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ORIGINAL ARTICLE

Evaluation of Intralesional 5-Fluorouracil Versus Intralesional Interferon Alpha in Treatment of Warts

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Abstract

Background: ***Infection with the human papillomavirus (HPV) causes warts, sometimes called verrucae, which are benign growths on the skin and mucous membranes. Feelings of shame and rage often accompany it, and it can have a major influence on patients' quality of life.***

Aim and objectives: ***Efficacy of intralesional 5-FU vs intralesional interferon alpha in treating warts in two separate groups of patients.***

Patients and methods: ***The sixty patients who were chosen for this cohort had wart diagnoses and were seen in the outpatient clinics of Al-Azhar University Hospitals in Cairo's Dermatology, Venereology, and Andrology Department. The study's recruitment phase began in April 2022 and ended in April 2023.***

Results: ***With respect to the ultimate answer, group A and group B differed significantly (P=0.005) from one another. Only seven patients (23.3%) in group A (5-fluorouracil) had a partial response, while twenty-three patients (76.7%) attained complete clearance. This group did not exhibit any signs of resistance. On the other hand, out of 30 patients in group B (Interferon alpha), 36.7% achieved full clearance, 53.3% showed partial response, and 10.0% showed resistance.***

Conclusion: ***Palmar, planter, and common warts can be effectively treated with intralesional 5-fluorouracil (5-FU), which is also readily available, inexpensive, and of good quality. For intralesional interferon alpha to be more effective, it may be necessary to increase the number of sessions, decrease the intervals between them, or change the dosage. It is possible that people with resistant warts will benefit more from a combination of the two therapies.***

Keywords: Intralesional 5-Fluorouracil; Intralesional Interferon Alpha; Warts

1. Introduction

Skin and mucosal warts or verrucae, which are benign epidermal proliferations, can be caused by herpes simplex virus (Hpv).[1]

Patients may experience emotions of shame and unhappiness as a result of its possible negative influence on their quality of life.[2]

The Food and Drug Administration (FDA) has authorized a wide variety of medicinal treatments for warts. Nevertheless, it is unfortunate that current research shows that many of these options are either ineffective or linked to various negative effects. Another option for therapy was surgical excision or electro-cautery; however, both of these procedures are invasive, expensive, and fraught with danger. Therefore, it is critical to investigate complementary and alternative medicine.[3]

A class of antimetabolite medications, intralesional (5-FU) has inhibitory effects on DNA and RNA production and may also function as an immunomodulatory agent.[4]

The impact of interferon alpha (IFNα) is achieved by upregulating genes related to immunological processes; it is produced by plasmacytoid dendritic cells. This is accomplished by binding type I IFN receptors and recognizing immunological complexes and nucleic acids of microbes. Thus, interferon beta (IFNα) prevents the replication of viruses and enhances the responses of B cells.[5]

Several inflammatory illnesses, including HIV-associated Kaposi's sarcoma, cutaneous neoplasms, and viral infections, have been managed with the use of interferons. Furthermore, there are other methods of administration for interferons that have been used to treat patients with resistant warts.[6]

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Various groups of patients with warts will be compared to determine which is more effective: intralesional 5-fluorouracil or intralesional interferon alpha.

2. Patients and methods

Sixty patients having a clinical diagnosis of warts between April 2022 and April 2023 were recruited from the dermatology, venereology, and andrology outpatient clinics at Cairo's Al-Azhar University Hospitals. Each patient's informed permission was double-checked before they were enrolled in the study. To put it simply, two groups of patients were randomly assigned to receive different treatments. Group (A) consisted of 30 male and female patients who were administered intralesional 5-FU solution, while Group (B) consisted of 30 patients who were administered intralesional interferon alpha 2b

Ethical consideration:

Everyone who took part in the study gave their official approval before it began. The research protocol has been green-lit by the Ethical Scientific Committee at Cairo's Al-Azhar University. Patients gave their verbal and written consent before they could participate in the study.

Inclusion criteria: The patient was found to have several lesions, specifically two or more warts, on the palmar, planter, and common surfaces.

Exclusion criteria: Patients who are immunocompromised, have a history of allergy to interferon alpha or other components of 5-FU solution, or have undergone other treatment methods for warts in the last three months are not eligible. Furthermore, individuals who were pregnant or nursing, as well as those with impaired wound healing, cardiovascular illness, renal disease, or liver disease were not included.

