A Meta-Analysis of Efficacy and Safety Evaluation Between Desloratadine Citrate Disodium Versus Loratadine Tablets in Patients with Chronic Urticaria

Objective To summarize the available evidence and assess the efficacy and safety of desloratadine citrate disodium versus loratadine in patients with chronic urticaria (CU).

Methods Databases PubMed (Medline), Web of knowledge, MEDLINE, VIP, Wanfang and CNKI databases were systematically searched for articles. The search results were last updated in June 2017. Quality assessment and data extraction were performed according to the Cochrane Handbook. The meta-analysis was performed using Stata 14.0.

Results Nine randomized controlled trials involving 950 patients were identified. In terms of efficacy, the pooled ORs for the overall responder rate and the complete remission rate were 2.37 (95% CI: 1.77–3.16) and 2.86 (95% CI: 2.25–3.64), respectively. The pooled ORs for 7 days overall responder rate, 14 days overall responder rate, 28 days overall responder rate were 1.92 (95% CI: 1.32–2.79), 3.71 (95% CI: 1.98–6.95), 2.64 (95% CI: 1.32–5.27) respectively. The pooled ORs for 7 days complete remission rate, 14 days complete remission rate, 28 days complete remission rate were 2.29 (95% CI: 1.38–3.79), 3.46 (95% CI: 2.28–5.23), 2.78 (95% CI: 1.93–4.01) respectively. In the terms of safety, the pooled OR for adverse events (AEs) was 0.42 (95% CI: 0.24–0.71), with statistical significance. The most common AEs were somnolence, thirst, dizziness, weakness and nausea.

Conclusion Desloratadine citrate disodium is more efficacious and safer than loratadine in patients with CU.

KEYWORDS chronic urticaria, loratadine, desloratadine citrate disodium, meta-analysis

INTRODUCTION

Chronic urticaria (CU) is a common skin disease defined by spontaneously occurring wheals pruritus for longer than 6 weeks, which afflicts twice as many women as men. The prevalence rates of CU among European and American are about 0.1–3% \(^2\). Many CU patients are severely impaired in their quality of life, Guo et al. have assessed the quality of life in CU patients, the result shown that CU had a significant impact on quality of life.\(^3\)

At present, second-generation H1-antihistamines has been widely used as first-line treatment for CU. Loratadine is atircyclic H1 receptor antagonist, as well as a potent long-acting second-generation antihistamines. Its electively binds to peripheral H1 receptors, whereas show low affinity to central H1 receptors, which make no obvious inhibitory effect and anticholinergic activity.\(^4\)

Desloradine citrate disodium is a novel second-generation antihistamines consisting of desloradine and sodium citrate, and is converted to desloradine in vivo to produce healing efficacy. The solubility was 100 times compared to loratadine, and is thus able to antagonize peripheral H1 receptor powerfully and selectively and plays its antihistamine and anti-inflammatory role.\(^5\)

Both desloradine citrate disodium and loratadine are the first choices for urticaria. However, due to the inconsistent quality of clinical studies, no final agreement and conclusion were drawn on comparison between desloradine citrate disodium and loratadine. In this study, we assessed the efficacy and safety of novel desloradine citrate disodium and traditional loratadine in order to support clinical medication and practice for CU.
Efficacy and safety evaluation between desloratadine citrate disodium versus loratadine tablets

METHODS

Search strategy

This examination was performed in accordance with the favoured reporting items for systematic reviews and meta-analysis (PRISMA) statement. We systematically searched databases PubMed (Medline), Web of knowledge, MEDLINE, VIP, Wanfang and CNKI databases to identify clinical trials by using the following key words: (chronic urticaria) and (desloratadine citrate disodium) and (efficacy OR randomized). Only papers written in English and Chinese were included. We also searched the reference lists of these publications for more articles relevant to the topic. As indicated by the search strategy, two authors (LNZ and ZRL) performed the literature search independently and merged all the searched papers. The search results were last updated in June 2017.

Inclusion and exclusion criteria

In this study, the inclusion measures were set as follows: (1) Types of study: the eligible studies were randomized controlled trials; (2) Types of participants: adults (>18 years) with CU were included in the study without restriction of any sex, any ethnicity and any type; (3) Intervention: studies that compared desloratadine citrate disodium 8.8 mg and loratadine 10 mg for CU were included.

