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Efficacy and Safety of Oral Isotretinoin in the Treatment of Viral Warts- A Hospital Based Interventional Study

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Abstract: Warts are caused by infection of keratinocytes (the predominant cell type in the epidermis) by human papillomavirus (HPV). The development of epidermal thickening a hyperkeratinization occurs following infection at the basal layer and clonal proliferation, which eventually results in a visible wart, weeks or even months later. To assess the efficacy and safety of oral isotretinoin in the treatment of viral warts and to assess the recurrence rate/relapse rate of viral warts with oral isotretinoin. This prospective interventional uncontrolled study was conducted on 50 patients of viral warts attending the outpatient department of dermatology and venerology department and will be given oral isotretinoin for a period of 3 months to 6 months. The data regarding patient particulars, diagnosis was collected in a specially designed case recording form and transferred to a master chart subjected to statistical methods like mean, standard deviation, proportion, percentage calculation and wherever necessary chi square test for proportion are used. 43 patients completed the study. 22 patients (51%) in the study population took treatment for 3 months while 21 patients (49%) for 6 months. 18 (42%) patients had a complete response. Out of the 18 patients, complete response was obtained in 10 (55.6%) patients at 3 months and in 8 patients (44.4%) at 6 months of therapy. 15 (35%) patients had a partial response. 10 (23%) patients had no response. In conclusion, oral isotretinoin is a safe and effective modality of treatment forViral Warts especially when painful destructive procedures are to be avoided which lead to theresultant painful and lengthy process of wound healing and trauma to the patient. Also whendealing with patients with multiple plane warts, especially in aesthetically sensitive areasrecalcitrant to standard therapy, systemic isotretinoin should be considered.
Keywords: Warts, human papillomavirus (HPV), a hyperkeratinization.

INTRODUCTION

Viral warts are benign growths caused by the human papilloma virus (HPV) which can occur anywhere on the body. These clinically manifest as verruca vulgaris (common warts), filiform verrucae (digitate warts), verruca plana (flat warts), verruca pedis (plantar warts), palmar verrucae, condyloma accuminata (anogenital warts), oral and laryngeal papillomas. They can either be localized or widespread, depending on the immunity of the individual. For long, they have been seen as a social stigma and cause significant social embarrassment to the patients implying the need to treat it. Minor abrasions and infections promoted by maceration of the epithelia most frequently serve as conduits for HPV to the basal keratinocytes, the primary targets for HPV infection [1, 2]. The development of epidermal thickening and hyperkeratinization occurs following infection at the basal layer and clonal proliferation, which eventually results in a visible wart, weeks or even months later[3]. There are over 150 genotypically different types of HPV, with classification based on defined variation of the viral DNA [3].

Although some warts regress spontaneously, most require treatment. Treatment is challenging mainly due to recalcitrance to standard therapy, unpredictable response, and high recurrence rates. No single treatment being known to be a hundred percent effective. Currently available options include destructive therapies, systemic therapies, and immunomodulatory.

Isotretinoin is capable of dramatically affecting epithelial cell differentiation and proliferation [4]. As

HPV replication is related to the state of keratinocyte differentiation, it is possible that this retinoid may inhibit the replication and assembly of HPV [5]. Trials and case reports have shown systemic retinoids, especially synthetic isotretinoin, to have an effect on a variety of warts, particularly genital warts [6-9]. A great deal of interest has been expressed in the use of retinoids as a potential chemopreventive and/or therapy in HPV-related cervical cancer [10].

Systemic isotretinoin has been used to treat severe acne vulgaris. However, isotretinoin also represents a potentially useful choice in many dermatological diseases such as psoriasis, pityriasis rubra pilaris, condyloma accuminata, skin cancers and rosacea [11].

Therefore, we attempted this study in order to assess the efficacy and safety of oral isotretinoin in the treatment of viral warts.

