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# Efficacy of *Viola odorata* flower decoction in chronic rhinosinusitis

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## ABSTRACT

Chronic rhinosinusitis (CRS) is one of the most frequent otorhinolaryngologic diseases encountered in daily practice with an estimated prevalence of 14% of the global population. This study aimed to explore the efficacy of *Viola odorata* flower decoction against CRS.

In this prospective randomized controlled trial, 30 patients with CRS were randomly assigned to receive either test drug (10 g of *V. odorata* flower in the form of decoction administered orally empty stomach in the morning daily) or active control drug (single nasal spray of fluticasone propionate 50 µg/spray in each nostril daily) for 30 days. The primary outcome measure was an improvement in sinonasal symptoms assessed using a 22-item sinonasal outcome questionnaire (SNOT-22). Reduction in absolute eosinophil count (AEC) and improvement in x-ray paranasal sinus were secondary outcome measures. The significance level was kept as 5%.

After completing the therapy, the SNOT-22 score was significantly low in the test group compared with the control group and a significant difference was found in AEC between the groups. Also, the SNOT-22 score remained significantly low after completion of the treatment on the 45th and 60th days compared with the control drug. Changes in x-ray paranasal sinuses were not significant between the groups. These results suggested that *V. odorata* flower was effective in reducing the symptoms of CRS.

Trial Registration No. Clinical Trial Registry of India CTRI/2017/09/009788 (01/09/2016)

**Key words:** Flower; herbal medicine; quality of life; sinonasal; *Viola odorata*

## INTRODUCTION

Rhinosinusitis is a group of disorders characterized by inflammation of the nasal mucosa and the mucosa of the paranasal sinuses [1]. The inflammation of the nasal and sinus mucosa often coexists in this condition, and hence the term "rhinosinusitis" has been given [2]. Rhinosinusitis is considered as chronic when symptomatic inflammation of the nasal and sinus mucosa persists for more than >12 weeks, with or without exacerbations [1-4]. Chronic rhinosinusitis (CRS) is one of the most frequent otorhinolaryngologic diseases encountered in daily practice [3] with an estimated prevalence of 14% of the global population [5].

In the medical management of CRS, topical administration of corticosteroids is considered as the first-line therapy. Nasal irritation, mucosal bleeding, and crusting have been found to be associated with the daily use of topical nasal steroids. Further long-term systemic steroid use is associated with significant side effects [1]. Surgery is usually considered as a last option for patients not responding to medical management. Recurrence has been noted with surgical treatment and is often not successful. Therefore, no effective medical or surgical treatment is available to provide complete cure for CRS. So, alternative therapeutic strategies need to be explored for the same [6].

*Viola odorata*, popularly known as "Banafsha" in Asia [7] and frequently recognized as wood violet, sweet violet, English violet, common violet, florist's violet, or garden violet [7-10], is cultivated and grows spontaneously on six continents with Mediterranean and temperate climates [11]. In India, it is distributed in Kashmir, Western Himalayan region, at an altitude of 1500–1800 m [12]. According to Unani literature, *Viola odorata* flowers (gulebanafsha) possess anti-inflammatory, analgesic, blood-purifying, and expectorant properties [13,14]. It is a remedy for respiratory problems such as bronchitis,

cough, and asthma [13,15]. Several experimental studies have been conducted showing its anti-inflammatory, antimicrobial, sedative, and pre-anesthetic properties. In clinical studies, the adjuvant use of violet syrup with short-acting β-agonist was found to enhance cough suppression in children with intermittent asthma [16]. Also, the frequencies of tonsillitis and peritonsillar abscess reduced with the administration of decoction of *V. odorata* flowers [17]. The objective of this study was to investigate the effect of *V. odorata* flowers in reducing the symptoms of CRS.

## METHODOLOGY

### Study design

This randomized controlled trial was conducted in the Department of Moalajat, Luqman Unani Medical College (LUMC) Hospital and Research Center, Vijaypur, Karnataka, from November 2016 to March 2018 conforming to the tenets of the Declaration of Helsinki. The study protocol was approved by the Institutional Ethical Committee (IEC), LUMC, Vijaypur, under.IEC No: BJP/LUMC/PG/IEC/2015-16/01/MOALAJAT/02. The trial was registered by the Clinical trial Registry of India with registration number CTRI/2017/09/009788. All patients were required to sign a consent form before participating in the trial.

