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Shadman Nemati, Fatemeh Yousefbeyk, Seyedeh Matin Ebrahimi, Ali Faghih Habibi, Maryam Shakiba, Hedieh Ramezani

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Effects of Chamomile Extract Nasal Drop on Chronic Rhinosinusitis Treatment: a Randomized Double Blind Study

Running Title: Effects of Chamomile Extract on Chronic Rhinosinusitis

Shadman Nemati\textsuperscript{a}, Fatemeh Yousefbeyk\textsuperscript{b}, Seyedeh Matin Ebrahimi\textsuperscript{c}, Ali Faghih Habibi\textsuperscript{*a}, Maryam Shakiba\textsuperscript{d}, Hedieh Ramezani\textsuperscript{c}

\textsuperscript{a}Otorhinolaryngology Research Center, Department of Otolaryngology and Head and Neck Surgery, Amiralmomenin Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran.
\textsuperscript{b}Department of pharmacognosy, school of pharmacy, Guilan University of Medical Sciences, Rasht, Iran.
\textsuperscript{c}Otorhinolaryngology Research Center, Amiralmomenin Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran.
\textsuperscript{d}Cardiovascular Diseases Research Center, Guilan University of Medical Sciences, Rasht, Iran.

* Corresponding author: Ali Faghih Habibi, MD, Associate Professor, Otorhinolaryngology Research Center, Department of Otolaryngology and Head and Neck Surgery, Amiralmomenin Hospital, 17 Shahrivar Ave, Rasht, Guilan, Iran.

Email1: dr.faghih.habibi@gmail.com \hspace{1cm} Email2: ent_rc@yahoo.com

Telephone number: +981333225242 \hspace{1cm} Postal code: 4139637459
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ABSTRACT

Objectives: Recently, more attention has been paid to herbal treatment in chronic rhinosinusitis (CRS) patients. Chamomile (Matricaria chamomilla) has extensive clinical uses in traditional-Persian medicine for its therapeutic properties. This study aimed to evaluate the effects of chamomile extract on the clinical symptoms of patients with CRS in a university hospital.

Materials and methods: In a randomized double-blind placebo-group clinical trial, 74 CRS patients were examined by an otolaryngologist blinded to the study groups, and the effects of treatment (according to SNOT-22 questionnaire) and possible complications recorded. Statistical analysis performed using SPSS software version 21, and level of significance considered as P<0.05.

Results: Of the 74 patients (31 females and 43 male), 37 cases randomized in the intervention and 37 cases in the placebo group. The Lund-Mackay score, clinical findings in endoscopic nasal examination and mean score of the SNOT-22 were not significantly different at baseline visit between the two study groups. The adjusted mean score of quality of life during the four time periods in the intervention group (34.3, confidence interval of 95%: 31.8-36.7) was significantly lower than that of control group (45.9, confidence interval of 95%: 43.5-48.4)  (P-value=0.001). Also, clinical improvement in endoscopic nasal examination was significant in intervention group compared with placebo group.

Conclusion: Chamomile extract is effective in further reducing the clinical symptoms and improving the quality of life of CRS patients.

Key Words: Chronic Rhinosinusitis, Chamomile, SNOT-22, Traditional Persian medicine.
1. Introduction

Chronic Rhinosinusitis (CRS) is one of the most common causes of patients’ referrals to physicians. It causes long-term discomfort for patients [1-3]. It is the fifth diagnostic disease for which antibiotics are prescribed [2]. In a study conducted in 2014 in the United States, the prevalence of the disease in North America was about 5-16 percent. In total, direct cost related to its treatment was estimated at $ 9.6 to $ 9.9 billion per year and its indirect cost was estimated at about $ 13 billion, drug cost was estimated at about $ 1500 to $ 2700 per person, and the total cost of the disease was estimated at $ 22 billion [4]. If left untreated, it can result in important complications such as bone abscess, abscess formation, sinus cellulitis and meningitis [5]. In cases of unsuccessful medical treatment or in some cases of rhinosinusitis complications, surgery is used, which requires a high cost and possibility of surgical complications. Due to the frequent recurrences and dissatisfaction of patients with conventional treatments, increasing attention has been paid recently to herbal remedies in CRS patients [5-6].