MATERIALS AND METHODS

This prospective interventional uncontrolled study was conducted in the out-patient department of dermatology and venerology department in a tertiary care hospital in India. 50 patients who are afflicted with viral warts after obtaining prior ethics committee approval were enrolled on the basis of inclusion and exclusion criterias.

Inclusion Criteria

- Patients in the age group 15-40 years.
- All males and those females who have provided consent to practice contraception and who had 2 negative urine pregnancy tests before the onset of therapy (wherever appropriate).
- 3 or more lesions on any part of the body.

Exclusion Criteria

- Female patients unwilling to practice contraception as mentioned above.
- Pregnant and lactating females.
- Patients with dyslipidemia.
- Patients with deranged liver function tests.
- Patients with pancytopenia or Hb <10gm.
- History of suicidal tendencies, depression.
- History of convulsions.
- Patients receiving other drugs like vitamin A, tetracyclines, oral steroids, cyclosporine, gemfibrozil, macrolides, azoles or anti-tubercular drugs.

A total of 50 Patients were selected for the study and were given 0.5mg/kg oral isotretinoin initially for a period of 3 months. Patients were followed up every 2 weeks. The number and size of the lesions were assessed clinically.

At the end of 3 months of treatment, patients who had complete resolution of the warts were called as responders, patients who had a decrease in the number and the size of the warts were called as partial responders and those who did not have any change in size or number were called as non-responders.

Partial responders, were treated with dose 1mg/kg for another 3 months i.e. a total of 6 months. Non-responders after 3 months of treatment were treated by other methods such as radiofrequency/electrocautery/ autoinoculation.

The laboratory investigations, done every monthly for 3 months and at the end of 6 months were haemoglobin (Hb), complete blood counts (CBC), liver function tests (LFT), renal function tests (RFT) and lipid profile.

Patients were instructed to apply vaseline jelly on the lips to prevent cheilitis and emollients over the body to prevent xerosis.

Monthly follow ups for 3 months were done for the patients post treatment. At the end of 3 and 6 months the number of lesions showing complete response, partial response and no response was noted.

Analysis

The data thus collected were statistically analyzed- categorical variables by chi-square test and continuous variables by Mann-Whitney U or Kruskal-Wallis tests. Linear and logistic regressions were performed for continuous and binary dependent variables, respectively.

RESULTS

Out of 50 patients, 7 were lost to follow up. Out of 43 patients, 35 patients (81%) were male and 8(19%) were Female 21-25 years (32 %) was the most common age group followed by 15- 20 years of age (30%).

Table-1: depicts the type of verrucae in affected study population

Diagnosis		Frequency	Percent
Valid	Anogenital Warts	5	10.0
	Filiform Warts	8	16.0
	Palmoplantar Warts	10	20.0
	Plane Warts	12	24.0
	Verucca Vulgaris	15	30.0
	Total	50	100.0

All patients on treatment, had cheilitis (100%) which did not require discontinuation of treatment and it resolved after the course of the therapy, 31 (74%) patients had xerosis and 1 (2%) patient developed stye.

Table-2 and 3: Depict the lab investigations. Various blood Parameters amongst study population at various time intervals

Parameters	Day 1	1 month	2 month	3 month	6 month
Hb	13.5 ± 1.18	13.7 ±1.16	13.66 ± 1.04	13.71 ± 1.15	13.52 ± 1.1
P value		0.675	0.623	0.260	0.539
SGOT	27.54 ± 10.67	29.53 ± 9.02	31.70 ± 8.79	30.74± 6.6	31.38 ± 9.3
P value		0.0001	0.0001	0.0001	0.0001
SGPT	24.26 ± 6.39	26.63 ± 5.76	28.36 ± 5.31	29.55± 4.83	29.23 ± 5.5
P value		0.0001	0.0001	0.0001	0.0001
Total bilirubin	0.93 ± 0.06	0.9 ± 0.07	0.92 ± 0.06	0.91 ± 0.08	0.95 ± 0.1
P value		0.0281	0.4365	0.1933	0.2640
Direct bilirubin	0.4 ± 0.05	0.4 ± 0.09	0.35 ± 0.05	0.36 ± 0.10	0.36 ± 0
P value		1.0000	0.0001	0.0213	0.0001
Creatinine	0.79 ± 0.16	0.84 ± 0.16	0.86 ± 0.15	0.88 ± 0.16	0.89 ± 0.1
P value		0.1332	0.0394	0.0108	0.0008