### Sample size estimation

The sample size of this study was calculated by taking assumptions needed to demonstrate a difference by a new treatment in terms of costs and risks: assumed effect size of 9 and assumed standard deviation of 8.44. Based on these assumptions, a sample containing 28 participants, 14 in each group, was found to be sufficient to rule out a clinically important difference of 9 between the 2 groups in reducing 22-item sinonasal outcome questionnaire (SNOT-22) score, assuming a standard deviation of 8.44 and using a two-tailed t test of the difference between means with 80% power and a 5% level of significance. After considering 10% as a dropout rate, the sample size required was approximately 30 (15 in each group).

### Participant selection and criteria

The male and female patients aged 18–50 years fulfilled the diagnostic criteria for CRS of the American Academy of Otolaryngology-Head and Neck Surgery. According to this criteria, a patient was diagnosed with CRS if 12 weeks or longer of two or more of signs and symptoms of mucopurulent drainage, nasal obstruction, facial pain/pressure/fullness, or reduced sense of smell were observed, besides inflammation documented by one or more of the findings of purulent mucus or edema in the middle meatus or anterior ethmoid region, polyps in the nasal cavity or the middle meatus, and/or radiographic imaging showing inflammation of the paranasal sinuses. Patients were excluded if they had known systemic and metabolic diseases, external injuries, nasal polyps, and nasal growth. Pregnant and lactating women were also excluded. Patients were randomized as 1:1 into the test or control group, 15 patients in each group, using an open list of random numbers produced from an online randomization list generator (www.randomization.com). The sequence of random numbers was concealed from the researcher collecting the data until the interventions were assigned to each patient.

### Intervention

The gule banafsha (*V. odorata* flower) was purchased from a local drug market of Vijaypur city and identified and authenticated by Professor Syed Saleemuddin Ahmed, Department of Pharmacology. The voucher specimen has been stored in the laboratory of the Department of Pharmacology, LUMC Hospital and Research Center, Vijayapur, Karnataka. Small sachets were made, each containing 10 g dried gule banafsha. Patients were instructed to prepare a decoction by adding each sachet in 250 mL of water, followed by boiling it for 5 min, sieving it, and use it empty stomach in the morning daily for 30 days. In the control group, a single nasal spray of fluticasone propionate (50 µg/spray) in each nostril in the morning daily was given for 30 days. Compliance was assessed at every follow-up by examining the lock bags in which the medication was dispensed at the previous visit.

### Study procedure

During the first visit, a detailed history, including the onset and duration of nasal blockage, running nose, sneezing, facial pain, decreased sense of smell, ear pain, ear fullness, history of allergy, and any previous treatment, was taken, and a complete physical examination was done. Systemic examination of Central Nervous System (CNS), Cardiovascular System (CVS), and Respiratory System (RS), and abdominal examination was performed in each patient. Following the evaluation, the patients were advised to go for necessary investigations, including absolute eosinophil count (AEC) and x-ray (Water's view). Serum Glutamic-Ocaloacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase

(SGPT), blood urea, and serum creatinine levels were also determined to assess the safety of the drug. Patients meeting the inclusion criteria were provided an information sheet containing details regarding the nature of the study. Patients were given enough time and opportunity to read and understand the details of the study mentioned in the information sheet and ask any questions. They were given the right to deny or withdraw the treatment during any part of the study without sharing any reason. After obtaining the willingness, they were asked to take part in the study and sign the consent form. The patients were followed up on the 15th and 30th days during the treatment. The sinonasal symptoms were assessed on each visit using the SNOT-22 score. AEC and x-ray of the paranasal sinuses were repeated after completion of the treatment. Two follow-ups were done on the 45th and 60th days to see the recurrence of symptoms and persistence of the therapeutic effect of the drugs by assessing the SNOT-22 score. Inquiries regarding any side effects were made and documented properly. Reduction in the SNOT 22 score was used as the primary outcome measure, while a reduction in AEC and improvement in x-ray paranasal sinuses (PNS)findings were analyzed as secondary outcome measures. Changes in maxillary sinus opacity, frontal sinus opacity, and ethmoidal sinus opacity in patients with rhinosinusitis were assessed and graded arbitrarily as severe, moderate, mild, and nil.

