AT, CC and EH alone and EH combined with CC nasally. The treatment effect of EH was enhanced by combining it with a CC. The saline volume control (vehicle) showed the action of EH was principally from the active pharmaceutical ingredients. AT instillation had similar effectiveness to a CC application used in isolation (Table 1).

Ocular Surface Temperature

There was a significant difference in ocular surface temperature between each of the treatments ($F=11.680$, $p<0.001$; Table 2), with a change in temperature toward baseline with time ($F=17.952$, $p<0.001$), although this recovery differed for each treatment ($F=144.816$, $p<0.001$). CC in combination with an AT or EH lowered the antigen-raised ocular surface temperature below the pre-exposure baseline. AT instillation alone or in combination to a CC or EH significantly, but only slightly (<0.5ºC), reduced the temperature ($p < 0.05$; Table 2). CC combined with either a AT or EH had a similar cooling effect. The saline vehicle volume control to EH had a similar cooling effect to an AT and no beneficial cooling effect over EH of the same volume but containing active pharmaceutical agents.

Discussion

In the first phase of the study, the efficacy of artificial tears (AT), cold compress (CC) and in combination (AT+CC) was investigated by measuring conjunctival hyperemia, ocular surface temperature and ocular symptoms following exposure to grass pollen in an environmental chamber model to produce the response signs and symptoms of an acute ocular seasonal allergic conjunctivitis. Subjects were exposed over a 5 minute interval in the environmental chamber to a predetermined threshold of reactivity, to ensure that subjects had sufficient signs and symptoms in order to detect any treatment effect. There was no significant difference in hyperemia, ocular surface temperature or ocular symptoms at each visit following the multiple exposures separated by at least a week (and between each eye for hyperemia and ocular surface temperature), demonstrating that the environmental chamber model produces a bilaterally homogenous and reproducible ocular allergic reaction. The data show that all treatments provided benefit in relieving hyperemia, restoring physiological ocular temperature and reducing ocular symptoms during an acute episode of stimulated SAC compared to no treatment.

Although artificial tears (AT) are principally formulated to relieve ocular surface signs and symptoms in dry eye, they have been advocated to have a beneficial effect in SAC [11, 12]. The reduction in signs (conjunctival hyperemia) and symptoms of SAC in this study are likely to have been principally caused by diluting and washing away the allergen from the eye, and the AT acting as a barrier to further exposure by preventing the allergen from binding to the ocular surface [7, 8, 11, 12]. This barrier effect to allergens has also been observed in contact lens wear, where patients wearing soft contact lenses exhibited reduced signs and symptoms of ocular allergy compared to non-contact lens wearing control visits following exposure in an allergen chamber, with a further benefit from using contact lenses with sustained release of a lubricating agent from within the material matrix [20]. ATs are generally stored at room

temperature, which could give them an additional soothing effect, but this study demonstrated that any benefit from the temperature change from AT is minor compared to its other properties such as lubrication, with the temperature reduction and consistency over time higher in the nasal region, compared to the cornea and lower still temporally, following the excretion pathway of the tear film.

In environmental studies of anti-allergy drug efficacy, the use of artificial tears as a control have been shown to have a drug effect of up 50-70% and this is considered to be a placebo effect [13, 21, 22, 23]. However, as artificial tears may produce a real physical effect on the binding of allergens to the ocular surface, this mechanism cannot be considered purely as placebo and therefore should not be considered as an effective control in studies of acute SAC, whereas their use is warranted in investigating the prophylactic effect of an ocular anti-allergy drugs [23].

The use of cold compresses (CC) has previously been recommended as supportive therapy in ocular allergy [11, 24, 25] but no studies relating to the efficacy of cold compress treatment has been reported in the scientific literature. Therefore, this study has demonstrated the beneficial effects of cold compress therapy in ocular disease for the first time. The application of CC may reduce hyperemia and relieve signs and symptoms by causing vasoconstriction of conjunctival blood vessels and subsequently prevent or minimize swelling and leakage of and inflammatory mediators involved in the allergic response [7, 10, 26]. A potential limitation of the CC data was the ability to control the application to the closed eyelids, although the gel mask was held in place over the eyes with an attached elastic headband. This, however, mimicked the clinical reality where the exact area and location of contact of the compress with the eyelid will vary between patients owing to differences in facial structure.

In the second phase of the study, the effectiveness of non-pharmaceutical treatments was compared to a dual action antihistamine / mast cell stabilizer pharmaceutical (EH), with or without the addition of a CC, in a randomly selected subgroup of subjects using the same acute induced-SAC methodology. Comparison over the 60 minute observation period showed that the combination of artificial tears and cold compress was superior to all other treatments in reducing hyperemia including over the pharmaceutical agent, although the antigen induced ocular redness could be improved to the equivalence effectiveness by combining EH with a CC. An AT or a CC used alone was more effective that the pharmaceutical used in isolation. The pharmaceutical agent effect, however, was confirmed as being derived from the active ingredients rather than any ocular lubricating effect of its fluid vehicle and this was also the case for the pharmaceutical effect on ocular comfort.

A CC alone or in combination with an AT or EH pharmaceutical lowered the ocular surface temperature below baseline from the increased level caused by exposure to the antigen, whereas an AT alone had relatively little effect over ocular temperature, particularly over the temporal conjunctiva. As this treatment result differed from that of conjunctival hyperemia and ocular symptoms, it could suggest that the inflammatory events causing increased ocular surface temperature following antigen exposure could differ from those driving other signs and symptoms or the results could be confounded by tear film thickness variations across the ocular surface and with time as this would have affected the radiated heat imaged by the thermal camera.

Ocular symptomology improved faster with EH compared to all other treatment modalities, reducing symptoms to baseline levels after 60 minutes, and the recovery profile was enhanced initially by the application of a CCs. Although none of the non-pharmaceutical treatments reduced symptoms to baseline levels, the mean scores were low, falling within

the “hardly troubled at all” category. These data suggest that AT and CC, either alone or in combination, are effective methods of relieving the signs and symptoms of SAC during the active phase of the condition.

EH displays anti-histamine, anti-inflammatory and mast cell stabilizing properties in animal and in-vitro studies [27, 28]. Conjunctival-allergen-challenge-model clinical trials of EH have shown that it is significantly more effective in preventing the signs and symptoms of allergic conjunctivitis compared to its vehicle as confirmed in this study [29, 30]. The efficacy of EH has also been demonstrated to be effective in an environmental clinical trial [31], but these study designs are subject to variations in exposure and therefore limit their ability to detect the efficacy of drugs. Thus, there has been a lack of studies investigating the efficacy of EH in acute SAC. In the present study, the combination of EH combined with CC was superior to EH alone in reducing ocular surface temperature ($p<0.001$), superior to EH in reducing hyperemia both nasally ($p<0.001$) and temporally ($p<0.001$), and enhanced the symptom recovery profile within the first 20 minutes. This suggests that clinically, EH should be prescribed together with advice on applying cold compresses in acute episodes. EH mast cell stabilizing properties are only likely to enhance the pharmaceutical effect after a few days use which should be considered if the patient is likely to be exposed to multiple episodes of acute pollen exposure over a short time period.

