

Efficacy and safety of oral isotretinoin in treatment of plane warts



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ABSTRACT

Introduction: Plane warts is one of the commonest viral infections which may be resistant to many treatment modalities, isotretinoin has been shown effectiveness in many HPV (human papilloma virus) infections. This study aimed to assess the efficacy and safety of oral isotretinoin in the treatment of plane warts.

Methods: A prospective clinical trial study was conducted in Erbil Dermatology Center in Erbil city, Kurdistan region through the period from 1st of July 2019 to 5th of January 2020. Forty patients with plane warts included. All patients received isotretinoin in a dose of 0.5 mg/kg/day in two divided doses for three months and patients were assessed monthly clinically and by investigations. After last dose patients were followed up for three months to see any recurrence.

Results: After three months of therapy 15 patients (37.5%) showed complete response while only 2 patients (5%) showed partial response and the remaining had significant reduction in number of their plane warts during this period. During the 3 months therapy, comparing the results after 1st, 2nd and 3rd month, there was significant increase in number of patients who achieved complete response at the end of three months with ($p=0.003$). At the end of three months follow up, only 2 patients out of 15 who achieved complete response revealed recurrence while remainder 13 were still free of disease. All the adverse effects of isotretinoin during treatment period were mild and reversible with no recorded serious adverse effects.

Conclusion: Oral isotretinoin is effective and safe in treatment of plane warts.

Keywords: Plane warts, Oral isotretinoin, Erbil city.

Cite This Article: Nooruldeen, A.D., Saeed, M.Y. 2021. Efficacy and safety of oral isotretinoin in treatment of plane warts. *Bali Medical Journal* 10(3): 1076-7080. DOI: 10.15562/bmj.v10i3.1806

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Received: 2021-04-28
Accepted: 2021-11-26
Published: 2021-12-30

INTRODUCTION

Plain warts are virus induced benign growths caused by Human Papilloma Virus (HPV) which are pleomorphic and can affect any part of the body. Depending on the immunity of the individual the disease can be localized or widespread.¹⁻³

There are over 150 genotypes of HPV that infect the epithelia of skin or mucosa. Plane warts are mainly due to HPV 3 and HPV 10, which primarily affect children and young adults.⁴ Clinically, they are smooth, flat or slightly elevated skin, grayish yellow colored but may be pigmented, round or polygonal in shape, varying from 1 to 5 mm in diameter; their number ranges from 2-3 to hundreds.⁵ Face, dorsum of hands and shins in female are sites of predilection which are sun exposed areas in human body so that sun exposure may play a role in acquiring flat warts.⁶

Although some warts regress

spontaneously, most require treatment which is challenging as some warts are recalcitrant to standard therapy and there are high recurrence rates.³ Currently available treatment modalities include destructive therapy, systemic therapy and immunomodulatory.³

Isotretinoin is synthetic derivative of vitamin A, which was first approved as treatment for severe acne by the US Food and Drug Administration (FDA) since 1982.⁷ In addition to this, it has been advocated for treatment of Seborrhea, gram negative folliculitis, severe rosacea, many disorders of fortification, inflammatory and neoplastic skin conditions.^{5,6} Despite this, careful patient selection and monitoring are required due to their teratogenicity and other potential toxicities.⁸

One of the mechanisms of action of systemic isotretinoin is promoting cell differentiation and proliferation. Furthermore, skin treated by retinoid

histologically shows epidermal hyperplasia which is caused by increased proliferation of basal keratinocytes, in addition to increase in differentiation markers of skin like involucrin, loricrin, filaggrin and epidermal transglutaminase,⁷ all these changes collectively induce skin desquamation and peeling and as HPV replication is related to the state of keratinocyte differentiation, it's possible that this retinoid may inhibit replication and assembly of HPV.^{7,9} This study aimed to assess the efficacy and safety of oral isotretinoin in the treatment of plane warts.

METHODS

A prospective clinical trial study conducted in Erbil Dermatology Center in Erbil City, Kurdistan region through the period from 1st of July 2019 to 5th of January 2020. Study population were patients with plane warts. The inclusion criteria included

were multiple facial plane warts who were resistant to previous treatment modalities, the patient must have not received any systemic treatment for at least 3 months and no topical treatment for at least 2 weeks for plane wart, aged 12 years and above, males and those females that have provided consent to practice contraception during the course of treatment and for at least 1 month following cessation of treatment and had 2 negative urine pregnancy tests before onset of therapy. Patients aged less than 12 years, single or less than 7 plane warts, female patients unwilling to practice contraception, pregnant or lactating women, patients with abnormal baseline investigations including complete blood picture, liver function tests and lipid profile, and patients with history of psychological problems including depression were excluded from the study.

