Abstract

Objective: To evaluate the efficacy and tolerability of a fixed dose combination of oxymetazoline 0.5 mg in buffered aqueous solution with menthol, eucalyptol and xylitol (OM) versus fixed dose combination containing oxymetazoline 0.05% plus dexamethasone 5% (OD), fixed dose combination containing xylometazoline 0.1% plus sorbitol 2% (XS), and xylometazoline 0.1% drops (XL) in patients with nasal congestion due to acute exacerbation of allergic rhinitis.

Methods: In this prospective, four-arm, open-label, randomized, comparative study conducted at single site with 160 patients (40 in each treatment arm), patients of either sex between 18 and 60 years of age with acute allergic rhinitis presenting with signs and symptoms of nasal congestion who gave informed written consent were enrolled. Patients with known hypersensitivity to nasal decongestants, having hypertension, history of myocardial infarction, angina or stroke, hyperthyroidism or hypothyroidism, and those taking any nasal or systemic decongestant up to 2 days prior and patients on topical nasal steroids 2 weeks prior were also excluded.

The study period for each patient was of 5 days and assessments were made for congestion, nasal irritation, nasal discharge and nasal blockade evaluated on a 4-point rating scale. Time to complete clinical recovery and global assessment was done for response and tolerability at end of therapy on a scale of Excellent, Good, Satisfactory and Poor.

Results: Mean symptom scores for nasal congestion with OM (oxymetazoline + Menthol) were significantly (p < 0.006) lower than all the other groups from as early as day 3. Also, the mean symptom scores for nasal irritation, nasal discharge, and nasal blockade are significantly lower with OM as compared to all other groups on day 5 (p < 0.05). For global efficacy evaluation, therapy with OM was reported as ‘Excellent’ in 78.57% patients which was far better as compared to all the other treatment arms (p < 0.0001). For global tolerability evaluation, OM was reported as ‘Excellent’ (61.90%) which was far better as compared to all other treatment groups (p < 0.0001).

Conclusions: Nasal drops containing oxymetazoline, menthol, eucalyptol and xylitol are having better efficacy and tolerability profile compared to xylometazoline containing nasal drops for the treatment of symptoms of allergic rhinitis.

Introduction

Allergic rhinitis is characterized by sneezing, rhinorrhea, blockade of the nasal passage, nasal and pharyngeal itching, lacrimation, all occurring in a temporal relationship to allergen exposure. Although commonly seasonal due to elicitation by airborne pollens, it can be perennial in an environment of chronic exposure. Significant congestion may interfere with sleep, can lead
to snoring, and can be associated with sleep apnoea. A blocked nose can also cause facial pain and headache, and a degree of discomfort.\(^1\)

Although allergen avoidance is the most cost effective means of managing allergic rhinitis, treatment with pharmacological agents represents the standard approach to allergic rhinitis.\(^2\)

Oral antihistamines are effective for itching, lacrymation and erythema, but they are not efficacious for nasal congestion. Some antihistamines are sedative and they induce psychomotor impairment. Their anti-cholinergic effect also includes visual disturbance, urinary retention and constipation. Because antihistamines have little effect on congestion, \(\alpha\)-adrenergic agents such as phenylephrine or oxymetazoline are generally used topically to alleviate nasal congestion.

Oxymetazoline is a direct acting sympathomimetic with marked \(\alpha\)-adrenergic activity. It is a vasoconstrictor which reduces swelling and congestion when applied to nasal mucous membrane. It acts within a few minutes and the effects last for 12 hours. It is used as the hydrochloride for the symptomatic relief of nasal congestion. In adults and children over 6 years, a 0.05% solution of oxymetazoline hydrochloride is applied topically as nasal drops or nasal spray, usually two to three times daily\(^3\) to each nostril as required.\(^4\)

**Material and Methods**

**Study Design**

The study was a prospective, four-arm, open-label, randomized, comparative, efficacy and tolerability study conducted at single site with 40 patients in each treatment arm (total 160 patients). The study was approved by independent ethics committee.

