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EFFICACY AND SAFETY OF INTRALESIONAL 5-FLUOROURACIL IN THE TREATMENT OF CUTANEOUS WARTS

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Abstract

OBJECTIVE

To determine the efficacy and safety of Intralesional 5-fluorouracil in the treatment of cutaneous warts.

METHODOLOGY

A descriptive cross-sectional investigation was undertaken at the Department of Dermatology, Chandka Medical College & Hospital, Larkana, with the objective of elucidating the therapeutic efficacy and tolerability profile of intralesional 5-fluorouracil (5-FU) in the management of cutaneous warts. The study population consisted of males and females aged between 18 and 65 years, all presenting with cutaneous warts of a minimum duration of one month. Participants received bi-weekly intralesional injections of 5-FU (50 mg/ml) until a maximum of six treatment sessions were administered. The therapeutic outcomes were classified as excellent (75-100% of cure), good (50-74% of improvement), fair (25-49% of improvement), or poor (<25% of improvement). The collected data were analyzed utilizing SPSS version 26, employing a significance level of 0.05.

RESULTS

The study involved a sample of 129 subjects with an average age of 31.60±11.28 years. A substantial proportion of the participants (62.0%) fell within the age bracket of 18 to 30 years, and 64.3% of the individuals were classified as female. Following the administration of six intralesional injections of 5-fluorouracil, a remarkable 75.2% of the subjects exhibited considerable improvement, whereas 10.9% demonstrated a positive response, 7.8% a satisfactory result, and 6.2% an unfavorable outcome. Regarding safety, pain was the most frequent adverse effect (72.8%), followed by erythema (20.1%), and irritation (15.5%).

CONCLUSION

Interlesional administration of 5-fluorouracil (5-FU) has been demonstrated to be an efficacious and safe intervention for the management of cutaneous warts; a majority of patients experienced significant clearance of lesions. The findings of

this investigation further substantiate 5-FU as a cost-effective therapeutic alternative in the treatment of obstinate warts particularly in settings with limited resources. Furthermore, larger scale with long follow-up randomized controlled trials are necessary to validate these findings.

INTRODUCTION

Warts, also known as verrucae, are caused by the human papillomavirus, a member of the Papovaviridae family. Morphologically, they can manifest as verruca vulgaris (common warts), verruca plana (plane or flat warts), plantar warts, filiform warts, digitate warts, and anogenital warts (condyloma acuminata), among other types [1].

The lesions present as rough and keratotic and are seen primarily on lower extremities. The inoculation of the virus into keratinocytes implies epidermal damage and a weakened immune system in this disease [2].

Many time-honoured methods of treatment for cutaneous warts include occlusion, curettage, cautery, diathermy, trichloroacetic acid (TCA), cryotherapy, radiofrequency ablation, electrofulgration, laser treatment, hypnosis, podophyllin, keratolytic agents, antiproliferative agents and immunotherapy [3]. In spite of the evidence of a significant clear-out rate to these modalities, paradoxically it is also characterized by a confusing, almost seemingly unjustified law of the recurrence or the treatment failure [4].

Among the common treatment methods applied to warts is the removal of the epidermis which is affected by the viral infection. These modalities include local agents such as salicylic acid, glutaraldehyde, and retinoic acid, as well as electrocoagulation, cryotherapy, and CO2 laser treatment [3-5]. The choice of treatment strategy can be substantially influenced by treatment-related pain, side-effects and financial considerations [6].

5-FU (5-fluorouracil) belongs to the antimetabolites, which act as an antagonist of cellular proliferation and cause cell cycle arresting [7]. The use of topical 5-FU is also used for warts, but with moderate efficacy [8]. It not only concentrates the drug, 5-FU inside the lesion, but previous studies also have proven its efficacy by showing the cure rates of 75% and 86%, respectively [9,10].

In clinical practice, a thorough assessment of the patient's medical history, features of the wart and patient preferences should drive the choice. As in the case of all medical interventions, the relative risks, benefits, and alternatives should be discussed with the patient to permit an informed decision between treatment options.

This study was designed because there is a need to critically evaluate the effectiveness and safety of Intralesional 5-fluorouracil as a treatment for cutaneous warts. The scarcity of strong evidence on this treatment warrants serious consideration of the benefits. We hope to offer dermatologists and patients a deeper understanding of treatment choices through a review of its efficacy and side effects that would enable them to make more informed clinical decisions. This research contributes to existing medical literature, promotes a patient-centred approach to care, and fills a current gap in the non-invasive management of cutaneous warts.

