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Review Article

Meta-analysis of the effect and safety of recombinant human interferon α-2b combined with Baofukang suppository in the treatment of HPV infection

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Abstract: Persistent infection of human papilloma virus (HPV) increases the risk of cervical precancerous lesions turning into cervical cancer, which seriously affects women's reproductive health and quality of life. This meta-analysis analyzed the effect and safety of recombinant human interferon α-2b (rhIFNα-2b) combined with Baofukang suppository in the treatment of HPV infection. Online databases were used to search for randomized clinical trials (RCTs) on the treatment of HPV infection with the deadline of January 2022 and the effects of treatment were analyzed by the odds ratio (OR) of treatment outcomes (total effective rate, HPV clearance rate and adverse reaction rate). The interval estimation was expressed by 95% confidence interval (CI). The searching results showed that there were 15 RCTs, including 1786 HPV-infected cases meeting the criteria for meta-analysis, of which 893 received combination therapy. In terms of total effective rate, combination therapy was superior to monotherapy (OR = 4.82, 95% CI 3.43-6.75, $P < 0.001$). In terms of increasing the HPV clearance rate and reducing the adverse reaction rate, combination therapy also showed obvious advantages over monotherapy (OR = 4.51, 95% CI 3.18-6.39, $P < 0.001$; OR = 0.60, 95% CI 0.40-0.91, $P < 0.02$). Our findings suggested that rhIFNα-2b combined with Baofukang suppository is safe and effective in the treatment of cervical HPV infection. Due to the limited quality of the included studies, the results need to be further studied and validated by more high quality RCTs.

Keywords: Cervical human papilloma virus infection, recombinant human interferon α-2b, Baofukang suppository, HPV clearance rate

Introduction

Cervical cancer is the most common gynecologic malignant tumor of parous women in underdeveloped parts of the globe [1]. Almost all cases of cervical cancer can be attributed to human papilloma virus (HPV) infection, which is a key factor triggering cervical cancer. Current researches confirm that approximately 80% of cervical cancers worldwide are associated with HPV type 16 and HPV type 18 infections [2], which release viral particles in the mature epithelial cells by infecting the cervical mucosal epithelium, resulting in disruption of normal cell cycle control and constant abnormal cell division [3]. Most genital tract HPV infections are short-term illness and are self-healing. However, treatments are required once they develop into a severe and persistent infection. Studies have shown that strengthening the prevention of HPV infection is very beneficial for the prevention of malignant tumors [4].

Drug therapy is a method of high safety and high compliance in the treatment of HPV infection. Recombinant human interferon α-2b has a broad-spectrum antiviral effect, which can hinder the replication of HPV virus ribonucleic acid and is conducive to tissue regeneration and repairing and improving the immune function of the vagina. The short-term efficacy of monotherapy is acceptable, but the risk of recurrence is high. In addition, long-term medication may also affect the patient's tolerance and compliance [5]. In China, a large number of papers on the treatment of HPV infection with the combination of Baofukang suppository (traditional Chinese medicine preparation) and recombi-

nant human interferon α-2b have been published in recent years, showing satisfactory therapeutic effects. However, with uneven paper quality and unified treatment standard, the efficacy of the combination of Baofukang suppository and recombinant human interferon α-2b remains to be confirmed. Therefore, literatures on the treatment of high-risk HPV infections by Baofukang suppository in combination with recombinant human interferon α-2b were extensively searched in various databases and meta-analysis was conducted to objectively evaluate the effect and safety of this method in the treatment of HPV infection, trying to provide evidence-based medical proof for clinical application.

Materials and methods

Source of materials

PRISMA statement was followed in meta-analysis [6].

Published literatures on the treatment of high-risk HPV infections by Baofukang suppository in combination with recombinant human interferon α-2b from the establishment of the databases to January 2022 were searched in databases including *China national knowledge infrastructure (CNKI), Vip database (VIP),* Wanfang, The Cochrane Library, Google Scholar, Embase, Medline, and PubMed. The search strategy contained 3 core parts, using the operator "AND" to link each part. Taking CNKI as an example: (1) HPV infection (e.g., Papillomavirus Infection, Human Papillomavirus Infection, HumanPapillomavirus Infections, Human, Papillomavirus Infections, HPV Infection). (2) Baofukang suppository (e.g., Baofukang bolt). (3) Recombinant human interferon α-2b (e.g., IFN-α2b, rhIFN-α2b, Xinfuning, Youjingan).

