

Original Article

Meta-analysis of randomized controlled trials of podophyllotoxin nanogel in the treatment of condyloma acuminatum

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Abstract: Objective: To evaluate the clinical effect of podophyllotoxin nanogel in the treatment of condyloma acuminatum by meta-analysis. Methods: PubMed, CNKI, Wanfang data journal paper resources, Springer databases were searched using “condyloma acuminata”, “liposome ointment”, “podophyllotoxin”, “Genital warts”, “Genital nodule” as the search terms, from 1979 to January 2019. Randomized controlled trials (RCT) comparing Podophyllotoxin nanogel with podophyllin tincture ointment in treatment of condyloma acuminata was included. The quality of the included RCT was evaluated according to the criteria in the Cochrane Systematic Review Manual. The results reported by randomized controlled trials (cure rate, medication time, recurrence rate, adverse reactions (edema, erosion, pain) and HPV subclinical infection rate) were analyzed using Review Manager (5.1.0.). Results: Thirteen RCTs were eventually included, with 1716 patients. Meta-analysis showed that Podophyllotoxin nanogel can improve the cure rate of patients with condyloma acuminatum (pooled OR=1.76, 95% CI=1.65-1.87, Z=17.80, P<0.00001) compared with traditional podophyllotoxin in the treatment of condyloma acuminatum. Reduced recurrence rate (pooled OR=-0.32, 95% CI=-0.36-0.28, Z=16.21, P<0.00001), shortened course of the patient's illness (95% CI=-9.41-9.14, Z=135.67, P<0.00001), and reduced incidence of adverse event, including edema (pooled OR=-0.26, 95% CI=-0.29-0.22, Z=13.63, P<0.00001), erosion (pooled OR=-0.25, 95% CI=-0.34- of 0.17, Z=5.76, P<0.00001), pain (pooled OR=-0.35, 95% CI=-0.42-0.28, Z=10.13, P<0.00001) were also observed. Podophyllotoxin nanogel can effectively control subclinical infection of HPV compared with traditional podophyllotoxin in the treatment of condyloma acuminatum (pooled OR=0.46, 95% CI=0.31-0.67, Z=4.03, P<0.0001). Conclusion: Meta-analysis showed that Podophyllotoxin nanogel has the following advantages in the treatment of condyloma acuminata, including improving cure rate, shorting treatment cycle, reduced recurrence rate and adverse reactions, etc.

Keywords: Podophyllotoxin nanogel, condyloma acuminata, META analysis, recurrence rate, adverse reactions

Introduction

Condyloma acuminata (CA) is a sexually transmitted disease caused by HPV infection [1]. According to epidemiological data in the United States, approximately 20 million sexually active adults in the United States are infected with condyloma acuminata, and about 20% of them are infected with HPV [2]. In recent years, as the number of homosexuals has increased, the number of infections in the anorectal has increased rapidly [3]. As a kind of infectious disease, the disease has the characteristics of high incidence and high recurrence rate, which brings many problems to CA patients. The se-

lection and improvement of treatment methods is one of the hotspots in the medical field.

Genital warts are often treated by ablation or cell destruction. Podophyllotoxin and trichloroacetic acid are cell destructive therapies. These treatments are often associated with pain and high recurrence rates. If there is latent HPV in the clinically normal epithelium outside the treatment area, the risk of recurrence is higher. Currently, podophyllotoxin is a drug that can inhibit the proliferation of lesions [4]. However, because the tincture can only treat visible skin lesions, it cannot treat the infection of latent subclinical viruses. Therefore, the disadvan-

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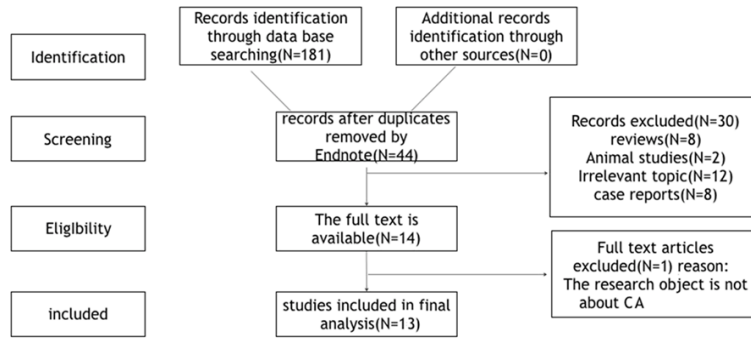


Figure 1. Flow chart of Literature inclusion.

tage of the treatment of podophyllotoxin is that the recurrence rate is high, and the constant recurrence is accompanied by suffering. Studies have shown that prolonging the drug application time in the lesion and increasing the drug concentration in the lesion can effectively treat condyloma acuminata and reduce adverse reactions caused by drugs. Liposomes allow the drug to form a reservoir at the site of the lesion and the drug is slowly released. Only a small amount of drug enters the blood circulation, which is an ideal therapeutic dosage form [5].

To further compare the efficacy of Podophyllotoxin nanogel and traditional podophyllotoxin in the treatment of condyloma acuminata, this paper summarized the comparative study.

Materials and methods

This study strictly follows the PRISMA guidelines

Search strategy

We use the following MeSH words to search: "Warts", "Buschke-Lowenstein Tumor", "Sexually Transmitted Diseases, Viral", "Skin Diseases, Viral", "Papillomavirus Infections", "Tumor Virus Infections", "liposome ointment", "podophyllotoxin", "Genital warts", "Genital nodule". Search criteria apply to other bibliographic databases. The initial search was re-run before the final analysis to retrieve further studies. The selected literature was studied by human participants.

Inclusion criteria

(1) Study type: Randomized Controlled Trial (RCT); (2) Patients with condyloma acuminata between the ages of 18 and 40; (3) Intervent-

ion: Experimental group: podophyllin liposome ointment was applied to the affected area. (4) Control group: podophyllin tincture ointment was used in the affected area. (5) Outcomes: the results included one or more of; the cure rate, medication time, recurrence rate, adverse reactions (edema, erosion, pain) and HPV subclinical infection rates.

