Evaluation of efficiency and safety of combined loratadine and budesonide in patients with anaphylactic rhinitis

A protocol for systematic review and meta-analysis

Jing Zhang, BD, Dan Kan, MD

Abstract

Background: Among the most prevalent allergic conditions that affect children is anaphylactic rhinitis (AR). It is capable of leading to physical as well as mental health issues. Concomitant use of loratadine and budesonide may improve symptoms of AR more than treatment with either drug alone. To assess the efficacy and safety of combined loratadine and budesonide for patients experiencing AR is the aim of this study.

Methods: We will apply 2 independent authors in six databases, including EMBASE, Pub Med, Web of Science, China National Knowledge Infrastructure, WanFang Database, Chinese Scientific Journal Database (VIP database). Studies evaluating the efficacy and safety of combined loratadine and budesonide in patients with AR will include studies published between inception and Dec 2021. Accordingly, the data will have to be in English and Chinese. For the selection of data extraction, the studies and risk of bias assessment will be completed by 2 independent authors. Accordingly, data synthesis will be conducted through RevMan 5.3 software. The study will establish heterogeneity using the $I^2$ test. Without correct data or information, there is a need for Publication bias, which is assessed by performing the Begg and Egger test and generating a funnel plot.

Results: The study provides a trustable clinical foundation for loratadine and budesonide for AR treatment.

OSF registration number: DOI 10.17605/OSF.IO/M2RFG

Ethics and dissemination: Because the present study is founded on existing studies, it does not require ethics approval.

Abbreviation: AR = anaphylactic rhinitis.

Keywords: anaphylactic rhinitis, budesonide, efficiency, loratadine, meta

1. Introduction

Anaphylactic rhinitis (AR) has a substantial global health issue. In essence, it is 1 of the most typical forms of non-infectious rhinitis, accounting for an estimated 10 to 30 percent of all adults as well as 40 percent of young persons. Past epidemiological studies have demonstrated that AR continues to increase globally. For example, the WHO has estimated that about 400 million people suffer from AR worldwide.\(^1\) Accordingly, AR is caused by a specific IgE-mediated allergic reaction, mainly in the nasal mucosa; hence, characterized by “stuffy, itchy, runny or runny nose, and sneezing.”\(^2\) Apart from specific allergen immunotherapy, currently available therapeutic approaches, such as antihistamines and corticosteroids, tend to focus on symptom relief, and although they do not provide a permanent solution, they remain first-line treatment.\(^3\)

Loratadine refers to a medication with high permeability and low water solubility, and it is usually used to treat allergic symptoms.\(^4\) Essentially, by oxidized low-density lipoproteins, the drug is capable of reducing endothelial inflammation produced and has some level of protective impacts.\(^5\) Accordingly, loratadine can selectively inhibit H1 receptors situated primarily on respiratory smooth muscle cells and those that do not cross the blood-brain obstruction. At the same time, it is
helpful in many situations for relieving allergic symptoms.\textsuperscript{[8]}
Even though \textit{loratadine} displays a clinical efficacy to treat AR, it is
necessary to enhance its effect.\textsuperscript{[9]}

\textit{Budesonide} entails a nebulized glucocorticoid utilized in
treating asthma and AR. It caused substantial decreasing
adhesion molecules levels, including MIP-2 and ICAM-1,
released from endothelial cells and wounded epithelial; thus,
triggering neutrophil infiltration and macrophages.\textsuperscript{[10,11]} Ac
correspondingly, \textit{budesonide} is capable of decreasing proinflammatory
cytokines (IL-1\textbeta, TNF-\textalpha, IL-6), increasing the levels of IL-10;
thus, antagonizing the impacts of earlier cytokines as well as
reducing cell apoptosis.\textsuperscript{[11-13]} However, the safety and efficiency
of combining \textit{loratadine} and \textit{budesonide} in patients with AR
have not been systematically verified. To this end, this review
aims to empirically assess the safety and efficacy of combining
\textit{loratadine} and \textit{budesonide} to treat patients experiencing AR and
build reliable evidence and valuable references for clinicians and
researchers to make better medical decisions. This will help n
conducting further studies on the topic.

