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Studying the effect of Scrophularia striata extract on the improvement of recurrent oral ulcers: A clinical trial study

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Abstract

Background and purpose

Recurrent aphthous lesions are one of the most common pathological ulcerative conditions in the oral mucosa. Various studies are seeking to find an appropriate treatment with few complications. This study aimed to investigate the effect of the extract of the medicinal plant Scrophularia striata in reducing pain and improving recurrent oral ulcers.

Materials and methods

In this clinical trial study, 100 patients with oral ulcers complaints referring to the dental clinic of Ilam University of Medical Sciences were investigated. Patients were randomly assigned to two intervention groups with 10% and 15% hydroalcoholic extract and two control groups with simple diphenhydramine syrup and normal saline serum. The rate of wound healing on days 1 and 3 was assessed by direct examination and observation, and the severity of pain and inflammation on days 1, 2, 3, and 5 was assessed by VAS criteria. Data analysis was performed using SPSS 24 software and statistical tests of mean, standard deviation, Kruskal-Wallis, and Wilcoxon were analyzed at a significance level of 0.05.

Results

The mean standard deviation of the participants' age was 28.15 ± 29 years, 3% smoked cigarettes, and 59% reported stress. 56% had a wound, and 31% had it on the lower lip. On the first day, the wound size did not differ significantly between the groups ($p = 0.266$), but on the third day, the mean rank difference in wound size between the groups increased significantly ($p < 0.001$); There was also no significant difference in the severity of inflammation on the first day ($p = 0.042$), but from the second day onwards, the differences increased significantly (second day $p < 0.001$, third day $p < 0.001$, and fifth day $p < 0.001$).

Conclusion

A solution prepared from the Scrophularia striata plant is effective in accelerating the healing process of recurrent oral ulcers and the severity of its inflammation. Given the favorable effects and low complication rate of a solution containing the extract of the Scrophularia striata plant, its use can be recommended to people with recurrent minor oral thrush.

1. Introduction

Recurrent aphthous stomatitis (RAS) is a recurrent inflammatory disease of the oral mucosa that presents as single or multiple painful ulcers in patients without systemic disease. These ulcers are one of the most common oral diseases, occurring in 20% of the world's population (1, 2) and, after traumatic

ulcers, are the most common cause of recurrent oral mucosal lesions (3). These lesions usually heal within 10–14 days without scarring (1, 3). Heredity, blood factors, and immunity are the three main factors in the occurrence of aphthous ulcers (4). In addition, various factors such as local trauma, smoking, viruses, stress, drugs, and allergies have been implicated in the development of RAS (5).

Although many drugs and treatments have been used to treat this disease, there is currently no definitive curative treatment for canker sores, and there are only a few drugs and treatments that have been clinically proven to improve RAS through clinical trials (6, 7). In fact, RAS treatment is mainly focused on relieving symptoms, with pain relief from canker sores being one of the main goals (8). Topical steroids, mouthwashes, antibiotics, local anesthetics, silver nitrate pens, cryotherapy, and lasers are some of the treatments used to reduce the pain of canker sores (9–12). In a clinical trial study conducted by Femiano et al. comparing systemic prednisolone and montelukast treatments in patients who had failed topical treatments, the results showed that the drugs had similar effects in patients, but due to fewer side effects, montelukast is recommended in patients (13).

In some studies, various medicinal plants have been used to reduce pain intensity and wound healing, including seed, licorice root, chamomile, rose, and purslane (14–16). Rad et al. compared the therapeutic effect of topical intraoral triamcinolone ointment and a topical herbal solution in the treatment of minor aphthous oral lesions, and the results showed that there was no significant difference in the response rate between the two groups (17).

