

A Prospective Multi-Center Controlled Study of Gaoweikang (Chinese Multi-Herb Extracts Based Potion) On High-Risk HPV Infection

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Abstract

Objective: To investigate the safety and anti-viral efficacy of Chinese multi-herb extracts-based potion (GWK) on a population of high-risk human papilloma (hrHPV) infection and hrHPV caused cervical Low-grade Squamous Intraepithelial Lesion (LSIL).

Methods: Patients with persistent hrHPV infection were enrolled in-group A including A1 received intervention and A2 as control. Patients with hrHPV infection caused cervical LSIL were enrolled in-group B which including B1 received intervention and B2 as control. For group A1 and B1, hrHPV were tested at 3 months (M3) and 6 months (M6) after intervention. The side effects were also analyzed.

Results: At baseline (D0), a total of 99 cases were enrolled in group A, with 50 cases in group A1 and 49 cases in group A2. A total of 91 cases were enrolled in group B, with 45 cases in group B1 and 46 cases in group B2. There was no significant difference in the characteristic including average age, age stratification, HPV genotype. At M6, both group A1 and group B1 had a higher hrHPV clearance rate than the control group respectively (A1/A2:80.0%VS20.4%; B1/B2:64.4%VS 15.2%, $P<0.001$). At M6, the effective rate of group A1 and group B1 were 84% (42/50) and 68.9% (31/45) respectively. The side effect rate of group A1 and B1 is 11.5% (6/52) and 11.1% (5/45). Most of adverse reaction were local discomfort including vulvar erythema, vulvar itch, vaginal increased discharge, cervical bleeding and mild pain of lower abdomen. Univariate logistic regression analysis showed that intervention had a OR of 12 (95% CI 4.431-32.50) to clear persistent HPV infection ($P<0.001$). For the cervical LSIL, the intervention had a OR of 10.1 to clear persistent HPV infection (95% CI 3.68-27.7) ($P<0.001$).

Conclusions: The results of this study suggest that Chinese multi-herb extracts-based potion (GWK) is safe and well tolerated. Furthermore, this preliminary study showed that Chinese multi-herb extracts-based potion is helpful for promoting HPV clearance for persistent HPV and HPV caused LSIL.

Keywords: high-risk human papilloma, persistent infection, Low-grade Squamous Intraepithelial Lesion (LSIL), HPV clearance; Chinese multi-herb extracts.

Persistent high risk human papillomavirus (hrHPV) is considered as a necessary cause for the development of cervical precancerous and cancer, as well as several other anogenital precancers and cancers including vulval, vaginal, penile, anal precancers and cancers [1]. The worldwide prevalence of HPV infection in women is 11-12% with higher rates in sub-Saharan Africa (24%), Eastern Europe (21%) [1]. this number will decrease with the widely application of HPV prophylactic vaccine [2-3]. For most people, HPV infections are usually subclinical, self-limiting and transient. A large double-blind, randomized controlled PATRICIA trial showed a natural clearance of 53%, 79%, 87% and 89% of all HPV infections at 12, 24, 36 and 48 months, respectively[4]. Thus, for the women with persistent HPV infection, especially with risk factor including immunosuppression and tobacco exposure, it tend to develop squamous intraepithelial lesion including low grade squamous intraepithelial lesion (LSIL), high grade squamous intraepithelial lesion(HSIL) and adenocarcinoma in situ(AIS). Both HSIL and AIS were regarded, as the precancerous lesion, which mostly need to be removed by cervical conization and regular follow up [5-6]. But for the persistent HPV infection and LSIL, there, is few active treatments or interventions in our clinical practice. Some literatures have reported that interferon or Carrageenan (CG), a sulfated polysaccharide compound extracted from red algae can contribute to the clearance of HPV infection [7-10], and the research on therapeutic vaccine is also in the ascendant [11]. Although the effect of the above on HPV has not been recognized and popularized on a large scale, both clinical and basic research and enthusiasm for the effective intervention to clear HPV have never stopped. In this study, we aimed to assess safety and efficacy of a Chinese multi-herb extracts-based potion (GWK), which was used to eliminate condyloma the caused by low-risk HPV infection, on the persistent hrHPV infection and hrHPV caused LSIL. We recorded the rate of clearance of HPV genital infection after the treatment, comparing these data with the HPV genital infection clearance rate in the control group which didn't subject to any therapy.

