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A prospective multicentre controlled study of Gaoweikang (Chinese multiherb extract-based tincture) used in high-risk HPV infections

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Abstract. – OBJECTIVE: The aim of the study was to investigate the safety and antiviral efficacy of a Chinese multiherb extract-based tincture (GWK) on a population of patients with high-risk human papilloma (hrHPV) infections and hrHPV-caused cervical low-grade squamous intraepithelial lesions (LSILs).

PATIENTS AND METHODS: Patients with persistent hrHPV infection were enrolled in Group A, including A1 subjects, who received the intervention, and A2 subjects, who received the control. Patients with hrHPV infection causing cervical LSIL were enrolled in Group B, which included B1 subjects, who received the intervention, and B2 subjects, who served as the control. For Groups A1 and B1, hrHPV was tested at 3 months (M3) and 6 months (M6) after the intervention. The side effects were also analyzed.

RESULTS: At baseline (D0), a total of 99 patients were enrolled in Group A, with 50 subjects in Group A1 and 49 subjects in Group A2. A total of 91 patients were enrolled in Group B, with 45 subjects in Group B1 and 46 subjects in Group B2. There was no significant difference in the characteristics, including average age, age stratification, and HPV genotype. At M6, both Group A1 and Group B1 had a higher hrHPV clearance rate than the control group (A1/A2: 80.0% *vs.* 20.4%; B1/B2: 64.4% *vs.* 15.2%, $p<0.001$). At M6, the effective rates of Group A1 and Group B1 were 84% (42/50) and 68.9% (31/45), respectively. The side effect rates of Groups A1 and B1 were 11.5% (6/52) and 11.1% (5/45), respectively. Most adverse reactions involved local discomfort, including vulvar erythema, vulvar itch, increased vaginal discharge, cervical bleeding, and mild pain in the lower abdomen. Univariate logistic regression analysis showed that the intervention had an OR of 12 (95% CI 4.431-32.50) for clearing persistent HPV infection ($p<0.001$). For cervical LSIL, the intervention had an OR of 10.1 for clearing persistent HPV infection (95% CI 3.68-27.7) ($p<0.001$).

CONCLUSIONS: The results of this study suggest that the Chinese multiherb extract-based tincture GWK is safe and well tolerated. Furthermore, this preliminary study showed that this Chinese multiherb extract-based tincture is helpful for promoting HPV clearance in cases of persistent HPV and HPV-induced LSIL.

Key Words:
High-risk human papilloma, Persistent infection, Low-grade squamous intraepithelial lesion (LSIL), HPV clearance, Chinese multiherb extracts.

Introduction

Persistent high-risk human papillomavirus (hrHPV) is considered a necessary cause for the development of cervical precancerous lesions and cancer, as well as several other anogenital precancers and cancers, including vulval, vaginal, penile, anal precancers and cancers1. The worldwide prevalence of HPV infection in women is 11-12%, with higher rates in sub-Saharan Africa (24%) and Eastern Europe (21%)[1]. This number

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will decrease with the wide application of HPV prophylactic vaccines[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, women with persistent HPV infection, especially with risk factors including immunosuppression and tobacco exposure, tend to develop squamous intraepithelial lesions, including low-grade squamous intraepithelial lesions (LSILs), high-grade squamous intraepithelial lesions (HSILs) and adenocarcinoma in situ (AIS). Both HSIL and AIS are regarded as precancerous lesions that mostly need to be removed by cervical conization and regular follow-up[5,6]. However, for persistent HPV infection and LSIL, there are few active treatments or interventions in our clinical practice. Some studies 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 research on therapeutic vaccines is also increasing[11]. Although the effect of the above treatment on HPV has not been recognized and popularized on a large scale, both clinical and basic research and enthusiasm for effective interventions to clear HPV have never stopped. In this study, we aimed to assess the safety and efficacy of a Chinese multiherb extract-based treatment (GWK), which was used to eliminate condyloma caused by low-risk HPV infection on persistent hrHPV infection and hrHPV-induced 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 was not subject to any therapy.

