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The Effect of Vitamin C on Histamine and Dust Mite Epicutaneous Test Responses: A Randomized Control Trial

Wan Abdul Aziz Wan Azhar[1], Husna Hasri[1], Sze Ying Tan[1], Divaharan Subramanie[1], Anasuhah Musa[2], Farah Dayana Zahedi[1,2], Samirah Taufiq Abdul Wahid[3], Norwahidah Abdul Karim[4], Shamsul Azhar Shah[5], Aneeza W Hamizan[1,2], Salina Husain[1,2]

[1]Department of Otorhinolaryngology, Malaysia, Faculty of Medicine, Kuala Lumpur, Malaysia
[2]Allergy Unit, Hospital Canselor Tuanku Mukhriz, Kuala Lumpur, Malaysia
[3]Universiti Kebangsaan Faculty of Allied Health Care and Science, Kuala Lumpur, Malaysia
[4]Department of Biochemistry, Universiti Kebangsaan Faculty of Medicine, Kuala Lumpur, Malaysia
[5]Department of Public Health, Universiti Kebangsaan Faculty of Medicine, Kuala Lumpur, Malaysia

Abstract

Objective: Vitamin C has antihistamine properties, but its effect on allergic skin responses is unclear. This study aimed to evaluate the effect of vitamin C on skin wheal reactions to exogenous histamine and a known allergen during skin prick tests (SPTs).

Methods: In this single-blinded randomized controlled trial, adults with allergic rhinitis and known positive SPT toward house dust mites were randomized into 2 groups: the intervention group received vitamin C (1000 mg daily for 7 days) and the control group kept a diet journal only. Repeat testing was conducted on day 8, and wheal sizes were measured using Image J software. Mean differences in wheal area (mm^2) between groups were compared, and treatment effect sizes within groups were calculated using Cohen's *d* formula.

Results: Of 103 participants, 44 in the vitamin C group and 45 in the control group completed the study. Vitamin C led to a small, non-significant reduction in histamine-induced wheal size (-2.5 ± 11.57 mm^2, Cohen's $d=0.30$ vs. -0.92 ± 14.24 mm^2, $P=.56$, Cohen's $d=0.08$), but no reduction was seen for dust mite allergens ($+4.48 \pm 25.08$ mm^2, Cohen's $d=-0.20$ vs. -0.16 ± 26.17 mm^2, Cohen's $d=0.01$, $P=.40$).

Conclusion: Short-term vitamin C supplementation had a minor, non-significant suppressing effect on exogenous histamine but did not attenuate the skin allergen responses. Vitamin C may be useful for histamine intolerance, but this requires larger studies.

Keywords: Ascorbic acid, vitamins, histamine antagonists, rhinitis, allergic, histamine, hypersensitivity, immediate

INTRODUCTION

Vitamin C, also known as ascorbic acid, is a water soluble micronutrient with known antihistamine effects.[1] Prior studies have shown that vitamin C levels are inversely correlated with blood histamine levels, where its supplementation leads to histamine.[2] Oral vitamin C at 1000 mg per day taken for 7 days was also reported to improve nasal symptoms among patients with allergic rhinitis, making it a popular supplement in this group of patients.[3] Patients with allergic rhinitis may undergo a skin prick test (SPT) to confirm the presence of an allergy. This test involves introducing histamine as a positive control and suspect allergens epicutaneously, and its wheal response will be recorded. A lack of skin wheal response toward histamine indicates the use of medications with antihistamine properties.[4] In a historical crossover study, Fortner et al[5] demonstrated that 7 out of 8 patients had less skin reactivity to histamine after taking oral vitamin C at 500-600 mg daily for 3 days, compared to when they were on a placebo. Larger studies are needed to investigate the antihistamine effect of vitamin C. This may lead to improved allergy diagnosis and management.

This study aims to evaluate the effect of oral vitamin C supplementation on skin reactions (measured by wheal area or diameter) toward histamine and dust mite allergens during SPT among individuals with prior documented allergies.

