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RESEARCH ARTICLE

COMPARATIVE EVALUATION OF EFFICACY OF TOPICAL SALICYLIC ACID OINTMENT AND 5-FLUOROURACIL CREAM IN WARTS PATIENTS

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Abstract

Context: Warts are one of the common diseases in India. There are various modalities used for the treatment of warts. Very few studies have been done which compare the efficacy of topical salicylic acid and 5-Fluorouracil cream in warts patients.

Aim: To compare the efficacy of topical salicylic acid ointment and 5% 5-fluorouracil cream in warts patients.

Settings and Design: Completely randomized design.

Methods and Material: Total 300 clinically diagnosed patients of warts which were divided into three groups (each contains 100 patients) depending on the treatment modalities which includes modality I treated with 16% salicylic acid, modality II treated with 5% 5-fluorouracil and modality III treated with the combination of 16% salicylic acid and 5% 5-fluorouracil. The evaluation of therapy was done by estimating the reduction in wart volume, complete regression of lesion, absence of recurrence of treated lesion after 3 months follow up.

Statistical analysis used: Significant conclusion was drawn after applying the one way Anova test of significance.

Results and conclusion: In Modality III, 99.95 % clearance was seen in warts volume at 12 weeks of treatment followed by Modality I (99.67% clearance in warts volume) and Modality II (99.31% clearance in warts volume) which were statistically significant at p value <0.01 level. Combination of 5-Fluorouracil and 16% salicylic acid is best for the treatment of warts with maximum recovery from warts with minimum adverse effect.

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Introduction:-

Warts are benign epithelial proliferation of skin and mucosa caused by human Papilloma virus¹. Human Papilloma viruses (HPV) is species specific, undeveloped, double stranded DNA virus, belonging to Papovaviridae family². It affects almost every part of skin, genital and oral mucosa^{3, 4}. The incubation period of wart is variable between few weeks to few years^{5, 6}. Subclinical infection may occur during early childhood leading to development of cell mediated immunity^{7, 8}. The management of warts may be with topical podophyllin, bleomycin, with 5-Fluorouracil, with imiquimod, formaldehyde, glutaraldehyde, cidofovir and keratolytics^{9, 10}. The combination of topical 5-Fluorouracil and salicylic acid has a synergistic effect on the warts which is due to the anti-proliferative effect of the 5-Fluorouracil and keratolytic effect of the salicylic acid^{11, 12}. There are only a few studies done for these modalities. Therefore, this study has been intended to determine the efficacy of topical 16 %salicylic acid ointment and 5% 5-Fluorouracil cream in warts patients.

Material and Methods:-

As per the sample size formula (sample size= Z^2PQ/M^2 where, $Z = 1.96$ at 95 % confidence interval, P is the prevalence of warts in India¹³, i.e. $P = 0.2$ (20%), Q is $1-P$, i.e. $Q = 0.80$ and M is margin of error. Minimum sample size with 5% margin of error (precision) was 245.86. So, total 300 clinically diagnosed patients of warts were enrolled from outpatient department of Dermatology, M.R.A. Medical College, Ambedkar Nagar. Patients of warts were divided into three groups based on the modalities of treatment. Patients fulfilling inclusion criteria after taking informed consent were selected for study. Ethical approval was taken from institutional ethical Committee.

Type of study:

Completely randomized design

Inclusion criteria: Diagnosed cases of warts on trunk and extremities with age of 18 to 50 years from Ambedkar Nagar or around.

Exclusion criteria: Subjects with warts on face, scalp and genital areas, pregnant and lactating women, patients under immunosuppressive therapy and other systemic diseases were excluded from the study.

Pre-treatment workup:

Clinical history: A detailed history of the patient was taken regarding name, age, sex, occupation, total duration of disease, site, history of trauma etc.