Materials and Methods

Patients and Procedure

This multicentre prospective controlled study was conducted at 8 hospitals (5 specialized gynecology and obstetrics hospitals and 3 general hospitals) in Shanghai, China, from January 2021 to December 2021. This study was approved by the Institutional Review Board of the Obstetrics and Gynaecology Hospital of Fudan University, Shanghai, China.

The inclusion criteria of Group A were as follows: (1) 25-50 years old, (2) Hr-HPV infection persisting > 6 months, and (3) no lesions on colposcopy-guided biopsy.

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

The exclusion criteria of Groups A and B were as follows: (1) any suspicion of cervical HSIL and more serious lesions in 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 other dysfunction.

At baseline (D0), all participants signed informed consent forms and were asked to use condoms during all sexual activities. The flow chart is shown in Figure 1. Patients were divided into different groups according to the patients' preferences. Group A had persistent hrHPV infection without lesions; this group included A1 subjects who received treatment with Gao Wei Kang (GWK), which is a kind of tincture that includes multi-Chinese herb extracts (Feitan Biomedical Co., Ltd., Shanxi, China) and A2 subjects (control), who did not receive any intervention. Group B had hrHPV infection with cervical LSIL; this group included B1 subjects, who received GWK treatment, and B2 subjects (control), who did not receive any intervention.

The Intervention of Chinese Multiherb Extracts

Group A1

One milliliter of GWK was diluted with 9 ml of purified water and placed into the vagina with the hips raised so that the tincture could fully cover the cervix and vagina for 20 minutes. The solution was used once per day for 10 days, which was considered to be one course. Then, sea buckthorn oil was applied at intervals of 3 days to promote repair. The above treatment was repeated for 6 courses. If the patient encountered a menstrual period during the intervention, the intervention was postponed.

Group B1

One milliliter of the original GWK tincture was poured on a cotton strip with a tail line and placed 1.5-2 cm into the cervical canal. Three to four milliliters of the original GWK tincture were poured into the cotton ball, which was specially made with a hollow inside. This cotton ball was placed on the cervix surface. Three hours later, the cotton strip