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Corresponding author:
Aneeza W Hamizan
E-mail: draneeza@gmail.com

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MATERIALS AND METHODS

Study Design

This was an investigator-blinded randomized controlled trial, conducted at the otorhinolaryngology outpatient clinic at a tertiary hospital. This study was approved by the Ethics Committee of Universiti Kebangsaan Malaysia (Approval no.: JEP-2023-329, Date: 26th June 2023 and registered in a public clinical trial registry (no. NCT05810233). All participants gave written informed consent. This study was written according to the Consolidated Standards of Reporting Trials (CONSORTS) guideline.[6]

Participants

This study included adults between 18 and 60 years old with a history of at least 2 symptoms of allergic rhinitis triggered by dust for more than 3 months. They must have prior valid positive SPT within the past year with a wheal reaction of at least 3 mm toward house dust mite (*Dermatophagoides pteronyssinus* (DP)). Participants were excluded if they had smoked cigarette or vaped in the past 6 months, had skin conditions affecting the volar aspect of the arm, were on beta-blockers, dietary supplements or immunosuppressants, had autoimmune disease, had pre-existing renal diseases, or a history of vitamin C allergy.

Those without available prior SPT reports or without a clear pen-outlined scotch tape-transferred wheal tracing were also excluded.

Study Proforma

All participants were given a study proforma to collect their basic demographic details, rhinitis symptoms (type, duration, allergic comorbidities), and to assess the severity of their nasal symptoms using the visual analogue scale (VAS). The VAS assessed overall nasal symptoms from 0 to 100 mm (no symptoms to worst ever symptom).

The prior SPT reports were retrieved, and the wheal tracings were scanned for measurement.

Intervention Arms

Participants were randomized to either receive a vitamin C tablet, 1000 mg once daily (Citrex, Pharmaniaga Sdn Bhd, Malaysia) (vitamin C group) or not (control group). Vitamin C was taken each morning, beginning the next day, for the next 7 days. All participants were scheduled to return on day 8. Participants in the intervention group took their final dose of vitamin C on the morning of day 8, before returning for their follow-up appointment. During the intervention period, all participants were allowed to continue their intranasal corticosteroids but were prohibited from taking any antihistamines or other health supplements.

Randomization and Blinding

A randomization sequence was generated by Microsoft Excel Randomizer by a research assistant not involved in the study. The vitamin C with instruction form (for the vitamin C group) or the instruction form alone (for the control group) was placed in a sealed opaque envelope based on the randomization sequence and serially labeled with the research identification number. The participants each received an envelope with their corresponding research number. The group assignment was only revealed after data analyses were completed.

Main Points

- *Vitamin C at a dose of 1000 mg daily over 7 days did not have any significant effect in reducing histamine or allergen response during the SPT.*
- *Vitamin C had a small effect size (Cohen's d = 0.3), suppressing the skin response toward exogenous histamines, but larger studies are needed.*
- *Vitamin C at this dose did not attenuate the skin response to a known allergen.*

Monitoring for Compliance and Side Effect

Participants filled out a compliance card to record their daily intake of vitamin C tablets. They were contacted by the same research assistant who dispensed the envelope on day 3 of the intervention to assess any adverse effects and ensure compliance. Participants were also required to return the envelope on day 8 for tablet counting.

Food Diary

All participants were asked to continue their regular diet without making any drastic changes for the next 7 days to control for dietary factors. They were also required to record their daily food intake in a food diary, which included the type of food and the amount they consumed daily. Foods that are high in vitamin C, such as guavas, bell peppers, kiwifruits, strawberries, oranges, papayas, tomatoes, snow peas, kale, and Cruciferous vegetables (e.g., broccoli, Brussels sprouts, cabbage, and cauliflower), were identified from the diet, and the total vitamin C consumed from the diet was estimated using a dietary reference atlas.[7]

Skin Prick Test

All participants returned on day 8 after randomization and were subjected to a post-intervention skin prick test (SPT). Standard screening for this procedure was utilized, and there were no participants on tricyclic antidepressants, oral steroids, or beta-blockers. All withheld antihistamines for 7 days before the SPT and were not on any other supplements. The post-intervention SPT was performed by 1 investigator blinded to the intervention group, with more than 5 years of experience in allergy (AH). The SPT was performed using the standardized SPT protocol which had been in effect for the past 5 years. All tests were performed in the same room at the allergy unit, using the same allergen and metal lancet type (Inmunotek, Spain). The post-intervention SPT only included dust mite (DP), together with positive and negative controls. The resulting wheal diameter was traced with a fine-tip pen and the tracing transferred to the reporting sheet. A wheal diameter of 3 mm or larger for dust mite, in the absence of a reaction for the negative control and a positive histamine reaction (≥3 mm), was considered valid and positive.[4] All participants were monitored in the clinic for 15 minutes after completion of the SPT. A test is considered valid if the negative control is less than 3 mm and the positive control is 3 mm or more. A valid and positive response is recorded if this included a 3 mm wheal reaction for the house dust mite extract.

