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Short Communication

Oxymetazoline plus Dexpanthenol in Nasal Congestion

Jagade Mohan V · Langade Deepak G · Pophale Rupesh R · Prabhu Arun

Abstract *Aims:* To compare the efficacy and tolerability of Oxymetazoline 0.05 % plus Dexpanthanol 5% versus Xylometazoline 0.1 % nasal drops in patients with nasal congestion due to allergic rhinitis and following nasal surgery.

Methods: An investigator-blind, randomized, controlled, phase IV clinical trial conducted in 100 patients with acute allergic rhinitis or patients post-nasal surgery. Patients received either Oxymetazoline 0.05% with Dexpanthanol 5% (OD) or Xylometazoline 0.1% (XO) nasal drops.

Results: Relief from nasal congestion was significantly better in the OD group then in the XO group (mean nasal scores 1.24 vs 1.86). Significantly more improvement in sneezing and decrease in nasal discharge was seen in the OD group than the XO group. Nasal irritation in the OD group was significantly less as compared to XO group (0.38 v/s 1.12 on second day and 0.10 vs 0.36 on the fourth day). The recovery time for OD group was 1.08 hours, which was significantly (46 min) lesser than that of the XO group. Rebound congestion was significantly less in OD as compared to XO group (6.25% vs 82.98%). 93.75% of the physicians in the OD group and 51.28% in XO group reported response to therapy as good to excellent. 95.83% patients in the OD group and only 52.91% patients in the XO group rated tolerability to therapy as good to excellent.

Conclusion: Oxymetazoline and dexpanthenol combination has a better efficacy, shorter recovery time, causes lesser rebound congestion and has better tolerability than xylometazoline.

Key words: Oxymetazoline · dexpanthenol · xylometazoline · rebound congestion

Jagade Mohan V[1] · Langade Deepak G[2] · Pophale Rupesh R[3] · Prabhu Arun[4]

1. Dept of ENT
2. Dept of Pharmacology
3. Dept of Pharmacology
4. Dept of ENT
Grant Medical College & Sir J.J. Group of Hospitals, Mumbai

M.V. Jagade (✉)
Prof. & Head Dept of ENT
Grant Medical College & Sir J.J. Group of Hospitals
Byculla, Mumbai - 400 008
e-mail: mohanjagade@hotmail.com

Introduction

Among the leading causes of nasal congestion, allergic rhinitis, infective rhinitis and post-operative nasal congestion head the list. If untreated, it leads to deterioration of quality of life and can interfere with hearing and speech development. It causes loss of work days and productivity. Chronic nasal congestion can lead to sinusitis with its accompanying morbidity and complications. Nasal congestion is also a common problem in the post –operative period after nasal surgery.

Nasal decongestants induce vasoconstriction via alpha receptor activation and reduce swelling of the mucosa, thus assisting in nasal as well as sinus drainage. Oxymetazoline and xylometazoline are commonly used long acting nasal decongestants. Rebound congestion and local irritation on instillation are the two factors that can limit their use. Dexpanthenol, a precursor to pantothenic acid, has lately been tried in combination with nasal decongestants in order to overcome some of the shortcomings of the latter. The combination of nasal decongestants with dexpanthenol has been proven to have a synergistic effect, which is clinically superior to that of the decongestant alone and also shortens the treatment time in allergic rhinitis.[1] It is also an epithelial protective agent and is also known to accelerate wound healing[1-3], an effect which could be useful in the postoperative period. The present study was undertaken to verify the validity of the above claims.

Objective

To compare the efficacy and tolerability of Oxymetazoline 0.05 % plus Dexpanthanol 5% versus Xylometazoline 0.1 % nasal drops in patients with nasal congestion due to allergic rhinitis and following nasal surgery.

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Patients And Methods

The study was an investigator-blind, randomized, controlled, phase IV clinical trial conducted in 100 patients attending the OPD at the ENT department at JJ Hospital, Mumbai. The study was initiated after an approval from the IRB of SNC and Sir JJ Group of Hospitals. Patients of either sex between 18 to 60 years of age with acute allergic rhinitis presenting with signs & symptoms of nasal congestion or patients post-nasal surgery like septoplasty or polypectomy, who gave their informed consent and can could come for follow-up as per the study schedule.

Exclusion Criteria

- Patients with known hypersensitivity to nasal decongestants,
- Patients having hypertension,
- Patients with a previous history of myocardial infarction, angina or stroke,
- Patients with known hyperthyroidism or hypothyroidism,
- Severe concurrent renal or hepatic illness,
- Any other condition that, in the opinion of the investigator, did not justify the inclusion of he subject in the study,
- Patient taking any nasal or systemic decongestant upto 2 days prior,
- Pregnant or lactating females.