2. Materials and methods

The study is registered with the Open Science Framework (OSF,
accession number DOI 10.17605/OSF.IO/M2RFG). Systematic
reviews and meta-analyses as required by the project statement
are our preference.

2.1. Inclusion criteria

2.1.1. Type of study. We only included randomized controlled
trials published or registered before December 2021. However,
we will exclude prospective randomized controlled trials, review
articles, case reports and other studies that do not meet this
requirement.

2.1.2. Type of participants. We will include participants of
different age ranges, participants of all types of AR, regardless of
their nationality, gender, race, occupation, education, severity,
or etiology.

2.1.3. Type of interventions. We will give the therapy of
\textit{loratadine} combined with \textit{budesonide} to the treatment group,
whereas the control group will receive only \textit{loratadine},
\textit{budesonide}, placebo, or they will not receive any form of
treatment. We will have no limit to dose, frequency, or treatment
duration.

2.1.4. Types of outcome measures. The clinical improvement
of AR symptoms, rhinoconjunctivitis-related quality of life,
ocurrence of adverse events, and utilization of rescue
treatment is our anticipated outcome.

2.2. Search methods for identification of studies

2.2.1. Electronics searches. We will use 2 independent in six
distinct databases: Web of Science, PubMed, EMBASE,
WanFang Database, China National Knowledge Infrastructure,
and Chinese Scientific Journal Database (VIP database). They
will assess the evaluation of efficacy as well as safety of combined
\textit{loratadine} and \textit{budesonide} in patients with AR, published from
inception to December 2021. We will only regard articles
published in English and Chinese. A search in PubMed was
performed using the following terms “(loratadine* OR
budesonide*) AND (rhinitis* OR ‘allergic rhinitis’ OR
‘anaphylactic rhinitis’) AND (random* OR trial OR ‘random-
ized controlled trial’ OR ‘randomized controlled trial’).

2.2.2. Searching other resources. The following clinical trial
registries are what we will use to establish ongoing trials: The
ClinicalTrials.gov, the Chinese clinical registry, and Google
Scholarship. We will also retrieve helpful but incomplete
information from the contact trial personnel.

2.3. Data extraction and management

We will use 2 independent authors to double-check and gather
all the qualifying studies and transfer them into RevMan
software. We will use a pre-defined data acquisition form to
enter details, for instance “author, journal, treatment indication,
population characteristics, total and per-arm sample size,
publication year, comparator dose and omalizumab, study
duration, and mode of administration.” In case of a disagree-
ment between the authors, a third author will mediate to help
reach a consensus.

2.4. Assessment of risk of bias

Two independent authors will be used to perform a systematic
review of each of the studies for the bias risk. The authors will
use the Cochrane Handbook. In particular, they will rely on 6
domains, including “reporting, the bias of selection, detection,
performance, attrition and other sources.” They will rate trials
for every field as “high risk, low risk or unclear after evaluation.”
The authors involved in the study will also be contacted to clear
any missing information. In case of a disagreement between
the authors, a third author will mediate to help reach a consensus.

2.5. Measures of treatment effect

We pooled the study-specific estimates by utilizing fixed and
random-effects models and estimated the standardized summary
mean differences and the relative risks, as well as the 95% confidence intervals correspondingly. We noticed that the
standardized mean difference was the mean change per standard
development, which is critical for comparing scores in various
scales.

2.6. Dealing with missing data

We will get in touch with respective authors where there is
missing information or incompleteness of data. We will wait for
1 month after sending an email to the original author to reply.
After 1 month, we will exclude the incomplete data from the
analysis if the author does not respond or provide the necessary
data.

2.7. Heterogeneity assessment and subgroup analysis

We use $I^2$ (ranging from 0\% to 100\%) to assess the presence and
degree of heterogeneity. We used a subgroup analysis for further
investigation where there is high heterogeneity. We intend to use
the formal test for subgroup interactions in RevMan V.5.3.

2.8. Sensitivity analysis

A sensitivity analysis will be used to conduct the robustness of
the critical decisions made during the monitoring review process.
2.9. Publication bias
We used a visual inspection of the Egger test and Begg funnel plots to evaluate all potential small study effects, such as an indication of publication bias.

