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*Original Article*

# Treatment with paiteling for cervical high-risk human papillomavirus infection

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**Abstract:** Objective: The present study evaluated the efficacy of Paiteling to eliminate Human papillomavirus (HPV) infection from cervix. Method: The patients were divided into loop electrosurgical excision procedure group (LEEP group, n=82) and non-LEEP group (n=239) in light of the cervical intrapithelial neoplasia classification. The two groups were subgrouped to paiteling group and control group by using random number table. All patients underwent thinprep cytologic test (TCT) and HR-HPV test every three months for one year. The negative conversion rate of HR-HPV and the regression rate of cervical lesions were compared between the two subgroups. Results: The negative conversion rate was higher than those in control subgroup at 6-, 9- and 12-month in non-LEEP group and LEEP group with paiteling, respectively. The regression rate of cervical lesions was significantly higher than those in control subgroup at 6-, 9- and 12-month in non-LEEP group with paiteling, respectively, while it did not differ between the two subgroups in LEEP group with paiteling. Conclusion: Paiteling can reverse early Paiteling cervical HR-HPV infection, shorten the duration of HPV infection, promote lesions subsided. To a certain extent, the removal of the residual virus and the disappearance of the disease can be accelerated.

**Keywords:** Papillomavirus infection, LEEP, Chinese medicines, paiteling, outcome, clearance rate

## Introduction

To date, with the increase of cervical high-risk paplomavirus (HR-HPV) infection, the incidences of cervical cancer is increasing annually among women worldwide [1-3]. HR-HPVs (16, 18, 31, 33, 35, 45, 51, 52, 53, 56, 58, 59, 66, 68 and CP8304) are considered as HR-HPVs, and HPV 16 and 18 infections are one of the most commonly associated with cervical cancer [4-7]. Therefore, reducing HR-HPV infection in such patients is the key to reduce the morbidity of cercical cancer. Loop electrosurgical excision procedure (LEEP) is currently one of the most common techniques for conization in China [8, 9]. Although this treatment is generally sufficient, existing analyses showed that an average of 10% residual or recurrent disease in the treated cases [7]. It is important to develop an effective and safe method in clearing established HR-HPV infection.

Traditional Chinese medicines possess good anti-virus activities and have been used for prevention and treatment of virus infection in China. Accordingly, Chinese medicine paiteling reprents are one of the most promising agents in the treatment of condyloma acuminatum. Paiteling, composed of folium, sophora, cnidium, gall and javanica oill, is an anti-virus agent, which exerts its effect through the degeneration and necrosis of abnormal cell [10]. The aim of this study was to estimate the therapeutic efficacy of paiteling on outcome of HR-HPV infection of the cervix.

## Materials and methods

### *Study population and inclusion criteria*

All patients diagnosed as HR-HPV subclinical infection by using TCT and HR-HPV test in People's Hospital of Shaoxing between January 2011 and June 2013 were selected in the study. The inclusion criteria were as followed: i) Women in reproductive age; ii) The women should positive for HR-HPV; iii) The woman should give written informed consent to partici-