1. Materials and Methods

1.1 Patients and Procedure

This multi-center prospective controlled study was conducted 8 Hospitals (5 specialized gynecology and obstetrics hospitals and 3 general hospitals) of Shanghai in China from January 2021 to December 2021. This study was approved by the Institutional Review Board of the Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China. The inclusion criteria of group A were as follows: (1) 25-50 years old, (2) with Hr-HPV infection persisted > 6 months, (3) with no lesions in the colposcopy guided biopsy.

The inclusion criteria of group B were as follows: (1) 25-50 years old, (2) with hrHPV infection, (3) with cervical LSIL and without any other lesion in the colposcopy guided biopsy.

The exclusion criteria of group A and B were as follows:(1) any suspicion of cervical HSIL and more serious lesions in the cytology or colposcopy impression or colposcopy guided biopsy. (2) patients with vaginal or vulvar intraepithelial lesions. (3) those who have severe immune dysfunction or need long-term use of glucocorticoids and immunosuppressants. (4) Patients with severe liver or kidney or another dysfunction.

At the basetime(D0), all participants signed informed consent and were asked to take condoms during the whole sexual life. The flow chart was arranged as figure 1. Patients were divided into different groups according to patients' preference: Group A were persistent hrHPV infection without lesion including A1 received treatment of Gao Wei Kang (GWK), which is a kind of potion which include multi-Chinese herb extracts. (Kunbao biomedical Co., Ltd. Shanxi, China) and A2 (control: didn't receive any intervention). Group B were hrHPV infection with cervical LSIL including B1 received treatment of GWK and B2 (control: didn't receive any intervention).

1.2 The intervention of Chinese multi-herb extracts

Group A1:

Dilute 1ml GWK with 9ml purified water and put it into the vagina with hip raised so that the potion can fully reach the cervix and vagina for 20 minutes. Use it once per day for 10 days, which was considered to be one course. Then the intervals were 3 days with seabuckthorn oil were applied to promote repair. Then repeat the above for 6 courses. If it encounters menstrual period during intervention, the intervention would be postponed.

Group B1:

1 ml of the original GWK potion was poured on a cotton strip with tail line and put 1.5-2 cm into the cervical canal. 3-4 ml of the original GWK potion was poured on the cotton ball, which was specially made with hollow inside. This cotton ball was put on the cervix surface. 3 hours later, the cotton strip and cervical cotton ball would be removed by pulling the tail line. 3 days of intervention and 4 days of interval was considered one course. Then repeat the above for 6 courses. If it encounter menstrual period during intervention, the intervention would be postponed.

After 5 cycles

1.3 Follow up

During treatment, recording the adverse effect if there is any complaint. Post-treatment follow-up: the first follow up was arranged at 1-2 months after treatment (M4). Gynecological examination, hrHPV testing were performed for group A1 and B1. For all enrolled patients, LCT, hrHPV testing will be arranged at 6 months (M6) after treatment. For those who had HPV16 positive or HPV18 positive or with cytology ASCUS and above, colposcopy would be carried out.

For patients with multiple genotypes of HPV infection, if the HPV genotype decreases but does not completely turn negative, it is called HPV reduction. The effective rate = HPV clearance rate + HPV reduction rate.