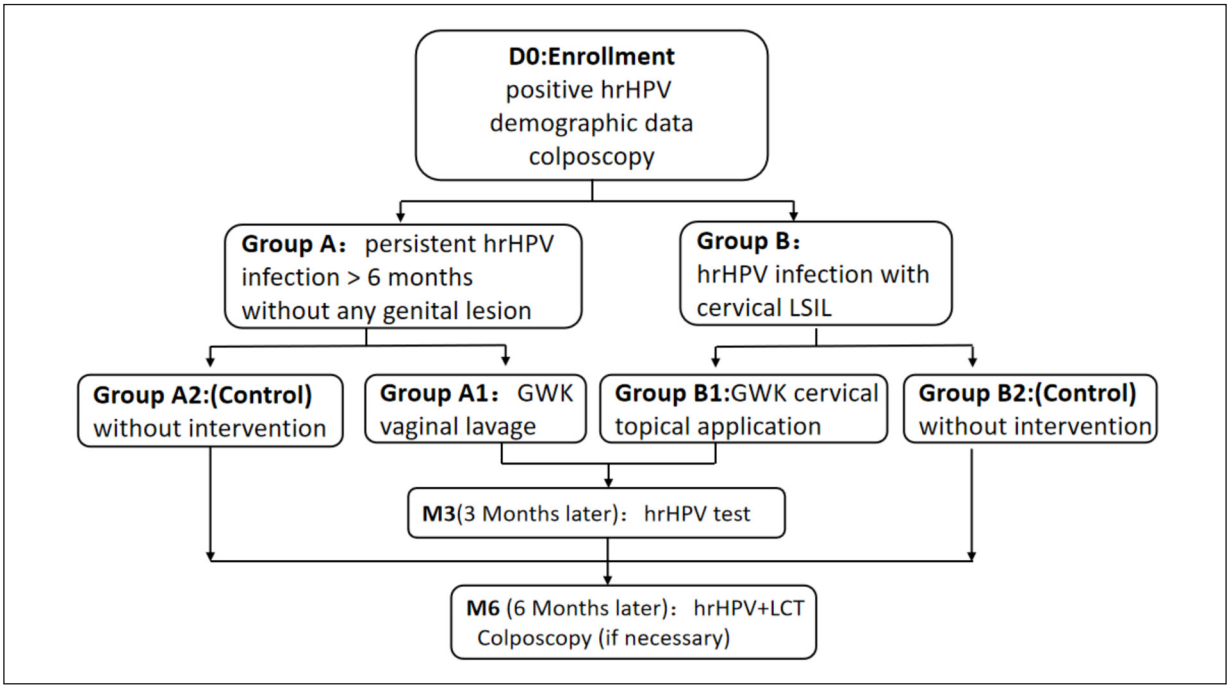

Figure 1. The flow chart of this study.

and cervical cotton ball were removed by pulling the tail line. Three days of intervention and a 4-day interval were considered to be one course. The above treatment was repeated for 6 courses. If the patient encountered a menstrual period during the intervention, the intervention was postponed.

During treatment, adverse effects were recorded if there was any complaint. Posttreatment follow-up: The first follow-up was arranged at 1-2 months after treatment (M4). Gynecological examination and hrHPV testing were performed for Groups A1 and B1. For all enrolled patients, LCT and hrHPV testing were arranged at 6 months (M6) after treatment. For those who were HPV16 positive or HPV18 positive or had cytology ratings of ASCUS and above, colposcopy was carried out.

For patients with multiple genotypes of HPV infection, if the HPV genotype decreased but did not completely turn negative, this status was called HPV reduction. The effective rate = HPV clearance rate + HPV reduction rate.

Statistical Analysis

The skewness and kurtosis tests were used to assess the normality of the distribution of quantitative variables. Normally distributed quantitative variables were summarized as the mean ± standard deviation. The association of normally distributed quantitative variables (age) was evaluated with Student's *t*-test. The clearance of HPV infection [expressed as percentage (%)] and the distribution of HPV genotypes were compared with the x2 test. A univariate logistic analysis model was used to analyze intervention efficacy. All collected data were analyzed using Stata 17.0 (Stata Corp, College Station, TX, USA).

Results

General Parameters

At baseline (D0), a total of 102 patients were enrolled in Group A, with 52 subjects in Group A1 and 50 subjects in Group A2. Thirty-eight patients in Group A1 had HPV infections longer than 12 months. Twenty-five patients had HPV infections longer than 24 months. A total of 93 patients were enrolled in Group B, with 45 subjects in Group B1 and 48 subjects in Group B2. The characteristics of the enrolled patients are described in Table I. Two patients in Group A1 dropped out of this study because of adverse events. One patient in Group A2 and 2 patients in Group B2 were lost to follow-up. The follow-up rate of all cases was 97.4% (190/195). Comparing the A1 and A2 groups and the B1 and B2 groups, there was no significant difference in average age, age stratification, HPV genotype, or tobacco exposure.

At M6, 8 patients in Group A1 were transferred for colposcopy. The proportion of referral

Table I. 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

colposcopy was significantly lower than that in the control group (16.0% *vs.* 51.0%, $p<0.001$).

At M6, 25 patients in Group B1 did not 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 that progressed to cervical HSIL.