Criteria for inclusion

(1) Type of research: RCTs: not limited by languages and publication types. (2) Research subjects: women who were diagnosed with cervical HPV infection (refer to the 2010 *Guidelines for the Treatment of HPV Infection by Centers for Disease Control and Prevention* [7]); women who were married or unmarried but with a history of sexual life; not limited by nationality, race or source of cases. (3) Interventions: recombinant human interferon α-2b combined with Baofukang suppository was adopted in experimental group, while blank control or only recombinant human interferon α-2b was adopted in control group. (4) Outcome indicators: total effective rate, HPV clearance rate, and rate of adverse reaction (vaginal discomfort, increased vaginal discharge, abnormal leukorrhea, fever, frequent urination, rash, and gastrointestinal discomfort).

Exclusion criteria

(1) Literature reviews, meta-analyses, systematic reviews, animal experiments, non-randomized controlled trials and literature with unavailable full text. (2) Patients who were also affected with cervical intraepithelial neoplasia (CIN1/CIN2/CIN3), cervicitis, or who were pregnant or breastfeeding. (3) Intervention: in addition to recombinant human interferon α-2b or Baofukang suppository, other adjuvant treatments methods were also adopted. (4) Repeatedly published studies or studies with duplicate data. (5) For studies published by the same author, only his/her latest one was selected. And for studies with duplicate data, only 1 study with the most comprehensive data was selected.

Literature screening

Literature screening was conducted independently by 2 trained staff (Changfu He, Chunyan Song) according to uniform screening criteria and the results were cross-checked. If two staff have inconsistent views on the screening results of certain literature, the opinion of a third-person (Min Li) will be adopted to assist in the judgement and resolution.

Data extraction

NoteExpress software was used for literature management and Excel was used to make tables for data extraction. The extracted literature data mainly included title, name of the first author, publication time, sample size (experimental group/control group), diagnostic criteria, baseline comparability, intervention, drug name, dosage, course of treatment, outcome indicators and adverse events. In the event of incomplete data, the author of that literature was contacted.

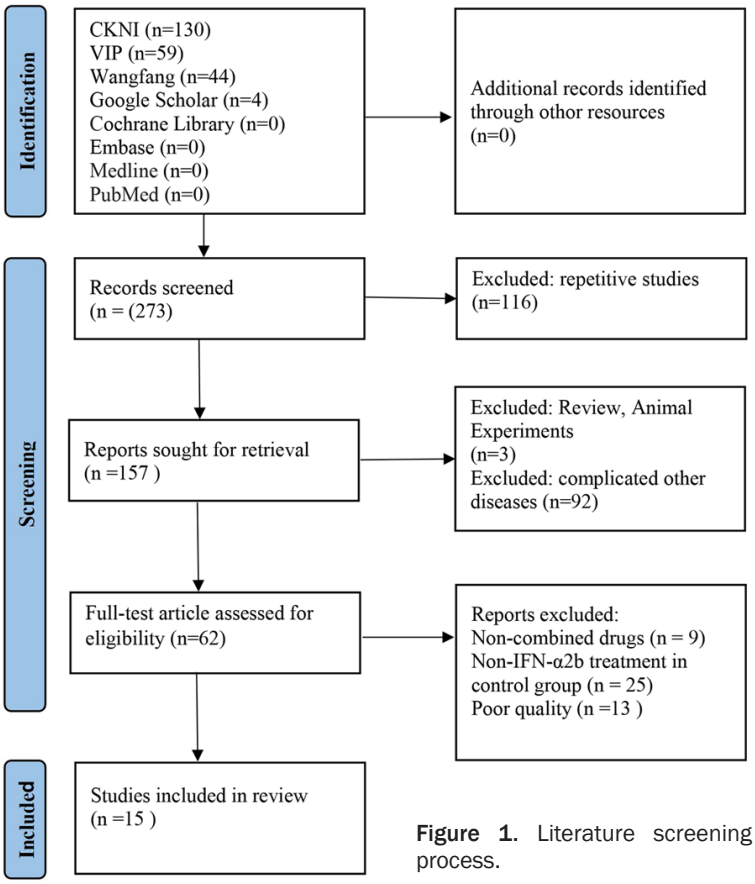

Figure 1. Literature screening process.

Quality evaluation of literature

As to the criteria for evaluating the quality of the included literature, Cochrane Handbook was followed [8]. The risk of bias was evaluated mainly from 7 parts: random sequence generation (selection bias), allocation cancellation (selection bias), blinding of patients and researchers participating in the study (implementation bias), blinding of those assessing outcomes (measurement bias), incomplete outcome data (withdrawal bias), selective reporting of outcomes, and other biases. In the end, the risk of bias in the literature was classified into three categories: low, high, and unclear.