The results of the present study are applicable only on the ability of the treatments to relieve the signs and symptoms of simulated SAC during the acute phase of the ocular allergic response, thus it has no bearing on their ability to prevent signs and symptoms from developing through prophylactic treatment. It is not expected that the application of cold compress or artificial tears will have any effect before the ocular allergic response develops, unless they are applied frequently. These data suggest that although EH resolves symptoms

of SAC earlier, it appears to be less efficacious in resolving ocular signs of inflammation such as conjunctival hyperemia and ocular surface temperature increases compared to an artificial tear or cold compress alone, or better in combination, during an acute episode of SAC. Therefore for occasional sufferers such self-management, with reduced risks of drug interactions and reduced patient expense, should be considered. For more frequent SAC sufferers, the benefits of a cold compress in addition to prophylactic pharmaceuticals should be considered as part of patient management when symptoms still occur. Further study is required to measure the immunologic response to ocular signs and symptoms induced by the environmental chamber and treatment strategies.

Word Count: 3,257

Acknowledgements, Conflicts of Interest

We would like to thank Dr Richard Armstrong for his invaluable advice relating to the statistical analysis of the study data.

The Authors declare no competing or conflicting interest and no competing or conflicting or competing financial relationships relating to the subject matter in the study.

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Title Page

Full Title: Effectiveness of Non-Pharmacological Treatments for Acute Seasonal Allergic Conjunctivitis

Condensed Title: Seasonal Allergic Conjunctivitis Non-Pharmacological Treatments

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Abstract

Objective: To investigate whether artificial tears and cold compress alone or in combination provide a treatment benefit, whether they were as effective as, or could enhance topical anti-allergic medication.

Design: Randomized masked clinical trial.

Participants: Eighteen subjects (aged 29.5 ± 11.0 years) allergic to grass pollen

Intervention: Controlled exposure to grass pollen using an environmental chamber to stimulate an ocular allergic reaction followed by artificial tears (AT), 5 minutes of cold compress (CC), AT combined with CC, or no treatment applied at each separate visit in random order. A subset of 11 subjects also had epinastine (EH) applied alone and combined with CC in random order or instillation of a volume matched saline control.

Main Outcome Measures: bulbar conjunctival hyperemia, ocular surface temperature, ocular symptoms repeated before and every 10 minutes after treatment for 1 hour

Results: Bulbar conjunctival hyperemia and ocular symptoms decreased and temperature recovered to baseline faster with non-pharmaceutical treatments compared to no treatment ($p < 0.05$). AT combined with CC reduced hyperemia more than other treatments ($p < 0.05$). The treatment effect of EH was enhanced by combining it with a CC ($p < 0.001$). CC combined with AT or EH lowered the antigen-raised ocular surface temperature below the pre-exposure baseline. AT instillation alone or CC combined with AT or EH significantly reduced the temperature ($p < 0.05$). CC combined with AT or EH had a similar cooling effect ($p > 0.05$). At all measurement time intervals, symptoms were reduced for both EH and EH combined with CC than CC or AT alone or in combination ($p < 0.014$).

Conclusions: In a controlled exposure to grass pollen, cold compresses and artificial tears showed therapeutic effect on the signs and symptoms of allergic conjunctivitis. A cold compress enhanced the use of epinastine alone and was the only treatment to reduce symptoms to baseline within an hour of antigenic challenge. Signs of allergic conjunctivitis were generally reduced most by a combination of a cold compress in combination with artificial tears or epinastine.

Ocular allergy represents a group of hypersensitivity disorders that primarily affects the conjunctiva. The most common form of ocular allergy is seasonal allergic conjunctivitis (SAC), accounting for 90% of cases [1, 2]. The most prevalent allergens in SAC are grass, tree, and weed pollen and outdoor moulds [2]. In the United Kingdom (UK), the prevalence of ocular allergy to grass pollen in patients attending optometric practice is estimated to be 8% [3]. Although the signs and symptoms of SAC are usually mild, it may hinder school performance, work productivity and everyday tasks such as driving [4, 5, 6].

The primary treatment strategy for SAC involves avoidance of the offending allergen to prevent the initiation of the allergic response. However, complete avoidance is not often possible and use of topical anti-allergic medications is required when signs and symptoms occur [7, 8, 9]. It has been suggested that non-pharmacological treatments such as artificial tears and cold compresses may be used in conjunction with allergen avoidance strategies and anti-allergic medications to help bring about symptomatic relief [9, 10, 11, 12]. However, there appears to be no evidence in the scientific literature which demonstrates the efficacy of using artificial tears or cold compresses for treating SAC. Therefore the aim of this study was to investigate the efficacy of instillation of artificial tear substitutes (AT) and application of cold compresses (CC) alone and in combination in patients with confirmed ocular allergic sensitivity to a controlled exposure of grass pollen using an environmental chamber model. In addition, the effectiveness of these treatments compared to a topical dual action antihistamine-mast cell stabilizer licensed for the treatment of SAC alone and in combination with CC was investigated.

Materials and Methods

The study received ethical approval from the Aston University Research Ethics Committee and was registered as a clinical trial (NCT01569191 ClinicalTrials.gov). The research was conducted in accordance this the principles expressed in the Declaration of Helsinki.

Subjects

All participants were ≥18 years old volunteers from a University population with no history of asthma, any active eye pathology and were not using ocular or systemic medications known to affect the eye. None of the participants experienced any form of allergic conjunctivitis at least 1 month before the study took place or used anti-allergic medication over the 14 days prior to testing.

Screening Protocol

Subjects underwent skin prick (SPT) and bilateral conjunctival challenge tests (CCT) to confirm systemic and ocular allergic sensitivity to grass pollen [13, 14, 15] . SPT was performed on the forearm using grass pollen solution (10 HEP, Soluprick SQ, ALK-ABELLO, Denmark) and positive (histamine solution) and negative (saline) controls. After 20 minutes, the size of the wheal response was measured and a positive result was recorded for diameters ≥3mm. CCT was performed by applying 20µL of grass pollen (Soluprick SQ, ALK-ABELLO, Denmark) solution in two-fold increasing concentrations from 3IR/mL to 100IR/mL to one eye (selected at random to be the experimental eye) and saline solution to the contralateral (control) eye every 10 minutes until a composite score of ≥5 using a standardized scoring method was reached [13, 14, 16]. Eligible subjects who had a positive SPT and CCT proved sensitivity to grass pollen were enrolled into the study with written informed consent.