At M3, 36 cases in Group A1 were HPV negative (72%, 36/50), and 26 cases in Group B1 were HPV negative (57.8%, 26/45). At M6, 40 cases in Group A1 were HPV negative (80%, 40/50), and 29 cases in Group B1 were HPV negative (64.4%, 29/45). Both Group A1 and Group B1 had a higher HPV clearance rate than the respective control groups (A1/A2: 80.0% *vs.* 20.4%; B1/B2: 64.4% *vs.* 15.2%, both $p<0.001$). At M6, 2 cases in Group A1 and 2 cases in Group B1 were alleviated. Therefore, the effective rates of Group A1 and Group B1 were 84.0% (42/50) and 68.9% (31/45), respectively (Table II).

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 infections were negative at M6. In Group B1, 4 cases with HPV16 infection, 2 cases with HPV18 infection and 24 cases with other hrHPV infections were negative at M6.

Regarding side effects, one patient dropped out of Group A1 because of vulvar erythema and vulvar itch, and the other dropped out of Group A1 because of mild pain in the whole body. In addition to these 2 cases, 4 cases in Group A1 complained of increased vaginal discharge and vaginal discomfort, but these symptoms could be relieved by themselves and did not affect the completion of the in-

Table II. The HPV clearance rate of intervention and control groups.

Variable	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	

tervention. Therefore, the side effect rate of Group A1 was 11.5% (6/52).

In Group B2, 2 patients had cervical bleeding, 2 patients had increased vaginal discharge, and 1 patient had mild pain with lower abdomen bleeding. Therefore, the side effect rate of Group B1 was 11.1% (5/45).

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

Discussion

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[12]. In addition to HPV vaccination in young girls, cervical cancer screening is ultimately important for the elimination of cervical cancer. In 2019, ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors suggested that management should be based on 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 current cervical screening, for women without CIN3+ but with hrHPV infection, how to actively eliminate HPV is both the doctors' and patients' most concerning 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 various degrees of psychological anxiety that affect their quality of life, especially their sexual life[14-16]. Chronic worrying is also considered to be related to the presence of hrHPV infection and may thus play a role in HPV-associated cervical carcinogenesis[17]. Therefore, in addition to routine education, including recommending the use of condoms and improving immunity[18], looking for effective methods to eliminate HPV has become a primary goal of worldwide research in the last decade. The currently available HPV vaccines are mainly used to prevent HPV infection, while therapeutic vaccines are expected to lead to a breakthrough in eliminating HPV. Nevertheless, research on therapeutic vaccines is still ongoing without satisfactory results. Moreover, the current therapeutic vaccine is only for HPV16 and 18 without targeting other hrHPV. In addition to vaccines, some studies have reported that interferon or carrageenan (CG), a sulfated polysaccharide compound extracted from red algae, can contribute to the clearance of HPV infection.

Chinese Herb Extracts Made Vaginal Microbicide's Possible Role in HPV Infection

In this study, we found that a Chinese multiherb extract-based tincture (GWK) had an excellent effect on patients with persistent HPV infection, with an HPV clearance rate of 72% at 3 months (Figure 1) and 80% at 6 months (Figure 2). It also had an evident therapeutic effect on LSIL caused by HPV infection. Although the control group without any intervention also had a certain possibility of self-regression, their HPV clearance was much lower than that of the intervention group. Such extraordinary efficacy is a great surprise for us and beyond our expectations. The efficacy was not only much higher than that in our control group but also higher than the 57.7%-64.3% efficacy of carrageenan in the published report[9]. The intervention of this study had an OR of 10-12, which was also higher than the 4.9 OR for carrageenan[9].