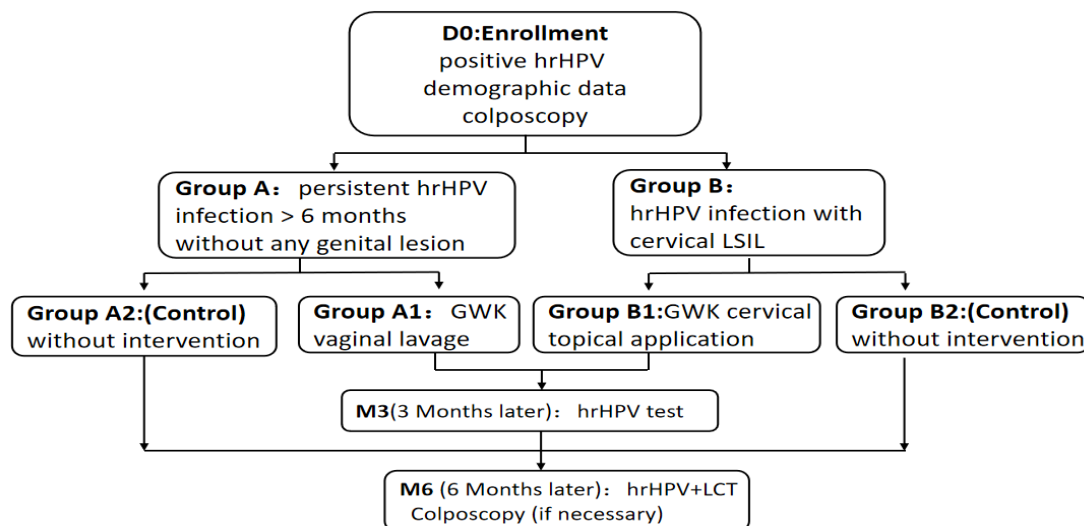


Figure 1: The flow chart of this study.

1.4 Statistical methods:

The Skewness and Kurtosis tests were used to assess the normality of the distribution of quantitative variables. Normally distributed quantitative variables were summarized as mean ± (standard deviation). The association of normally distributed quantitative variables (age) was evaluated with the student’s t-test. The clearance of HPV infection (expressed as percentage (%)) and the distribution of HPV genotype were compared with X² test. Univariate logistic analysis model was used to analyse intervention efficacy. All collected data were analysed using Stata 17.0 (Stata Corp, College Station, TX).

2. Results

2.1 General Parameters

At baseline (D0), a total of 102 cases were enrolled in-group A, with 52 cases in group A1 and 50 cases in group A2. 38 cases of group A1 had the HPV infection longer than 12 months. 25 cases had HPV infection longer than 24 months. A total of 93 cases were enrolled in group B, with 45 cases in group B1 and 48 cases in group B2. Characteristic of enrolled cases are described in table1. There were 2 cases in group A1 dropping out of this study because of adverse advent. 1 case in group A2 and 2 case in group B2 lost follow up. The follow up rate of all cases were 97.4% (190/195). Compare

A1 with A2 groups, B1 with B2 groups, there was no significant difference in average age, age stratification, HPV genotype, tobacco exposure.

At M6, there were 8 cases in-group A1 was transferred to colposcopy. The proportion of referral colposcopy was significantly lower than that in the control group (16.0% VS 51.0%, P<0.001).

At M6, there were 25 cases in-group B1 didn’t undergo colposcopy. For the other 20 cases, there were 14 cases whose histology was cervical LSIL, 2 cases with vaginal LSIL, 3 cases with no lesion and 1 case progressed to cervical HSIL.

At M3, 36 cases of group A1 turned HPV negative (72%, 36/50) and 26 cases of group B1 turned HPV negative (57.8%, 26/45). At M6, 40 cases of group A1 turned HPV negative (80%, 40/50) and 29 cases of group B1 turned HPV negative (64.4%, 29/45). Both group A1 and group B1 had a higher HPV clearance rate than the respectively control group (A1/A2:80.0%VS20.4%; B1/B2:64.4%VS 15.2%, both P<0.001). At M6, there were 2 cases in group A1 and 2 cases in group B1 got alleviated. So, the effective rate of group A1 and group B1 were 84.0% (42/50) and 68.9% (31/45) respectively.

Table 1: Characteristic of study population of intervention and control groups.

| Variable | A1(HPVI) | A2(control) | P _{A1-A2} | B1(LSIL) | B2(control) | P _{B1-B2} |
|------------------------------|----------|-------------|--------------------|----------|-------------|--------------------|
| No. | 50 | 49 | | 45 | 46 | |
| Age(X±SD) | 37.5±7.0 | 35.4±8.5 | 0.182 | 35.0±7.9 | 37.9±8.2 | 0.090 |
| 25-30(n) | 6 | 11 | 0.355 | 11 | 15 | 0.650 |
| 31-40(n) | 27 | 25 | | 19 | 16 | |
| 41-50(n) | 17 | 13 | | 15 | 15 | |
| T0:HPV16+ (n, %) | 16 | 12 | 0.602 | 12 | 9 | 0.685 |
| T0:HPV18+ (n, %) | 6 | 4 | | 5 | 4 | |
| T0: Other hrHPV+ (n, %) | 34 | 37 | | 35 | 39 | |
| Tabacco exposure (n, %) | 3 | 6 | 0.233 | 1 | 4 | 0.181 |
| Having sexual partner (n, %) | 38 | 44 | 0.093 | 34 | 40 | 0.188 |