Measurement of Skin Prick Test Wheal Size

The wheal size was measured in mm using (1) the area in mm^2 and (2) longest diameter in mm. The measurement was performed using the software, Image J.[8] The scanned copy of the SPT wheal tracing was uploaded into the software, and the measurement scale was set as millimeter (mm) and calibrated on a ruler scale. Measurement of the area (mm^2) was done by selecting the area using the tool in Image J software. Measurement of the wheal diameter (mm) was done by drawing a line between the 2 widest points.[9] The mean of 3 consecutive measurements was taken for each participant for every baseline and post-intervention prick test and recorded. The values were recorded on a datasheet, and the difference in values between the post-intervention period and baseline were compared.

Statistical Analysis

All statistical analyses were performed per protocol using the Statistical Package for Social Science (SPSS) version 26 (IBM SPSS Corp.; Armonk, NY, USA). The wheal area and diameter before and after the intervention within each group were assessed using a Paired *t*-test. The difference in the wheal area and diameter pre- and post-intervention were calculated by subtracting the post-intervention with baseline measurements. The values were recorded, and the mean difference between groups was assessed using a Student *t*-test. The effect size per intervention was calculated using Cohen's *d* formula utilizing an online calculator (https://goodcalculators.com/effect-size-calculator/).

RESULTS

Participants

A total of 103 participants were randomized into the vitamin C (n=51) and the control group (n=52). Of these, 44 participants from the vitamin C group and 45 participants from the control group respectively completed the study protocol (Figure 1).

There were no differences in the characteristics and baseline SPT between the vitamin C and control groups. The dietary intake of vitamin C during the intervention period was also similar for both groups (Table 1).

Wheal Size Within Group

The changes between baseline and after intervention for the vitamin C group and the control group are depicted in Figure 2.

In the vitamin C group, the wheal area (23.94 ± 9.28 vs. 21.41 ± 7.74 mm^2, P=.16, Cohen's d=0.30) and longest diameter (6.50 ± 1.41 mm vs. 6.15 ± 1.01 mm, P=.20, Cohen's d=0.29) for histamine were similar between baseline and after the intervention (Figure 2A(i-ii)). Similarly, the wheal area for dust mite did not change significantly (30.86 ± 21.62 mm^2 and 35.34 ± 22.88 mm^2, P=.20, Cohen's d = −0.20) (Figure 2A(iii)). However, the dust mite wheal diameter was larger after ingesting 7 days of vitamin C (7.36 ± 2.59 mm vs. 8.36 ± 3.05 mm, (P=.03), Cohen's d = 0.35) (Figure 2A(iv)).

In the control group, the histamine wheal area (25.23 ± 12.05 mm^2 and 24.31 ± 11.47 mm^2, P=.67, Cohen's d = 0.08) and diameter (6.49 ± 1.51 mm and 6.39 ± 1.57 mm, P=.84, Cohen's d=0.07) also remained similar (Figure 2B(i-ii)). This was also seen for the dust mite wheal area (34.36 ± 19.53 mm^2 and 34.19 ± 22.09 mm^2, P=.97, Cohen's d = 0.01) and diameter (7.88 ± 2.53 mm vs. 8.11 ± 3.19 mm, P=.67, Cohen's d=0.08) (Figure 2B (iii-iv)).

Wheal Size Between Groups

The mean difference in the histamine wheal area between the vitamin C group and the control group was similar (−2.51 ± 11.57 mm^2 vs. −0.92 ± 14.24 mm^2, P=.56). This was mirrored by the mean differences in wheal diameter (−0.36 ± 1.70 mm vs. −0.06 ± 1.96 mm, P=.48) (Figure 3A).

The mean difference in dust mite wheal area (4.48 ± 25.08 vs. −0.16 ± 26.17 mm^2, P=.40) and diameter (1.00 ± 2.98 vs. 0.23 ± 3.54 mm, P=.27) between the vitamin C group and the control group was also not statistically significant (Figure 3B).

