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Original Article

The effect of chronic cigarette smoking on the response of anogenital wart in male Chinese patients to topical 25% podophyllin therapy

長期吸煙對男性肛門生殖器疣患者接受 25% 鬼臼樹脂治療的影響

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A prospective study was carried out from December 1998 to May 1999 in two social hygiene clinics in Hong Kong to evaluate the effect of chronic smoking on clinical response of anogenital wart (AGW) to topical 25% podophyllin therapy. Male smokers and non-smokers with newly diagnosed AGW were recruited for the study. Each patient was treated once every five days consecutively for a maximum of five months and assessed monthly for disappearance of AGW. A total of 178 patients were recruited and 155 patients completed the study. Among these 155 patients, 83 (53.6%) were smokers while 72 (46.4%) were non-smokers. At the end of the first two months, 57 non-smokers but only 30 smokers had their lesions cleared. The difference between the smokers and non-smokers in responding to topical 25% podophyllin therapy at two months interval was statistically significant ($\chi^2 = 29.0$, $p < 0.01$). In addition, the association between smoking and susceptibility to AGW was also evaluated. One hundred and ten healthy patients without AGW were served as a control group. A significant association of AGW with chronic cigarette smoking was noted (odds ratio = 1.7, confidence intervals = 1.05-2.92, $p < 0.02$). We conclude that smokers gave a less favourable response to topical podophyllin treatment compared to the non-smoker counterparts. Further, chronic smokers were more susceptible than non-smokers to development of AGW.

筆者於1998年12月至1999年5月期間於香港兩間社會衛生科診所進行一項前瞻性研究，評估長期吸煙對以25%鬼臼樹脂治療肛門生殖器疣的影響，募集長期吸煙與非吸煙患者進行研究。患者連續每五天接受治療一次，以五個月為限。每月一次評估疣的消退情況。共募集178人，155人完成研究，其中83人(53.6%)為吸煙者，72人(46.4%)為非吸煙者。於首兩個月末，非吸煙治癒者有57人，而吸煙治癒者則僅有30人。此外，對吸煙與罹患肛門生殖器疣的相關性也作了研究。以

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110 位非肛門生殖器疣患者作對照，經排除混淆性因素後，發現肛門生殖器疣與長期吸煙有相關性，其機率比(OR)為 1.7，置信區間(CI)為 1.05-2.92，P 值 < 0.02。我們發現吸煙人仕對局部鬼臼樹脂治療的療效較非吸煙者差，而且也更易罹患肛門生殖器疣。

Keywords: Anogenital wart, chronic cigarette smoking, podophyllin

關鍵詞：肛門生殖器疣、長期吸煙、鬼臼樹脂

Introduction

Anogenital wart (AGW) is one of the commonest viral sexually transmitted infections (STI) worldwide. Although the prevalence of AGW cannot be ascertained in Hong Kong, caseload statistics from the Social Hygiene Service has shown that an estimated 3000 cases were reported annually and a rising incidence of AGW is evident.[1] Human papillomavirus types 6, 11, 16, 18, 31, 33, 35, 39, 42, 43, 44, 45, 51, 52, 55 and 56 have been implicated as the aetiological agent of AGW. AGW not only could be symptomatic, producing meatal obstruction, haemorrhage and disfigurement; it also increases the likelihood of cervical intraepithelial neoplasia (CIN) and anal intraepithelial neoplasia. CIN has been reported to be associated with high risk oncogenic HPV types of 16, 18, 31, 33, 35 and 58 in Hong Kong.[2,3] The effect of chronic smoking on the treatment response of AGW is not well documented in the past. In this study, the effects of chronic cigarette smoking on the treatment of male AGW using 25% topical podophyllin therapy is examined and analysed.

Methods

The prospective study was carried out in Yaumatei and South Kwai Chung Social Hygiene Clinics from December 1998 to May 1999. Male patients with newly diagnosed AGW and who met the inclusion criteria were recruited. These were age 16 to 75, good general health, not taking any immunosuppressive therapy, not received any form of therapy for their AGW for the past two weeks, co-operative, and consent for the study was given. The location, number and size of the AGW were documented. They were divided into two groups of smokers (currently smoking, daily consumption of at least ten cigarettes) and non-smokers (never smoked, or occasional smokers and no more than ten cigarettes per day). The basic demography and sexual behaviour of these recruited patients were also obtained. Another 110 healthy patients without AGW who attended these two clinics were served as a control group to evaluate the association of AGW with smoking behaviour. Patients with AGW were standardised to receive 25% topical podophyllin therapy to their genital warts once every fifth day for a maximum of five months. The lesion was washed to remove podophyllin four hours after application. Each patient was assessed monthly by the attending clinician for successful treatment as indicated by complete disappearance of AGW. The number of treatments required and the number of patients with successful treatment in the smoker and non-smoker groups were compared. The difference between the smoker and non-smoker's group in response to therapy was tested by the chi-square statistics using Epi-info version 6 software, CDC, $p < 0.01$ was taken as statistically significant. The odds ratio between smoking and AGW was determined by the two by two table analysis.