Patients on screening were assigned a serial number as per the chronological order. After the patient was found to be eligible and satisfying the inclusion criteria, the sealed study medication pack was opened to reveal the study medication. Randomization was done on the basis of a PC based software (Rando version 1.2, © R.Raveendran 2004)

and the patients were randomized into two groups. The study was conducted for a period of 6 days. Patients could withdraw from the study at their own request or at the discretion of the investigator anytime during the study. In all cases, the reasons for the patient's withdrawal were entered in the CRF. One group received Oxymetazoline HCl 0.05 % with Dexpanthanol 5% (OD) and the second group received Xylometazoline HCl 0.1 % (XO) in the form of nasal drops which were administered four times a day.

Patients were not allowed to take the following medications:
- Any other systemic or nasal decongestants,
- Glucocorticosteroids in any form.

Patients were allowed to take the following preparations, provided they were prescribed by the investigator:

- Antimicrobial agents for post nasal surgery patients,
- Antihistaminic agents.

Any concomitant treatment given to or taken by the patient was recorded in the case record form. Patients were assessed clinically during screening and then on days 2, 4 & 6 of study therapy. On the first day, the patients were provided a diary and they were required to fill the symptom severity in the diary to assess the symptom relief after first dose & rebound congestion.

Statistical methods

The two treatments groups were analyzed for baseline comparability using unpaired 't' test. After they were found comparable, the change in clinical parameters between groups was analyzed by Mann-Whitney 'U' test (non-parametric). Change in clinical parameters from baseline values at follow-up visits in the treatment groups was analyzed by Friedman test (non-parametric). Adverse events will be compared using Chi-Square test.

Results

Out of a total of 100 patients enrolled in the study, five were lost to follow up (two in OD group and 3 in XO group). A total of 95 patients were evaluated for the study (48 OD and 47 XO group). Both the treatment groups were comparable as far as age, weight and height were concerned. There was no significant difference between the two groups with respect to sex of the patients or to the indication for therapy. [Table –1]

Table 1 patient profile of patients enrolled

	Oxymetazoline + Dexpanthenol (n=48)*	Xylometazoline (n=47)*	'p' Chi-Square
Gendre			
• Male	28 (58.33)	30 (63.83)	>0.05
• Female	20 (41.75)	17 (36.17)	
Type of Patient			
•Allergic Rhinitis	38 (79.17)	36 (76.60)	>0.05
• Post Nasul Surgery	10 (20.83)	11 (23.40)	
• No. (%)			

Nasal congestion

Nasal congestion was relieved as early as the first hour by both the medications. It was observed that as early as the second hour, relief from nasal congestion was significantly more ($p< 0.05$) in the OD group then the XO group. This difference was maintained till the end of the observation period of six hours. When nasal congestion was assessed over six days, the improvement seen in the OD group (mean score of 1.24) was significantly more than that in the XO group (mean score of 1.86) on the second day ($p<0.05$) as well as on the fourth day (0.25 in OD group Vs 0.64 in the XO group, $p<0.05$). The relief in nasal congestion is significantly better in the OD group then in the XO group.

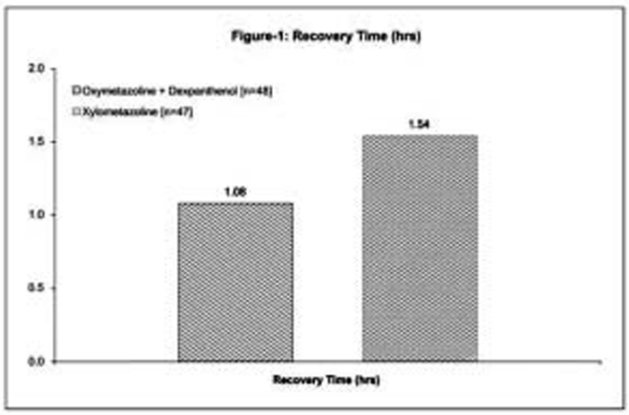
Sneezing: There was a considerable improvement in sneezing in both the treatment groups within the first hour. The mean sneezing scores were 0.40, 0.30 and 0.20 for the OD group at the end of one, two and three hours respectively whereas mean sneezing scores for the XO group were 0.70, 0.43 and 0.45 at the end of one, two and three hours respectively. The difference between the two groups was statistically significant

