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Original Article

Efficacy, safety, and serum cytokine modulation by olopatadine hydrochloride and desloratadine citrate disodium combination therapy in urticaria

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Abstract: Objectives: To assess the efficacy, safety, and impact on serum cytokines of olopatadine hydrochloride (OLP) combined with desloratadine citrate disodium (DES) in treating urticaria. Methods: We retrospectively analyzed 114 urticaria patients treated at the Affiliated Hospital of Xinyang Vocational and Technical College from March 2020 to March 2023. The control group (55 patients) received DES, while the research group (59 patients) received OLP+DES combination therapy. We compared efficacy, safety (including epigastric pain, dry mouth, lethargy, dizziness, and fatigue), changes in serum cytokines (interleukin [IL]-2, IL-4, and interferon [IFN]-γ), symptom resolution (wheal number, wheal size, and itching degree), and 3-month recurrence rates. A univariate analysis was also conducted to identify factors influencing urticaria recurrence. Results: The research group exhibited a significantly higher overall efficacy rate, lower incidence of adverse events, and reduced recurrence rates at 3 months (all $P<0.05$) compared to the control group. Post-treatment, the research group showed significant increases in IL-2 and IFN-γ levels and reductions in IL-4 levels, wheal number, wheal size, and itching degree (all $P<0.05$). Factors such as history of drinking/smoking, IL-2 levels, and treatment method were associated with urticaria recurrence (all $P<0.05$). Conclusions: The combination of OLP and DES is an effective and safe treatment option for urticaria, significantly improving serum cytokine profiles, alleviating symptoms, and reducing recurrence risk.

Keywords: Olopatadine hydrochloride, desloratadine citrate disodium, urticaria, efficacy

Introduction

Urticaria, a prevalent allergic dermatological condition, not only incurs high healthcare costs but also significantly diminishes patient quality of life [1, 2]. The condition is triggered by numerous factors including mechanical stresses - such as friction, pressure, and vibration - and environmental stimuli like temperature extremes and electromagnetic radiation, leading to symptoms like intense pruritus, wheals, and edema in subcutaneous or interstitial tissues [3, 4]. The pathophysiology of urticaria involves both immunoglobulin E (IgE) and non-IgE mediated pathways, which excessively activate histamine release from mast cells and basophils and elevates other inflammatory serum mediators [5]. Epidemiologically, the lifetime prevalence of urticaria can reach up to 20%, with episodes typically resolving within 24 hours, though risk increases with age [6]. If not managed promptly and effectively, urticaria can exacerbate, potentially affecting gastrointestinal and respiratory functions, and impacting the patient's health as severely as ischemic heart disease [7]. Currently, the cornerstone of urticaria treatment includes second-generation H1 antihistamines, aimed at complete symptom resolution [8]. However, despite advancements, achieving an optimal inflammatory balance in the skin remains challenging. Thus, enhancing the efficacy of H1 antihistamines through combination therapies is critical for effective urticaria management [9]. Continued research into these therapies is essential for improved treatment outcomes.

As a potent long-acting histamine inhibitor, Desloratadine citrate disodium (DES) has demonstrated efficacy in upregulating helper T (Th)

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1 cytokines and suppressing Th2 responses in allergic rhinitis models in rats, while regulating inflammatory cytokines such as interleukin (IL)-4, IL-12, and interferon (IFN)-γ to reduce nasal inflammation [10, 11]. In patients with chronic sinusitis, DES has been shown to modulate various inflammatory mediators, effectively halting disease progression [12]. Furthermore, a study by Zheng et al. revealed DES's role in treating chronic urticaria, potentially through the down-regulation of cytokines like IL-4, IL-18, IL-23, and IL-33 [13]. Olopatadine hydrochloride (OLP), also an H1 antihistamine and mast cell stabilizer, has proven more effective than placebo in treating allergic rhinoconjunctivitis [14], and has managed symptoms such as itching, papules, and erythema in atopic dermatitis by modulating Ig E and IL-6 levels [15]. Sil et al. reported the use of OLP in chronic urticaria, highlighting its superior safety and efficacy compared to levocetirizine [16]. Despite these findings, there remains a significant gap in research regarding the combined clinical benefits of OLP and DES in treating urticaria. This study aims to evaluate the combination therapy's efficacy, safety, and impact on serum cytokines, thereby elucidating its therapeutic value.