### SNOT-22

SNOT-22 is a questionnaire related to a sinonasal symptom, which is extensively used in the literature to assess the quality of life in sinonasal diseases. It assesses nasal, paranasal, and psychological symptoms, and also symptoms associated with sleep [8].

### Statistical analysis

The results on categorical variables were presented as number (%), while continuous variables were presented as mean ± standard deviation (SD) (min–max). The level of significance was kept at 5%. To analyze the significance of study parameters on a continuous scale, Student t test (two tailed, independent) and Student t test (two tailed, dependent) were used for inter- and intragroup analyses, respectively. To analyze the significance of study parameters on categorical scale between two or more groups, the chi-square/Fisher Exact test was used. The statistical software used for the analysis of data were SPSS 18.0 and R environment ver.3.2.2. Microsoft Word and Excel were used to generate graphs and tables.

## RESULTS

### Participant selection

A total of 151 patients were screened; 19 patients denied to participate in the study, and 132 were subjected to investigation. Of these, 102 patients were excluded from the study and 30 patients were randomly allocated (Figure 1).

### Baseline characteristics

At baseline, patients were assessed for different variables such as age sex, diet, occupation, and socioeconomic condition. Both groups were found to be statistically similar (Table 1).

### Primary outcome

The baseline SNOT-22 score was not significantly different between the two groups with a *P* value of 0.08. In the test group, the mean of the SNOT-22 score was reduced from 62.53 ± 5.21 to 41.87 ± 4.41 and 14.07 ± 8.64 after 15-day and 30-day treatment with a mean difference of 20.667 and 48.467, respectively. After treatment, the score remained low from the baseline with a mean difference of 52.533 and 51.267 on the 45th day and 60th day, respectively. These changes in the SNOT-22 score within the group were statistically significant with a *P* value <0.001. When changes in the SNOT-22 in the test group were compared with those in the control group, a statistically significant difference was observed in the SNOT-22 score on the 15th, 45th, and 60th days between the groups, showing the long-term efficacy of the test drug (Table 2).

### Secondary outcome measures

As shown in Table 2, after a 1-month treatment, the mean score of eosinophil count was reduced from 823.33 cells/mm$^3$ to 360.00 cells/mm$^3$ with a mean difference of 463.333 in the test group, which was statistically significant with a *P* value <0.001. When the test group was compared with the control group statistically using the unpaired t test, after completion of treatment, a significant difference was found between the two groups with a *P* value <0.001, where the test drug decreased eosinophil count more prominently compared with the control drug.

Changes in maxillary sinus opacity, frontal sinus opacity, and ethmoidal sinus opacity in patients with rhinosinusitis were assessed and arbitrary graded as severe, moderate, mild, and nil. In the test group, sinus opacity was resolved completely after 30 days of treatment in four patients and partially in six patients; PNS opacity was reduced from grades severe and moderate

