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Original Article

A clinical analysis of the outcome of microwave therapy in treating cervical HPV subclinical infection

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Abstract: Objective: This study aimed to investigate the effectiveness of microwave therapy in clearing HPV infection. Methods: A retrospective study was performed on 181 HPV subclinical infection patients who were admitted to the Third Affiliated Hospital of Sun Yat-sen University from April 2011 to July 2015. The patients were divided into a microwave therapy group and a control group according to the therapeutic method they had received. Age, gravidity (G), parity (P), squamocolumnar junction (SCJ) types, HPV types, and HPV clearance and removal time were analyzed. The outcome of microwave therapy, the natural laws of HPV infection spontaneous clearance, and the influencing factors of HPV clearance were studied. Results: Ultimately, 165 patients were included in the study, with 47 cases in the microwave therapy group and 118 cases in the control group. There were no statistically significant differences in the baseline characteristics, including age, gravidity times, parity times, HPV types, and SCJ. The HPV clearance rate of microwave group was significantly higher than the rate of the control group. The median HPV clearance time of the microwave group was significantly shorter than the clearance time of the control group. There were no significant differences in age for the HPV clearance rate and clearance time. No significant differences were found in the high-risk HPV and low-risk HPV patients for the HPV clearance rate and clearance time and no significant differences were found in the clearance rate and clearance time between the most common types of HPV. Conclusion: Microwave therapy is a safe and reliable treatment for cervical HPV subclinical infection, which can not only increase the clearance rate but also reduce the clearance time.

Keywords: Microwave therapy, cervix, HPV infection, clearance

Introduction

Cervical human papilloma virus (HPV) subclinical infection refers to the special state in which HPV has not been cleaned by the body or caused any clinical symptoms after infecting the cervix. According to Centers for Disease Control (CDC), the probability that women are infected with genital HPV is greater than 80% before the age of 50; however, the probability of genital warts and genital tract tumors is less than 5% [1], indicating that subclinical infection is far more common than the symptoms of infection. Subclinical infection is an intermediate process subsequent to infection, after which HPV in the body can be naturally removed. It stimulates the local formation of verrucous tissue or sustains the infection and leads to additional tumors according to the different infection types [2].

As the vast majority of HPV infections are transient, HPV and mild lesions can be self-cleared, and persistent HPV infection still lacks a specific treatment. Infection with oncogenic (or high-risk) HPV usually is a necessary but not sufficient factor for the development of squamous cervical neoplasia. Therefore, only a minority of women infected with high-risk HPV will develop significant cervical abnormalities and cancer [3]. To date, there are no guidelines for asymptomatic, high-risk HPV infection treatment [4]. Selectively local treatment has been suggested for the clinical manifestations of anal genital warts and low-grade intraepithelial neoplasia which is mainly for the clinical disease but not for the HPV virus itself [5]. Currently, the clinical HPV treatment method is divided into local drug therapy, immunotherapy, surgical treatment, and local physical therapy. Unfortunately, there is no satisfactory treat-

ment. Usually the therapeutic regimen depends on the clinical situation and the tendencies of the patient [6]. Although the effect of surgical treatment for HPV clearance is more satisfactory, it has several defects, including cumbersome steps, a higher cost, and a series of recent and long-term complications, such as cervical stenosis, cervical insufficiency, and premature birth. These risks are more serious than those caused by HPV infection [7]. The clinical application of physical therapy has been used for decades and developed into cryotherapy, laser ablation and microwave therapy. It has been reported that the rate of cryotherapy and laser treatment for HPV clearance has reached nearly 90% [8]. Microwave treatment is the latest type of invented physical therapy. Its uses electromagnetic radiation focused on tissue to produce heat, so that the tissue from the inside to the outside is instantly solidified, so the boundary of the damage parts is clear, the site is heated evenly, and the ability of the lesioned tissue to absorb microwaves is greater than that of normal tissue [9]. Therefore, microwave treatment can be considered a selective treatment, which is applied relatively widely. Unfortunately, there is no reliable treatment that removes HPV infection and inhibits its recurrence.

A clinical treatment for HPV infection which is simple, effective, safe, and easy for patients to accept will be quite meaningful for the prevention and treatment of cervical lesions and ease patient anxiety. In this study, a retrospective analysis of HPV subclinical infection patients was performed so as to unravel the clinical characteristics and curative effects of microwave treatment for HPV subclinical infection.

