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# Histopathological evaluation of Nd: YAG laser versus Tuberculin Purified Protein Derivative in treatment of palmoplantar warts

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**Abstract**
**Background:** Warts are benign epithelial proliferations caused by HPV, characterized histopathologically by hyperkeratosis, papillomatosis, and koilocytes in the epidermal layer. Nd: YAG laser offers photothermal destruction of warts, while PPD offers an immunotherapeutic approach for treatment of palmoplantar warts.
**Objective:** The evaluation of the histopathological effects of Nd: YAG Laser monotherapy versus Tuberculin purified protein derivative in treatment of palmoplantar warts.
**Methodology**: Sixteen patients were recruited and divided into 2 equal groups; the first group received Nd: YAG laser sessions only every 4 weeks for 4 sessions while the other group received intralesional PPD every 2 weeks for 6 treatment sessions. Two biopsies were taken, one before treatment, the other at the end of the treatment protocol at 4 months. Using image analysis a histopathological image was analyzed by H&E stains and another sample was immunohistochemically evaluated with p16.
**Results:** In Group A (Nd: YAG laser), the mean koilocyte count decreased from 142.67±55.4 to 24.5±42.1 ($p < 0.028$), while in Group B (PPD), the reduction 143.5±50.2 to 130.3±80.0 was not statistically significant ($p = 0.753$). Elongated rete ridges in Group A were reduced from 17.83±6.6 to 8.17±8.8 ($p < 0.027$), whereas Group B showed a reduction from 11.67±4.7 to 6.33±7.33 ($p = 0.115$). For p16 expression, Group A exhibited a significant reduction from 54.39±4.6 to 13.9±16.4 ($p = 0.028$), while Group B showed a nonsignificant change from 40.167±9.19 to 32.139±16.9.
**Conclusion**: Nd: YAG laser demonstrated superior efficacy compared to PPD in reducing koilocytes, rete ridges, and p16 expression.

**Keywords**—p16, palmoplantar warts, Tuberculin PPD, Nd: YAG Laser, Koilocytes.

## I. Introduction

Warts are benign epithelial proliferations caused by the human papillomavirus (HPV), infecting both skin and mucosal tissues transmission occurs by contact and/or autoinoculation. Histopathologically, these lesions are characterized by hyperkeratosis, papillomatosis, and vacuolated keratinocytes with pyknotic nuclei (koilocytes), features typically observed in the epidermal layer, especially in cases of common and plantar warts. These keratinocyte alterations are evidence of HPV's influence on cellular structure and are key markers for diagnosing different wart types [1].

Deep palmoplantar warts (PPW), with their dermal prominent endophytic growth and surrounding collar of calloused skin, explains their greater tenderness compared to superficial warts. Histologically, these warts display dilated blood vessels in the papillary dermis; a characteristic feature that can be exploited in laser treatments [2].

Following an incubation period ranging from 1 to 6 months, histological changes may develop, including thickening of the stratum corneum and the formation of papillomatous projections, particularly in deeper, weight-bearing sites on the plantar surface [3].

The therapeutic approach to warts is often challenging due to their variable histopathological presentations and potential for recurrence. Effective treatments should aim to reduce pain, enhance quality of life, and address both superficial and deep structural involvement. Physical destruction methods like cryosurgery, pulsed-dye lasers, and Nd: YAG lasers target dilated vessels in the dermis, inducing coagulation or vascular collapse, these lasers can alleviate wart symptoms through selective photothermolysis [4].

The Nd: YAG laser (1064 nm) offers deep tissue penetration and thermal coagulation, effectively debulking large lesions through photothermal destruction, where light

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energy is converted into heat energy to target and destroy tissue [5]. In addition to physical methods, immunotherapy with intralesional injections, such as purified protein derivative (PPD), has shown effectiveness in eliciting a cell-mediated immune response. The PPD activates cytotoxic T-cells and NK cells, inducing an immune response against HPV-infected cells. Histopathological evidence of treatment efficacy includes increased lymphocytic infiltration around keratinocytes in treated lesions, contributing to wart regression across multiple types, including recalcitrant palmoplantar warts [6,7].