Statistical analysis

RevMan 5.3 was used for meta-analysis. The enumeration data were expressed by OR, the continuous variable data were expressed by mean difference (MD) and the interval estimation was expressed by CI. Heterogeneity was evaluated by using I^2 and P. When P was ≥ 0.1 and I^2 was ≤ 50%, the heterogeneity was small, so the fixed-effect model (FEM) was used for meta-analysis. When P was < 0.1 and I^2 was > 50%, the heterogeneity was large, so the random-effect model (REM) was used for meta-analysis. When the number of literature included in the outcome indicators was over 10, a funnel plot was used to analyze whether there was publication bias.

Ethical statement

All analyses were conducted based on previously published studies. Therefore, ethical approval and patient's consent were not required.

Results

Overview of literature retrieval and screening

Two hundred and seventy-three studies were found in the initial search and there were 157 left after duplicates checking by NoteExpress. After reading the title and abstract, 62 of them were selected for full text reading. Studies with non-combination drugs, unreasonable experimental design, incomplete data and those that IFNα-2b was not adopted in control group and those that were not compliant with inclusion criteria were excluded. Finally, 15 studies [9-23] were included, all of which were written in Chinese (**Figure 1**).

Basic features of the included studies

A total of 15 studies [9-23] were included, all of which were Chinese and the study subjects were either infected with HPV or high-risk human papillomavirus (HR-HPV), with a sample size of 1786 cases (893 cases in the experimental group and 893 cases in the control group). The maximum sample size of the experimental group and the control group was 150 cases and the minimum sample size was 30 cases (**Table 1**).

Table 1. Basic features of included literature

Studies	Diagnosis	Study design	Number of researchers	Ages	Intervention		Outcome
			E/C	E/C	E	C	
Liang N 2019 [9]	HR-HPV(+)	Random	30/30	35.4±4.2/35.6±1.1	Based on C group + Baofukang, 1.74 g/d, qd, 15 days/courses, for 3 courses (ad us, ext)	rhIFN-α2b, 8×10^5 IU/d, qd, 9 days/courses, for 3 courses (ad us, ext)	①②
Fang Y 2021 [10]	HPV(+)	Random number table	50/50	42.29±6.37/42.31±6.28	Based on C group + Baofukang, 1.74 g/d, qod, for 3 months (ad us, ext)	rhIFN-α2b, 5×10^5 IU/d, qod, 12 days/courses, for 3 courses (ad us, ext)	①②
Zhu W 2020 [11]	HPV(+)	Random number table	42/42	32.45±3.39/32.51±3.31	Based on C group + Baofukang, 1.74 g/d, qd, 18 days/courses, for 3 courses (ad us, ext)	rhIFN-α2b, 10 g/d, qd, 18 days/courses, for 3 courses (ad us, ext)	①③
Huang J 2017 [12]	HR-HPV(+)	Random	40/40	35.31±2.13/35.25±2.45	Based on C group + Baofukang, 1.74 g/d, qd, for 3 weeks (ad us, ext)	rhIFN-α2b, 1×10^5 IU/d, qd, for 3 weeks (ad us, ext)	①
Yang J 2016 [13]	HR-HPV(+)	Random number table	73/73	35.56±4.39/35.79±4.42	Based on C group + Baofukang, 1.74 g/d, qd, 15 days/courses, for 3 courses (ad us, ext)	rhIFN-α2b, 8×10^5 IU/d, qd, 9 days/courses, for 3 courses (ad us, ext)	①②
Wu Y 2015 [14]	HR-HPV(+)	Random number table	35/35	34.6±4.1/33.9±4.3	Based on C group + Baofukang, 3.48 g/d, qod, for 3 months (ad us, ext)	rhIFN-α2b, 10 g/d, qod, for 3 months (ad us, ext)	①
Shun X 2022 [15]	HPV(+)	Random number table	150/150	45.39±3.75/45.36±3.74	Based on C group + Baofukang, 1.74 g/d, qd, for 3 months (ad us, ext)	rhIFN-α2b, 1 g/d, for 3 months (ad us, ext)	①③
Li C 2018 [16]	HR-HPV(+)	Random	100/100	36.62±2.19/35.92±2.61	Based on C group + Baofukang, 3.48 g/d, qod, 16 days/courses, for 3 courses (ad us, ext)	rhIFN-α2b, 10 g/d, qd, 16 days/courses, for 3 courses (ad us, ext)	①②③
Liu H 2016 [17]	HR-HPV(+)	Random	60/60	39.3±4.1/39.23±4.16	Based on C group + Baofukang, 3.48 g/d, qod, for 2 weeks (ad us, ext)	rhIFN-α2b, 10 g/d, qod, 10 times/courses, for 3 courses (ad us, ext)	①②③
Lai Z 2021 [18]	HR-HPV(+)	Random	39/39	46.2±3.5/42.2±3.5	Based on C group + Baofukang, 1.74 g/d, qod, 10 times/courses, for 3 courses (ad us, ext)	rhIFN-α2b, 5×10^5 IU/d, qod, 10 times/courses, for 3 courses (ad us, ext)	①②③
Li X 2020 [19]	HR-HPV(+)	Random number table	35/35	35.3±5.0/36.3±4.4	Based on C group + Baofukang, 1.74 g/d, qod, 10 times/courses, for 3 courses (ad us, ext)	rhIFN-α2b, 1×10^5 IU/d, qod, 10 times/courses, for 3 courses (ad us, ext)	③
Wang L 2021 [20]	HR-HPV(+)	Random number table	60/60	35.26±4.86/35.56±5.10	Based on C group + Baofukang, 1.74 g/d, qod, 10 times/courses, for 3 courses (ad us, ext)	rhIFN-α2b, 1 ga time, qod, 10 times/courses, for 3 courses (ad us, ext)	①②③
Lai X 2022 [21]	HR-HPV(+)	Random	40/40	35.12±4.08/35.32±4.31	Based on C group + Baofukang, 3.48 g/d, qod, 16 days/courses, for 3 courses (ad us, ext)	rhIFN-α2b, 8×10^5 IU/d, qd, 16 days/courses, for 3 courses (ad us, ext)	①②③
Yi B 2021 [22]	HPV(+)	Random number table	109/109	38.9±6.7/38.6±6.6	Based on C group + Baofukang, 1.74 g/d, qd, 10 days/courses, for 3 courses (ad us, ext)	rhIFN-α2b, 8×10^5 IU/d, qd, 10 days/courses, for 3 courses (ad us, ext)	①②③
Zhou J 2020 [23]	HPV(+)	Grouped by medication	30/30	38.86±2.95/37.24±2.35	Based on C group + Baofukang, 1.74 g/d, qd, for 3 months (ad us, ext)	rhIFN-α2b, 10 g/d, qd, for 3 months (ad us, ext)	①