Sample Size:

According to prior research and taking into account the average (±standard deviation) of intralesional interferon alpha versus intralesional 5-FU in two sets of wart patients. With a significance level of less than 0.05 and a high level of significance of 0.0001, the sample size was calculated using Stata® 17. There were a total of sixty participants in the study. There ought to be thirty people in each group.

Every single patient had gone through the following:

Details on the population's demographic makeup, including age, gender, hobbies, and health background. Confirmation of the diagnosis, type, and quantity of warts was also achieved through dermatological and general tests. Digital images were taken both before and four weeks after the treatment ended.

Study Procedures:

Thirty male and female patients were randomly assigned to Group A and given intralesional (5-FU)solution after isopropyl alcohol was used to clear the lesions. The medicine was packaged in a 10-milliliter container and was supplied by Al Hikma Pharmaceutical of Cairo, Egypt. A 0.25 ml local anesthetic was prepared by mixing 20 mg/ml lidocaine with 0.0125 mg/ml epinephrine. This was then mixed with 1 ml of 50 mg/ml 5-FU to generate the solution. The patients were administered intralesional injections of the freshly prepared solution until the lesions turned white, with a maximum dosage of two milliliters per session. The maximum number of sessions allowed throughout the twelve weeks was two per week, or until the warts were completely gone, whichever came first.

Interferon alpha (Recombinant Human Interferon Alpha 2b, Intalfa 3MIU/1.0 mL, manufactured by Intas Pharmaceutical, Ahmadabad, India) was delivered intralesionally to thirty patients (male and female) in Group B. After the patients in this group cleaned their lesions with isopropyl alcohol, they were given a series of intralesional injections of interferon alpha. Every wart, up to a limit of five per patient per session, was treated with a dose of one million IU. After the first two weeks, or until the warts were all gone, these injections were given three times weekly. All patients in groups A and B had revisions four weeks after therapy ended, and they were followed up for three more months to check for recurrence.

Follow-up and Prognosis:

Full responsiveness is achieved when all warts have been removed. The patient was considered to be responding partially when certain warts did not change. Treatment was considered unsuccessful when no lesions showed indications of clearance.

Data management and statistical Analysis:

The data was analyzed using SPSS version 24, which stands for Statistical Package for the Social Sciences. Reports were made regarding the percentage and frequency of the qualitative data. The expression for regularly distributed quantitative data was mean ± standard deviation, while for non-normally distributed data it was median (IQR). Standard deviation: Dividing the total of all variables by the total of all values gives the central tendency of that particular collection of numbers. We have standard deviation (SD): Statistically speaking, it is the measure of the dispersion of a set of values. When the standard deviation is little, it means that the values are tightly clustered around the set average, but when it's large, it means that the values span a wider range.

The tests that were described earlier were performed: Random sample When comparing two groups with normally distributed data, the T-test (T) is used. To compare non-parametric variables, the chi-square test was used. The likelihood, or p-

value: A p-value of 0.001 was considered extremely significant, while a p-value of 0.05 was considered statistically significant. Statistical significance was determined to be absent when the p-value was higher than 0.05.

3. Results

Table 1. Comparative analysis of demographic information among the groups under study.

		GROUP A (N=30)		GROUP B (N=30)		STAT. TEST	P-VALUE
AGE(YEARS)	Mean	32.1		32.4		T=0.1	0.917
	±SD	9.5		10.2			NS
SEX	Male	13	43.3%	9	30%	X^2=1.14	0.284
	Female	17	56.7%	21	70%		NS
SMOKING	No	23	76.7%	24	80%	X^2=0.09	0.754
	Smoker	7	23.3%	6	20%		NS
SYSTEMIC ILLNESS	No	24	80%	25	83.3%	X^2=0.11	0.739
	Yes	6	20%	5	16.7%		NS

T:independent sample T test. X2:Chi-square test. NS:p-value>0.05 is considered non-significant.

There was no statistically significant disparity observed between the two groups in terms of age, gender, smoking behavior, and systemic illness, *Table 1*.

Table 2. Types of warts compared amongst the groups under study.