CRS means inflammation of the mucosa covering nose and paranasal sinuses around it that lasts for more than twelve weeks. Symptoms of CRS include 7 major symptoms and 7 minor symptoms. When more than two major symptoms or one major symptom and two minor symptoms are seen, CRS is diagnosed [7, 8]. Principles of medical treatment of CRS include the treatment of predisposing factors (allergic rhinitis, immunodeficiency, diabetes, nasal septal deviation, nasal septal spurs, anemia, and malnutrition), nasal washing with normal saline, intra-nasal corticosteroids, and oral antibiotics [8]. Because of complications and harmful effects of chemical drugs, return to herbal and natural drugs has been considered and new approaches have emerged in the past decades to study medicinal plants and examine their physiological, pharmacological and cytological effects. In this regard, chamomile (Matricaria chamomilla L.) has a special status, because of its therapeutic properties and extensive clinical uses. Its clinical advantages include anti-anxiety, anti-spasm, sedative, anti-allergic, anti-inflammatory, antibacterial, antifungal, antiviral and various other effects. The active chemical compounds of chamomile flowers include flavonoids, terpenoids, and coumarins. Based on previous studies, no significant side effects, other than allergic reactions to chamomile and its family, have been observed and only drug interferences with several drugs such as cyclosporine, aspirin, warfarin and heparin have been reported [9-13]. To the best of our knowledge, no study has been conducted on this issue so far, so we decided to investigate the effect of chamomile on the
clinical symptoms of patients with CRS based on the SNOT-22 questionnaire in a university-referral Hospital in north of Iran.

2. Materials and methods

In this randomized double blind clinical trial study with placebo control, 74 patients referred to Amiralmomenin University hospital in Rasht (a metropolitan city in north of Iran) were examined in 2017-2018. The proposal of the study was approved in Otorhinolaryngology Research Center and Research and Technology Deputy and the Ethics Committee of Guilan University of Medical Sciences with registration code number IRCT20080831001138N27. Patients with chronic rhinosinusitis (CRS) referred to the ENT clinic of Amiralmomenin hospital were selected based on diagnostic criteria [8]. Inclusion criteria of the study were age more than 18 years, having reading and writing skills, and having CRS based on diagnosis of ENT physician. Pregnant patients, people with a history of sinus and nasal surgery, people who have used corticosteroids continuously and daily in the last 3 weeks, and patients with acute exacerbation or complications of CRS who needed antibiotics, those who had an acute cold during the study, patients with severe nasal polyposis (grade 2 or 3) in endoscopic nasal exam, or a Lund-Mackay score more than 14 on the CT scan of the sinus, and those who did not follow the researcher's drug regimen during the study for seven consecutive days were excluded from the study. Also, people who have a history of allergies to chamomile or its compounds or have used drugs such as cyclosporine, aspirin, warfarin, and heparin (due to drug interferences) were not included into study [21-24]. At the beginning of the study, informed consent was obtained from all of the participants and they could withdraw from the study if they did not tolerate the drug, pregnancy or fever above 38.5 ºC occurred, and if they were not inclined to continue participating in the study.

After receiving explanations about the project and signing the informed consent, the patients were randomly allocated in two groups by the random block method, using a list of random numbers that were evenly divided into groups A and B by Random Allocation software, and each of them was included in a separate closed envelope. For each patient, one of the envelopes would be given according to the number, and after filling out the forms, he or she was treated and received the relevant drug. Patients and researchers were unaware of the type of drug they were receiving. Chamomile (Matricaria chamomilla L.) flower was prepared in May and June from the heights of Talesh mountains in Guilan province by botanical experts. It dried at 25°C
and in shady conditions. Then, the extract was prepared by maceration method. For extracting, after grinding, the dried plant was poured into special containers and kept in 300 g / liter of 70% ethanol for 48 hours. Finally, after filtering, 8 g of extract was obtained. After filtering, ethanol was removed from the solution by the evaporator rotary device. Spectrophotometry method was used for standardization of the extract. The extract was dissolved in normal saline and then poured into 10 cc drippers and kept away from light and in a cool environment all the time. For clinical uses, three drops of the drug were poured into each nostril for 3 times a day after washing the nose passage with normal saline solution for 3 weeks, and for the control group, each nostril was washed with normal saline and then 3 drops of sesame seed oil, as placebo, was administrated to each nostril for three times a day for three weeks. The correct way of using drug (first lie on the bed in an arched position and get close to the edge of the bed so that the head is hanging, and then pour three drops of the drug into each nostril from near the tip of the nose and stay in that position for three minutes and then get up) was taught to all patients. None of the patients took any other drug during these three weeks of study course.

