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Evaluation of intralesional 5-fluorouracil versus intralesional interferon alpha in treatment of warts

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***Abstract*---**Background: Warts are non-malignant growth of the skin and mucous membranes resulting from infection with human papillomavirus (HPV). It can significantly impact the quality of life for patients and elicit feeling of embarrassment. Aim and objectives: A comparative analysis of the efficacy of intralesional 5-FU and intralesional interferon alpha among distinct groups of patients diagnosed with warts. Patients and methods: This is a cohort of sixty individuals diagnosed with warts were selected from the period of early April 2022 to the end of April 2023. Results: There was a statistically significant difference (P-value=0.005) seen between the two groups, namely group A and group B, in relation to the final

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response. In group A (5-Fluorouracil)), complete clearance was achieved by 23 patients (76.7%), with 7 patients (23.3%) showing partial response. No instances of resistance were observed in this group. Conversely, in group B (Interferon alpha), only 11 patients (36.7%) attained complete clearance, while 16 patients (53.3%) exhibited partial response, and resistance was evident in 3 cases (10%). Conclusion: Intralesional *5-Fluorouracil* (5-FU) is highly effective, cheaper, and easily available in treating warts. The combination of the both treatments may deliver a greater benefit to patients with resistant warts.

***Keywords*---**5-Fluorouracil, Interferon Alpha, Warts, Verruca, Human Papillomavirus.

Introduction

HPV is responsible for the development of benign epidermal proliferations known as warts or verrucae on the skin and mucosa (Lynch et al., 2014) [6]. It has the potential to significantly impact the quality of life for patients, leading to feelings of humiliation and dissatisfaction (Kannambal et al., 2019)[5]. The FDA, or food and drug administration, has granted approval for many medical treatment choices for different types of warts. However, it is regrettable that a significant portion of these options exhibit limited efficacy or are associated with numerous detrimental effects, as evidenced by existing research. Additional treatment modalities encompassed electro-cautary and surgical excision; however, it is important to note that both surgical interventions are intrusive, costly, and pose inherent risks. Therefore, it is imperative to explore alternate therapy modalities (Rafique et al., 2023)[8]. 5-FU is classified as an antimetabolite medication that exerts inhibitory effects on the synthesis of DNA and RNA, while also potentially serving as an immunomodulatory agent (Ghonemy et al., 2020) [3].

Interferon alpha (IFNα) is derived by plasmacytoid dendritic cells and exerts its effects by upregulating genes associated with immunological processes. This is achieved through the recognition of microbial nucleic acids and immune complexes, as well as the binding of type I IFN receptors. Consequently, (IFNα) inhibits viral replication and augments B cell responses (Chen et al., 2023) [2]. The administration of interferons has been employed in the management of viral infections, cutaneous neoplasms, HIV-associated Kaposi's sarcoma, and various inflammatory disorders. Additionally, patients with resistant warts have received interferons through several administration routes (Park et al., 2002)[7].

The current study aims to compare between the safety and effectiveness of intralesional 5-fluorouracil and intralesional interferon alpha in different groups of patients with warts.

Patients and Methods

Outpatient’s clinics in Dermatology, Venereology, and Andrology at Al-Azhar University Hospitals in Cairo were used to recruit sixty patients who had been

clinically diagnosed with warts between April 2022 and April 2023. Prior to the study's enrollment, each participant provided their informed consent. A committee from Al-Azhar University in Cairo's Ethical Scientific Committee has approved the study plan. Before the patients were included in the trial, their informed written and verbal agreement was acquired. Simply said, two groups of patients receiving distinct treatments were randomly assigned. Thirty patients of both genders were enrolled in Group (A), which got intralesional 5-FU solution, and thirty patients in Group (B), which received intralesional interferon alpha 2b. The patients who had a clinical diagnosis of palmar, planter, or common warts recruited as a part of the study. The patients with multiple lesions (i.e. ≥2 warts) were also included. Exclusion criteria encompassed patients who had undergone alternative wart treatments within the preceding three months, individuals with compromised immune systems, those with known allergies to interferon alpha or any constituents of 5-FU solution, as well as pregnant or lactating women. Furthermore, individuals with a solitary wart, impaired wound healing, or underlying cardiovascular, renal, or hepatic conditions were also excluded from the study. Demographic data such as age, gender, special habits, and medical history was obtained. Dermatological examinations were also done to confirm the diagnosis, type, and number of warts. Digital pictures were captured at baseline and four weeks following the end of the treatment.