Table no 2 showing there was significantly increase in the SGOT, SGPT at 1,2,3, and 6 month, creatinine at 2,3,6 month interval and direct bilirubin at 2,6 month interval amongst study population

Table-3: Various blood Parameters amongst study population at various time intervals

Parameters	Day 1	1 month	2 month	3 month	6 month
CHOLESTEROL	106.76 ± 22.43	119.1 ± 2316.	133.56 ±24.57	144.9 ± 20.51	145.0 ± 18.9
P value		0.0001	0.0001	0.0001	0.0001
TG'S	70.48 ± 22.01	84.78 ± 21.37	99.27 ± 20.44	110.0± 16.91	112.5 ± 18.1
P value		0.034	0.0001	0.0001	0.0001
LDL	107.4 ± 13.20	109 ± 14.22	110 ± 14.33	110 ± 13.60	111.86 ± 13
P value		0.5732	0.3785	0.0001	0.0001
HDL	49.58 ± 4.09	49.78 ± 4.34	49.21 ± 4.36	49.09 ± 3.52	48.53 ± 2.7
P value		0.8187	0.6824	0.0001	0.0001

Table no 3 showing there was significantly increase in the CHOLESTEROL at 1, 2,3, and 6 month interval, TGs at 2,3, and 6 month interval, LDL and HDL levels at ,3 and 6 month interval amongst study population.

RESULTS

43 patients completed the study. 22 patients (51%) in the study population took treatment for 3 months while 21 patients (49%) for 6 months.

18 (42%) patients had a complete response. Out of the 18 patients, complete response was obtained in 10 (55.6%) patients at 3 months and in 8 patients (44.4%) at 6 months of therapy.15 (35%) patients had a partial response. 10 (23%) patients had no response.

Table-4: The final outcome is depicted in

		Frequency	Percent
	Complete response	18	36.0
	Incomplete Response	15	30.0
	Lost to Follow Up	7	14.0
	No Response	10	20.0
	Total	50	100.0

Table no 4 showing most of the study population showed complete response (36%), incomplete response was observed in 30%, no response in 20% and 14% were lost to follow up.

On follow up, recurrence was observed at 3 months, most commonly in verucca vulgaris (31.6%) and plane warts(31.6%)

DISCUSSION

Treatment of warts has been an enigma to most practitioners with not a single definitive approach against the HPV virus.

Conventional therapies for HPV infection are often associated with unsatisfactory response rates and high recurrence rates. The various modalities of treatment include cytodestructive therapies, immunotherapy and systemic therapies. Destructive therapies like cryotherapy, electrocoagulation, radiofrequency, laser etc are designed to damage or remove the lesion, rather than to kill the virus. They treat only the existing verrucae and require multiple sessions and adverse effects like ulcerations, secondary infection, dyspigmentation and scarring. Immunotherapy includes autoimplantation, needling, using intralesional antigens, contact sensitizers like diphencyprone, dichloronitrobenzene, HPV vaccines;but have an unpredictable outcome.Systemic options include oral zinc,cimetidine, levamisole and oral retinoids. The use of a systemic agent may more effectively control the virus [3].

Oral retinoids, by reducing epidermal proliferation, can help to debulk warts. Etretinate, acitretin and isotretinoin have been reported to be helpful in cases of extensive and hyperkeratotic warts in immunosuppressed patients [6,12-14].