Clinical examination: Patients were examined in day light. A routine dermatological examination was done. The variants of the warts were noted and morphological details of the lesions in terms of number, site, size and its distribution over the body were recorded. Consent: Proper written consent was taken from each individual explaining the drugs, possible outcomes and complications.

Treatment modalities given:

Patients were instructed to soak the warty area by putting wet towel on it for 5-10 minutes and then remove the upper dead layer of the warts by gentle scrubbing. This was done in the morning and at bedtime. Timings of application of different modalities were as following

1. Modality I: In this modality 16% salicylic acid was applied daily in the morning and at bedtime.
2. Modality II: In this modality 5% 5-Fluorouracil was applied daily in the morning and at bedtime.
3. Modality III: In this modality 5% 5-Fluorouracil was applied daily in the morning and 16% salicylic acid was applied at bedtime.

Criteria for successful therapy: The evaluation of therapy was based on complete regression of lesion, absence of recurrence of treated lesion after 3 months follow up (All the patients were followed up once a week up to four weeks then once in two weeks for next eight weeks. After completion of first three months of study all the patients were followed every month for any recurrence of illness for next three months). Responses of all treatment modalities were assessed by the measurement of reduction in the average volume of warts on subsequent follow up.

Warts volume was calculated by measuring maximum and minimum diameter of the lesions using formula $\pi r^2 h$ (where r denotes the radius and h denotes height of the wart while value of π is $22/7$). The diameters of the warts

were measured by using divider and the corresponding gap was interpreted on horizontal scale while height was measured directly using vertical scale. Then average volume of the warts was calculated as the sum of volumes of all warts divided by number of warts.

Statistical method used: After collecting the information, data was compiled, tabulated and sort out in SPSS version 23. The variables were presented as mean \pm standard deviation. Categorical variables were presented as percentage. One way Anova test was applied to compare the significance of difference in continuous variables. A P-value < 0.05 was considered as statistically significant for statistical tests.

Results:-

Total 300 clinically diagnosed patients of warts were enrolled in this study and 16 were lost during follow up. Out of 300 warts patients, 168 (56%) were male and 132 (44%) were female. Other socio-demographic characteristics were shown below (Table-1).

Outcome assessment: 99.95 % clearance was seen in warts volume at 12 weeks of treatment using Modality III, followed by Modality I (99.67% clearance in warts volume) and Modality II (99.31% clearance in warts volume) which were statistically significant at p value < 0.01 level (shown in Table-3 and figure-1) by using one One way Anova test for significant difference between groups.

Cure according to Modalities: Very good response was seen with all modalities but among them Modality III (5% 5-Fluorouracil was applied daily in the morning and 16% salicylic acid was applied at bedtime) was excellent for warts patients.

Table 1:- Socio-demographic characteristics of the warts patients.

Variables		No. of patients (n=300)	Percentage (%)
Sex	Male	168	56.00 %
	Female	132	44.00 %
Education	Illiterate	10	3.33 %
	Primary	24	8.00 %
	Junior high school	34	11.33 %
	High school	116	38.67 %
	Intermediate	70	23.33 %
	Graduate	44	14.67 %
	Post- graduate	2	0.67 %
Occupation	Service	18	6.00 %
	Business	32	10.67 %
	Labor	82	27.33 %
	Teaching	14	4.67 %
	Housewife	38	12.67 %
	Agriculture	78	26.00 %
	Not working	38	12.67 %
Type of Warts	Common warts	154	51.33 %
	Flat warts	62	20.67 %
	Planter warts	60	20.00 %
	Periungue warts	24	8.00 %

Table 2:- Adverse Effects of the treatment of different modalities.

Adverse effect	Modality I	Modality II	Modality III
Erythema	5	1	1
Irritation	2	2	1
Burning	6	2	1
Hyperpigmentation	3	1	0
Allergic contact dermatitis	2	1	1
Total	18	7	4

Skin markings/dermatoglyphics: After 12 weeks of treatment, 235 (78.33%) patients had complete reappearance of normal skin marking or dermatoglyphics. Maximum complete reappearance of normal skin was seen with modality III treatment (Figure no.-2).

