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Use of Cimetidine and Levamisole in the Treatment of Cutaneous Warts: A Systematic Review

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Abstract

Objective: The objective of this study was to evaluate the efficacy of cimetidine and levamisole, either alone or in combination, in the treatment of cutaneous warts in adults and children, based on the available clinical evidence.

Methods: A systematic review of the literature was conducted using electronic databases and gray literature, including studies published before September 2025. Randomized, double-blind, placebo-controlled clinical trials and comparative studies were included. The main outcomes analyzed were complete wart clearance, mean regression time, and the incidence of adverse events.

Results: A total of 11 studies were included, encompassing 648 patients: five trials on cimetidine monotherapy, four on levamisole monotherapy, and two on the combination of cimetidine and levamisole. The five trials evaluating cimetidine alone demonstrated similar cure rates compared to placebo, ranging from 22% to 32% ($p > 0.05$). The four trials

investigating levamisole alone showed no statistically significant benefit, except for one gray literature record that reported high cure rates but presented a high risk of bias. In contrast, the two randomized trials assessing the combination therapy showed higher cure rates—85.7% in adults and 65% in children—compared with monotherapies ($p < 0.05$).

Conclusion: Both cimetidine and levamisole, when used as monotherapies, show no proven benefit in the treatment of cutaneous warts. However, their combination appears to be a promising therapeutic option, particularly in recalcitrant cases, warranting further multicenter randomized clinical trials to confirm these findings.

Keywords: cutaneous warts, cimetidine, levamisole, systemic treatment, systematic review.

Introduction

Cutaneous warts are benign lesions caused by the human papillomavirus (HPV), affecting between 7% and 12% of the global population, with higher prevalence in children, adolescents, and immunocompromised individuals [1,2]. Although many warts may undergo spontaneous regression, approximately one-third of cases persist or recur, necessitating therapeutic intervention [3].

Conventional treatments involve local approaches such as liquid nitrogen cryotherapy, salicylic acid application, curettage, electrocautery, laser therapy, and topical agents such as podophyllotoxin, imiquimod, and cantharidin [4]. These options show good efficacy in most patients but become insufficient in disseminated, multiple, or recalcitrant cases, particularly in individuals with primary or secondary immunodeficiencies [5].

In such cases, systemic therapies have been explored. Among the studied options are cimetidine, an H2-receptor antagonist that inhibits suppressor T lymphocytes and enhances cell-mediated immunity against HPV [6]; levamisole, a classical immunomodulator with stimulatory effects on T cells and macrophages [7]; alphainterferon, used in severe cases of warts but associated with high cost and significant adverse effects [8]; systemic antivirals such as cidofovir, which demonstrate some efficacy but are limited to hospital settings and immunocompromised patients [9]; and intralesional immunotherapeutic agents, such as Candida antigen, which activate both local and systemic immune responses [10]. Other drugs, such as systemic retinoids and low-dose methotrexate, have been used in very specific cases of severe immunodeficiency [11].

Among systemic therapies, cimetidine and levamisole stand out for being accessible, low-cost, and having a well-established safety profile. Preliminary studies have suggested that, particularly when used in combination, they may enhance therapeutic response in patients with recalcitrant or disseminated warts. However, the literature still presents conflicting results, and no consensus exists regarding their routine use [12,13].

The objective of this systematic review is to critically evaluate the efficacy and safety of cimetidine and levamisole, whether used alone or in combination, in the treatment of cutaneous warts.

Methods

A comprehensive systematic review was conducted, encompassing publications up to September 2025. Searches were performed in PubMed/MEDLINE, Cochrane Library, Embase,

LILACS, and clinical trial registries such as ClinicalTrials.gov and HERDIN. Combined descriptors were used, including the terms *"warts"*, *"cimetidine"*, *"levamisole"*, *"treatment"*, and *"recalcitrant warts"*. Additional references were identified through manual search and screening of grey literature, including unpublished

trial records and technical reports.

Inclusion criteria comprised randomized, double-blind, placebo-controlled clinical trials or comparative studies involving adult or pediatric patients with common, flat, plantar, or recalcitrant warts. The primary outcome assessed was the complete clearance of warts, while secondary outcomes included the mean time to regression and reported adverse events. Studies exclusively involving genital warts, isolated case reports, narrative reviews, or investigations combining systemic therapies with topical agents without an appropriate control group were excluded.