Several studies have suggested that p16 protein can serve as a reliable marker for the detection of HPV-associated lesions. The p16 gene, also known as cyclin-dependent kinase (CDK) inhibitor 2A, is located on chromosome 9p21 and has repeatedly shown diverse alteration in many primary tumors [8]. Overall, histopathology and immunohistochemical evaluation not only aids in the diagnosis and classification of warts but also underpins the rationale for treatment choices, highlighting cellular and vascular targets within the lesions that can be specifically addressed by both immunologic and laser-based therapies [9]. So, this study aimed at the evaluation of the histopathological effects and immunohistochemical evaluation of Nd: YAG Laser monotherapy versus Tuberculin purified protein derivative in treatment of palmoplantar warts.

## II. MATERIALS AND METHODS

This is a randomized comparative controlled and prospective clinical study that involved 16 patients suffering from palmoplantar warts. Participants were randomly assigned to either the Nd: YAG laser (Group A) or intralesional PPD (Group B) treatment group using the envelope randomization method. Patients were recruited from the dermatology and venereology outpatient clinic of Medical Research Centre of Excellence. The study was approved by National Research Centre's ethical committee (MREC 17/049) and all patients signed an informed consent. Inclusion criteria involved patients older than 18 years diagnosed with more than one PPW, and no concurrent topical and systemic therapy of warts. Patients with chronic diseases or fever or hypersensitivity to Tuberculin PPD constituents, lactating or pregnant females, as well as immunosuppressed patients were excluded.

Patients were divided into 2 groups where group A received Nd: YAG laser sessions only, every 4 weeks for a maximum of 4 treatment sessions, while group B: received intralesional injection of tuberculin PPD, every 2 weeks for a maximum 6 treatment sessions.

All patients were examined at the end of the study to evaluate the response to treatment and another biopsy was taken at 4 months after the first treatment session.

### Procedures

Prior to laser treatment and in biopsy excision, warts and surrounding skin were anesthetized using EMLA cream under occlusion or a local lidocaine injection and were shaved with a sterile disposable surgical blade.

Long pulsed Nd: YAG (1064 nm) laser (Cutera, Inc., Brisbane, CA, USA) was used. The parameters used were: spot size (5 mm), pulse duration (20 ms) and fluence (100 - 200 j/cm2 Not less than two overlapping laser pulses were applied to each wart, covering the wart itself and a 1mm margin of the surrounding skin. Tuberculin PPD (VACSERA®, Egypt 2ml vial) was injected intralesional at a dose of 10 IU (0.1ml) only, into the largest wart at the first visit. The same procedure was repeated into the same lesion every 2 weeks until the lesion disappeared for a maximum of 6 treatments.

### Histopathological Evaluation

A four mm biopsy was taken before the first treatment session and after 4 months from the beginning of treatment, biopsies were preserved in 10% formalin solution.

### General histological examination

The procedure for histological preparation was done as described by Bancroft and Stevens (2016). Briefly, skin tissues were sliced to 3-4 mm thick, fixed in 10% neutral buffered formalin (10% NBF), dehydrated in graded concentrations of ethanol, cleared in xylene, and embedded in paraffin. The paraffin blocks were sectioned with a microtome at (4-6μm) thickness and dyed with Hematoxylin and Eosin stain to study general tissue structure. H&E-stained sections were examined via using Leica microscope (CH9435 Hee56rbrugg) (Leica Microsystems, Switzerland) [10].

Histopathological scoring was evaluated in skin tissue for number of koilocytes, number and rete ridges per cross-sectional area using the image analysis system Leica QWin DW3000 (LEICA Imaging Systems Ltd., Cambridge, England). The most representative six fields were assessed for each section in all groups using 400x magnification via light microscopy transferred to the screen.

### Immuno-histochemical Evaluation

A cyclin-dependent kinase inhibitor 2A also known as p16 was used to detect its correlation with HPV in the lesion.

*Immunohistochemistry Staining Protocol*

Immunohistochemistry was applied on paraffin tissue sections and fixed on positively charged slides by using avidin-biotin-peroxidase complex (ABC) method. P16 Polyclonal Antibody (Elabscience Cat# E-AB-40264, Dilution: 1:50) has been tested. Sections from each studied group were incubated with the formerly stated antibodies, subsequently the chemicals involved for ABC technique (Vectastain ABC-HRP kit, Vector laboratories) were inserted. Marker expression was identified with peroxidase and stained with diaminobenzidine (DAB, produced by Sigma) to distinguish antigen-antibody complex. Negative controls were integrated using non-immune serum instead of the primary or else secondary antibodies. Immuno-stained sections were checked and photographed via using Leica microscope under different magnification powers (CH9435 Hee56rbrugg) (Leica Microsystems, Switzerland).