Forty patients with multiple facial plane warts were included. The ethical considerations were obtained from Helsinki Declaration regarding informed consent, confidentiality of patients, and patient informed about possible side effects of current drug. The ethical committee of Kurdistan Board for Medical Specialties granted the ethical approval for this study. Clinical parameters including name, age, gender, duration of the disease, response to prescribed treatment, side effects of isotretinoin and patient's satisfaction, in addition to follow up assessment for recurrence 3 months after last dose were obtained. Diagnosis of plane warts was made clinically then Isotretinoin treatment was prescribed accordingly in a dose of 0.5 mg/kg/day in two divided doses. The patients were assessed monthly on clinical bases for response under good illumination and photograph were taken for documentation. Also in each visit CBC, LFT and lipid profile were performed to check for adverse effects of the drug. The response of treatment was assessed by classifying the response as shown in [Table 1](#). The interpretation of response to treatment was accomplished by two dermatologists. The satisfaction of patients to treatment outcome of isotretinoin was classified in scale as shown in [Table 2](#). After completing treatment, patients were followed up for further 3 months looking for any recurrence. The data collected were analyzed statistically by Statistical Package

of Social Sciences (SPSS) software version 22. The Fischer's exact test was applied for analyzing the data as suitable. Level of significance (p value) was regarded statistically significant if it was 0.05 or less.

RESULTS

This study included forty patients with plane warts. The ages of the patients ranged from 12 to 49 years, with mean age of 18 years; 70% of them were less than 18 years old. Females with plane warts were more than males (67.5% vs. 32.5%).

The duration of warts was 1-5 years with mean duration of 2.1 years. Mean dose of isotretinoin treatment was 27.5 mg; 50% of patients received 20 mg of isotretinoin and less ([Table 3](#)).

A total of fifteen patients (37.5%) showed complete response after 3 months therapy with further 10 patients (25%) showed excellent response and 9 patients (22.5%) showed very good response. These results show 85% effectiveness of oral isotretinoin in treatment of plane warts. A significant difference in the treatment response was observed regarding different

Table 1. Response to treatment of patients

Response to treatment	No	No improvement
	Partial	25% of lesions resolved
	Good	50% of lesions resolved
	Very good	75% of lesions resolved
	Excellent	90% of lesions resolved
	Complete	100% of lesions resolved

Table 2. Satisfaction of patients

Satisfaction of patients	Not satisfied	No satisfaction
	Partially satisfied	50% satisfaction
	Completely satisfied	100% satisfaction

Table 3. General characteristics of patients with plane warts

Variables	Value
Age, n (%)	
<20 years	28 (70)
20-29 years	6 (15)
30-39 years	2 (5)
≥40 years	4 (10)
Gender, n (%)	
Male	13 (32.5)
Female	27 (67.5)
Duration, n (%)	
1 year	18 (45)
2-3 years	14 (35)
4-5 years	8 (20)
Dose of isotretinoin, n (%)	
≤20 mg	20 (50)
30 mg	9 (22.5)
40 mg	11 (27.5)

follow up periods; there was a significant increase ($p = 0.003$) in number of patients who reached complete response at the end of three months with (Table 4 and Figure 1).

After the 3 months period of follow up from the end of treatment course, 13 (86.7%) patients out of 15 who reached complete response were still free of the disease and only 2 (13.3%) of them had gotten recurrence (Table 5).

There were no significant adverse effects as hyperlipidemia or abnormal LFT. Thirty percent (30%) of patients experienced mild and reversible side effects; commonly dry lip (33.3%), cheilitis (25%), headache and low mood (16.7%), dryness of skin (16.7%) and cheilitis with dry lip (8.3%) (Figure 2, Figure 3 and Table 6).

Patients treated with oral isotretinoin showed high degree of satisfaction regarding treatment compliance and response of drug with 75% of them being completely satisfied and 15% of them were partially satisfied with only 10% of them being unsatisfied (Table 7). The result of a patient before and after isotretinoin treatment depicted in Figure 4.