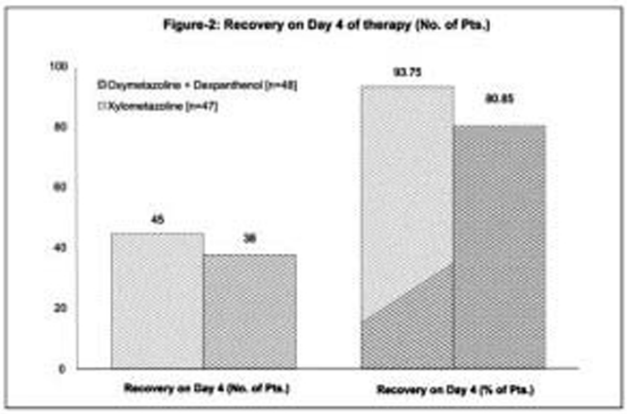
(p<0.05) for all the three hours with the OD group showing a higher improvement. This improvement in mean sneezing scores was maintained in the subsequent days with OD group showing a significantly higher improvement than the XO group on the second as well as the fourth day. The mean sneezing scores in the OD group were 0.42 and 0.11 on the second and fourth days respectively, whereas those in the XO group were 1.12 and 0.63 on the second and fourth days respectively (p<0.05 for day 2 as well as day 4). Thus it was inferred that improvement in sneezing is more significant in the OD group than the XO group.

Nasal discharge: There was a marked improvement in nasal discharge within the first hour in the OD group compared to XO group which was maintained throughout the six hour observation period. The values at first (1.10 in OD Vs 1.98 in XO), second (0.70 in OD Vs 1.40 in XO) and third hours (0.54 in OD Vs 0.78 in XO) attained statistical significance. (p<0.05) When this parameter was assessed over a six day period, it was observed that the nasal discharge scores were markedly lesser in the OD group than in the XO group. This difference was statistically significant for the second day, (p<0.05) OD causes a more significant decrease in nasal discharge as compared to XO.

Nasal irritation: Lesser nasal irritation was observed in the OD group as compared to the XO group throughout the six hour observation period. This achieved statistical significance (p<0.05) in the first two hours. The scores for nasal irritation in the OD group were 0.86 and 0.32 for the first and second hours respectively, whereas the scores for the XO group were 1.04 and 0.86 for the first and second hours respectively. The nasal irritation scores remained lower in the subsequent visits also in the OD group (0.38 on second day and 0.10 on the fourth day) than in the XO group (1.12 on the second day and 0.36 on the fourth day). This difference was statistically significant on both the days (p < 0.05). As is evident from the above data, OD causes lesser nasal irritation as compared to XO

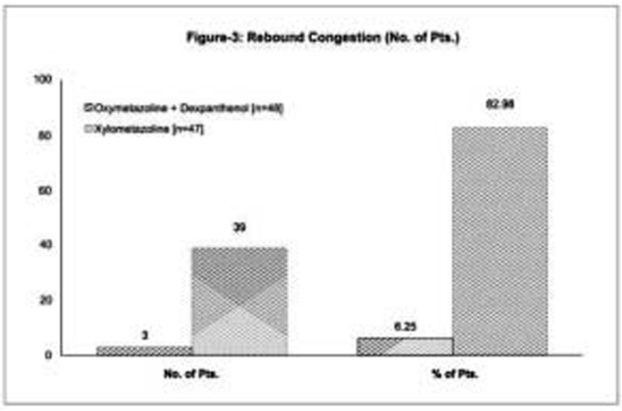
***Recovery time*:** The recovery time for OD group was 1.08 hours, which was 46 minutes lesser than that of the XO group, which showed a recovery time of 1.54 hours. [Figure- 1] (p<0.05) The percentage of patients who were considered recovered at the end of four days was 93.75 % in the OD group and 59.57% in the XO group. [Figure – 2] (p < 0.05) OD





causes a significantly faster recovery (46 minutes faster) than XO and a larger percentage of patients (93.75%) were fully recovered by day four as compared to XO (59.57%).

Rebound congestion: Rebound congestion was reported by only 6.25% of the patients in the OD treatment arm, whereas it was seen in 82.98% of patients in the XO treatment arm. [Figure – 3]. It follows that OD causes lesser rebound congestion than XO. Physicians Global Assessment of Response to Therapy (PGART) 93.75% of the physicians reported the response with OD as good to excellent as compared to 51.28% who thought that the response to therapy good to excellent in the XO group. (p<0.05) The data quoted above goes to show that more physicians rated OD higher than XO as far as efficacy is concerned. Patients Global Assessment of Tolerability to Therapy (PGATT) The results of the PGATT showed that 95.83% patients rated the tolerability to therapy for the OD group as good to excellent whereas only 52.91% patients in the XO group rated tolerability to therapy as good to excellent (p<0.05). The PGATT rating points towards a better patient tolerability for OD than XO.