### Quantitative scoring of immunohistochemical results "Area Percentage"

Six high power fields (x 400) exhibit positive brown immunostaining were selected for evaluation in each serial section of the studied groups. Area % was determined for p16-stained sections via Leica QWin 500 image analyzer computer system (England). This image analyzer entails of Leica microscope, a colored video camera, colored monitor and a

hard disc of a Leica IBM personal computer linked to the microscope and managed by Leica QWin 500 software. Records were statistically described in terms of mean and standard deviation (mean ± SD) for area %.

**Statistical analysis**

Data were examined for normality via Kolmogorov-Smirnov test of normality. The outcomes of this test pointed that most data were normally distributed (parametric data), accordingly descriptive analysis, One Way-Anova, and Post Hock tests were operated for intergroup relationship. P-values less than 0.05 were represented as statistically significant. Statistical analysis was conducted with SPSS 26.0 (Statistical Package for Scientific Studies, SPSS, Inc., Chicago, IL, USA) for Windows.

## III. RESULTS

Firstly, the demographic data of both groups are interpreted in **table. 1.**

Table. 1. Demographic data of both groups

| | | Nd-YAG (n = 8) | PPD (n = 8) | *P value* |
|---|---|---|---|---|
| **Age (years)** Mean ± SD | | 25.27 ± 4.35 | 23.73 ± 7.06 | 0.078 |
| **Gender** n (%) | **Male** | 7(46.7%) | 6(40.0%) | 0.713 |
| | **Female** | 8(53.3%) | 9(60.0%) | |
| **Disease duration (years)** Mean ± SD | | 11.87 ± 5.46 | 8.67 ± 4.58 | 0.075 |

**Histopathological examination results**

The marked histopathological and immuno-histochemical changes are demonstrated in **table. 2.**

Table. 2. Histopathological and immuno-histochemical results

| | Nd-YAG (n = 8) | PPD (n = 8) | *P value* |
|---|---|---|---|
| **Koilocytes change** | -118.2 ± 73.7 | -13.2 ± 73.5 | 0.055 |
| **Koilocytes %change** | -80.6 ± 35.9 | -9.3 ± 61.4 | 0.037 |
| **Elongated rete ridges change** | -9.7 ± 7.4 | -5.3 ± 7.9 | 0.335 |
| **Elongated rete ridges %change** | -57.4 ± 36.2 | -18.1 ± 114.6 | 0.873 |
| **Dilated blood vessels change** | -15.4 ± 8.9 | 2.1 ± 10.6 | 0.002 |
| **Dilated blood vessels % change** | -73.9 ± 33.2 | 134.7 ± 392.8 | 0.002 |
| **P16 change** | -40.5 ± 18.1 | -8.0 ± 14.6 | 0.016 |
| **P16 %change** | -73.8 ± 31.8 | -20.6 ± 42.5 | 0.078 |

Those can be summarized as following:

1. Koilocytes number: In Group A, Koilocytes number had a mean of 142.67±55.4 before treatment and a mean of 24.5±42.1 after treatment with a highly statistical difference of p value < 0.028. While In group B, Koilocytes number before commencing treatment was 143.5±50.2 that was reduced to a mean of 130.3±80.0 after treatment with p value of 0.753 which is not statistically significant. Between both groups Koilocytes number reduction was highly significant in favor of Nd: YAG, p value of 0.016 **(Fig 1).**

In an attempt to compare the effect of each treatment through calculating the change in Koilocytes between before and after treatment in each group, the mean and SD of dilated koilocytes change in group A showed a reduction by 80.6 ± 35.9% while group B showed a reduction in koilocytes by 9.3 ± 61.4% with a statistically significant difference (p = 0.037) **(Table 2).**