3. Discussion
AR is 1 of the most common allergic diseases worldwide, affecting 10% to 40% of the global population. In particular, many people seem to experience the effects of the negative impacts of AR. Therefore, patients might resort to using medication to relieve these uncomfortable symptoms. Nevertheless, some of the most common adverse events with intranasal formulations were “poor taste, nasal burning, sedation, increased cost relative to oral formulations and more frequent dosing.” In most cases, doctors consider side effects based on the initiation of intranasal antihistamines. On this foundation, we need to strengthen our randomized controlled study on the safety and effectiveness of combining loratadine and budesonide to treat patients with AR in future studies. We also need to establish a significant scientific basis to apply this approach to clinical treatment. This will be crucial in the provision of a solid scientific foundation to use this approach in the clinical therapy of AR.

Author contributions
Conceptualization: Jing Zhang, Dan Kan.
Data curation: Jing Zhang, Dan Kan.
Formal analysis: Jing Zhang, Dan Kan.
Funding acquisition: Jing Zhang, Dan Kan.
Investigation: Jing Zhang.
Methodology: Jing Zhang, Dan Kan.
Project administration: Jing Zhang.
Resources: Dan Kan.
Software: Jing Zhang, Dan Kan.
Supervision: Jing Zhang.
Validation: Jing Zhang, Dan Kan.
Visualization: Jing Zhang.
Writing – original draft: Jing Zhang, Dan Kan.
Writing – review & editing: Dan Kan.

References
[1] Pawankar R. Allergic diseases and asthma: a global public health concern and a call to action. World Allergy Organ J 2014;7:12–12.
[2] Small P, Kim H. Allergic rhinitis. Allergy Asthma Clin Immunol 2011; 7:53.
[3] Hossenbaccus L, Linton S, Garvey S, Ellis AK. Towards definitive management of allergic rhinitis: best use of new and established therapies. Allergy Asthma Clin Immunol 2020;16:1–17.
[4] Wang J, Chang R, Zhao Y, et al. Coamorphous loratadine-citric acid system with enhanced physical stability and bioavailability. AAPS PharmSciTech 2017;18:2541–50.
[5] Iesce MR, Lavorgna M, Russo C, et al. Ecotoxic effects of loratadine and its metabolic and light-induced derivatives. Ecotoxicol Environ Saf 2019;170:664–72.
[6] Armakovic S, Armakovic SJ, Abramovic BF. Theoretical investigation of loratadine reactivity in order to understand its degradation properties: DFT and MD study. J Mol Model 2016;22:240.
[7] Zhou Y, Gao C, Wang H, Liu L, Huang Z, Fa X. Histamine H1 type receptor antagonist loratadine ameliorates oxidized LDL induced endothelial dysfunction. Biomed pharmacother 2018;106:1448–53.
[8] Kim YJ, Kim KS, Kim BS, Yoon S. Histamine receptor antagonists, loratadine and azelastine, sensitize P-gp-overexpressing antimitotic drug-resistant KBV20C cells through different molecular mechanisms. Anticancer Res 2019;39:3767–75.
[9] Ozoh OB, Aderibigbe SA, Ayuk AC, et al. The prevalence of asthma and allergic rhinitis in Nigeria: a nationwide survey among children, adolescents and adults. PLoS One 2019;14:e0222281.
[10] Li LF, Liao SK, Lee CH, Huang C-G, Quinn DA. Involvement of Akt and endothelial nitric oxide synthase in ventilation-induced neutrophil infiltration: a prospective, controlled animal experiment. Critical Care 2007;11:1–13.
[11] Miyao N, Suzuki Y, Takeshita K, et al. Various adhesion molecules impair microvascular leukocyte kinetics in ventilator-induced lung injury. Am J Physiol Lung Cell Mol Physiol 2006;290: L1059–68.
[12] Ju NY, Gao H, Huang W, et al. Therapeutic effect of inhaled budesonide (Pulmicort® Turbuhaler) on the inflammatory response to one-lung ventilation. Anaesthesia 2014;69:14–23.
[13] Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterology 2010;139:1526–37. 1337.e1.
[14] Bouquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008; 63(Suppl 86):8–160.