METHODOLOGY

This investigation constituted a cross-sectional descriptive analysis undertaken within the Department of Dermatology at Chandka Medical College and Hospital in Larkana. A non-probability consecutive sampling methodology was employed to recruit participants for the study. The subjects group included both males and females, aged between 18 and 65 years suffering from cutaneous warts of duration more than one month and who voluntarily participated after obtaining informed consent. Patients were ineligible if they had a past medical history that may significantly impact the efficacy or safety of the treatment, known allergy to 5-fluorouracil or related cytotoxic agents, had history of systemic immunosuppression, enrolled in other investigational therapy study, history of treatment with 5-fluorouracil for cutaneous warts within 3 months before entering the study, and pregnant or lactating women. Baseline demographic details were well recorded. All subjects underwent intralesional injection of 5-FU (50 mg/ml) at a dose of 0.1 ml/cm² using insulin syringes (0.25 mm x 6 mm) at the base of each wart, after appropriate skin disinfection with isopropyl alcohol. Injections

were repeated every 2 weeks, to a maximum of 6 sessions or until the lesions were resolved. Patients underwent biweekly follow-up for assessment of dimensions, clearance, irritation, erythema, and discomfort at lesion injection sites; efficacy and safety were evaluated 3 months after treatment. The effectiveness of the intervention was classified into four categories: excellent (75-100% improvement), good (50-74%), satisfactory (25-49%), and poor (<25% improvement). An excellent response was deemed representative of an effective treatment outcome.

The data were analyzed using the SPSS software system (Ver. 26). Descriptive statistics are shown as means ± standard deviations, and frequencies with percentages. The Chi-square test was employed to ascertain the statistical test of significance, with a significance level established at 5% to evaluate statistical relevance.

RESULTS

A total of 129 participants were incorporated into the study, with an average age of 31.60 ± 11.28 years. Among the participants, 62.0% were in the 18-30 years age range, while 38.0% were above 30 years. The mean Body Mass Index (BMI) was recorded at 25.89 ± 3.53 kg/m², with 62.8% exhibiting a BMI within the range of 20 to 26 kg/m², and 37.2% presenting a BMI that exceeds 26 kg/m². The average duration of wart presence was determined to be 6.98 ± 2.67 months, with 66.7% of patients experiencing a duration of 4–7 months; conversely, 33.3% had a duration extending beyond 7 months. Females constituted the majority of the study cohort, accounting for 64.3%, whereas males represented 35.7%. The distribution of affected anatomical sites indicated that the feet were the most frequently impacted region (46.5%), followed by the hands (34.9%), and the genital area (18.6%). Regarding safety, pain was the most frequent adverse effect (72.8%), followed by erythema (20.1%), and irritation (15.5%). as shown in TABLE I.

After the sixth intralesional 5-fluorouracil injection, the majority of patients (75.2%) demonstrated an excellent treatment response, showing 75–100% improvement. A good response, with 50–74% improvement, was observed in 10.9% of patients, while 7.8% showed a satisfactory response with 25–49% improvement. A poor response, defined as less than 25% improvement, was noted in 6.2% of the cases as shown in TABLE II.

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Table I: Demographic, Clinical, and Safety Characteristics of Patients (n=129)	
Variable	**n** (%)
Age (Mean ± SD) = 31.60 ± 11.28	
18-30 years	80 (62.0)
>30 years	49 (38.0)
Body Mass Index (Mean ± SD) = 25.89 ± 3.53	
20-26 kg/m^2	81 (62.8)
>26 kg/m^2	48 (37.2)
Duration of Warts (Mean ± SD) = 6.98 ± 2.67	
4-7 months	86 (66.7)
>7 months	43 (33.3)
Gender	
Male	46 (35.7)
Female	83 (64.3)
Site of Involvement	
Genital	24 (18.6)
Hand	45 (34.9)
Feet	60 (46.5)
Safety	
Erythema	26 (20.1)

Irritation	20 (15.5)
Pain	94 (72.8)

Table II: Frequency of Treatment Response After the 6th Intralesional 5-Fluorouracil Injection

Treatment Response	Frequency	Percentage (%)
Excellent (75-100% Improvement)	97	75.2
Good (50-74% Improvement)	14	10.9
Satisfactory (25-49% Improvement)	10	7.8
Poor (<25% Improvement)	8	6.2

DISCUSSION

The present study aimed at evaluating the efficacy and safety of 5-fluorouracil (5-FU) intralesional therapy for treating cutaneous warts. The findings demonstrated a high rate of therapeutic success, including an excellent response (75–100% clearance) in 75.2% of patients, a good response (50–74%) in 10.9%, a satisfactory response (25–49%) in 7.8% and a poor response (<25% clearance) in only 6.2% of patients. These results were statistically significant ($p = 0.0001$), providing further evidence of the efficacy of IL 5-FU in treating warts.

