



## Role of Diosmin-Hesperidin Combination (Daflon® Tablets Servier) in Treatment of Vasomotor Rhinitis

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**Abstract: Background:** Rhinitis is defined as inflammation of the membranes lining the nose, characterized by nasal symptoms including itching, rhinorrhea and nasal congestion. Rhinitis represents a global health problem affecting between 10% and 25% of the world population. **Objectives:** To review the efficacy of combination of diosmin and hesperidin effect on vasomotor rhinitis symptoms versus intranasal steroids only on improvement scale in improvement of symptoms of Vasomotor Rhinitis. **Patients and Methods:** A meta-analysis examining the use of Diosmin hesperidin combination in treatment of vasomotor rhinitis in combination or in comparison with intranasal steroids. As our study involved examining only the existing peer-reviewed literature, Institutional Review Board approval was deemed unnecessary. Comparison between group A and group B regarding percentage of recovery: Group A: received Diosmin, Hesperidin combination (Daflon 500 mg tablets), group B: received intranasal steroids inhalers. **Results:** This study proved that Diosmin Hesperidin combination has a venotonic action on the nasal mucosa that decrease its secretions and decreases nasal obstruction and rhinorrhea and sneezing from vasomotor rhinitis patients. Our study is a collective analysis of retrospective and prospective cohort studies done separately in diosmin hesperidin combination in treatment of vasomotor rhinitis versus intranasal steroids in treatment of it. The data analysed and results showed statistically significant difference between two modalities of treatment between diosmin hesperidin combination (flavonoids) which showing efficacy 86.96% and intranasal steroids showing efficacy 72.5%. **Conclusion:** The cost benefit relation validates the trial of use of Diosmin Hesperidin combination (Daflon ® Servier) in cases of vasomotor rhinitis non responsive to other lines of therapy.

[Ezzat W.F., Sobhy T.S., Mady O.M., Shendy G.M., Ezzat W.F., Sobhy T.S., Mady O.M., Shendy G.M. **Role of Diosmin-Hesperidin Combination (Daflon® Tablets Servier) in Treatment of Vasomotor Rhinitis.** *N Y Sci J* 2020;13(1):1-5]. ISSN 1554-0200 (print); ISSN 2375-723X (online). <http://www.sciencepub.net/newyork>. 1. doi:[10.7537/marsnys130120.01](https://doi.org/10.7537/marsnys130120.01).

**Keywords:** Diosmin-Hesperidin, Daflon, Vasomotor Rhinitis

### 1. Introduction

VMR is characterized by prominent symptoms of nasal obstruction, rhinorrhea, and congestion. These symptoms are excessive at times and are exacerbated by certain odors (e.g., perfumes, cigarette smoke); alcohol; spicy foods; emotions; pregnancy and environmental factors such as temperature, and barometric pressure changes (Ezzat et al., 2009).

The diagnosis of VMR is based on a detailed medical history and exclusion of airborne allergens, and exclusion of clinical signs of rhinosinusitis (Hellings et al., 2017).

VMR is a heterogeneous disorder comprising several pathophysiological entities. The etiology of some of these disorders (e.g. drug-induced rhinitis, non allergic rhinitis with eosinophilia syndrome [NARES], occupational rhinitis, hormonal rhinitis, emotion-induced rhinitis, physical/chemical irritant-induced rhinitis) is well established (Hellings et al., 2017).

There is evidence that localized inflammation is the underlying cause of symptoms in drug-induced

rhinitis and NARES, since eosinophilia is an important pathophysiological component in these conditions. In contrast, neurogenic reflex mechanisms initiated by environmental factors appear to be involved in idiopathic rhinitis. It has been suggested that there may be an imbalance of the sympathetic and parasympathetic nervous systems, with parasympathetic hyper-activity and sympathetic hypo-activity resulting in nasal congestion and rhinorrhoea. Indirect evidence suggests that C-fibres may also play an important role in the pathophysiology of idiopathic rhinitis (Hellings et al., 2017).

### Aim of the Work

To review the efficacy of combination of diosmin and hesperidin effect on vasomotor rhinitis symptoms versus intranasal steroids only on improvement scale in improvement of symptoms of Vasomotor Rhinitis.

### 2. Methodology

Study was done in the following steps:

- Methods used in the study.

- Identification and location of articles.
- Screening and evaluation of articles.
- Data collection.
- Data analysis.
- Reporting and interpretation (Results).
- Discussions and conclusion.

### I) Methods used in the study:

A meta-analysis examining the use of Diosmin hesperidin combination in treatment of vasomotor rhinitis in combination or in comparison with intranasal steroids.

As our study involved examining only the existing peer-reviewed literature, Institutional Review Board approval was deemed unnecessary.

### II) Identification and location of articles:

A database search of the Cochrane Review, and PubMed (1949 to November 2019) were performed to identify articles. Search terms included:

- Vasomotor Rhinitis.
- Diosmin Hesperidin Combination (Daflon Tab).
- Intranasal Steroids.

