INTRODUCTION
Warts are benign proliferation of skin and mucosa that result from infection with human papilloma virus (HPVs)\(^6\). There are many types of HPV ranging from 100-150 with distinct regional predeliction and specific histopathology. Although any age group can be affected but plane warts occur mostly in children and young adults. Treatment of verrucae in children is difficult, may be painful using traditional methods, especially if they are multiple or on the face. The objective of the current study was to compare the safety and efficacy of topical 5-fluorouracil 5% ointment with topical tretinoin 0.05% in treatment of plane wart. Sixty patients; 33 males (55%) and 27 females (45%) were enrolled in this randomized controlled comparative therapeutic trial. They were divided into two groups: Group A: Patients treated with topical 5-Fluorouracil (Efudix\(^\text{R}\) 5%) skin ointment and group B: Patients were treated with topical tretinoin cream (Retin-A\(^\text{R}\) 0.05%). Both treatments were applied once daily at night for 4 weeks duration to be evaluated for the response (grading response) at the end of 4th and 8th week. After 4 weeks of treatment, 13 patients (43%) showed an excellent response while 7 patients (23%) showed a significant response in group A. The corresponding values in group B were 10 patients (33%) and 6 patients (20%). At the end of 8 weeks, the number of patients with excellent responses raise to 23 (76%) in group A and to 21 (70%) in group B. Both of treatments (ointment and cream) were safe and effective therapy for plane warts.

ABSTRACT
There are many types of HPV ranged from 100-150 with distinct regional predeliction and specific histopathology. Any age group can be affected\(^4\). Plane warts occur mostly in children and young adults\(^5\). The face, hands and lower legs. Widespread flat warts occurs on the hands and lower legs. Plane warts are 2 to 4 mm, slightly elevated, flat-topped papules that are slightly erythematous or brown on pale skin and hypopigmented on darker skin\(^6\). Useful finding is the tendency of warts to koebnerize forming linear, slightly raised papular lesions\(^6\). Warts are benign proliferations of skin and mucosa that result from infection with papilloma viruses. Flat warts or verruca plana are 2 to 4 mm, slightly elevated, flat-topped papules that have minimal scale. These are most frequent on the face, hands and lower legs. Widespread flat warts occurs in patients with epidermodysplasia verruciformis (EV) that are usually caused by the same human papilloma virus (HPV) types as those found in flat warts in the general population (e.g., HPV 3, 28 and 49)\(^4,\, 7\). Many modalities of treatment were used to treat plane warts, but none is uniformly effective. Cryotherapy\(^6\), salicylic acid\(^6\), retinoids\(^4\), 5-Fluorouracil\(^8\), imiquimod\(^6\), laser\(^6\), oral cimetidine\(^4\) and adapaline\(^13\). 5-Fluorouracil (5-FU) is a pyrimidine analogue that interferes with DNA synthesis by irreversibly inhibiting thymidylate synthetase, which prevents cellular proliferation and results in cell death (preferentially affecting rapidly dividing cells)\(^12\). It is also incorporated into DNA and RNA, leading to DNA breakage and decreased protein synthesis, and it disrupts the exosome complex that degrades RNA. The primary dermatologic use of topical 5-FU is the treatment of actinic keratoses\(^11\). 5-FU is particularly helpful in treating numerous AKs and sites of severe actinic damage without clinically evident lesions. It is less effective for hypertrophic AKs owing to decreased percutaneous absorption through the thickened stratum corneum. Additional dermatologic applications of topical 5-FU include the treatment of actinic cheilitis, squamous cell carcinoma in situ (Bowen’s disease), superficial basal cell carcinoma, cutaneous and genital warts, porokeratoses, nail psoriasis and extramammary Paget’s disease 38. It can also improve the appearance of photoaged skin via epidermal injury and subsequent dermal remodeling (similar to that seen following laser therapy)\(^14\). 5-FU is available in both cream (0.5%, 1% and 5%). Retinoids exert their physiologic effects on DNA transcription by binding to two distinct families of nuclear receptors, RARs and RXRs. These receptor families belong to a super family of nuclear receptors, RARs and RXRs. These receptor families belong to a super family of nuclear receptors that act as ligand-activated transcription factors and include the steroid, vitamin D3 and thyroid hormone receptors as well as peroxisome proliferator-activated receptors (PPAR). Local skin irritation can be expected, and noticeable beneficial effects may take weeks or months to appear. Administration of topical retinoids should be titrated depending on cutaneous irritation\(^15\). The FDA-approved indications for the use of topical retinoid include: acne vulgaris, photoaging, psoriasis, Cutaneous T-cell lymphoma, Kaposi Sarcoma.