Research were excluded when they met the following criteria: (1) Duplicate records; (2) Not clinical trials; (3) Not CU; (4) Irrelevant intervention; (5) Irrelevant outcome measures; (6) non-Chinese or English language.

Outcome measures

Outcome measures included primary outcome measures and secondary outcome measures.

Symptom score reduce index (SSRI)

\[
100\% \times \left( \frac{\text{the total score before the treatment} - \text{the total score after the treatment}}{\text{the total score before the treatment}} \right)
\] (SSRI)

According to SSRI, we defined the overall responder rate, the primary efficacy outcomes, as the proportion of patients with an SSRI score ≥ 60% during the treatment period. The secondary efficacy outcomes were the complete remission, which is defined as the percentage of participants with an SSRI score ≥ 90% during the treatment period.

Safety outcome was adverse event (AE) rate (defined as the proportion of patients who experienced AEs among total observed patients).

Data extraction

Two authors (LNZ and ZRL) independently assessed trials for inclusion and extracted data using a standardized data extraction form from included trials.

Any discrepancies were resolved by discussion with a third review author (TTZ). The extracted data included the following: (1) information about participation, including age, the number of patients and the type of disease; (2) basic characteristics about the study, including authors, publication year, trial design; (3) data on outcomes, including the complete remission rate, the overall responder rate and AE rate.

Study quality evaluation

The Cochrane Collaboration’s apparatus was used to assess the risk of bias of the identified RCT articles by two authors (LNZ and ZRL) independently. Any contradictions were settled by discussion with a third review author (TTZ). The risk of bias was used to assess the quality of each study. The risk of bias picture included the seen parts as follows: (A) Random sequence generation (selection bias); (B) Allocation concealment (selection bias); (C) Blinding of participants and personnel (performance bias); (D) Blinding of outcome assessment (detection bias); (E) Incomplete outcome data (attrition bias); (F) Selective reporting (reporting bias); (G) Other bias. The red meant high risk and green represented low risk, meanwhile, the yellow is not clear.

Statistical analysis

The meta-analysis was performed using Stata (v14). Heterogeneity among the trials was evaluated by the \( \chi^2 \) test and the \( I^2 \) statistics for heterogeneity. A \( P \) value < 0.1 or an \( I^2 \) value > 50% was considered significant heterogeneity and the results were synthesized during a random effect model. Heterogeneity will determine the choice of a fixed or random effects model (for \( I^2 < 50\% \) or \( I^2 > 50\% \), respectively). Mantel-Haenszel odds ratios (ORs) with 95% confidence intervals (CIs) were used as measures of the associations between treatment and outcomes. The publication bias was assessed using the Egger test and visual inspection of the funnel plot. The intent-to-treat (ITT) population data were chosen for the analysis. We planned to perform sub-group analysis by duration of follow-up (7 days, 14 days, and 28 days).

RESULTS

Results of study collection

Literature retrieved and extracted from the main database of Chinese and English languages by using the retrieval strategy. The English language database included PubMed (Medline), Web of knowledge, MEDLINE, the Chinese database included VIP, Wanfang and CNKI databases. The study selection process was as follows. The initial search identified a total of 1065 records by a database and trial registers search, no study were identified by searching the reference lists of publications. After titles and abstracts screened, 144 articles were retained for full review. Nine remaining records were retrieved after full texts screened (Fig. 1). Figures 2 and 3 summarized the risks of bias of the included trials. No RCT was excluded after quality analysis.
Characteristics of included studies

Of these nine studies, the efficacy of desloratadine citrate disodium and loratadine on the treatment of CU was compared. Characteristics of the nine studies included in this meta-analysis were demonstrated in Table 1. The most recent study was from 2017, and the oldest was published in 2015, all were RCTs. Nine articles involving 960 patients were identified. Of the nine articles, two studies were chronic idiopathic urticaria. The sample sizes of these studies ranged from 50 to 202 and all the treatment periods was 28 days.