Sample Size:

Based on evidence from previous study and by considering the mean (±SD) of intralesional interferon alpha versus intralesional 5-FU in two groups of patients with warts. Stata® 17 was used to calculate the sample size with<0.05 level of significance and 0.0001 high level of significance. Total sample size was 60 participants. Each group should have 30 participants.

Study Procedures:

The patients were simply randomized and separated into; ***Group A*** that included thirty patients of both genders who were treated with intralesional (IL) 5-FU solution after cleaning the lesions with isopropyl alcohol. A 10 ml bottle of Utoral-500 mg/10 ml-from Al Hikma Pharmaceutical in Cairo, Egypt contained the medication. A mixture of 20 mg/ml lidocaine and 0.0125 mg/ml epinephrine was used to make 0.25 ml of local anesthetic, which was then combined with 1 ml of 50 mg/ml 5-FU to create the solution. With a maximum dosage of two milliliters of the solution per session, the patients received intralesional injections of the freshly made solution until the lesions blanched. The sessions repeated every two weeks. The maximum number of sessions was 6 sessions that may be conducted during the twelve-week period or until all warts were totally resolved, whichever happened first.

The other one is ***Group B*** that included thirty patients of both genders who were administered intralesional interferon alpha (Recombinant Human Interferon Alpha 2b, Intalfa 3MIU/1.0 mL, produced by Intas Pharmaceutical, Ahmadabad, India). The patients in this group received a series of intralesional interferon alpha injections after cleaning the lesions with isopropyl alcohol. Each wart received a dose of one million IU, up to a maximum of five warts per patient every

session. These injections were administered three times a week for two weeks in a row, or until all warts were completely removed, whichever occurred first. After the therapy was stopped, all of the patients in groups A and B underwent revisions four weeks later, and they were then monitored for an additional three months to look for any recurrence.

Follow up and Prognosis:

When every wart has been cleared, the patient is deemed fully responsive. When some warts did not alter, the patient was deemed to be partially responding. When none of the lesions showed signs of clearing, the treatment was deemed ineffective.

Data management and statistical Analysis:

The statistical package for social science (SPSS) versions 24 was used to examine the data. The frequency and proportion of the qualitative data were reported. For quantitative data that were normally distributed, the expression was mean ±SD, and for data that were not normally distributed, it was median (IQR). Mean (average): The central tendency of an individual set of numbers refers to the concept of dividing the sum of variables by the total number of values. Standard deviation (SD): The measurement of dispersion of a group of values is referred to as it. A low standard deviation suggests that the values cluster closely around the average value of the set, whereas a high standard deviation shows that the values are more widely dispersed throughout a larger range.

The aforementioned tests were conducted: Independent sample T test (T): When conducting a comparison between two groups using data that follows a normal distribution. Chi-square test: Was employed for the purpose of comparing non-parametric variables. Probability (P-value): The p-value of 0.05 was deemed to be statistically significant, while a p-value of 0.001 was regarded to be very significant. A p-value greater than 0.05 was deemed to be statistically insignificant.

Results

There was no statistically significant difference observed between the two groups in terms of age, gender, smoking behavior, and systemic illness (table 1). In group A, the participants' ages spanned from 18 to 58 years, with a mean age of 32.1 years. While in group B, the participants' ages spanned from 18 to 52 years, with a mean age of 32.4 years.

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 NS
	±SD	9.5		10.2			
Sex	Male	13	43.3%	9	30%	X^2=1.14	0.284 NS
	Female	17	56.7%	21	70%		
Smoking	No	23	76.7%	24	80%	X^2=0.09	0.754 NS
	Smoker	7	23.3%	6	20%		
Systemic illness	No	24	80%	25	83.3%	X^2=0.11	0.739 NS
	Yes	6	20%	5	16.7%		

T: independent sample T test. X^2:Chi-square test. NS: p-value>0.05 is considered non-significant.