Adverse effects: Minimum adverse effects were seen with modality III treatment in warts patients followed by modality II and modality I (Table-2).

Discussion and conclusions:-

HPVs can infect and cause disease at any site in stratified squamous epithelium, either keratinizing (skin) or non-keratinizing (mucosa). The clinical problems encountered with such infections can be broadly divided into cutaneous warts, genital warts, oral warts and laryngeal warts¹⁴. The present study was done on 300 patients of warts selected randomly from outpatient department of Dermatology, M.R.A. Medical College and Hospital, Ambedkar Nagar. In present study, there were 168 males (56%) and 144 females (44%). Similar results were obtained by Bhargawa et al¹⁵, and Ammen et al¹⁶. Contrary to our finding, Rulison and Coles found that warts were more common in women than men^{17, 18}. Various researchers had shown that the prevalence of warts were more in male than female¹⁹⁻²². In the present study, the majority of wart patients were from rural areas. This can be explained by the fact that the rural population is more prone to trauma due to involvement in agricultural work. This can also be attributed to the dominance of agricultural workers and laborers in our study. Warts were more prevalent in people who were illiterates and having qualification of high school. In our study, Common wart was the most common variant (51.33%), followed by flat warts (20.67%), plantar wart (20%) and periungual warts (8%). Similar result was reported by various scientists^{20, 21}.