KEYWORDS: Plane wart, 5-Fluorouracil 5%, Retin-A cream 0.05% etc.
While the selected non-FDA approved indications are limited disorders of keratinization such as: Darier disease, ichthyoses, pityriasis rubra pilaris, rosacea, pigmentedary disorders, lentigines, actinic keratoses, striae, wound healing, lichen planus, verrucae planae (plane warts) and corticosteroid-induced atrophy therapy and in the prevention of skin cancer (basal cell carcinoma in xeroderma pigmentosum)[15].

MATERIAL & METHODS

Study Design

Randomized controlled comparative therapeutic trial was conducted at the Department of Dermatology and Venereology in Al-Kindy Teaching Hospital/ Baghdad during the period from January 2012 to December 2012. All patients with plane warts attending the Outpatient Department of Dermatology & Venereology in Al-Kindy Teaching Hospital were included in this study. Patients with one or more of the following were excluded from this study: those who received treatment for plane warts in the last two months, patients neither with any immunosuppressive state nor on immunosuppressive medications.

Sixty patients; 33 males (55%) and 27 females (45%) were enrolled in this study.

A full history was taken from each patient according to written questionnaire regarding the name, age, sex, occupation, marital status, duration of disease, family history of warts, past medical history (states of immune suppression, organ transplantation or any chronic diseases), drugs history especially for corticosteroids and other immune suppressants or any previous treatment modality received for their warts. Physical examination was performed for each patient to assess the number, presence of other types of warts, the examination was aided by taking several photos for each patient using the same digital camera (Sony cyber shot) from approximately the same view and distance. The numbers of lesions were calculated. After a full explanation to each patient about the nature of the disease, course, prognosis and full information related to the therapy including; the side effects, action and the way of application, the patients were randomly divided into two groups: those who received treatment for plane warts in the study: 33 males (55%) and 27 females (45%). Their ages range from 11 to 25 years with a mean ± SD of 15.3 ± 4.65 years. Table (1) & figure 1

Group A: Patients treated with topical 5-Fluorouracil (5-FU) skin ointment 5%.

Group B: Patients were treated with topical tretinoin cream 0.05%.

In both groups, patients were instructed to apply the drug once daily at night for 4 weeks duration to be evaluated for the response to treatment and to record any possible local and systemic side effects at the end of 4th and 8th week of therapeutic regimen respectively.

The response to treatment was graded as follows:
0= no response
1= mild response (1-25% reduction in lesion no.)
2= moderate response (26-50% reduction in lesion no.)
3= significant response (51-75% reduction in lesion no.)
4= excellent response (76-100% reduction in lesion no.)

At the end of 4th week, if no or mild response observed, the patients were instructed to continue using the treatment to be re-evaluate at the end of 8th week.

All patients were reexamined at the end of 4th week and 8th week to evaluate the response to treatment depending on clinical and photographic assessment and to record any possible local & systemic side effects.

Statistical Analysis

Data were analyzed by using Minitab software. Chi-square and t-test were used to test the significance differences between proportions and means respectively. The p-value less than 0.05 were considered significant.

RESULTS

During the period from January 2012 to December 2012, a total of 60 patients with plane warts were included in this study; 33 males (55%) and 27 females (45%). All Patients were randomly divided into two groups:

Group A: Patients were treated with topical 5-Fluorouracil (5-FU) skin ointment 5%.

Group B: Patients were treated with topical tretinoin cream 0.05%.