Materials and methods

Patients

A total of 181 patients who visited the Third Affiliated Hospital of Sun Yat-sen University from April 2011 to July 2015 were included in this study. They were all confirmed to have HPV subclinical infection through a gynecological clinic colposcopy. The inclusion criteria were as follows: HPV positive patients; patients who did not have cervical precancerous lesions and tumors; patients without a history of gynecological precancerous lesions and tumors; patients without previous cervical related treatment and surgery; patients with good compliance and regular follow-up. Patients with acute vaginitis, pregnant and lactating women, patients with acute or subacute inflammation, and patients with severe medical diseases such as cardiovascular or cerebrovascular diseases or diabetes were excluded. This study was approved by the ethics committee of the Third Affiliated Hospital of Sun Yat-sen University.

Grouping

The age, gravidity (G), parity (P), squamocolumnar junction (SCJ) type, HPV type, HPV positive time, treatment time, the first review time and results, and the second review time of each case were studied. According to the treatment, the patients were divided into the microwave treatment group and the control group.

As for the microwave treatment group, the patients were treated at the lithotomy position. Microwave therapy was performed from about 0.15 cm deep into the cervical canal outward to the cervical mouth with the whole squamocolumnar junction area burned. Sex and bathing were forbidden for two months. If there were any new symptoms or changes in the original condition at any time, the patients were asked to record them and come to the clinic for review. A follow-up of the HPV test was carried out at 6 months and 12 months post-operation. As for the patients in the control group, no special treatment was performed, and the follow-up was the same as in the microwave group.

Statistical analysis

SPSS13.0 software (SPSS Inc, Chicago, IL, USA) was applied to process the data. The categorical data was described with frequencies and frequency distributions. For quantitative data, the mean and the standard deviation were used when it was a normal distribution, and the median and percentiles were utilized when it was a non-nomal distribution. The comparison of quantitative data between the two gro-ups was carried out with a *t* test, rank sum test and Z test. The comparison of the subgroups of quantitative data was carried out using a variance analysis, a Kruskal-Wallis rank sum test, and Bonferroni method. A comparison of the classified data was done with a χ^2 test and a rank sum test. $P<0.05$ was considered statistically significant.

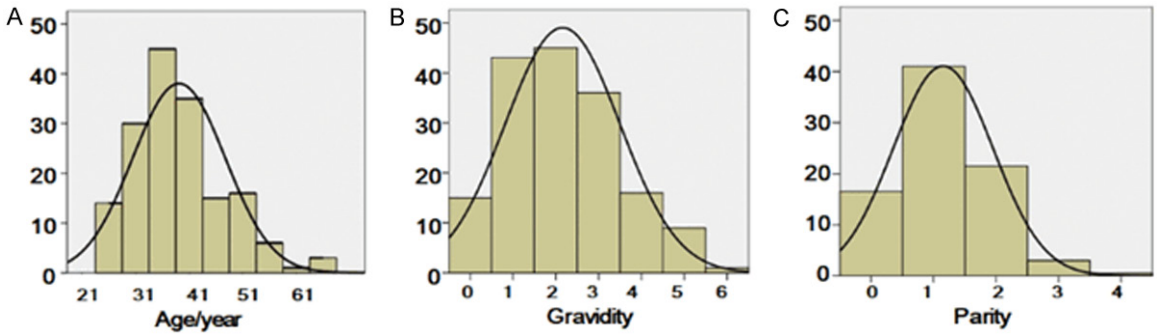

Figure 1. The overall age (A), gravidity (B), and parity (C) distributions of the patients showed a positive peak distribution.

Results

General condition of the participants

According to the above criteria, 10 patients were excluded for lack of follow-up information, and 6 patients were removed due to pregnancy. Finally, a total of 165 cases were included in this study. Forty-seven cases were in the microwave treatment group and 118 cases were in the control group. No patient in the microwave treatment group experienced any serious side effects in this study. Two patients (2/47, 4.2%) had mild leucorrhea bleeding but without massive hemorrhage, an indication of the safety and reliability of the microwave treatment.

The overall age, G, and P distributions of the subjects did not satisfy the normality, all showing a positive peak distribution (**Figure 1**). Since some patients (23 cases, accounting for 13.9% of the total) were treated outside the hospital, those hospitals only processed the HPV quantitative sub-type detection, or only had the low-risk detection but without the sub-type detection, thus resulting in some unknown types of virus. For these patients, "+" "HR" and "LR" were used instead (**Table 1**). In this study, HPV single virus infection was the most common type. The combined statistics of the infection types showed that Type 52 was the most common type of the high-risk types, while Type 18 was the least common. The most common type of low-risk type was the CP8304 type and the most synergistic infection was the 53/58 type. The frequency distribution of HPV at high and low risk illustrated that most of the patients had the high-risk types (81.8%). The cervical transformation areas had individual differences, and with hormone level fluctuations and age changes, the transformation areas shifted inward or outward. All visible transformation areas were found in most of the patients (41.2%), while areas not visible were identified in 27.9% of the patients.