To evaluate the disease and the effects of treatment, we used SNOT-22 standard questionnaire as a valid scale. SNOT-22, consisted of 22 questions. Each question is scored from zero to five and a score of zero means that the patient lacks that symptom and a score of five means that the symptom has appeared in its most severe form. In total, the score range of the questionnaire is from zero to 110. SNOT-22 answered by the patient is currently the simplest and most common standard questionnaire used for assessing CRS all around the world, and the Persian version of the questionnaire was first translated and validated by Jalessi M. et al in 2012 [8, 14-16]. One way to measure outcomes is to determine the threshold for a particular outcomes measure that represents the smallest change in a measure or domain of interest that patients perceive as beneficial, termed the minimal clinically important difference (MCID) [8]. For several CRS-specific QOL measures, the MCID has been directly evaluated, as with the SNOT-22, and the published approximate MCID for SNOT-22 totally is ≥8.9 [8].

All the subjects in the case and control group visited and underwent endoscopic nasal examination at the beginning and also, at the end of the study, but answering about SNOT-22 questionnaire and adverse drug reactions and irritations were repeated weekly during the study course. Demographic data, included the patients’ age and gender and history of smoking, SNOT-22 questionnaire data before and after treatment, and other data in medical history, CT and clinical/endoscopic examination were recorded for every subject. After beginning the treatment,
the first, second and third examinations of patients was performed at the end of the first, second, and the third weeks of treatment by an ENT specialist who was blinded to study groups and didn't know what kind of nasal drops received by the patients, and the effect and possible complications of treatment were recorded.

Statistical analyses performed using SPSS software version 21, and the graphs were plotted using Excel software. Data description was performed with indices of mean and standard deviation and absolute and relative frequency. The normality of quantitative data was measured by Kolmogorov Smirnov test. Baseline characteristics were compared using chi-square, T-test or Mann-Whitney U test as appropriate. The repeated measure analysis of covariance (RMANCOVA) was used to compare the mean changes in the quality of life scores between the two groups at different time periods. The level of significance was considered as P <0.05.

3. Results

Out of 149 patients with CRS who referred to the ENT clinic of Amiralmomenin Hospital, 62 had severe nasal polyposis, 4 did not meet age criteria and 7 used drugs that interfered the results of the study and a total of 76 cases were identified as eligible for this study (44 male and 32 female) and 38 of them were included in each study groups (the drug and placebo groups). During the study, two patients were excluded from the study, one from the drug group due to irritation after using the drug and one from the placebo group due to the use of other common drugs in the treatment of CRS, and a total of 74 subjects completed the study course. Figure 1 illustrates flow diagram of the study.