The Medical Subject Headings database—a controlled vocabulary system used for indexing articles for MEDLINE—was used to maximize our search yield.

### Criteria of considering studies for this review:

#### Type of studies:

Randomized control trials on patient suffering from Vasomotor Rhinitis (VMR), cohort studies, and retrospective studies.

#### Type of participants:

Patient suffering from non-allergic vasomotor rhinitis.

#### Types of intervention:

Combination between Diosmin Hesperidin complex (Daflon 500 mg tablets) versus intranasal steroids as a medical treatment of vasomotor rhinitis.

#### Type of outcome measures:

The improvement of symptoms on administration of daflon tablets and intranasal steroids of vasomotor rhinitis on SNOT scale.

#### Search strategy for identification of study:

The study will include published medical articles about Diosmin Hesperidin complex, intranasal steroids, Vasomotor Rhinitis, through searching the Medline data base ([www.pubmed.com](http://www.pubmed.com)) using a combination of the following keywords:

Vasomotor rhinitis, diosmin hesperidin combination, intranasal steroids.

### Methods of review:

#### Locating and selecting studies:

The study was limited to articles published in English language, conducted to humans, in the last 30 years.

### Data extraction:

Data was independently extracted by two reviewers and cross-checked.

### Evidence of publication bias:

A funnel plot is a simple scatter plot of the intervention effect estimates from individual studies against some measure of each study's size or precision.

### Design:

A retrospective non company sponsored randomized case control study.

### III) Screening and evaluation of articles:

Studies were included if they utilized ( Diosmin Hesperidin combination) Daflon tablets or Bioflavinoids as a line of treatment for vasomotor rhinitis also using intranasal steroids in treatment of vasomotor rhinitis.

Studies must have focused on Diosmin Hesperidin combination and Bioflavinoids and intranasal steroids in treatment of vasomotor rhinitis only original research articles written in English and published in peer-reviewed journals were included. The patient population of the study must have been adult patients ( $\geq 18$  years of age). Any included study must have contained at least 10 cases.

Table (1): Example of Included articles:

Article	Cases no.	Type of study
Blair W. Saylor (1949)	53	Retrospective study
Phanindra-Kumar (1995)	76	Double Blind Clinical Trial
Ezzat W, et al (2009)	60	Case Control Study
Korhan et al, (2019)	30	RCT
Eli (2009)	39	RCT

### Exclusion criteria:

Studies or cases from studies were excluded if:

- Any prior nasal allergy or chronic nasal disease or allergic nasal polypi.
- Also any nasal surgery, irrespective of its nature.
- History of hypersensitivity to corticosteroids or food allergy in a need for a regular use of inhaled glucocorticoids for asthma and any systemic renal, endocrine, cardiovascular, gastrointestinal and hematological diseases or neuropsychiatric disorders.
- Unpublished studies (eg, conference abstracts) were excluded.
- Studies published before 1940 were excluded.
- Missing one or more of inclusion criteria.

### Statistical methods

Statistical analysis was done using Comprehensive meta-analysis version 2.2.046 (Bio stat© Englewood, NJ). Studies included in meta-analysis were tested for heterogeneity of the estimates. P-values <0.05 are considered statistically significant.

### 3. Results

The previous table shows that there was highly statistically significant difference found between group A and group B regarding percentage of recovery which was 86.96% in group A versus 72.55% in group B with p-value = 0.012.

**Table (2):** Comparison between group A and group B regarding percentage of recovery

	Group A		Group B	
	Total number	Recovered	Total number	Recovered
Blair W.Saylor (1949)	53	45 (84.9%)	-	-
Phanindra-Kumar 1995	76	68 (89.5%)	-	-
Ezzat W, et al (2009)	48	43 (89.6%)	12	8 (66.7%)
Korhan et al. (2019)	30	24 (80.0%)	-	-
Eli (2009)	-	-	39	29 (74.4%)
<b>Total</b>	<b>207</b>	<b>180 (86.96%)</b>	<b>51</b>	<b>37 (72.55%)</b>
Chi-square test	<b>6.355</b>			
P-value	<b>0.012 (S)</b>			

**Table (3):** Incidence of Symptom recovery among group A treatment

Symptom recovery	No.	%
Rhinorhea	70	92.11%
Sneezing	68	89.47%
Obstruction	64	84.21%

### 4. Discussion

The most common form of nonallergic rhinitis is idiopathic rhinitis also known as vasomotor rhinitis. Individuals categorized as such are those who not only lack conventional evidence of allergic disease but are also devoid of any evidence of sinusitis/nasal polyposis, anatomic abnormalities, or a known infection. In addition, pharmacological (iatrogenic) or endocrine causes need to be ruled out. Their nasal symptoms are chronic, without a seasonal pattern (although some cases of seasonal symptomatology may appear) and are more likely to include nasal congestion and clear rhinorrhea and less likely sneezing and pruritus. Patients with idiopathic/vasomotor rhinitis report a family history of rhinitis less frequently than patients with allergic disease.