Eighteen subjects (one third male) took part in the study with a mean age of 29.5±11.0 (age range 20-65). At each visit subjects underwent slit lamp bio-microscopy to ensure signs and symptoms of SAC were not present prior to testing. This was followed by a series of measurements on both eyes including slit lamp examination and grading of nasal and temporal bulbar conjunctival hyperemia using a grading scale (Jenvis Research, Germany), and ocular surface temperature of the cornea and temporal and nasal bulbar conjunctiva (5mm^2 area, 2 seconds post-blink) using an infra-red camera (Thermo Tracer TH7102, NEC, Japan) where a series of digital markers were used to ensure the temperature was measured at the same location for each subject[17]. Ocular allergy symptomology was also measured using the eye symptom section from the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) on a 0 to 6 scale, with the summed score for itching, watering, swelling and soreness resulting in a score between 0 and 24 [18].

Subjects were exposed to between 251 and 500 grains/m^3 of Timothy grass pollen (*phleum pratense*; equivalent to a “very high” pollen count classification; concentration monitored using a Burkard continuous air sampler) in a computer controlled environmental chamber (Design Environmental, 32 Rassau Industrial Estate, Ebbw Vale, Gwent) at a temperature of 20°C and 70% ambient humidity (average local conditions in June in the UK) on separate visits with the concentration established that caused ocular itching graded ≥3 (RQLQ grade) and a ≥0.5 unit change (Jenvis scale) in nasal and temporal bulbar conjunctival hyperemia occurred in both eyes after 5 minutes of exposure.

Once the concentration of pollen for each individual had been established, on separate occasions separated by at least one week, out of the allergy season, the subjects had baseline measurements taken and were then exposed to pollen at this concentration for 5 minutes and 5 minutes post exposure the same measurements were repeated. This was

followed by application bilaterally of either an AT applied to the temporal conjunctiva (Blink Refreshing Eye Drops 0.5ml single use vial, Abbot Medical Optics, USA), CC applied to the closed eye lid for 5 minutes (frozen gel-pack: Boots Pharmaceuticals, Nottingham, UK), AT combined with CC (for 5 minutes, 5 minutes after AT instillation) or no treatment (NT) to the eyes in random order (computer generated) at each visit (examiner masked). The same measures were then repeated every 10 minutes for 1 hour at each visit.

A subgroup of 11 randomly selected subjects (mean age of 29.1±12.9 years, range 20-65) attended for three further identical visits receiving 1 drop of Epinastine Hydrochloride (EH, Relestat 0.5mg/ml, Allergan, USA), 1 drop of EH combined with CC (for 5 minutes, 5 minutes after instillation of EH), or a single drop of saline (termed vehicle, equivalent to the same volume as the drug but without the active ingredients to determine how much of the effect was lubrication compared to pharmaceutical) in random order to assess the efficacy of non-pharmaceutical agents, against a dual action antihistamine/mast cell stabilizer licensed for seasonal allergic conjunctivitis.

Statistics

The randomization code was held by a non-masked researcher and the code broken after data entry by the statistician. Statistical analysis was performed using SPSS for Microsoft Windows. As ocular surface temperature and conjunctival hyperemia were found to be normally distributed (Kolmogorov-Smirnov Test > 0.05), their changes over time were evaluated by repeated measures Analysis of Variance (ANOVA), and where statistical significance was identified, post-hoc analysis was performed using paired t-tests. This approach limited the number of statistical comparisons to minimize the chance of Type I statistical errors. Changes in ocular symptomology were evaluated by the Friedman test and post-hoc analysis where statistical significance was identified was performed using Wilcoxon signed-rank tests. Statistical significance was taken as $p < 0.05$. Sample size, even of the

pharmaceutical comparison subgroup, met the requirements for sufficient replicates for a repeated measures design.[19]

Results

Non-Pharmaceutical Treatment Efficacy versus No Treatment

Ocular Symptomology

Although the symptoms differed in overall magnitude, with itching rated as the severest symptom and swelling the least, the profile with time after treatment and recovery was similar for each of the symptoms so they were averaged for analysis. The global ocular symptom scores were similar at baseline at each visit ($X=6.091$, $p=0.107$) as was the post exposure effect ($X=2.729$, $p=0.435$). They decreased with time after treatment (CC: $X=88.489$, $p<0.001$; AT: $X=88.258$, $p<0.001$; AT+CC: $X=87.639$, $p<0.001$; Figure 1), with all treatments reducing symptoms more than no treatment ($p < 0.001$), but none of the treatments returned global ocular symptom scores to baseline levels within 1 hour after antigen exposure (no treatment 58.6% relative return to baseline, CC 71.6%, AT 84.8%, AT+CC 86.9%; $p<0.001$).

Bulbar Conjunctival Hyperemia

Hyperemia was similar at baseline at each visit ($F=0.955$, $p=0.438$) as was the post exposure effect ($F=0.267$, $p=0.898$). There was no difference in conjunctival hyperemia between the eyes ($F=0.112$, $p=0.742$), however, the nasal conjunctiva was more red than the temporal conjunctiva over the measurement period (1.71±0.62 versus 1.47±0.56 Jenvis units; $F=33.711$, $p<0.001$). There was a significant difference in conjunctival hyperemia following each of the treatments ($F=68.211$, $p<0.001$; Figure 2), with a reduction in redness with time ($F=302.764$, $p<0.001$), although this recovery differed with treatment ($F=9.469$, $p<0.001$) and none of the treatments achieved complete recovery to baseline within 60 minutes (no treatment 16.5% relative return to baseline, CC 57.9%, AT 73.3%, AT+CC 76.5%; $p<0.001$). However, all treatments produced a significant improvement in hyperemia over time compared to no treatment both nasally and temporally ($p<0.05$).

Ocular Surface Temperature

Ocular surface temperature was similar at baseline at each visit ($F=0.685$, $p=0.605$) as was the post exposure effect ($F=0.636$, $p=0.639$). There was no difference in temperature between the eyes ($F=0.017$, $p=0.897$), however there were significant differences in temperature between corneal, nasal and temporal locations ($F=97.899$, $p<0.001$). There was a significant difference in temperature following each of the treatments ($F=19.684$, $p<0.001$; Figure 3), with the temperature converging toward baseline over time ($F=32.955$, $p<0.001$), although this recovery differed with treatment ($F=122.796$, $p<0.001$). Temporal bulbar conjunctival and corneal temperatures returned to baseline levels (was no longer significantly different; $p>0.05$) with the application of cold compress (within 50 minutes), artificial tears (within 40 minutes) and artificial tears combined with cold compress (within 40 minutes), whereas for the nasal bulbar conjunctiva the return to baseline temperature was generally faster (40, 30 and 40 minutes respectively). Ocular surface temperature did not return to baseline levels without treatment at any location (relative return to baseline 57.0%; $p<0.05$).