Retinoids affect cellular growth, differentiation, and morphogenesis, inhibit tumor promotion and malignant cell growth, exert immunomodulatory actions, and alter cellular cohesiveness [15] An inverse relationship was observed between concentrations of retinoids and HPV deoxyribonucleic acid within infected epithelial cells, suggesting an effect on viral replication[16,17].

Several Mechanisms can be responsible for its effects against the viral warts:

- Epidermal growth factor receptor as a retinoid target: Epidermal growth factor receptor activation promotes cellular growth and transformation as well as produces other biological effects. Retinoids repress epidermal growth factor receptor expression through a transcriptional mechanism [18].
- Induction of differentiation: Tretinoin and other retinoids can induce differentiation in certain cell lines.The carboxylic acid end group may be critical for this capability of retinoids because it is crucial for binding and activation of retinoic acid receptors[19].
- Inhibition of proliferation: In addition to differentiation induction, retinoids also have a direct anti-proliferative effect which is also linked to their carboxylic acid end group
- Inhibition of ornithine decarboxylase: Retinoids promote apoptosis by inhibition of Ornithine decarboxylase which is the rate-limiting enzyme in the synthesis of polyamines. Polyamines play important roles in stabilizing DNA structure and in the DNA double-strand break repair pathway.
- Immunomodulation can be a possible mechanism of action.Retinoids also stimulates killer T-cell production and cell-mediated cytotoxicity which may contribute to the treatment of warts.

Comparison with other studies

Demographic profile

In our study, maximum (32 %) patients were in the age group of 21-25 years followed by the age group of 15- 20 years (30 %). The mean age in our study was 24.48 ±5.81, while in a similar study conducted by Hayder R *et al*. the mean age of study population was found to be 15.28 ± 8.51 years [20].

In our study 78% of study population was males while 22% were females which suggest a higher affection in male population. This is contrary to the study conducted by Hayder R *et al*. in which 57.69% patients were females, and 42.30% were males. This can be explained by the reluctance of the female patients to use contraception because of which these patients could not be enrolled in the study [20].

Side effects

In the present study, 43 (100%) patients had cheilitis, 31 (74%) had xerosis and 1 (2%) patient developed stye. In a study conducted on 50 patients by Rao et al where isotretinoin (0.3-0.4mg/kg) was used for 3 months, 49 (98%) patients had cheilitis and 42 (84%) patients had xerosis which is similar to our study. The controversial adverse events that have emerged, such as associations of isotretinoin use with depression, suicidal ideation, and inflammatory bowel disease, have not been definitively substantiated as being caused by isotretinoin, and if a causative association with isotretinoin exists, such reactions are rare and idiosyncratic[21].

Laboratory Investigations

We found in our study significant elevations from baseline levels of liver enzymes, serum creatinine, triglycerides and cholesterol at monthly intervals but all within the normal limits which was similar to the study conducted by María Guadalupe Olguin-García *et al*. [22] similarly, rao *et al*. in his study reported similar changes in the lab investigations [21]. We also found no significant changes in the levels of hemoglobin, white blood cells count and platelet count before and after treatment. But the results varied in the study conducted by Young lee et al where a statistically significant change in the mean value of white blood cell count was found although the proportion of patients with laboratory abnormalities was low[23].

Response

In the present study, 43 patients completed the study. 18(42%) patients had a complete response, 15(35%) patients had an incomplete response, 10 (23%) patients had no response. Individually, complete response was observed in 100 % of anogenital Warts, 25% of filiform Warts, 20% of Palmoplantar Warts, 25% of Plane Warts and 33.33% of verucca vulgaris.