There was no statistically significant variation observed in the types of warts among the groups under investigation, as indicated by a p-value of 0.743. The distribution of wart types among the individuals in each group is presented in Table 2. Also there was no statistically significant variance in the number of warts at baseline (p-value = 0.748) between the groups under investigation, table 3. In the context of the treatments administered, a statistically significant difference (P-value=0.005) was observed in the final outcomes among the groups under investigation. Within group A (5-Fluorouracil), 23 patients (76.7%) achieved complete clearance, while 7 patients (23.3%) displayed partial response, with no instances of resistance noted. In contrast, group B (Interferon alpha) saw only 11 patients (36.7%) achieving complete clearance, with 16 patients (53.3%) demonstrating partial response, and resistance was evident in 3 cases (10%), as indicated in table 4.

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 NS
	Common	5	16.7%	5	16.7%		
	Palmar	3	10%	5	16.7%		

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

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 ±SD	5.2 4.6	4.9 3.2	T= 0.32	0.748 NS

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%		
	Partial response	8	26.7%	0	0%	X^2 =9.2	0.002 S
Response after 3rd session	No response	1	3.4%	27	90%		
	Partial response	24	82.8%	3	10%		
	Complete response	4	13.8%	0	0%	X^2=44.4	<0.001HS
	Complete response in previous session	1	3.3%	0	0%		
Final response (after 4 weeks from final session)	No response	0	0%	3	10%		
	Partial response	7	23.3%	16	53.3%		
	Complete response	23	76.7%	11	36.7%	X^2=10.7	0.005S

The study revealed a notable disparity in the total number of sessions between the two groups, with group A exhibiting a highly significant lower average number of sessions (5±1.23) in contrast to group B (5.9±0.18), as indicated by a p-value of less than 0.001. In group A (5-FU), one patient (3.3%) achieved complete response after 2 session, 4 Patients (13.3%) achieved complete response after 3 sessions, 3 Patients (10%) achieved complete response after 4 sessions and 5 patients(16.7%) achieved complete response after 5 session. Only 17 patients (56.7%) needed to complete 6 sessions then. On the other hand, in group B (INF), 29 patients (96.7%) needed to complete all programmed sessions and only one patient achieved compete response after 5 sessions.

As regard side effects, in group A (5-FU), all patients 100% experienced local pain, 56.7% developed local eschar formation, 23.3% had temporary local hyperpigmentation that subsided during follow-up, 3.3% experienced local hypopigmentation, 6.7% had local ecchymosis or swelling, and 13.3% had local erythema.

In group B (INF alpha), 83.3% of patients experienced flu-like symptoms, which were related to the dosage and ranged in severity from mild to moderate. These symptoms gradually subsided over subsequent sessions. Additionally, 13.3% of patients reported local itching, 30% reported local pain, and 3.3% reported local swelling. In general, side effects were tolerable.

There was no statistically significant correlation found between the final response and factors such as age, sex, smoking, and types of wart in both groups. However, in group B, a statistically significant (p-value = 0.048) increase in the percentage of systemic illness was observed in patients with no response (66.7%) compared to patients with partial response (12.5%) and complete response (9.1%). Throughout the three-month follow-up period, neither group had any recurrences.