Data and methods

General information

This retrospective study evaluated 114 patients with urticaria treated at the Affiliated Hospital of Xinyang Vocational and Technical College from March 2020 to March 2023. The study was approved by the Ethics Committee of the Affiliated Hospital of Xinyang Vocational and Technical College. Patients were divided into two groups: 55 received DES monotherapy (control group) and 59 received combined DES and OLP therapy (research group).

Inclusion criteria: (1) Confirmed diagnosis of urticaria based on established diagnostic guidelines [17]. (2) No use of other antihistamines, anticholinergics, receptor agonists, aspirin, or glucocorticoids within the previous two weeks. (3) Willingness to participate and ability to comply with study requirements. (4) No known contraindications to the study drugs. (5) Availability of complete clinical data.

Exclusion criteria: (1) Pregnant or lactating women, or women with childbearing potential not using effective contraception. (2) Severe comorbid conditions including respiratory, circulatory, digestive, endocrine, hematologic, immune, neurologic, or psychiatric disorders. (3) Presence of other skin conditions or non-classic forms of urticaria such as factitious or cholinergic urticaria. (4) Known drug allergies or hereditary angioedema. (5) Severe mental illness or cognitive impairment.

Medication methods

The control group received 8.8 mg of DES tablets (Shanghai LMAI-Bio Co., Ltd., Z101036) orally, once daily. The research group additionally received OLP tablets (5 mg; Shanghai Yuno Biotech Co., Ltd., BDG-110734-100), two tablets per dose, administered once in the morning and once in the evening. Treatment for both groups continued for two months.

Analysis indexes

(1) Efficacy [18]: Efficacy was assessed as follows: Marked effectiveness: Complete symptom and sign resolution with no recurrence within 6 months. Improvement: Significant symptom and sign reduction with occasional recurrence within six months. Ineffectiveness: No response to treatment or the need for a change in prescription. The total effective rate was calculated as the sum of cases with marked effectiveness and improvement divided by the total number of cases.

(2) Safety [19]: Post-treatment side effects such as epigastric pain, dry mouth, lethargy, dizziness, and fatigue were recorded, and the total incidence was calculated.

(3) Serum Levels of inflammatory factors [19]: 3 mL of fasting cubital venous blood was collected from each patient before and after treatment. Serum IL-2, IL-4, and IFN-γ levels were measured using ELISA kits (Shanghai Fuyu Biotech Co., Ltd., FY-03183H2, FY-03181H2, FY-03173H1) following the manufacturer's instructions.

(4) Symptom recovery [20]: Itching severity and number and size of wheals were scored as follows: Itching severity: Asymptomatic (0), mild (1), moderate (2), severe (3). Wheal number: 0 (0), 1-2 (1), 3-12 (2), >12 (3). Wheal size: None (0), ~1.5 cm (1), 1.5-2.5 cm (2), >2.5 cm (3).

Table 1. Comparison of general information

Indicators	Control group (n=55)	Research group (n=59)	χ^2/t	P
Age (years old)	37.40±6.91	38.51±8.86	0.742	0.460
Sex (male/female)	29/26	34/25	0.276	0.599
Disease duration (years)	6.38±2.25	6.54±2.43	0.364	0.717
Body mass index (kg/m^2)	23.31±1.05	23.71±1.13	1.954	0.053
Drinking history (yes/no)	11/44	9/50	0.443	0.506
Smoking history of (yes/no)	15/40	12/47	0.757	0.384

Table 2. Comparison of efficacy

Indicators	Control group (n=55)	Research group (n=59)	χ^2	P
Marked effectiveness	30 (54.55)	40 (67.80)		
Improvement	19 (34.55)	18 (30.51)		
Ineffectiveness	6 (10.91)	1 (1.69)		
Total effective rate	49 (89.09)	58 (98.31)	4.193	0.041

Table 3. Comparison of safety

Adverse events	Control group (n=55)	Research group (n=59)	χ^2	P
Epigastric pain	2 (3.64)	2 (3.39)		
Dry mouth	1 (1.82)	1 (1.69)		
Lethargy	4 (7.27)	0 (0.00)		
Dizziness	3 (5.45)	1 (1.69)		
Fatigue	4 (7.27)	2 (3.39)		
Total	14 (25.45)	6 (10.17)	4.597	0.032

(5) Follow-up [21]: The 3-month recurrence rates for both groups were statistically analyzed through medical record reviews, clinic visits, and telephone interviews.

Statistical analyses

Measurement data were expressed as mean ± standard deviation ($\bar{x}$±sd) and analyzed using the independent sample t-test for inter-group comparisons and the paired t-test for intra-group comparisons. Count data were presented as n (%) and analyzed using the χ^2 test. Univariate analysis was utilized to identify factors influencing recurrence in urticaria patients. Statistical analyses were conducted using SPSS version 21.0, with P<0.05 considered statistically significant.