Results

One hundred and seventy-eight male patients with newly diagnosed AGW were successfully recruited.

Their stratified characteristics are shown in Table 1. Ninety-nine percent of these patients were ethnic Chinese. Twenty-three (12 were smokers and 11 were non-smokers) did not complete the study and were excluded. For the 155 patients (83 smokers and 72 non-smokers) who completed the study, their results of evaluation for AGW disappearance in the two groups are shown in Figure 1. At the end of the second month of treatment, the AGW in 47 patients (79.1%) of the non-smoker group but only 25 (36.1%) of the smoker group disappeared. The smoker group showed a delayed response to treatment as illustrated by the lag response to successful treatment after 3, 4 and 5 months. The difference between the two groups at the end of two months interval was statistically significant. ($\chi^2 = 29.0$, $p < 0.01$) However, there was no significant difference in treatment response between the two groups at the conclusion of our study after five months.

A comparison made with 110 healthy male Chinese patients without AGW using a crude two

Table 1. Stratified characteristics of the smoker group with AGW and non-smoker group with AGW compared with control

	Overall study Group with AGW N = 178	**Control Group without AGW N = 110**	**Smoker Group with AGW N = 83**	**Non Smoker Group with AGW N = 72**
Mean age + SD (Year)	37.9 + 12.9	41.7 + 14.2	36.1 + 13.5	38.9 + 12.1
Marital status (%)	58.7	57.3	56.7	61.0
Ethnicity Chinese (%)	98.9	95.5	99.0	99.0
VEP (%)				
No VEP	0	25.5	0	0
China	50.0	34.5	51.6	48.0
Hong Kong	44.3	39.1	44.0	44.3
VEt (%)				
No VEt	0	26.4	0	0
1 month	50	50	51.6	48.1
2 months	10.9	9.1	9.5	12.6
3 months	16.1	8.2	14.7	12.6
Number of sex partners* (%)				
No recent sex partner	0	22.7	0	0
One	35.4	35.5	34.5	36.4
Two	64.6	38.2	65.4	63.6
STI history (%)**				
No	65.5	60.0	66.2	64.9
One STI	23.8	35.5	28.0	28.5
Two STIs	9.4	4.5	5.8	5.1
Three STIs	1.3	0	1.2	1.4
Condom usage rate* (%)**	38.0	60.0	40.2	38.6

*The proportion of patients who reported to have the number of sex partners in the past three months; **The proportion of patients who reported to have the number of STI in the past one year; ***The proportion of condom use in the past 3 months reported by the patients. VEP = Place of venereal exposure of last episode of sexual activity reported by the patients, VEt = Time of venereal exposure of last sex reported by the patients. The difference between the characteristic variables between the smoker group with AGW and non-smoker group without AGW was statistically insignificant ($p > 0.05$).

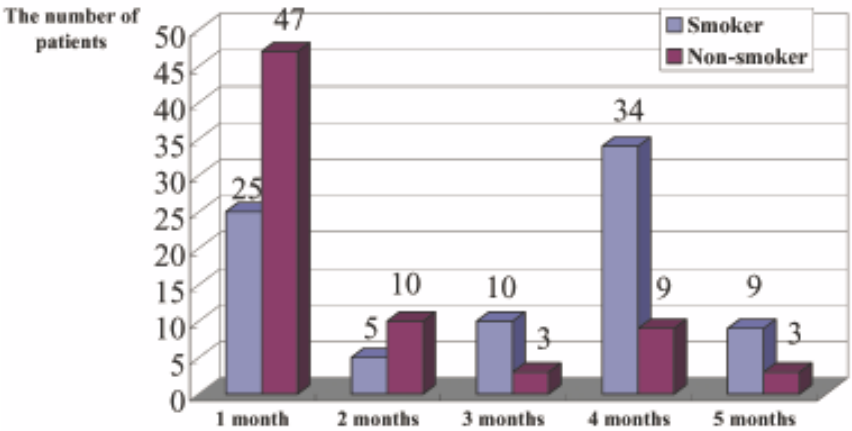

Figure 1. The number of patients successfully treated at different intervals in the smoker and non-smoker group.

by two table analysis without controlling for confounding variable showed that the odds ratio in the association between AGW and chronic smoking was 1.7 (95% confidence interval 1.05-2.92, $p < 0.02$). In the control group without AGW, 43 were smokers and 67 were non-smokers.