**Study subjects**

Patients of either sex between 18 and 60 years of age with acute allergic rhinitis presenting with signs and symptoms of nasal congestion who gave informed written consent and who were willing to follow-up as per the study schedule were enrolled.

Patients with known hypersensitivity to nasal decongestants, those having hypertension, previous history of myocardial infarction, angina or stroke, hyperthyroidism or hypothyroidism, severe concurrent renal or hepatic illness were excluded from the study. Patients taking any nasal or systemic decongestant up to 2 days prior and patients on topical nasal steroids 2 weeks prior were also excluded.

**Randomization and Interventions**

All enrolled patients were randomized to receive either of the following four treatments as per the pre-determined randomization code. Randomization was done on a PC based programme Rando\(^\circ\) (v.1, 1998). The investigator was provided with randomization codes for each patient in a separate sealed envelope. After enrolment each patient was assigned a serial number and only then the randomization code for that patient was opened to reveal the treatment allocated to the patient.

- **OM**: Drops containing oxymetazoline HCl 0.05% in buffered aqueous solution, menthol, eucalyptol and xylitol as inactive (New Nasivion Care, mfg. Merck Ltd.)
- **OD**: Drops containing oxymetazoline HCl 0.05% and dexpanthanol (NASIVION CARE, mfg. Merck Ltd.)
- **XL**: Xylometazoline HCl 0.1% drops
- **XS**: Drops containing xylometazoline HCl 0.1% w/v and Sorbitol Solution 2.0%

All treatments were administered as intranasal drops three times a day for a period.
of 5 days. Patients were not being allowed to receive any other systemic or nasal decongestants, glucocorticosteroids and antihistaminic agents during the study period. However, patients were allowed any concomitant treatment provided they were prescribed by the trial investigator.

**Assessment Parameters**

The study period for each patient was of 5 days and assessments were made at baseline, day 3 and on day 5.

Primary efficacy variable was the improvement in nasal congestion evaluated on a 4-point rating scale of ‘0, no congestion; 1, mild congestion; 2, moderate congestion; and 3, severe congestion’.

Secondary efficacy variable included improvement in other symptoms of allergic rhinitis like nasal irritation, nasal discharge and nasal blockade evaluated on a 4-point rating scale similar to that for the nasal congestion.

Rebound congestion occurring in the patients after first dose was also recorded. Time to complete clinical recovery was evaluated as the time needed for complete resolution of all local symptoms of allergic rhinitis.

Also, the global assessment of response to therapy (PGART) was assessed by physician at end of therapy on a scale of Excellent, Good, Satisfactory and Poor.

Safety variables were the adverse events, either spontaneously reported by the patient, or noticed by the physician during the trial, and global assessment of tolerability to therapy (PGATT) assessed by patient at end of therapy on a scale of Excellent, Good, Satisfactory and Poor.

**Compliance to therapy**

Patient compliance was assessed at each visit by the investigator by open questioning about the study medication consumption.

**Statistical Analysis**

Measurement (parametric) data and ranking (non-parametric) data was expressed as means and one standard deviation. Categorical data was expressed as numbers and proportions. Four groups were compared at baseline for demographics and baseline values of efficacy parameters using One Way ANOVA (parametric) and Kruuskall Wallis test (non-parametric). For all statistical tests, the significance level is taken as p < 0.05.

**Results**

**Patient population**

A total of 160 patients were enrolled between March 2009 and May 2009 (OM, 46; OD, 44; XL, 40; and XS, 30).

**Baseline characteristics**

The baseline and demographic data of the patients enrolled in the study are given in Table 1. The age, body weight and other demographic parameters were similar in all the four treatment groups. Also the patients were comparable with respect to the mean baseline symptom scores for all four nasal symptoms.

**Nasal symptoms**

Mean nasal symptom scores for all four groups of treatment on day 3 and day 5 of giving treatment are shown in Table 2. Mean symptom scores for nasal congestion with OM (oxymetazoline + menthol) are 1.16 and 0.41 on day 3 and day 5 respectively which are significantly (p < 0.006) lower than all the other groups from as early as day 3. Also, the mean symptom scores for nasal irritation, nasal discharge, and nasal blockade are significantly lower with OM as compared to all other groups on day 5 (p < 0.05).