In a similar study of oral isotretinoin in flat warts conducted by María Guadalupe Olguin-García *et al*. 2016 all patients (n=16) in the isotretinoin group showed complete clearance, while none of the patients in the placebo group (n=15) showed any improvement (p¼0.0001). This result was different from that reported in the study of Al-Hamamy, where only 19 (73.07%) patients achieved complete response with 0.5mg/kg/day of isotretinoin for 8 weeks and 7 patients showed no response (26.92%) suggesting the variability in patient response. These studies did not include follow up of patients for recurrence which influences the result significantly as flat warts are known to recur and be recalcitrant[20,22].

Tsambaos *et al*. treated 56 male patients with condyloma acuminata using isotretinoin 1 mg/kg for 3 months where in 22 (39.6%) patients responded completely and 7 (13.2%) patients responded partially. Two recurrences (9.5%) occurred during the 1 year follow up. We found similar results in our study with complete response in 2(40%) patients with condyloma acuminata at 3 months interval and partial response in 3(60%) patients. All the partial responders showed complete resolution of the lesion at 6 months interval when dose was increased to 1mg/kg [23].

The duration of the study conducted by Tsamboas *et al*. was for a period of only 3 months implying a need for a higher dose and a longer duration of treatment for complete resolution of common warts.

Comparision with other systemic therapies

We found in our study that 18(42%) patients had a complete response,15(35%) patients had an incomplete response, 10(23%) patients had no response Individually, Complete response was observed in 100 % of anogenital Warts, 25% of filiform Warts, 20% of Palmoplantar Warts, 25% of Plane Warts and 33.33% of verucca vulgaris.

The comparison of isotretinoin with other oral therapies for verruca like Cimetidine, Levamisole and Zinc sulphate is discussed below.

Studies comparing the clearance rate of warts with cimetidine and placebo, showed 26 % and 5 % clearance rates respectively in the first study [24] and 27 % and 22% clearance rates in the second study [25].The study investigators proposed a placebo effect for cimetidine.

In an open labeled study conducted by Mun 50 % of the patients with multiple, non-genital viral warts showed complete resolution of their warts after 2 months of treatment with oral zinc sulfate (10 mg/kg to a maximum dose of 600 mg/day) oral zinc sulphate. Complete responders remained free of lesions at 6-month follow-up[26].

Reza Yaghoobi *et al.* conducted a randomized, placebo controlled, and double-blinded clinical trial in 32 patients to evaluate the effectiveness of zinc sulfate in the treatment of patients with recalcitrant multiple warts, where complete response was seen in 78.1% (25/32) patients after a 2-month course of treatment. After 6 months of follow-up, no instance of recurrence was noticed [27].

Saúl A*et al*. conducted a study using levamisole and a placebo. It was found that both groups showed some improvement but results were not statistically different. Similarly in a study conducted by Schou M*et al*. patients receiving levamisole did not show significant clinical regression of warts [28,29].

To the best of our knowledge this is the first study using isotretinoin for the treatment of all types of warts. The limitation of the study was the small sample size on which the study was conducted.

