Efficacy of NB-UVB as Add-on Therapy to Antihistamine in the Treatment of Chronic Urticaria: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Narrow-band ultraviolet B (NB-UVB) phototherapy has been used for the treatment of chronic urticaria (CU), but the clinical efficacy of this treatment modality requires further evidence. A systematic review and meta-analysis of randomized clinical trials were conducted to evaluate the efficacy and safety of NB-UVB as add-on therapy in the treatment of CU.

Methods: A literature search was conducted in the Cochrane, Embase, PubMed, Web of Science, CNKI, CBM, VIP and WanFang databases up to October 2020. A total of nine studies involving 713 participants met the inclusion criteria.

Results: Two trials showed a significant difference in the Urticaria Activity Score between therapy with NB-UVB + antihistamines and that with antihistamines alone (mean difference 8.23, 95% confidence interval [CI] 5.78–10.68, \( p < 0.00001 \)). Six trials (563 participants) showed a significant benefit of NB-UVB as add-on therapy to antihistamines in the total effective rate (risk ratio [RR] 1.56, 95% CI 1.39–1.75, \( p < 0.00001 \)). In terms of adverse events, no statistically significant differences were found for NB-UVB + antihistamines versus antihistamines alone (RR 1.10, 95% CI 0.67–1.79, \( p = 0.71 \)). Combination therapy of NB-UVB + antihistamines yielded a significantly lower risk of recurrence (RR 0.25, 95% CI 0.14–0.44, \( p < 0.00001 \)).

Conclusion: Our meta-analysis suggests that combination therapy of NB-UVB + antihistamines is significantly more effective in treating CU than antihistamines alone.

Keywords: Antihistamine; Chronic urticaria; Efficacy; Meta-analyses; Narrow-band UVB
**Key Summary Points**

**Why carry out this study?**

Second-generation H1-antihistamines are typically the first-line drugs in the treatment of chronic urticaria (CU), but they are associated with a low efficacy.

Some studies have suggested narrow-band UVB (NB-UVB) phototherapy can be added to H1-antihistamine treatment for CU.

No systematic review of NB-UVB therapy for treating CU has been carried out to date.

**What was learned from the study?**

Combination therapy of NB-UVB + antihistamines may potentially be more effective for improving CU than antihistamines alone, with lower recurrence.

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**DIGITAL FEATURES**

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14096253.

**INTRODUCTION**

Chronic urticaria (CU) is a common skin disease that is defined as the recurrent occurrence of wheals with or without angioedema on most of the days during a period exceeding 6 weeks [1]. The prevalence of CU in children and adults across the world has been established to be around 0.1–1.6%, and the condition can last ≥ 2 years [2–4]. CU is known to have a substantial impact on the quality of life. People with recurrent CU often suffer from fatigue, pain, lack of sleep or insomnia due to persistent itching, and these conditions may in turn be a source of anxiety, depression, irritability and social dysfunction [3, 5, 6]. The second-generation H1-antihistamines (sgAH) are typically the first-line drugs used to treat CU, but almost 5–50% of patients do not respond adequately to sgAH even at fourfold the standard dose [7, 8]. Omalizumab should be added to the therapeutic regimen when long-term use of sgAH fails to achieve the desired results. Different agents, including cyclosporine, methotrexate and short-term systemic corticosteroids, are among the different treatment options for patients not responding to antihistamines [1]; however, their high cost and systemic adverse effects limit patient access to these agents.

Phototherapy is a major effective therapeutic modality in dermatology and has influenced the treatment of different skin diseases dramatically [9, 10]. Ultraviolet B (UVB) phototherapy has different effects, including anti-inflammatory, immunosuppressive and cytotoxic effects [11]. The mechanisms of its action are unclear but reducing skin mast cell reactivity, degranulating and releasing histamine and other pro-inflammatory mediators are possible modes of action [12, 13]. Other plausible mechanisms include apoptosis of dermal mast cells, immunomodulatory action and the production of anti-inflammatory cytokine [14]. The Korean Academy of Asthma, Allergy and Clinical Immunology (KAACAI) and the Korean Dermatological Association (KDA) Evidence-Based Practice Guideline suggests that narrow-band UVB (NB-UVB) phototherapy can be added to H1-antihistamine treatment for the treatment of chronic spontaneous urticaria (CSU) and symptomatic dermographism [15]. However, to date, there has been no systematic review of NB-UVB phototherapy for treating CU. The aim of this meta-analysis was to summarize the current literature on the use of NB-UVB in CU, especially in terms of evaluating the efficacy and safety of NB-UVB phototherapy.