Scrophularia striata, locally known as Scrophularia striata, is a perennial plant from the genus of the monkeywort that grows in Ilam province and parts of Khuzestan province (16). For many years, the people of Ilam province have been experimentally using this plant in various forms such as edible decoction, incense, and poultice to treat various diseases including eye and ear inflammation and infection, skin burns, infected wounds, episiotomy, pain and digestive disorders, colds, hemorrhoids, boils, etc. (18). Researchers have used the aqueous and alcoholic extracts of this plant in a few clinical trials. The alcoholic extract of Scrophularia striata does not contain antifungal compounds (Candida Albicans), but the aqueous extract of this plant at the highest concentration has a weak inhibitory effect, which is due to the presence of effective compounds in the plant (19). Abbasi et al. studied the effect of Scrophularia striata extract on Staphylococcus aureus and Pseudomonas aspergillus bacteria in a laboratory environment and found that its antibacterial effect is equivalent to Betadine (20). In another study, it was found that the use of the herb Scrophularia striata was 10% more effective in healing skin wounds in rabbits compared to other groups that received treatments with phenytoin and esrin (21).

Considering the recurrent nature of oral ulcers, their painful nature, and the use of multiple methods for pain relief that are often costly, ineffective, and have drug side effects, and in order to achieve a more effective treatment method, the present clinical trial study investigated the effect of the herb Scrophularia striata extract in reducing the pain of oral ulcers.

2. Materials and Methods

2.1. Study Design

In this triple-blind clinical trial study, the study population was selected from among patients with RAS referred to the Department of Oral and Dental Diseases, Faculty of Dentistry, Ilam University of Medical Sciences.

2.2. Setting and Participants

The study population was selected from among patients with RAS referred to the Department of Oral and Dental Diseases, Faculty of Dentistry, Ilam University of Medical Sciences. Selected patients over 10 years of age, after conducting complete clinical examinations and taking a detailed medical history and confirming the diagnosis of minor RAS, were accepted into the study sample if no more than three days had passed since their RAS appeared, they had not used any other treatment method for RAS before the visit, at the time of the visit the intensity of their RAS pain and burning had not decreased compared to the first few days, and they had consented to participate in the study.

2.3. Randomization and allocation concealment

The study was conducted in a triple-blind manner using a continuous sampling method, and the selected patients were randomly assigned to one of the intervention groups of 10% or 15% of the extract of the Scrophularia striata, the control group with the administration of diphenhydramine syrup, or the control group with the administration of physiological saline based on the inclusion criteria. The following measures were taken to blind the patients: the bottles containing the solution were only marked with control and intervention labels, and the selection of the solution for the participants was random; the researcher and the participants were unaware of the contents of the bottles; and the data analysis was completely blind.

2.4. Sample Size calculation

Where p_1 and p_2 denote the initial estimates of the proportion of complete recovery in the intervention and control groups, respectively, and $\mathrm{p}^{\prime}$ represents their average. The values $\mathrm{Z}_{1-\beta}$ and $\mathrm{Z}_{\alpha\ /2}$ correspond to the desired statistical power (1 − β) and the two-sided type I error rate (α), respectively. In this study, a design effect of 20% was applied to account for potential variability between groups and to ensure the ability to detect small yet clinically meaningful differences in outcomes. This assumption reflects a conservative approach, whereby even modest differences between the intervention and control groups could be identified. The statistical power was set at 80% (yielding $\mathrm{Z}_{1-\beta}\ = 0.84$), and the type I error rate was fixed at 5% ($\mathrm{Z}_{\alpha\ /2}\ = 1.96$). Based on these parameters and considering a four-group parallel study design, the required sample size was calculated as 25 participants per group (Fig. 1). Consequently, a total of 100 participants were deemed sufficient to achieve the study objectives.

2.5. Data Collection Tools and Techniques

The data collection method was based on direct observation and examination and questioning the patient. After explaining the purpose of the study, the written consent form for participation in the study

and demographic and health characteristics, including age, sex, education, occupation, marital status, medical history, and stress, were completed.

2.5.1. Wound Characteristics Questionnaire

The wound characteristics questionnaire, including the number, size, and location of wounds after the examination, was recorded by the examiner by measuring the wound using a periodontal probe in millimeters.

2.5.2. Pain and Burning Assessment Tool

The pain or burning sensation was also measured using the VAS scale (22), with zero indicating absolute painlessness and 10 indicating unbearable pain.