Discussion

Nasal decongestants are used topically to alleviate the mucosal congestion in a variety of conditions like allergic rhinitis, infective rhinitis and in post nasal surgery cases, to name a few. Systemic decongestants do not have much advantage over the topical decongestants and are not so frequently used for these indications. Nasal decongestants

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decrease the resistance to airflow by decreasing the volume of nasal mucosa due to activation of alpha receptors in the venous capacitance vessels in nasal tissues, thereby causing prompt reversal of symptoms of congestion. The receptors that mediate this action seem to be mainly of the alpha 1 type. Alpha 2 receptors may mediate the constriction of the arterioles that provide nutrition to the nasal mucosa. Intense constriction of these arterioles may cause damage to the nasal mucosa.[6] Oxymetazoline and xylometazoline are more frequently used and preferred over the other nasal decongestants due to their longer duration of action and alpha 1 selectivity. These drugs have two main limitations, namely, rebound congestion and nasal irritation on instillation. Rebound hyperemia, or 'rhinitis medicamentosa 'are some of the terms used to describe the loss of efficacy and worsening of symptoms that is seen with prolonged use or stoppage of nasal decongestants.

The mechanisms involved may be receptor desensitization and damage to the mucosa. It is possible that damage to mucosa as well as rebound congestion is lesser with alpha 1 selective drugs. The second important factor that effects compliance and hence efficacy is the nasal irritation in the form of stinging or burning which is felt by the patient when the nasal decongestant is instilled into the nose. It has been attributed in part to the presence ofbenzalkonium chloride, which is used frequently as a preservative in nasal drops.[7] In the present study, the combination of oxymetazoline and dexpanthenol (OD) has shown superior results in all the efficacy parameters (congestion, sneezing, discharge, recovery time, PGART rating) as well as the tolerability parameters (rebound congestion and PGATT rating) as compared to xylometazoline (XO). This better efficacy and tolerability of oxymetazoline could probably be due to the addition of dexpanthenol to it.

It has been shown in earlier studies that the addition of dexpanthenol to nasal decongestants significantly reduces nasal obstruction, rhinorrhea, hyperplasia of nasal concha and redness of the nasal mucous membrane as compared to plain nasal decongestants.[1] Dexpanthenol is rapidly converted to pantothenic acid in vivo, which is widely distributed throughout the body, primarily as coenzyme A. Many varied functions have been attributed to it. Dexpanthenol, when added to nasal decongestants, could diminish the risk of a "rebound effect".[1] and can significantly increase the cell growth and normalize the ciliary beat frequency[3 2]which are important in recovery. In accordance with these findings, in the present study it was observed that the oxymetazoline and dexpanthenol combination when compared with xymetazoline, resulted in a significantly lower incidence of rebound congestion (6.25% v/s 82.98%, $p<0.05$) and a significantly shorter recovery time (1.08 hours v/s 1.54 hours, $p<0.05$).

The addition of dexpanthenol (5%) given before nasal decongestants or preserved nasal sprays is shown to improve the tolerability of these substances and to counteract the toxic effects.4,5This could be the reason for lesser nasal irritation on instillation of the medication containing dexpanthenol. Lesser irritation and lesser rebound congestion translate into better compliance on part of the patient and a better efficacy in the long run. Moreover, dexpanthenol has a favorable effect on wound healing and this will aid in the quicker healing of a post operative wound in the nose along with the decongestant action of xylometazoline. Hence, the combination proves to be synergistic. There is another factor which could also explain the better efficacy and tolerability of the oxymetazoline and dexpanthenol combination. Oxymetazoline is stated to possess antiinflammatory properties which are partially mediated by the inhibition of proinflammatory cytokines as well as reduced T-cell stimulatory capacity which gives rise to an immunomodulating effect and will aid in recovery.[8] Oxymetazoline also has an antioxidant effect. Since oxidants play a role in tissue damage in inflammation, it has been hypothesized that especially oxymethazoline may have an additional beneficial effect, due to their anti-oxidant properties, in the topical treatment of nasal inflammation. This effect could minimize the damage to nasal mucosa that is caused by alpha vasoconstrictor action and also hasten wound healing in the postoperative period. This antioxidant property of oxymetazoline has been rated much higher than that of xylometazoline.[9]

Conclusion

Oxymetazoline and dexpanthenol combination has a better efficacy, shorter recovery time, causes lesser rebound congestion and has better tolerability than xylometazoline. Oxymetazoline and dexpanthenol combination also has secondary effects on wound healing and antioxidant properties which may aid in early recovery and lesser adverse effects,

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