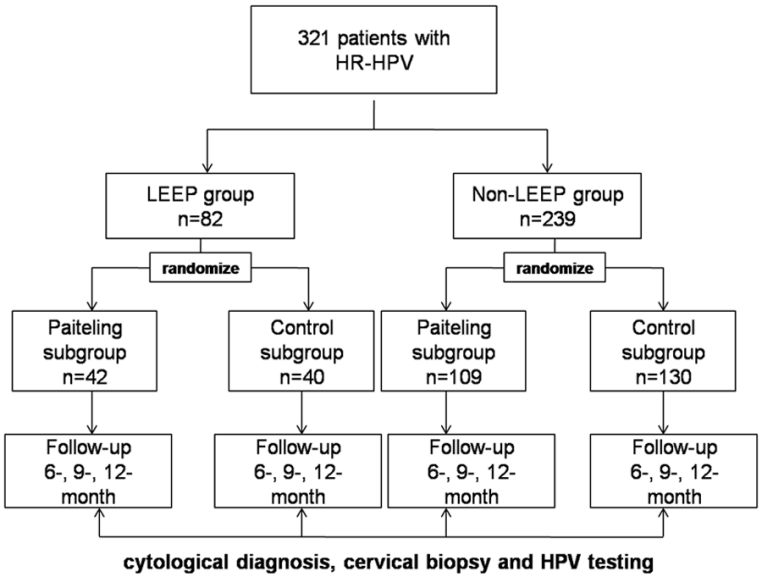


**Figure 1.** Flow diagram showing the progress through the study.

pate in the study voluntarily; iv) Absence of a history of physical therapy or surgical procedure for treatment of cervical; v) Absence of a history liver, kidney and heart disease. Exclusion criteria: i) Pregnant or lactating woman; ii) Subjects treated earlier for cervical precancer or cancer. Overall, the mean age (± standard deviation) of all patients was 36.07 ± 8.8 years (range 23-58 years) and 30.3 ± 5.6 years (range 24-58 years) in LEEP group and non-LEEP group, respectively.

*HPV test*

All patients underwent HPV testing with the HPV typing kit (Guangdong Hybribio Biotech). Cervical samples for the HPV test were obtained with a ctyobrush and tested according to the manufacturer's instructions. High-risk HPV types (16, 18, 31, 33, 35, 45, 51, 52, 53, 56, 58, 59, 66, 68 and CP8304) were all tested and samples with positive results were called HR-HPV infection.

For all cases in the study with HPV-positive, cervical scrapings were collected for cytological diagnosis by gynecologists. Cytology was performed using TBS 2001. The screening of cytology slides was confirmed according to the abnormal squamous cells of uncertain significance (ASCUS) criteria.

Patients with abnormal cytology underwent coloscopy-directed cervical biopsy by using a Leica microscope (Leica, Germany).

*Treatment and follow-up*

Overall, 82 patients were divided into loop electrosurgical excision procedure group (LEEP group). 239 patients were divided into non-loop electrosurgical excision procedure (non-LEEP group). The two groups were subgrouped to paiteling group and control group by using random number table. In LEEP group, 42 patients in paiteling and 40 in control subgroups; and in non-LEEP group, 109 in paiteling and 130 in control subgroups.

In LEEP group, LEEP was performed in LEEP group. The cervix was exposed using an adapted speculum allowing smoke eacuation. After delineating the area of abnormality with Lugol's iodine, 1 ml of local anesthetic was injected in each quadrant. The loop was selected according to the size of the area to be excised. When an endocervical extension was suspected, a second selective endocervical sweep was performed. Exceptionally, when the exocervical lesion was too large to be accommodated by a single sweep, excision was achieved with two or more systematic sweeps. The base of the resulting crater was then coagulated by ball diathermy. Paiteling was used in the cervix when the wound healing process was finished according to the instructions (Patborn, Beijing, China).

In non-LEEP group, paiteling was used in the cervix according to the instructions. The control subgroup had follow-up observation.

All patients underwent TCT and HR-HPV test every 3 months for 1 year. At each follow-up visit, patients underwent cytological diagnosis, cervical biopsy and HPV testing with the HPV typing kit. For patients who underwent treatment with paiteling were diagnosed with positive following visit for 12 months, the patient was considered unresponsive to treatment (**Figure 1**).

**Table 1.** Comparison of HR-HPV negative conversion and regression in non-LEEP group

| Subgroup | Negative conversion rate (%) | | | Regression rate (%) | | |
|---|---|---|---|---|---|---|
| | 6-month | 9-month | 12-month | 6-month | 9-month | 12-month |
| Paiteling (109) | 83.9 (88/105)[a] | 89.5 (94/105) | 95.2 (98/103)[b] | 84.8 (89/105) | 85.7 (90/105) | 91.3 (94/103)* |
| Control (130) | 27.8 (35/126)[c] | 38.3 (46/120)[d] | 71.3 (82/115)[e] | 30.2 (38/126) | 46.7 (56/120) | 55.7 (64/115) |
| $X^2$ | 70.000 | 60.270 | 19.834 | 66.799 | 35.783 | 32.778 |
| p | P<0.0001 | P<0.0001 | P<0.0001 | P<0.0001 | P<0.0001 | P<0.0001 |

[a]Cases with vaginitis at the one month follow-up visit were excluded from calculations, 3 patients were lost to follow-up visit. [b]Cases with residual or recurrent disease at 9-month follow-up visit were excluded from calculations. [c-e]4, 10, 15 patients were lost to follow-up at 6-, 9- and 12-month follow-up visit, respectively.