2.6. Intervention

Each participant was given a bottle containing 100 cc of solution, coded I1, I2, C1, C2, and the examiner and patient were unaware of its contents. The contents of these bottles in each group were:

1. I1 containing 15% solution of hydroalcoholic extract of the Scrophularia striata plant
2. I2 containing 10% solution of hydroalcoholic extract of the Scrophularia striata plant
3. C1 containing normal saline serum
4. C2 containing diphenhydramine syrup

The patients were instructed to gargle the desired solution three times a day, 15–30 minutes before meals and 2–3 times before bedtime, and to hold the solution in the mouth for 30–60 seconds each time, so that the solution came into contact with the surface of the lesion and its surroundings. The size of the wound and the healing time using a periodontal probe were recorded in the first session and on the third day, and the amount of pain or burning was recorded using the VAS (22) scale in the first session and on days 2, 3, and 5. Also, if one of the following conditions occurred, the patient was excluded from the study:

1. Simultaneous use of another drug for the treatment of aphtha
2. Failure to use the drug as recommended according to the patient's own statement
3. Failure of the patient to return for a repeat examination

The necessary instructions on how to use the drug, hygiene tips, number and date of care days were provided to the individual in the form of a brochure, and the address and contact number of the research units were recorded, as well as the researcher's contact number so that they could be contacted in case of questions or any problems during the use of the drug. In the case of children, the necessary instructions were given to the parents accompanying the child in addition to the child.

2.7. Statistical Analysis

Data were analyzed using SPSS version 24. Descriptive statistics (mean, standard deviation, frequency, and percentage) were used to describe baseline characteristics. Group comparisons for demographic

variables were performed using one-way ANOVA for age and the chi-square test for categorical variables. Due to the non-normal distribution of clinical outcomes, the Kruskal–Wallis test was used to compare wound size and inflammation severity among groups at different time points. Pairwise group comparisons were conducted using the Wilcoxon rank-sum test. All tests were two-tailed, and a p-value < 0.05 was considered statistically significant (Fig. 1).

3. Results

In this study, 100 patients were equally divided into four groups (two control groups and two intervention groups). The mean age of the participants was 28.15 years (standard deviation 8.29, range 10 to 50 years). In terms of gender, 40% were male and 60% were female. Most of the people were unemployed (72%) and the predominant level of education was a bachelor's degree (62%). Only 3% of the people smoked cigarettes and 59% of the patients reported the presence of stress. Also, in terms of the number and location of the wounds, 56% had one wound and 31% had it on the lower lip.

Examination of the distribution of basic variables showed that some variables had significant differences between the groups. Education level ($p = 0.004$), employment status ($p = 0.009$), location of the lesion ($p = 0.012$) and the presence of stress ($p = 0.039$) were significantly different between the groups. In contrast, gender distribution ($p = 0.506$) and smoking history did not differ significantly.

According to the results of Table 1, the mean age of participants in all groups was almost the same and no significant difference was observed in terms of age between groups ($p = 0.059$). This indicates that the age distribution in the four studied groups was homogeneous and the age variable could not have an interfering role. In terms of gender, the distribution of women and men in the groups was also similar ($p = 0.506$), so gender is not considered a confounding variable. However, some demographic variables showed significant differences between the groups. The level of education between the groups was significantly different ($p = 0.004$), such that the percentage of people with university education in the control groups was higher than in the intervention groups. On the other hand, employment status also showed a statistically significant difference ($p = 0.009$), such that the proportion of unemployed people in the intervention groups was higher than in the control groups. Also, the presence of stress was more common in the intervention groups ($p = 0.039$), which could contribute to the occurrence or exacerbation of clinical symptoms. Overall, the results in Table 1 show that the groups were similar in terms of most demographic characteristics and there were only differences in some background indicators such as education, employment status, and stress. These differences were considered as potential background variables in the final analysis to reduce their impact on the intervention results.