Patient of Verruca vulgaris on oral isotretinoin and its response

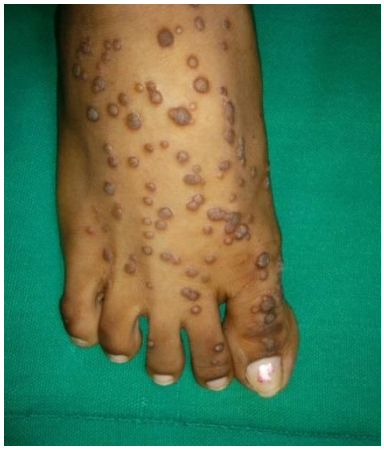

Fig-1: First Day of Presentation

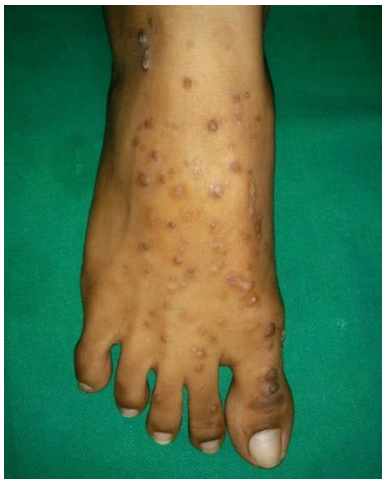

Fig-2: 1 Month After Treatment

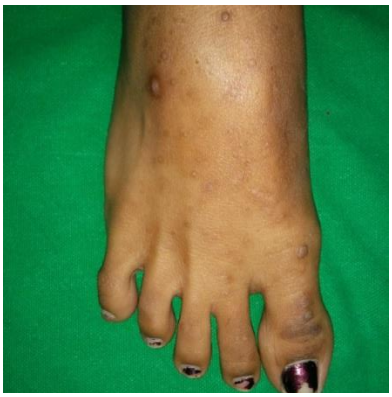

Fig-3: 3 Months After Treatment

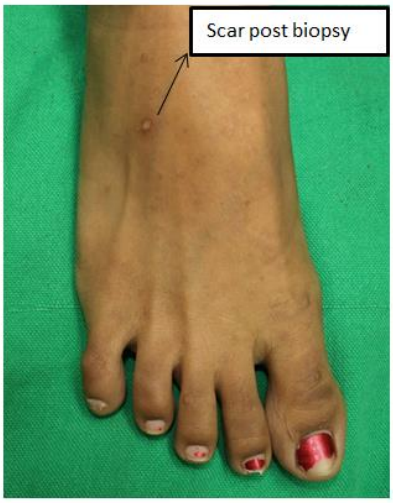

Fig-3: Complete Resolution on 6 months After Treatment

CONCLUSION

Oral isotretinoin seems to be a reasonably effective modality of treatment clearing 42 % of the disseminated warts, with acceptable cost and wide availability. In further 35 % patients, debulking of the warts was seen which provides an opportunity to use other forms of cytodestructive modalities more effectively. Therefore, it seems to be a safe option when used for a relatively short period of time with reversible side effects.

REFERENCES

1. Leman JA, Benton EC. Verrucas. Guidelines for management. Am J Clin Dermatol 2000;143-149.
2. Ciconte A, Campbell J, Tabrizi S, Garland S, Marks R. Warts are not merely blemishes on the skin: A study on the morbidity associated with having viral cutaneous warts. Australas J Dermatol. 2003;44:169-173.
3. Armstrong DK, Maw RD, Dinsmore WW, Blaakaer J, Correa MA, Falk L, Ferenczy AS, Fortier M, Frazer I, Law C, Moller BM. Combined therapy trial with interferon alpha-2a and ablative therapy in the treatment of anogenital warts. Sexually Transmitted Infections. 1996 Apr 1;72(2):103-7.
4. Akyol M, Özçelik S. Non-acne dermatologic indications for systemic isotretinoin. American journal of clinical dermatology. 2005 Jun 1;6(3):175-84.
5. TsambaosD, Zimmermann B Effects of synthetic retinoids on cellular systems. In :Roegnigk HJ, Maibach ,eds. Psoriasis,2ndedn.NewYork:Marcel Dekker.1991:659-707.
6. González FU, Gil MD, Martinez AA, Rodriguez PG, de Paz FS, García-Pérez A. Cutaneous toxicity of intralesional bleomycin administration in the treatment of periungual warts. Archives of dermatology. 1986 Sep 1;122(9):974-5.
7. Miller RA. Nail dystrophy following intralesional injections of bleomycin for a periungual wart. Archives of dermatology. 1984 Jul 1;120(7):963-4.
8. Shelley WB, Shelley ED. Intralesional bleomycin sulfate therapy for warts. A novel bifurcated needle puncture technique. *Arch Dermatol* 1991; 127: 234–6.
9. Munn SE, Higgins E, Marshall M, Clement M. A new method of intralesional bleomycin therapy in the treatment of recalcitrant warts. British Journal of Dermatology. 1996 Dec;135(6):969-71.
10. Agius E, Mooney JM, Bezzina AC, Yu RC. Dermojet delivery of bleomycin for the treatment of recalcitrant plantar warts. Journal of dermatological treatment. 2006 Jan 1;17(2):112-6.
11. Bedell MA, Hudson JB, Golub TR, Turyk ME, Hosken M, Wilbanks GD, Laimins LA. Amplification of human papillomavirus genomes in vitro is dependent on epithelial differentiation. Journal of virology. 1991 May 1;65(5):2254-60.
12. Hursthouse MW. A controlled trial on the use of topical 5-fluorouracil on viral warts. British Journal of Dermatology. 1975 Jan;92(1):93-6.
13. Zschocke I, Hartmann A, Schlöbe A, Cummerow R, Augustin M. Wirksamkeit und Nutzen eines 5-FU-/Salicylsäure-haltigen Präparates in der Therapie vulgärer und plantarer Warzen–systematische Literaturübersicht und Metaanalyse: Efficacy and benefit of a 5-FU/salicylic acid preparation in the therapy of common and plantar warts–systematic literature review and meta-analysis. JDDG: Journal der Deutschen Dermatologischen Gesellschaft. 2004 Mar;2(3):187-93.
14. Lee S, Kim JG, Chun SI. Treatment of Verruca plana with 5% 5-FIuorouraciI Ointment. Dermatology. 1980;160(6):383-9.
15. Salk RS, Grogan KA, Chang TJ. Topical 5% 5-fuorouracil cream in the treatment of plantar warts: a prospective, randomized, and controlled clinical study. J Drugs Dermatol 2006; 5: 418–24.
16. Lutzner MA, Blanchet-Bardon C, Puissant A. Oral aromatic retinoid (Ro 10-9359) treatment of two patients suffering with the severe form of