Although the pathogenesis of intrinsic rhinitis remains unknown, it is believed to be the result of autonomic imbalance, with a relative dominance of the parasympathetic nervous system in the nasal mucosa.

Ezzat W, It was hypothesized in this study that the action of micronized flavinoids, which included

increasing vascular tone, protection of vascular endothelium and decreasing edema, together with their anti-inflammatory effects would act on the nasal endothelium. In a similar fashion as it does on the diseased venous system in cases of varicosities. The theory based on the fact that various factors leading to nasal congestion, vascular pooling, increased extracellular volume, peripheral vascular dilatation, smooth muscle relaxation, vascular distension and osmolar changes with their subsequent effects would at least in part be reversed or reduced by the effect of micronized flavinoids.

Diosmin a bioflavonoid found to be anti-edematous and physiological antagonist to histamine. It increases capillary resistance and decreases capillary permeability. The preparations used in treating allergic diseases may have three pharmacological effects; modifying mediator effects in sensitive target organs and mediator release. Diosmin affects the microcirculation and on certain inflammatory reaction mediators. The physiological antagonism to histamine, inhibition of synthesis of prostaglandins, the lymphagogue property and anti-edematous effects might have responsible in relieving rhinorrhoea, sneezing and nasal obstruction. In addition Diosmin has shown a decrease in eosinophils in the nasal smear at the end of seven days of treatment. Bioflavonoids have mast cell stabilisation action. The administration of Diosmin may be beneficial in the treatment of rhinitis as indicated by rapid clinical recovery.

None of the patients complained of nasal crusting, rebound rhinitis, muscular palsy, hyposmia, vision changes, or dry eyes.

MPFF, an oral phlebotropic and vascular protective agent consisting of 90% micronised diosmin and 10% flavonoids expressed as hesperidin, increases venous tone, improves lymphatic drainage and reduces capillary hyperpermeability. By reducing the expression of some endothelial adhesion molecules, MPFF inhibits the activation, migration and adhesion of leukocytes, which leads to a reduction in the release of inflammatory mediators and thereby a reduction in capillary hyperpermeability.

These findings implicate that Diosmin-hesperidin combination, as a micronized flavinoid drug, can and should be used in Vasomotor Rhinitis as an effective line of treatment, whether alone instead of local nasal steroid to give the same improvement also, in combination with other lines in severe cases to give better response.

Also some studies proved significance difference in response of rhinorrhea, sneezing is decreased and nasal obstruction is released.

Phanindra Kumar, revealed that one hundred and fifty patients (87 men, 63 women), 76 in the Diosmin group and 74 in the placebo group, completed the trial. There were no significant differences in clinical and biochemical parameters between the two groups before treatment. This randomized double blind study with Diosmin and placebo lasted for one week and the follow up period for one week. Diosmin was given 300 mg three times a day and placebo was also administered in the same dose as identical capsules as Diosmin. Significant difference in the response between the two groups for the individual parameters was observed. With Diosmin rhinorrhoea subsided in 58 patients (51-100%) while it was in 19 patients (51-100%) in placebo group. Sneezing were decreased in 76 patients (51-100%) ( $P < 0.001$ ) in Diosmin group and 19 patients in placebo group. There was considerable reduction in eosinophilic count of Diosmin group compared to placebo group, there were eleven drop outs (6males, 5 females). No side effects were observed in placebo group but one female and three males complained mild fever in Diosmin group.

Our study proved that Diosmin Hesperidin combination has a venotonic action on the nasal mucosa that decrease its secretions and decreases nasal obstruction and rhinorrhea and sneezing from vasomotor rhinitis patients.

Our study is a collective analysis of retrospective and prospective cohort studies done separately in diosmin hesperidin combination in treatment of vasomotor rhinitis versus intranasal steroids in treatment of it.

The data analysed and results showed statistically significant difference between two modalities of treatment between diosmin hesperidin combination (flavinoids) which showing efficacy 86.96% and intranasal steroids showing efficacy 72.5%.

Also Diosmin Hesperidin administration improves symptoms of vasomotor rhinitis rhinorrhea improved by 92 % from total number of patients and sneezing improved by 89.5 % from total number of patients and nasal obstruction is improved by 84.5 %.

#### Limitation of study

1. Paucity of comparative randomized clinical trials.
2. Most of included studies were retrospective or prospective cohort studies.
3. No definite age group was detected in most of those studies.
4. No randomization in study sample.
5. Diversity of sample size between the two techniques.
6. Absence of similarity in experimental conditions among those techniques.

#### Conclusion

The available data favors the efficacy of usage of Diosmin and Hesperidin combination (Daflon servier) either as a monotherapy or combination with intranasal steroids for cases of Vasomotor Rhinitis, further randomized controlled studies must be conducted in the future.

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12/20/2019