

# Intralesional ionic contra virus therapy versus 5-fluorouracil in treatment of plantar warts: clinical and dermoscopic evaluation

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**Received:** 15 March 2025

**Revised:** 22 April 2025

**Accepted:** 12 May 2025

**Published:** 8 January 2026

**Egyptian Journal of Dermatology and Venereology** 2026, 46:83–95

## Background

Plantar warts represent a therapeutic challenge for dermatologists.

## Aim and objectives

To evaluate the effectiveness of intralesional injection of ionic contra virus therapy (ICVT) (combined digoxin and furosemide) versus intralesional 5-Fluorouracil (5-FU) in the treatment of plantar warts.

## Patients and methods

This study involved 50 patients with plantar warts divided into two equal groups, group I (25 patients) treated with intralesional ICVT (combined digoxin and Lasix) and group II (25 patients) treated with intralesional 5-FU. The injection was repeated every 2 weeks to a maximum of six sessions (baseline, 2, 4, 6, 8, and 10 weeks). Dermoscopic examination to all patients was done to confirm the diagnosis of wart and also to follow-up the response to treatment.

## Results

Complete/partial response was observed at higher rates among patients of group-II (96%) compared with group-I (72%). No response was higher among group-I (28%) than group-II (4%). Regarding a number of sessions, group II patients had significantly ( $P < 0.001$ ) lower mean number of sessions ( $3.5 \pm 1.9$ ) than group I ( $5.98 \pm 0.4$ ). Respecting the side effects of treatment, a significant difference ( $P < 0.001$ ) in the rate of side effects between the two treatment modalities was recorded. The majority (92%) of group-II patients had pain for 12 h after injection, and only one (4%) case had small ulcer while all cases of group-I had no side effects.

## Conclusion

Both intralesional ICVT and 5-FU were effective, safe, and well-tolerated methods for the treatment of plantar warts clinically and dermoscopically, however, intralesional 5-FU had relatively higher efficacy.

## Keywords:

wart, 5-fluorouracil, ionic contra virus therapy

Egypt J Dermatol Venereol 46:83–95

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1110-6530

## Introduction

Warts are a frequent epidermal growth that affect people of all ages and are primarily asymptomatic. They are caused by different strains of the human papilloma virus (HPV) [1]. Viral warts were the commonest viral skin infection in Egypt as it represented 2/3 of all cases diagnosed with viral skin infection and this was observed in a study done on patients who attended a dermatology clinic at Sohag University Hospitals [2].

The majority of HPV strains prefer certain anatomical locations and produce unique wart shapes. Extragenital cutaneous warts include common warts, sometimes called verrucae vulgares, plane warts, which are usually found on the hands and face, and plantar warts, which are warts on the soles of the feet [3].

There are many methods to treat plantar warts, but no one approach is universally successful. Intralesional

immunotherapy eliminates all lesions and boosts the immune system. Recent studies have shown the effectiveness of ionic contra virus therapy (ICVT) against HPV, which involves the use of digoxin and furosemide [4]. DNA viruses such as HPV need an influx of  $K^+$  for their replication process. Both digoxin, a cardiac glycoside, and furosemide, a loop diuretic, interact with cell membrane ion co-transporters ( $Na^+/K^+-ATPase$  and  $Na^+-K^+-2Cl^-$  co-transporter-1) to decrease potassium influx. Consequently, it is believed that these two compounds might be beneficial in treating warts caused by HPV. This innovative approach aims to target the wart virus throughout the body, rather than only in the locally treated lesion [5].

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One of the therapeutic options for the treatment of warts is intralesional 5-Fluorouracil (5-FU). It is an antitumor drug that, through indirectly inhibiting DNA synthesis, prevents the synthesis of pyrimidine and thymidine, which in turn prevents cellular proliferation and replication [6].

In our research, we investigated the efficacy of intralesional administration of ICVT (a combination of digoxin and furosemide) compared with intralesional 5-FU for treating plantar warts.

### Patients and methods

This study was conducted in the outpatient clinics of the Dermatology, Venereology, and Andrology Department at Sohag University Hospitals, during the period from January 2023 to January 2024. This study involved 50 patients with plantar warts divided into two equal groups, group I (25 patients) treated with intralesional combined digoxin and Lasix and group II (25 patients) treated with intralesional 5-FU.

Approval for this study was obtained from the Research and Ethical Committee at Faculty of Medicine, Sohag University before study execution (Soh-Med-22-07-01), and clinical trial registration was awarded (NCT05520658). In addition, a written informed consent was obtained from all participants after explaining the nature of the study.

### Study design

Randomized clinical trial (conducted by the simple randomized method by using closed envelop).

### Sample size calculation

Sample size calculation was carried out using G\*Power-3 software [7]. A calculated sample of 50 patients with plantar warts would be needed. The sample was randomly assigned to one of two equal groups: (group-I (n=25): patients received intralesional combined digoxin and furosemide and (Group-II (n=25): patients received intralesional 5-FU.

**Patient selection:** Patients with clinically and dermoscopically confirmed plantar warts, aged more than or equal to 18 years, and of both sexes were included in the study. On the other hand, pregnant or lactating females, patients with a known hypersensitivity to any substances involved in this research, those undergoing immune suppressive treatment, and those who have had wart treatment within the two months before joining the study were not included in our study. Additionally, participants

with systemic diseases, particularly those with cardiac conditions, as well as those who declined to take part in the study, were also excluded.