Exclusion criteria

(1) Patients did not use podophyllotoxin ointment as a control group; (2) Subjects were animals; (3) Non-clinical randomized controlled trials.

Literature screening

Two researchers independently screened the initial literature based on the literature headings and abstracts in strict accordance with the inclusion and exclusion criteria. After that, all selected documents that may be included were carefully read. Two researchers cross-checked the results of the included studies, fully discussed the divergent findings or invited a third researcher to join in the discussion.

Data extraction and outcome measures

The following information was extracted from the included RCTs: first author, publication year, sample size, baseline characteristics of patients, GON block intervention, control, pain score, number of headache days, duration of headache per four weeks (hour), and medication consumption (day). The author would be contacted to acquire additional data when necessary.

The general data included in the study is recorded using a consolidated table which contains the following items: author, publication year, country, multicenter or single centered, published journal, number of cases per group, study time, study design.

Statistics: cure rate, medication time, recurrence rate, adverse reactions (edema, erosion, pain) and HPV subclinical infection rate.

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Table 1. Data summary

Study	Study period	Country	Multi-center or single center	Study design	Case	Control	Cure Number		Recurrence Number		Medication time (d)		Edema		Erosion		Pain		Skin lesion	
							Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
Beutner KR 2009	2007-2008	U.K.	Single center	RCT	74	72	72	54	6	29	9.5±2.5	18.9±4.2	9	31			9	31	4	14
Bin He 2013	2011-2012	China	Single center	RCT	49	46	48	19	3	12	9.5±1.5	19.7±3.3	10	32			10	32	5	9
Cheng Wang 2018	2015-2017	China	Single center	RCT	85	87	83	41	4	25	15.3±5.1	26.1±7.3	13	29					9	18
Fangming Xie 2007	2004-2006	China	Single center	RCT	35	32	30	10	3	12	8.4±1.7	17.6±3.1	11	20			11	20	4	8
Greenberg MD 2001	1999-2000	U.K.	Single center	RCT	62	58	60	44	4	25	7.5±1.06	16.6±1.22	7	29			7	29	2	6
Hu Nan 2018	2013-2016	China	Single center	RCT	75	75	74	38	14	35	8.22±1.03	17.5±1.01	2	13	11	27	2	13	9	19
Kang Zeng 1998	1996-1997	China	Single center	RCT	49	32	47	13	5	11	8.6±1.7	18.6±3.6	0	0						
Kirby P 2010	2007-2009	USA	Single center	RCT	48	46	46	25	5	22	8.62±1.04	17.76±1.42	6	23			6	23		
T.A. Syed 1994	1992-1993	USA	Single center	RCT	214	206	211	121	16	31	8.79±0.86	18.02±1.17	20	56						
Xiaohong Li 2018	2015-2016	China	Single center	RCT	36	36	34	14	2	10	10.3±1.12	19.5±0.92	0	14						
Xiaohong Liu 2006	2003-2005	China	Single center	RCT	51	58	18	43	2	11	9.4±2.7	18.4±2.2	9	24	7	28	9	24		
Xiaoqun Li 2018	2015-2016	China	Single center	RCT	44	44	40	22	6	23	9.8±1.7	19.6±3.1	1	7	3	12				
Zhenhui Yang 2018	2016-2017	China	Single center	RCT	54	48	54	25	3	18	9.1±1.9	19.5±3.2	10	32						

Table 2. Quality evaluation of the 13 studies and evaluations

Study	Random sequence generation	Distribution of hidden	Blinded for the object of study or intervention	Blinded for the outcome measure	Incomplete data report	Select the report	Other sources of bias	The quality of evidence
Beutner KR 2009	High	High	High	Low	Low	Low	Low	B
Bin He 2013	Low	Low	High	Low	Low	Low	Low	B
Cheng Wang 2018	High	High	High	Low	Low	Low	Low	B
Fangming Xie 2007	Low	Low	Low	Low	Low	Low	Low	A
Greenberg MD 2001	High	High	High	Low	Low	Low	Low	B
Hu Nan 2018	High	High	High	Low	Low	Low	Low	B
Kang Zeng 1998	High	High	Low	Low	Low	Low	Low	B
Kirby P 2010	High	Low	High	Low	Low	Low	Low	B
T.A. Syed 1994	High	High	High	Low	Low	Low	Low	A
Xiaohong Li 2018	High	Low	High	Low	Low	Low	Low	B
Xiaohong Liu 2006	High	High	High	Low	Low	Low	Low	A
Xiaoqun Li 2018	Low	High	High	Low	Low	Low	Low	B
Zhenhui Yang 2018	High	High	High	Low	Low	Low	Low	A

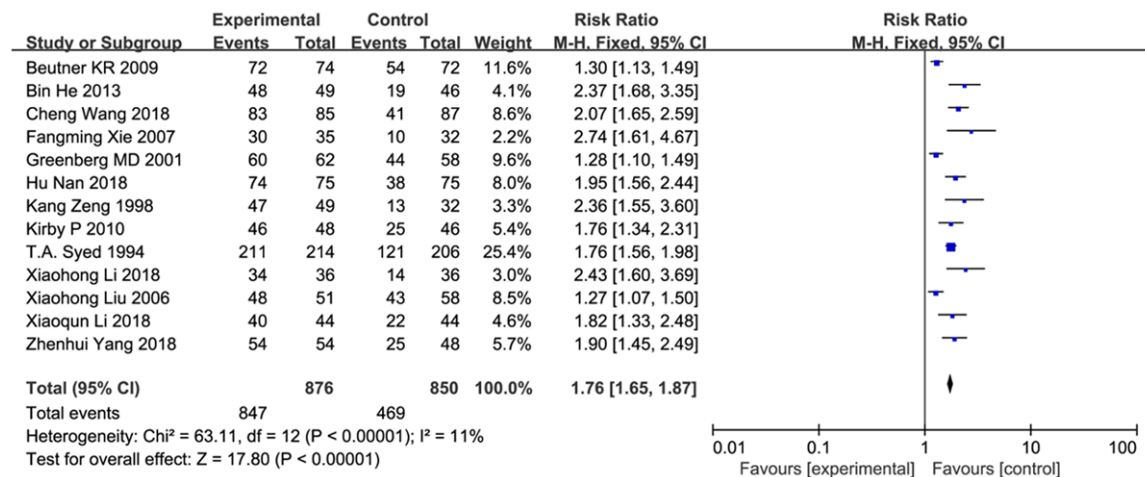


Figure 2. Effect of Podophyllotoxin nanogel on the cure rate of patients with CA (Forest plot).