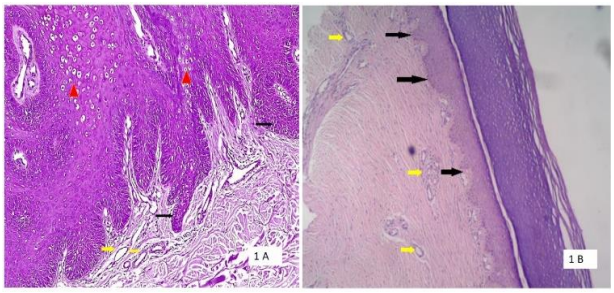


***Figure. 1.*** *(H&E x 200). On the left, histopathological image before treatment showed marked elongated rete ridges (black arrows), and marked Koilocytes (red arrows) and high vascularity (yellow arrows). On the right, after treatment by Nd: YAG laser at 4 months interval, the image showed normal appearance of the rete ridges (black arrows), no obvious Koilocytes, and moderate vascularity (yellow arrows).*

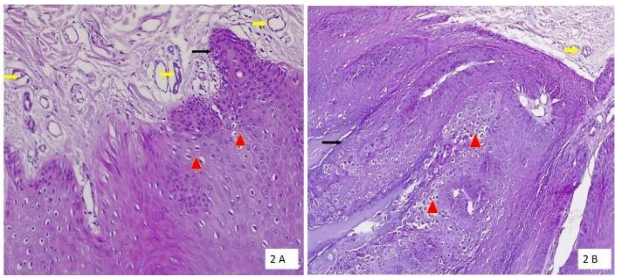


***Figure. 2.*** *(H&E x 200). The left image shows elongated rete ridges (black arrows), and Koilocytes (red arrows) and markedly dilated blood vessels (yellow arrows). On the right, after treatment by Nd: YAG laser at 4 months interval, the image showed rete ridges (black arrows), Koilocytes (red arrows), and mild vascularity (yellow arrows).*

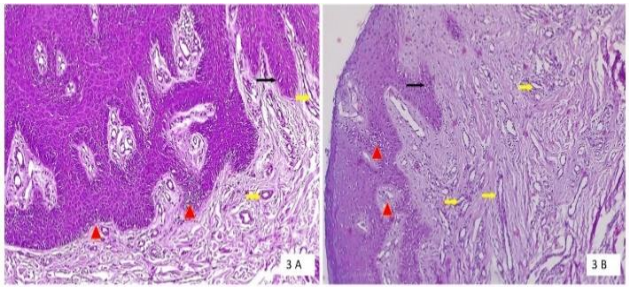


***Figure. 3.*** *(H&E x 200): The left image shows, elongated rete ridges (black arrows), marked vacuolated cells (Koilocytes, red arrows) and high vascularity (yellow arrows). On the right, after treatment by PPD at 4 months interval, the image shows few rete ridges (black arrows), many Koilocytes (red arrows) and dilated blood vessels (yellow arrows).*

2. Elongated rete ridges: In group A were of mean and SD of 17.83±6.6 that was reduced to 8.17±8.8 after treatment with p value of <0.027 which is highly significant. While elongated rete ridges, in Group B were measured at 11.67±4.7 and were reduced after treatment to 6.33±7.33 which is not significant at p value of 0.115. Between both groups a p value of 0.037 showing a significant difference in favor of Nd: YAG Laser treatment **(Figures 2 & 3).**

In an attempt to compare the effect of each treatment through calculating the change in elongated rete ridges between before and after treatment in each group, the mean and SD of elongated rete ridges change in group A showed a reduction by 57.4 ± 36.2% while group B showed a reduction in elongated rete ridges by 18.1 ± 114.6% with no statistically significant difference (p = 0.873) **(Table 2).**

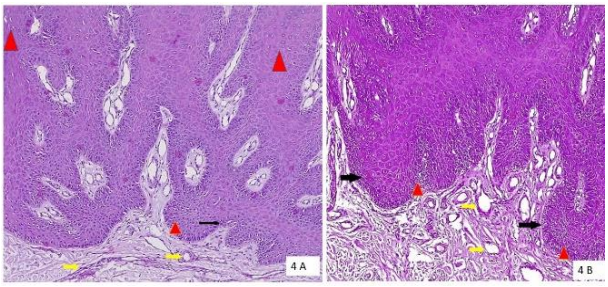


***Figure. 4.*** *(H&E x 200): The left image shows, elongated rete ridges (black arrows), Koilocytes cells (red arrows) and high vascularity (yellow arrows). On the right, after treatment by PPD at 4 months interval, the image shows minimal rete ridges (black arrows), moderate Koilocytes (red arrows) and high vascularity (yellow arrows).*