**Methods:** All patients were subjected to complete history taking which include: Personal history as name, sex, age, residence, occupation, and marital status. Present history of wart as onset, course, duration, and sites of lesions. Past history of similar condition or any chronic medical conditions. Therapeutic history of any treatment modalities of warts (topical, surgical, laser and immunotherapy).

General examination of all patients was done to assess the general condition of the patients, as well as, to exclude any systemic diseases. All patients were subjected to careful local clinical examination to define the site, number, and size of warts. Also dermoscopic examination to all patients was done to confirm the diagnosis of wart (dermoscopic features of palmoplantar warts including well circumscribed area of papillomatous growth, interrupted skin lines, dotted spots from thrombosed vessels and bleeding spots that may be surrounded by whitish halo known as frogspawn pattern) and also to follow-up the response to treatment (for 6 months from last session) by using dermoscope DermLite1 (DL1) with magnification 10×.

ECG and serum K level had been done for all participants who received intralesional combined digoxin and furosemide before the study to exclude any subclinical cardiac patients.

Patients clinically and dermoscopically diagnosed with plantar wart were randomly divided into two groups, group (I) treated by intralesional combined digoxin and furosemide, one session every 2 weeks for maximum sixsessions and patients in group (II) treated by intralesional 5-FU mixed with 1 ml of 2% lignocaine and epinephrine one session every 2 weeks for maximum six sessions.

Our study was conducted in the following manner: Digoxin for injection was be sold in ampoules (Lanoxin, manufactured by the GlaxoSmithKline firm) that hold 0.5 mg/2 ml of the drug. Injectable furosemide is sold in vials with a 20 mg/2 ml capacity (Lasix, a product of the Sanofi Aventis corporation). The total dose of digoxin and furosemide injected into the base of each wart was 0.0008 mg/0.1 ml (per lesion) [8].

Our goal was to prepare a 20 ml solution containing a combination of digoxin and furosemide, which would

yield a dose of 0.025 mg/ml topical (0.125 mg × 20 ml) ÷ 100. A dose of 0.025 ÷ 3 = 0.0083 mg/1 ml is injectable. 0.16 mg of furosemide and 0.16 mg of digoxin, computed as follows: In all, 20 ml of the injected solution contains 0.16 mg of furosemide and 0.16 mg of digoxin, calculated as 0.0083 × 20. The injectable solution was prepared by dilution using iso-osmotic saline and vaporization. Accordingly, each wart received a dose of 0.0008 mg/0.1 ml every session, with a maximum of five warts per session [8].

A 5 ml ampule containing 250 mg/5 ml of injectable 5-FU was available. In a 5 ml syringe, 4 ml of 50 mg/ml 5-FU were combined with 1 ml of a combination of 20 mg/ml (2%) lidocaine and 0.0125 mg/ml epinephrine [The combination was designed to reduce the pain (lidocaine) and sustain high local drug concentrations for longer periods than with fluorouracil alone as a result of vasoconstriction (epinephrine)]. Several warts (maximum five warts) were intralesionally injected for with the freshly prepared solution using an insulin syringe until the lesion blanched. Two weeks later a dark, ecchymosed eschar appeared, which was pared. A second injection was given for any remaining warts, if any were found [9].

#### (A) Therapeutic response evaluation:

##### *I-Clinical evaluation*

All patients were evaluated by a decrease in number or decrease in size of warts (measured by ruler) with photographic and dermoscopic documentation after every session and at the end of treatment. The clinical response was evaluated as follows [9]:

- (a) Complete response: Disappearance of the wart and return of the normal skin markings.
- (b) Partial response: 50–99% reduction in wart size
- (c) No response: 0–49% decrease in wart size.

##### *II-Dermoscopic evaluation*

According to dermoscopic evaluation, treatment response was scored as follows:

1. Score 0: One month following the last session, there is no clinical or dermoscopic evidence of wart removal.
2. Score 1: One month after the last session, there is clinical improvement with a reduction in the size of the wart but no dermoscopic clearing of warts.
3. Score 2: Warts disappear clinically (clinical clearance), but a month later, dermoscopic examination revealed remnants of warts.
4. Score 3: 1 month following the last session, participants had clinical and dermoscopic eradication of warts [10].

(B) Evaluation of safety and tolerability: were be evaluated throughout the study by assessment of adverse effects (pain, erythema, hypopigmentation, hyperpigmentation, scar formation or any systemic adverse effect as vasovagal attacks or anaphylaxis).

(C) Patients' satisfaction was assessed according to whether the patient was not satisfied, slightly satisfied, or very satisfied.

Following the final session and for a maximum of six months, patients in both groups who had shown a complete response would get monthly follow-up visits to identify any recurrence.

#### Statistical analysis

(a) The collected data were verified, coded by the researcher, and analyzed using the Statistical Package for Social Sciences (IBM-SPSS/PC/VER 24.0) program for Windows. Descriptive statistics: mean, standard deviation, median, range, frequencies, and percentage were calculated.