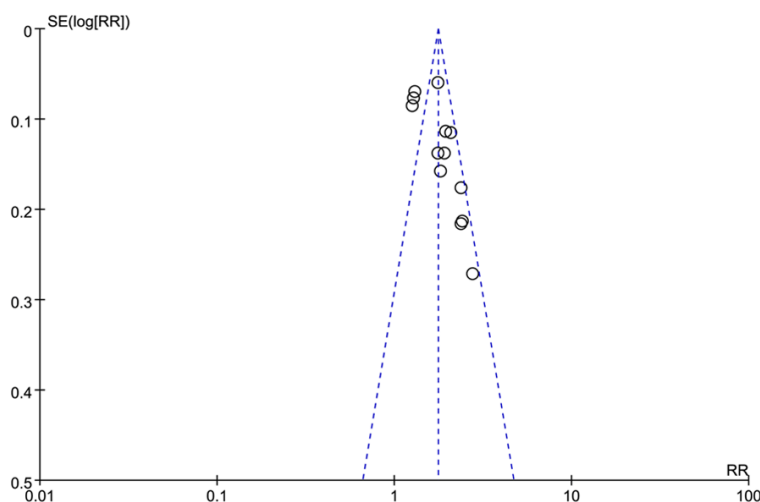


Figure 3. Effect of Podophyllotoxin nanogel on the cure rate of patients with CA (Funnel plot).

The primary outcomes were the pain score, and number of headache days. Secondary outcomes included duration of headache per four weeks (hour), and medication consumption (day).

Quality evaluation

The Review Manual Version 5.1.0 was selected as the tool to include RCT's bias risk assessment to assess the specific quality of the final included literature. Specifically, the following seven evaluation criteria were included: (1)

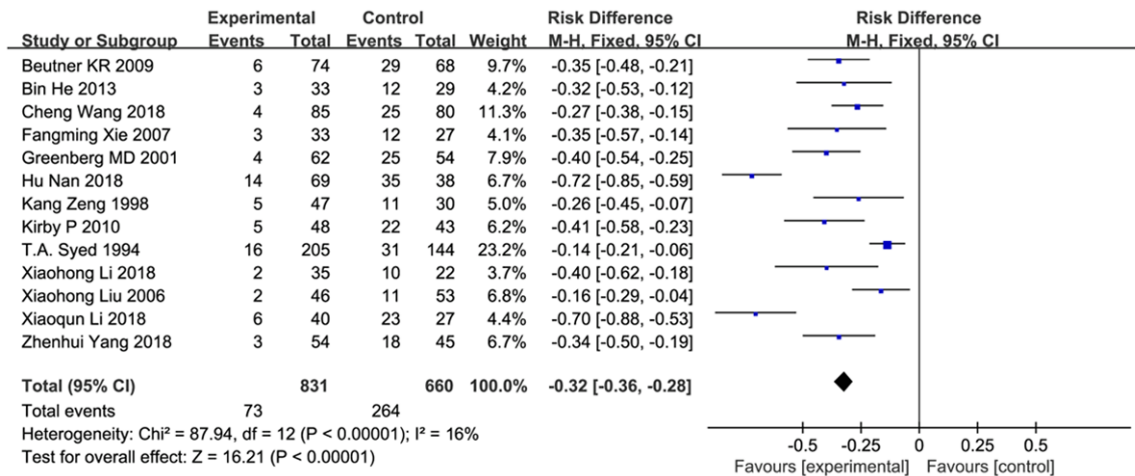


Figure 4. Effect of podophyllotoxin liposome ointment on recurrence rate in CA patients (Forest plot).

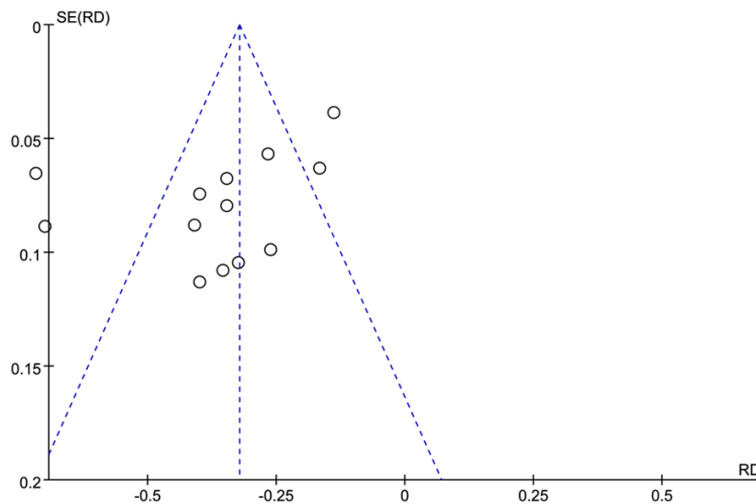


Figure 5. Effect of podophyllotoxin liposome ointment on recurrence rate in CA patients (Funnel plot).

random sequence generation; (2) allocation concealment; (3) double blindness of implementers and participants; (4) blind method of result evaluation; (5) integrity of result data; (6) select reports; (7) other sources of bias. We used the SIGN method (<http://www.sign.ac.uk/methodology/checklists.html>) to summarize the overall level of potential bias for each study: the judgment of bias is expressed as “low risk”, “high risk” or “risk unclear”. “All differences are resolved by consensus”. (1) “A” means that all or most of the quality standards are met. Implementation (allowed in the assessment of all potential sources of bias section); (2) “B” indicates that certain criteria are met; (3) “C” means that there is little or no satisfac-

tion. In the article, we use “A” to indicate that the article is evaluated as “high quality research” and B to indicate that the article is evaluated as “medium quality research”.