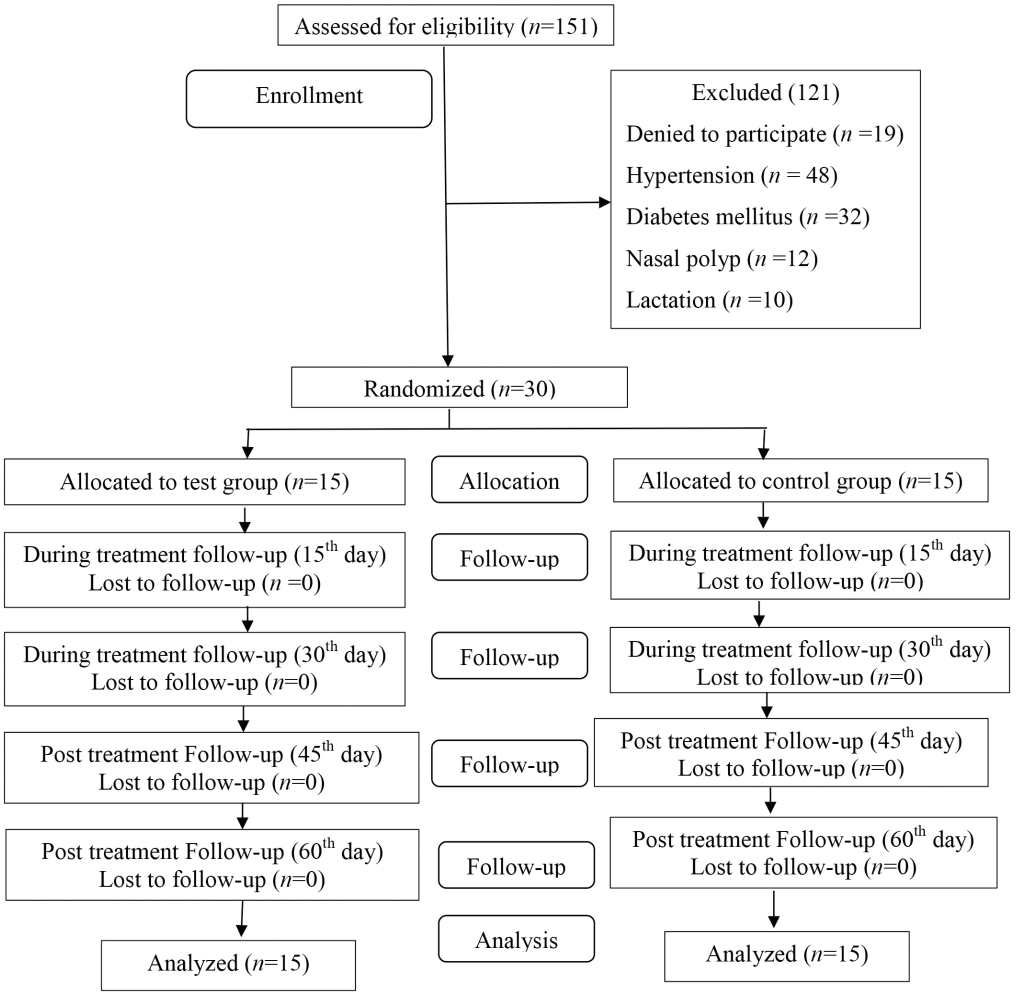


Figure 1 Flow chart as per the CONSORT statement.

to mild with a percentage change of 40%. However, in the control group, no patient was relieved completely; however, three patients were relieved partially as PNS opacity was reduced from grades severe and moderate to mild with a percentage change of 20%. When these observations were compared between the two groups, no significant difference was found with a *P* value of 0.123. In the test group, after completion of the treatment, frontal sinus opacity was resolved completely in four patients with a percentage change of 26.7%. However, in the control group, no patient was relieved completely or partially. When these observations were compared between the two groups, a significant difference was found with a *P* value of 0.042. In the test group, after completion of the treatment, two patients were relieved partially because PNS opacity was reduced from grades severe and moderate to mild with a percentage change of 13.3%. However, in the control group, two patients were relieved completely after the treatment with a percentage change of 13.3%. When these observations were compared between the two groups, no significant difference was found with a *P* value of 0.483 (Table 4).

## DISCUSSION

The results of this study showed that both test and control drugs significantly reduced the SNOT-22 score after a 1-month treatment. CRS is considered as a multifactorial disease characterized by a variety of disorders leading to inflammation of nasal and sinus mucosa. It may also include bacterial, viral, fungal, allergic, nonallergic, inflammatory, pharmacologic, neural, genetic, and hormonal causes (18-20). An ionone-like compound known as 3-acrylic acid from the aerial parts of *V. odorata* at 6 mg/disk concentration showed significant antibacterial efficacy against