		GROUP A (N=30)		GROUP B (N=30)		STAT. TEST	P-VALUE
WART TYPES	Planter	22	73.3%	20	66.6%	X^2=0.59	0.743
	Common	5	16.7%	5	16.7%		NS
	Palmar	3	10%	5	16.7%		

X2:Chi-square test. NS:p-value>0.05 is considered non-significant.

There was no statistically significant difference in the types of warts between the tested groups (p-value = 0.743). Twenty patients (66.6%) with plantation wart, five patients (16.7%) with common wart, and three patients (10%) with palmar wart were in group A; in group B, there were twenty patients (66.6%) with planter wart, five patients (16.7%) with common wart, and five patients (16.7%) with palmar wart, Table 2.

Table 3. Comparison of number of warts at baseline between studied groups.

		GROUP A (N=30)	GROUP B (N=30)	STAT. TEST	P-VALUE
NUMBER OF WARTS AT BASELINE	Mean	5.2	4.9	T=	0.748
	±SD	4.6	3.2	0.32	NS

There was no statistically significant variance in the number of warts at baseline (p-value = 0.748) between the groups under investigation, Table 3.

Table 4. Comparison of response to treatment at different sessions.

		GROUP A (NO=30)		GROUP B (NO=30)		STAT. TEST	P-VALUE
RESPONSE AFTER 1ST SESSION	No response	22	73.3%	30	100%	X^2 =9.2	0.002 S
	Partial response	8	26.7%	0	0%		
RESPONSE AFTER 3RD SESSION	No response	1	3.4%	27	90%	X^2=44.4	<0.001HS
	Partial response	24	82.8%	3	10%		
	Complete response	4	13.8%	0	0%		
	Complete response in previous session	1	3.3%	0	0%		
FINAL RESPONSE (AFTER 4 WEEKS FROM FINAL SESSION)	No response	0	0%	3	10%	X^2=10.7	0.005S
	Partial response	7	23.3%	16	53.3%		
	Complete response	23	76.7%	11	36.7%		

With a p-value of 0.005, the difference in the final response between the research groups was statistically significant. Only seven patients (23.3%) in group A (5-fluorouracil) had a partial response, whereas twenty-three (76.7%) attained complete clearance. This group did not exhibit any signs of resistance. On the other hand, out of 30 patients in group B (Interferon alpha), 36.7% achieved full clearance, 53.3% showed partial response, and 10.0% showed resistance, Table 4.

Table 5. Correlation between final response and other data into group-A.

GROUP A		FINAL RESPONSE				STAT. TEST	P-VALUE
		Partial (n=7)		Complete (n=23)			
AGE(YEARS)	Mean	33.7		31.6		F=0.49	0.624
	±SD	10.7		9.3			NS
SEX	Male	4	57.1%	9	39.1%	X^2=0.7	0.4 NS
	Female	3	42.9%	14	60.9%		
SMOKING	No	7	100%	16	69.6%	X^2=2.77	0.096
	Yes	0	0%	7	30.4%		NS
SYSTEMIC ILLNESS	No	6	85.7%	18	78.3%	X^2=0.18	0.666
	Yes	1	14.3%	5	21.7%		NS
WART TYPE	Planter	5	71.4%	17	73.9%	X^2=0.2	0.903
	Common	1	14.3%	4	17.4%		NS
	Palmer	1	14.3%	2	8.7%		

X2:Chi-square test. F:F value of ANOVA test. NS:p-value>0.05 is considered non-significant.

The total number of sessions in group A was substantially lower (5±1.23) (p-value<0.001) compared to group B (5.9±0.18). There were three patients (10%) and four patients (13.3%) in group A (5-FU) who reached full response after four sessions; one patient (3.3%) reached full reaction after two sessions, and five patients (16.7%) reached full response after five sessions. Six sessions were necessary for just 17 individuals (56.7%).

In contrast, 29 patients (96.7% of the total) in group B (INF alpha) were required to finish all of their sessions, and after 5 sessions, just one patient showed a full recovery.

Group A (5-FU) patients had the following side effects: 100% local pain, 56.7% local eschar formation, 23.3% local hyperpigmentation that faded with follow-up, 3.3% local hypopigmentation, 6.7% local ecchymosis or swelling, and 13.3% local erythema.

Group B (INF alpha) had manageable side effects overall; however, 83.3% of patients had flu-like symptoms, the intensity of which varied with dosage and was mild to moderate. As time went on, these symptoms started to go away. Thirty percent of patients also reported local discomfort, three percent local swelling, and thirteen percent local itching. Age, sex, systemic illness, smoking, and wart type were not observed to have a statistically significant link with final response in group A (5-FU), Table 5.