Statistical analysis

All data were analyzed using Review Manager version 5.1.0, and $P < 0.05$ was considered statistically significant. The pooled effect was estimated using the standard mean difference (SMD) of continuous results and the 95% confidence interval (95% CI). The dichotomous variables uses the ratio (RR) and

95% CI. Heterogeneity was evaluated by χ^2 and I^2 . A fixed-effects model was used to calculate relevant data for insignificant heterogeneity ($I^2 > 50\%$, $P < 0.1$). The random effects model was used to calculate heterogeneous data ($I^2 < 50\%$, $P < 0.1$). The funnel plot was used to visually assess the publication bias.

Results

After a comprehensive search of the database, a total of 181 articles were obtained. EndNote software was used to check for duplicates and found 44 articles. By reading the title of the article, 18 articles were obtained. By carefully studying the full text of the literature, we finally

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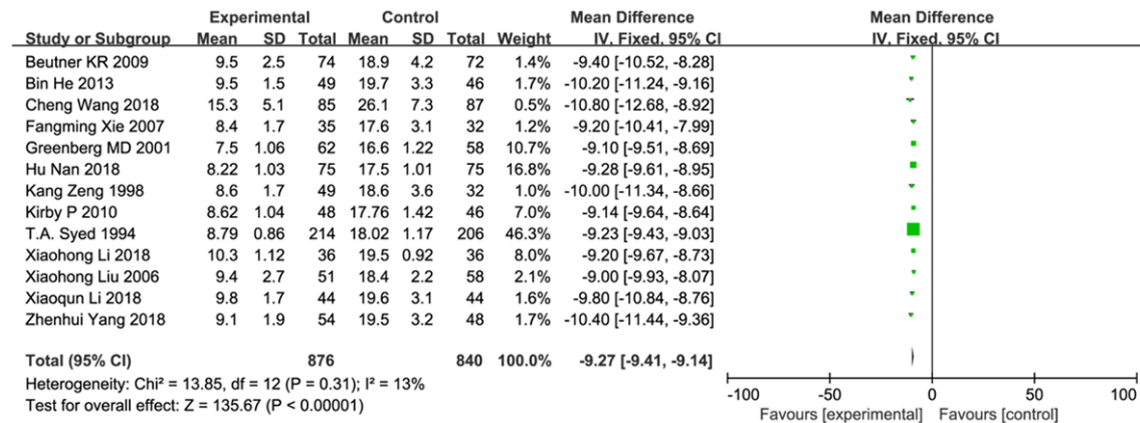


Figure 6. Effect of podophyllotoxin liposome ointment on the course of patients (Forest plot).

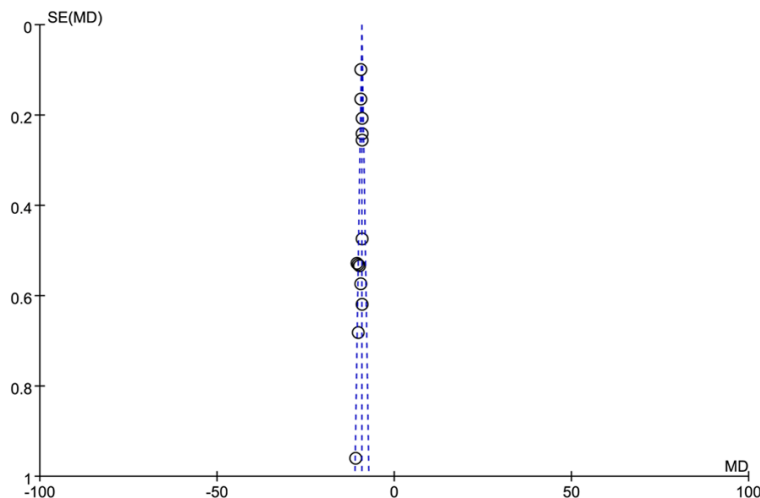


Figure 7. Effect of podophyllotoxin liposome ointment on the course of patients (Funnel plot).

included 13 eligible studies (Syed, TA 1994 [6], Zeng K 1998 [7], Greenberg MD 2001 [8], Liu XH 2006 [9], Xie FM 2007 [10], Beutner KR 2009 [11], Kirby P 2010 [12], He B 2013 [5], Nan H 2018 [13], Ye WZ 2018 [14], Yang ZH 2018 [4], Li XY [15], Li XH 2018 [16]). Search for relevant literature was according to the following process (**Figure 1**). **Table 1** summarized the characteristics of these 13 studies with a total of 1716 patients.

Quality assessment

Based on the Cochrane Handbook 5.1 Assessment Tool, **Table 2** shows the risk of bias among studies, which were judged by the 7 criteria. Results showed that most of the trials had reported a random design method but few

reported an allocation concealment scheme; some of the trials reported a detailed blind design. According to the quality assessment, the quality evaluation of 4 articles is A, and the quality evaluation of 9 articles is B. The specific results are shown in **Table 2**.

Outcome measures

Effect of podophyllotoxin nanogel on the cure rate of patients with condyloma acuminata

The effects of Podophyllotoxin nanogel and common podophyllotoxin on the cure rate of patients with condyloma acuminata was studied in 13 papers. Podophyllotoxin nanogel can significantly improve the cure rate of patients with condyloma acuminata.

The heterogeneity test result was (chi-squared = 63.11, P < 0.00001, I² = 11%), so 95% CI was used. The results showed that Podophyllotoxin nanogel had a higher cure rate than normal podophyllotoxin (Z = 17.80, P < 0.00001) (**Figures 2, 3**).