Relative Efficacy of Non-Pharmaceuticals versus a Dual Action Pharmaceutical

Ocular Symptomology

All ocular symptom changes with time were similar so they have been averaged for presentation and analysis. At all measurement time intervals, symptoms were reduced for both EH and EH in combination with a CC compared to a CC or AT alone or in combination ($p < 0.01$; Figure 4). Only EH alone and in combination with a CC reduced global ocular symptom scores to baseline levels within the post-antigen exposure hour over which subjects were monitored (after 60 minutes: $p=0.414$, $p=0.705$). A CC enhanced the pharmaceutical benefit of EH alone up to 20 minutes ($p<0.05$), where thereafter they were similarly efficacious ($p>0.05$). A CC also further reduced symptoms when combined with AT

compared to AT use alone up to 20 minutes ($p < 0.05$). The drug effect was from the active ingredients rather than the saline vehicle control ($p < 0.001$).

Bulbar Conjunctival Hyperemia

There was a significant difference in conjunctival hyperemia between each of the treatments ($F=11.728$, $p<0.001$; Table 1), with a reduction in redness with time ($F=581.320$, $p<0.001$), although this recovery differed with treatment ($F=9.463$, $p<0.001$). AT combined with CC outperformed AT, CC and EH alone and EH combined with CC nasally. The treatment effect of EH was enhanced by combining it with a CC. The saline volume control (vehicle) showed the action of EH was principally from the active pharmaceutical ingredients. AT instillation had similar effectiveness to a CC application used in isolation (Table 1).

Ocular Surface Temperature

There was a significant difference in ocular surface temperature between each of the treatments ($F=11.680$, $p<0.001$; Table 2), with a change in temperature toward baseline with time ($F=17.952$, $p<0.001$), although this recovery differed for each treatment ($F=144.816$, $p<0.001$). CC in combination with an AT or EH lowered the antigen-raised ocular surface temperature below the pre-exposure baseline. AT instillation alone or in combination to a CC or EH significantly, but only slightly (<0.5ºC), reduced the temperature ($p < 0.05$; Table 2). CC combined with either a AT or EH had a similar cooling effect. The saline vehicle volume control to EH had a similar cooling effect to an AT and no beneficial cooling effect over EH of the same volume but containing active pharmaceutical agents.

Discussion

In the first phase of the study, the efficacy of artificial tears (AT), cold compress (CC) and in combination (AT+CC) was investigated by measuring conjunctival hyperemia, ocular surface temperature and ocular symptoms following exposure to grass pollen in an environmental chamber model to produce the response signs and symptoms of an acute ocular seasonal allergic conjunctivitis. Subjects were exposed over a 5 minute interval in the environmental chamber to a predetermined threshold of reactivity, to ensure that subjects had sufficient signs and symptoms in order to detect any treatment effect. There was no significant difference in hyperemia, ocular surface temperature or ocular symptoms at each visit following the multiple exposures separated by at least a week (and between each eye for hyperemia and ocular surface temperature), demonstrating that the environmental chamber model produces a bilaterally homogenous and reproducible ocular allergic reaction. The data show that all treatments provided benefit in relieving hyperemia, restoring physiological ocular temperature and reducing ocular symptoms during an acute episode of stimulated SAC compared to no treatment.

Although artificial tears (AT) are principally formulated to relieve ocular surface signs and symptoms in dry eye, they have been advocated to have a beneficial effect in SAC [11, 12]. The reduction in signs (conjunctival hyperemia) and symptoms of SAC in this study are likely to have been principally caused by diluting and washing away the allergen from the eye, and the AT acting as a barrier to further exposure by preventing the allergen from binding to the ocular surface [7, 8, 11, 12]. This barrier effect to allergens has also been observed in contact lens wear, where patients wearing soft contact lenses exhibited reduced signs and symptoms of ocular allergy compared to non-contact lens wearing control visits following exposure in an allergen chamber, with a further benefit from using contact lenses with sustained release of a lubricating agent from within the material matrix [20]. ATs are generally stored at room

temperature, which could give them an additional soothing effect, but this study demonstrated that any benefit from the temperature change from AT is minor compared to its other properties such as lubrication, with the temperature reduction and consistency over time higher in the nasal region, compared to the cornea and lower still temporally, following the excretion pathway of the tear film.

In environmental studies of anti-allergy drug efficacy, the use of artificial tears as a control have been shown to have a drug effect of up 50-70% and this is considered to be a placebo effect [13, 21, 22, 23]. However, as artificial tears may produce a real physical effect on the binding of allergens to the ocular surface, this mechanism cannot be considered purely as placebo and therefore should not be considered as an effective control in studies of acute SAC, whereas their use is warranted in investigating the prophylactic effect of an ocular anti-allergy drugs [23].

The use of cold compresses (CC) has previously been recommended as supportive therapy in ocular allergy [11, 24, 25] but no studies relating to the efficacy of cold compress treatment has been reported in the scientific literature. Therefore, this study has demonstrated the beneficial effects of cold compress therapy in ocular disease for the first time. The application of CC may reduce hyperemia and relieve signs and symptoms by causing vasoconstriction of conjunctival blood vessels and subsequently prevent or minimize swelling and leakage of and inflammatory mediators involved in the allergic response [7, 10, 26]. A potential limitation of the CC data was the ability to control the application to the closed eyelids, although the gel mask was held in place over the eyes with an attached elastic headband. This, however, mimicked the clinical reality where the exact area and location of contact of the compress with the eyelid will vary between patients owing to differences in facial structure.

In the second phase of the study, the effectiveness of non-pharmaceutical treatments was compared to a dual action antihistamine / mast cell stabilizer pharmaceutical (EH), with or without the addition of a CC, in a randomly selected subgroup of subjects using the same acute induced-SAC methodology. Comparison over the 60 minute observation period showed that the combination of artificial tears and cold compress was superior to all other treatments in reducing hyperemia including over the pharmaceutical agent, although the antigen induced ocular redness could be improved to the equivalence effectiveness by combining EH with a CC. An AT or a CC used alone was more effective that the pharmaceutical used in isolation. The pharmaceutical agent effect, however, was confirmed as being derived from the active ingredients rather than any ocular lubricating effect of its fluid vehicle and this was also the case for the pharmaceutical effect on ocular comfort.

A CC alone or in combination with an AT or EH pharmaceutical lowered the ocular surface temperature below baseline from the increased level caused by exposure to the antigen, whereas an AT alone had relatively little effect over ocular temperature, particularly over the temporal conjunctiva. As this treatment result differed from that of conjunctival hyperemia and ocular symptoms, it could suggest that the inflammatory events causing increased ocular surface temperature following antigen exposure could differ from those driving other signs and symptoms or the results could be confounded by tear film thickness variations across the ocular surface and with time as this would have affected the radiated heat imaged by the thermal camera.