Comparison of general conditions of the microwave treatment group and the control group

In order to learn about the general conditions between the two groups, the age, gravidity (G), parity (P), type of HPV infection, type of HPV at high or low risk, type of SCJ of the microwave treatment group and the control group were compared. According to the Shapiro-Wilk normality test, the ages and the G, and P distributions of both groups had a non-normal distribution ($P<0.001$). The non-normal independent quantitative data of the two groups were compared with a Wilcoxon rank-sum test, and the result demonstrated that the age distribution of the two groups was not statistically significant. We utilized the χ^2 test to compare two sets of independent qualitative data and $P>0.05$. We found that there was no significant difference in the distribution between the high-risk and low-risk types of HPV. There was no statistical difference in the SCJ-type distribution found by a line χ^2 test ($P>0.05$). Together, the results showed that there were no differences between the two groups pre-operation, and the grouping was reasonable.

Comparison of HPV clearance between the microwave and control groups

To study the HPV clearance between the two groups, a comparison was performed. There were no significant differences in age, gravidity (G), parity (P), type of HPV at high or low risk, or

Table 1. Frequency distribution of HPV infection type and merged frequency of infection type

		Frequency	Percentage (%)			Merged frequency	Merged percentage (%)
HPV	52	34	20.6	HPV	52	40	24.2
	16	15	9.1		58	19	11.5
	58	12	7.3		16	18	10.9
	39	8	4.8		53	13	7.9
	56	8	4.8		18	11	6.7
	51	7	4.2		39	9	5.5
	53	6	3.6		56	8	4.8
	18	5	3		31	7	4.2
	31	5	3		51	7	4.2
	cp8304	5	3		cp8304	6	3.6
	33	4	2.4		33	4	2.4
	53/58	4	2.4		66	3	1.8
	66	3	1.8		68	3	1.8
	16/18	2	1.2		59	2	1.2
	44	2	1.2		6	2	1.2
	52/58	2	1.2		44	2	1.2
	6	2	1.2		11	1	0.6
	68	2	1.2		45	1	0.6
	11	1	0.6		66	1	0.6
	16/52	1	0.6		35	1	0.6
	18/31/58	1	0.6		42	1	0.6
	18/45	1	0.6		47	1	0.6
	18/53	1	0.6		+	20	12.1
	18/66	1	0.6		HR	3	1.8
	31/52	1	0.6		LR	1	0.6
	35	1	0.6				
	39/52	1	0.6				
	42	1	0.6				
	47	1	0.6				
	52/53	1	0.6				
	53/59	1	0.6				
	59	1	0.6				
	68/cp8304	1	0.6				
	+	20	12.1				
	HR	3	1.8				
	LR	1	0.6				
	Total	165	100.0				

type of SCJ between the microwave group and the control group (**Table 2**). The HPV clearance was 93.6% and 77.1% for the microwave and control groups, and a line χ^2 test showed that the difference was statistically significant (P = 0.013, **Table 3**). The data suggested that microwave therapy could promote the removal of HPV. A Shapiro-Wilk normality test showed that the HPV clearance times formed non-normal distributions in both groups (**Figure 2**). With a Wilcoxon rank-sum test, all the 135 patients were enrolled, and the HPV clearance statistics were calculated, and the results showed a statistically significant difference (P<0.001). It indicated that the time of HPV removal after the microwave treatment was shorter (**Table 3**). We divided the microwave treatment group into 3 subgroups based on the type of SCJ, and then we compared the clearance rate and clearance time (**Table 4**). The χ^2 test results showed that P = 0.424, indicating that the type of SCJ in the microwave group had no obvious contact with the HPV clearance rate. A rank sum test indicated that the type of SCJ in the microwave group and the HPV clearance time were not significantly correlated (P> 0.05). In conclusion, the results indicated that microwave therapy could remove the HPV infection.