Effect of podophyllotoxin nanogel on recurrence rate of patients with condyloma acuminata

The effect of Podophyllotoxin nanogel on the recurrence rate of patients with condyloma acuminata (1 month after the wart body was completely cleared to half a year recurrence)

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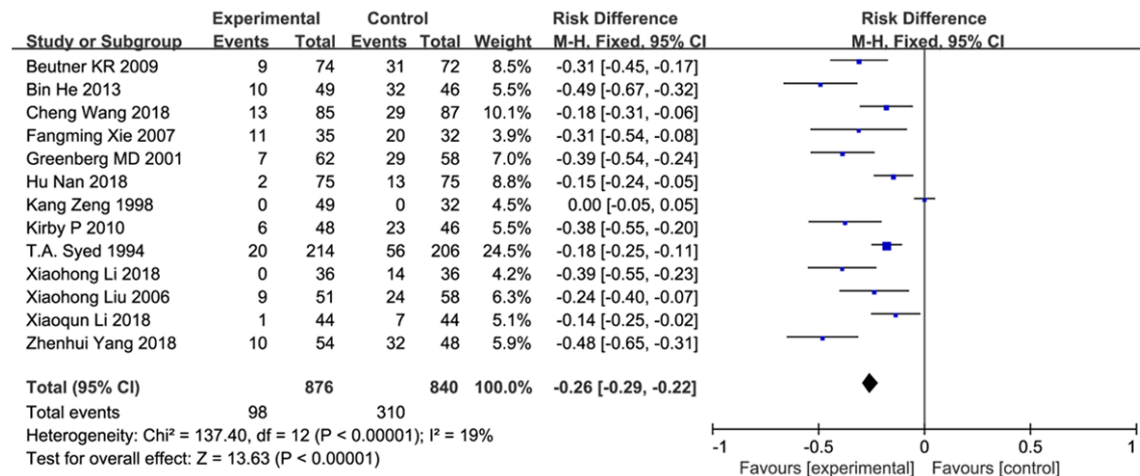


Figure 8. Correlation between podophyllotoxin liposome ointment and edema (Forest plot).

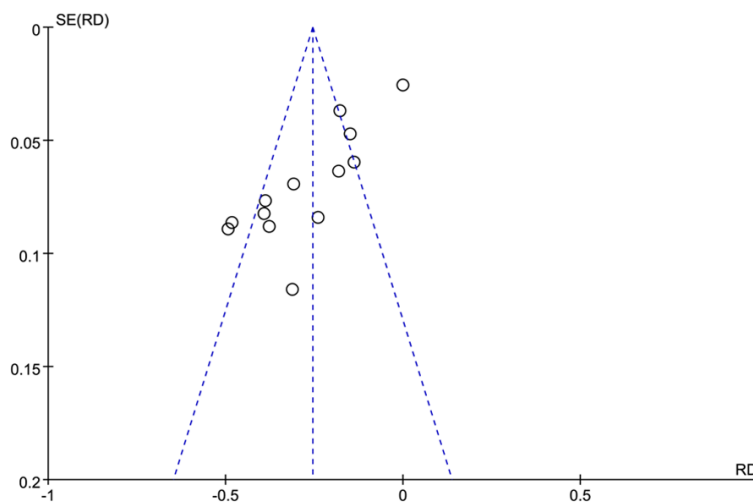


Figure 9. Correlation between podophyllotoxin liposome ointment and edema (Funnel plot).

was studied in 13 papers. Podophyllotoxin nanogel can reduce the recurrence rate of patients with condyloma acuminata. The heterogeneity test result was chi-squared = 87.94, $P < 0.00001$, $I^2 = 16\%$, so fixed model was used. The results showed that Podophyllotoxin nanogel can reduce the patient's recurrence rate ($Z = 16.21$, $P < 0.00001$) (Figures 4, 5).

Effect of podophyllotoxin nanogel on the course of patients with condyloma acuminata

The effect of podophyllotoxin solid nanoparticle gel on the patient's course of disease was studied in 13 papers, and Podophyllotoxin nanogel can reduce the administration course.

The heterogeneity test result was (chi-squared = 13.85, $P = 0.31$, $I^2 = 13\%$), so fixed model was used. The results showed that Podophyllotoxin nanogel can reduce the patient's medication time ($Z = 135.67$, $P < 0.00001$) (Figures 6, 7).

Effect of podophyllotoxin nanogel on adverse reactions of patients with endothelial reactions

Correlation between Podophyllotoxin nanogel and edema: The correlation between Podophyllotoxin nanogel and edema after use was analyzed in 13 papers. The heterogeneity test result was (chi-squared = 137.4, $P < 0.00001$, $I^2 = 19\%$), so fixed model was used. The results showed that Podophyllotoxin nanogel can reduce the risk of edema ($Z = 13.63$, $P < 0.00001$) (Figures 8, 9).

The correlation between Podophyllotoxin nanogel and erosion after use was analyzed in 3 papers. The heterogeneity test result was (chi-squared = 2.02, $P = 0.37$, $I^2 = 1\%$), so fixed model was used. The results showed that the use of Podophyllotoxin nanogel did not increase the risk of erosion ($Z = 5.76$, $P < 0.00001$) (Figures 10, 11).

Effect of podophyllotoxin nanogel on correlation of patients with condyloma acuminata

The correlation between Podophyllotoxin nanogel and erosion after use was analyzed in 3 papers. The heterogeneity test result was (chi-squared = 2.02, $P = 0.37$, $I^2 = 1\%$), so fixed model was used. The results showed that the use of Podophyllotoxin nanogel did not increase the risk of erosion ($Z = 5.76$, $P < 0.00001$) (Figures 10, 11).