Baseline characteristics of the two study groups are illustrated in table 1. There was no significant difference in terms of age, sex, and history of medical conditions between the two groups. All of the subjects had CT scan of paranasal sinuses, and the mean of Lund-MacKay score in the treatment group was 8.6±5.0, and in the placebo group it was 8.4±4.8 (P=0.93). On endoscopic nasal examination at the start of study, 20 and 19 out of 38 subjects in case and control group, respectively, had no obvious nasal polyposis and only demonstrated mucosal inflammation and muco-purulent discharges (CRSsNP), and 18 and 19 cases had grade 1 nasal polyposis that was mild in severity and confined to the middle meatus of the lateral nasal wall (47% and 50% of cases and controls, respectively: P=0.96). Also, the mean score of quality of life (i.e. SNOT-22 questionnaire score) at the baseline was 49.54±10.90 and 50.7±9.12 in the case and control groups, respectively, (P= 0. 620) that was not significantly different (table 1).
As mentioned earlier, only one patient showed significant nasal irritation and left the study in the treatment group; and only 3 cases (8%) and 2 controls (5%) declared minimal irritation in their nose during the use of the nasal drops that was not so severe that would interfere continuing the treatment. SNOT-22 questionnaire score in each week of the study were decreased in the two groups, but especially in the treatment group, the changes were more significant and noticeable. It is important to be noticed that the control group did not reach to MCID, but the intervention group did reach to MCID even after 1 week of treatment (i.e. the difference in totally SNOT-22 scores at the beginning of study and 1, 2, and 3 weeks after the treatment were more than 8.90 in all the subjects in intervention group, except in one case who had SNOT-22 score of 52 at the beginning of study, and reached to the scores of 45 at the end of the first week, but reached to the score of 37 and 30 at the end of the second and the third weeks).

Endoscopic nasal examination at the end of the 3rd week revealed very mild inflammation/discharge in 9 cases (24%) and grade 1 polyposis in 8 patients (21.6%) from treatment group, while it showed inflammation/discharge in 17 subjects (45.9%) and grade 1 nasal polyposis in 18 cases (48.6%) from placebo group, both of changes in frequency of the findings were statistically significant.

According to table 1 contents, despite non-significant differences in baseline visit scores, at the end of the treatment and also in time periods (weekly visits), the clinical/ endoscopic examination findings, and also the quality of life scores in the intervention group were significantly better than those of the placebo group. Using RMANOVA analysis of variance, the trend of changes in mean scores of quality of life between the two groups was evaluated. The assumption of symmetric sphericity was not met, therefore the multivariate test were used to evaluate the trend of quality of life over time. The results of the relevant test showed that the trend of changes in the two groups was significant (P-value <0.001). Fig 2 shows the trend of changes in mean scores of quality of life at different time points in the two groups. Examination of marginal mean adjusted for age showed that the mean score of quality of life during the four time periods in the intervention group (34.3, confidence interval of 95%: 31.8-36.7) was significantly lower than that of control group (45.9, confidence interval of 95%: 43.5-48.4) (P-value=0.001).

In major symptoms of feeling of pain or pressure on the face (P = 0.00), feeling of congestion or fullness on the face (P = 0.00), nasal congestion (P = 0.00), presence of pus or discharge in the
nose (P = 0.00), there was a significant difference between days 7, 14, 21 in the two groups of intervention and control.

4. Discussion

Chronic rhinosinusitis (CRS) means inflammation of mucosa covering the paranasal sinuses that lasts for more than twelve weeks. The clinical symptoms of the disease vary and if left untreated, it can result in important complications such as bone abscess, orbital cellulitis and abscess, meningitis, and cavernous sinus thrombophlebitis [5]. CRS is not a serious threat to life per se, but it can cause serious problems and complications due to its proximity to the orbit and brain.

Principles of medical treatment of CRS include the treatment of predisposing factors (allergic rhinitis, immunodeficiency, diabetes, nasal septal deviation, nasal septal spurs, anemia, and malnutrition), nasal washing with normal saline, intra-nasal corticosteroids, and oral antibiotics [8]. In cases of unsuccessful medical treatment or in some cases of rhinosinusitis complications, surgery is used, which requires a high cost and possibility of surgical complications. Due to the frequent recurrences and dissatisfaction of patients with conventional treatments, increasing attention has been paid recently to herbal remedies in CRS patients [5-6].

It has been reported that chamomile contains Apigenin and Luteolin (similar role to indomethacin in reduction of leukocyte infiltration), a-Bisabolol (anti-inflammatory role), Chamazulene (anti-inflammatory and anti-fever role), Guaiazulene (anti-inflammatory and anti-fever role), Matricin (Anti-inflammatory role) [17-18]. Several studies have indicated that chamomile flowers are effective in treatment and alleviating symptoms of CRS [19-21].