**METHODS**

We conducted this systematic review and meta-analysis according to the Preferred Reporting
Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and an a priori established protocol. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Search Strategy/Selection Criteria

The following electronic databases were systematically searched up to October 2020: Cochrane Central Register of Controlled Trials (CENTRAL), Embase, PubMed, the Chinese National Knowledge Infrastructure (CNKI), the Chinese Biomedical Literature Database (CBM), the Chinese Scientific Journal Database (VIP) and the Wanfang Database. The search terms included the keyword “NB-UVB” OR “narrow-band ultraviolet B” combined with the Medical Subject Headings (MeSH) “urticaria.” The search strategy was “NB-UVB” OR “narrow-band ultraviolet B” AND “urticaria.” The reference lists of all relevant articles were searched for additional information.

We included studies that met all of the following criteria: (1) the study design was a randomized controlled trial (RCT); (2) the publication language was Chinese or English; (3) the study involved patients with CSU or chronic idiopathic urticaria; (4) the treatment groups were treated with NB-UVB phototherapy in combination with antihistamine, and antihistamine was given to control groups. Exclusion criteria were: studies with duplicate information published elsewhere; studies that could not be adequately interpreted; and nonoriginal data such as reviews, commentaries and editorials.

Study Selection and Data Extraction

In accordance with the PRISMA guidelines (Fig. 1), the potentially relevant studies were first screened by two authors (JQC and ZX) independently according to the titles and the abstracts from the electronic databases for inclusion in the review. Duplicates were removed. Full-text articles of potentially eligible studies were assessed. The discrepancy for inclusion as well as quality assessment was resolved by discussion with a third review author (QC). Data were then extracted from the included studies using a data extraction form. The following information from primary trials were retrieved in the data extraction table: lead author, publication year, sample size (treatment group, control group), age of subjects, course of disease, interventions (treatment group, control group), course of treatment and outcome criteria. The final results were reviewed by all the reviewers.

Bias Assessment

To assess for bias, two authors independently (JQC and ZX) completed the Cochrane assessment of bias comparison for each study. The following domains for risk of bias were assessed: sequence generation, allocation sequence concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias. The assessments were classified into three levels: low risk, high risk and unclear risk. Any disagreements were discussed and arbitrated by the third author (QC).

Outcomes

Primary outcomes included symptom scores, such as total effective rate (TER), Urticaria Activity Score (UAS), Reduction of Urticaria Activity Score (RUAS), and Symptom Score Reduction Index (SSRI). Adverse events and recurrence rate (RER) were also included.

Statistical Analysis

RevMan V.5.3 statistical software (The Nordic Cochrane Center, Copenhagen, Denmark) was applied for data synthesis when a meta-analysis was allowed. The results were expressed as risk ratio (RR) with 95% confidence interval (CI) for dichotomous data and the standard mean difference (SMD) with 95% CI for continuous data.
Statistical significance was defined as a $P$ value < 0.05. Heterogeneity was assessed by $I^2$ statistics, with $I^2 = 25\%$, $I^2 = 50\%$ and $I^2 = 75\%$ considered as low, moderate and substantial heterogeneity, respectively. The first random effects model was used, and if $I^2$ was < 50\%, then the fixed effects model was used.

**RESULTS**

**Study Selection and Study Characteristics**

Based on the literature search strategy explained in the Methods section, a total of 244 articles were retrieved from the online databases.
considered in this study. Ultimately, nine RCTs with 713 participants were included in the systematic review and meta-analysis after stepwise screening [16–24] (Fig. 1). These nine RCTs were conducted and published in Chinese or in English between 2008 and 2020, with seven originating from China. All nine RCTs were all single-center randomized controlled studies. Characteristics, design, number of patients and other parameters of the nine RCTs are reported in Table 1.