Discussion

Our study showed that smokers suffering from AGW responded less favourably than non-smokers to topical 25% podophyllin therapy. In the latter, the response rate is statistically significant better at the end of two months. Male STI patients who smoked were also shown to have a higher chance of having AGW. These two observations enabled us to postulate that chronic cigarette smoking or some factors associated with chronic cigarette smoking promote symptomatic human papillomavirus (HPV) infection or decrease healing. Under this premise, we hypothesise that chronic cigarette smoking can either increase manifestation of HPV infection or decrease healing. However, since HPV is a sexually transmitted infection and there is a link between cigarette smoking and sexual activity;[4] the effect of smoking on HPV infection may be a result of the latter. In order for our hypothesis to be valid, we have to control the main confounding factors in sexual activity; namely the number of recent sexual partners, the proportion of condom use and past history of STI. Thus what we need to verify is whether smoking has any residual effect on HPV infection after controlling these confounding factors. Confounding is the distortion of an exposure or disease association by the effect of some third factor. In our study, we have collected sexual behavioural characteristics of the recruited subjects, which enabled us to carry out a stratified analysis in comparing these confounding parameters between the smokers and non-smokers group (Table 1). The stratified results showed that the confounding characteristics between the two groups were similar; the delayed healing of AGW by topical 25% podophyllin therapy was therefore due to chronic cigarette smoking.

Biological plausibility is commonly appealed to in the explanation and interpretation of epidemiological association; in this case, the association between chronic cigarette smoking and HPV infection.[5,6] The hypothesis that chronic cigarette smoking promotes symptomatic HPV infection is biologically plausible. Cigarette smoke contains carcinogens that may impair the body immune system; these include nicotine,

cotinine, dimethyl-1,2-benzanthrancene and benzapyrene.[7-10] One of the targets of these carcinogens may be the Langerhans' cells which have been shown to be reduced in the cervix and genital epithelium in patients with cervical cancer.[11,12] Cervical cancer has been shown to be more common in patients with the high risk oncogenic type 16 HPV infection and chronic smoking.[13] Without these antigen presenting cells, the activity of the T-lymphocytes would be impaired. As T-lymphocytes are an important cellular defence to the control of HPV infection, HPV infection may act synergistically with chronic smoking in suppressing the body immune surveillance system; hence a delay in healing of the AGW. The immunological mechanisms is also evidenced by the fact that patients who are immunocompromised also have more HPV infection.[14-16]

The promotional effect of smoking on the manifestation of HPV infection including anogenital cancer has been documented in the literature.[17,18] HPV infection was shown to have been increased in chronic cigarette smokers by PCR methods.[19] In addition, Daling et al reported an association of increased risk of cancer in anal, penile, cervical and vulval areas in current smokers of more than 10 cigarettes per day when compared with control.[20] Hellberg also documented that the relative risk of having penile cancer for smokers for more than 10 cigarettes per day was 2.2 compared with non-smokers.[20] All these provide further evidence that HPV infection with its consequence of squamous malignancy may well be mediated through immune depression by chronic cigarette smoking. The odds ratio that was shown in our study in the association between AGW and smoking is also compatible with those reported in the literature.[17,21]

Our study has the following limitations. Sexual behavioural characteristics and smoking habits of the recruits were self-reported; the data may suffer from recall bias. Although the results may be more representative by a larger sample size, the current sample has already shown a 50% difference in response to therapy between non-smokers and smokers with AGW. The confounding effects have been dealt with by stratification, which showed no difference in the sexual characteristics between the two groups of smokers and non-smokers. Regression modelling is another mean to eliminate the confounding effects. Finally, the end point of the study is the disappearance of AGW after two months of topical treatment; the cumulative effect of topical therapy with 25% podophyllin in fact is similar between the non-smoker and smoker group. Our study has not assessed the relapse rate of AGW between the two groups, which would provide another perspective in looking at the promotional effect of smoking on HPV infection in STI patients.

Conclusion

In conclusion, our prospective study has shown that HPV infection is more common in STI patients who smoke. The response of HPV infection manifesting as AGW to topical 25% podophyllin therapy is less favourable in smokers than non-smokers. The exact mechanism of such a difference in response is unknown. Inhibition of the immune system through depletion of epidermal Langerhans' cells by carcinogens released by chronic smoking is a postulated explanation.

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