GWK was used to eliminate condyloma, which was caused by low-risk HPV infection. The mechanism of GWK is not completely clear. The theory of traditional Chinese medicine is completely different from that of Western medicine[19]. Traditional Chinese medicine pays more attention to the overall and macro roles than to the molecular and cellular levels[20]. The Chinese multiherb extracts we used in this study were prepared from nine traditional Chinese medicines, including *Java brucea, Fritillaria thunbergii (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 antiviral, antitumor, anti-inflammatory, and corrosive; it clears away toxins, resists bacteria, and dispels dampness. *Java brucea* and *Fritillaria thunbergii* were considered to be the main effective components. In recent years, Chinese scholars have also performed research on the molecular mechanism of action of traditional Chinese medicine. *Java brucea*, which was recently reported to be able to induce apoptosis

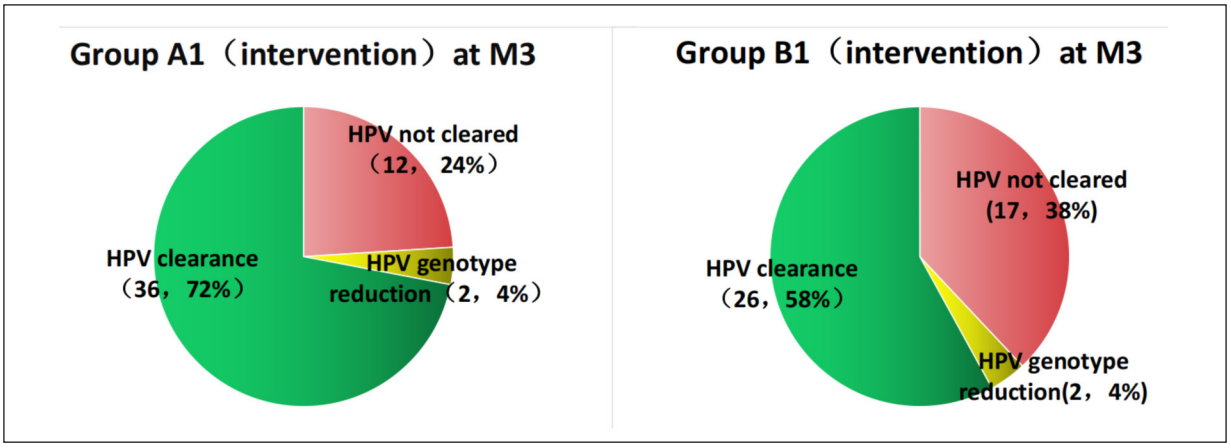

Figure 2. HPV infection clearance 3 months after intervention in persistent HPV infection (left) and LSIL (right).