Ocular symptomology improved faster with EH compared to all other treatment modalities, reducing symptoms to baseline levels after 60 minutes, and the recovery profile was enhanced initially by the application of a CCs. Although none of the non-pharmaceutical treatments reduced symptoms to baseline levels, the mean scores were low, falling within

the “hardly troubled at all” category. These data suggest that AT and CC, either alone or in combination, are effective methods of relieving the signs and symptoms of SAC during the active phase of the condition.

EH displays anti-histamine, anti-inflammatory and mast cell stabilizing properties in animal and in-vitro studies [27, 28]. Conjunctival-allergen-challenge-model clinical trials of EH have shown that it is significantly more effective in preventing the signs and symptoms of allergic conjunctivitis compared to its vehicle as confirmed in this study [29, 30]. The efficacy of EH has also been demonstrated to be effective in an environmental clinical trial [31], but these study designs are subject to variations in exposure and therefore limit their ability to detect the efficacy of drugs. Thus, there has been a lack of studies investigating the efficacy of EH in acute SAC. In the present study, the combination of EH combined with CC was superior to EH alone in reducing ocular surface temperature ($p<0.001$), superior to EH in reducing hyperemia both nasally ($p<0.001$) and temporally ($p<0.001$), and enhanced the symptom recovery profile within the first 20 minutes. This suggests that clinically, EH should be prescribed together with advice on applying cold compresses in acute episodes. EH mast cell stabilizing properties are only likely to enhance the pharmaceutical effect after a few days use which should be considered if the patient is likely to be exposed to multiple episodes of acute pollen exposure over a short time period.

The results of the present study are applicable only on the ability of the treatments to relieve the signs and symptoms of simulated SAC during the acute phase of the ocular allergic response, thus it has no bearing on their ability to prevent signs and symptoms from developing through prophylactic treatment. It is not expected that the application of cold compress or artificial tears will have any effect before the ocular allergic response develops, unless they are applied frequently. These data suggest that although EH resolves symptoms

of SAC earlier, it appears to be less efficacious in resolving ocular signs of inflammation such as conjunctival hyperemia and ocular surface temperature increases compared to an artificial tear or cold compress alone, or better in combination, during an acute episode of SAC. Therefore for occasional sufferers such self-management, with reduced risks of drug interactions and reduced patient expense, should be considered. For more frequent SAC sufferers, the benefits of a cold compress in addition to prophylactic pharmaceuticals should be considered as part of patient management when symptoms still occur. Further study is required to measure the immunologic response to ocular signs and symptoms induced by the environmental chamber and treatment strategies.

Word Count: 3,257

Acknowledgements, Conflicts of Interest

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The Authors declare no competing or conflicting interest and no competing or conflicting or competing financial relationships relating to the subject matter in the study.

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Table

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Table 1: Statistical comparison of nasal (n) and temporal (t) hyperemia between the non-pharmaceutical and pharmaceutical treatments.

		Significance (p)					
Treatment	Mean*	EH	EH+CC	CC	AT	AT+CC	Vehicle
EH	$1.46\pm0.43_n$	X	<0.001	0.378	0.045	0.042	<0.001
	$1.35\pm0.40_t$	X	<0.001	<0.001	<0.001	<0.001	<0.001
EH+CC	$1.33\pm0.41_n$		X	0.002	<0.001	0.559	<0.001
	$1.19\pm0.37_t$		X	0.929	0.220	0.014	<0.001
CC	$1.51\pm0.30_n$			X	0.349	<0.001	<0.001
	$1.19\pm0.29_t$			X	0.162	<0.001	<0.001
AT	$1.55\pm0.38_n$				X	<0.001	<0.001
	$1.24\pm0.35_t$				X	<0.001	<0.001
AT+CC	$1.36\pm0.31_n$					X	<0.001
	$1.08\pm0.37_t$					X	<0.001
Vehicle	$2.00\pm0.39_n$						X
	$1.65\pm0.38_t$						X

Treatments: epinastine hydrochloride (EH), epinastine hydrochloride combined with cold compress (EH+CC), cold compress (CC), artificial tear (AT), artificial tears combined with cold compress (AT+CC) and vehicle. Nasal and temporal regions significantly interacted with treatment and so have been presented separately.* = mean hyperaemia grade (Jenvis units) of right and left eyes averaged (n=11, 22 eyes) over 60 minutes.

Table 2: Statistical comparison of ocular surface temperature between the non-pharmaceutical and pharmaceutical treatments.

		Significance (p)					
Treatment	Mean*	EH	EH+CC	CC	AT	AT+CC	Vehicle
EH	35.31±0.48	X	<0.001	<0.001	<0.001	<0.001	0.057
EH+CC	34.72±0.63		X	0.228	<0.001	0.089	<0.001
CC	34.81±0.55			X	<0.001	<0.001	<0.001
AT	35.52±0.67				X	<0.001	0.319
AT+CC	34.57±0.34					X	<0.001
Vehicle	35.44±0.41						X

Treatments: epinastine hydrochloride (EH), epinastine hydrochloride combined with cold compress (EH+CC), cold compress (CC), artificial tear (AT), artificial tears combined with cold compress (AT+CC) and vehicle. Ocular temperature was similar between eyes and did not interact with ocular surface region, so average data is presented. * = mean ocular surface temperature of right and left eyes and region combined (n=11, 22 eyes) over 60 minutes.