Our findings are consistent with a number of previous investigations. Kamal et al. reported an excellent response of 75% of their patients, and good, satisfactory, and poor responses were 12.5%, 7.5%, and 5%, respectively, which is almost commensurate with our results [9]. Similarly, Fatima et al. reported that 75.3% of their group of patients had an excellent response and a good response was seen in 12.9%, satisfactory in 7.1%, and poor in 4.7%, which was also confirmed by our findings [11]. These reproducible results in subsequent studies affirm the reproducibility and clinical reliability of IL-5-FU in the management of warts.

However, Basavarajappa et al. compared the efficacy of topical 5% 5-fluorouracil (5-FU) combined with needling versus 30% trichloroacetic acid (TCA) plus needling, demonstrating a reduced excellent response rate of 23.3% and a higher good response rate of 46.7%. The rate of satisfactory response and poor response was reported to be 26.7% and 3.3% respectively [10]. The relatively reduced excellent response rate noted in this study can be attributed to the topical 5-FU application and not by intralesional 5-FU, which suggests that the enhanced drug delivery into the lesion by intralesional route might improve the bioavailability of the drug and hence better treatment results.

In terms of safety, pain emerged as the most frequently reported adverse effect in our study, affecting 72.8% of participants, followed by erythema (20.1%) and irritation (15.5%). In a separate clinical trial, pain was also the predominant side effect, reported in 60% of cases, with burning sensation being the next most common at 6.67% [10].

Also, Bdaiwi and Abdul-Saheb assessed the differences in clinical response based on various types and localizations of warts in Iraqi patients, revealing a significant range in response to treatment, implying that the clinical criteria of the lesions, as well as host factors, could be critical for predicting treatment success [12]. Zoheir et al. compared intralesional 5-FU and methotrexate and found that both drugs were effective in the treatment of plantar warts, with 5-FU giving a slightly better response [13]. Furthermore, Khattab et al. compared the effectiveness of intralesional 5-FU with a combination therapy using digoxin and furosemide, in the treatment of resistant plantar warts, and found both therapies effective, but 5-FU was still considered as a good alternative with lower adverse effect [14].

Treatment options have included microneedling as an adjunctive treatment modality. Ghonemy et al. analyzed microneedling alonge compared to 5-FU combined with microneedling, and found that efficacy was more favorable with the combination approach, however substantial clearance was also obtained with intralesional injection alone [15]. These findings indicate that interventionist implementations could be useful to enhance therapeutic effects in refractory or extensive cases.

Concerning the safety of 5-FU injection, our study showed limited side effects, which supports Mullen et al.'s systematic review stating that intralesional therapies, including 5-FU, are mostly safe with low rate of significant side effects [16]. Other treatment approaches for 5-FU such as the salicylic acid– based preparation for periungual warts were also evaluated by Kim et al, who found that the combination regimen was effective but less potent when compared to intralesional injection [17].

This study provided insight into the therapeutic efficacy, and safety profile of intralesional 5-fluorouracil in the treatment of cutaneous warts, however, there are several limitations that need consideration. First, the study has adopted non-probability consecutive sampling approach that might explain the results which were not fully generalizable to the general population as a result of possible selection bias. Second, 5-FU vs a control group (i.e., a placebo or another therapy) is not conducted, and thus no further conclusion can be made regarding how effective 5-FU is compared with other treatment. In addition, the observation period was short-term, only 3 months, which is probably not enough to retrieve long-term recurrence rate or delayed adverse effects. Furthermore, the exclusion of the most severely immunosuppressed, pregnant women and those with previous 5-FU exposure, might also limit the generalization of the results in more complex clinical settings.

Despite these limitations, studying has a number of strengths. It was a clinical, pragmatic trial with strict inclusion and exclusion criteria for increased internal validity. The application of same standardized protocol of administration, same duration of follow-up and treatment response assessed objectively assured comparable outcome parameters. Furthermore, the use of an inexpensive and widely available drug like 5-FU emphasizes its applicability in developing countries.

According to the observations, future randomized controlled trials with larger sample size and longer follow-up time should be conducted to assess recurrence rate and relative efficacy. Deeper investigation of combination regimens or different doses may improve treatment responses. Moreover, addition of heterogeneous patient populations, such as immunosuppressed or refractory wart types might increase the clinical applicability of the results.

In conclusion, the available data support intralesional 5-FU as a safe, effective, and reproducible treatment for the management of warts. The direct cytotoxic effect, the low cost, and the low systemic absorption make it a reasonable first line or second line agent, even in resistant cases. It will remain for other future research studies to explore its place in combination therapy or to evaluate long-term recurrence rates.

CONCLUSION

Interlesional administration of 5-fluorouracil (5-FU) has been demonstrated to be an efficacious and safe intervention for the management of cutaneous warts; a majority of patients experienced significant clearance of lesions. The findings of this investigation further substantiate 5-FU as a cost-effective therapeutic alternative in the treatment of obstinate warts particularly in settings with limited resources. Furthermore, larger scale with long follow-up randomized controlled trials are necessary to validate these findings.

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