Table 1
Demographic characteristics of participants in the study groups

Variable	Total sample (n = 100)	Control 1 (n = 25)	Control 2 (n = 25)	Intervention 1 (n = 25)	Intervention 2 (n = 25)	p-value
Age (mean ± SD)	28.15 ± 8.29	27.9 ± 8.4	28.2 ± 7.8	28.6 ± 8.1	28.0 ± 8.7	0.059[1]
Gender (Female/Male)	60/40	14/11	18/7	13/12	15/10	0.506[2]
Educational level (≤ Diploma / ≥ Bachelor's degree)	27/73	7/18	2/23	8/17	10/15	0.004[2]
Employment status (Employed/Unemployed)	28/72	12/13	2/23	9/16	5/20	0.009[2]
Stress (Yes/No)	59/41	11/14	12/13	20/5	16/9	0.039[2]

The results of Table 2 show the changes in wound size and inflammation severity in the four study groups. At the beginning of the study (day 1), wound size did not differ significantly between the groups ($p = 0.266$), indicating that the initial condition of the patients was equivalent. However, on the third day, the mean rank difference in wound size between the groups increased significantly ($p < 0.001$); so that the intervention groups (especially the second intervention/10% extract) had a significant reduction in wound size compared to the control groups. This pattern indicates the positive effect of the intervention on the healing process of the lesion. A similar trend was observed regarding the severity of inflammation. On the first day, there was no significant difference between the groups ($p = 0.042$) at the border of significance, but from the second day onwards, the differences increased significantly (day 2 $p < 0.001$, day 3 $p < 0.001$ and day 5 $p < 0.001$). The severity of inflammation in the intervention groups decreased significantly, especially on the third and fifth days, while in the control groups the decrease was slower and more limited. Overall, Kruskal–Wallis analyses confirm that there is a significant difference between the intervention and control groups in terms of clinical indicators and that these differences are in favor of improving the treatment results in favor of the intervention groups.

Table 2
Comparison of clinical variables among groups using the Kruskal–Wallis test

Clinical variable	Control 1 (Mean rank)	Control 2 (Mean rank)	Intervention 1 (Mean rank)	Intervention 2 (Mean rank)	p-value
Wound size on day 1	59.24	46.56	50.74	45.46	0.266
Wound size on day 3	78.86	66.94	35.06	21.14	< 0.001
Inflammation severity on day 1	46.08	57.80	58.80	39.32	0.042
Inflammation severity on day 2	62.20	66.80	48.88	24.12	< 0.001
Inflammation severity on day 3	72.82	62.72	43.50	22.96	< 0.001
Inflammation severity on day 5	76.44	67.06	37.50	21.00	< 0.001

The results of the Wilcoxon paired comparison test showed that the reduction in inflammation severity in both intervention groups was significantly greater than in both control groups ($p < 0.001$). This finding indicates that the intervention had an effective therapeutic effect in accelerating the process of reducing inflammation at both levels used. A significant difference was also observed between the two control groups ($p < 0.001$), so that control group 1 showed the lowest improvement. In contrast, the comparison between the two intervention groups showed that the difference between them in terms of the reduction in inflammation was not significant ($p = 0.992$), meaning that although the average rank of intervention group 2 was slightly better, this difference did not reach a significant level. Therefore, it can be concluded that the nature of the intervention created the main effect and the difference in the dose/level of intervention did not have a significant additional effect and both performed better than the control groups (Table 3).

Table 3
Pairwise comparison of the reduction in inflammation severity between groups based on the Wilcoxon test

Group comparison	N per group	Mean rank	U	p-value
Control 1 vs. Control 2	25 / 25	33.92 vs. 17.08	102.000	< 0.001
Control 1 vs. Intervention 1	25 / 25	35.30 vs. 15.70	67.500	< 0.001
Control 1 vs. Intervention 2	25 / 25	36.36 vs. 14.64	41.000	< 0.001
Control 2 vs. Intervention 1	25 / 25	32.88 vs. 18.12	128.000	< 0.001
Control 2 vs. Intervention 2	25 / 25	36.54 vs. 14.46	36.500	< 0.001
Intervention 1 vs. Intervention 2	25 / 25	25.48 vs. 25.52	312.000	0.992

4. Discussion

In this triple-blind clinical trial, 100 patients were divided into two intervention groups with 10% and 15% extracts of the Scrophularia striata plant and two control groups receiving simple hydramine syrup and normal saline. The aphthous ulcers were examined for size on the first and third days and for the severity of inflammation and pain on the first, second, third and fifth days.