Validity of Skin Prick Test Pre- and Post-Intervention

All participants' SPTs remain valid and positive for post-intervention SPTs.

Compliance

All participants complied with the rules and medication checklist.

Adverse Effect

There were no side effects reported among participants taking vitamin C and the control at day 3 and day 8. There were no adverse events after the SPT among all participants.

DISCUSSION

This study revealed that 7 days of oral supplementation with 1000 mg of vitamin C did not produce any significant changes in the wheal size measurements. This was seen both within the vitamin C group before and after the intervention, as well as between the vitamin C and control groups. Although there was no statistically significant difference in wheal size in the vitamin C group, there appears to be a small effect size in reducing the skin reactivity toward exogenous histamines (Cohen's d = 0.3), when contrasted to the consistently low effect size of the control group (Cohen's d range 0.01-0.08). However, this attenuating effect was not observed when a known allergen was applied to the skin; instead, this allergen application seemed to aggravate the skin reaction among those taking vitamin C. Larger studies are needed to examine the role of

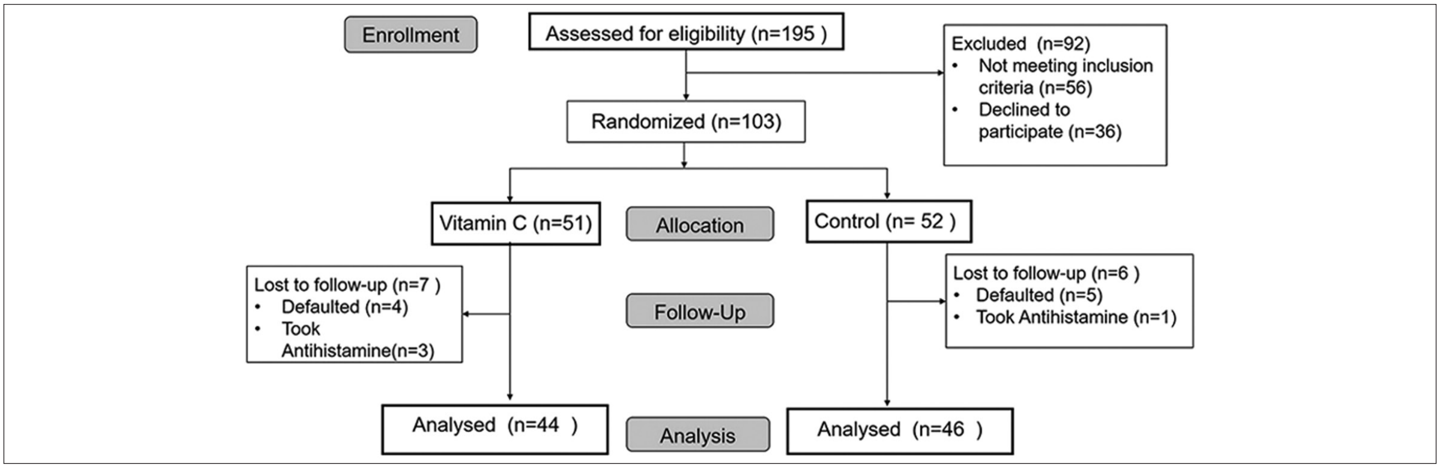

Figure 1. The CONSORT flowchart showing the number of participants assessed for eligibility, randomized, and subsequently completed the study, and analyzed (per-protocol).

Table 1. The Baseline Characteristics of Allergic Rhinitis Participants Randomized into the Vitamin C Intervention Group or Control