Table 1 Demographic profile of the patients in the test and control groups

| Basic variables | Test group (n = 15) | Control group (n = 15) | aP value |
|---|---|---|---|
| **Age (year)** | | | |
| 20–30 | 6 (40%) | 8 (53.3%) | 0.087 |
| 31–40 | 8 (53.3%) | 7 (46.7%) | |
| 41–50 | 1 (6.7%) | 0 (0%) | |
| Mean ± SD | 32.80 ± 5.80 | 29.07 ± 5.73 | |
| **Sex** | | | |
| Female | 1 (6.7%) | 3 (20%) | 0.598 |
| Male | 14 (93.3%) | 12 (80%) | |
| **Occupation** | | | |
| Business | 5 (33.3%) | 2 (13.3%) | 0.672 |
| Student | 3 (20%) | 4 (26.7%) | |
| Unskilled worker | 3 (20%) | 2 (13.3%) | |
| Professional | 1 (6.7%) | 4 (26.7%) | |
| Skilled worker | 2 (13.3%) | 2 (13.3%) | |
| Housewife | 1 (6.7%) | 1 (6.7%) | |
| **Diet** | | | |
| Mixed | 12 (80%) | 12 (80%) | 1 |
| Vegetarian | 3 (20%) | 3 (20%) | |
| **Socioeconomic status** | | | |
| Upper class | 4 (26.7%) | 5 (33.3%) | 1 |
| Upper middle class | 8 (53.3%) | 7 (46.7%) | |
| Lower middle class | 2 (13.3%) | 3 (20%) | |
| Upper lower class | 1 (6.7%) | 0 (0%) | |
| Lower class | 0 (0%) | 0 (0%) | |
| **Duration of illness (month)** | | | |
| <12 | 3 (20%) | 6 (40%) | 0.823 |
| 12–24 | 12 (80%) | 8 (53.3%) | |
| >24 | 0 (0%) | 1 (6.7%) | |
| Mean ± SD | 14.27 ± 4.57 | 14.80 ± 7.91 | |

[a] Chi square test/Fisher exact test

selected respiratory bacteria (9). *V. odorata* has been found to be active against different bacterial species in several animal studies (21,22-25). The antimicrobial effect of *V. odorata* was found to be high in flowers compared with leaves and roots (25). Prophylactic administration of the *V. odorata* extract was found to be partially effective in preventing lung damage, while it was found to be equally effective in hydrocortisone in aiding the resolution of formalin-induced lung damage (26). In vivo, the injections of different dosages of the ethanolic and chloroform extracts of *V. odorata* were found to increase sleeping time and also showed better sedation and pre-anesthetic effects in a dose-dependent manner compared with diazepam (27). The aqueous extract of the aerial parts of *V. odorata* showed significant diuretic activity (28). Clinically the adjuvant administration of *V. odorata* syrup along with short-acting β-agonist showed cough suppression in children with intermittent asthma (16). Frequencies of tonsillitis and peritonsillar abscess were reduced with administration of the decoction of *V. odorata* flowers (17). Nasal drops of *V. odorata* were found to be efficacious in patients of insomnia because they showed significant improvements in sleep and insomnia severity index scores after a 1-month treatment (29). The SNOT-22 questionnaire comprised several parameters, including cough, nasal blockage, ear fullness, ear pain, facial pain, sleep disturbances, sneezing, and running nose. Thus, the reduction in the SNOT-22 score could be explained on the basis of the aforementioned effects of *V. odorata* in animal studies as well as clinical trials.

Eosinophils are considered to play a major role in the pathogenesis of eosinophilic CRS through the release of noxious secretary granules. They also cause the release of major basic proteins, eosinophil-derived neurotoxins, eicosanoids, and various cytokines. The eosinophils histologically infiltrate into the epithelium out to the sinus cavity through the thickened basement membrane. Continuous eosinophilic inflammation causes the disruption of mucociliary clearance systems resulting in impaired immune capabilities and raises the possibility of infectious damage to the host (30). Sreeparvathi et al. demonstrated a significant correlation between eosinophil counts in tissues and blood with increased severity of symptoms in patients suffering from eosinophilic CRS with nasal polyps in the Indian population (31). Prophylactic administration of the *V. odorata* extract was found to be partially effective in preventing lung damage, while it was found to be equally effective to hydrocortisone in aiding the resolution of formalin-induced lung damage (26). Generally, eosinophilic CRS is related to steroid responsiveness (32). Dahl et al did not observe any effect of the administration of nasal corticosteroids for 6 weeks on airway reactivity or induced sputum eosinophilia (33). Lee et al observed that the *V. odorata* extract caused considerable inhibition of the effect of the total serum level of IgE and cytokines IL-3 and IL-4 on the inflammation of respiratory tracts in allergic mice. It also effectively reduced the overactivity of the airways, eosinophilia, and excessive secretion of mucus (16).