Table 2: The HPV clearance rate of intervention and control groups.

| Variables | A1(HPVI) n=50 | A2(control) n=49 | P _{A1-A2} | B1(LSIL) n=45 | B2(control) n=46 | P _{B1-B2} |
|-------------------------|------------------|---------------------|--------------------|------------------|---------------------|--------------------|
| M3: hrHPV- | 36 | - | | 26 | - | |
| M3: hrHPV+ | 14 | - | | 19 | - | |
| M3:HPV16+ (n, %) | 4 | - | | 9 | - | |
| M3:HPV18+ (n, %) | 5 | - | | 4 | - | |
| M3: other hrHPV+ (n, %) | 5 | - | | 11 | - | |
| M3: HrHPV clearance (%) | 72.0% | - | | 57.8% | - | |
| M6: hrHPV- | 40 | 10 | | 29 | 7 | |
| M6: hrHPV+ | 10 | 39 | | 16 | 39 | |
| M6:HPV16+ (n, %) | 3 | 11 | 0.538 | 8 | 7 | 0.210 |
| M6:HPV18+ (n, %) | 3 | 4 | | 3 | 4 | |
| M6: other hrHPV+ (n, %) | 8 | 25 | | 11 | 28 | |
| M6: hrHPV clearance (%) | 80.0% | 25.6% | <0.001 | 64.4% | 15.2% | <0.001 |
| M6: colposcopy (n, %) | 8(16.0%) | 25(51.0%) | <0.001 | 20(44.4%) | 27(58.7%) | 0.125 |
| M6: Histology | | | 0.737 | | | 0.359 |
| No lesion | 6 | 20 | | 3 | 7 | |
| LSIL or VaIN | 2 | 4 | | 16 | 20 | |
| HSIL | 0 | 1 | | 1 | 0 | |

Considering the genotype of HPV infection clearance, in group A1, 13 cases with HPV16 infection, 3 cases with HPV18 infection and 26 cases with other hrHPV infection were negative at M6. In group B1, 4 cases with HPV16 infection, 2 cases with HPV18 infection and 24 cases with other hrHPV infection were negative at M6.

For the side effect, one drop out of group A1 because of vulvar erythema and vulvar itch; the other one drop out of group A1 because mild pain in the whole body. Besides these 2 cases, there were 4 cases in group A1 complained of vaginal increased discharge and vaginal discomfort, but these symptoms can be relieved by themselves, and do not

affect the completion of intervention. So, the side effect rate of group A1 is 11.5% (6/52)

In-group B2, there were 2 cases had cervical bleeding, 2 cases had vaginal increased discharge and 1 case had mild pain of lower abdomen bleeding. So, the side effect rate of group B1 is 11.1% (5/45).

Univariate logistic regression analysis showed that intervention had a OR of 12(95% CI 4.431-32.50) to clear HPV persistent infection (P<0.001) in group A1. In particular, for the cervical LSIL, the intervention had a OR of 10.1 (95% CI 3.68-27.7) (P<0.001).