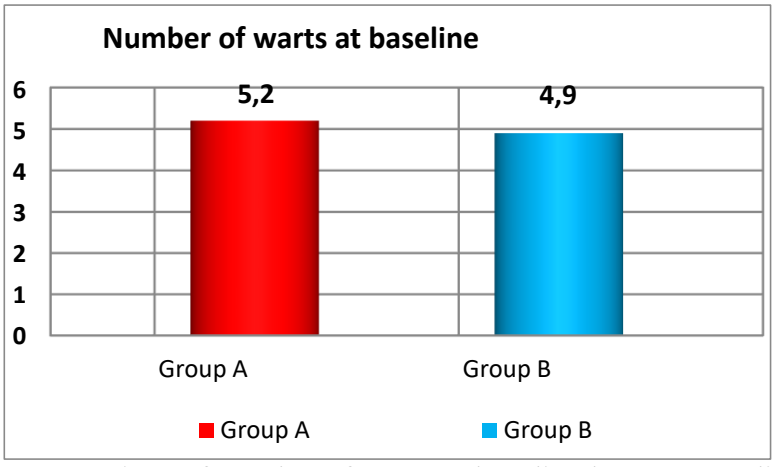

Figure (1): Comparison of number of warts at baseline between studied groups

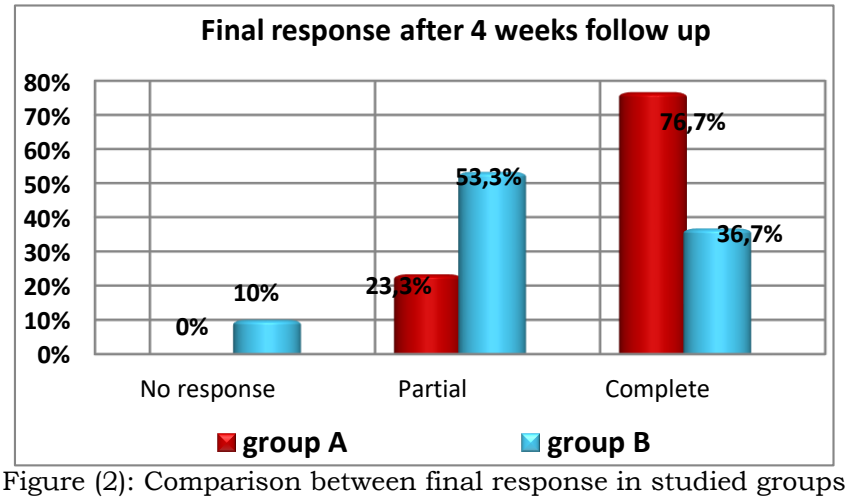

Figure (2): Comparison between final response in studied groups

Figure (3): A male patient, age 46, had planters' warts prior to and following receiving 5-FU treatment; he showed a partial response. He received six sessions of treatment in total. The picture on the right was taken at a four-week follow-up appointment.

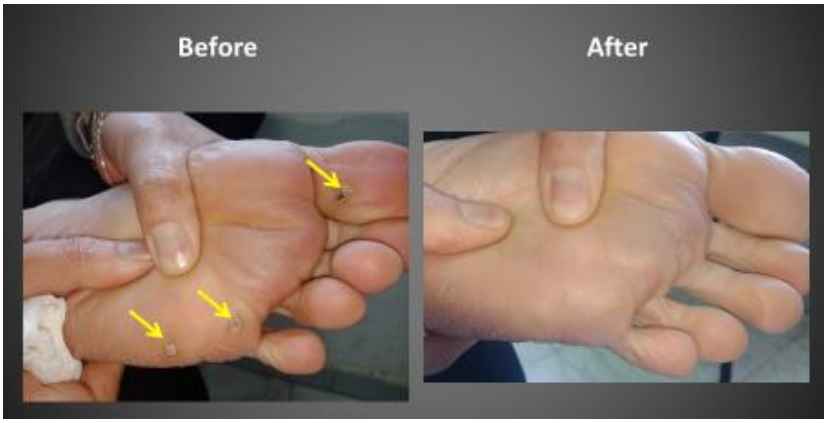

Figure (4): Following three treatment sessions, a 39-year-old female patient with planter warts demonstrated a full response to 5-FU treatment. The image to the right was captured during the four-week check-in.

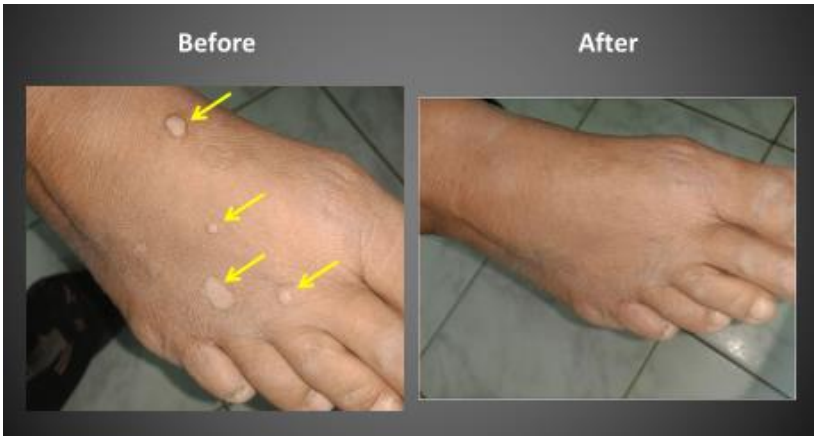

Figure (5): One woman, forty-three with common warts showing a complete clearance of all warts after treatment with 5- FU for 4 successful sessions. The right picture was taken after a 3-month-follow-up period.

Figure (6): A 18-year-old female with multiple planter warts that were treated with intralesional INF alpha 2b for 6 sessions over 2 weeks, showing complete clearance of all warts. The right picture was taken during a 4-week follow-up visit.