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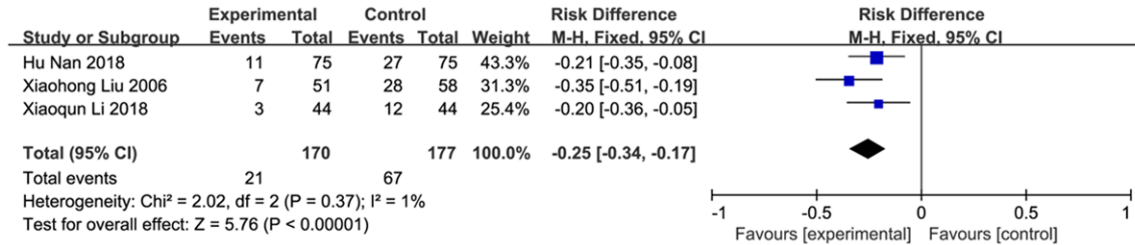


Figure 10. Correlation between podophyllotoxin liposome ointment and erosion (Forest plot).

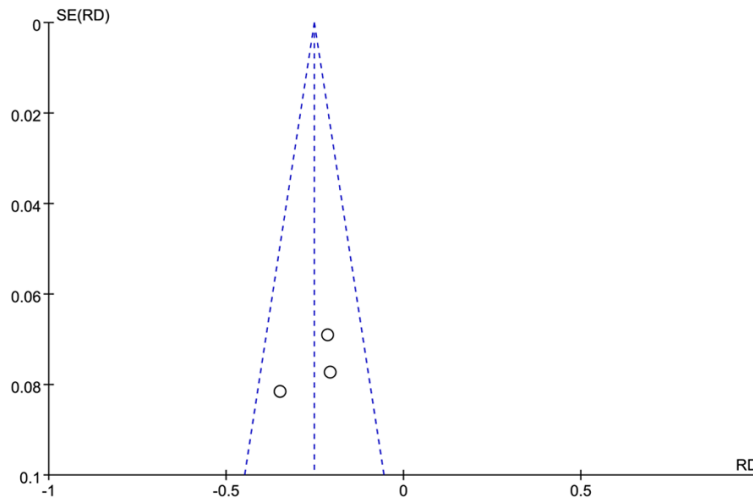


Figure 11. Correlation between podophyllotoxin liposome ointment and erosion (Funnel plot).

Effect of podophyllotoxin nanogel on pain of patients with condyloma acuminata

The correlation between Podophyllotoxin nanogel and pain after use was analyzed in 7 papers. The heterogeneity test result was (chi-squared = 5.11, $P = 0.40$, $I^2 = 2\%$), so fixed model was used. The results showed that the use of Podophyllotoxin nanogel did not increase the risk of pain ($Z = 10.13$, $P < 0.00001$) (**Figures 12, 13**).

Effect of podophyllotoxin nanogel on HPV infection of patients with condyloma acuminata

Correlation between Podophyllotoxin nanogel and HPV infection after use was analyzed in 6 papers. The heterogeneity test result was (chi-squared = 1.16, $P = 0.95$, $I^2 = 0\%$), so fixed model was used. The results showed that the use of Podophyllotoxin nanogel reduced the risk of HPV infection in patients ($Z = 4.03$, $P < 0.00001$) (**Figures 14, 15**).

Publication bias

No publication bias was found in the included studies for all the above mentioned results.

Discussion

At present, there are many methods for treating condyloma acuminata. However, due to the lack of antiviral means, all treatments have been accompanied by higher recurrence rates. Repeated episodes of genital warts cause great mental and physical pain, and some genital warts can also be converted to cervical or penile cancer. Although

the treatment of condyloma acuminata is very mature, high recurrence rate is still a very difficult problem that restricts clinical treatment.

Podophyllotoxin is extracted from the grass, and the clinical effect of treating condyloma acuminata is achieved by inhibiting the proliferation of HPV-infected cells.

However, the surface tension of tincture is very low, and it is easy to diffuse into the mucosa of normal skin during treatment, causing damage to the skin in the normal area, leading to side effects.

As a new type of drug carrier with sustained release effect, liposomes can be used in the treatment of condyloma acuminata to exert better targeting and reduce side effects.

In a double-blind randomized, controlled clinical trial, Gilson et al found no significant differ-

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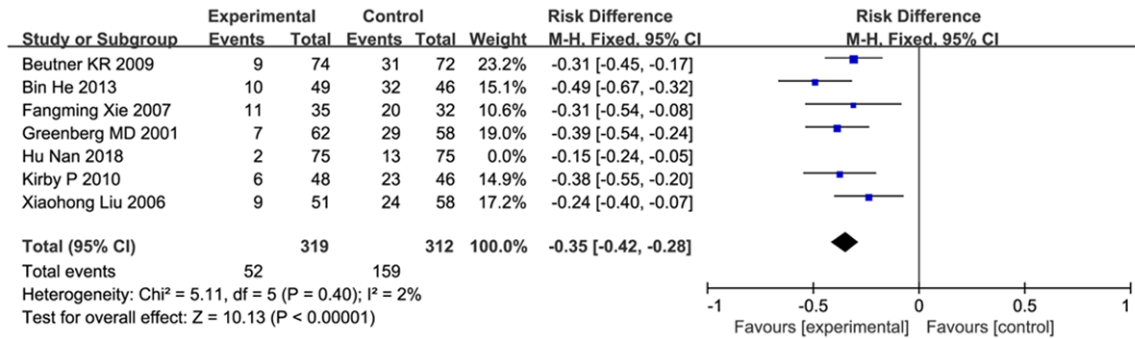


Figure 12. Correlation between podophyllotoxin liposome ointment and pain (Forest plot).