Notes: HR-HPV stands for high-risk human papillomavirus infection; E stands for experimental group; C stands for control group; qd stands for once a day; qod stands for once every other day; ad us, ext stands for external use; ① stands for total effectiveness of treatment; ② stands for HPV clearance rate; ③ stands for adverse reaction rate.

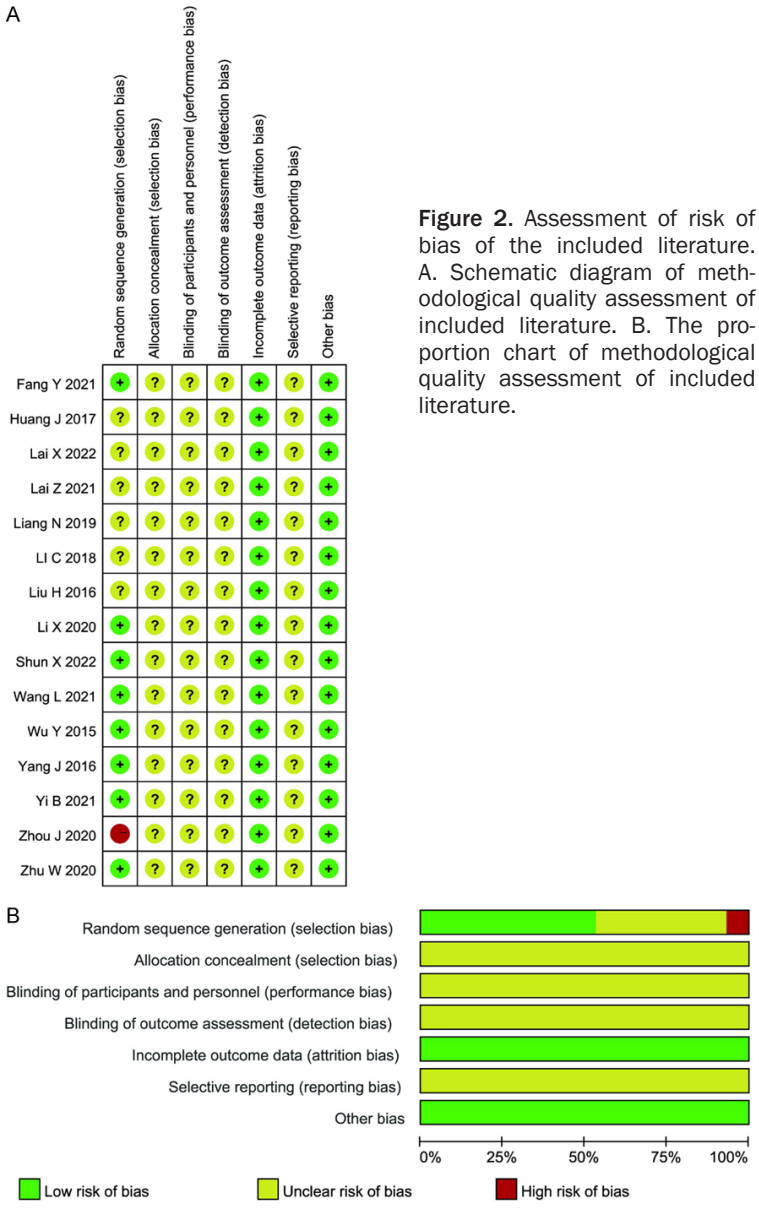

Figure 2. Assessment of risk of bias of the included literature. A. Schematic diagram of methodological quality assessment of included literature. B. The proportion chart of methodological quality assessment of included literature.

Assessment of risk of bias of the included studies

The included studies were all RCTs, of which 8 [10, 11, 13-15, 19, 20, 22] reported that the random number table method was adopted and were rated as low risk; 6 [9, 12, 16-18, 21] did not report a specific method of randomization and only stated that the methods were random, so their risks were identified as unclear; 1 [23] was rated as high risk because the grouping was based on different medications; 15 did not state the allocation concealment, so their risks were rated as unclear. In terms of the blinding of the study results, none of the studies mentioned this and their risks of bias were therefore rated as unclear. In terms of the incompleteness of results data, all were complete and were therefore rated as low risk. In terms of selective reporting, according to the studies recorded by the China Clinical Trials Registry, none of them had reported and therefore rated as unclear. All studies that did not have any other biases were rated as low risk (**Figure 2**).