Figure 1

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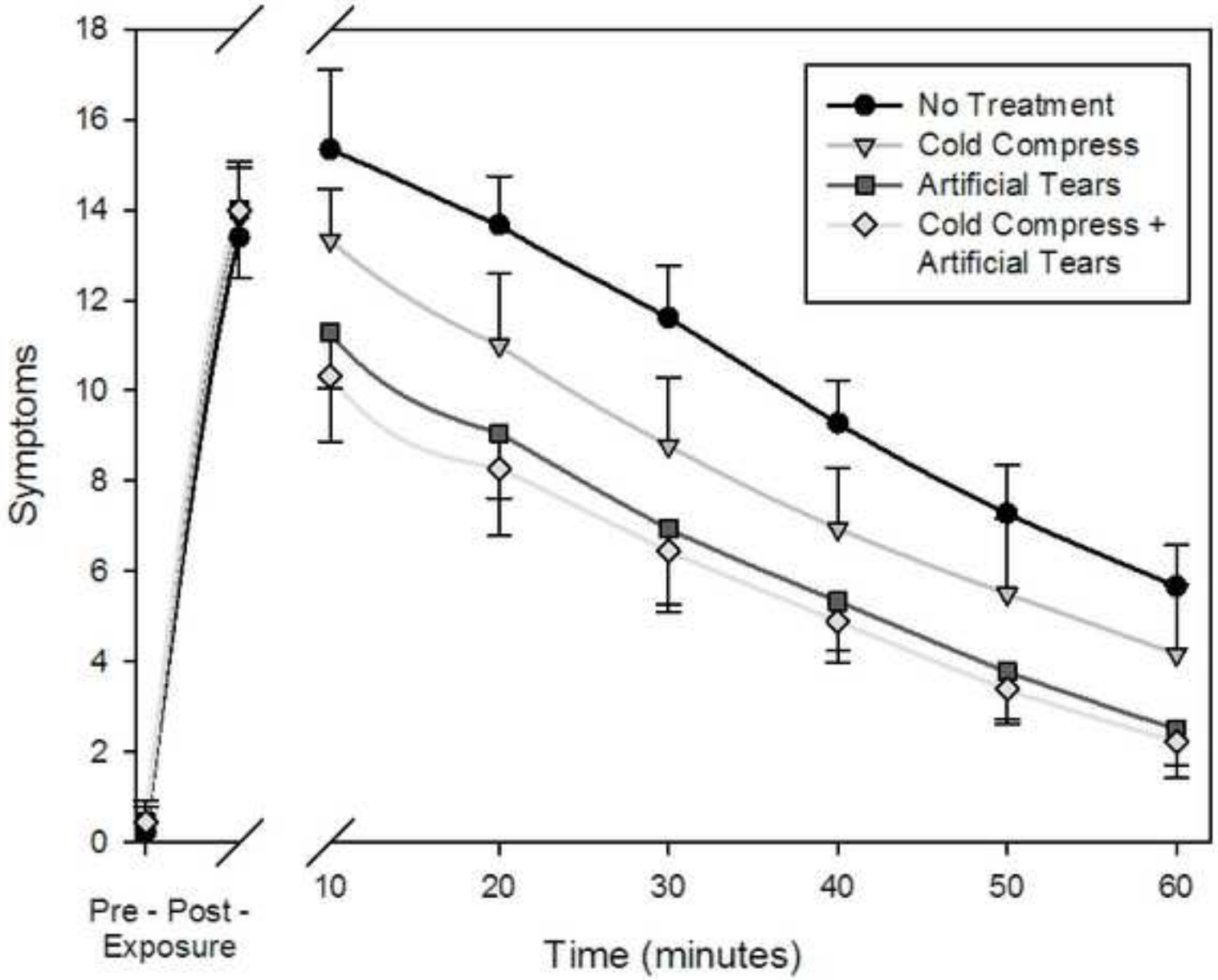

Figure 2

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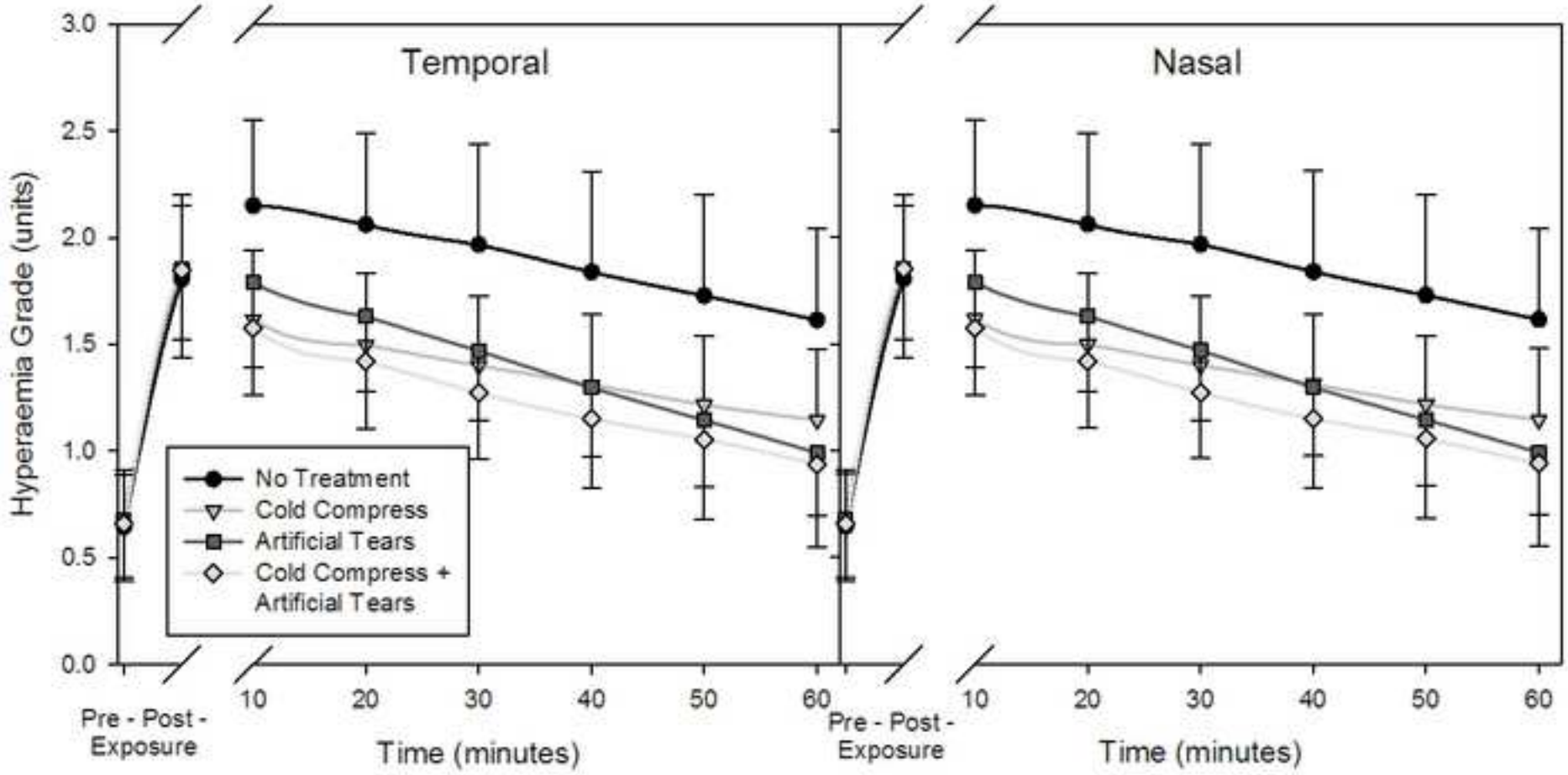