**Table 2.** Comparison of HR-HPV negative conversion and regression in LEEP group

| Subgroup | Negative conversion rate (%) | | | Regression rate (%) | | |
|---|---|---|---|---|---|---|
| | 6-month | 9-month | 12-month | 6-month | 9-month | 12-month |
| Paiteling (42) | 83.3 (35/42) | 90.0 (36/40)[a] | 95.0 (38/40) | 92.9 (39/42) | 92.5 (37/40) | 92.5 (37/40) |
| Control (40) | 60.0 (24/40) | 68.5 (24/35)[b] | 74.3 (26/35) | 77.5 (31/40) | 85.7 (30/35) | 88.6 (31/35) |
| $X^2$ | 4.431 | 4.101 | 4.851 | 2.736 | 0.330 | 0.034 |
| p | P=0.0353 | P=0.0428 | P=0.0276 | P=0.0981 | P=0.565 | P=0.852 |

[a]2 patients were lost to follow-up visit. [b]Cases with residual or recurrent disease at 9-month follow-up visit were excluded from calculations.

Negative conversion rate was canculated based on the results of HPV testing during the follow-up observation. Regression rate was canculated based on the results of cytological diagnosis.

*Statistical analysis*

Statistical analyses were performed with SPSS software. Percentage was used to predict the negative conversion of HR-HPV. A chi-square test and Fisher's exact test were used to compare between-group differences in negative conversion rate and regression rate of lesion of HR-HPV at each follow-up time. The *p* values less than 0.05 were considered statistically significant.

## Results

*Effects of paiteling in the non-LEEP group*

A total of 239 patients were assigned to the non-LEEP group. Then these patients were subgrouped to paiteling subgroup (109) and control subgroup (130). As shown in **Table 1**, the negative conversion rate of HR-HPV at 6, 9 and 12 months were 83.9%, 89.5% and 95.2% in non-LEEP group with paiteling, respectively, which was higher than those in control subgroups with significant differences ($X^2$=70.000, P<0.0001; $X^2$=60.270, P<0.0001; $X^2$=19.834, P<0.0001, respectively). HR-HPV regression rate were 84.8%, 85.7% and 91.3%, respectively at 6, 9 and 12 months follow-up. There was a statistically difference between two subgroups ($X^2$=66.799, P<0.0001; $X^2$=35.783, P< 0.0001; $X^2$=32.778, P<0.0001; respectively). When pathological diagnosis were performed, we did not observe significant differences in cytological and biopsy assay. Our results also showed that the HR-HPV natural negative conversion rate of control subgroup from non-LEEP group was 27.8%, 38.3% and 71.3%, respectively without any intervention procedure at 3, 6 and 9 months follow-up (**Table 1**), indicating that HPV infection can be cleared to some extend by the body within a period.

*Effects of paiteling in the LEEP group*

A total of 82 patients were assigned to the LEEP group. Then these patients were subgrouped to paiteling subgroup (42) and control subgroup (40). As shown in **Table 2**, at 6, 9 and 12 months follow-up, 83.3%, 90.0% and 95.0% of the negative conversion rate in the paiteling subgroup after LEEP procedure were archived, the difference was statistically significant compared with the control subgroup ($X^2$=4.431, p=0.0353; $X^2$=4.101, p=0.0428; $X^2$=4.851, P=0.0276, respectively). Whereas for HR-HPV