Meta-analysis results

Meta-analysis of the total effective rate of treatment: Fourteen [9-18, 20-23] studies reported the total effective rate of treatment. The differences in heterogeneity tests were not statistically significant (P = 0.96, I^2 = 0%), so fixed-effects model was applied. The results showed that the total effective rate of recombinant human interferon α-2b combined with Baofukang suppository in the treatment of HPV infection was higher than that of recombinant human interferon α-2b alone [OR = 4.82, 95% CI (3.43-6.75), P < 0.00001; **Figure 3**].

Meta-analysis of HPV clearance rate: Eight studies [9, 10, 13, 16-18, 20-22] reported the HPV clearance rate. The differences in heterogeneity tests were not statistically significant (P = 0.94, I^2 = 0%), so a fixed-effects model was applied. The results showed that the HPV clearance rate of recombinant human interferon α-2b combined with Baofukang suppository in the treatment of HPV infection was higher than that of recombinant human interferon α-2b alone [OR = 4.51, 95% CI (3.18-6.39), P < 0.00001; **Figure 4**].

Meta-analysis of adverse reaction rate: Ten studies [11, 15-22] reported adverse reactions

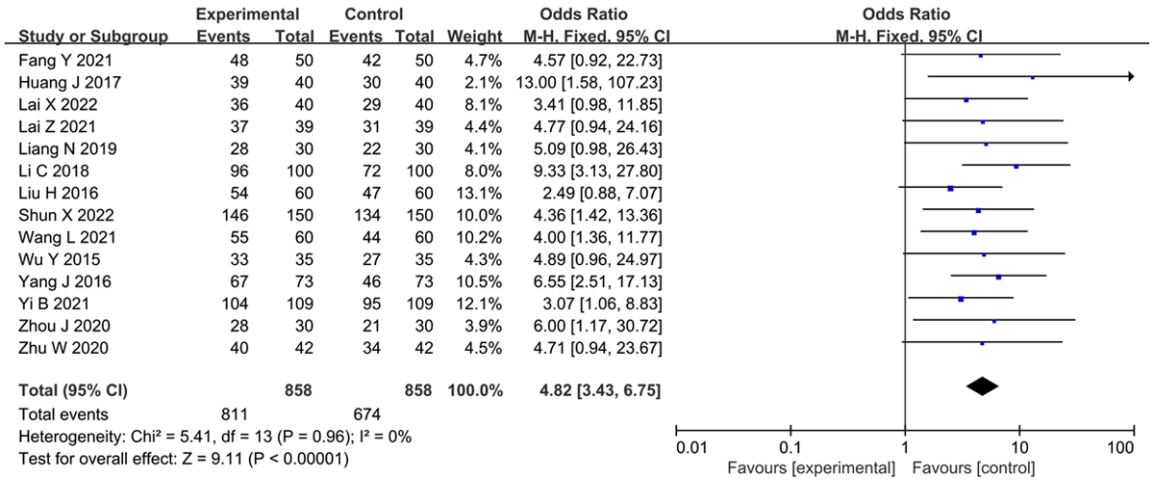

Figure 3. Forest plot of total effective rate of recombinant human interferon α-2b combined with Baofukang suppository vs. recombinant human interferon α-2b only.