Figure 3

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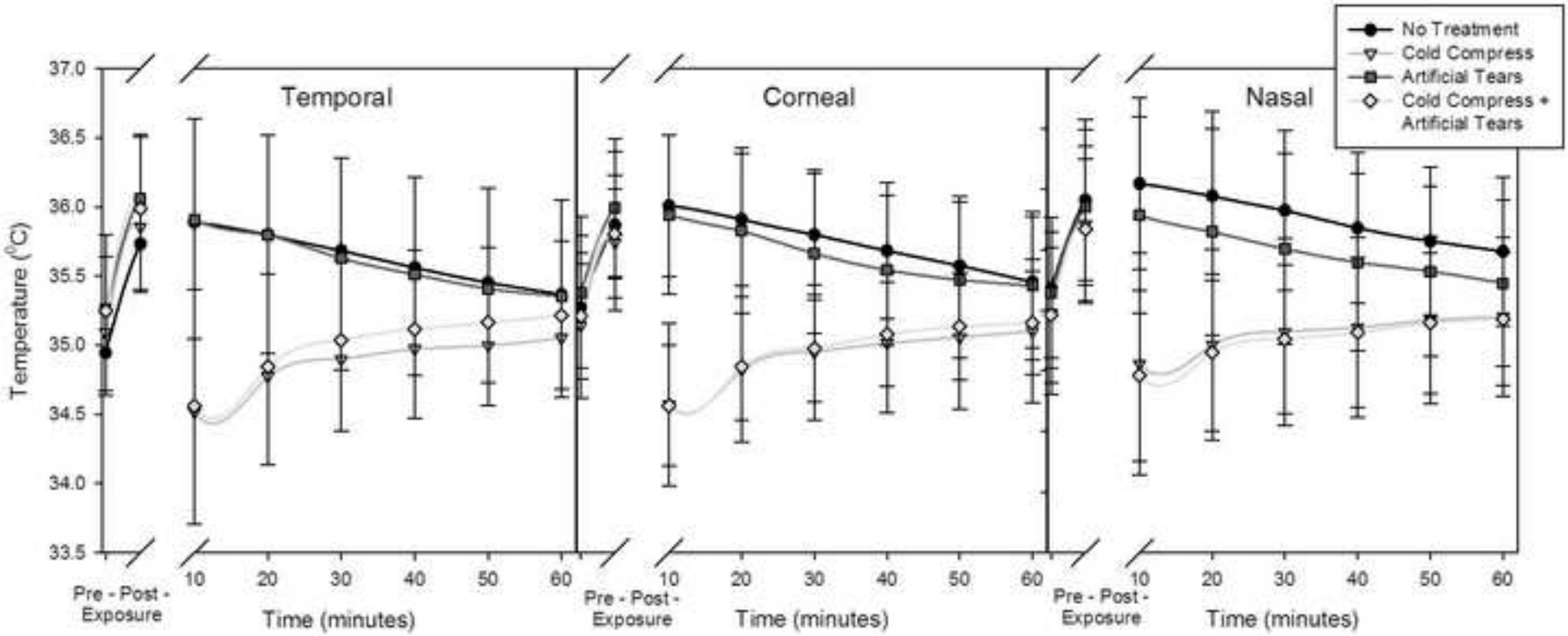

Figure 4

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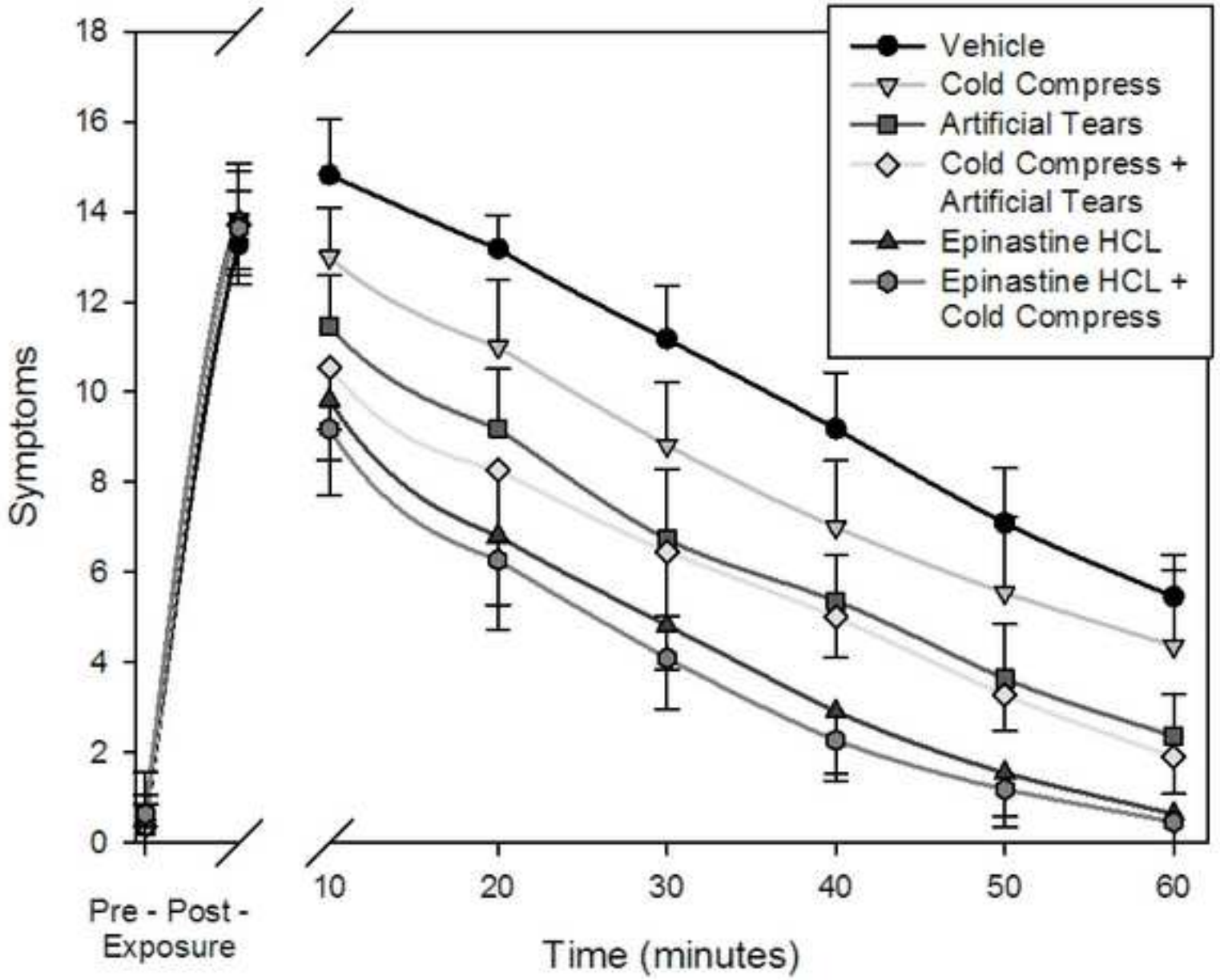

Figures Legends

Figure 1: Ocular symptoms pre and post pollen exposure and every 10 minutes thereafter up to 60 minutes for no treatment, cold compress, artificial tears and artificial tears combined with cold compress. Although the symptoms differed in overall magnitude the profile with time after treatment and recovery was similar for each of the symptoms so they were averaged for analysis. n = 18. Error bars represent ±1 standard deviation.