According to the results, the size of the ulcer had decreased on the third day. However, in the intervention groups that received the Scrophularia striata plant extract (especially the 10% extract group), there was a significant reduction in the size of the ulcer compared to the control groups. This pattern indicates the positive effect of the intervention on the healing process of the lesion. Several studies have investigated the effects of various drugs and treatment methods on wound healing and reducing inflammation of recurrent oral ulcers, and different results have been obtained. The results of the study by Rad et al. (17) showed that the solution of the plant in question is better than topical intraoral triamciolone ointment in the treatment of minor oral aphthae. Khatibi et al. (15) stated that the use of two drugs, rose extract and diphenhydramine, can have similar therapeutic effects on aphthous lesions of the oral mucosa, and considering the greater benefits of rose extract and its low complication rate, the use of this drug is recommended for the improvement of aphthous lesions of the oral mucosa. The results of the study by Najafi et al. (14) on the effectiveness of purslane in the treatment of recurrent aphthous stomatitis show that the drug in question was superior to common drugs in terms of both patient tolerance and ease of use, as well as the absence of side effects and a significant effect on the improvement of lesions. Also, in examining the effect of laser irradiation duration at the same dose in the treatment of recurrent oral aphthae, Aghakhani et al. (23) showed that lower power and longer irradiation time of the 660 nm diode laser are effective for the treatment of oral aphthous ulcers.

Although there is no similar study on the effect of the extract of the Scrophularia striata plant on oral ulcers, the extract of this plant has been used in other studies. Sharifi et al. (24) concluded in their study of the effect of the Scrophularia striata plant on the healing of episiotomy wounds in primiparous women

that this plant can be used as an accelerator of episiotomy wound healing. The extract of this plant has also been used in animal studies. Azhdari Zarmehri et al. (25) studied the effect of hydroalcoholic extract of Scrophularia striata on burn wound healing in rats and reported that hydroalcoholic extract of Scrophularia striata at doses of 2.5% and 5% was effective in wound healing. However, the 5% dose was more effective. Alimohammadi et al. (26) also studied the effect of hydroalcoholic extract of Scrophularia striata on pain reduction using the hot plate test in mice and showed that the extract of Scrophularia striata caused a weak analgesic effect in the hot plate test as a model for assessing acute pain and claimed that the hydroalcoholic extract of Scrophularia striata has analgesic properties and can be a suitable alternative to chemical analgesic drugs. Shohani et al. (27) also investigated the healing effect of hydroalcoholic extract of the plant Scrophularia striata on open skin wounds in rabbits and reported that 10% Scrophularia striata ointment was effective in healing skin wounds in rabbits.

The results of this study showed a similar trend in the severity of inflammation as wound healing. On the first day, there was no significant difference between the groups, but from the second day onwards, the differences increased significantly and the severity of inflammation in the intervention groups decreased significantly, especially on the third and fifth days, while in the control groups the decrease was slower and more limited. These findings indicate that the research intervention had an effective effect on reducing the severity of inflammation and reducing the size of the wound. The progressive decrease in clinical indicators during the follow-up days confirms that the improvement in the intervention groups was not only faster but also more stable than in the control groups.