Analysis of factors affecting HPV clearance

To unravel the factors affecting the HPV clearance, a further comparison was undertaken. We divided the microwave group and the control group into 2 subgroups according to age (≤35 years old or >35 years respectively), and then we analyzed the correlation between the HPV clearance rate and time and age. There was no significant association between the age and the HPV clearance rate or HPV clearance

Table 2. Comparison of the general conditions between the microwave group and the control group

	Microwave group	Control group	Statistical method	*P* value
Age (years): mean value	36: (22~51)	34: (22~65)	Wilcoxon rank-sum test	0.461
Gravidity: mean value	2: (0~6)	2: (0~5)	Wilcoxon rank-sum test	0.793
Parity: mean value	1: (1~3)	1: (1~4)	Wilcoxon rank-sum test	0.633
HPV high risk ratio (%)	87.2	79.7	χ^2 test	0.377
SCJ1, 2, 3 ratio (%)	36.2, 36.2, 27.7	41.2, 30.9, 27.9	χ^2 test	0.608

Table 3. Comparison of the HPV clearance rate and the clearance time between the two groups

	Microwave therapy group (n=47)	Control group (n=118)	χ^2/Z value	*P* value
HPV clearance rate	93.6% (44/47)	77.1% (91/118)	6.15	0.013
HPV clearance time Median (Range)	258 (91-878)	290 (119-777)	2.592	0.019

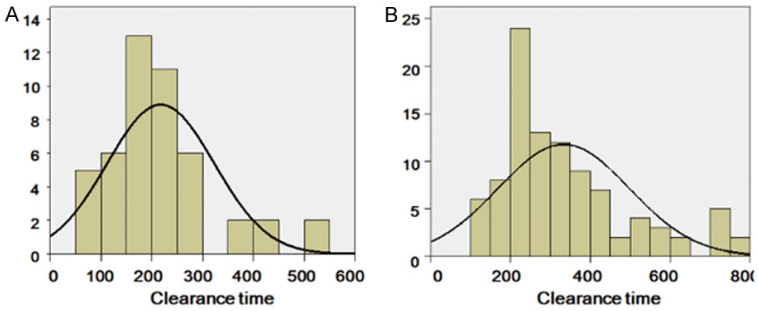

Figure 2. The HPV clearance time showed a non-normal distribution in both groups. A. Microwave group; B. Control group.

time in the two groups (**Table 5**). After excluding the 4 unknown type cases, the remaining 43 cases in the microwave group were divided into 2 subgroups of high and low risk of HPV. There was no significant difference in the HPV clearance rates between high-risk and low-risk HPV (**Table 6**). The correlation between high or low risk of HPV and natural clearance time was analyzed by a rank sum test. The results showed no significant correlation between HPV type and HPV clearance time. In the control group, 11 unknown cases were excluded, and the remaining 107 cases were divided into high and low risk subgroups. Results similar to those of the microwave group were obtained (**Table 6**).

For the microwave group and control groups, the comparisons of the clearance rates and clearance times among the most common HPV types (16, 18, 52, 53, 58) in this study are presented in **Table 7**. The Bonferroni calibration test level was 0.01. The comparisons of the clearance rate of each of the two types using the χ^2 test were not statistically significant (P>0.01). A rank sum test showed no statistically significant difference between the HPV type and the clearance time for both of the two groups (P>0.05, **Table 8**).

Collectively, the results illustrated that microwave therapy is an effective treatment for cervical HPV subclinical infection, a therapy that not only increases the clearance rate but also reduces the clearance time.

Discussion

Age is an important factor affecting HPV epidemics, and the age distribution of HPV infection varies from country to country [10]. According to a study taking 30 as the age boundary, there were no significant differences in the HPV infection rate and the high-risk HPV infection rate between the two groups [11]. In this study, among the patients with subclinical infection using 30 years old as the boundary, the high-risk HPV infection rate showed no statistically significant difference as well. A large sample of international studies showed that the median duration of all HPV infections was 9.8 months, and the rate of persistent infection rapidly declined during the first 6 months and then decreased more slowly over the next 36 months [12]. Our study showed that HPV clearance had a positive peak distribution, reaching

Table 4. Comparison the HPV clearance rate and clearance time based on three types of SCJ in the microwave group

Microwave HPV clearance rate					Microwave HPV clearance time			
Group	Cases	Clearance cases	Clearance rate	P	Group	Cases	Mean time (day)	P
SCJ1	17	15	88.2	0.424	SCJ1	15	203.0	0.444
SCJ2	17	16	94.1		SCJ2	16	186.5	
SCJ3	13	13	100.0		SCJ3	13	214.0	

Table 5. Comparison of age and HPV clearance rate/time

HPV clearance rate						HPV clearance time				
Group	Age (year)	Cases	Clearance cases	Clearance rate	P	Group	Age (year)	Cases	Mean time (day)	P
Microwave group	~35	20	19	95.0	1.000	Microwave group	~35	19	198.5	0.455
	36~	27	25	92.6			36~	25	195.0	
Control group	~35	66	52	78.8	0.627	Control group	~35	52	308.0	0.253
	36~	52	39	75.0			36~	39	253.0	

a peak between 150 and 250 days, and rapidly declining thereafter. The curve tended to be straight, which is consistent with previous studies.