#### Test of significances

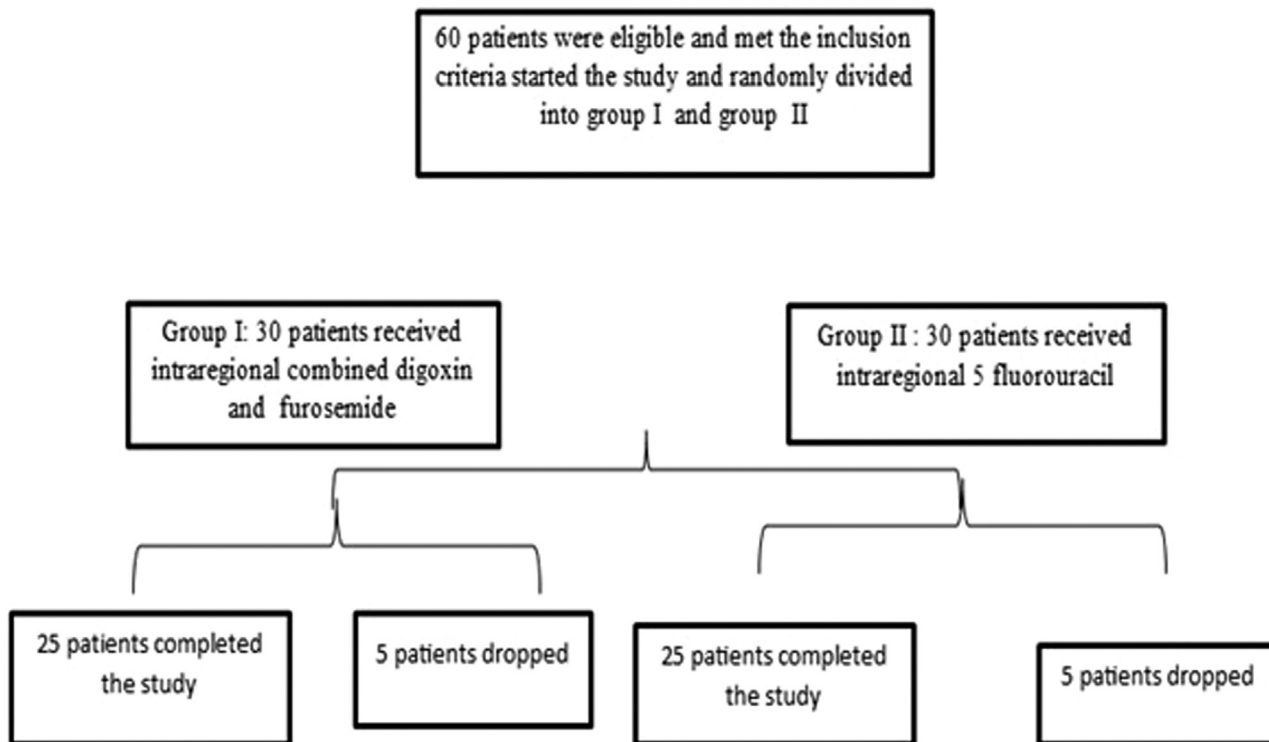
- (a) Independent Sample *t*-test was used to compare the mean difference between groups.
- (b)  $\chi^2$  and Monte Carlo Exact tests were used to compare the difference in distribution of frequencies among different groups.
- (c) Mann-Whitney *U* test was calculated to test the median differences in continuous variables between groups and related samples.
- (d) ANOVA test was used to compare the mean difference between groups
- (e) Post-hoc test was used for pairwise comparison with Bonferroni correction.
- (f) A *P* value considered statistically significant when *P* less than 0.05.

\* IBM\_SPSS. Statistical Package for Social Science. Ver. 24. Standard version. Copyright SPSS Inc., 2012–2016. New York, USA. 2016.

#### Results

The study included 60 patients with plantar warts selected from the outpatient clinic of the Dermatology, Venereology, and Andrology department at Sohag University Hospitals. Sixty patients were randomly divided into two groups: group (I): 30 patients received intralesional combined digoxin and furosemide, one session every

Figure 1



Flow diagram of participants and their allocation

2 weeks for maximum 6 sessions, five of them dropped throughout the study and group (II): 30 patients received intralesional 5-FU one session every 2 weeks for maximum six sessions and five of them dropped throughout the study (Fig. 1).

The sociodemographic characteristics of the two studied groups included age, sex, occupation, and residence were shown in Table 1. Both groups of our study were age and sex matched.

The clinical characteristics of the studied groups (I, II) included disease duration, side of the wart, and

multiplicity of the lesion. There was no statistically difference between both groups as regard to disease duration, side of the wart, and multiplicity of the lesion. This was demonstrated in Table 2.

Treatment-related characteristics of the two studied groups with regard to treatment response, number of sessions, side effects, and patients' satisfaction, were shown in Table 3.

For the response to treatment, there was a significant difference ( $P=0.044$ ) in the response between the two treatment modalities. Complete/partial response was

Table 1 Sociodemographic characteristic differences among the studied groups:

	Group I (Digoxin & Furosemide) (n=25)	Group II (5-FU) (n=25)	P value
Age/year Mean±SD	36.20±10.8	32.20±8.9	0.162
Sex n (%)			0.089
Female	9 (36)	15 (60)	
Male	16 (64)	10 (40)	
Occupation n (%)			0.355
Nonworker/housewife	6 (24)	9 (36)	
Worker	19 (76)	16 (64)	
Residence			0.894
Urban	16 (64)	17 (68)	
Rural	9 (36)	8 (32)	

\*Independent Sample t-test was used to compare the mean difference between groups; \*\*Chi-square test was used to compare the proportion difference between groups; P value less than 0.05 was significant. (5-FU, 5-flourouracil).