In addition, the degree of reduction in the severity of inflammation in both intervention groups was significantly greater than in both control groups. The intervention at both levels used had an effective therapeutic effect in accelerating the process of reducing inflammation, so it can be concluded that the nature of the intervention created the main effect and the difference in dose/level of intervention did not have a significant additional effect and both performed better than the control groups. In the control groups, control group 1 (normal saline solution) showed the least improvement. A study by Ardeshiri Lagimi (2009) showed that the extract of the Scrophularia striata plant has a stimulating effect on the growth of human fibroblast cells and the extract of this plant at different concentrations has different effects in the field of healing (28). One way to facilitate wound healing is to use fibroblast growth stimulants (29). For this reason, the extract of the Scrophularia striata plant, by inducing the growth of fibroblast cells, causes positive changes in order to accelerate the process of wound contraction and wound healing. A study by Shohani et al. (2010) also showed that the effective components of the Scrophularia striata plant stimulate collagen production and faster wound contraction and reduce wound inflammation (27). Also, in a study by Sharafati-Chaleshtori (2014), it was reported that the Scrophularia striata y plant has significant antibacterial properties (30). A study by Stevenson et al. (2002) in London showed that the compounds present in the ripe seeds of the Scrophularia striata plant are the reason for wound healing (31). In a study by Jafary et al. (2013), it was shown that among the three types of extracts extracted from this plant, the hydroalcoholic extract has the best result in healing open wounds on the skin of mice (32).

Although the results of various studies with different drugs show the effect of different extracts and other methods in wound healing, the present study is the first study on the effect of the Scrophularia striata plant extract on wound healing and the severity of inflammation and pain of recurrent oral ulcers, and there is no similar study for comparison in a human sample, and this study can be used as a baseline study for other studies.

The Scrophularia striata plant contains active antioxidant and antibacterial compounds that are effective in wound healing (32), and studies have shown its positive effect on two strains of Staphylococcus aureus and Pseudomonas aeruginosa (33, 34). The combination of these extraordinary therapeutic properties has made this plant have a very high capacity for treating inflammation and wound healing.

4.1. Limitations and Strengths

One of the strengths of the present study is that it is the first human study conducted in Iran and the world on the effect of plant extract on wound healing and inflammation of recurrent oral ulcers. Also, considering the positive anti-inflammatory effects and acceleration of wound healing, this extract can replace existing chemical drugs, which is another advantage of this study. Among the limitations of the present study is the inability to control individual differences in terms of wound healing power, nutritional status, and health level of the subjects, which can be effective in wound healing. However, an attempt was made to control these issues to some extent by randomly selecting participants and randomly assigning them and using the same training in using the solutions.

5. Conclusion

The changes in wound size and inflammation severity in the four study groups indicated the effect of the intervention on wound healing and reduced inflammation severity. The intervention groups (especially the 10% extract) had a significant reduction in wound size compared to the control groups. This pattern indicates the positive effect of the intervention on the healing process of the lesion. A similar trend was observed regarding the severity of inflammation. The severity of inflammation in the intervention groups decreased significantly, especially on the third and fifth days, while in the control groups the decrease was slower and more limited. It can be concluded that the solution prepared from the Scrophularia striata y plant is effective in accelerating the healing process of recurrent oral ulcers and the severity of its inflammation. Given the favorable effects and low complication rate of the solution containing the Scrophularia striata y plant extract, its use can be recommended to people with minor recurrent oral ulcers. However, further clinical trials are recommended, considering the limitations of this study.

Declarations

Ethics approval and consent to participate

Reassurances were made in terms of medical ethics regarding the preservation of information and results, the voluntary nature of participation in the study, and that no names of the individuals would be

given. written informed consent from all participants according to the Declaration of Helsinki's announcement, and interventional human principles. The ethics code number IR.MEDILAM.REC.1397.159 was obtained from the Academic Committee on Ethics in Biomedical Research of Ilam University of Medical Sciences. The research project was also registered with the Iranian Clinical Trials Center with the code IRCT20180327039152N1 at 2018-04-28.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed during the current study are available upon reasonable request from the corresponding author.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

Conceptualization, Methodology, writing– Original Draft Preparation: M.S.H., N.A., M.A.R., M.R., Validation, Supervision, Visualization: M.S.H., A.V., Formal Analysis, Data Curation, Software: M.S., N.G.H., Investigation, Writing– Review & Editing, Resources, Project Administration: M.S.H., M.R., A.V. All authors read and approved the final manuscript.

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Author statement

Authorsdeclare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors. We understand that the Corresponding Author is the sole contact for the Editorial process. She is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

Declaration on the use of AI

The authors of the article state that they did not use any artificial intelligence tools in the process of writing and revising the article.

