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*Research article*

# Respule or metered-dose inhaler for eosinophilic esophagitis treatment? A dose-ranging, randomized clinical trial study on efficacy, safety, and relapse rate

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**Abstract:** Background: Eosinophilic esophagitis (EoE) is a chronic allergen/immune-mediated disease known by eosinophil infiltration into the esophagus. Topical steroids are used for its treatment. We investigated the efficacy, side effects, and symptom relapse after discontinuation of two budesonide forms in EoE patients. Methods: In this prospective, dose-ranging, randomized trial, 35 EoE patients under 18 years who received two budesonide forms were assigned to low-dose oral respule (17 patients) and swallowed metered-dose inhaler (MDI) (18 patients) groups. Both groups received low-dose budesonide for eight weeks. Doses were doubled after the first eight weeks if symptom remission was not achieved, but the previous dose was continued for the next eight weeks for the subjects with symptom relief. At the end of week 16, budesonide was discontinued in all patients. The following

outcomes were assessed: The primary outcome was symptom relief, assessed by Pediatric EoE Symptom Scores (PEESS®v2.0). Secondary outcomes included safety, side effects, and histological changes, based on repeated endoscopy at weeks 0, 8, 16, and 32. Results: Non-response to low-dose treatment in the first eight weeks was observed in 2 cases (13.3%, 95% CI: 2.6%–35.2%) in the respule group and 7 cases (50.0%, 95% CI: 22.7%–77.3%) in the MDI group, indicating a significant difference between the groups ($p = 0.033$). In the $16^{th}$ week, the treatment failure rate was 13.3% and 26.6% in the oral respule and swallowed MDI groups, respectively ($p = 0.048$). The therapeutic response during the $8^{th}$ week was significantly higher in oral respule group than swallowed MDI group (OR = 8.418, $p = 0.046$). Conclusion: This study indicates that the oral respule formulation of budesonide is more effective than the swallowed MDI in alleviating symptoms of eosinophilic esophagitis (EoE) in children. The oral respule not only resulted in a higher rate of symptom relief but also exhibited a better safety profile, with fewer incidents of oral thrush and adrenal suppression.

**Keywords:** Eosinophilic esophagitis; EoE treatment; budesonide oral respule; swallowed topical corticosteroids

## 1. Introduction

Eosinophilic esophagitis (EoE) is a chronic allergen/immune-mediated disease known by abnormal infiltration of eosinophils into the esophagus and their activation, leading to esophageal dysfunction. The EoE can develop in early childhood and its clinical manifestation may be different in children, adolescents, and adults [1–3]. Diagnostic delay is common due to similarity between EoE and gastroesophageal reflux, which may lead to progressive esophageal fibrosis, strictures, and narrowing [4,5]. The incidence and prevalence of EoE are rapidly increasing; however, the exact prevalence is unknown [6]. Therefore, it is valuable to study the risk factors affecting the clinical manifestations of the disease to provide more appropriate and targeted approaches for the management or treatment of the disease. Evidence suggests that EoE is associated with Th2 cytokines seen in allergic patients [7–10]. Uncertainty about the nature of the disease and the lack of long-term clinical studies have led to indefinite treatment for this disease. The current therapies try to prevent the progression of the disease with anti-inflammatory drugs, among which steroids play an important role. However, the progression of the disease may lead to fibrosis and narrowing of the esophagus in a group of patients, leaving no choice except for performing mechanical dilation. To the best of our knowledge, long-term treatment is needed due to chronic nature of EoE [11]. In this regard, the type of drug should be chosen in a way that not only does not lead to side effects in children but also does not lead to problems in their development and maturity. General nutritional and pharmacological treatments for EoE include dietary changes, proton pump inhibitors, and topical administration of corticosteroids to reduce esophageal inflammation [12]. Systemic corticosteroids can improve the acute inflammation seen in EoE, but systemic use of corticosteroids may lead to side effects some of which are comprised of osteoporosis, infection, adrenal insufficiency, vascular necrosis, and growth problems [13,14]. Topical corticosteroids are widely used for the treatment of EoE. Along with the elemental diet, which most of the studies confirmed its effect, the following drugs were studied, although the results about the effectiveness of these drugs have had contradictory and even disappointing results [15,16]. Inhaled budesonide is available in two forms, metered-dose inhaler (MDI) and respule. They are used as an