In the present study, the difference between the mean of SNOT-22 questionnaire score in days zero and 21 in the placebo group decreased by 7 numbers, and this difference in the intervention group showed a decrease of 24 numbers, that is much more than MCID, and this indicate that the efficacy of the treatment is not only statistically, but also "clinically" significant. It is interesting to be noted that the intervention group did reach to MCID even after 1 week of treatment (i.e. the difference in totally SNOT-22 scores at the beginning of study and 1, 2, and 3 weeks after the treatment were more than 8.90 in all the subjects in intervention group, except in one case).

In a large study conducted on patients with CRS who underwent sinus surgery in the United Kingdom and Wales, the average test score preoperatively was 41.5 (group with nasal polyposis) and 44.4 (group without nasal polyposis). This decreased to 18.3 and 14.1, respectively, 3 months after surgery (P < 0.001) [22]. As stated, in our study this change shows a decrease of 24
scores in the intervention group and 7 in the placebo group, which is consistent with the above mentioned study. Also, the means of the intervention and control groups in the first visit at the beginning of the study were not significant and the means in the two groups on days 7, 14, and 21 were significant (P = 0.000), which this significant difference was remained after moderating the baseline conditions (P=0.000). This may indicate a positive effect of chamomile flower extract on patients' quality of life. The obtained results are consistent with those of the study conducted by Snidvongs et al [23]. The results are also consistent with those of other studies conducted to improve the quality of life measured with SNOT-22 [24-25].

Patients also reported an improvement in pain or pressure during intervention in the drug group, which was significant compared to the placebo group. One of the properties of chamomile flowers is its anti-inflammatory effects, and if one patient had pain or pressure due to inflammation of the nasal mucosa and sinuses, it would be stated that this property of chamomile extract would be effective in reducing the symptoms [17,18].

In a study conducted in 2018 on the effect of rhinosinusitis treatment with lavender and marjoram and its comparison with standard treatment, it was observed that in the group received herbal treatment, the reduction in SNOT score was 56% after 6 weeks of treatment. Clinically, the difference between the means of systemic symptoms such as confusion with 1.05 (p = 0.05) and fatigue with 1.63 (p = 0.01) in the herbal treatment group improved more and the difference between the means of local symptoms such as nasal congestion with 2.37 (p=0.78) and nasal discharge with 1.95 (p = 0.14) in the standard treatment group showed more decrease [26]. In the present study, the difference between the means of day zero and day 21 of the SNOT-22 scores in the placebo group decreased by 7 points and in the drug group showed a decrease of 24 points, indicating the significant effect of chamomile extract on the symptoms of CRS, comparable with other studies. Also, in major symptoms such as pain or pressure on the face (P = 0.00), feeling of congestion or fullness on the face (P = 0.00), nasal congestion (P = 0.00), the presence of pus or discharge in rhinoplasty (P = 0.00), a significant difference was found on days 7, 14 and 21 in two groups.

5. Conclusion
The results of our study showed that the use of chamomile extract significantly improved the symptoms of CRS and increased the quality of life of patients. The effects of chamomile extract may probably be due to its anti-inflammatory and antimicrobial properties. Since this study revealed meaningful clinical and quality-of-life improvements in the course of the treatment,
along with no any significant complications, it is recommended that complementary clinical and laboratory studies be conducted using this new drug solely or in combination with other common treatments to control the symptoms of the CRS. Also, as we excluded severe forms of CRSwNP (i.e. CRS with nasal polyposis), it is suggested including these spectrum of CRS patients in the future studies.

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**Compliance with ethical standards**

**Conflict of interest:** The authors declare that they have no conflict of interest.

**Ethical approval:** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Guilan University of Medical Sciences, IR.GUMS.REC.1396.513) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent:** All participants signed the written informed consent.

**References**


Fig. 1. CONSORT 2010 Flow Diagram of the study groups. From 149 Chronic Rhinosinusitis patients, 38 subjects allocated randomly in each study groups and 37 of cases and controls analyzed eventually.