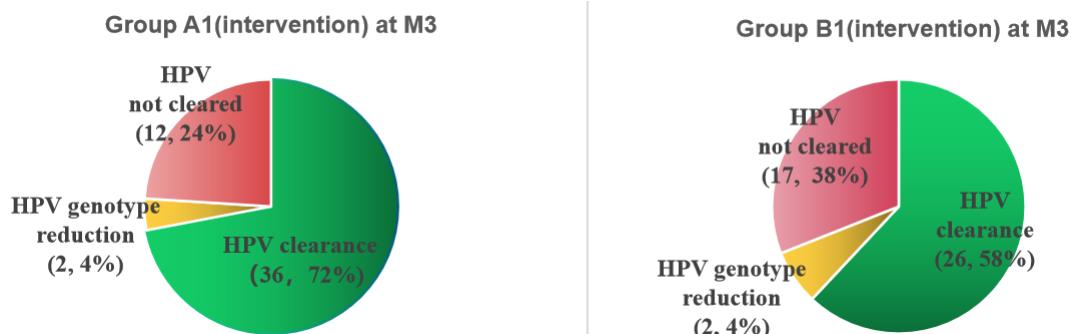


Figure 2: HPV infection clearance 3 months after intervention in persistent HPV infection (left) and LSIL (right).

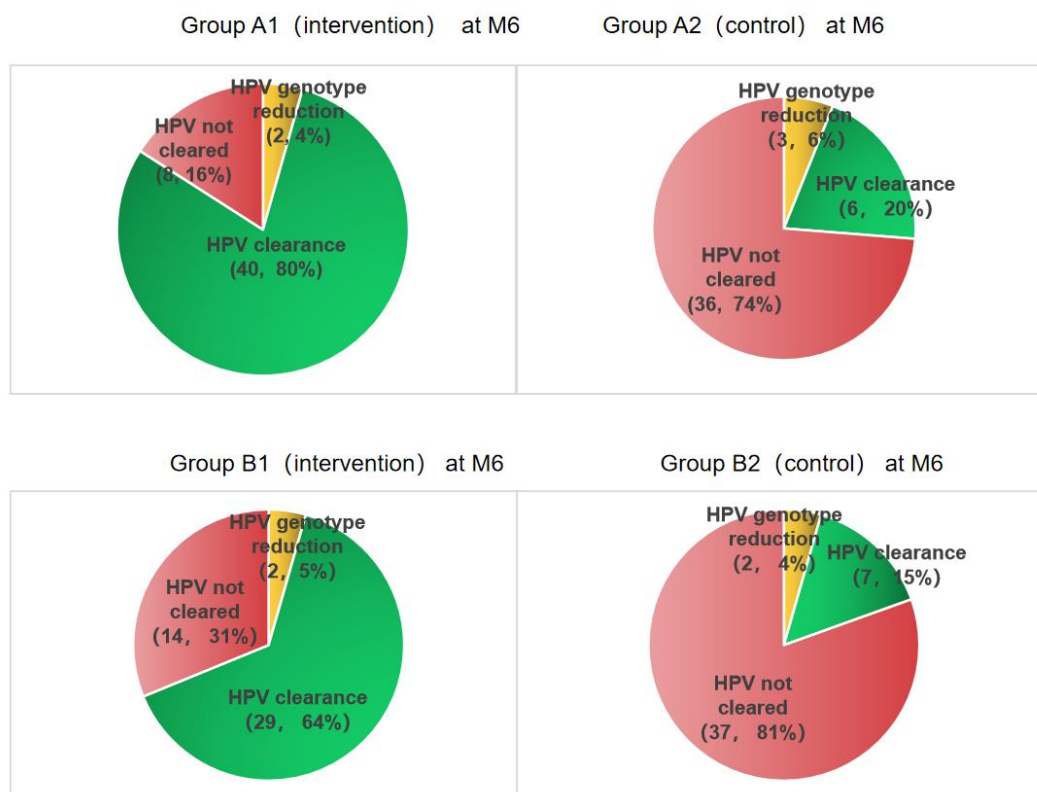


Figure 3: HPV infection clearance 6 months after intervention in persistent HPV infection (upper left) and LSIL (lower left) and the control groups (right).

3. Discussion

3.1 The current clinical management of hrHPV infection

In May 2018, the World Health Organization (WHO) put forward the global call for action to eliminate cervical cancer, which was responded by most countries in the world [12]. Besides the HPV vaccination in the young girl, cervical screening is In addition to HPV vaccination, cervical cancer screening is ultimate important for the elimination of cervical cancer. In 2019, ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors suggest that the management should base on the the immediate CIN3+ risk [13].