	Vitamin C	Control	*P*
N	44	45	–
Age (years)	26.07 ± 6.08	26.82 ± 8.88	.64
Gender (female %)	63.6	64.4	.94
Race (%)			.62
- Malay	59.1	68.9	
- Chinese	22.7	22.2	
- Indian	13.6	6.7	
- Others	4.5	2.2	
Rhinitis status (intermittent %)	79.5	71.1	.36
Severity of allergic rhinitis (moderate to severe %)	68.2	60	.42
Trigger (dust %)	100	88.9	.06
Family history of allergic comorbidities (%)	70.5	84.4	.11
Visual analog score (VAS)			
- Overall symptoms	41.07 ± 27.45	39.89 ± 29.56	.85
- Runny nose	37.32 ± 28.32	36.18 ± 30.56	.86
- Sneezing	39.73 ± 28.56	41.47 ± 28.96	.78
- Blocked nose	38.52 ± 31.75	34.58 ± 30.81	.55
- Itchy nose	35.20 ± 27.39	38.16 ± 29.39	.73
Baseline histamine diameter (mm)	6.50 ± 1.41	6.49 ± 1.51	.98
Baseline histamine area (mm^2)	23.94 ± 9.28	25.23 ± 12.05	.57
Baseline DP[†] diameter (mm)	7.36 ± 2.59	7.88 ± 2.53	.33
Baseline DP area (mm^2)	30.86 ± 21.62	34.36 ± 19.53	.43
Total vitamin C intake (mg)	134.92 ± 163.40	107.64 ± 148.27	.41

[†]DP, *Dermatophagoides pteronyssinus.*

vitamin C in modifying the skin response towards exogenous histamine and allergens. Despite these findings, the SPTs remained valid regardless of vitamin C supplementation.

Vitamin C at this maximum commercially available dose did not have any substantial effect on the skin wheal reaction. Similarly, Newbold[10] did not observe any difference in skin reaction after a 6-day intervention with 1000 mg of oral vitamin C. In this current study, 1 week was deemed sufficient for the antihistamine effect. This was supported by Clemetson,[11] who showed that 1000 mg of vtamin C taken orally for 3 days had already translated into reduced blood histamine levels. Levine et al[12] also reported a reliable increase in serum vitamin C levels with 1000 mg supplementation which plateaued within 1 day. However, this dose is recommended for reducing the severity and duration of the common cold, but its effect on allergies still requires further studies.[13]

In this study, vitamin C seems to have a small effect in attenuating the skin response towards exogenous histamine, but this requires confirmation with a larger sample size. Vitamin C supplementation has also been tested for a protective effect against inhaled exogenous histamine, but the results have been conflicting. [16,17] Exogenous histamine response may be reduced by vitamin C through enhanced histamine degradation. This is because vitamin C is a cofactor of Diamine Oxidase (DAO), an enzyme responsible for metabolizing extracellular histamine.[14] The inability to degrade histamine leads to systemic symptoms which may mimic allergy. This group of diseases has been termed histamine intolerance, and low histamine diet with vitamin C supplement is a suggested therapy.[15] This postulates that vitamin C may be beneficial in reducing symptoms from high dietary histamine found in fermented products or crustaceans which may aggravate allergy symptoms.

In this current study, vitamin C did not reduce the skin wheal reaction towards a culprit allergen. In this case, the skin is not exposed to exogenous histamine, but to a known allergen that will crosslink with the FcεRI receptor on mast cells, leading to the release of endogenous