**Table 2 Clinical characteristic differences among the studied groups.**

	Group I (Digoxin and Furosemide) (n=25)	Group II (5-FU) (n=25)	P value
Disease Duration (month)			
Mean±SD	11.60±8.3	18.36±24.6	0.486
Median (Range)	9 (–36)	12 (3–120)	
Disease duration category			0.183
< 1 year	15 (60)	10 (40)	
1–3 year	10 (40)	13 (52)	
> 3 years	0	2 (8)	
Multiplicity			0.333
Multiple	5 (20)	8 (32)	
Single	20 (80)	17 (68)	

\*Mann–Whitney *U* test was used to compare the median difference between groups; \*\*Chi-square test was used to compare the proportion difference between groups; *P* value less than 0.05 was significant. (5-FU, 5-flourouracil).

**Table 3 Treatment data differences among the studied groups.**

	Group I (Digoxin and Furosemide) (n=25)	Group II (5-FU) (n=25)	P value
Clinical and dermoscopic response to treatment			0.044**
No response (score 0)	7 (28)	1 (4)	
Partial response (score 1)	3 (12)	5 (20)	
Complete response (score 2, 3)	15 (60)	19 (76)	
Session number			
Mean±SD	5.98±0.4	3.52±1.9	0.001*
Median (Range)	6 (3–6)	3 (1–6)	
Side effects			0.001***
No	25 (100)	1 (4)	
Pain for 12 h after injection	0	23 (92)	
Small ulcer	0	1 (4)	
Patients' satisfaction			0.039**
Unsatisfied	9 (36)	2 (8)	
Slightly satisfied	4 (16)	7 (28)	
Very satisfied	12 (48)	16 (64)	

\*Mann–Whitney *U* test was used to compare the median difference between groups; \*\*Chi-square test was used to compare the proportion difference between groups; \*\*\*Monte Carlo exact test was used to compare the proportion difference between groups; *P* value less than 0.05 was significant. (5-FU, 5-flourouracil).

observed at higher rates among patients of group-II (Case 6, 7, 8, 9, and 10) (96%) compared with group-I (Case 1, 2, 3, 4, and 5) (72%). No response was higher among group-I (28%) than group-II (4%). Regarding number of sessions, group II patients had significantly ( $P<0.001$ ) lower mean number of sessions ( $3.5\pm 1.9$ ) than group I ( $5.98\pm 0.4$ ).

Respecting the side effect of treatment, significant difference ( $P<0.001$ ) in the rate of side effect between the two treatment modalities was recorded. The majority (92%) of group-II patients had pain for 12 h after injection and only one case (4%) had small ulcer while all cases of group-I had no side effects.

For the patients' satisfaction, significant difference ( $P=0.039$ ) in the rate of satisfaction between the two treatment modalities was recorded. About two-thirds (64%) of group-II were very satisfied compared

with about one-half of group-I (48%) whereas only 8% of group-II were unsatisfied than 36% of group-II.

Regarding recurrence, following a 6-month monthly follow-up, no recurrence had been noted in patients in either group who had seen a complete response.

The relationship between response and disease determinants as regard age, sex and multiplicity was represented in Tables 4 and 5. Respecting disease duration, group-II patients with complete response had shorter disease duration (<3 years) (100%) compared with those with partial response (80%) and those with no response (0%) ( $P=0.012$ ). On the other hand, group-I cases had an insignificant correlation ( $P=0.264$ ).

#### Group I (ICVT treated group)

Figure 2, Fig. 3, Fig. 4 represent group I.

**Table 4 Relationship between response to treatment and disease determinants (G-I) (combined digoxin and furosemide treated group)**

	Response to Treatment			P value
	No response (score 0) (n=7)	Partial response (score1) (n=3)	Complete response (score 2,3) (n=15)	
Age/year	29.71±8.4	35.33±7.5	39.40±8.9	0.149
Sex				0.118
Female	4 (57.1)	2 (66.7)	3 (20)	
Male	3 (42.9)	1 (33.3)	12 (80)	
Duration of disease				0.264
< 1 year	5 (71.4)	2 (66.7)	8 (53.3)	
1–3 year	2 (28.6%)	1 (33.3%)	7 (46.7)	
> 3 years	0	0	0	
Multiplicity				0.390
Multiple	1 (14.3)	0	4 (26.7)	
Single	6 (85.7)	3 (100)	11 (73.3)	

\*ANOVA test was used to compare the mean difference between groups; \*\*Post-hoc test was used for pairwise comparison with Bonferroni correction;\*\*\*Chi-square test was used to compare the proportion difference between groups;P value less than 0.05 was significant.

**Table 5 Relationship between response to treatment and disease determinants (G-II) (5-Flourouracil treated group)**

	Response to Treatment			P value
	No response (score 0) (n=1)	Partial response (score1) (n=5)	Complete response (score 2,3) (n=19)	
Age/year	48	29.80±8.2	32.01±8.7	0.543
Sex				0.384
Female	0	3 (60)	12 (63.2)	
Male	1 (100)	2 (40)	7 (36.8)	
Duration of disease				0.012***
< 1 year	0	1 (20)	9 (47.4)	
1–3 year	0	3 (60)	10 (52.6)	
> 3 years	1 (100)	1 (20)	0	
Multiplicity				0.514
Multiple	0	1 (20)	7 (36.8)	
Single	1 (100)	4 (80)	12 (63.2)	

\*ANOVA test was used to compare the mean difference between groups; \*\*Post-hoc test was used for pairwise comparison with Bonferroni correction;\*\*\*Chi-square test was used to compare the proportion difference between groups; P value less than 0.05 was significant.

### Group II (5-FU treated group)

Figure 5, Fig. 6, Fig. 7 represent group II.