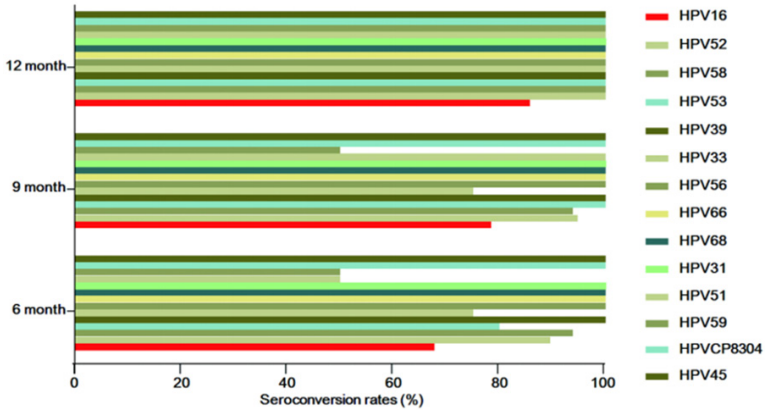


**Figure 2.** The seroconversion rates of HPV subtypes at different points after paiteling applying.

regression rate between two subgroups, there was no statistically differences ($X^2$=2.736, P=0.0981; $X^2$=0.330, P=0.565; $X^2$=0.034, p=0.852, respectively). At 6 month follow-up, 2 out of 42 patients with abnormal TCT in the paiteling subgroup converted to normal and HR-HPV negative was archived. However, at 9 month follow-up, HR-HPV converted to positive, and ASC-H or ASCUS could not be excluded according to the TCT.

*Correlation between HPV subtypes and the effects of paiteling*

To test whether the effects of paiteling is linked to HPV subtypes, seroconversion rates among the drug subgroup were compared. The top 5 HPV subtypes infecting human were HPV16 (38 cases), HPV52 (20 cases), HPV58 (16 cases), HPV53 (10 cases) and HPV39 (9 cases). Wherein the seroconversion cases (rates) of HPV16 at 6, 9 and 12 month were 25 cases (67.7%), 29 cases (78.4%) and 30 cases (85.7%), respectively. In contrast to HPV16, the remaining subtypes all reached 100% at 12 month, while there were cases remaining HPV-positive at 6 and 9 month. However, 5 cases were lost and it was possible that the lost cases didn't convert to negative (**Figure 2**). During the follow-up, about 5.3-25% cases infected with HPV52, HPV58, HPV33 or HPV39 did not convert to negative at 6 and 9 month, whereas all became negative at 12 month. The seroconversion rates of HPV39, HPV56, HPV66, HPV68, HPV31, HPVCP8304, and HPV45 all were 100% when reviewed the first time after applying the drug, and the HPV-negative status continued until the end of follow-up (**Table 3**). In summary, the results argued that the effects of paiteling on different HPV subtypes were various.

## Discussion

In present study, we investigated the efficacy of paiteling in eliminating HPV infection from cervix. We found that higher negative conversion rate and regression rate of HR-HPV were significantly obtained in the paiteling subgroup of LEEP and non-LEEP group, respectively. Our results showed that paiteling in the treatment of HR-HPV was a safe and highly effective method.

Persistent HR-HPV infection is a risk factor of cervical cancer, present in 99% of all cases. Previous studies showed that HPV infections are common, 90% of HPV infection are cleared within 2 years, but abnormal cells can begin to appear if infection persists among these patients [11, 12]. Our results also revealed that the HR-HPV negative conversion rate of control subgroup from non-LEEP group was 27.8%, 38.3% and 71.3%, respectively without any intervention procedure at 3, 6 and 9 months follow-up. However, if these cervical cells cross the basal membrane and spread into the tissues beneath does the situation become cervical cancer, indicating the necessarity of clinical intervention for patients with persistent HR-HPV.

Traditional Chinese medicines possess good anti-virus activities and have been used for prevention and treatment of HPV related cancer in China [10]. Paiteling composed of folium, sophora, cnidium, gall and javanica oill can eliminate or inhibit virus infection by destroying mitovhondria and other membrane system selectively and then result in cell degeneration and necrosis [10]. Paiteling had been applied to cure condyloma acuminatum in vagina by its antivirus anctivities [13, 14]. Therefore, we investigated the efficacy of paiteling in eliminating HR-HPV infection. In this study, the HR-HPV negative conversion rate of non-LEEP group with paiteling were 83.9%, 89.5% and 95.2% at 6, 9 and 12 months follow-up. Comparison of the negative conversion rate between the 2