The current model of cervical carcinogenesis posits that HPV infection results in either transient or persistent infection [13]. Most HPV infections are transient and have little risk of progression. Only a small fraction of infections are persistent, but a persistent infection at 1 year and 2 years after the initial infection strongly predicts a subsequent risk of cervical intraepithelial neoplasia (CIN) 3 or cancer, regardless of age [14]. Most HPV-related types of cervical neoplasia progress very slowly. As low-grade neoplasia (or CIN 1) is a manifestation of acute HPV infection, there is a high rate of regression to normal histology results, which could lead to following the current recommendations for observation rather than treatment of these cases [15, 16]. The time from the development of CIN 3 to cancer is not precisely known, but the 10-year difference in the age of diagnosis between screen-detected CIN 3 and cancer suggests long average latency in the precancerous state [17]. In line with this, we gave the control group no treatment but strict screening. A follow-up HPV test was carried out at 6 months to 12 months so as to ensure the safety of the control group.

The body's immune system can naturally remove infected HPV. Almost all sexually active populations have been infected with HPV in the short term, but most HPV infections can subside by themselves [1]. Rosary et al. [18] systematically reviewed and completed a meta-analysis indicating that the median duration of high-risk HPV persistent infection was 9.3 months (range: 6.0-14.8), and the median duration of low-risk HPV persistent infection was 8.4 months. The types with the longest durations were (HPV-33), HPV-33 (12.5 months), and HPV-16 (12.4 months). And half of the HPV infections continued for 6 to 12 months. The median duration of all cytology-negative HPV infections was 11.5 months, while that of the high-risk types was 10.9 months. Our results showed that the median clearance time of high-risk HPV was 276 days and 427 days for low-risk HPV. There was no significant difference (P = 0.091), and the reasons might be as follows: (1) This study did not focus on a high and low risk type comparison, so the choice of cases might have a certain degree of bias; (2) Doctors would be more inclined to recommend colposcopy to low-risk patients with long-term persistent infections; (3) As the low-risk viruses had a shorter natural clearance time and were less harmful, the doctor usually did not recommend microwave treatment, leading to fewer cases of low-risk patients; (4) Because of the introduction of colposcopy, patients who had excluded the intraepithelial neoplasia resulted in having their long-term persistent infection cases relatively reduced, thereby leading to an overall shorter clearance time; (5) In this study, there were fewer low-risk cases. For the LR type in the microwave group, there were only 2 cases and P = 0.465, but in the control group, 13

Table 6. The association between HPV clearance rate/time and the risk type in both groups

HPV clearance rate						HPV clearance time				
Microwave group	Group	Cases	Clearance cases	Clearance rate (%)	*P* value	Microwave group	Mean time (day)	Shortest time (day)	Longest time (day)	*P* value
	High risk type	41	38	92.7	0.864	High risk type	212.0	88.0	559.0	0.419
	Low risk type	2	2	100.0		Low risk type	164.0	79.0	249.0	
Control group	Group	Cases	Clearance cases	Clearance rate (%)	*P* value	Control group	Mean time (day)	Shortest time (day)	Longest time (day)	*P* value
	High risk type	94	69	73.4	0.595	High risk type	289.0	119.0	745.0	0.091
	Low risk type	13	11	84.6		Low risk type	411.0	148.0	777.0	

Table 7. Comparison of the HPV clearance rate and the HPV type in both groups

Group	HPV type	Cases	Clearance cases	Clearance rate (%)
Microwave group	16	8	8	100.0
	18	5	5	100.0
	52	11	8	72.7
	53	3	3	100.0
	58	3	3	100.0
	Others	17	17	100.0
Control group	16	10	8	80.0
	18	6	6	100.0
	52	29	21	72.4
	53	10	4	40.0
	58	16	12	75.0
	Others	47	40	85.1%

Table 8. Comparison of the HPV clearance time and the HPV type in both groups

Group	HPV type	Mean time (day)	Shortest time (day)	Longest time (day)
Microwave group	16	208.5	91.0	409.0
	18	203.0	101.0	532.0
	52	249.0	154.0	559.0
	53	354.0	179.0	532.0
	58	207.0	142.0	452.0
Control group	16	347.0	119.0	547.0
	18	250.0	162.0	590.0
	52	311.0	144.0	745.0
	53	257.0	191.0	417.0
	58	247.0	151.0	708.0

cases of the LR type made the P value decrease significantly to 0.091. Therefore, the removal time might be statistically significant if we were to increase the total sample size to amplify the LR cases.