Risk of Bias in Included RCTs

All included RCTs mentioned randomization. The random allocation methods reported in the articles include: random number tables (4 RCTs), rolling a dice (1 RCT), drawing a lot (1 RCT), order of visit (1 RCT); the remaining two RCTs did not mention specific randomization methods. The details of the allocation concealment were not reported in all nine studies included in the meta-analysis, which resulted in an unclear risk. Only one study [16] reported the blindness of the treatment options. We graded eight studies as having high risk in this domain. There was also no discussion of blinding in the outcome assessments, and these were judged as “unclear” for evidence of bias. We considered nine studies to be at low risk of bias for incomplete outcome data, according to the reports of dropouts or intention to-treat analysis. In the selective reporting section, seven studies [16–18, 21–24] were judged to have a high risk of bias, because adverse events or the RER of CU were not described, while the remaining two studies [19, 20] were considered to have a low risk of bias. The risk of bias assessment is presented in Fig. 2.

Efficacy of NB-UVB Treatment for CU

Urticaria Activity Score

Two studies [16, 22] (150 participants) compared NB-UVB therapy + antihistamine medication with the same antihistamine alone using the UAS at baseline and after treatment. The change in the UAS change from baseline to after treatment was calculated as the RUAS. The mean difference (MD) was 8.23 (95% CI 5.78–10.68, \(p < 0.00001\)) using the fixed model (Fig. 3). In this analysis, combined therapy with NB-UVB + antihistamines was more effective than theapy with antihistamines alone.

Total Effective Rate

Seven trials [17–21, 23, 24] (563 participants) reported the TER in the proper manner (Fig. 4). In this analysis, NB-UVB therapy combined with antihistamines was associated with a higher TER than antihistamines alone (RR 1.56, 95% CI 1.39–1.75, \(p < 0.00001\)).

Adverse Events and RER

Adverse events were reported in six of the nine RCTs, but no serious adverse events were reported in these trials [16, 17, 19–22]. As presented in Fig. 5, the pooled results indicate that the adverse events associated with interventions with NB-UVB were similar to those of the control groups (RR 1.19, 95% CI 0.72–1.98, \(p = 0.49\)). For the combined therapy, six studies reported five cases of erythema, seven cases of drowsiness, nine cases of itching, three cases of dry mouth, four cases of dizziness and one case of pain. For the antihistamine medication alone treatment, three studies reported eight cases of drowsiness, four cases of dry mouth, seven cases of dizziness, two cases of gastrointestinal discomfort and two cases of headache. Only two trials [19, 20] reported recurrence of urticaria; this involved 60 patients, including 12 in the combined treatment group and 48 in the antihistamine alone group (Fig. 6). This analysis demonstrated an apparent benefit in a lower RER when NB-UVB therapy was added to antihistamine therapy (RR 0.13, 95% CI 0.06–0.28, \(p < 0.00001\)).

DISCUSSION

This systematic review, which included nine trials with 713 participants, evaluated the efficacy and safety of NB-UVB in the treatment of CU. Although the quality of these studies was not highly satisfactory, the results showed that, compared to treatment with antihistamines alone, combination therapy of histamines and
| Study (first author/year) | Composition of sample (male/female) | Age (years, T/C) | Course of the disease (T/C) | Interventions | Dose of NB-UVB | Course of treatment | Outcomes |
|--------------------------|------------------------------------|----------------|---------------------------|---------------|----------------|-------------------|----------|
|                         | Treatment group | Control group |                           |               |                |                   |          |
| Engin 2008 [16]          | 11/34                  | 14/19          | 34.2/32.6                 | 14.2/12 months | NB-UVB + levocetirizine (10 mg/day) | Initial dose: 200 mJ/cm\(^2\) | 3 months | TER, RUAS, VAS, ADE |
|                          |                       |                |                           |               | Levocetirizine (10 mg/day)          | Dose increments: 10%-20% |          |                |
|                          |                       |                |                           |               |                | Frequency: 3 times weekly |          |                |
|                          |                       |                |                           |               |                | Maximum dose: 1300 mJ/cm\(^2\) |          |                |
| Zhao 2011 [18]           | 23/18                  | 22/19          | 34.12/34.13               | 1.16/1.16 years | NB-UVB + desloratadine (5 mg/day) | Initial dose: 250 mJ/cm\(^2\) | 4 weeks | TER |
|                          |                       |                |                           |               | Desloratadine (5 mg/day)          | Dose increments: 10% |          |                |
|                          |                       |                |                           |               |                | Frequency: every other day |          |                |
|                          |                       |                |                           |               |                | Maximum dose: MED |          |                |
| Zuo 2011 [17]            | 42                    | 39             | 39                        | 3.1 years     | NB-UVB + mizolastine (10 mg/day) | Initial dose: 300 mJ/cm\(^2\) | 8 weeks | TER, SSRI, ADE |
|                          |                       |                |                           |               | Mizolastine (10 mg/day)          | Dose increments: 10-20% |          |                |
|                          |                       |                |                           |               |                | Frequency: 3 times weekly |          |                |
|                          |                       |                |                           |               |                | Maximum dose: 1500 mJ/cm\(^2\) |          |                |
| Study (first author/year) | Composition of sample (male/female) | Age (years, T/C) | Course of the disease (T/C) | Interventions | Dose of NB-UVB | Course of treatment | Outcomes |
|--------------------------|------------------------------------|-----------------|----------------------------|---------------|----------------|-------------------|----------|
| Dal 2014 [19]            | 26/22                              | 34.48 ± 6.79/33.12 ± 6.53 | 34.18 ± 6.43/10.32 ± 6.36 months | NB-UVB + desloratadine (5 mg/day) | Desloratadine (5 mg/day) | 4 weeks | TER, SSRI, RER, ADE |
| Fan 2016 [20]            | 40/40                              | 37              | 8 months                   | NB-UVB + mizolastine (10 mg/day) | Mizolastine (10 mg/day) | 12 weeks | TER, SSRI, RER, ADE |
| Wang 2018 [21]           | 32/32                              | 27.31 ± 6.8     | NR                         | NB-UVB + cetirizine hydrochloride (10 mg/day) | cetirizine hydrochloride (10 mg/day) | 4 weeks | TER, SSRI, ADE |