Efficacy evaluation

The overall responder rates for desloratadine citrate disodium versus loratadine

A total of 502 participants from five RCTs were included. A $\chi^2$ test for heterogeneity indicated no significant statistical heterogeneity between trials, $\chi^2 = 9.27, I^2 = 0.0\%$, ($P = 0.597 > 0.1$), and a fixed-effects model was used. The overall OR was 2.37 (95% CI: 1.77–3.16) with statistical significance ($P = 0.000 < 0.05$), suggesting desloratadine citrate disodium group were more effective than loratadine group. The overall responder rates of patients with CU on 7 days, 14 days and 28 days were investigated. The estimated ORs were 1.92 (95% CI: 1.32–2.79), 3.71 (95% CI: 1.98–6.95), 2.64 (95% CI: 1.32–5.27), respectively, which were shown in Fig. 4. In the meta-analysis of the overall responder rate, no evidence of publication bias was noted (Egger test, $P = 0.087 > 0.05$; A funnel plot evaluated the publication bias of the studies was shown in Fig. 5).

The complete remission rates for desloratadine citrate disodium versus loratadine

A total of 704 participants from six RCTs were included. A $\chi^2$ test for heterogeneity indicated no significant statistical heterogeneity between trials, $\chi^2 = 9.82, I^2 = 0.0\%$, ($P = 0.632 > 0.1$), and a fixed-effects model was used. The overall OR was 2.86 (95% CI: 1.32–2.79), 3.71 (95% CI: 1.98–6.95), 2.64 (95% CI: 1.32–5.27), respectively, which were shown in Fig. 4. In the meta-analysis of the overall responder rate, no evidence of publication bias was noted (Egger test, $P = 0.087 > 0.05$; A funnel plot evaluated the publication bias of the studies was shown in Fig. 5).
Table 1  Characteristics of included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Subject no. ITT</th>
<th>Age, mean (years)</th>
<th>Treatment period (days)</th>
<th>Diseases type</th>
<th>Intervention (t/c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang 2013(9)</td>
<td>RCT</td>
<td>122</td>
<td>39</td>
<td>28</td>
<td>Chronic urticaria</td>
<td>Desloratadine citrate disodium 8.8 mg vs loratadine 10 mg</td>
</tr>
<tr>
<td>Chen 2015(10)</td>
<td>RCT</td>
<td>50</td>
<td>41</td>
<td>28</td>
<td>Chronic urticaria</td>
<td>Desloratadine citrate disodium 8.8 mg vs loratadine 10 mg</td>
</tr>
<tr>
<td>Hu 2016(12)</td>
<td>RCT</td>
<td>202</td>
<td>30</td>
<td>28</td>
<td>Chronic idiopathic urticaria</td>
<td>Desloratadine citrate disodium 8.8 mg vs loratadine 10 mg</td>
</tr>
<tr>
<td>Yang 2017(13)</td>
<td>RCT</td>
<td>60</td>
<td>33</td>
<td>28</td>
<td>Chronic urticaria</td>
<td>Desloratadine citrate disodium 8.8 mg vs loratadine 10 mg</td>
</tr>
<tr>
<td>Ren 2016(14)</td>
<td>RCT</td>
<td>70</td>
<td>32</td>
<td>28</td>
<td>Chronic urticaria</td>
<td>Desloratadine citrate disodium 8.8 mg vs loratadine 10 mg</td>
</tr>
<tr>
<td>Chen 2016(15)</td>
<td>RCT</td>
<td>76</td>
<td>41</td>
<td>21</td>
<td>Chronic urticaria</td>
<td>Desloratadine citrate disodium 8.8 mg vs loratadine 10 mg</td>
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<tr>
<td>Hua 2016(16)</td>
<td>RCT</td>
<td>110</td>
<td>40</td>
<td>28</td>
<td>Chronic idiopathic urticaria</td>
<td>Desloratadine citrate disodium 8.8 mg vs loratadine 10 mg</td>
</tr>
<tr>
<td>Deng 2017(17)</td>
<td>RCT</td>
<td>96</td>
<td>33</td>
<td>28</td>
<td>Chronic urticaria</td>
<td>Desloratadine citrate disodium 8.8 mg vs loratadine 10 mg</td>
</tr>
<tr>
<td>Liang 2015(11)</td>
<td>RCT</td>
<td>174</td>
<td>33</td>
<td>28</td>
<td>Chronic urticaria</td>
<td>Desloratadine citrate disodium 8.8 mg vs loratadine 10 mg</td>
</tr>
</tbody>
</table>

Fig. 4 The meta-analysis of the overall responder rates about desloratadine citrate disodium and loratadine in the treatment of chronic urticaria.