Fig. 2. Trend of mean score in quality of life at different time points in the two study groups
Table 1. Baseline characteristics, endoscopic nasal examination findings at the baseline and at the end of study, and mean score of quality of life at the baseline, weekly surveys, and at the end of the study course in the Chamomile and placebo groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention (n=37)</th>
<th>control (n=37)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years [mean ± SD]</td>
<td>44.41±10.699</td>
<td>46.27±11.77</td>
<td>0.478</td>
</tr>
<tr>
<td>Women [n (%)]</td>
<td>16 (43.2)</td>
<td>15 (40.5)</td>
<td>0.814</td>
</tr>
<tr>
<td>Past medical history [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes [n (%)]</td>
<td>4 (10.8)</td>
<td>3 (8.1)</td>
<td>0.704</td>
</tr>
<tr>
<td>Hyperlipidemia [n (%)]</td>
<td>2 (5.4)</td>
<td>4 (10.8)</td>
<td></td>
</tr>
<tr>
<td>Hypertension [n (%)]</td>
<td>2 (5.4)</td>
<td>3 (8.1)</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>0 (0)</td>
<td>1 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Smoking, yes [n (%)]</td>
<td>7 (18.9)</td>
<td>9 (24.3)</td>
<td>0.778</td>
</tr>
<tr>
<td>Lund-Mackay score in CT scan</td>
<td>8.6±5.0</td>
<td>8.4±4.8</td>
<td>0.93</td>
</tr>
<tr>
<td>Frequency of grade 1 polyposis in endoscopic exam (baseline)</td>
<td>18 (47%)</td>
<td>19 (50%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Frequency of inflammation/discharge in endoscopy (baseline)</td>
<td>20 (52.6%)</td>
<td>19 (50%)</td>
<td>0.95</td>
</tr>
<tr>
<td>QOL* at baseline [mean ± SD]</td>
<td>49.54±10.90</td>
<td>50.7±9.12</td>
<td>0.620</td>
</tr>
<tr>
<td>QOL at week 1 [mean ± SD]</td>
<td>33.94±9.44</td>
<td>46.27±9.03</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>QOL at week 2 [mean ± SD]</td>
<td>27.89±6.17</td>
<td>43.67±7.33</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>QOL at week 3 [mean ± SD]</td>
<td>25.89±3.96</td>
<td>43.18±7.59</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Frequency of grade 1 polyposis in endoscopic exam (week 3)</td>
<td>8 (21.6%)</td>
<td>18 (48.6%)</td>
<td>0.046</td>
</tr>
<tr>
<td>Frequency of inflammation/discharge in endoscopy (week 3)</td>
<td>9 (24%)</td>
<td>17 (45.9%)</td>
<td>0.030</td>
</tr>
</tbody>
</table>

*Quality of life
Author Statement

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Shadman Nemati: Investigation- Conceptualization- Writing- Original draft preparation- Supervision -Writing - Review & Editing

Fatemeh Yousefbeyk: Investigation

Seyedeh Matin Ebrahimi: Investigation-Original draft preparation-

Ali Faghih Habibi: Investigation- Conceptualization- Project administration- Writing-

Original draft preparation-Writing - Review & Editing

Maryam Shakiba: Investigation - Formal analysis

Hedieh Ramezani: Investigation
Figure 1

Enrollment

Assessed for eligibility (n=149)

Excluded (n=73)
- Not meeting inclusion criteria (n=73)
- Declined to participate (n=0)
- Other reasons (n=0)

Randomized (n=76)

Allocation

Allocated to intervention (n=38)
- Received allocated intervention (n=37)
- Did not receive allocated intervention (due to irritation after using the drug) (n=1)

Allocated to placebo (n=38)
- Received allocated placebo (n=37)
- Did not receive allocated placebo (due to the use of other common drugs in the treatment of CRS) (n=1)

Follow-Up

Lost to follow-up (n=0)
Discontinued intervention (n=0)

Lost to follow-up (n=0)
Discontinued placebo (n=0)

Analysis

Analysed (n=37)
- Excluded from analysis (n=0)

Analysed (n=37)
- Excluded from analysis (n=0)