3. Dilated blood vessels: In Group A, the mean and SD of dilated blood vessels before treatment was 21.4 ± 7.9 and after treatment it became 6.0 ± 7.0, with a statistically significant difference (p value < 0.05). In group B, the mean and SD of blood vessels before treatment was 18.8 ± 8.8 that increased to 20.9 ± 8.8 after treatment, with no statistically significant difference (p > 0.05). Between both groups, dilated blood vessels showed an insignificant difference before treatment (p = 0.494), while the difference was statistically significant after treatment (p = 0.004). This result showed that Nd-YAG laser had better effect than PPD. In an attempt to compare the effect of each treatment through calculating the change in blood vessels between before and after treatment in each group, the mean and SD of dilated blood vessel change in group A showed a reduction by 73.9 ± 33.2% while group B showed an increase in blood vessel by 134.7 ± 392.8% with a statistically significant difference (p = 0.002) **(Figures 3&4, Table 2).**

4. Immunohistochemical results: In group A, p16 value was 54.39±4.6 before treatment that was reduced to 13.9±16.4 with p value of 0.028 which is highly significant. While In group B, p16 value before treatment was 40.167±9.19 and was reduced to 32.139±16.9 which is insignificant with a p value of 0.249.

In an attempt to compare the effect of each treatment through calculating the change in p16 expression between before and after treatment in each group, the mean and SD of p16 expression change in group A showed a reduction by 73.8 ± 31.8% while group B showed a reduction in p16 expression by 20.6 ± 42.5% with no statistically significant difference (p = 0.078) **(Figures 5 &6, Table 2).**

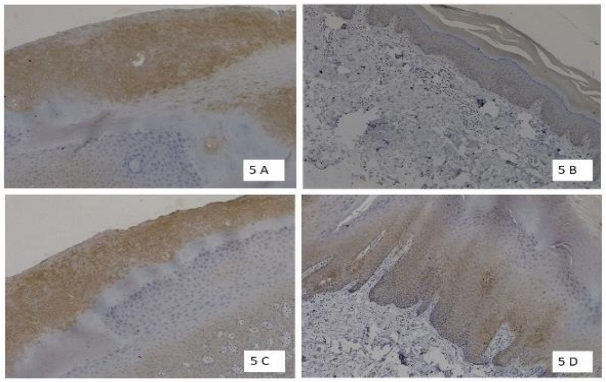


***Figure. 5.*** *Images 5 A and 5C showed immunohistochemical staining with p16 before treatment which were strongly positive, while images 5 B and 5D showed negative expression of p16 after 4 treatment sessions by Nd: YAG laser.*

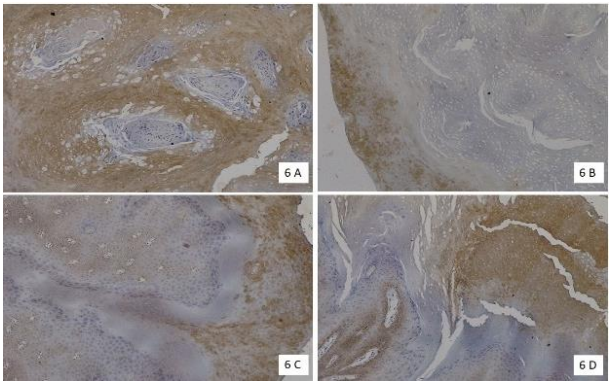


***Figure. 6.*** *Images 6A and 6C showed immunohistochemical staining with p16 before treatment which were strongly positive, while images 6B and 6D still showed expression of p16 after 4 treatment sessions by PPD.*

## IV. DISCUSSION

To the best of our knowledge, our study is the first to evaluate the histopathological and immunochemical difference before and after treatment with Nd: YAG versus PPD in palmoplantar warts. In this prospective comparative study, long-pulsed Nd: YAG showed a higher cure rate than PPD for palmoplantar warts. On the histopathological level the difference was statistically significant.

The use of lasers for the treatment of warts is based on their ability to target certain chromophores in the papillary dermis. Photocoagulation and microvascular hemorrhage occur when the chromophore absorbs light. The long-pulsed Nd: YAG laser has a wavelength that allows deeper penetration depths than other lasers. Minimal destruction of the surrounding tissue is anticipated with long-pulsed Nd: YAG lasers as they may obliterate the nutrient supply to the wart or destroy the rapidly dividing epidermal cells that contain HPV [10].