anti-inflammatory agent in the maintenance treatment of asthma [17]. Recently, several studies have shown the efficacy of oral respule and swallowed forms of this drug in improving EoE [12]. We chose these two formulations due to their differing delivery mechanisms; oral respule provides direct esophageal coating, while swallowed MDI offers localized action, which may result in varying efficacy and side effect profiles. Despite the use of budesonide in various forms for EoE treatment, there is a lack of direct comparison of oral respule and swallowed MDI formulations in pediatric patients, creating a gap in evidence-based treatment guidelines. In this study, the efficacy, safety, side effects (local and systemic), and symptom relapse after discontinuation of oral respule form of budesonide were compared with the swallowed MDI form of budesonide in EoE patients.

## 2. Materials and methods

### *2.1. Patient selection*

This study was a prospective, dose-ranging, randomized clinical trial study conducted on children under 18 years with confirmed EoE based on AGREE criteria [18]. Randomization was performed using a random number table with allocation concealment ensured by sealed, opaque envelopes. Children with a history of cardiovascular disease, moderate to severe asthma, uncontrolled allergic rhinitis, and other congenital or genetic defects were excluded from this study. A history of systemic corticosteroid usage in the last two weeks or during the study and incomplete adherence to the study protocol were also considered exclusion criteria. Adherence was monitored through patient diaries, monthly in-person check-ins, and weekly phone calls to ensure correct use of the treatment.

### *2.2. Study protocol*

Before starting the study, a questionnaire was prepared in which demographic information about the patients was recorded. Many of our patients had asthma and allergic rhinitis. Individuals with moderate to severe were excluded and only mild asthma or allergic rhinitis were enrolled. Considering that some of the participants in the study suffered from allergic rhinitis or asthma, and to avoid the possible confounding effects of nasal corticosteroid spray (INS) or inhaled corticosteroid spray (ICS), these subjects were treated with oral antihistamine as an alternative treatment to INS and Montelukast instead of ICS, and to avoid the confounding effects of these two drugs, along with the use of PPI and diet, it was applied to all participants so that the only difference between the two groups was only the type and dose of local budesonide.

Although we are almost certain that food allergy plays a prominent role in this disease, studies on how to find food allergens are directed in two different ways: Experimentally or test-guided; however, studies provided different results [19–21]. In this study, food elimination was done based on the skin prick test, prick-to-prick, and atopic patch test results [22]. After selecting patients based on inclusion and exclusion criteria, basic results related to endoscopy, histology, and eosinophil counts, as well as routine hematological and biochemical laboratory results, and a PEESS®v2.0 questionnaire, were assessed in all subjects. Then, patients were randomly divided into two groups receiving oral respule form of budesonide (Pulmicort respule, Astra Zeneca) or budesonide inhaled MDI (Budecort 200 µg, CIPLA) using a random number table. The initial dose was adjusted based on the patient's weight and classified as low and high doses. All patients started with a low dose, based on their weight for the first

eight weeks. Individuals with good responses continued the low dose but the dose was doubled in the non-responders (high dose) for the next eight weeks. Patients in the oral respule group weighing less than 30 kg received a dose of 0.5 mg/day as a low dose and patients weighing more than 30 kg received a dose of 1 mg of drug daily (low dose) for eight weeks. If the efficacy of the drug is not observed after eight weeks, doses were changed to 1 and 2 mg, respectively (high dose). Respule should be consumed in its pure form without combining it with another substance, and for half an hour after that, they were not allowed to eat or drink food. Patients in the MDI group received one puff daily (as a low dose) or twice daily (as a high dose). Budesonide spray without a container was put inside the mouth and swallowed, and the patients were asked to wash their mouths with water after that. Patients underwent follow-up during weeks 8, 16, and 32 of the intervention. Anti-leukotriene, antihistamine (H1-blocker), PPI, and food elimination were continued during 32 weeks, but local steroid (MDI or respule) was discontinued after 16 weeks. During the follow-up period, disease response to treatment was monitored by asking about vomiting, abdominal pain, appetite, nausea, and any symptoms using Symptom relief based on Pediatric EoE Symptom Scores (PEESS®v2.0) and any possible side effects of the drug (MDI and respule) such as nausea, diarrhea, headache, allergies and vomiting, and oral complications like thrush and tongue burning were recorded. At the beginning of the study and after week 16, patients in both groups were referred to the center again for endoscopy and were examined for histological histology as well as eosinophil counts. Serum cortisol levels at 8 AM were measured as a predictor of adrenal suppression at the beginning of 8, 16, and 32 weeks. The flow diagram of the study is illustrated in Figure 1. After explaining the research and its objectives to the participants, written informed consent was obtained from all patients to participate in the study. All patients were regularly monitored by phone (weekly) and in-person visits (monthly) and were evaluated on how to take the medicine and adhere to the prescribed diet and medication. Moreover, a 24-hour phone number for emergencies was provided. Patients were also assured that all their information was kept confidential and that their names and addresses would never be unraveled. Also, this study was approved by the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.FMD.REC.1398.371) and registered at IRCT (IRCTID: IRCT20191211045703N1).