Discussion

This is the first study to assess the efficacy of intralesional 5-fluorouracil and interferon alpha in the treatment of warts in various patient populations. The two treatments have never been compared in single study before.

Consistent with the current study, *Kamal et al.,* carried out research on 40 patients to determine the safety and effectiveness of intralesional 5-FU in the treatment of warts. They used the same mixture we used with the same concentration. The type of warts included in the study were planter, palmar and genital warts, their percentage were 52.5%, 32.5% and 15% respectively. The findings showed that thirty patients (75%) had a fully excellent response, seven

patients (17.5%) had a partial reaction (good to satisfactory), and three patients (7.5%) had a bad response (Kamal et al., 2018) [4].

Kannambal et al., compared intralesional 5-FU with placebo in 2 groups of patients with common, palmar and plantar warts included 20 patients for each. Their study showed a complete response in 12 (60%) of 20 patients, while partial response observed in 8 patients (40%). This discrepancy in results between our study and theirs may be attributed to the difference between the number of sessions and the interval between them as they did maximally 3 sessions with 3 weeks interval (Kannambal et al., 2019) [5].They stated that, when it is applied to warts close to the nails, possible adverse effects include discomfort and onycholysis were obtained.

Yazdanfar et al., assessed the effectiveness of 34 patients with 68 verrucae against placebo. They combined 5-FU with a lignocaine and epinephrine combination in their investigation. Weekly injections were administered to the patients until the warts disappeared. They displayed a 64.7% thorough response (Yazdanfar et al., 2008) [10]. They found unfavorable effects that were comparable to ours, with the exception of ulceration, necrosis, and scarring, which our investigation did not uncover.

Chen, L. et al., carried out a retrospective research with 2415 wart-diagnosed individuals, of which 540 individuals received treatment with interferon alpha. They found that, a cure rate was 85.93% (464/540) in the group that received interlesional interferon alpha. These results in their study were completely different from the results of our study, and it is likely that the reason for this difference is that they did not mind giving patients some medications that stimulate the immune system like zinc sulphate and some topical medications that are used as a treatment for warts, such as imiquimod. Perhaps the difference was also due to number of sessions which was significantly more than number of sessions in our study (Chen et al., 2023) [2].

Aksakal., et al., a study evaluating the efficacy of interferon alpha in the treatment of warts was carried out on 53 patients who had been diagnosed with them. Four groups of patients were created from their patient population: group 1 consisted of patients with a single verruca plantaris lesion; group 2 consisted of multiple verruca vulgaris lesions localized to the finger; group 3 consisted of multiple verruca plantaris lesions; and group 4 was a control group made up of patients with single lesion. Sublesional IFN-alpha 2 a was administered as a single dosage (4.5 MU) to the patients in the first three groups (experimental groups), whereas the control group had an injection of physiological saline placebo. According to their findings, 6.6% of patients in group 1 experienced treatment failure, 8.3% saw a partial response, and 79.2% of patients had a complete response. The percentages 22.2% and 33.3% of groups 2 and 3, respectively, had complete response rates. The control group received zero responses. 55.5% of all verruca kinds in their study were successful overall (Aksakal et al., 2009) [1]. However, these findings are somewhat inconsistent with the results of our study, especially since they injected volunteers for a single session only. Upon reviewing their methodology, we found that they utilized cryocautery for 3-4 seconds prior to injection to serve as local anesthesia, this

procedure certainly influenced their results. Acute side effects, such as headache and mild to moderate flu-like symptoms, were reported by them. 32 (71.1%) of the patients experienced flu-like symptoms following IFN treatment, this could be a little different from the frequency in our research (Aksakal et al., 2009) [1].

Vance et al., conducted a study on one hundred patients who had been prescribed varying doses of interlesional interferon alpha 2 b for their warts. Of the patients treated with IFN, 13% responded well to 106 IU of IFN, 22% responded well to 105 IU of IFN, and 21% responded poorly to placebo. The warts treated with a placebo appeared to respond better than those treated with a high dosage of interferon, this was at odds with what we found (Vance et al., 1986) [9].

Conclusion

The efficacy of intralesional 5-FU is significantly high, cheaper, and easily available in treating palmar, planter, and common warts. Intralesional interferon alpha may need more sessions, adequate time between sessions or dose adjustment to show more efficacies. The combination of the both treatments could deliver a greater benefit to patients with warts.

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