Percentage change from baseline to day 3
and day 5 in total symptom score for all four treatment groups is shown in Fig. 1. Percentage change from baseline to day 3 and day 5 in total symptom score is significantly (p < 0.01 and p < 0.001 respectively) higher with OM s compared to all other groups.

Mean total symptom score for all four groups are shown in Fig 1. Mean total symptom score on day 5 is 1.99 with OM which is significantly (p < 0.0001) lower than OD (4.82), XL (5.57) and XS (5.17). Mean total symptom score even on day 3 are significantly lower in OM as compared to all other groups (p < 0.02).

Fig. 2 shows the per cent reduction in the total symptom score from baseline on day 3 and day 5. There is significantly greater reduction in the total symptom score with OM (oxymetazoline plus menthol) as compared to other treatment groups (p < 0.05).

**Global evaluation**
For efficacy evaluation, therapy with OM was reported as 'Excellent' in 78.57% patients which was far better as compared to all the other treatment arms (p < 0.0001). Therapy was reported as excellent in 17.07% patients in OD, 13.16% patients of XL group, and 3.45% of patients in XS group. For tolerability evaluation, OM was reported as 'Excellent' (61.90%) which was far better as compared to all other treatment groups (p < 0.0001). Therapy was reported as excellent in 12.20% patients of OD, 7.89% patients of XL group and 3.45% patients of XS group.

**Rebound congestion**
Rebound congestion was observed with
xylometazoline containing treatments (XL and XS) in 20% patients on day 3 and 17.5% on day 5 with XL, 26.67% on day 3 and 23.33% on day 5 with XS. The rebound congestion was 18.18% on day 3 as well as on day 5 with OD, whereas no rebound congestion was observed with OM. The difference being statistically significant (p < 0.006 for day 3; p < 0.013 for day 5).

Non-compliance

Compliance was good with oxymetazoline containing treatments (OM and OD), whereas it was poor with xylometazoline containing treatments (XL and XS). Non-compliance was seen in 2 patients of xylometazoline 0.1% and 2 patients in xylometazoline 0.1% + sorbitol 2%.

Discussion

Oral use of nasal decongestants are modestly effective in the allergic rhinitis for the short term relief of symptoms, and these drugs provide benefit in some individuals after regular use over three to five days. Adverse events in adults are rare and mild.5

In a prospective placebo-controlled double-blind study with 247 pts investigated whether oxymetazoline has a clinically relevant impact on the duration of acute rhinitis. The effect of oxymetazoline set in after 25 seconds, as compared with 90 seconds for physiological saline (p < 0.001). The duration of the rhinitis decreased significantly under oxymetazoline in comparison with the control group (4 vs. 6 days). All the parameters investigated revealed oxymetazoline to be significantly superior to physiological saline solution. Treatment with the former significantly shortened the duration of the rhinitis by one-third (2 days).6

In another investigator-blind, randomized, controlled, phase IV clinical trial conducted in 100 patients with acute allergic rhinitis or patients post-nasal surgery Oxymetazoline and dexpanthenol combination has a better efficacy, shorter recovery time, causes lesser rebound congestion and has better tolerability than xylometazoline. Rebound congestion was significantly less as compared to Xylometazoline group (6.25% vs 82.98%).7