### Discussion

HPV) is the source of benign cutaneous and occasionally mucosal lesions known as viral warts that may cause pain, bleeding, and cosmetic disfigurement [11]. The degree and location of lesions, the type of contact, the amount of viral load, the exposed person's immunologic condition specific to HPV, and other factors all play a role in the acquisition of HPV [12].

Cutaneous warts are a common skin disease as they develop in 7–12% of the population infected with HPV, and it markedly affect patient's quality of life so most of patients with warts seek medical treatment [13]. It represented two-thirds of all cases diagnosed with viral skin infection in Egypt [2].

No specific treatment for HPV infection is available right now. However, the destructive techniques that cause keratolysis or epidermal damage are the only ones offered as therapy choices [14]. Because intralesional therapy increases the local immune response with few side effects, it is superior to topical application in the treatment of warts due to its promising success and low or absent recurrence [15].

Intralesional ICVT (combined digoxin and furosemide) was the efficient and safe way in treatment of wart [16]. 5-FU is an antimetabolite that reduces cell division, induces cell cycle arrest, cytotoxicity and death. Recently, 5-FU used as intralesional injection which can induce high concentration inside the wart lesion, recent study had shown its effectiveness in treatment of warts [17].

In order to evaluate the safety and efficacy of intralesional injection of ICVT (combined digoxin

Figure 2



A and B : Clinical picture of plantar wart before and after treatment with intralesional ICVT (Respectively) showing complete response. C: Dermoscopic picture before treatment showing bleeding spots. D: Dermoscopic picture shows complete clearance of bleeding spots and return of normal skin markings after treatment (score 3).

and furosemide) versus intralesional injection of 5-FU in the treatment of plantar warts. we conducted the current study on 60 patients who were diagnosed with plantar warts both clinically and dermoscopically. These patients were divided into two groups: group I was treated with 30 patients receiving intralesional combined digoxin and furosemide, and group II was treated with 30, patients receiving intralesional 5-FU, only 25 patients in each group completed the study. The injections were performed every two weeks for a total of six sessions (baseline, 2, 4, 6, 8, and 10 weeks).

After the end of the treatment course, both groups demonstrated a statistically significant improvement of the injected warts, however the improvement was better in group II (5-FU) than group I (ICVT) as we found that, most of patients in group II achieved a complete clinical response while about two third of patients in group I had a complete clinical response and this was statistically significant.

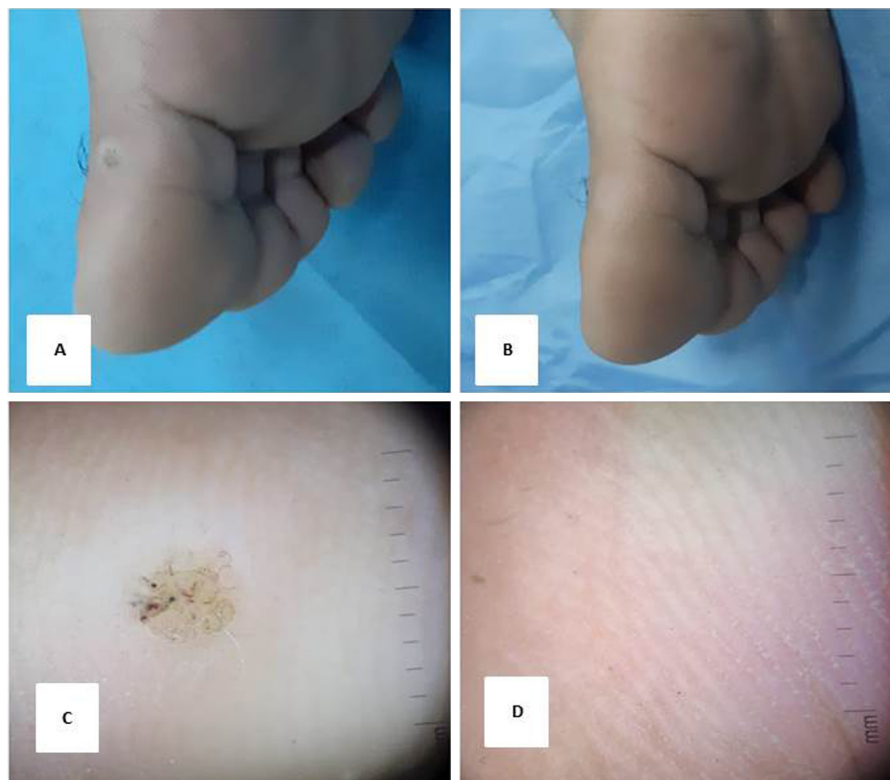
Regarding studies relevant to the use of intralesional injection of combined digoxin and furosemide compared with other modalities in treatment of viral warts, Nasr and colleagues, did a comparative study on

75 patients with numerous warts divided to one of three equal groups, to measure and compare the effectiveness and safety Utilizing intralesional injection of vitamin D3, Candida antigen, and a combination of furosemide and digoxin to treat several warts. At the end of the study, they found that the intralesional Candida antigen group had the greatest overall therapeutic response, whereas the vitamin D3 group and the combination digoxin and furosemide therapy group showed the least amount of response [4]. This was in line with our findings, as we found significantly higher response in 5-FU group than ICVT (combined digoxin and furosemide) group.

The results of our study comes in agreement also with a study by Siddiqui *et al.*, who conducted a randomized controlled trial on 80 patients, to compare the efficacy of cryotherapy versus combined digoxin and furosemide in the treatment of viral warts and concluded that excellent response rate was in both groups with no significant difference between them [18].