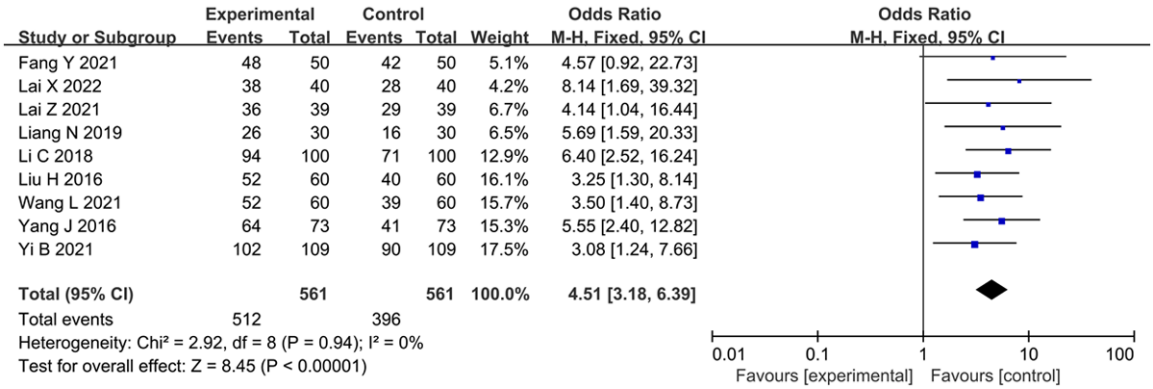

Figure 4. Forest plot of HPV clearance rate of recombinant human interferon α-2b combined with Baofukang suppository vs. recombinant human interferon α-2b only.

in patients, mainly including vaginal pain, fever, vaginal secretion increase, vaginal discomfort, anorexia, etc. (**Table 2**). The differences in heterogeneity tests were not statistically significant (P = 0.49, I^2 = 0%), so a fixed-effects model was applied. The results showed that the adverse reaction rate of recombinant human interferon α-2b combined with Baofukang suppository in the treatment of HPV infection was lower than that of recombinant human interferon α-2b alone [OR = 0.60, 95% CI (0.40-0.91), P < 0.02; **Figure 5**].

Assessment of publication bias

Total effective rate of treatment: The funnel plot analyzed the total effective rate of recombinant human interferon α-2b combined with Baofukang suppository and that of recombinant human interferon α-2b alone in the treatment of HPV infection, the results of which showed that the data were completely distributed inside the graph with obvious asymmetry, indicating that there existed a certain large degree of publication bias in the studies (**Figure 6**).

Occurrence of adverse reactions: The funnel plot analyzed the adverse reaction rate of recombinant human interferon α-2b combined with Baofukang suppository and that of recombinant human interferon α-2b alone in the treatment of HPV infection, and the results showed that the data were distributed within the range, and the graph was considerably symmetrical (**Figure 7**), indicating that there was basically no publication bias in the studies.

Table 2. Incidence of adverse reactions

Study	Adverse reaction	
	E	C
Zhu W 2020 [11]	Vaginal pain 1 case	Vaginal pain 1 case, pruritus 1 case, fever 1 case
Shun X 2022 [15]	Abdominal distension 3 cases, pruritus 2 cases, vaginal pain 2 cases	Abdominal distension 3 cases, pruritus 3 cases, vaginal pain 2 cases
Li C 2018 [16]	Vaginal uncomfortable 4 cases, fever 3 cases, urine frequency 2 cases	Vaginal uncomfortable 5 cases, fever 3 cases, urine frequency 3 cases
Liu H 2016 [17]	Irritability 1 case	Irritability 1 case, gastrointestinal reaction 1 case
Lai Z 2021 [18]	Vaginal pain 3 cases, vaginal dryness 2 cases	Vaginal pain 1 case, vaginal dryness 3 cases
Li X 2020 [19]	leucorrhea increasing 1 case, rash 1 case	leucorrhea increasing 2 cases, rash 1 case
Wang L 2021 [20]	Vaginal secretion increase 1 case, abnormal leukorrhea 2 cases, vaginal uncomfortable 2 cases	Vaginal secretion increase 3 cases, abnormal leukorrhea 4 cases, vaginal uncomfortable 6 cases
Lai X 2022 [21]	Vaginal uncomfortable 1 case, fever 1 case	Vaginal uncomfortable 3 cases, fever 2 cases, urine frequency 1 case
Yi B 2021 [22]	Vaginal pain 5 cases, abdominal distension 2 cases, vaginal secretion increase 1 case	Vaginal pain 3cases, abdominal distension 2 cases, vaginal uncomfortable 1 case, vaginal secretion increase 1 case
Zhou J 2020 [23]	Pruritus 1 case	Vaginal pain 2 cases, pruritus 3 cases, urine frequency 3 cases

E: experimental group; C: control group.