The present study is a a randomized comparative study of “new nasivion care drops” (oxymetazoline 0.5 mg in buffered aqueous solution with menthol, eucalyptol and xylitol) versus “nasivion care” (oxymetazoline 0.05% plus dexpanthenol 5%) versus xylometazoline 0.1% drops versus xylometazoline 0.1% and sorbitol 2.0% combination in patients with nasal congestion due to acute exacerbation of allergic rhinitis. New nasivion care group showed significantly (p < 0.006) lower mean symptom scores for nasal congestion, nasal irritation, sneezing, nasal discharge and nasal blockade on day 3.
as well as day 5 as compared to nasivion care group, xylometazoline 0.01% and xylometazoline 0.01% + sorbitol 2% which is the primary efficacy variable. Maximum improvement in symptoms as measured by percentage change in mean symptom score from baseline to day 3 and day 5 was also higher with new nasivion care as compared to all other groups which is significant (p < 0.01 on day 3 and p < 0.0001 on day 5). Also significant improvement was seen in New nasivion care group in all the symptoms of allergic rhinitis as measured by total symptom score which was significantly lower on day 3 (p < 0.02) and more significant difference on day 5 (p < 0.0001).

The major problem with nasal-delivery decongestants, particularly long-acting forms is the rebound effect. The longer acting agents pose a particular risk for this effect. Rhinitis medicamentosa is a condition of nasal hyperreactivity, mucosal swelling and tolerance induced, or aggravated, by the overuse of topical vasoconstrictors with or without a preservative. Nasal imidazoline include oxymetazoline, naphazoline, xylometazoline, and clonidine mimic the actions of the sympathetic nervous system through the presynaptic release of norepinephrine in sympathetic nerves. Norepinephrine then binds postsynaptically to receptors and results in vasoconstriction. They are also mild ß-receptor agonists and cause rebound vasodilation after the effect has waned. Several studies demonstrate that rebound congestion does not develop with up to 8 weeks of topical decongestant use while others have suggested that the onset of RM occurs after the use of topical sympathomimetics for 3 to 10 days.11

There was no incidence of rebound congestion in patients with OM (new nasivion care) group which probably could be due to the longer effects of menthol, eucalyptol and xylitol. Rebound congestion was seen with xylometazoline containing treatments and OD (nasivion care) on day 3 as well as on day 5. Compliance was poor with xylometazoline containing treatments but the difference was not significant.

In investigator-blind, randomized, controlled, phase IV clinical trial conducted in 100 patients with acute allergic rhinitis or patients post-nasal surgery. Oxymetazoline and dexpanthenol combination has a better efficacy, shorter recovery time, causes lesser rebound congestion and has better tolerability than xylometazoline. Rebound congestion was significantly less as compared to Xylometazoline group (6.25% vs. 82.98%). Efficacy evaluation at end of therapy in ‘New Nasivion Care’ Group was ‘Excellent’ in 78.57% patients which was far better as compared to all the other treatment arms (p < 0.0001). Tolerability evaluation at end of therapy in New Nasivion Care Group was ‘Excellent’ in 61.90% patients which was far better as compared to all other treatment groups (p < 0.0001).

Thus, the nasal drops containing oxymetazoline, menthol, eucalyptol and xylitol are having better efficacy and tolerability profile compared to xylometazoline containing nasal drops for the treatment of symptoms of allergic rhinitis.

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Bibliography


**SHALL WE PUT THE WORLD ON FOLATE?**

The purpose of folate fortification is to increase peri-conceptional folate concentrations in women of child-bearing age to prevent neural tube defects and potentially other malformations (cardiac defect, or cleft lip and palate) in their babies. Because the prevention effort targets only women of reproductive age before conception, is it justifiable to expose the entire population to mandatorily fortified foods with an uncertain risk associated with this enrichment?

Folate deficiency is associated with high plasma concentrations of homocysteine, a potential risk factor for the development of atherosclerosis and consequently cardiovascular disease. Some evidence suggests that folate depletion fosters the development of cancer, particularly colorectal cancer. Folate might also negate the increase of breast cancer risk associated with alcohol intake.

Despite the proposed beneficial effects of folate, there are rising health concerns about an excessive intake of this vitamin. High intake of folic acid might mask vitamin B₁₂ deficiency, especially in elderly individuals.

Two mechanisms could underlie an apparent cancer promoting effect of high-dose folic acid.

Conversely, death rates from cardiovascular disease have fallen in the USA and Canada during the past decade, and are concurrent with several changes including a decline in smoking, reduction of intake of trans fatty acids, more aggressive treatment of hypertension, and folate fortification.