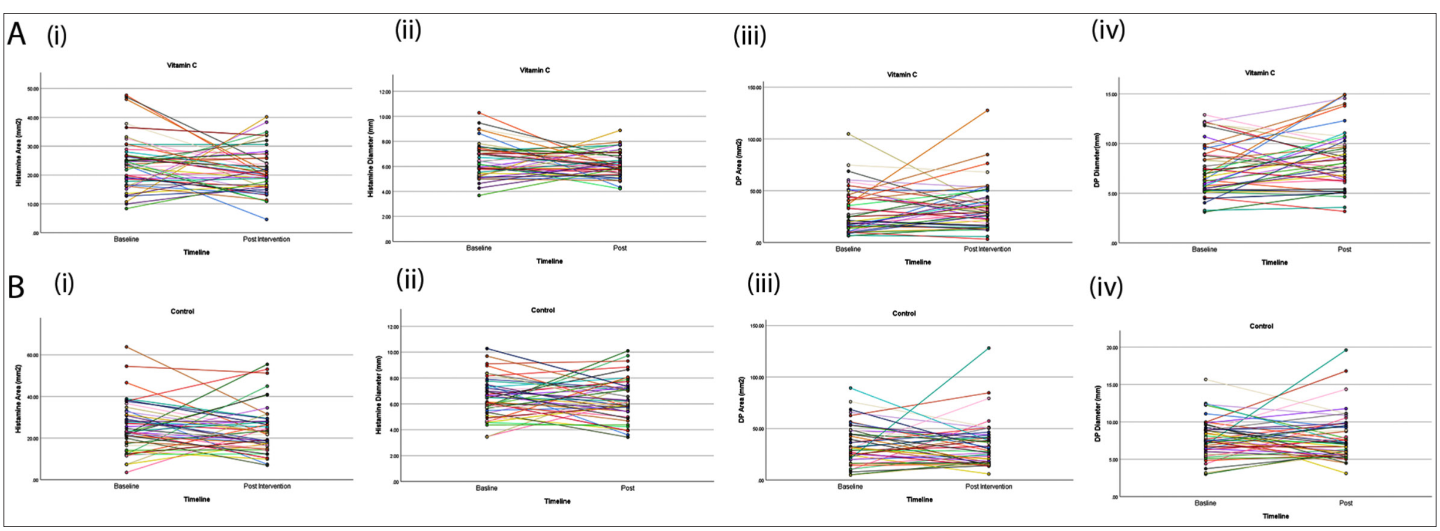

Figure 2. The skin prick test wheal area and diameter for each participant at baseline and after intervention period. Each circle represents a patient's wheal size at baseline (left) and after intervention (right) with the connecting line showing either an increase (upward slope) or decrease (downward slope) in wheal size. (A) Overall, participants in the vitamin C group showed no marked changes in histamine wheal area (i) or diameter (ii). The wheal area for dust mite allergen (*Dermatophagoides pteronyssinus* (DP)] remained similar (iii) but the wheal diameter showed an increased trend (iv). (B) Among the controls there were no changes in the histamine wheal area (i), diameter (ii) as well as dust mite (DP) wheal area(iii) or diameter (iv).

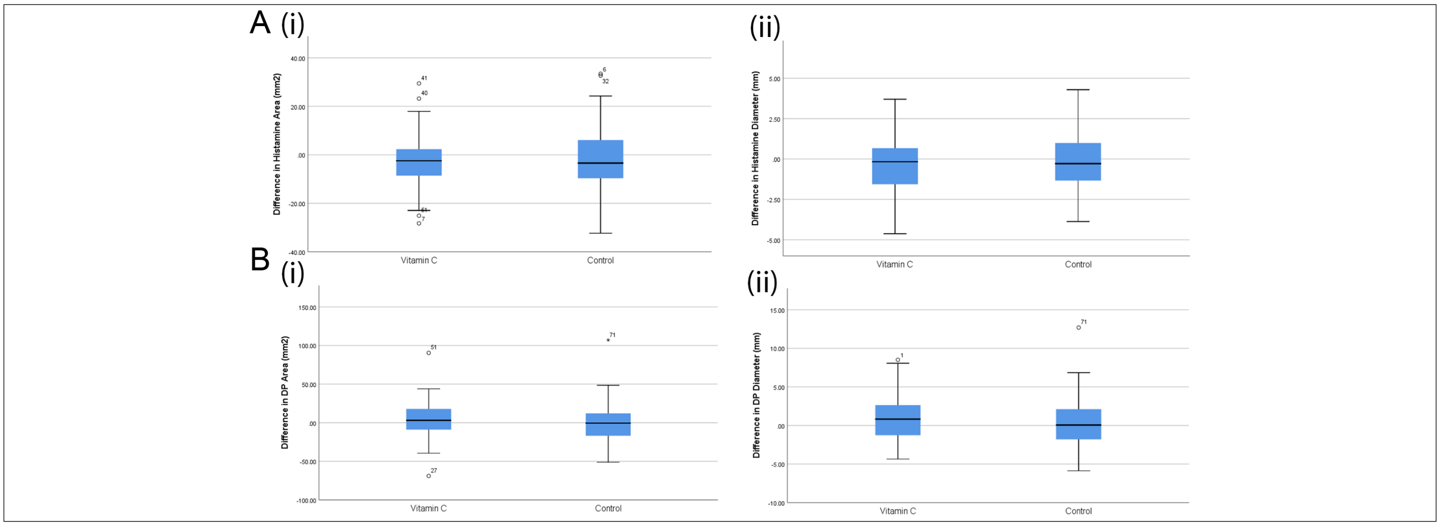

Figure 3. Comparison of the wheal size change (mean difference) in (A) histamine and (B) *Dermatophagoides pteronyssinus* (DP): (i) wheal area (mm^2) and (ii) diameter (mm) between the vitamin C group and the control group. The graph depicts the mean wheal area (mm^2) and diameter (mm) for histamine and DP allergens for both groups, with bars representing the standard deviation. There were no differences in the wheal size change (area or diameter) after intervention between the vitamin C and control group.