### *2.3. Statistical analysis*

Quantitative data were reported as Mean ± standard deviation (SD). Qualitative data were reported as numbers and percentages. Comparison of the mean of parametric data between the two groups was done using an independent sample T-test; otherwise, a non-parametric Mann-Whitney U test was employed. The categorical variables were compared using the Chi-square test. Comparison of the change in quantitative parameters after treatment was also performed using a paired T-test or Wilcoxon test. The effect of independent variables on the dependent variable as the endpoint was also investigated using multivariable logistic or linear regression modeling. For the statistical analysis, the statistical software IBM SPSS Statistics for Windows version 22.0 (IBM Corp. Released 2013, Armonk, New York) was used. P-values $< 0.05$ were considered statistically significant.

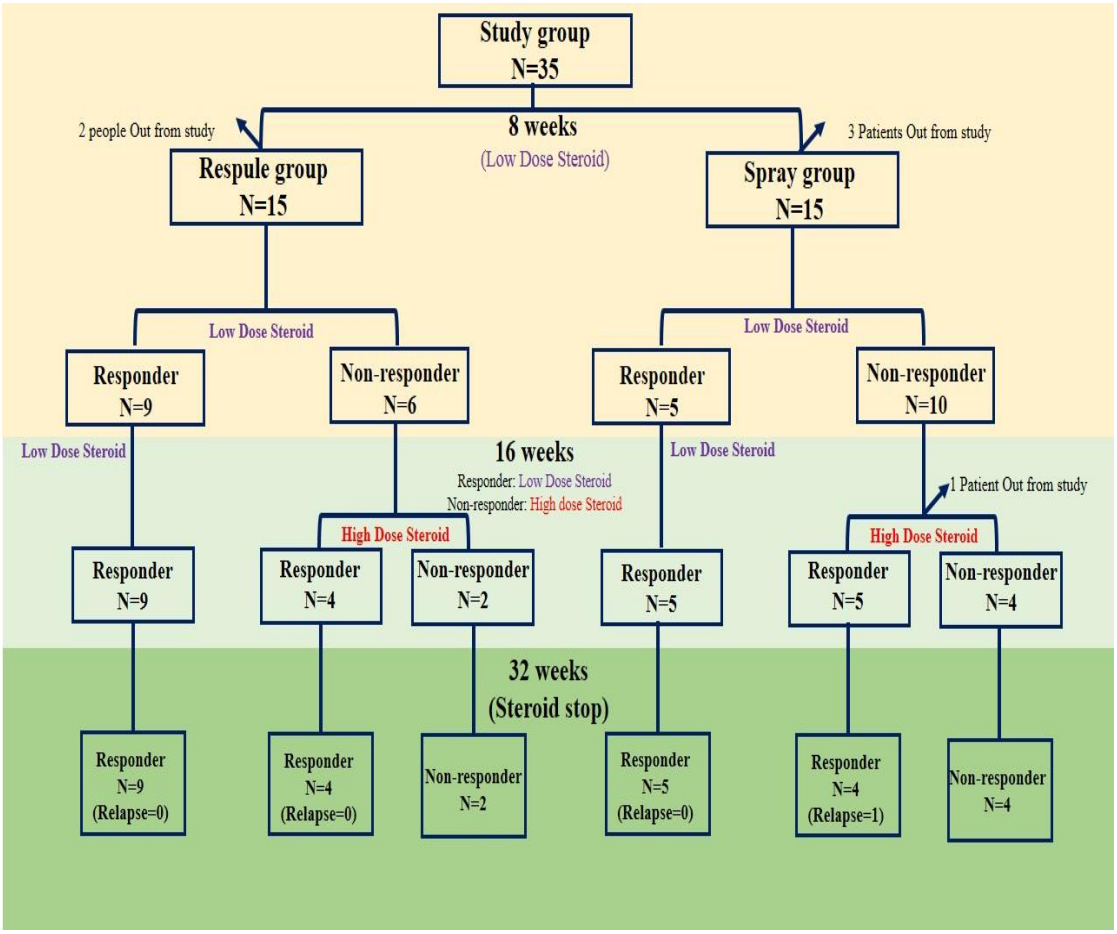


**Figure 1.** Flow diagram of the respule and MDI groups and the results of treatment in 8, 16, and 32 weeks after the steroids are shown.

## 3. Results

In this study, 35 (19 males and 16 females) patients were enrolled who were randomly treated with oral respule (n = 17) and swallowed MDI (n = 18). Of these, two patients in the respule group (one patient due to an asthma attack and the second patient due to non-compliance) and three patients in the MDI group (two patients due to asthma attack and one patient due to non-compliance) were excluded from the study during the first eight weeks, respectively. Finally, 15 patients in the respule group and 15 cases in the MDI group finished the first eight weeks. The two groups were similar in gender, mean age, mean body weight, and history of allergic disorders (Table 1). The mean frequency of eosinophils before the intervention was 31.13 ± 14.07 and 30.67 ± 13.44 in the respule and MDI groups, respectively, which did not show a significant difference between the two groups ($p = 0.467$). Similarly, the mean frequency of eosinophils in the $16^{th}$ week of the intervention was 6.33 ± 2.14 and 5.85 ± 2.12, respectively, which did not show a significant difference ($p = 0.487$). No difference was observed in adrenal