Age and Gender Distribution

Group A: (5-Fluorouracil ointment (Efudix® 5%): a total of 30 patients 16 males (53%) & 14 females (47%). Their ages range from 10 to 25 years with a mean ± SD of 15.3 ± 4.65 years. Table (1) & figure 1

Group B: (topical tretinoin cream (Retin-A® 0.05%) A total of 30 patients 17 males (56.7%) and 13 females (43.3%). Their ages range from 11 to 25 years with a mean ± SD of 15.86 ± 4.58 years. Table (1) & figure 1

The difference between the two groups in the age and gender distribution was statistically insignificant which implies a good randomization.

| TABLE 1: The distribution of patients according to the age and gender in both groups. |
|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| Gender                           | Group A 5 -Fluorouracil          | Group B Topical Tretinoin         |
| No                               | Mean ± SD                        | No                               | Mean ± SD                        |
| Male                             | 16 16.38 ± 4.94                  | 17 17.12 ± 4.73                  |
| Female                           | 14 14.07 ± 4.14                  | 13 14.23 ± 3.98                  |
| TOTAL                            | 30 15.3 ± 4.65                   | 30 15.86 ± 4.58                  |
Response to therapy

Group A (5-Fluorouracil 5%): After 4 weeks of treatment, all of the patients showed response to treatment. Thirteen patients (43%) showed an excellent response while 7 patients (23%) showed a significant response. Patients with mild and moderate response were 4 (13%) and 6 (20%) respectively. After 8 weeks, the number of patients with excellent responses raise to 23 (76%), Table 2. The overall number of patients achieved significant to excellent response after 8 weeks was 27 (90%).

<table>
<thead>
<tr>
<th>Response</th>
<th>No response No. (%)</th>
<th>Mild response No. (%)</th>
<th>Moderate response No. (%)</th>
<th>Significant response No. (%)</th>
<th>Excellent response No. (%)</th>
<th>Total No. (%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 4 weeks</td>
<td>0 (0)</td>
<td>4 (13.3)</td>
<td>6 (20)</td>
<td>7 (23.3)</td>
<td>13 (43.4)</td>
<td>30 (100)</td>
<td>P=0.03</td>
</tr>
<tr>
<td>After 8 weeks</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (10)</td>
<td>4 (13.3)</td>
<td>23 (76.7)</td>
<td>30 (100)</td>
<td></td>
</tr>
</tbody>
</table>

In Group B (topical tretinoin): after 4 weeks of treatment, all of the patients showed response to treatment. Ten patients (33%) showed an excellent response while 6 patients (20%) showed a significant response. Patients with mild and moderate response were 6 (20%) and 8 (27%) respectively. After 8 weeks, the number of patients with excellent responses raise to 21 (70%). Table (2). The overall number of patients achieved significant to excellent response after 8 weeks was 25 (83%) patients.

<table>
<thead>
<tr>
<th>Response</th>
<th>No response No. (%)</th>
<th>Mild response No. (%)</th>
<th>Moderate response No. (%)</th>
<th>Significant response No. (%)</th>
<th>Excellent response No. (%)</th>
<th>Total No. (%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 4 weeks</td>
<td>0 (0)</td>
<td>6 (20)</td>
<td>8 (27)</td>
<td>6 (20)</td>
<td>10 (33)</td>
<td>30 (100)</td>
<td></td>
</tr>
<tr>
<td>After 8 weeks</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (16.7)</td>
<td>4 (13.3)</td>
<td>21 (70)</td>
<td>30 (100)</td>
<td>P=0.03</td>
</tr>
</tbody>
</table>

Difference in response to therapy between the two groups registered in Table (4) & Table (5). The response to treatment to 5-Fluorouracil 5% was higher than that of topical tretinoin after 4 weeks. Patients with excellent response were 43.4% and 33% in both groups respectively. However, this difference was statistically insignificant (P-Value= 0.76) similarly, after 8 weeks, patients with excellent response in both groups were comparable and statistically insignificant (P-Value= 0.7)