Results

Comparison of general data

No significant differences were observed between the two groups in terms of age, sex, disease duration, body mass index, and histories of drinking and smoking (all P>0.05). See **Table 1**.

Comparison of efficacy

The total effectiveness rates were 89.09% in the control group and 98.31% in the research group, demonstrating higher efficacy in the research group (P<0.05). See **Table 2**.

Comparison of safety

Adverse events, including epigastric pain, dry mouth, lethargy, dizziness, and fatigue, were recorded. The overall incidence of adverse events was 10.17% in the research group, significantly lower than 25.45% in the control group (P<0.05). See **Table 3**.

Comparison of serum cytokines

Initial levels of IL-2, IL-4, and IFN-γ showed no significant differences between groups prior to treatment (all P>0.05). Post-treatment, signifi-

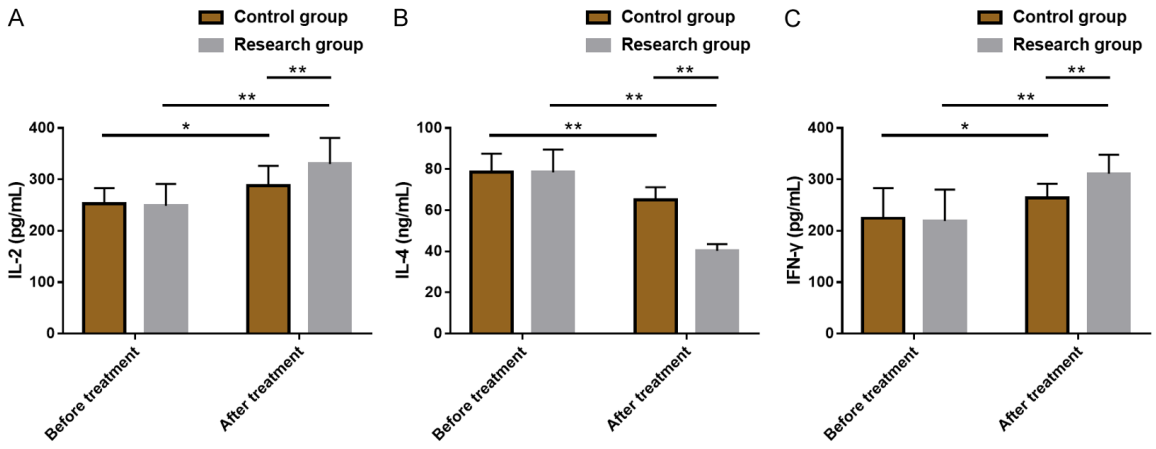

Figure 1. Comparison of serum cytokines. A. Changes in pre- and post-treatment IL-2 levels. B. Changes in pre- and post-treatment IL-4 levels. C. Changes in pre- and post-treatment IFN-γ levels. Note: * and ** represent P<0.05 and P<0.01, respectively. IL, interleukin; IFN, interferon.

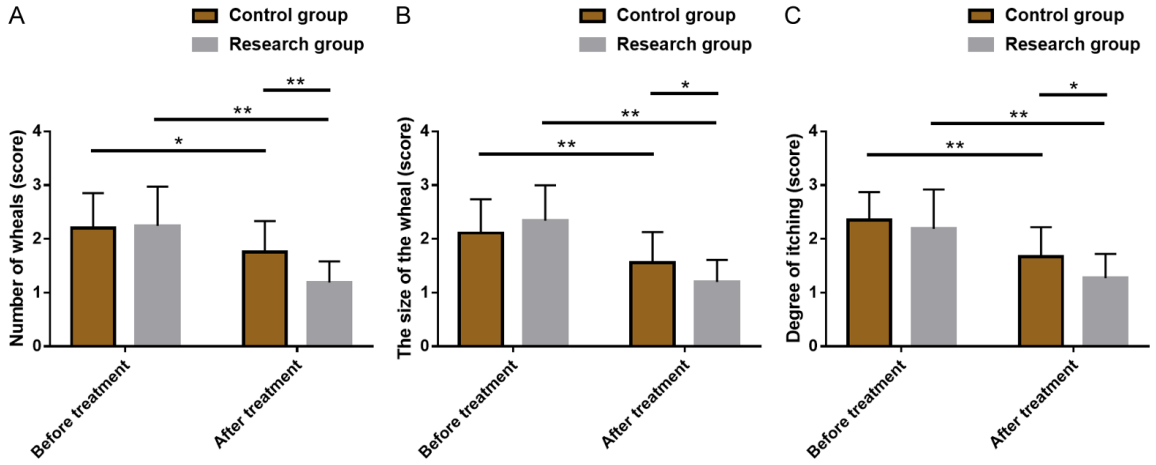

Figure 2. Comparison of symptom recovery. A. Changes in pre- and post-treatment scores of the wheal number. B. Changes in pre- and post-treatment scores of the wheal size. C. Changes in pre- and post-treatment scores of the degree of itching. Note: * and ** represent P<0.05 and P<0.01, respectively.