DISCUSSION

Treatment of flat warts is common therapeutic problem and some of warts are recalcitrant to standard therapy with high recurrence rate and there is no single treatment option that is 100% effective.^{10,11} Although spontaneous regression is common, cosmetic reasons dominate on its treatment reasons.¹² Treatment methods for warts such as chemical or destructive procedures mainly focuses in destruction of the lesions, as flat warts

Table 4. Distribution of isotretinoin treatment response according to follow up periods

Variable	After one month	After two months	After three months	P
Response, n (%)				0.003*
Partial	2 (5)	2 (5)	2 (5)	
Good	8 (20)	4 (10)	4 (10)	
Very good	21 (52.5)	11 (27.5)	9 (22.5)	
Excellent	9 (22.5)	14 (35)	10 (25)	
Complete	0 (0)	9 (22.5)	15 (37.5)	

*Significant

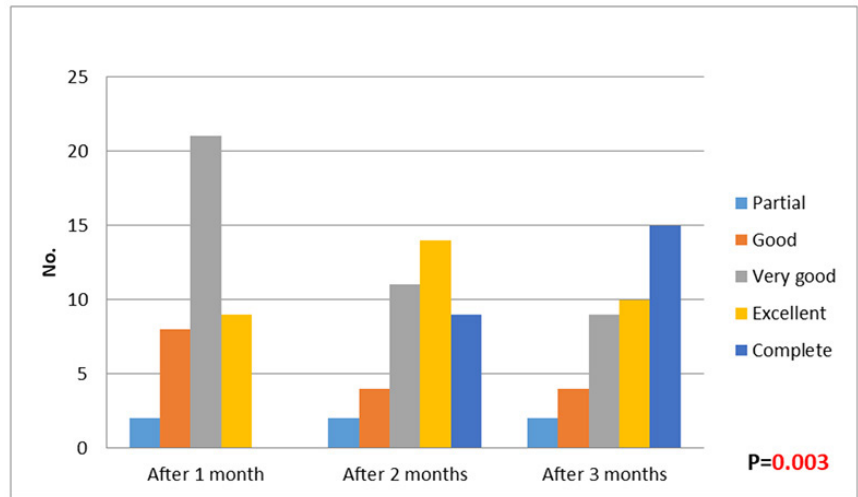


Figure 1. Isotretinoin treatment response according to follow up periods.

Table 5. Recurrence of the disease in patients with complete response after 3 months

Variable	Value
Follow up after 3 months of last isotretinoin treatment, n (%)	
Recurrence	2 (13.3)
No recurrence	13 (86.7)
Total	15 (100)

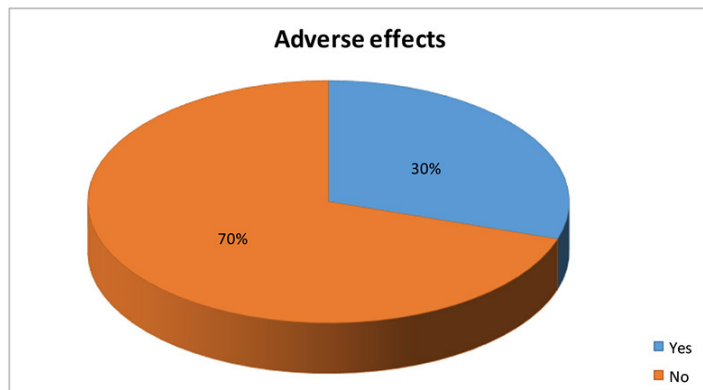


Figure 2. Adverse effects of isotretinoin treatment

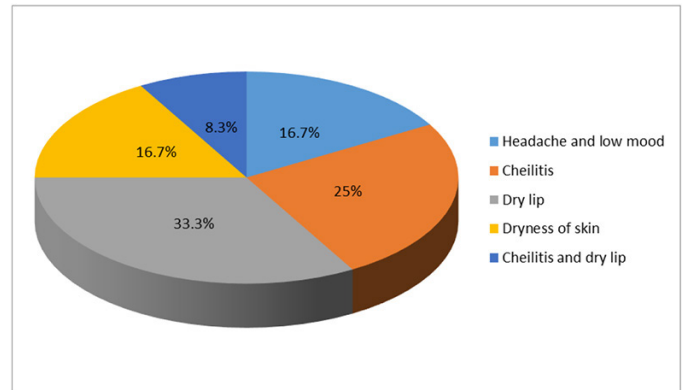


Figure 3. Types of adverse effects of isotretinoin treatment

readily koebnerize, destructive techniques may even exacerbate the problem.¹² Where as lack of efficient systemic therapy in treatment of plane warts enhanced many clinical trial checking the effectiveness and safety of oral isotretinoin.¹³⁻¹⁵ It was firstly described in treatment of warts in eighties of last century.¹⁶