Figure 2: Hyperemia grade pre and post pollen exposure and every 10 minutes thereafter up to 60 minutes for no treatment, cold compress, artificial tears and artificial tears combined with cold compress on the temporal and nasal bulbar conjunctiva. Data from right and left eyes were similar so were averaged (n=18 subjects, 36 eyes). Error bars represent ±1 standard deviation.

Figure 3: Ocular surface temperature pre and post pollen exposure and every 10 minutes thereafter up to 60 minutes for no treatment, cold compress, artificial tears and artificial tears combined with cold compress on the corneal and temporal and nasal bulbar conjunctival surfaces. Data from right and left eyes were similar so were averaged (n=18 subjects, 36 eyes). Error bars represent ±1 standard deviation.

Figure 4: Ocular symptoms pre and post pollen exposure and every 10 minutes thereafter up to 60 minutes for the saline vehicle volume control, cold compress, artificial tears and artificial tears combined with cold compress, epinastine hydrochloride (HCL) and epinastine HCL combined with a cold compress. Although the symptoms differed in overall magnitude the profile with time after treatment and recovery was similar for each of the symptoms so they were averaged for analysis. n = 11. Error bars represent ±1 standard deviation.

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Ophthalmology Study Design Worksheet #1
Randomized Controlled Trial (RCT)

Ophthalmology requires compliance with the CONSORT statement (Begg C, Cho M, Eastwoods S, et al. Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA* 1996;276:637-9. See also *JAMA*, 1997;227:76-7).

Randomized (controlled) trial. A human trial that involves at least one experimental treatment group and one control treatment group, concurrent enrollment, and follow-up of the test and control groups, and in which the assignment to experimental and control groups is by a randomization process. Neither the subjects nor the persons responsible for treatment can influence the assignments, and the assignments remain unknown to the subjects and staff until eligibility has been determined.

Manuscript #: _____
(For Office Use)

First Author's Name: _____Paramdeep Bilkhu_____

Manuscript Title: _____ Effectiveness of Non-Pharmacological Treatments for Acute Seasonal Allergic Conjunctivitis
_____

Heading	Descriptor	Yes/No	Page/¶	N/A	Comments
Title:	1. Content of paper clarified within 135 character limit.	__yes___	___1____	_____	_____
Abstract:	2. Structured per Instructions For Authors. Design identified as randomized controlled trial.	_____yes___	___2____	_____	_____
Introduction:	3. States hypothesis, clinical objectives, and planned subgroup or covariate analyses.	___yes_____	___3____	_____	_____
	4. Brief review of pertinent literature.	___yes_____	___3____	_____	_____
Methods:	5. Describe therapeutic intervention.	__yes_____	___5____	_____	_____
	6. Describe the study population and clarify whether one or both eyes of patients were included.	__yes_____	__4-5__	_____	_____

7. Define inclusion/exclusion criteria.	__yes_____	___4____	_____	_____
8. Describe primary and secondary outcome measure(s) and the minimum important (statistically significant) difference(s).	__yes_____	___5-6__	_____	_____
9. Indicate how the target sample size was calculated.	__yes_____	___6____	_____	_____
10. IRB approval and informed consent requirements completed.	__yes_____	___4____	_____	_____
11. Clarify the method of collecting patients (e.g., consecutive cases from clinic population, etc.).	___yes_____	___4____	_____	_____
12. Detail the main comparative analyses and whether data were analyzed according to the group to which they were originally assigned (e.g., by intention to treat or by treatment as administered).	___yes_____	___6____	_____	_____
13. Defined stopping rules (if warranted).	_____	_____	___n/a___	_____

(Randomization/Masking Issues)

14. Describe assignment by unit of randomization (e.g., eye, individual, cluster, geographic area).	__yes_____	__6_____	_____	_____
15. Describe the method used to generate the assignment schedule.	__yes_____	__6_____	_____	_____
16. Describe the method of assignment concealment and timing of assignment.	__yes_____	__6____	_____	_____

	17. Describe mechanism (e.g., drops, parenteral, tablets), and similarity/dissimilarity of experimental and control treatment characteristics (e.g., appearance, discomfort).	___yes_____	__6_____	_____	_____
	18. Describe the allocation schedule and methods for security (location of code during trial and when broken).	___yes_____	__6_____	_____	_____
Results:	19. Describe evidence for successful masking (blinding) among participants, persons doing intervention, outcome assessors, and/or data analysts.	___yes_____	__6_____	_____	_____
	20. Provide a chart summarizing participant flow, numbers and timing of randomization assignments, interventions, and measurements for each randomized group, and completeness of follow-up. Detail reasons for loss to follow-up.	_____	_____	__na____	_no loss to follow up and all patients had all treatments
	21. Summarize eligibility of available data or character of ineligibles (e.g., refusal, not meeting criteria, etc.).	_____	_____	__na____	All data used
	(Statistical Issues/Data Management)				
	22. State estimated effect of intervention on primary and secondary outcome measures, including a point estimate (e.g., mean, odds ratio, relative risk, etc.) and measure of precision	_____	_____	__na___	Repeated measures design

	(e.g., confidence interval).				
	23. State results in absolute numbers when feasible [e.g., 33 of 50 eyes (66%), rather than 66% alone].	_____	_____	__na____	Repeated measures design
	24. If both eyes of each patient were studied, indicate whether they were analyzed separately or averaged, indicate what methods were used for correlated data.	_____	_____	__na____	_only 1 eye data analysed
	25. Present summary data and appropriate descriptive and inferential statistics in sufficient detail to permit alternative analyses and calculation replication.	__yes_____	__7-9___	_____	_____
	26. Describe prognostic variables by treatment group and any attempt to adjust for them.	_____	_____	___na___	Repeated measures design
	27. Describe protocol deviations from the study together with the reasons/explanations.	_____	_____	___na___	_none____
	28. Describe any adjustments in the alpha level for multiple comparisons.	_____	_____	___na___	_none made__
Discussion:	29. State specific interpretation of study findings, including sources of bias and imprecision (internal validity) and discussion of external validity, including appropriate quantitative measures when possible.	__yes_____	_10-13_	_____	_____
	30. Assess the possibility that chance	__yes_____	__6_____	_____	_____

accounts for any statistically significant differences between groups.				
31. If "no difference" is reported, provide the power to detect a difference of meaningful clinical magnitude or provide a confidence interval for the treatment effect noted.	__yes_____	___6____	_____	_sample size required justified__
32. State general interpretation of the data in light of the totality of the available evidence.	_____	_____	_____	_____
33. Discuss the biological plausibility of results.	_____	_____	_____	_____
34. Discuss the clinical applications/relevance of the findings.	__yes_____	_13_____	_____	_____
35. Contrast or compare the results to previous studies.	__yes_____	_12-13	_____	_____
36. Discuss the need for specific additional studies if appropriate.	___yes_____	__13____	_____	_____

Form completed by: __J S Wolffsohn_____

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