suppression test results when assessing serum cortisol levels. In the respule group, six patients who did not respond to a low dose of the drug were treated with a double dose (high dose), of which 4 responded to the drug, and 2 did not respond. In the MDI group, 10 cases did not respond to low dose, one case was excluded due to asthma attack, and 9 cases were finally administered at high dose, of which five cases responded to high-dose and four cases ultimately did not respond to high-dose treatment. Therefore, non-response to low-dose

treatment in the first eight weeks was observed in 2 cases (13.3%, 95% CI: 2.6%–35.2%) in the respule group and 7 cases (50.0%, 95% CI: 22.7%–77.3%) in the MDI group, indicating a significant difference between the groups (p = 0.033). In the 16th week, the treatment failure rate with high dose was shown to be 13.3% in the respule group and 26.6% in the MDI group (p = 0.048) (Table 2). In the multivariate logistic regression model in the presence of underlying factors including sex, age, weight and history of rhinitis, asthma or eczema, the therapeutic response in the treatment by oral respule during the eighth week was significant after treatment with swallowed MDI (OR = 8.418, p = 0.046) (Table 3). Symptom relapse after discontinuation of local steroid was 0 (0%) and 1 (6.7%) in the respule and MDI groups, respectively, without significant P-value (p = 0.999). The Final response to the treatment independent of the dose was 13/15 (86.3%) and 10/15 (66.7%) without significant P-value (p = 0.637%) in the respule and MDI groups, respectively. Oral thrush frequency, independent of the dose, was 1/15 (6.7%) and 6/15 (40%) without a significant difference (p = 0.113) in the respule and MDI groups, respectively, all of which were resolved in the 32th week. Adrenal suppression rate independent of the dose was 4/15 (26.7%) and 3/15 (20%) in the respule and MDI groups, respectively, which was not significant (p = 0.789). One of them in MDI group was not resolved in the 32th week. Adverse events, such as oral thrush and adrenal suppression, were more frequent in the MDI group. Severity ranged from mild to moderate, and all cases were managed with appropriate interventions.