cant changes were observed in both groups: increases in IL-2 and IFN-γ levels and a decrease in IL-4 levels (P<0.05). Notably, the research group exhibited higher levels of IL-2 and IFN-γ and lower levels of IL-4 compared to the control group after treatment (P<0.05). See **Figure 1**.

Comparison of symptom recovery

The assessment of wheal number, size, and itching severity revealed no significant differences between groups before treatment (all P>0.05). However, post-treatment scores decreased significantly in both groups, with more pronounced improvements in the research group (all P<0.05). See **Figure 2**.

Comparison of recurrence rate

During a three-month follow-up, the recurrence rate was significantly lower in the research group (8.47%) compared to the control group (21.82%, P<0.05). See **Figure 3**.

Univariate analysis of recurrence

Analysis indicated that age, gender, disease duration, body mass index, IL-4, and IFN-γ were not significantly associated with recurrence (all P>0.05). However, factors such as drinking history, smoking history, IL-2 levels, and treatment method showed significant associations with recurrence rates (all P<0.05). See **Table 4**.

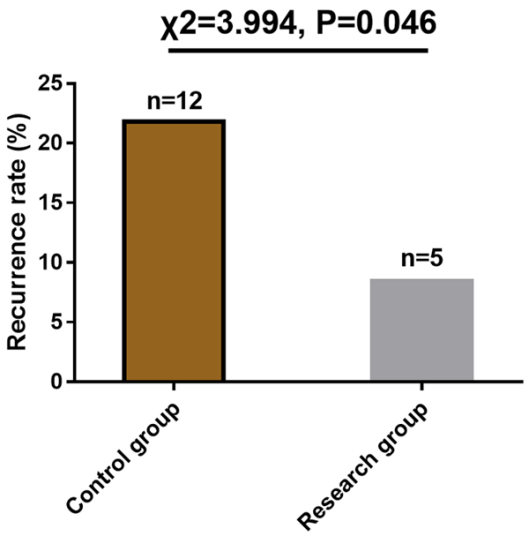

Figure 3. Recurrence rate of urticaria patients in two groups.

Discussion

Urticaria, predominantly a mast cell-mediated histaminergic condition, is broadly categorized into acute and chronic forms, with chronic spontaneous urticaria constituting the majority of cases [22]. Despite the availability of several effective treatments, patients achieve desired outcomes in only 60-80% of patients [23], highlighting the need for further exploration of therapeutic strategies to enhance treatment efficacy. In our study, the combination of OLP and DES demonstrated a higher total effectiveness rate (98.31% vs. 89.09%) compared to DES alone, suggesting enhanced clinical efficacy in managing urticaria. Safety assessments revealed lower incidences of side effects such as epigastric pain, dry mouth, lethargy, dizziness, and fatigue in the combination therapy group (10.17% vs. 25.45%), indicating a favorable safety profile for OLP+DES. Furthermore, OLP has been shown to be more effective and cost-efficient than rupatadine in treating chronic spontaneous urticaria, which is associated with a significant reduction (52.8%) in cell-associated platelet-activating factor, a key mediator of vascular permeability and inflammation [24-26]. A randomized, double-blind, placebo-controlled study by Yamamoto et al. corroborates the safety of OLP, reporting no serious adverse reactions during treatment for seasonal allergic rhinitis [27], aligning with our findings on its safety profile.

Furthermore, post-treatment serum cytokine analysis revealed significant increases in IL-2 and IFN-γ, and a significant decrease in IL-4 in the research group compared to the control, suggesting that the combination of OLP and DES effectively maintains the serum inflammatory balance in patients with urticaria. Notably, single nucleotide polymorphisms in IL-2 are linked to an increased susceptibility to chronic spontaneous urticaria, with IL-2 and IFN-γ predominantly secreted by Th1 cells [28, 29]. IFN-γ also inhibits Th2 cell proliferation and differentiation and reduces IL-4 release [30], which is primarily secreted by Th2 cells to stimulate B cells for Ig E synthesis, thereby exacerbating urticaria [31]. The synergistic effects of OLP and DES may thus correct abnormal immune responses more effectively than DES alone. This is supported by Tamura et al., who found that OLP significantly reduced IL-4 levels in a mouse model of oxazolone-induced chronic contact hypersensitivity, mirroring our results [32].