Data extraction was performed independently by two reviewers, collecting information on population characteristics, study design, dosage, treatment duration, clinical outcomes, and adverse effects. Methodological quality was assessed according to the GRADE approach, classifying the level of evidence as high, moderate, low, or very low.

Results

A total of 11 clinical studies comprising 648 patients were included: five trials investigating cimetidine alone, four assessing levamisole alone, and two evaluating the combination of cimetidine and levamisole. All studies were prospective, most of them randomized and

double-blind, involving children and adults with common, flat, plantar, or recalcitrant cutaneous warts.

Cimetidine Monotherapy

Five randomized, placebo-controlled trials evaluated the efficacy of cimetidine as a single systemic treatment. The studies by Yilmaz et al. [7], Rogers et al. [8], and Kharfi et al. [6], including between 50 and 86 patients, reported cure rates ranging from 22% to 32%, with no statistically significant difference compared to placebo ($p > 0.05$).

In adult populations, Yilmaz et al. [7] observed complete regression in 32% of patients treated with cimetidine versus 30% in the control group, while Rogers et al. [8] reported 27% versus 22%, respectively. In children, Kharfi et al. [6] described a 28% response rate in the cimetidine group compared to 24% in the placebo group, also without statistical significance.

In comparative studies by Parsad et al. [4,5], which analyzed cimetidine alone against its combination with levamisole, cure rates reached 45.5% in adults [4] and 31.5% in children [5] treated exclusively with cimetidine, confirming its limited efficacy as systemic monotherapy. Overall, the drug demonstrated good tolerability, with mild adverse effects such as nausea and mild abdominal discomfort (Table 1).

Levamisole Monotherapy

Four clinical studies evaluated levamisole as monotherapy. The trial by Schou et al. [12], which included 99 adults with common warts and condylomas, found no significant difference in lesion regression compared to placebo. The prospective controlled study by

Moncada et al. [13], involving 22 patients, reported partial improvement in some cases; however, the absence of a robust control group and lack of statistical significance limited its interpretability.

In the randomized trial by Amer et al. [14], with 40 patients treated for five months, only partial wart reduction was observed, with no significant difference relative to the placebo group. Conversely, the unpublished national registry by Abad-Casintahan [15], part of the grey literature, reported a cure rate of 77.5% with levamisole compared to 2.5% with placebo ($p < 0.05$). Nonetheless, this study presented a high risk of methodological bias, lack of peer review, and limited reproducibility.

Overall, the body of evidence indicates no consistent clinical benefit of levamisole alone in the treatment of cutaneous warts, despite its satisfactory safety profile and low incidence of adverse effects (Table 2).

Combination of Cimetidine and Levamisole

Two randomized, double-blind clinical trials evaluated the combined use of both agents. In the study by Parsad et al. [4], involving 48 adults with recalcitrant warts, the group receiving combination therapy (cimetidine 30 mg/kg/day plus levamisole 5 mg/kg/day for 12 weeks) achieved a cure rate of 85.7%, significantly higher than that observed in the group treated with cimetidine alone (45.5%, $p < 0.01$). The mean time to regression was also shorter (7 vs. 10 weeks).

In pediatric patients, Parsad et al. [5] reported a cure rate of 65% in the combination group and 31.5% in the cimetidine monotherapy group ($p = 0.015$), with mean regression

times of 7.8 weeks versus 11 weeks, respectively. In both studies, adverse events were mild, predominantly occasional nausea, and no serious events were reported.

These findings suggest a potential synergistic effect between cimetidine and levamisole, resulting in significantly improved clinical outcomes and faster resolution, particularly in cases of recalcitrant warts (Table 3).

Discussion

The present study provides a comprehensive overview of the available literature on the use of cimetidine and levamisole—individually and in combination—for the treatment of cutaneous warts. A joint analysis of the data reveals that, although the immunological rationale justified investigating the efficacy of these drugs when used separately, neither demonstrated superiority over placebo in multiple randomized clinical trials. In contrast, the combination of cimetidine and levamisole proved effective in two studies, significantly increasing cure rates and accelerating lesion regression in patients with recalcitrant warts, both in adults and children [4,5]. Thus, the combined therapy shows potential benefit in selected cases, although it is not yet recognized as a first-line treatment.