**Table 1.** Baseline characteristics of study groups.

| Parameters | Respule group | MDI group | P-value |
|---|---|---|---|
| Gender: Female/Male (%) | 9 (60.0)/6 (40) | 10 (66.7)/5 (33.3) | 0.70 |
| Age (year), Mean ± SD | 4.77 ± 1.88 | 4.80 ± 1.81 | 0.96 |
| Weight (kg), Mean ± SD | 14.67 ± 3.59 | 15.33 ± 3.59 | 0.62 |
| History of rhinitis (%) | 9 (60.0) | 10 (66.7) | 0.70 |
| History of asthma (%) | 6 (40.0) | 6 (40.0) | 0.99 |
| History of Atopic dermatitis (%) | 6 (40.0) | 6 (40.0) | 0.99 |

**Table 2.** The treatment failure (non-responder patients) and the results of adrenal suppression and oral candidiasis in 8, 16, and 32 weeks in MDI and respule groups.

| Time | Group | Low dose steroid | | | | |
|---|---|---|---|---|---|---|
| | | Responder (%) | Non-responder (%) | | Oral candidiasis | Adrenal suppression |
| 8 weeks | Respule group | 9 (60) | 6 (40) | | 0 | 4 |
| | MDI Group | 5 (34) | 10 (66) | | 1 | 3 |
| | | Low dose steroid | High dose steroid | | Low and High dose steroid | |
| | | Responder (%) | | Non-responder (%) | | |
| 16 weeks | Respule group | 9 (60) | 4 (27) | 2 (13) | 1 | 4 |
| | MDI Group | 5 (36) | 5 (36) | 4 (28)** | 5 | 3 |
| | | Stop steroid | | | | |
| | | Responder (%) | | Non-responder (%) | | |
| 32 weeks | Respule group | 13 (87) | | 2 (13) | 0 | 0 |
| | MDI Group | 9 (64) | | 5 (36)** | 0 | 1 |

Note: *: <0.05, **: <0.01; Adrenal suppression: serum cortisol level under 5 mcg/dL at 8 AM.

**Table 3.** Multivariate logistic regression model in determining the difference in the therapeutic effect of two drug protocols.

| Item | P value | OR | 95% CI for OR | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Group | 0.046 | 8.418 | 1.038 | 68.263 |
| Gender | 0.297 | 0.267 | 0.022 | 3.189 |
| Age | 0.967 | 1.027 | 0.295 | 3.577 |
| Weight | 0.852 | 1.061 | 0.569 | 1.980 |
| Rhinitis | 0.902 | 0.872 | 0.098 | 7.768 |
| Asthma | 0.877 | 1.199 | 0.121 | 11.912 |
| Atopic Dermatitis | 0.399 | 0.387 | 0.043 | 3.508 |

## 4. Discussion

So far, there is no standard therapeutic option for the treatment of EoE, but there is strong evidence for the therapeutic effects of a specific diet, as well as the use of PPIs and local or oral corticosteroids to improve clinical symptoms [23]. In order to reduce the confounding effects of other drugs, in this study, all groups received the same basic treatment including PPI, Monteleukast, antihistamine and food avoidance, so the type and the dose of local budesonide was the only factor compared in the two groups. Another challenging topic in this study was the food elimination method, as described in the method we used test-guided food avoidance [19–21], which we know may not be very accurate.

The budesonide molecule, either in the form of oral respule or in the form of MDI, showed its efficacy and safety in the treatment of these patients. If we judge based on the number of eosinophils in the tissue, which is an accurate criterion, there was no difference between the two groups after 16 weeks ($p = 0.467$), and if the clinical criteria based on Considering the PEESS®v2.0 questionnaire, a slight preference was shown in the oral respule group compared to MDI group ($p = 0.048$). In recent years, the efficacy of local corticosteroids (oral respule or swallowed MDI) in improving clinical symptoms, as well as histological findings, has been considered, though which form of the drug is the most effective and has the least side effects of the drug is debated [24,25].What we did evaluate and compare the efficacy of oral respule or swallowed MDI forms of budesonide in the treatment of EoE patients. In this study, it was shown that in evaluating the therapeutic response at both 8 and 16 weeks after treatment, the rate of therapeutic response to oral respule was significantly higher than the swallowed MDI form of the drug. This result was maintained even after adjustment of underlying variables such as gender, age, weight, and history of allergic diseases. We showed that in terms of local side effects such as oral thrush. Although the number of cases of oral thrush in the MDI group was more than in the respule group, there was no statistically significant difference between the two groups. There was no significant difference between the two groups in terms of systemic complications such as adrenal suppression. Budesonide, with predominant glucocorticoid activity, has inhibitory effects on mast cells, eosinophils, neutrophils, and macrophages and also inhibits the release of cytokines. Studies have shown that the drug is highly absorbed and rapidly metabolized if the oral form of the drug is used, which has not been observed in inhaled use. Therefore, based on this hypothesis, we predicted that the therapeutic effects of the respule form of the drug could be much more effective than its MDI form and it is more effective in eliminating eosinophilia [26,27]. Due to

