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 acuminatum 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=-0.34-0.17, 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 acuminatum, including improving cure rate, shorting treatment cycle, reduced recurrence rate and adverse reactions, etc.

Keywords: Podophyllotoxin nanogel, condyloma acuminatum, 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 selection and improvement of treatment methods is one of the hotspots in the medical field.

Genital warts are often treated by ablation or cell destruction. Podlo-phyllotoxin 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-
Advantage 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 Trail (RCT); (2) Patients with condyloma acuminata between the ages of 18 and 40; (3) Intervent-

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.
## Table 1. Data summary

<table>
<thead>
<tr>
<th>Study</th>
<th>Study period</th>
<th>Country</th>
<th>Multicenter or single center</th>
<th>Study design</th>
<th>Cure Number Case</th>
<th>Cure Number Control</th>
<th>Recurrence Number Case</th>
<th>Recurrence Number Control</th>
<th>Medication time (d) Case</th>
<th>Medication time (d) Control</th>
<th>Edema Case</th>
<th>Edema Control</th>
<th>Erosion Case</th>
<th>Erosion Control</th>
<th>Pain Case</th>
<th>Pain Control</th>
<th>Skin lesion Case</th>
<th>Skin lesion Control</th>
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<tbody>
<tr>
<td>Beutner KR 2009</td>
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<td>RCT</td>
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<td>9.5±2.5</td>
<td>18.9±4.2</td>
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<td>31</td>
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<td>31</td>
<td>4</td>
<td>14</td>
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<td>3</td>
<td>12</td>
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<td>3</td>
<td>12</td>
<td>3</td>
<td>12</td>
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<td>20</td>
<td>4</td>
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<td>75</td>
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<td>Single center</td>
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<td>44</td>
<td>6</td>
<td>23</td>
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<td>9.8±1.7</td>
<td>19.6±3.1</td>
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<td>7</td>
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<td>China</td>
<td>Single center</td>
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<td>9.1±1.9</td>
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<td>32</td>
<td>1</td>
<td>32</td>
</tr>
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</table>
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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)
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Table 1. Risk Differences and Meta-analysis Results

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Weight</th>
<th>M-H. Fixed. 95% CI</th>
<th>Risk Difference</th>
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<tbody>
<tr>
<td>Beutner KR 2009</td>
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<td>74</td>
<td>29</td>
<td>68</td>
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</tr>
<tr>
<td>Bin He 2013</td>
<td>3</td>
<td>33</td>
<td>12</td>
<td>29</td>
<td>-0.32 [-0.53, -0.12]</td>
</tr>
<tr>
<td>Cheng Wang 2018</td>
<td>4</td>
<td>85</td>
<td>25</td>
<td>80</td>
<td>-0.27 [-0.38, -0.15]</td>
</tr>
<tr>
<td>Fangming Xie 2007</td>
<td>3</td>
<td>33</td>
<td>12</td>
<td>27</td>
<td>-0.35 [-0.57, -0.14]</td>
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<tr>
<td>Greenberg MD 2001</td>
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<td>62</td>
<td>25</td>
<td>54</td>
<td>-0.40 [-0.54, -0.25]</td>
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<tr>
<td>Hu Nan 2018</td>
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<td>69</td>
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<td>38</td>
<td>-0.72 [-0.85, -0.59]</td>
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<td>Kang Zeng 1998</td>
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<td>47</td>
<td>11</td>
<td>30</td>
<td>-0.26 [-0.45, -0.07]</td>
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<tr>
<td>Kirby P 2010</td>
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<td>48</td>
<td>22</td>
<td>43</td>
<td>-0.41 [-0.58, -0.23]</td>
</tr>
<tr>
<td>T.A. Syed 1994</td>
<td>16</td>
<td>205</td>
<td>31</td>
<td>144</td>
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<tr>
<td>Xiaohong Li 2018</td>
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<td>35</td>
<td>10</td>
<td>22</td>
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<td>Xiaohong Liu 2000</td>
<td>2</td>
<td>46</td>
<td>11</td>
<td>53</td>
<td>-0.16 [-0.29, -0.04]</td>
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<tr>
<td>Xiaogun Li 2018</td>
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<td>40</td>
<td>23</td>
<td>27</td>
<td>-0.70 [-0.88, -0.53]</td>
</tr>
<tr>
<td>Zhenhui Yang 2018</td>
<td>3</td>
<td>54</td>
<td>18</td>
<td>45</td>
<td>-0.34 [-0.50, -0.19]</td>
</tr>
</tbody>
</table>

Total (95% CI): 831/660 = 100.0%; -0.32 [-0.36, -0.28]

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 satisfaction. 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 $\chi^2$ 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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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 the 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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The heterogeneity test result was (chi-squared =137.4, P=0.31, I²=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

The 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, I²=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).

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, I²=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 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.
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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, I² = 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, I² = 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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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] believed that podophyllotoxin liposomes can reduce the incidence of adverse reactions in patients 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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We can draw a conclusion that both products have significant clinical effects. However, podophyllotoxin flexible nanoliposomal gel significantly reduced the patient’s recurrence rate. The flexible nanoliposomal 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 nano-liposomal gel is more convenient to use, the wart is more thoroughly removed, with small damage and no scar. There were few adverse reactions during the treatment.

Disclosure of conflict of interest

None.

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