With a change in age, sexual activity and immune system function change correspondingly. A number of studies about the correlation between age and HPV duration did not reach a consistent conclusion [1]. Brisson et al. [19] found that women less than 25 years old were more likely to have a persistent infection than women of other ages, and some other studies reached to the same conclusion: older women have a lower persistent infection rate that younger women [1, 20]. On the other hand, the study by Castle et al. [21] concluded that younger women are less likely to have persistent infection than older women, and similar conclusions were drawn from four other studies [22-24]. In our study, the HPV clearance rates were compared using the 35 years old as the boundary, and no statistical differences were found between the microwave group and the control group. The possible reason was that the purpose of this study was definitely different from other studies, which screened cases directly from colposcopy patients, leading to selective bias. And we knew that many HPV-infected women under 25 years old had low-risk HPV, cytologically negative results, or no abnormal clinical manifestations. According to the guidelines, they were recommended for regular review rather than further colposcopy [1], so this cohort of women would not be included in this study. Nevertheless, this cohort of women with HPV infection accounted for a large part of the HPV-infected population.

In theory, microwave therapy is mainly indicated for HPV infection in high-risk areas of SCJ, and as a result, the SCJ of Type 1 and Type 2 that exposed outside can be treated well, while for the SCJ of Type 3, which is in the cervical canal, microwave treatment is difficult to carry out, affecting its efficacy [25]. In our study, treatment for Type 1 and Type 2 were mainly aimed at the cervical transformation area and the surface of the outer cervix. For Type 3 SCJ, because the transformation zone was inside the cervical canal, the treatment probe could not reach the treatment site perfectly, and as a result, the treatment also proceeded on the surface of the outer cervix. Currently, there are few studies on SCJ type and HPV clearance rates, and there is no literature available for reference [26, 27]. In this study, the clearance rates of HPV in SCJ of Type 1, 2 and 3 were 88.2%, 94.1%, and 100.0% respectively. There was no significant difference in HPV clearance rates among these three SCJ types in the microwave group. However, we found that the theoretical frequencies of 3 cells were less than 5; that is, the number of theoretical frequencies was not cleared in the SCJ of Type 1, 2 and 3 and were 1.1, 1.1 and 0.8, accounting for 50% of the total. According to the statistical requirements, the use of the contingency table

χ^2 test requires that the number of theoretical frequencies fewer than 5 does not exceed 1/5 of the total lattice number. Therefore, the reason why the clearance rates on the different SCJ types of HPV in the microwave treatment group in this study was not statistically significant might be the smaller sample size. Further study is needed to increase the sample capacity in follow-up studies to get more convincing statistical data.

Li et al. [28] proved that microwave therapy could effectively inhibit DNA amplification of Type 6 and Type 11 HPV. In the control group, the DNA doubled by 100%, while in the CO2 laser group and microwave group, the DNA only increased by 83.3% and 50%. What is more, clinicians often combine microwave therapy and drug therapy, getting a better efficacy than by using one of these two methods alone. Tang Zhiying et al. [29] found that the HPV negative rate was 95.4% after 6 months through the combination of Paul Fu Kang turunda and microwave treatment, and the single microwave negative conversion rate was 85.6%.

In this study, we used microwave treatment on HPV subclinical infection. The HPV clearance rate was 93.6%, and the median time to clear was 194 days, or about 6.5 months. Compared with the control group in terms of the clearance rate and removal time, the microwave treatment showed a significant advantage, and its treatment effect was no less than the other treatments. The advantages of microwave therapy include short treatment time, low cost, repeatability, and easy implementation. The side-effects of microwave treatment are pain, cervical bleeding, adhesions, stenosis, and so on. No one in this study experienced serious side effects. A small number of patients had mild leucorrhea bleeding but without massive hemorrhage, an indication of the safety and reliability of microwave treatment. In view of the better efficacies of combined treatment in other studies, we suggest the combination of drug therapy and microwave therapy.

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Disclosure of conflict of interest

None.

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