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Figures

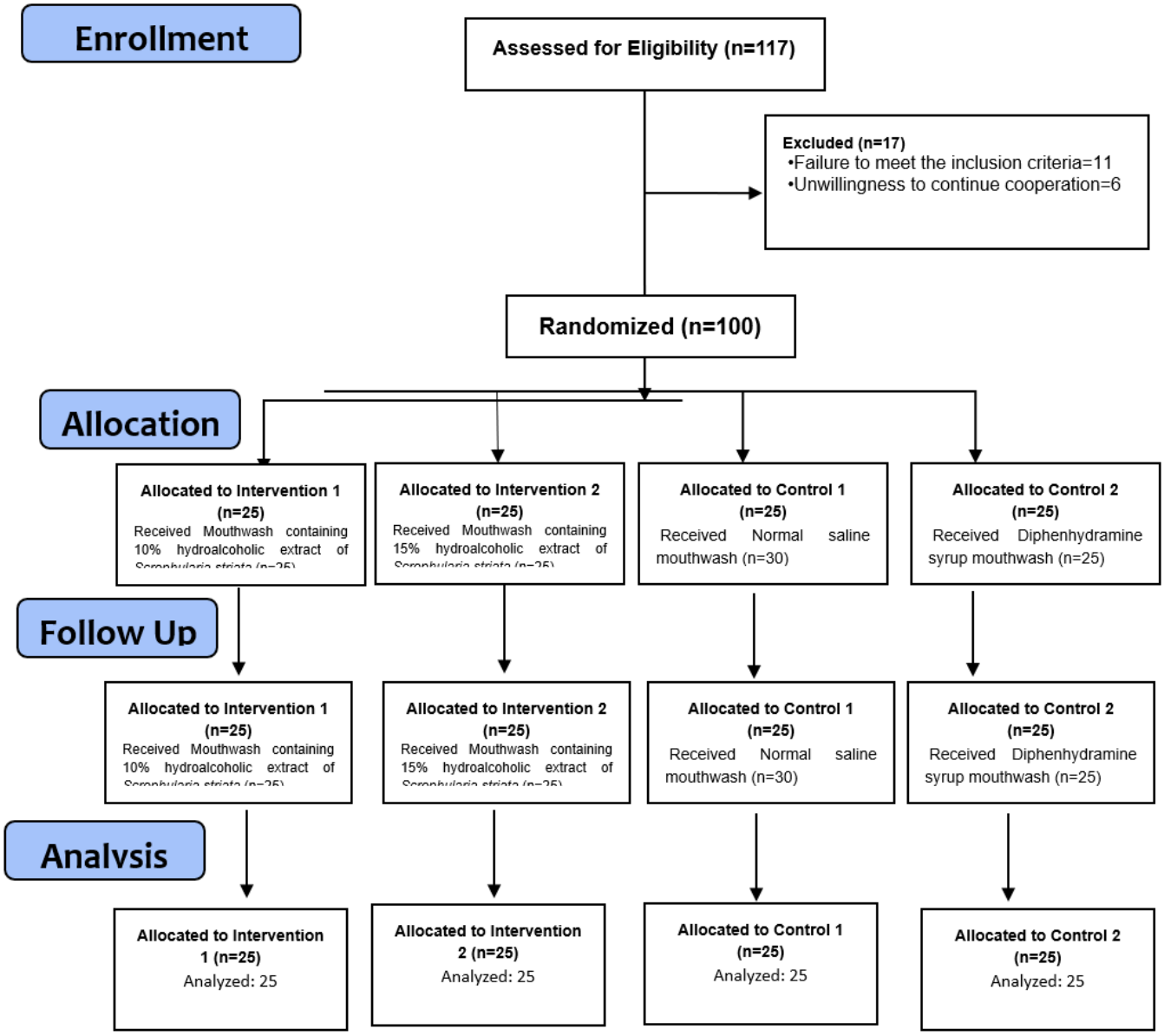


Figure 1

Participant flow in patients with Recurrent aphthous stomatitis