NB-UVB: Narrowband Ultraviolet B therapy; SSRI: Serotonin Reuptake Inhibitors; RER: Retinoids; ADE: Adverse Effects; NR: Not Reported.
Table 1 continued

| Study (first author/year) | Composition of sample (male/female) | Age (years, T/C) | Course of the disease (T/C) | Interventions | Dose of NB-UVB | Course of treatment | Outcomes |
|---------------------------|-------------------------------------|-----------------|----------------------------|---------------|----------------|-------------------|----------|
|                           | Treatment group                     | Control group   |                            |               |                |                   |          |
|                           | T                                    | C               |                            |               |                |                   |          |
| Chen 2019 [23]            | 9/6                                  | 8/7             | 35.48 ± 4.35 / 35.46 ± 4.36| NB-UVB + loratadine citrate (5 mg/day) | NB-UVB           | 4 weeks TER, SSRI |          |
|                           | 35.05 ± 3.12 / 9.03 ± 3.13 months   |                 |                            | loratadine citrate (5 mg/day) | Irradiation intensity: 10.5 mW/cm² | Frequency: every other day |          |
|                           |                                      |                 |                            |               |                |                   |          |
|                            | The first irradiation time was 45 s, followed by an increase of 7 s, for 7 times for one course | | | | | |          |
|                            |                                      |                 |                            |               |                |                   |          |
| Sheikh 2019 [22]          | 10/27                                | 13/22           | 30.54/33.4                 | NB-UVB + loratadine (10 mg/day) | Loratadine (10 mg/day) | 8 weeks UAS, RUAS, ADE |          |
|                           |                                      |                 | 18.95/15.66 months         |               | Dose increments: 10%-20% | Frequency: twice weekly |          |
|                           |                                      |                 |                            |               |                |                   |          |
|                            | Maximum dose: 1630 mJ/cm²             |                 |                            |               |                |                   |          |
| Study (first author/year) | Composition of sample (male/female) | Age (years, T/C) | Course of the disease (T/C) | Interventions | Dose of NB-UVB | Course of treatment | Outcomes |
|--------------------------|-------------------------------------|------------------|----------------------------|---------------|----------------|-------------------|----------|
| Han 2020 [24]            | 25/40                               | 33.0 ± 7.2/30.0 ± 8.1 | 12.6 ± 8.4/11.8 ± 7.6 weeks | NB-UVB + mizolastine (10 mg/day) | Initial dose: 200 mJ/cm² | 4 weeks | TER, SSRI |
|                          | 26/36                               |                   |                            | Mizolastine (10 mg/day)       | Dose increments: 10% |        |           |
|                          |                                     |                   |                            |               | Frequency: 2–3 times weekly |    |           |
|                          |                                     |                   |                            |               | Maximum dose: 3000 mJ/cm² |    |           |

Where data are available, values are presented as the mean ± standard deviation.