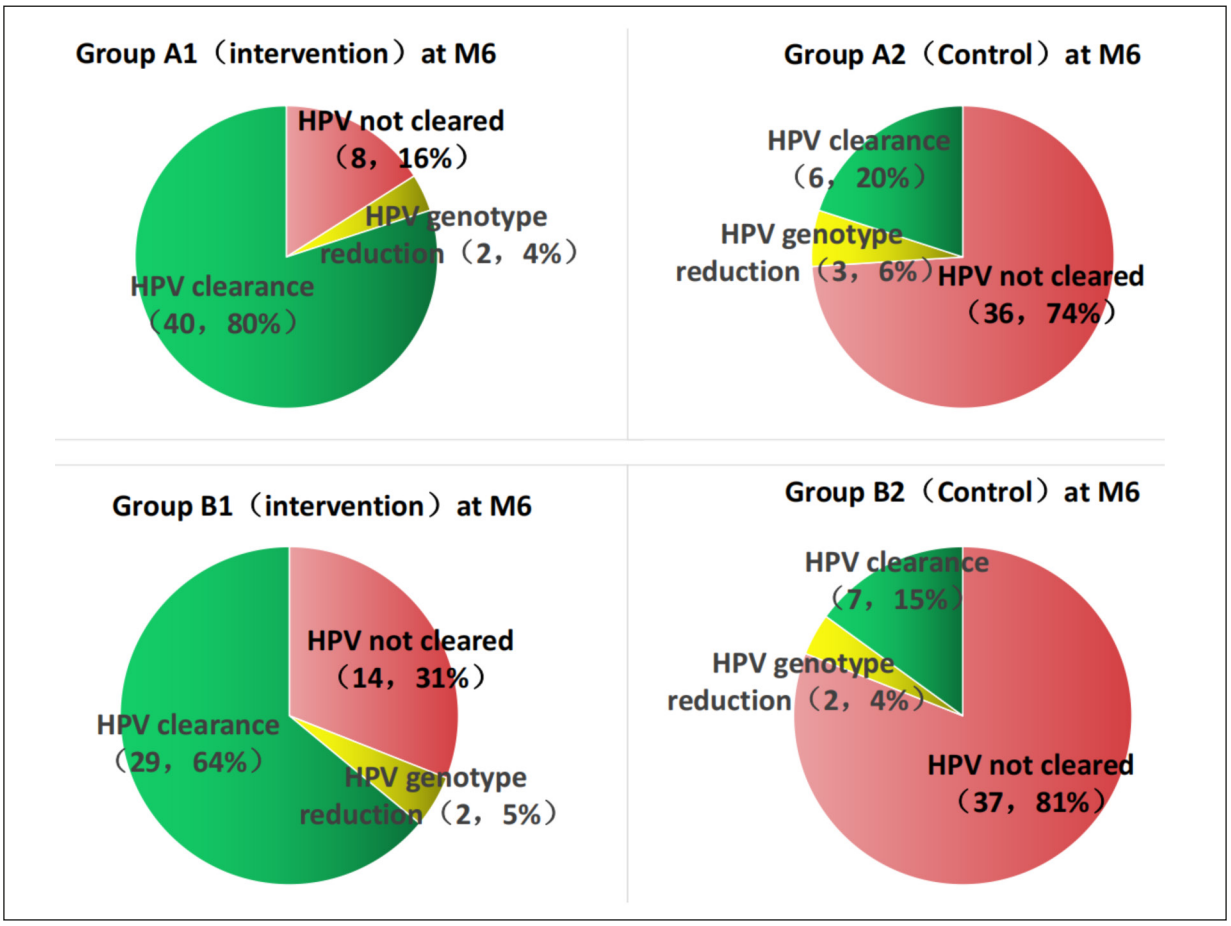

Figure 3. HPV infection clearance 6 months after intervention in persistent HPV infection (upper left) and LSIL (lower left) and the control groups (right).

and has selective cytotoxicities, is one of the main ingredients of this prescription[21,22]. FT extracts were reported to exert antiviral effects *in vitro, in vivo* and *in ovo*[23,24]. We speculate that in addition to 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 approximately 11% had local adverse reactions, which were

not serious. Generally, adverse reactions can be relieved by themselves. These local adverse reactions are somewhat similar to imiquimod[25], but the symptoms are lighter than those induced by imiquimod. Most patients could tolerate the treatment, except for 2 patients who dropped out of this study. No serious adverse reactions were found in this study. Therefore, we believe that the product is relatively safe.

Limitations

There are some limitations in this study, including the small number of cases included and the nonrandomized group. Although the follow-up effect of half a year shows that the Chinese multiherb extract-based tincture (GWK) is safe and effective, the longer-term effect and its internal mechanism need further research.

Conclusions

In conclusion, this study found that the Chinese multiherb extract-based tincture GWK is safe and well tolerated. Our preliminary study showed that GWK is helpful for promoting HPV clearance and treating HPV-induced LSIL.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

L.M. Chen and L. Sui designed the study, L.-M. Chen, Q. Cong, D. Wu, Y. Chen, L.-H. Qiu, Z.-B. Hong, Y.-B. Yang, L. Xu, L.-F Wang, L.-X. Huang, W.-R. Li, J.-P. Tang and Y.-G. Cao collected the data; L.M. Chen analyzed the data and wrote the manuscript. All authors read and approved the final manuscript.

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Ethics Approval

Ethics committee approval was granted by the Institutional Review Board of the Obstetrics and Gynaecology Hospital of Fudan University, Shanghai, China.

Informed Consent

An informed consent form was obtained from the patients before their participation in the study.

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