Present study revealed a significant treatment response after three months of oral isotretinoin treatment ($p = 0.003$) with 37.5% of patients having complete

response, 25% excellent response and 22.5% very good response finding that reached 85% effectiveness of oral isotretinoin in treatment of plane warts. This finding is similar to results of Al-Hamamy¹¹ open therapeutic trail in Iraq which included 31 patients with recalcitrant facial plane warts treated with oral isotretinoin (0.5 mg/kg/day) and found that (73.07%) of patients had a significant complete response in treatment after two months. Current study outcome

is also confirmed by Ozturk and a study in Turkey¹⁷ which reported higher efficacy of isotretinoin in treatment of flat warts in a dose of 30mg/day for three months and 80% of lesions were recovered. In addition to these studies, a systematic review and meta-analysis study conducted by Yang¹⁸ in Taiwan on eight randomized controlled trails stated that oral isotretinoin is effective in treatment of human papillomavirus infection with complete response rate of (67.7%). Another randomized controlled trial study by Kaur et al¹⁹ divided 29 patients with plane warts into two groups; A group (16 patients) treated with oral isotretinoin 0.5mg/kg/day and B group (13 patients) treated with topical isotretinoin for 3 months and found that oral isotretinoin was more effective with earlier treatment response than topical isotretinoin (69% complete response for group A and 38% complete response for group B). In comparing our study findings with cryotherapy outcome in treatment of plane warts, the cryotherapy needs longer treatment duration reaching six months with mean cure rate of 49% in addition to high recurrence rate reaching to 31% and many reported adverse effects such as pain, hyperpigmentation and hypopigmentation,¹⁰ while our study regarding isotretinoin showed better results in shorter duration and less recurrence rate and adverse effects.

In current study, the adverse effects of isotretinoin were shown in 30% of patients, however, these adverse effects are minor and confirmed the safety of isotretinoin, a finding that coincides with reports of British Association of Dermatologists' guidelines.¹⁰ While serious adverse effects had not been reported, the main adverse effects were dry lip and cheilitis. These findings are in agreement with results of Olguin-Garcia et al²⁰ study in Mexico which revealed that dry lip and cheilitis are most frequent adverse effects of isotretinoin after treatment of plane warts. The recurrence of plane warts after oral isotretinoin treatment was detected in two patients among 15 patients who achieved complete response in our study. This recurrence rate is close to recurrence rate for oral isotretinoin reported by Gupta et al²¹ study in India on 35 patients with plane warts which found that two

Table 6. Adverse effects of isotretinoin treatment

Variables	Value
Adverse effects of isotretinoin treatment, n (%)	
Yes	12 (30)
No	28 (70)
Types of adverse effects, n (%)	
Headache and low mood	2 (16.7)
Cheilitis	3 (25)
Dry lip	4 (33.3)
Dryness of skin	2 (16.7)
Cheilitis and dry lip	1 (8.3)

Table 7. Satisfaction of patients with outcome of isotretinoin treatment.

Variable	Value
Satisfaction of patients, n (%)	
Not satisfied	4 (10)
Partially satisfied	6 (15)
Completely satisfied	30 (75)



Figure 4. Seventeen years old female with plane warts: a).before oral isotretinoin treatment; b). complete treatment response 3 months after treatment

patients had recurrence among 17 patients with complete response. Despite that, our recurrence rate is lower than recurrence rate of 18% reported by Białecka et al.²² The complete satisfaction of patients regarding outcome and safety of isotretinoin was observed in 75% of patients in present study. Satisfaction in oral isotretinoin in treatment of plane warts and other dermatological diseases was reported high in many literatures.^{11,20,23}

Our study concluded that oral isotretinoin is effective therapy for recalcitrant warts with better cost and availability. Its use in pediatric age group with a low cumulative dose and relatively short period revealed no serious problem with most adverse effects being mild and reversible. It is important to enhance Dermatologists in selection of oral isotretinoin for treatment of plane warts.

CONCLUSION

Oral isotretinoin appears to be safe and effective treatment modality for multiple facial plane warts and it should definitely be given a trail before trying other destructive procedures. While serious adverse effects of oral isotretinoin have not been reported, this confirms its safety when used for short periods.

ACKNOWLEDGMENT

Special thanks and appreciation for all medical workers in Erbil Dermatology Center in Erbil City, Kurdistan for their support.

FUNDING

The authors are responsible for all of the study funding without the involvement of grant or any external source of funding.

ETHICAL STATEMENT

The ethical committee of Kurdistan Board for Medical Specialties granted the ethical approval for this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest regarding the publication of this article.

AUTHORS' CONTRIBUTION

All authors have contributed to all process in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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