Table 6. Correlation between final response and other data in group B.

GROUP B		FINAL RESPONSE						STAT. TEST	P-VALUE
		No (n=3)		Partial (n=16)		Complete (n=11)			
AGE(YEARS)	Mean	35.7		35.2		27.5		F=2.24	0.126
	±SD	7.02		10.5		8.9			NS
SEX	Male	2	66.7%	6	37.5%	1	9.1%	X^2=4.6	0.098
	Female	1	33.3%	10	62.5%	10	90.9%		NS
SMOKING	No	1	33.3%	13	81.3%	10	90.9%	X^2=4.6	0.086
	Yes	2	66.7%	3	18.8%	1	9.1%		NS
SYSTEMIC ILLNESS	No	1	33.3%	14	87.5%	10	90.9%	X^2=6.1	0.048 S
	Yes	2	66.7%	2	12.5%	1	9.1%		
WART TYPE	Planter	2	66.7%	9	56.2%	9	81.8%	X^2=4.1	0.380
	Common	0	0%	3	18.8%	2	18.2%		NS
	Palmer	1	33.3%	4	25%	0	0%		

X2:Chi-square test. S:p-value<0.05 is considered significant.

F:F value of ANOVA test. NS:p-value>0.05 is considered

The final reaction in group B (INF alpha) was not shown to be significantly related to age, sex, smoking status, or kind of warts. However, the percentage of systemic illnesses was considerably greater (p-value=0.048) in patients with no response (66.7%), as compared to patients with partial responses (12.5%) and complete responses (9.1%). Neither group experienced any recurrences throughout the three-month follow-up period, Table 6.

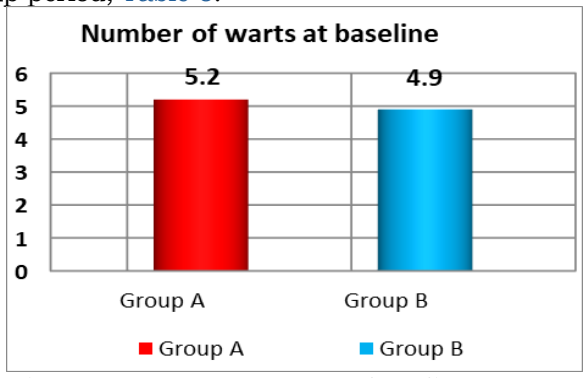

Figure 1. Wart count at baseline compared between groups.

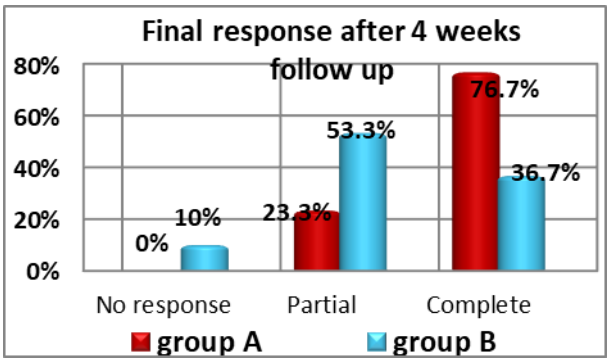

Figure 2. Evaluation of the research groups' final responses.

Figure 3. There was a partial response in a 46-year-old male patient who had planters' warts both before and after 5-FU treatment. In all, he underwent six sessions of therapy. The photo on the right was captured during a follow-up session four weeks later.

Figure 4. A female patient with planter warts who was 39 years old showed complete improvement after three sessions of 5-FU treatment. During the four-week check-in, the picture on the right was taken.

Figure 5. After receiving 5-FU for four effective

sessions, a woman with 43 common warts reported a full disappearance of all warts. After a three-month follow-up, the photo on the right was captured.

Figure 6. An 18-year-old woman's warts disappeared after 6 sessions of intralesional INF alpha 2b treatment spread out over 2 weeks. The photo on the right was taken during a follow-up appointment four weeks later.

4. Discussion

Intralesional 5-fluorouracil and interferon-alpha have never been tested for their effectiveness in treating warts in different patient populations until now. There is zero prior study that has compared the two treatments.