About research on the intralesional therapy of viral warts using combined digoxin and furosemide, 80 adult

Figure 3



A and B : Clinical picture of plantar wart before and after treatment with intralesional ICVT (Respectively) with complete response. C : Dermoscopic picture of plantar wart before treatment showing bleeding spots and hairpin vessels. D: Dermoscopic picture shows complete clearance of plantar wart and return of normal skin markings after treatment with intralesional digoxin and furosemide (score 3).

patients with multiple cutaneous warts took part in a double-blinded randomized clinical trial to assess the safety and efficacy of treating numerous cutaneous warts. The patients were randomized into two groups. As a control group, group II received intralesional normal saline solution once weekly for a maximum of five sessions, whereas group I received intralesional combination furosemide and digoxin. The majority of patients in the intralesional combined furosemide and digoxin group (group I) showed complete eradication of warts following the final treatment session, with a highly statistically significant difference [15].

Our results were comparable with, Fathy and colleagues in 2021, who, to assess the safety and effectiveness of intralesional injection of a combination of digoxin and furosemide in the treatment of plantar warts, randomly assigned 40 patients with multiple plantar warts ( $\geq 3$  warts) to two equal groups, were administered intralesionally to the first group (normal saline) and the second group (combination digoxin and furosemide). The second group had a statistically significant improvement and fewer warts overall, while the first group exhibited no changes at all [16].

Our findings closely matched those of Rijsbergen *et al.*, who administered a topical gel containing digoxin 0.125% and furosemide 0.125% instead of a placebo once a day for 42 days in a row. Topical digoxin and furosemide reduced the mean size of HPV-caused cutaneous warts by 3 mm, and these warts also showed a 94% drop in the mean HPV load [19].

The previous findings may be explained by the fact that for DNA viruses like HPV to replicate,  $K^+$  influx is necessary. By interacting with cell membrane ion co-transporters ( $Na^+/K^+$  ATPase and  $Na^+-K^+-2Cl^-$  co-transporter-1), the cardiac glycoside digoxin and the loop diuretic furosemide block the  $K^+$  inflow and prevent the replication of DNA viruses. Thus, it is hypothesized that these two substances could be beneficial in the management of warts caused by HPV [8].

Concerning studies relevant to the use of intralesional 5-FU in comparison to other modalities in treatment of viral warts, Rafique and colleagues in 2023, conducted an experimental trial on 102 patients to compare the outcomes of MMR vaccine V/S 5-FU in the treatment of palmo-plantar warts. It was concluded that

Figure 4



A and B : Clinical picture of plantar wart before and after treatment with intralesional ICVT (Respectively) with complete response. C: Dermoscopic picture of plantar wart before treatment showing scaly yellowish lesion with central bleeding spots. D: Dermoscopic picture shows complete clearance of plantar wart and return of normal skin markings after treatment with intralesional digoxin and furosemide (score 3).

intralesional 5-FU was safer and more effective treatment in comparison to injection MMR for palmo-planter warts as it showed a high response rate and this was in agreement with our results [6].

In accordance to the findings of our study, Zoheir and colleagues conducted a comparative study on 40 patients with at least one plantar wart, to assess the effectiveness of intralesional methotrexate (MTX) in comparison with 5-FU in treatment of Plantar Warts. About one-third of the patients in group A (MTX group) experienced complete resolution, but the majority of patients in group B (5-FU group) did [17].

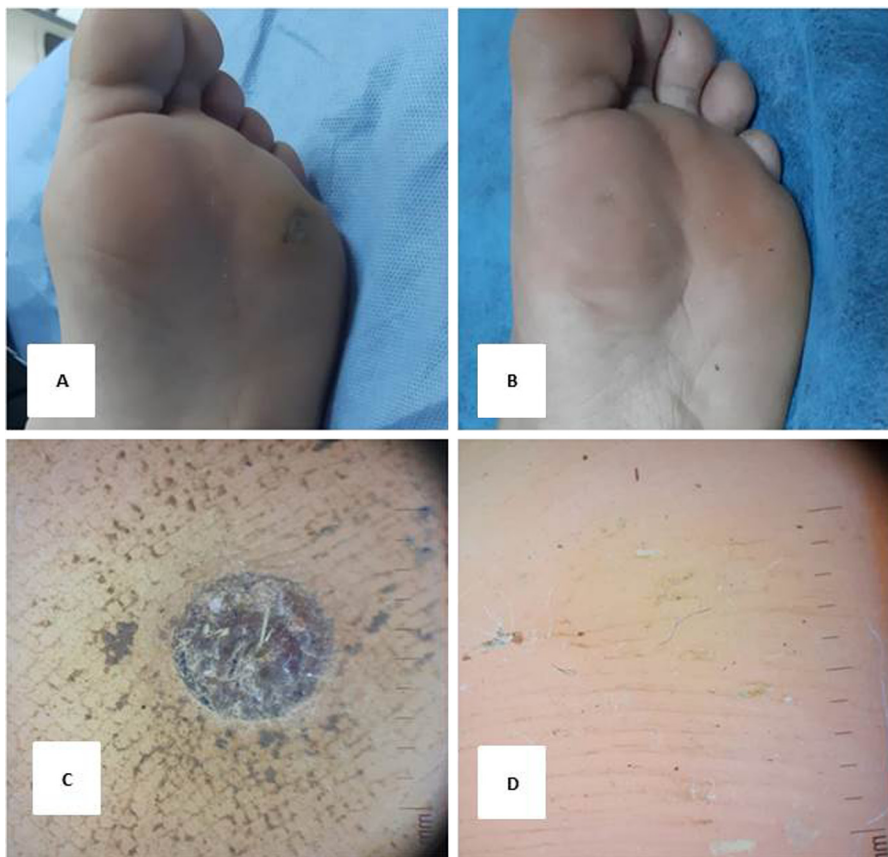
Our results also comes in agreement with a study by Sepaskhah and colleagues who conducted a randomized controlled trial on 50 patients with common and palmoplantar warts that were treated with either intralesional 5-FU admixed with lidocaine and epinephrine (5-FU+LE) or cryotherapy. After treatment the authors revealed that both 5-FU+LE and cryotherapy were effective