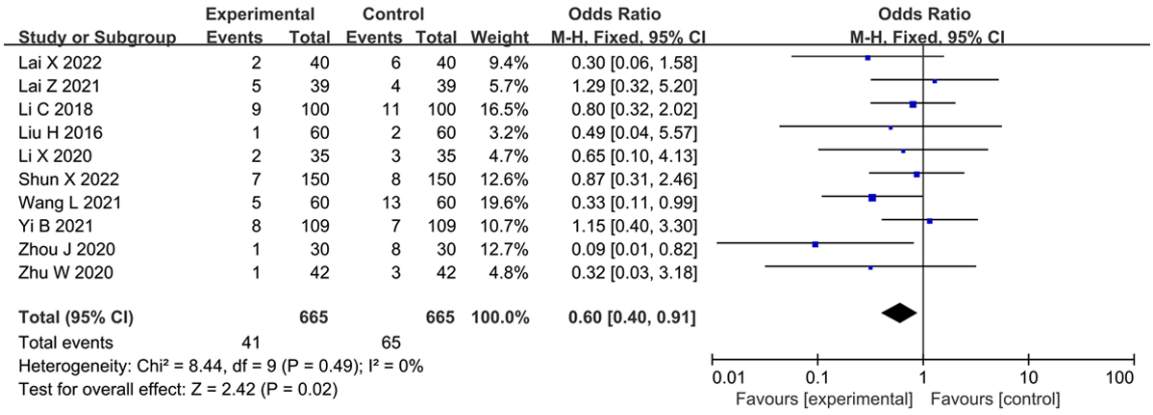

Figure 5. Forest plot of adverse reaction rate of recombinant human interferon α-2b combined with Baofukang suppository vs. recombinant human interferon α-2b only.

Discussion

This study comprehensively retrieved the RCTs of recombinant human interferon α-2b combined with Baofukang suppository in the treatment of HPV infection and evaluated the effect of treatment from 2 aspects: total effective rate and HPV clearance rate. From the results of meta-analysis, it can be seen that the treatment of HPV infection using recombinant human interferon α-2b combined with Baofukang suppository was better than using recombinant human interferon α-2b alone, which was mainly manifested in higher total effective rate and higher clearance rate of the experimental group. Adverse reactions of both treatment methods were also taken into consideration. Related reports indicated that the treatment of HPV infection by recombinant human interferon α-2b will lead to adverse reactions such as vaginal discomfort, increased vaginal discharge and abnormal vaginal leukorrhea. The results of the meta-analysis showed a decrease in the adverse reaction rate after using recombinant human interferon α-2b combined with Baofukang suppository in treatment.

HPV DNA testing is an important biological indicator for diagnosing HPV infection [24]. The types of infection can be divided into high-risk

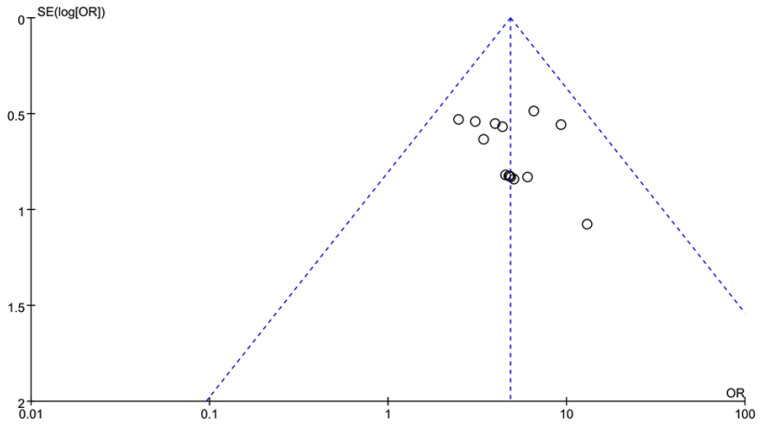

Figure 6. Funnel plot of total effective rate of treatment.