epidermodysplasia verruciformis. InRetinoids 1981 (pp. 407-410). Springer, Berlin, Heidelberg.

17. Hayder R. Al-Hamamy, HusamAli Salman and Nawar A. Abdulsattar, Treatment of PlaneWarts with a Low-Dose Oral Isotretinoin, *International Scholarly Research Network*, 2012, Article ID 163929, 1-3
18. Rao PK, Bhat RM, Nandakishore B, Dandakeri S, Martis J, Kamath GH. Safety and efficacy of low-dose isotretinoin in the treatment of moderate to severe acne vulgaris. Indian journal of dermatology. 2014 May;59(3):316.
19. Olguin-García MG, Jurado-Santa Cruz F, Peralta-Pedrero ML, Morales-Sánchez MA. A double-blind, randomized, placebo-controlled trial of oral isotretinoin in the treatment of recalcitrant facial flat warts. Journal of Dermatological Treatment. 2015 Jan 2;26(1):78-82.
20. Lee YH, Scharnitz TP, Muscat J, Chen A, Gupta-Elera G, Kirby JS. Laboratory monitoring during isotretinoin therapy for acne: a systematic review and meta-analysis. JAMA dermatology. 2016 Jan 1;152(1):35-44.
21. Tsambaos D, Georgiou S, Monastirli A, Sakkis TH, Sagriotis A, Goerz G. Treatment of condylomata acuminata with oral isotretinoin. The Journal of urology. 1997 Nov 1;158(5):1810-2.
22. Yaghoobi R, Sadighha A, Baktash D. Evaluation of oral zinc sulfate effect on recalcitrant multiple viral warts: a randomized placebo-controlled clinical trial. Journal of the American Academy of Dermatology. 2009 Apr 1;60(4):706-8.
23. Saúl A, Sanz R, Gomez M. Treatment of multiple viral warts with levamisole. International journal of dermatology. 1980 Jul;19(6):342-3.
24. Schou M, Helin P. Levamisole in a double-blind study: no effect on warts. Acta dermato-venereologica. 1977;57(5):449-54.