Research by Kamal et al. on the efficacy and safety of intralesional 5-FU for the treatment of warts was conducted on 40 patients, which is in line with the present study. They utilized an identical combination to ours, diluted to the same extent. The study comprised three different forms of warts: planter warts (52.5%), palmar warts (32.5%), and genital warts (15.5%). Thirty patients (or 75% of the total) had a completely fantastic reaction, seven (17.5%) had a partial reaction ranging from good to adequate, and three (7.5%) had a terrible reaction, according to the results.[7]

Twenty patients with common palmar and plantar warts were enrolled in the study by Kannambal et al., who compared intralesional 5-FU with placebo. Twelve patients, or 60% of the total, had a full recovery, while eight patients, or 40%, had a partial recovery, according to their study. Possible explanation for the disparity in findings between our study and theirs: they only conducted a maximum of three sessions, spaced three weeks apart.[2]

They reported experiencing discomfort and onycholysis as potential side effects when applying it to warts near the nails.

Yazdanfar et al. compared the efficacy of the treatment to a placebo in a study involving 34 individuals with 68 verrucae. In their experiment, they used a mixture of 5-FU, lignocaine, and epinephrine. The patients were given injections once a week until the warts vanished. They demonstrated an attentiveness level of 64.7%.[8]

Except for ulceration, necrosis, and scarring, which were not detected in our analysis, they discovered adverse effects that were similar to ours.

A retrospective study by Chen L. et al. included 2415 people with wart diagnoses; 540 of them people were given interferon-alpha. The group that got intralesional interferon-alpha had a cure rate of 85.93% (464/540). Their study's results were totally at odds with ours, and we suspect that this discrepancy is due to the fact that they routinely gave patients immune-system stimulants like zinc sulphate and topical wart treatments like imiquimod. We can't rule out the possibility that the vastly higher number of sessions may have contributed to the discrepancy.[5]

A study was carried out by Aksakal et al. to assess the effectiveness of interferon-alpha in treating 53 individuals afflicted with warts. They divided their patient population into four categories: The patients were divided into four groups: those with a single verruca plantaris lesion, those with several verruca vulgaris lesions concentrated on a single finger, those with multiple verruca plantaris lesions overall, and a control group of patients with no lesions at all. Patients in the first three groups (experimental groups) received a single dosage (4.5 MU) of sublesional IFN-alpha 2 a, whereas those in the control group received an injection of physiological saline placebo. The results showed that 6.6% of patients in group 1 had treatment failure, 8.3% had a partial response, and 79.2% had a complete response. Full responses were received by 33.3% of Group 3 and 22.2% of Group 2. No answers were obtained by the control group. The overall success rate for all verruca varieties in their study was 55.5%. Since they only injected the volunteers once, these results don't quite add up with our study's findings. We discovered that they used cryocautery as a local anesthetic for three or four seconds before injection; this technique definitely affected their findings when we reviewed their methods.[9]

They reported experiencing acute side effects such headaches and mild to moderate flu-like symptoms. Although our study found a somewhat lower prevalence of flu-like symptoms in 32 individuals (71.1%) after IFN treatment, this may be due to sampling bias.

One hundred patients with warts who had been given different dosages of intralesional interferon alpha 2 b were the subjects of the study by Vance et al. In the study involving interferon alfa (IFN), 13% of patients showed improvement with 106 IU of IFN, 22% with 105 IU of IFN, and 21% with placebo. Contrary to our findings, it seemed that

warts treated with a placebo responded better than those treated with a high dose of interferon.[10]

The smoking habit can influence the onset and persistence of HPV infections through mechanisms such as diminishing local immune response, stimulating cell proliferation, elevating proinflammatory mediators, or inducing harm to host DNA, thereby heightening susceptibility and persistence of infection with HPV.[11]

Nonetheless, there were no statistically significant differences in smoking behavior or outcome between the two groups in this study.

4. Conclusion

If you have palmar, planter, or common warts, you should use intralesional 5-FU because it is highly effective, inexpensive, and readily available. For intralesional interferon alpha to be more effective, it may be necessary to increase the number of sessions, decrease the intervals between them, or change the dosage. Patients suffering from warts may see even more relief if the two therapies are used together.

Disclosure

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Authorship

All authors have a substantial contribution to the article

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Conflicts of interest

There are no conflicts of interest.

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