**Table 3.** The seroconversion rates of HPV subtypes at different points after paiteling applying

| HPV subtypes | Total cases | Seroconversion rates (%) | | | Note |
|---|---|---|---|---|---|
| | | 6 month | 9 month | 12-month | |
| 16 | 38 | 25 (67.7) | 29 (78.4) | 30 (85.7) | One lost; Two lost at 12-months |
| 52 | 20 | 17 (89.5) | 18 (94.7) | 19 (100) | One lost; |
| 58 | 16 | 15 (93.8) | 15 (93.8) | 16 (100) | |
| 53 | 10 | 8 (80.0) | 10 (100) | 10 (100) | |
| 39 | 9 | 9 (100) | 9 (100) | 9 (100) | |
| 33 | 6 | 3 (75) | 3 (75) | 4 (100) | One lost; One with positive HPV merged with HPV59. |
| 56 | 5 | 5 (100) | 5 (100) | 5 (100) | |
| 66 | 5 | 5 (100) | 5 (100) | 5 (100) | |
| 68 | 5 | 5 (100) | 5 (100) | 5 (100) | Two merged with HPV16 and remained positive. Lost, while Others all negative. |
| 31 | 2 | 2 (100) | 2 (100) | 2 (100) | |
| 51 | 2 | 1 (50) | 2 (100) | 2 (100) | One with positive HPV at 6-months merged with HPV52. |
| 59 | 2 | 1 (50) | 1 (50) | 2 (100) | |
| CP8304 | 2 | 2 (100) | 2 (100) | 2 (100) | |
| 45 | 1 | 1 (100) | 1 (100) | 1 (100) | |

subgroups showed a statistically significant difference ($P<0.01$). The HR-HPV regression rate between the 2 subgroups at at 6, 9 and 12 months follow-up showed statistically difference ($P<0.01$). Thus, it was indicated that paiteling reversed HR-HPV infection and promoted regression of lesion. Currently, reports associated with the efficacy of paiteling in the treatment of HR-HPV were limited. Furthermore, there are no serious adverse reactions during or after the treatment course. Therefore, paiteling is a safe and effective for treating cervical HR-HPV infection.

Today, various conization procedures including the LEEP have been accepted as gold standards for treatment of CIN [15, 16]. However, existing reports showed a great variation the surgical extent and reported recurrence rates (up to 30%) [17, 18]. Alnoso et al. reported 35.3% and 27.1% of HPV test were still positive after treatment with the LEEP at 6 and 12 months respectively [19]. Kim et al. found that persistent HPV infections were detected in 45.6%, 14.3%, 6.3%, 2.2%, 1.5% and 1.1% at 3, 6, 9, 12, 18 and 24 months after LEEP, respectively. And some patients had recurrent disease revealed by biopsy [20]. Furthermore, the positive margin of LEEP specimen was a significant risk residual or recurrent disease after LEEP [21]. Therefore, HPV test during follow-up can offer timely information about recurrent disease and help for the risk control [21, 22]. Our finding of significant increased rate of negative conversion of LEEP group with paiteling indicated that paiteling could eliminate HR-HPV infection after the LEEP. In contrast, our results showed no significant difference in HR-HPV regression rate between two subgroups after LEEP, this may be due to complete clearance of HR-HPV infection and low viral loads after the LEEP treatment, which limited the efficacy of paiteling in eliminating cervical infection and allowed more time for infections to recur. Therefore, long-term follow-up time should be considered in our further study.

Although the trial design is very interesting, this study has several limitations and the following limitations must be acknowledged: whether the negative conversion of HR-HPV correlated with stage, HPV type was not determined yet. The study population was small, and the follow-up duration was short, comparisons between HR-HPV types and viral load are lacking. Despite these limitations, this study was one of exploration of combination therapy by using Traditional Chinese medicine.

In present study, we investigated the efficacy of paiteling in eliminating HPV infection from cervix. Our results showed that paiteling in the treatment of HR-HPV was a safe and highly effective method.

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## Disclosure of conflict of interest

None.

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