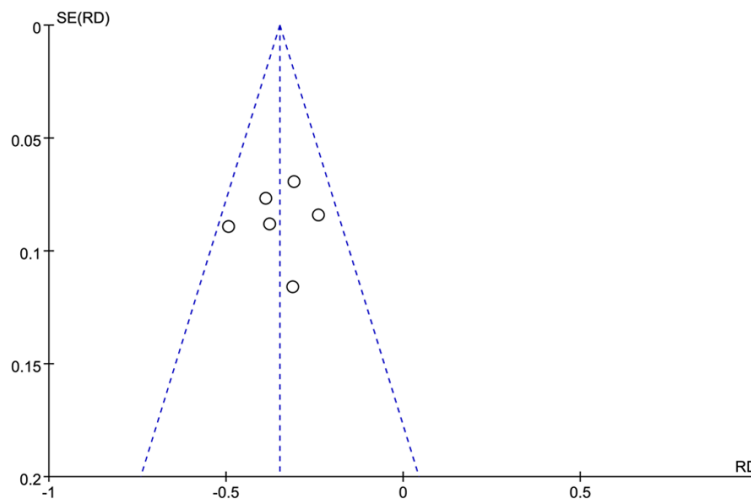


Figure 13. Correlation between podophyllotoxin liposome ointment and pain (Funnel plot).

ence in the cure rate of condyloma acuminata between podophyllotoxin flexible nanoliposomes and podophyllotoxin tinctures [17]. In a randomized clinical study, Happonen et al concluded that podophyllotoxin flexible nanoliposomes had a significantly better cure rate for condyloma acuminata than podophyllotoxin tinctures [18]. In addition, this article analyzed the patient's disease duration, and believed that podophyllotoxin flexible nanoliposomes can reduce the patient's disease course. *In vitro* experimental studies found that transdermally administered flexible nanoliposomes can not only reduce the local skin irritation, promote the penetration of drugs into the affected area, but also ensure the accumulation of drugs in the epidermis, improve the bioavailability of the drug and reduce the body's absorption [19]. Considering the above characteristics of liposomes, it may increase the cure

rate of condyloma acuminata and shorten the course of condyloma acuminatum patients.

Mistrangelo M [20] suggested the recurrence rate of podophyllotoxin liposome gel in the treatment of condyloma acuminata was significantly lower than that of the expectorant. In a related clinical randomized controlled trial, Krishna S [21] concluded that podophyllotoxin liposomes did not reduce the incidence of endothelial reactions in CA patients. Lacey CJ [22] believes that podophyllotoxin liposomes can reduce the incidence of adverse reactions in pa-

tients with CA. The results of this study showed that podophyllotoxin flexible nanoliposomes can significantly reduce the occurrence of edema, erosion, pain and other adverse reactions. Liposomes increased the transdermal action of the drug [23], which reduced the diffusion range of the drug and reduces local irritation, thereby reducing the occurrence of adverse reactions.

Küppers V [24] and Wilson N [25] suggest that podophyllotoxin liposomes can effectively control the subclinical infection of HPV, further confirming the results of this study, the pharmacodynamics and pharmacokinetics of podophyllotoxin liposomes.

There are some restrictions in this study. First, our analysis was based on only 13 RCT samples, all of which were small ($n < 200$), resulting

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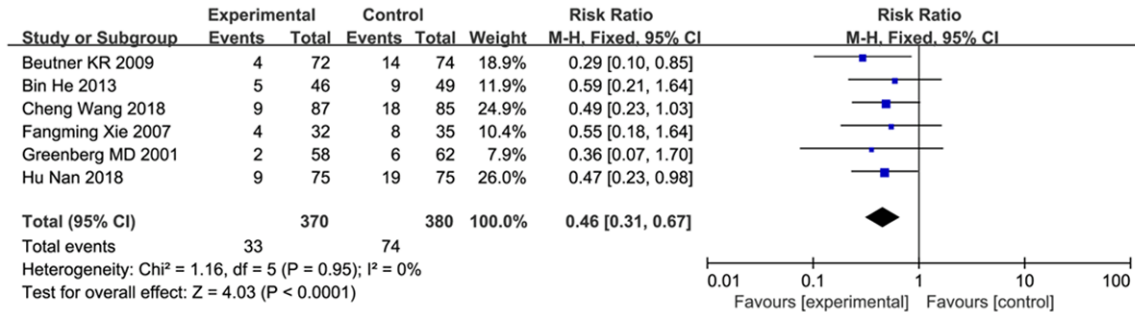


Figure 14. Correlation between podophyllotoxin liposome ointment and HPV infection (Forest plot).

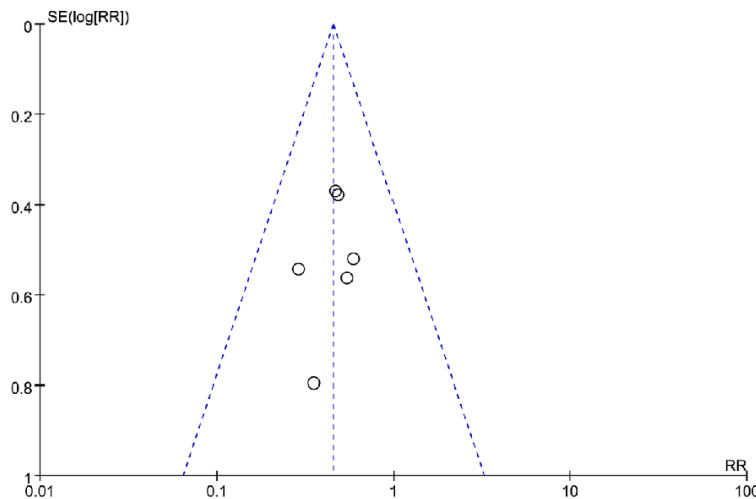


Figure 15. Correlation between podophyllotoxin liposome ointment and HPV infection (Funnel plot).

and no scar. There were few adverse reactions during the treatment.

Disclosure of conflict of interest

None.