ADE Adverse event, C Control group, MED minimum effective dose, NB-UVB narrow-band ultraviolet B, RER recurrence rate, SSRI Symptom Score Reduction Index, T treatment group, TER total effective rate, UAS Urticaria Activity Score, VAS visual analog scale, NR Not reported.
NB-UVB seemed to be more effective at improving the TER with no differences in adverse events; the RERs were actually lower with the combination therapy. In terms of the safety evaluation, no serious adverse reactions were reported to be associated with NB-UVB phototherapy.

The exact pathogenesis of CU remains unknown. The proposed pathogenesis involves degranulation of mast cells as an important phenomenon, with the release of numerous pro-inflammatory mediators and cytokines [25]. NB-UVB has a suppressive effect on systemic immune responses and reduces the release of...
histamine and other pro-inflammatory mediators from mast cells and the apoptosis of dermal mast cells, and regulates cytokine production by both Th1 (interleukin-2 [IL-2], interferon gamma) and Th2 (IL-10) T-cell populations [22, 26, 27]. NB-UVB has an inhibitory effect on these pro-inflammatory mediators and cytokines, which can explain its role in CU. Aydogan et al. [28] treated a cohort of 22 patients with NB-UVB and showed a benefit in all patients, with complete response in ten of these patients, with both VAS scores and total CU impact on the quality of life being significantly lower after treatment compared to baseline. Bishnoi et al. [29] published a randomized prospective observer-blinded comparative study and found that after 90 days of treatment with NB-UVB, there was a decrease in the UAS to a mean value of 1.4, which was statistically significant. Although only very low-quality evidence is available, the KAAACI/KDA Evidence-Based Practice Guideline [15] suggests that NB-UVB phototherapy be used as add-on therapy in patients unresponsive to H1-antihistamines. Despite the growing acceptance of NB-UVB as an effective treatment modality in CU, few studies have systematically reviewed the advantages of NB-UVB phototherapy added to guideline-recommended antihistamine drugs. In addition, in the latest EAACI/GA2LEN/EDF/WAO (European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization) guidelines [1] and other guidelines [30–32], there is no recommendation regarding the use of phototherapy in the treatment of CU. In the present study, we performed a meta-analysis of the existing RCTs to better elucidate the efficacy and safety of NB-UVB phototherapy in the treatment of CU. The strengths of this meta-analysis are that we analyzed the superior efficacy of a combination treatment of NB-UVB + antihistamines. If true, NB-UVB might be a useful treatment option applicable in certain selected contexts, such as cases that do not

![Fig. 5 Adverse events associated with NB-UVB phototherapy + antihistamine medication vs. antihistamine alone for the treatment of CU](image1)

![Fig. 6 Recurrence rate associated with NB-UVB therapy + antihistamine medication vs. antihistamine alone for the treatment of CU](image2)
respond well to omalizumab or when this drug is not available.

Although the data showed a potential effectiveness of NB-UVB phototherapy, there are several limitations that should be mentioned. Firstly, only nine trials were included in this meta-analysis, which prevented certain statistical investigations (such as subgroup analyses and meta-regression) from being carried out. Secondly, of these nine articles, seven were published in Chinese, and two were in English. Most of the participants were from China, resulting in geographical limitations. Thirdly, only one study reported the blindness of the treatment options; this may have affected the reporting of treatment results in favor of NB-UVB phototherapy. Fourthly, the outcome measurement varied across the studies, which weakened the strength of the identified associations. Several studies used different percentages of TER to evaluate the responses, whereas two studies used UAS; this discrepancy may lead to inevitable bias. In addition, only two of the nine RCTs reported the RER, thus not allowing any reflection of the characteristics of the interventions.

CONCLUSIONS

In conclusion, NB-UVB phototherapy + antihistamine therapy may potentially be more effective for improving CU than antihistamine alone, with a very low degree of quality of evidence. This combined therapy may be safe and achieved low recurrence when used to treat patients with CU, based on the limited evidence currently available. For future research, large-scale multicenter RCTs with proper outcome measurements and long-term follow-up should be conducted to provide convincing proof.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Date Availability. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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