Cimetidine, an H2-receptor antagonist, was first proposed as an immunomodulatory agent in the early 1990s, based on the hypothesis that the inhibition of suppressor T lymphocytes could enhance immune response against HPV. However, five randomized clinical trials in both children and adults failed to demonstrate significant improvement. For instance, the studies by Yilmaz et al. [7], Rogers et al. [8], and Kharfi et al. [6] reported cure rates ranging from 22% to 32% among patients treated with cimetidine, with

no statistical difference compared to placebo. Therefore, although this drug may exert theoretical immunological effects, these do not translate into meaningful clinical benefits. In comparative trials conducted by Parsad et al. [4,5], cimetidine monotherapy yielded response rates between 31.5% and 45.5%, significantly lower than those observed with the combination therapy, indicating that cimetidine alone has limited efficacy and may be more rationally employed within a combined regimen.

Levamisole, in turn, is a classical immunomodulator initially developed as an antihelminthic agent. It was later investigated in various autoimmune and infectious diseases due to its capacity to stimulate cell-mediated immunity via T lymphocytes and macrophages, in addition to increasing pro-inflammatory cytokines such as IL-2 and IFN-γ. Early studies suggested that, in patients with multiple or persistent warts—particularly immunocompromised or malnourished individuals—the drug might enhance immune response against HPV. However, well-controlled randomized trials, such as those by Schou et al. [12], Moncada et al. [13], and Amer et al. [14], demonstrated no significant clinical benefit. By contrast, an unpublished grey literature report from the Philippines by Abad-Casintahan [15] described a cure rate of 77.5%. Nevertheless, because it was not published in a peer-reviewed journal and presented methodological shortcomings, this result must be interpreted with caution due to the high risk of bias. Accordingly, levamisole alone is not recommended for the treatment of cutaneous warts.

The combination of cimetidine and levamisole represents the main positive finding of this review. In the two clinical trials conducted by Parsad et al. [4,5], both in adults and children, the combination regimen provided outcomes significantly superior to cimetidine

monotherapy. In adults, cure rates reached 85.7% in the combination group versus 45.5% in the control group, with faster regression (seven weeks versus ten). Similar results were observed in children, with 65% clearance in the combination group compared to 31.5% under monotherapy, along with earlier regression (7.8 weeks versus 11 weeks). These findings suggest a synergistic effect: while cimetidine reduces suppressor T-cell activity, levamisole stimulates effector T cells and macrophages, resulting in a more robust immune response against HPV. Pathophysiologically, warts reflect an imbalance between viral infection and host immune defense. In immunocompetent individuals, cytotoxic T lymphocytes eliminate infected cells; in immunosuppressed or immunodeficient patients, this response is inadequate, allowing lesion persistence. Thus, the combination of these two drugs has a plausible biological rationale for use in disseminated or recalcitrant cases.

Despite promising results, several limitations must be acknowledged. The small number of studies and limited sample sizes reduce statistical power and increase the risk of bias. Furthermore, the lack of long-term follow-up impairs assessment of wart recurrence after treatment. The heterogeneity across studies—regarding patient age, types of warts, and response criteria—also limits the generalizability of findings. On the other hand, this review has notable strengths, including a comprehensive search across multiple databases, inclusion of grey literature, and a critical methodological assessment using the GRADE system. The findings were also contextualized with other systemic and topical therapies, such as intralesional immunotherapy with Candida antigen [10] and systemic retinoids [11].

In general, the available data confirm that neither cimetidine nor levamisole alone should be considered first-line systemic therapy for cutaneous warts. However, their

combination is promising, particularly in resistant or extensive cases following failure of conventional treatments. To confirm efficacy and safety, larger multicenter clinical trials with prolonged follow-up are required. Therefore, cimetidine combined with levamisole may be regarded as an experimental, low-cost, and safe therapeutic approach for cutaneous warts. Nonetheless, its use should remain individualized and reserved for selected cases, until more robust evidence definitively validates its therapeutic role.

Declarations

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Table 1 – .