If this risk is 4% or greater, immediate management via colposcopy or treatment is indicated. If the immediate risk is less than 4%, regular follow up is recommended. Although CIN3 is the optimum screening target for the current cervical screening, for women without CIN3 + but with hrHPV infection, how to actively eliminate HPV is both the doctors and patients' most concerned problem. Although it was reported that 60-90% of HPV infections resolve spontaneously within one or two years, many women with HPV infection, especially those with persistent HPV infection, have varying degrees of psychological anxiety and affect their quality of life, especially sexual life [14-15]. Chronic worrying is also considered to related to the presence of hrHPV infection and may thus play a role in HPV associated cervical carcinogenesis [16].

Therefore, in addition to the routine education including recommending the use of condoms, improve immunity [17], looking for effective methods to eliminate HPV has become

a primary goal of worldwide research in the recent decade. The current available HPV vaccines are mainly used to prevent HPV infection, while therapeutic vaccines are expected to make a breakthrough in eliminating HPV. Nevertheless, the research about therapeutic vaccines still going on without satisfied result. Moreover, the current therapeutic vaccine is only for HPV16 18 without targeted for other hrHPV. In addition to vaccines, there were some researches reporting that interferon or Carrageenan (CG), a sulfated polysaccharide compound extracted from red algae can contribute to the clearance of HPV infection.

3.2 Chinese herb extracts made vaginal microbicide's possible role in HPV infection

In this study, we found Chinese multi-herb extracts-based potion (GWK) had an excellent effect on patients with persistent HPV infection with the HPV clearance rate of 72% at 3 months and 80% at 6 months. It also had obvious therapeutic effect on LSIL caused by HPV infection. Although the control group without any intervention also had a certain possibility of self-regression, the HPV clearance is much lower than that of the intervention group. Such an extraordinary efficacy is a huge surprise for us and beyond our expectation. The efficacy is not only much higher than our control group, but also higher than 57.7%- 64.3% of Carrageenan in the published report [9]. The intervention of this study had a OR of 10-12, which is also higher than 4.9 of Carrageenan [9].

GWK was used to eliminate the condyloma, which was caused by low-risk HPV infection. The mechanism of GWK is not completely clear. The action theroey of traditional Chinese medicine is completely different from the Western medicine mode [18]. Traditional Chinese medicine pays

more attention to the overall and macro role than the molecular and cellular level [19]. The Chinese multi-herb extracts we used in this study is prepared from nine traditional Chinese medicines, including java brucea, fritillaria thunbergia (FT), scutellaria barbata, sophora flavescens, arnebia, radix isatidis, radix scutellariae and saponin thorn. This formula is based on the theory of traditional Chinese medicine, playing the role of several main drugs, and highlighting the synergy of various traditional Chinese medicines. The overall function of this prescription in traditional Chinese medicine is anti-virus, anti-tumor, corrode, clear away toxin, resist bacteria, anti-inflammation and dispel dampness.

Java brucea and *Fritillaria thunbergii* were considered to be the main effective component. In recent years, Chinese scholars have also done research on the mechanism of action of traditional Chinese medicine from the perspective of molecular mechanism. Java brucea, which was recently reported to be able to induce apoptosis and had selective cytotoxicities [20-21] is one of the main ingredients of this prescription. FT extracts was reported to exert antiviral effects in vitro, in vivo and in ovo [22-23]. We speculate besides these two main ingredients, the function of the whole formula may be related to antiviral and immune regulation, but the specific mechanism needs further basic and clinical research.

In terms of safety, we found that about 11% had local adverse reactions, and they are not serious. Generally, the adverse reaction can relieve by themselves. These local adverse reactions are somewhat similar to imiquimod [24], but the symptoms are lighter than imiquimod. Most patients can tolerate it except 2 drop out of this study. No serious adverse reactions were found in this study. Therefore, we believe that the product is relatively safe.

There are some limitations in this study, including the limited number of cases included and non-randomized group. Although the follow-up effect of half a year shows that Chinese multi-herb extracts-based potion (GWK) is safe and effective, the longer-term effect and its internal mechanism needs further research.

Conclusion

In conclusion, this study found that Chinese multi-herb extracts-based potion (GWK) is safe and well tolerated. Our preliminary study showed that Chinese multi-herb extracts-based potion (GWK) is helpful for promoting HPV clearance and treating HPV caused LSIL.

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