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References

- [1] Yan J, Chen SL, Wang HN and Wu TX. Meta-analysis of 5% imiquimod and 0.5% podophyllotoxin in the treatment of condylomata acuminata. *Dermatology* 2006; 213: 218-223.
- [2] Heley S. Human papillomavirus: beware the infection you can't see. *Aust Fam Physician* 2003; 32: 311-5.
- [3] Ault KA. Human papillomavirus infections: diagnosis, treatment, and hope for a vaccine. *Obstet Gynecol Clin North Am* 2003; 30: 809-817.
- [4] Yang ZH and Chen X. Clinical observation of podophyllotoxin gel in the treatment of HPV16 condyloma acuminatum. *Clinical Report on Chinese Folk Therapy* 2018; 26.
- [5] He B and Lin ZF. Clinical observation of podophyllotoxin liposome gel in the treatment of recurrent condyloma acuminatum. *New Chinese Medicine* 2013; 61-62.
- [6] Syed TA, Lundin S and Ahmad SA. Topical 0.3% and 0.5% podophyllotoxin cream for self-treatment of condylomata acuminata in women. A placebo-controlled, double-blind study. *Dermatology* 1994; 189: 142-145.

in an overestimation of the clinical effects of podophyllotoxin nanogels, which required a large sample for later analysis. Second, in this study, the optimal therapeutic dose of the drug was not analyzed and further clinical studies were needed. Finally, some unpublished and missing data may affect the results of the analysis.

In summary, we can draw a clear conclusion that both products have significant clinical effects. However, podophyllotoxin flexible nanoliposomal gel significantly reduced the patient's recurrence rate. The flexible nanoliposome formulation has a higher encapsulation efficiency and less podophyllotoxin is in a free state. This feature also made it less irritating to the epidermis and therefore safer. Compared with the traditional dosage form, the flexible nanoliposomal gel is more convenient to use, the wart is more thoroughly removed, with small damage

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- [7] Zeng K, Li GF, Xu CY, Chen ZL and Wang CF. A double-blind randomized controlled trial of podophyllotoxin liposome ointment in the treatment of condyloma acuminatum. *Journal of First Military Medical University* 1998; 18: 246.
- [8] Greenberg MD, Rutledge LH, Reid R, Berman NR, Precop SL and Elswick RK Jr. A double-blind, randomized trial of 0.5% podofilox and placebo for the treatment of genital warts in women. *Obstet Gynecol* 1991; 77: 735-9.
- [9] Liu XH, Jiang BB, Zhao ZQ, Zhao D, Song LT and Yang H. Clinical study of podophyllotoxin liposome in the treatment of condyloma acuminatum. *Journal of Practical Medicine* 2006; 23: 1438-1440.
- [10] Xie FM, Zeng K, Chen ZL, Li GF, Lin ZF, Zhu XL and Sun LD. Treatment of recurrent condyloma acuminatum with solid lipid nanoparticle gel containing podophyllotoxin: a randomized double-blinded, controlled clinical trial. *Nan Fang Yi Ke Da Xue Xue Bao* 2007; 27: 657-659.
- [11] Beutner KR, Conant MA, Friedman-Kien AE, Illeman M, Artman NN, Thisted RA and King DH. Patient-applied podofilox for treatment of genital warts. *Lancet* 1989; 1: 831-4.
- [12] Kirby P, Dunne A, King DH and Corey L. Double-blind randomized clinical trial of self-administered podofilox solution versus vehicle in the treatment of genital warts. *Am J Med* 1990; 88: 465-469.
- [13] Nan H. Clinical effect of podophyllotoxin lipid in patients with condyloma acuminatum. *Sex Science in China* 2018; 27: 124-127.
- [14] Ye WZ, Li SJ, Wu YW, Wang SS and Wang L. Clinical efficacy of podophyllotoxin lipid in the treatment of recurrent condyloma acuminatum of female vulva. *Anhui Medical Journal* 2018; 297-299.
- [15] Li XY, Ding W, Zhou SL, Jin YE and Li L. Clinical effect of formaldehyde combined with interferon α 1B on condyloma acuminatum. *Journal of Military Surgeon in Southwest China* 2018; 20: 22-25.
- [16] Liu XH. Clinical study of podophyllotoxin liposome in the treatment of condyloma acuminatum. *Chinese Medicine* 2018; 11: 163-165.
- [17] Gilson RJ, Ross J, Maw R, Rowen D, Sonnex C and Lacey CJ. A multicentre, randomised, double-blind, placebo controlled study of cryotherapy versus cryotherapy and podophyllotoxin cream as treatment for external anogenital warts. *Sex Transm Infect* 2009; 85: 514-519.
- [18] Happonen HP, Lassus A, Santalahti J, Forstrom S and Lassus J. Combination of laser therapy with 0.5% idoxuridine cream in the treatment of therapy-resistant genital warts in male patients: an open study. *Sex Transm Dis* 1990; 17: 127-129.
- [19] Kacerovska D, Pizinger K, Kumpova M and Cetkovska P. Genital warts treated by photodynamic therapy. *Skinmed* 2007; 6: 295-297.
- [20] Mistrangelo M, Dal Conte I, Volpato S, Di Benedetto G, Testa V, Currado F and Morino M. Current treatments for anal condylomata acuminata. *Minerva Chir* 2018; 73: 100-106.
- [21] Krishna S. Comparison of podophyllotoxin and imiquimod as anal condyloma acuminata therapy. *Dermatol Online J* 2009; 15: 14.
- [22] Lacey CJ, Goodall RL, Tennvall GR, Maw R, Kinghorn GR, Fisk PG, Barton S and Byren I. Randomised controlled trial and economic evaluation of podophyllotoxin solution, podophyllotoxin cream, and podophyllin in the treatment of genital warts. *Sex Transm Infect* 2003; 79: 270-275.
- [23] Jablonska S. Traditional therapies for the treatment of condylomata acuminata (genital warts). *Australas J Dermatol* 1998; 39 Suppl 1: S2-S4.
- [24] Kuppers V, von Eckardstein S, Adomeit A, Wingartz C, Boddien-Heidrich R, Koldovsky U and Bender HG. Diagnostic and therapeutic concepts of HPV infection in HIV-positive women. *Zentralbl Gynakol* 1999; 121: 27-30.
- [25] Wilson N, Morgan J and Baker MG. Evidence for effectiveness of a national HPV vaccination programme: national prescription data from New Zealand. *Sex Transm Infect* 2014; 90: 103.