(95% CI: 1.38–3.79), 3.46 (95% CI: 2.28–5.23), 2.78 (95% CI: 1.93–4.01), respectively (Fig. 6). No obvious evidence of publication bias was shown in this meta-analysis (Egger test, \( P = 0.051 > 0.05 \); A funnel plot evaluated the publication bias of the studies was shown in Fig. 7).

Safety evaluation

The most common AEs were somnolence, thirst, dizziness, weakness and nausea. A total of 960 participants from nine RCTs were included. A \( \chi^2 \) test for heterogeneity indicated no significant statistical heterogeneity between trials, \( \chi^2 = 0.58, p = 0.00, (P = 1.000 > 0.1) \), and a fixed-effects model was used. The overall OR was 0.42 (95% CI: 0.24–0.71) with statistical significance (\( P = 0.001 > 0.05 \)); thus there was sufficient evidence to conclude that the incidence of desloratadine citrate disodium group was lower than loratadine group. The estimated ORs for desloratadine citrate disodium compared to loratadine were shown in Fig. 8. Egger test, \( (P = 0.864 > 0.05) \) and a funnel plot did not suggest evidence of publication bias (Fig. 9).

DISCUSSION AND CONCLUSION

CU, is a skin disease characterized by recurrent appearance of wheals and angioedema, occurring at least
twice a week for more than 6 weeks. H-antihistamines are the mainstay of treatment, which are divided into first- and second-generation drugs, such as desloratadine citrate disodium, loratadine, desloratadine, mizolastine, and soon.18,19

In our systematic review and meta-analysis, 950 patients from 9 studies were included. For efficacy assessment, desloratadine citrate disodium did appear to be superior to loratadine in CU with the pooled ORs for the overall responder rate and the complete remission rate and were 2.37 (95% CI: 1.77–3.16), 2.86 (95% CI: 2.25–3.64), respectively. The pooled ORs for 7 days overall responder rate, 14 days overall responder rate, 28 days overall responder rate were 1.92 (95% CI: 1.32–2.79), 3.71 (95% CI: 1.98–6.95), 2.64 (95% CI: 1.32–5.27). The pooled ORs for 7 days complete remission rate, 14 days complete remission rate, 28 days complete remission rate were 2.29 (95% CI: 1.38–3.79), 3.46 (95% CI: 2.28–5.23), 2.78 (95% CI: 1.93–4.01), respectively. In terms of safety, well-tolerated was also identified in the desloratadine citrate disodium group compared to loratadine. Pooled OR for AEs was 0.42 (95% CI: 0.24–0.71), with statistical significance. The most common AEs were somnolence, thirst, dizziness, weakness, and nausea. These evidences suggested that desloratadine citrate disodium might be more suitable than loratadine for CU.

Our systematic review and meta-analysis provided the most updated evidence for the efficacy and safety of desloratadine citrate disodium versus loratadine in patients with CU. Owing to the inclusion of nine RCTs, the statistical analysis was performed pooled a relatively large population and allowed us to better evaluate the real efficacy and safety of the drug. Besides, data extraction and statistical analysis were carried out by independent reviewers and carefully cross checked. Therefore, it is reasonable to assume that the results of our meta-analysis are of high quality. Furthermore, we performed targeted subgroups analysis according to the duration of follow-up—7 days, 14 days, and 28 days—
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which could have great clinical relevance and meaningful practical importance.

Several limits of this review should be taken into account. Firstly, the sample sizes of RCTs was relatively small, among these nine studies, only three studies have more than one hundreds observed patients. Secondly, only two included studies described the optimization method in detail and outcome measures off our studies were incomplete, which may induce selective bias and reporting bias. Thirdly, despite the need for long-term therapy of the participants with CU, the treatment period of the trials included in this review was only 28 days, treatment period of Meador et al.20 was only 21 days. Furthermore, this meta-analysis didn’t provide the estimated ORs of the most common types of AEs between desloratadine citrate disodium and loratadine, with reason of rare information of the incidence of AEs. Additional head-to-head studies are required to confirm clinical decision-making. RCTs and follow-up studies are ongoing and are necessary to validate our findings.

This meta-analysis showed that the use of desloratadine citrate disodium was demonstrated to be more effective with respect to the overall responder rate and the complete remission rate when compared with loratadine. The safety analysis showed that desloratadine citrate disodium was safer than loratadine. Further well-designed and large-scale RCTs will be needed to compare the long-term efficacy and safety of desloratadine citrate disodium and loratadine on chronic urticaria.

REFERENCES