in treating common and palmoplantar warts, without significantly different efficacy. However, the patients experiencing complete clinical response were mostly received 5-FU+LE injection [20].

Our findings were comparable with Ghonemy and colleagues, who conducted a randomized study on 90 patients with plantar warts were divided randomly into three groups, group A (intralesional 5-FU), group B (microneedling) while group C (microneedling and 5-FU solution) to assess their therapeutic efficacy, safety and tolerability. Group C treated with (5-FU and microneedling) showed the best response rate among all groups while group B treated with (microneedling) was the least one with no statistically significant difference among all groups [21].

Regarding studies relevant to intralesional use of 5-FU alone in treatment of viral warts Kannambal and colleagues in 2019 conducted a study on 40 patients of multiple recalcitrant cutaneous warts, to evaluate the

Figure 5



A and B : Clinical picture of plantar wart before and after treatment with intralesional 5-FU (Respectively) with complete response. C: Dermoscopic picture before treatment with raised papilliform scaly wart. D : Dermoscopic picture shows complete clearance of plantar wart and return of normal skin markings after treatment (score 3).

role of intralesional 5-FU in recalcitrant warts. Each patient administered 5-FU which was mixed with 2% lignocaine and epinephrine at an interval of every 3 weeks till the clearance or maximum of three sittings and they observed the complete response in common warts was more than in palmar warts and plantar warts respectively. So, they concluded that intralesional 5-FU injection was safe and efficacious in the treatment of multiple recalcitrant cutaneous warts [22].

These findings were almost similar to a study by, Kamal and colleagues who conducted an interventional study on 40 patients with warts who were treated with intralesional 5-FU at the base of each wart at two weeks interval for maximum six sessions to determine the efficacy and safety to intralesional 5-flourouracil in the treatment of warts. After treatment, they stated that intralesional 5-FU is an effective and safe treatment for treatment of common, plantar and genital warts, as overall most patients of the study showed excellent results [23].

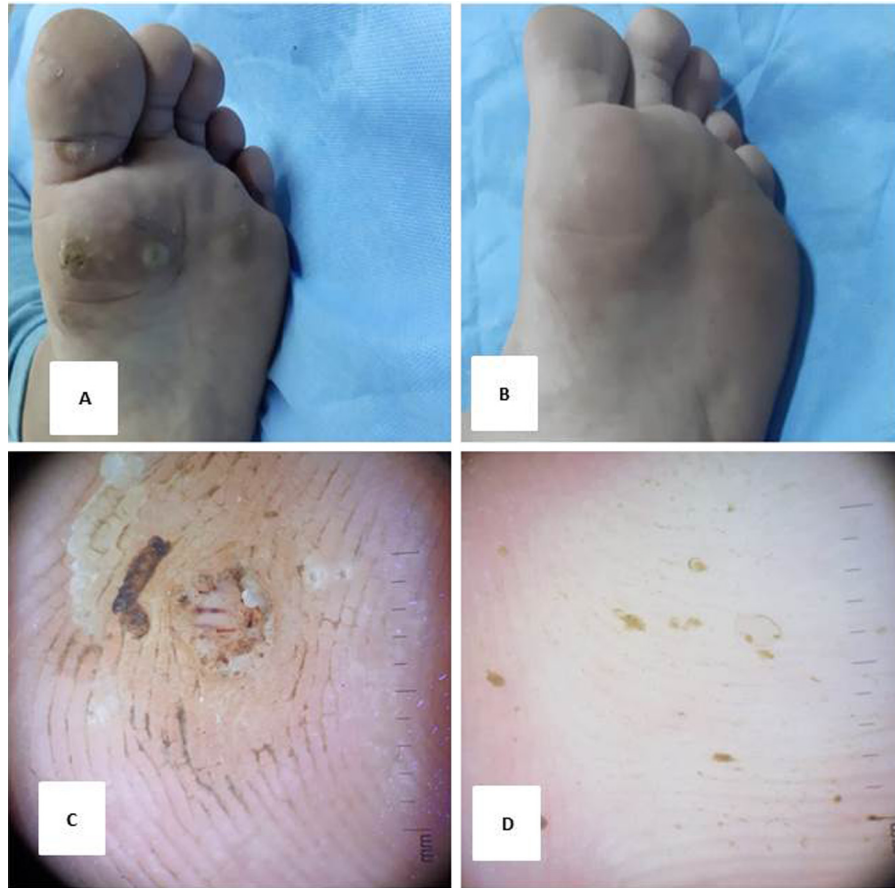
The previous findings may be explained by the fact that 5-FU is one of the pyrimidine analogue type. Due to its

structure, 5-FU disrupts nucleoside metabolism and can be integrated into the single and double helix of RNA and DNA, respectively, causing cell cytotoxicity and death [21]. Furthermore, 5-FU reduces epidermal proliferation, which aids in reducing the growth of wart tissue. Since 5-FU is an inhibitor of nucleic acid synthesis, it prevents the synthesis of pyrimidine thymidine, a nucleoside necessary for DNA replication, by inhibiting the nucleotide synthesizing enzyme thymidylate synthetize [22]. Because of this mode of action, intralesional 5-FU can be used to treat HPV-related viral warts [24].