Table 2 Comparison of SNOT 22 score in the two groups of the patients studied

| SNOT 22 | Test group | Control group | Total | P value |
|---|---|---|---|---|
| ***Before treatment*** | 62.53 ± 5.21 | 59.27 ± 4.62 | 60.90 ± 5.11 | 0.080 |
| 15th day | 41.87 ± 4.41 | 29.73 ± 4.22 | 35.80 ± 7.49 | <0.001a** |
| 30th day | 14.07 ± 8.64 | 18.87 ± 5.51 | 16.47 ± 7.53 | 0.080 |
| 45th day | 10.00 ± 7.56 | 17.80 ± 7.22 | 13.90 ± 8.28 | 0.007 a** |
| 60th day | 11.27 ± 7.39 | 23.87 ± 7.07 | 17.57 ± 9.57 | <0.001a** |
| ***Difference from BT*** | | | | |
| 15th day | 20.667 | 29.533 | 25.100 | - |
| 30th day | 48.467 | 40.400 | 44.433 | - |
| 45th day | 52.533 | 41.467 | 47.000 | - |
| 60th day | 51.267 | 35.400 | 43.333 | - |
| ***P value from BT*** | | | | |
| 15th day | <0.001b** | <0.001b** | <0.001b** | - |
| 30th day | <0.001b** | <0.001b** | <0.001b** | - |
| 45th day | <0.001b** | <0.001b** | <0.001b** | - |
| 60th day | <0.001b** | <0.001b** | <0.001b** | - |

[a] Student *t* test (unpaired); [b]Student t test (paired); **Strongly significant (*P* value: ≤ 0.01).

Table 3 Comparison of absolute eosinophil count (cells/mm$^3$) in the two groups of patients studied

| Absolute eosinophil count (Cells/mm$^3$) | Test group | Control group | *P* value |
|---|---|---|---|
| Before treatment | 823.33 ± 92.32 | 766.67 ± 97.59 | 0.114 |
| After treatment | 360.00 ± 60.36 | 486.67 ± 91.55 | <0.001**[a] |
| Difference | 463.333 | 280.000 | - |
| P value | <0.001**[b] | <0.001**[b] | - |

[a]Student *t* test (Unpaired); [b]Student *t* test (paired); **Strongly significant (*P* value: ≤ 0.01).

If history and physical examinations are equivocal, or if conventional treatment has failed, paranasal sinuses imaging is usually done to supports the clinical findings or confirm the diagnosis. Sinus ostial obstruction in sinonasal inflammatory disease is a very common cause of an opacified paranasal sinus (34). Water-soluble polysaccharides extracted from the grass of *V. odorata* possessed anti-inflammatory activity manifested by the suppression of the exudation and proliferation stages of inflammation (35). The safety profile was found to be within the normal limit in both the groups (Table 5). No adverse reactions were noted in both the groups. Also, in other clinical trials with *V. odorata* flowers, no adverse effects were noted (16,17,29). Small sample size and long-term follow-up were the limitations of this study. Further studies are recommended with a large sample size along with long-term follow-up.

## CONCLUSIONS

The test drug was found to be equally effective in reducing the SNOT-22 score compared with the control drug. Additionally, a statistically significant long-term effect of the test drug was noted. Regarding the changes in z-ray paranasal sinuses, both the test and control drugs were found to be equally effective. Therefore, it was inferred that the research drug controlled CRS.