the young age of the participants, our most important challenge in this study was ensuring the correct use of the drug, especially the MDI form, which was overcome by frequent training and continuous monitoring of how to use the drug. Various studies with similar results have shown significant effects of oral viscose budesonide in improving the symptoms of EoE. However, there have been very few studies comparing the efficacy of the oral respule and swallowed inhaled forms of the same drug. In the study of Albert et al, the efficacy and side effects of 8-week use of oral viscose budesonide in 75 EoE patients between 2–64 years old were evaluated and it was shown that the use of this drug was associated with a clinical response of 71%. which was almost the same as our study [15], except that we gave the drug in different doses for 16 weeks in the pediatric group under 18 years old. In the study of Fable et al., the efficacy and safety of budesonide (oral viscose) and fluticasone in the treatment of EoE in children were evaluated, which showed a therapeutic response of 75% compared to 40% in the use of these two drugs after eight weeks [28]. Our results showed similar benefits for budesonide respule but the efficacy in budesonide MDI was higher maybe because of the nature of budesonide molecule or the duration as we used for 16 weeks. Dellon et al. showed a similar finding with oral budesonide respule which, like fluticasone MDI, has been successful in controlling this disease, although it has not been statistically superior to the MDI form [29]. There have been many studies on the benefits of topical steroids. As Nenstiel et al. note in a review of the efficacy of fluticasone and budesonide, it seems our results are consistent with other studies[11]. However, in interpreting the studies, issues such as dose, duration and, most importantly, the criteria for evaluating the response to treatment should be considered. There is no direct relationship between clinical symptoms and histological findings, and for this reason, studies that considered both of these findings are of particular importance [30]. What distinguishes our study from others is the 16-week medication period, the use of different doses, and the evaluation of symptom recurrence after 16 weeks of drug discontinuation. However, in our study, the recurrence of symptoms was investigated after 16 weeks of discontinuation the topical steroid, which we know that this time cannot definitively predict the possibility of recurrence and the chance of recurrence may exist several months later. We used both clinical and histological findings. Overall, what can be seen from the present study is the far greater efficacy of the oral respule form of budesonide compared to the swallowed inhaled MDI form of the drug, which appears to be due to higher drug uptake and greater availability of drug metabolites to affect inflammatory indices such as eosinophils in the area. The occurrence of symptom relapse post-discontinuation underscores the chronic nature of EoE and the necessity for ongoing management strategies to prevent long-term complications. However, the small size of the study and, most importantly, the patients' dissatisfaction with the repetition of endoscopy at 16 weeks were the most important limitation of our study. Future larger-scale studies with blinding are warranted to validate these results. Moreover, blinding of participants and outcome assessors was not feasible due to the distinct characteristics of the interventions.

## 5. Conclusion

This study indicates that the oral respule formulation of budesonide is more effective than the swallowed metered-dose inhaler (MDI) in alleviating symptoms of eosinophilic esophagitis (EoE) in children. The oral respule not only resulted in a higher rate of symptom relief but also exhibited a better safety profile, with fewer incidents of oral thrush and adrenal suppression. Based on these results, the oral respule formulation may be a more advantageous treatment option for pediatric EoE patients,

especially when quick symptom relief is needed. However, considering the chronic nature of EoE and the risk of symptom recurrence after stopping treatment, further investigation into long-term management strategies is warranted.

## Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

## Conflict of interest

The authors declare no conflict of interest.

## Author contributions

FS, MF, NA conceived the study, drafted the manuscript, and gathered the data; MKh, SA, MN, MHB, SSh, AY, BR, FM, NE conducted statistical analysis and interpretation of data. FS revised the final manuscript for important intellectual content. All authors read and approved the final manuscript.

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## Ethical considerations

This study was approved by the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.FMD.REC.1398.371) and registered at IRCT (IRCTID: IRCT20191211045703N1). https://www.irct.ir/trial/44589

## Availability of data and material

Please get in touch with the corresponding author for data requests.

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