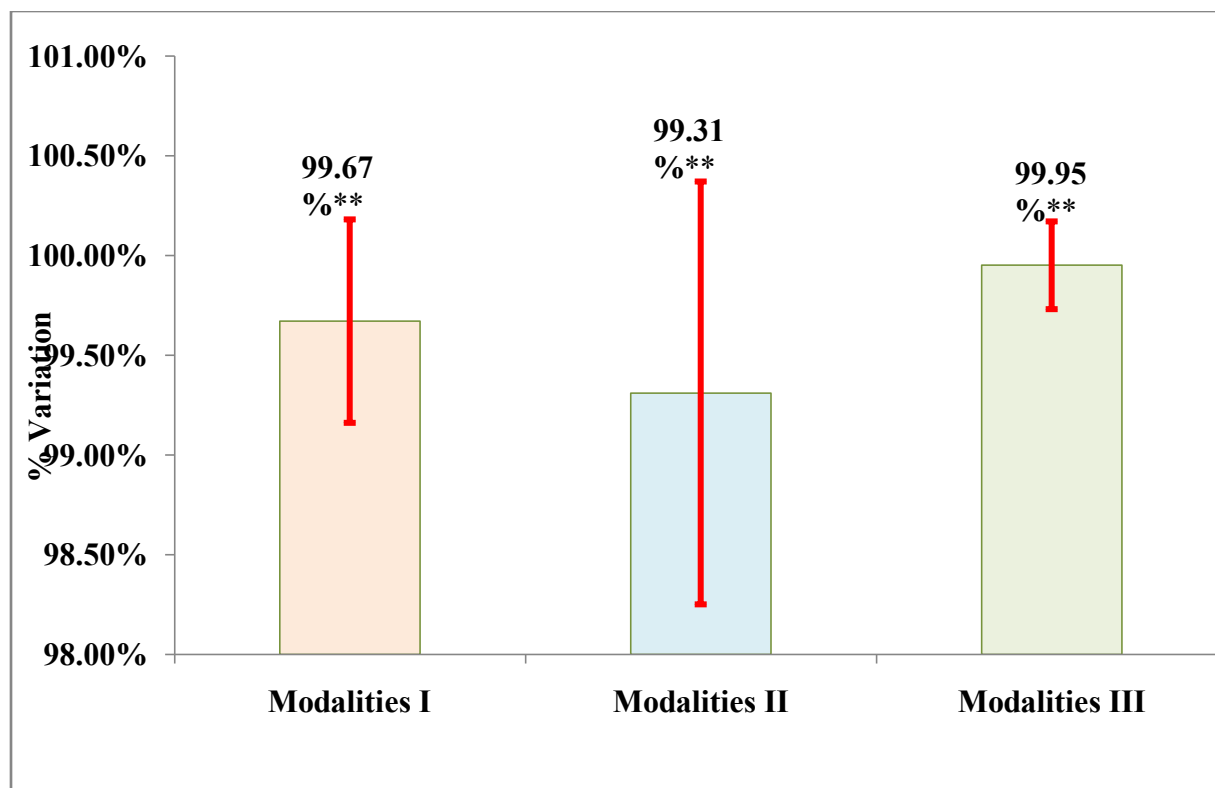
In the present study, 16% salicylic acid treatment was successful in warts patients with 99.67% recovery from warts. Similar result has been reported by various research studies²³⁻²⁵. One of the studies in Southern Illinois University School of Medicine, Springfield, Illinois, USA found that Salicylic acid is one of the most commonly used treatments for warts²⁶. There is consistent evidence that topical salicylic acid is an effective therapy for cutaneous warts. In Japan, a systematic review of local treatments of cutaneous warts found evidence that topical treatments with salicylic acid have a therapeutic effect, with a cure rate of 75 %²⁷. In present study, out of 100 patients, 5% 5-Fluorouracil treated 92 patients had 99.31% recovery from warts. One of the study conducted by Botacini et al., found that 5-Fluorouracil can be a good option for treatment²⁸. There is consistent evidence to support that the 5% 5-fluorouracil cream could completely eradicate all plantar warts within 12 weeks of treatment²⁹. Similarly, Goncalves reported 50% cure rates for common warts after 5-Fluorouracil therapy³⁰. In present study, modality III (combination of 5-Fluorouracil and 16% salicylic acid) cured 96 patients had shown 99.95 % recovery from warts. In Germany, the Systematic literature review and meta-analysis had shown similar finding that combination of 5-fluorouracil and 16% salicylic acid was an efficient and valuable remedy for common and plantar warts over 5-Fluorouracil or 16% salicylic acid alone³¹. One of the medical record reviews which was conducted in New York, USA also proved that the twice-daily applications of 5% topical 5-fluorouracil combined with topical 16% salicylic acid is a safe and effective treatment for warts with complete clinical resolution in all patients³². Combination of 5-Fluorouracil and 16% salicylic acid is best for the treatment of warts with maximum recovery from warts with minimum adverse effect over 5-fluorouracil or 16% salicylic acid alone.

Limitation of the Study:

This study had been conducted on small sample size so need more sample size for more elaborated study. It was very difficult to maintain follow up of same patients. Some of patients may lose during follow up.

Table 3:- Changes in average volume of warts at twelfth weeks.

	INITIAL AVERAGE VOLUME			AVERAGE VOLUME AT 12TH WEEKS			% Variation			STATISTICAL VALUES
MOD.	NO.	MEAN	S.D.	NO.	MEAN	S.D.	NO.	MEAN	S.D.	
I	100	143.86	110.46	96	0.82	1.64	96	99.67%	0.51%	
II	100	147.53	93.40	92	0.79	2.80	92	99.31%	1.06%	
III	100	89.45	85.13	96	0.13	0.63	96	99.95%	0.22%	
TOTAL	300			284			284			



* Significant at 0.01 level ($p < 0.01$).

Figure No.1:- Showing the Percentage (%) variation between Modalities I, II and III in warts patients at twelfth weeks of treatment.



Figure no.2 (a):- Image of the patient treated with 16% salicylic acid at baseline and after 12 weeks.



Figure no.2(b):- Image of the patient treated with 5% 5-fluorouracil at baseline and after 12 weeks.



Figure no.2(c):- Image of the patient treated with 16% salicylic acid & 5% 5-fluorouracil at baseline and after 12 weeks.

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