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Table 4 Comparison of x-ray PNS opacity between the groups

| Maxillary sinus | Before treatment | After treatment | % change |
|---|---|---|---|
| ***Test group (n = 15)*** | | | |
| No opacity | 0 (0%) | 4 (26.7%) | 26.70 |
| Mild opacity | 2 (13.3%) | 8 (53.3%) | 40.00 |
| Moderate opacity | 4 (26.7%) | 3 (20%) | –6.70 |
| Severe opacity | 9(60%) | 0(0%) | –60.00 |
| ***Control group (n = 15)*** | | | |
| No opacity | 3 (20%) | 3 (20%) | 0.00 |
| Mild opacity | 0 (0%) | 3 (20%) | 20.00 |
| Moderate opacity | 3 (20%) | 7 (46.7%) | 26.70 |
| Severe opacity | 9 (60%) | 2 (13.3%) | –46.70 |
| *P* value | 0.204a | 0.123a | - |
| Frontal grading | | | |
| ***Test group (n = 15)*** | | | |
| No opacity | 11 (73.3%) | 15 (100%) | 26.70 |
| Mild opacity | 1 (6.7%) | 0 (0%) | –6.70 |
| Moderate opacity | 3 (20%) | 0 (0%) | –20.00 |
| Severe opacity | 0 (0%) | 0 (0%) | 0.00 |
| ***Control group (n = 15)*** | | | |
| No opacity | 10 (66.7%) | 10 (66.7%) | 0.00 |
| Mild opacity | 0 (0%) | 0 (0%) | 0.00 |
| Moderate opacity | 5 (33.3%) | 5 (33.3%) | 0.00 |
| Severe opacity | 0 (0%) | 0 (0%) | 0.00 |
| *P* value | 0.682a | 0.042a* | - |
| Ethmoidal grading | | | |
| ***Test group (n = 15)*** | | | |
| No opacity | 13 (86.7%) | 13 (86.7%) | 0.00 |
| Mild opacity | 0 (0%) | 2 (13.3%) | 13.30 |
| Moderate opacity | 1 (6.7%) | 0 (0%) | –6.70 |
| Severe opacity | 1 (6.7%) | 0 (0%) | 6.70 |
| ***Control group (n = 15)*** | | | |
| No opacity | 12 (80%) | 14 (93.3%) | 13.30 |
| Mild opacity | 0 (0%) | 0 (0%) | 0.00 |
| Moderate opacity | 2 (13.3%) | 1 (6.7%) | –6.60 |
| Severe opacity | 1 (6.7%) | 0 (0%) | –6.7 |
| *P* value | 1a | 0.483a | - |

[a]Chi square/Fisher exact Test; *moderately significant (*P* value: $0.01 < P \leq 0.05$).


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Table 5 Comparison of safety profile in the two groups

| Safety parameter | Test group | Control group | Total | *P* valuea |
|---|---|---|---|---|
| ***Blood urea (mg/dL)*** | | | | |
| Before treatment | 19.40 ± 3.64 | 19.47 ± 3.60 | 19.43 ± 3.56 | 0.96 |
| After treatment | 16.73 ± 3.61 | 17.67 ± 3.66 | 17.20 ± 3.60 | 0.488 |
| **Serum creatinine (mg/dL)** | | | | |
| Before treatment | 1.15 ± 0.08 | 1.07 ± 0.12 | 1.11 ± 0.11 | 0.057 |
| After treatment | 1.00 ± 0.09 | 0.96 ± 0.10 | 0.98 ± 0.10 | 0.262 |
| ***SGOT (IU/L)*** | | | | |
| Before treatment | 23.00 ± 2.98 | 23.33 ± 2.85 | 23.17 ± 2.87 | 0.756 |
| After treatment | 21.07 ± 2.52 | 21.20 ± 3.61 | 21.13 ± 3.06 | 0.907 |
| ***SGPT (IU/L)*** | | | | |
| Before treatment | 25.40 ± 3.18 | 24.73 ± 2.94 | 25.07 ± 3.03 | 0.556 |
| After treatment | 23.33 ± 2.53 | 23.53 ± 3.48 | 23.43 ± 2.99 | 0.858 |

[a] Student *t* test (unpaired).


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