histamine. This mast cell degranulation is unlikely to be inhibited by this relatively low dose of vitamin C. A laboratory study using peritoneal mast cells found that lower concentrations of vitamin C do not have a mast cell stabilizing effect. However, higher concentration can dose-dependently prevent mast cell degranulation, and this effect is potentiated by other supplements.[18] Clinical studies have also supported the use of high doses to achieve an antiallergenic effect [19,20]. Vollbracht et al[20] found that 7.5 g of intravenous vitamin C for 3 weeks was able to reduce skin pruritus and rhinitis and this was supported by Hagel et al.[21] Taken together these studies support the use of high doses for the management of mast cell-related diseases.[19-21] However, vitamin C toxicity is a concern when administering such high doses.[12] Topical vitamin C may be an option, and this was proven in a study that found reduced skin allergy towards hair dye when the skin was pretreated with topical vitamin C.[22]

The high variability in the skin wheal sizes, as evidenced by the large standard deviations, may have masked the effect of vitamin C on the skin test reaction. This may also explain the slight increase in dust mite wheal diameter in the vitamin C group. This is difficult to control for as the skin response will vary by skin site, time of day, and individual responses (e.g., age, race, and skin condition).[23] Furthermore, operator technique can influence SPT outcomes, such as the angle of penetration, applied pressure, distance between SPT sites, and measurement of wheal diameter.[23] This study only took participants who had previously done SPT in the past year, due to ethical concerns. This led to operator variability between baseline and post-intervention tests. However, all SPTs done in our clinic followed the same protocol and used the same allergen from the same manufacturer. In this current study, the repeat SPT results remained positive and valid in both the vitamin C and control groups. This suggests, that despite the variabilities present, SPT remains a reliable test to confirm the presence of allergy.

Another limitation is that there was no documented serum vitamin C concentration due to a lack of resources. This was addressed by recording compliance with vitamin C as its intake is associated with increased plasma level.[12,24] We also recorded dietary intake using a food diary to estimate the usual vitamin C consumption. This was compared between groups, which showed similar vitamin C intake across groups.

The strength of this study is that it utilized the maximum over-the-counter dosage of vitamin C, which reflects the amount patients typically consume as dietary supplements.[24] High compliance was also observed in the vitamin C group without any reports of side effects reaffirming its good safety profile. We also used the SPT wheal, which is an objective outcome measurement to assess the antihistamine effect of vitamin C. In addition, the measurement of the SPT wheal reaction was done through computerized analysis to reduce measurement bias.

While previous studies have explored the antihistamine effects of vitamin C, this current study specifically addresses its potential impact on skin responses to exogenous histamines and allergens, an area with limited existing data. Vitamin C may be a useful adjunct for the treatment of allergies, but further research employing longer durations and higher dosages of vitamin C supplementation may be warranted.

CONCLUSION

Previous research has shown that vitamin C has antihistamine properties and can help reduce histamine levels in the body. However, the current study found that 7 days of 1000 mg vitamin C supplementation may have a small effect in attenuating exogenous histamine but not toward a known allergen. Further, larger studies are needed to assess the role of vitamin C in the management of histamine-related diseases.

Data Availability Statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics Committee Approval: This study was approved by the Ethics Committee of Universiti Kebangsaan Malaysia (Approval no.: JEP-2023-329, Date: 26th June 2023).

Informed Consent: Written informed consent was obtained from the patients/ patient who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Author Contributions: Concept – A.H., S.H., F.D.Z., W.K., S.T.; Design – A.H., F.D.Z., S.H.; Supervision – A.H., F.D.Z.; Resources – W.K., S.T., A.M.; Materials – S.T., A.M.; Data Collection and/or Processing – W.A.A., H.H., S.Y., D.S.; Analysis and/or Interpretation – W.A.A., H.H.; Literature Search – H.H., S.Y.; Writing Manuscript – W.A.A., H.H., S.Y., D.S Critical Review – A.H., F.D.Z., S.H.

Declaration of Interests: The authors have no conflict of interest to declare.

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