<table>
<thead>
<tr>
<th>Response</th>
<th>No response No. (%)</th>
<th>Mild response No. (%)</th>
<th>Moderate response No. (%)</th>
<th>Significant response No. (%)</th>
<th>Excellent response No. (%)</th>
<th>Total No. (%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>0 (0)</td>
<td>4 (13.3)</td>
<td>6 (20.0)</td>
<td>7 (23.3)</td>
<td>13 (43.4)</td>
<td>30 (100)</td>
<td></td>
</tr>
<tr>
<td>Group B</td>
<td>0 (0)</td>
<td>6 (20.0)</td>
<td>8 (27.0)</td>
<td>6 (20.0)</td>
<td>10 (33.0)</td>
<td>30 (100)</td>
<td>P=0.76</td>
</tr>
</tbody>
</table>
5-fluorouracil versus topical tretinoin 0.05% in treatment of plane wart

<table>
<thead>
<tr>
<th>Response</th>
<th>No response No. (%)</th>
<th>Mild response No. (%)</th>
<th>Moderate response No. (%)</th>
<th>Significant response No. (%)</th>
<th>Excellent response No. (%)</th>
<th>Total No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (10.0)</td>
<td>4 (13.3)</td>
<td>23 (76.7)</td>
<td>30 (100)</td>
<td></td>
</tr>
<tr>
<td>Group B</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (16.7)</td>
<td>4 (13.3)</td>
<td>21 (70.0)</td>
<td>30 (100)</td>
<td>P=0.7</td>
</tr>
</tbody>
</table>

**Side effects**

In general, the treatment in both groups was well tolerated. Side effects were trivial and transient and did not necessitate stopping the treatment. Patients who were treated with 5-fluorouracil showed relatively more side effects than those treated with topical tretinoin. Table 6.

**DISCUSSION**

Warts are benign proliferation of skin and mucosa that result from infection with human papilloma virus (HPVs). Plane warts occur mostly in children and young adults. The course of papilloma virus infection varies considerably. Plane warts seem to persist or disseminate in immune-compromised individuals. However, spontaneous resolution can be expected in immune-competent patients at a variable period of time. There are many modalities of therapy, reflecting that none was uniformly effective or directly antiviral. Whatever method is used in the treatment of warts, there will be failures and recurrences.[1]. 5-Fluorouracil (5-FU) is a pyrimidine analogue that interferes with DNA synthesis by irreversibly inhibiting thymidylate synthetase, which prevents cellular proliferation and results in cell death (preferentially affecting rapidly dividing cells).[12]. 5-Fluorouracil has been used in the treatment of plane warts.[16]. Retinoid exert their physiologic effects on DNA transcription by binding to two distinct families of nuclear receptors, RARs and RXRs. Topical retinoids had been used successfully in treatment of plane warts with a variable success rate.[11,17]. The present work aimed to compare the therapeutic efficacy and safety of topical 5-Fluorouracil ointment 5% to topical Retin-A cream 0.05% in the treatment of plane warts.

Topical 5-Fluorouracil was effective in the treatment of plane warts. An excellent response to treatment was recorded as early as the 4th week of treatment in 43.4% of patients. After 8 weeks, this figure raised to reach 76.6%. At the end of the course of therapy, patients with significant to excellent response were 90%. These results were comparable to what has been reported and in a shorter duration. Salk used 5-FU cream for 12 weeks with 95% clearance.[16]. Patients treated with topical Retin-A 0.05% showed a similar response to treatment. After 4 weeks 33% showed an excellent response to therapy. After 8 weeks, excellent response to treatment was observed in 70%. Patient with significant to excellent response to treatment were 83%. These results were also comparable to previous studies.[11,17].

Both 5-FU and topical retinoid were well tolerated by the patients. Side effects like erythema, scaling, burning, itching and dyspigmentation were recorded in both treatment groups. However, none of these side effects necessitate stopping the treatment. These side effects were comparable to the previously reported side effects in both drugs.[11,12,16,17].

When we compared topical 5-Fluorouracil 5% ointment to topical Retin - A cream 0.05%, we found that 5-FU had a better success rate 90% vs 83% for topiical retinoids at the end of the treatment course. Nevertheless, this difference was statistically insignificant. On the other hand side effects were more intense in patients treated with 5-Fluorouracil.

**CONCLUSION**

In conclusion, both topical 5-Fluorouracil 5%, and topical retin-A cream 0.05% were safe and effective therapy for plane warts.

**REFERENCES**