In terms of symptom recovery, both the numbers and size of wheals, as well as the degree of itching, were significantly reduced in the research group compared to the control group post-treatment, underscoring the effectiveness of the OLP and DES combination in managing urticaria symptoms. Notably, Abelson et al. demonstrated that OLP eye drops expedited and enhanced relief from eye itching in patients with acute allergic conjunctivitis [33]. Additionally, the research group exhibited a statistically lower recurrence rate of urticaria compared to the control group, suggesting that OLP+DES may help reduce the likelihood of recurrence. This aligns with findings by Shi et al., where a combination of tripterygium glycosides tablets and DES notably decreased recurrence rates, illustrating the benefits of combination therapy in minimizing urticaria recurrence risks [34]. Univariate analysis identified factors influencing recurrence; patients with a history of drinking/smoking, IL-2 levels below 300 pg/mL, and those treated with DES alone were more prone to urticaria recurrence.

This study faces several limitations. Firstly, as a single-center study with a limited sample size, its findings need confirmation through multicenter studies with larger populations to enhance their generalizability. Secondly, the

Table 4. Univariate analysis of recurrence in urticaria patients

Indicators	Recurrent group (n=17)	Non-recurrent group (n=97)	χ^2/t	P
Age (years)			2.833	0.092
<40 (n=68)	7 (41.18)	61 (62.89)		
≥40 (n=46)	10 (58.82)	36 (37.11)		
Gender			0.044	0.835
Male (n=63)	9 (52.94)	54 (55.67)		
Female (n=51)	8 (47.06)	43 (44.33)		
Disease duration (years)			0.010	0.919
<6 (n=39)	6 (35.29)	33 (34.02)		
≥6 (n=75)	11 (64.71)	64 (65.98)		
Body mass index (kg/m^2)			0.176	0.675
<24 (n=59)	8 (47.60)	51 (52.58)		
≥24 (n=55)	9 (52.94)	46 (47.42)		
Drinking history			38.861	<0.001
Yes (n=20)	12 (70.59)	8 (8.25)		
No (n=94)	5 (29.41)	89 (91.75)		
Smoking history			13.649	<0.001
Yes (n=27)	10 (58.82)	17 (17.53)		
No (n=87)	7 (41.18)	80 (82.47)		
IL-2 (pg/mL)			11.446	<0.001
<300 (n=45)	13 (76.47)	32 (32.99)		
≥300 (n=69)	4 (23.53)	65 (67.01)		
IL-4 (ng/mL)			0.604	0.437
<60 (n=70)	9 (52.94)	61 (62.89)		
≥60 (n=44)	8 (47.06)	36 (37.11)		
IFN-γ (pg/mL)			1.914	0.167
<300 (n=70)	13 (76.47)	57 (58.76)		
≥300 (n=44)	4 (23.53)	40 (41.24)		
Treatment method			3.994	0.046
Desloratadine Citrate Disodium Tablets (n=55)	12 (70.59)	43 (44.33)		
Olopatadine Hydrochloride plus Desloratadine Citrate Disodium Tablets (n=59)	5 (29.41)	54 (55.67)		

absence of prognostic analysis restricts our understanding of the long-term outcomes of OLP+DES treatment in urticaria patients. Future studies should include longitudinal follow-ups to assess the impact of this treatment on patient prognosis. Expanding the analysis of prognostic factors will be crucial in determining whether OLP+DES therapy serves as a protective factor in improving long-term outcomes for these patients.

The primary innovation of this study lies in its comprehensive evaluation of OLP+DES therapy, confirming its clinical superiority over DES monotherapy in treating urticaria across multiple dimensions: efficacy, safety, modulation of serum cytokines, symptom relief, and reduced recurrence rate within a three-month follow-up period.

In conclusion, the combination of OLP and DES Tablets demonstrated superior performance compared to DES alone in treating urticaria, as evidenced by higher effectiveness, enhanced safety, greater normalization of serum cytokine levels, faster symptom resolution, and a lower risk of recurrence. These findings suggest that OLP+DES combination therapy could offer a more effective treatment option for urticaria patients.

Disclosure of conflict of interest

None.

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