Before treatment, Histopathologic examination showed separation of the dermo-epidermal junction, epidermal necrosis, and red blood cell (RBC) extravasation, presence of koilocytes, elongated Rete ridges [11].

Our data concedes with the study by Devra et al., in 2022 that used hematoxylin and eosin-stained sections and revealed marked papillomatosis of epidermis with hyperkeratosis and focal parakeratosis. The keratinocytes in the middle showed intracytoplasmic eosinophilic inclusions of various sizes with nuclei at places showing nuclear enlargement, ground glass appearance, and focal viral inclusions also known as Koilocytes, scant dermal tissue identified shows dilated blood vessels [13].

These data was supported by that study performed by, Kimura et al. in 2014 where their histological evaluation showed separation of the dermis and epidermis at the basement membrane with coagulated necrosis of the wart tissue in the lower epidermis, as well as coagulation and destruction of the blood vessels in the papillary dermis following the laser irradiation [1].

Unlike various other treatment options, immunotherapeutic approaches upregulate the immune system to recognize and destroy the lesions at both the target site and distant locations. This approach has proven to be an inexpensive and effective method, particularly for individuals with multiple recalcitrant warts [14]. In comparison with conventional therapeutic methods, intralesional immunotherapy has demonstrated shorter treatment times, increased efficacy, a lower incidence of side effects, and reduced recurrence rates [15]. Intralesional immunotherapeutic agents work by introducing an antigen to promote T-cell–mediated immunity nonspecifically against HPV, resulting in clearance of HPV at local and distant sites [16]. More specifically, these therapies result in (i) delayed hypersensitivity reactions against HPV, and (ii) proliferation of peripheral mononuclear cells that then promote T helper 1 (Th1) cell cytokine responses [17].

Using H&E stains, our most outstanding results showed that Koilocytes number in the Nd: YAG group had a mean of 142.67±55.4 before treatment and a mean of 24.5±42.1 after treatment with a highly statistical difference of p value < 0.028. While the biopsies taken before and after treatment by PPD, the Koilocytes number were 143.5±50.2 that was reduced to a mean of 130.3±80.0 after treatment with p value of 0.753 that is insignificant. Comparing both groups after treatment showed a highly significant difference in favor of Nd: YAG with a p value of 0.016.

Our next significant result was the presence of Elongated rete ridges in group A were of mean and SD of 17.83±6.6 that was reduced to 8.17±8.8 after treatment with p value of <0.027 which is highly significant. While elongated rete ridges, in Group B were measured at 11.67±4.7 and were reduced after treatment to 6.33±7.33 which is not significant at p value of 0.115. Between both groups a p value of 0.037 which is a significant difference in favor of Nd: YAG Laser treatment. Using immunohistochemistry, we evaluated the expression of P 16 which is cyclin dependent kinas inhibitor that is sometimes used as an immunohistochemical marker in routine diagnosis of warts, where Mastutik et al., in 2021 used the detection of p16INK4A expression by immunohistochemistry as a biomarker for HPV infection diagnosis [18]. While Romagosa et al. in 2011 used the expression of p16INK4A as a marker to determine the prognosis of a malignancy caused by HPV infection following the work by Missaoui et al. in 2014, that suggested that p16INK4A can be a specific marker for HPV infection and may correlate with the type of high-risk HPV or low risk-HPV [19, 20].

In our study, we used p 16 as a marker for prognosis and correlation between both treatment modalities, showing focal expression of p 16 before treatment by both modalities while after treatment by Nd: YAG Laser, the expression dropped dramatically from a mean value of 54.39±4.6 to 13.9±16.4 with a p value of 0.028 which is significant. However, the samples treated by PPD, the p16 value before treatment was 40.167±9.19 and was merely reduced to 32.139±16.9 which is insignificant and showing a p value of 0.249. These results may suggest that P16 could be used not only as a diagnostic marker but also as a prognostic marker in HPV lesions. Although, this study was limited by the small sample size and short duration of follow up; results are interesting and promising. Our recommendations include adding more parameters in the histopathological evaluation, and adding other immunohistochemical markers that are specific and sensitive to HPV.

## V. CONCLUSION

Nd: YAG Laser offers a more effective method for treatment of palmoplantar warts in comparison to Tuberculin PDD as proven on the histopathological and immuno-histochemical grounds.

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