Summary of Studies on Cimetidine Monotherapy for Cutaneous Warts

Author / Year [Ref]	Study Design	Population (N, age range, type of warts)	Therapeutic Regimen	Main Outcomes	Adverse Events	Level of Evidence
Yilmaz et al., 1996 [7]	Double-blind RCT, placebo-controlled	86 adults with common/recalcitrant warts	Cimetidine 25–40 mg/kg/day, 3 doses/day, for 12 weeks	Complete cure in 32% vs. 30% with placebo ($p > 0.05$). No significant difference	Mild nausea, headache	Moderate
Rogers et al., 1999 [8]	Double-blind RCT, placebo-controlled	70 adults with multiple plantar warts	Cimetidine 40 mg/kg/day for 12 weeks	Complete cure in 27% vs. 22% with placebo ($p > 0.05$)	No severe events reported	Moderate
Kharfi et al., 2002 [6]	Double-blind RCT, placebo-controlled	50 children with multiple warts	Cimetidine 30–40 mg/kg/day for 12 weeks	Complete cure in 28% vs. 24% with placebo ($p > 0.05$). Not significant	Nausea, mild abdominal pain	Moderate
Parsad et al., 1999 [4]	Double-blind RCT, comparative	48 adults with recalcitrant warts	Cimetidine alone vs. Cimetidine + Levamisole	45.5% cure with cimetidine alone vs. 85.7% with combination ($p < 0.01$)	Mild nausea	Moderate
Parsad et al., 2001 [5]	Double-blind RCT, comparative	39 children with recalcitrant warts	Cimetidine alone vs. Cimetidine + Levamisole	31.5% cure with cimetidine alone vs. 65% with combination ($p = 0.015$)	Mild nausea	Moderate

Table 2 – .

RCT: Randomized Clinical Trial; N: Number of participants; p: Statistical significance value; kg/day: Kilogram per day **Summary of Studies on Levamisole Monotherapy for Cutaneous Warts**

Author / Year [Ref]	Study Design	Population (N, age range, type of warts)	Therapeutic Regimen	Main Outcomes	Adverse Events	Level of Evidence
Schou et al., 1977 [12]	Double-blind RCT, placebo-controlled	99 adults with common warts and condylomas	Levamisole 150 mg/day, 3 consecutive days, every 2 weeks, for 6 weeks	No difference in wart regression vs. placebo	Mild nausea	Moderate
Moncada et al., 1979 [13]	Prospective controlled series	22 patients with multiple warts	5 mg/kg/day, 3 days/fortnight, for 12 weeks	Partial improvement in some patients, no robust placebo group	Not reported	Low
Amer et al., 1991 [14]	Double-blind RCT, placebo-controlled	40 patients with various types of warts	Same regimen for 5 months	Partial, non-significant reduction vs. placebo	Headache, nausea	Moderate
Abad-Casintahan, 2001 [15]	National registry, unpublished (grey literature)	40 patients with common, flat, plantar warts	150 mg/day, 3 days/fortnight, for 12 weeks	77.5% cure vs. 2.5% placebo ($p < 0.05$). High risk of bias	Not reported	Very low

Table 3 – .

RCT: Randomized Clinical Trial; N: Number of participants; p: Statistical significance value; kg/day: Kilogram per day; IL-2: Interleukin-2; IFN-γ: Interferon-gamma.

Summary of Studies on Combined Cimetidine and Levamisole Therapy

Author / Study Year [Ref] Design	Population (N, age range, type of warts)	Therapeutic Regimen	Main Outcomes	Adverse Events	Level of Evidence
Parsad et al., 1999 [4] Double-blind RCT	48 adults with recalcitrant warts	Levamisole 5 mg/kg/day, 3 days/fortnight + Cimetidine 30 mg/kg/day continuously, both for 12 weeks	85.7% cure (18/21) vs. 45.5% (10/22) with cimetidine alone ($p < 0.01$). Mean regression: 7 vs. 10 weeks	Mild nausea	Moderate
Parsad et al., 2001 [5] Double-blind RCT	44 children (39 evaluated), recalcitrant warts	Same regimen	65% cure vs. 31.5% with cimetidine alone ($p = 0.015$). Mean regression: 7.8 vs. 11 weeks	Mild nausea, no severe events	Moderate

RCT: Randomized Clinical Trial; N: Number of participants; p: Statistical significance value; kg/day: Kilogram per day