In the current study, we found that patients in group-II (5-FU) with complete response had shorter wart duration (<3 years) compared with those with partial response and those with no response. So, the obtained results suggest that disease duration can affect the therapeutic response in our patients in this group.

Our results are matching to Xiao *et al.*, who conducted a multivariate analysis on patients with wart to explore the risk factors of cutaneous warts for the effectiveness of 5-FU. The results indicated that duration of

Figure 6



A and B : Clinical picture of plantar warts before and after treatment with intralesional 5-FU (Respectively) with complete response. C: Dermoscopic picture of plantar warts before treatment with bleeding spots and streaks. D: Dermoscopic picture shows complete clearance of plantar warts and return of normal skin markings after treatment (score 3).

cutaneous warts, lesions on foot and warts diameter greater than or equal to 5 mm adversely affected the effectiveness of 5-FU [25].

This comes in disagreement with a study by Khozeimeh *et al.* in 2017, that showed no significant relationship between the therapeutic response and wart duration before the treatment with 5-FU [26]. Similarly the results of study by Sepaskhah and colleagues, who reported that the therapeutic response of 5-FU was not related to the disease duration in their studied patients [20].

Not in line with our results Kenawi *et al.*, who conducted a comparative study on 60 patients with different types of warts (common, planter, genital, periungual warts). The selected patients were randomized into two treatment groups where group (A) received intralesional 5-FU and group (B) received intralesional BCG. After treatment the authors found that the longer the duration of warts, the better the response to either drugs [27].

These variations between the previous studies and ours may be due to differences in sample size, study type, study duration, different ethnic group and type of wart. Moreover, may be due to the difference in the mode of drug delivery as well as the concentration of the drug delivered.

As regard side effects in our study, we found that pain which resolved few hours after cessation of treatment was the commonest side effect reported in the majority of patient in group II (5-FU), also only one patient in the same group reported a small ulcer after receiving two sessions and this ulcer take about two weeks to improve with complete clearance of the wart. While group I (Digoxin and Furosemide) reported no side effects and this was statistically significant.

These findings suggest that intralesional injection of 5-FU as well as, ICVT (combined digoxin and furosemide) are safe methods for treatment of viral warts but less tolerable as regard to pain only in group II (5-FU).

Figure 7



A and B: Clinical picture of plantar wart before and after treatment with intralesional 5-FU (Respectively) with complete response. C: Dermoscopic picture before treatment showing papilliform scaly yellowish wart with bleeding spots. D: Dermoscopic picture shows complete clearance of plantar warts and return of normal skin markings after treatment (score 3).

In accordance to our findings, Ghonemy *et al.* found that pain at the injection site was the main adverse effects after 5-FU injection which differed in the intensity according to the patients and the group. It was ranged from moderate to severe, hemorrhagic eschar formation was affecting more than half of patients which resolved later after treatment [21]. Similarly, Zoheir and colleagues, found that the pain was observed among one third of patients in group B (5-FU group), mild bruises in two patients and mild bruises & pain in another two patients, which resolved later on, with no significant difference between them and group A (MTX group) [17]. As well, Kannambal and colleagues work, reported that most patients, experienced moderate pain during injection of 5-FU that was of short duration and was overcome by mixing with xylocaine with adrenaline [22].

Not in line with our results, Sepaskhah *et al.* in 2022 who compared intralesional 5-FU versus cryotherapy in treatment of common and palmoplantar warts, found that 5-FU injection accompanied less pain during treatment than cryotherapy [20].

As regards patients' satisfaction, more than two-thirds of patients in 5-FU group were very satisfied, and more than half of patients in the combined digoxin and furosemide group were very satisfied also and this was statistically significant.

With respect to recurrence, following a monthly follow-up for six months, no recurrence had been noted in patients who had responded completely in group I, and this comes in agreement with a study done by Lofty *et al.* who treated cutaneous warts with intralesional digoxin and furosemide [15]. Also group II patients that had been cured totally with intralesional 5-FU, showed no recurrence, and that comes in a line with study done by Ghonemy *et al.* in 2020 who evaluated the effectiveness of injecting 5-FU against using microneedling alone versus in combination with it to treat plantar warts [21]. This result suggests that intralesional injection of 5-FU and digoxin plus furosemide combination are useful and efficient treatments for viral warts.

Our study had some limitations, one of them is a relatively small sample size. In addition, selection

bias, as the study participants were primarily recruited from patients who attended our clinic only. Therefore, there is a need for larger multi-center research that would take into account age, sex, geographical and cultural differences, in order to assess the efficacy of intralesional 5-FU compared with intralesional combined digoxin and furosemide in treatment of planter warts.

In conclusion, Intralesional ionic contraviral therapy (combined digoxin and furosemide) as well as intralesional 5-FU are effective, safe and well tolerated methods for treatment of planter warts clinically and dermoscopically, however, intralesional 5-FU had relatively higher efficacy than combined digoxin & furosemide in the treatment of planter warts clinically, dermoscopically and regarding the patient satisfaction score.

### Conflicts of interest

There are no conflicts of interest.

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