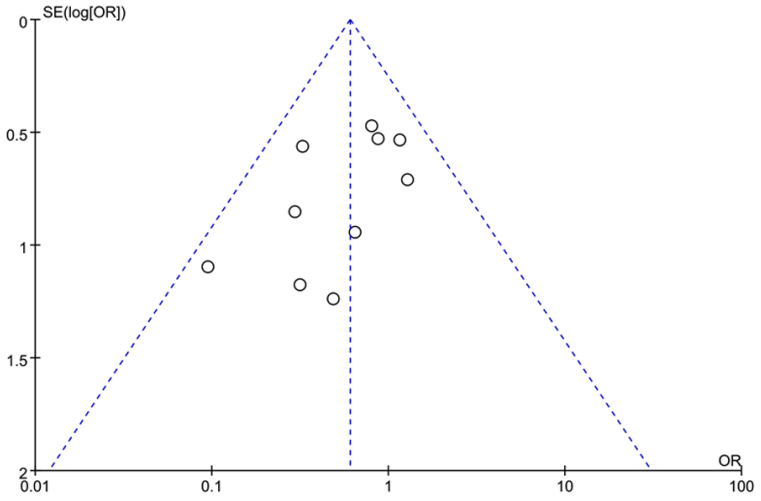

Figure 7. Funnel plot of adverse reaction rate.

and low-risk, depending on the subtype of the virus. HPV infection is associated with the cause of vaginitis and cervicitis. In addition, high-risk HPV infection has the potential to result in carcinogenesis and persistent high-risk HPV infection is closely related to the occurrence of cervical cancer [25]. Current treatments for cervical HPV infection vary according to the disease severity, including cryotherapy [26], laser therapy [27], carbon dioxide (CO_2) therapy [28], antivirals [29] and cervical loop electrosurgical excision procedure (LEEP) [30]. However, due to the latentness of HPV and limited treatment options, there is a chance that the infection will recur, which leads to unsatisfactory treatment results. Recombinant human interferon α-2b is a broad-spectrum antibacterial drug produced by human white blood cells with strong antiviral, antineoplastic and immunomodulatory effects [31]. It inhibits viral protein synthesis by inducing cells to produce antiviral proteins, thereby preventing the replication and transcription of virus [31]. However, due to its short half-life, clinical application is still limited. At present, the screening of antineoplastic and antiviral drugs from herbs and traditional Chinese medicines has become a hot topic related to the treatment of HPV infection. Scholars such as Nikakhtar [32] have reported that vaginal suppository, water extract of the myrtle, can speed up the clearance of HPV virus, thus effectively treating HPV infection. As a Chinese medicine with a long history of being used for treating gynecological diseases, Baofukang suppository has been repeatedly reported in recent decades that its combination with recombinant human interferon α-2b is good for the treatment of cervical HPV infection. It is mainly composed of two kinds of Chinese medicine: zedoary turmeric oil and borneol. Zedoary turmeric oil is a volatile oil distilled from turmeric that contains a variety of active ingredients, including curcumin, curcuminol and curcuminone, which are antibacterial, antineoplastic and antiviral [33]. Borneol is a kind of natural crystalline compound extracted from the resin of dipterocarpaceae tree containing bicyclic monoterpene alcohol, which has anti-inflammatory, analgesic and antibacterial properties and can accelerate percutaneous absorption of drugs and increase the bioavailability of drugs in brain tissue [34]. Moreover, Li and other researchers [35] reported that Baofukang suppository is a good antibacterial drug, because it can effectively inhibit the formation and proliferation of bacterial hyphae in the treatment of vulvovaginal candidiasis, boosting the immune system. Current studies have found that rhIFN-α2b can bind to

interferon receptors on the surface of target cells, promote the expression of antiviral proteins, inhibit the replication of HPV, reduce the expression level of viral proteins and restore the infection site to normal [36]. However, long-term use may cause adverse reactions, but adverse reactions will disappear after withdrawal [37]. Baofukang suppository has inhibitory effect on virus, mold, bacteria and so on [38]. Its combination with rhIFN-α2b in the treatment of HPV infection is beneficial to reduce the load of virus and improve the clinical symptoms of patients [39].

There are still some limitations in this study. First, the quantity and quality of the included studies need to be further improved. All studies mentioned the method of randomization, but none mentioned allocation concealment and blinding, which was prone to the risk of bias. The sample size of some studies was too small. Only 3 [15, 16, 22] of them had over 100 cases, the remaining 12 [9-14, 17-21, 23] had less than 80 cases and the minimum was only 30 cases, which could easily lead to unstable therapeutic effect indicators and low power of test that affect the extrapolation of results. Second, due to the different courses of treatment in different studies, there may be a large degree of bias in outcome indicators. Third, the included studies were conducted in China, resulting in geographical limitations.

Conclusion

This study aimed to systematically evaluate the effect of Baofukang suppository combined with recombinant human interferon α-2b in the treatment of cervical HPV infection, so as to provide evidence-based medical proof for the clinical treatment of HPV infection. The results of 15 studies showed that the application of Baofukang suppository combined with recombinant human interferon α-2b in the treatment of cervical HPV infection is effective and safe.

Disclosure of conflict of interest

None.

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