Research Article

Influence of Lacidophilin Vaginal Capsules plus rh-IFN-α2b on Efficacy, Vaginal Microecology, and Safety of Patients with HPV Infection

Yan Sun, Jianqun Xu, Hongya Zhou, Lina You, and Yan Zhu

Obstetrics and Gynecology, Xishan People’s Hospital of Wuxi City, Wuxi 214000, Jiangsu, China

Correspondence should be addressed to Yan Zhu; zhuyan9180@163.com

Received 5 June 2022; Accepted 9 July 2022; Published 3 August 2022

Academic Editor: Shoib Baba

Copyright © 2022 Yan Sun et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. Human papillomavirus (HPV) is a self-limiting disease, and there is no specific antiviral drug at present. Purpose. Here, we analyzed the influence of lacidophilin vaginal capsules plus recombinant human interferon α-2b (rh-IFN-α2b) on efficacy, vaginal microecology, and safety of patients with HPV infection. Two hundred cases of HPV infection admitted between January 2019 and December 2020 were retrospectively collected. Of them, 90 cases receiving rh-IFN-α2b intervention were assigned to the control group (CG), and 110 cases given lacidophilin vaginal capsules in addition to rh-IFN-α2b were included in the research group (RG). Baseline data, efficacy, vaginal microecology, microecological restoration recovery, and incidence of adverse events (AEs) were compared between the two groups.

Results. The analyses revealed nonsignificant difference in baseline data between RG and CG, indicating comparability. In terms of efficacy, RG showed a statistically higher negative conversion ratio (NCR) than CG (57.27% vs. 47.78%), as well as an obviously higher overall response rate (ORR) (90.90% vs. 72.22%). As far as the vaginal microecology was concerned, the incidence rates of catalase-positive, sialidase-positive, abnormal microbial density, and abnormal microbial diversity of RG were significantly lower compared with CG, but no evident differences were determined in Trichomonas vaginalis-positive and Candida-positive. As for microecological restoration, RG had an obviously higher vaginal microecological recovery rate than CG (90.00% vs. 65.56%), as well as notably lower vaginal secretion pH and Nugent score. On the other hand, RG and CG showed no statistical significance in the incidence of AEs (12.73% vs. 13.33%).

Conclusions. The main contributions of this study as follows: first, it is confirmed that lacidophilin vaginal capsules plus rh-IFN-α2b has better clinical effects than rh-IFN-α2b alone in HPV-infected patients; second, it demonstrates that the combination therapy can significantly improve NCR and ORR, without increasing the incidence of AEs, and is beneficial to improve patients’ vaginal microecology and promote its restoration from the multidimensional aspects of efficacy, safety, and vaginal microecology and its recovery. Our findings provide valuable clinical evidence for the drug treatment of HPV-infected patients.

1. Introduction

Human papillomavirus (HPV) infection is highly correlated with cervical cancer (CC, including squamous intraepithelial lesion (SIL)), in which persistent high-risk HPV can cause at least 90% of CC cases and is closely associated with squamous intraepithelial lesions [1, 2]. As a carcinogenic factor, HPV infection can also cause cancers in the vulva, anus, and oropharynx [3]. The carcinogenic mechanism of HPV infection is shown to be related to vaginal microecology, inflammatory factors, genetics, and immune function [4, 5]. This study analyses the clinical effect of drug therapy on HPV infection, aiming to provide novel references for the improvement of vaginal microecology and alleviation of inflammatory factors in HPV-infected patients.

Interferon α-2b is essentially a cytokine protein that is widely used in virtue of its broad-spectrum antitumor, antivirus, and immune-enhancing effects [6]. With the same biological function, recombinant human interferon α-2b (rh-IFN-α2b) can exert antitumor action in combination with other drugs [7]. In the research of Kaliki et al. [8], it is pointed out that rh-IFN-α2b can be used to treat ocular...
2. Data and Methods

2.1. Study Population. Inclusion criteria were as follows: diagnosis of HPV single infection or low-grade squamous intraepithelial lesion (LSIL); treatment-naive patients; nonpregnancy and nonlactating women; normal cognitive and mental conditions; premenopausal women; high compliance; and no contraindications to the medication used in this study.

Exclusion criteria were as follows: malignant tumors; one or more organ dysfunction; abnormalities of immune, hematopoietic or coagulation functions; distant metastasis; and presence of acute phase gynecological inflammation.

After rigorous screening, 200 HPV-infected patients admitted between January 2019 and December 2020 were enrolled, including 90 cases (control group, CG) treated with rh-IFN-α2b and 110 cases (research group, RG) additionally given lacidophilin vaginal capsules. The mean age and average course of disease of CG were 29.71 ± 5.68 years and 2.25 ± 1.05 years, respectively, while in RG, the data were 30.76 ± 8.14 years, and 2.49 ± 1.19 years, respectively. All subjects provided informed consent, and this study has been ethically ratified by our hospital.

2.2. Therapeutic Methods. CG received rh-IFN-α2b intervention. The subjects washed the vulva every night before going to bed since the third day after menstruation and placed the drug deep (one pill/time) in the vagina to the fornix near the cervical orifice once every two days. With ten times as a course of treatment, the patients were treated for a total of three courses.

RG was additionally intervened by the drug lacidophilin vaginal capsules, which was administered the second night after the use of rh-IFN-α2b intervention, two capsules at a time, using the same method as mentioned above. The patients received 4 courses of treatment, with seven times of medication as a course.

Antibiotics, vaginal irrigation, tub bath, and sexual life were prohibited in both the groups during treatment.

Efficacy assessment was performed three months after treatment.

2.3. Endpoints

(1) Curative effect: the negative conversion ratio (NCR) was assessed by cervical HPV-DNA, with the efficacy divided into three grades. Negative conversion: vaginal and cervical examinations at the follow-up visit showed that all high-risk HPV subtypes were negative; effective: some positive high-risk HPV subtypes turned negative and at least one HPV subtype remained positive; ineffective: all high-risk HPV subtypes were positive. The NCR was the percentage of negative cases in the total number of cases in the group, and the overall response rate (ORR) was the percentage of the sum of negative conversion and effective cases in the total number of cases in the group.

(2) Vaginal microecology: two sterile cotton swabs were used to collect vaginal secretions from the lateral wall of the patient’s vagina during the return visit. One was used to detect pH, catalase, and sialidase using the dry chemical method; the other was used for vaginal microecological examination through the microscope after smear, determining the presence of microbes such as Trichomonas vaginalis and Candida, as well as microbial density and diversity. It was considered positive when the concentration of catalase was less than 2 μmL/L and when the sialidase was greater than 9 units/mol.

(3) Microecological restoration: vaginal microecological restoration or normal was translated in vaginal secretion pH ≤ 4.5, and the microbial density and diversity within 10–999 bacteria/oil immersion lens, with Lactobacillus as the dominant flora, Nugent score ≤ 3 points [12], as well as catalase and sialidase-negative. In contrast, unrecovered vaginal microecology was indicated if the vaginal secretion pH was greater than 4.5, and microbial density and diversity were 1–9 or more than 1000 bacteria/oil immersion lens, with Gram-negative Brevibacterium, coccus, or miscellaneous bacteria as the dominant flora, Nugent score > 3, as well as catalase and sialidase-positive.

(4) Safety: we observed and counted the cases of vaginal redness and swelling, vaginal tingling, vaginal bleeding, and cervical or vaginal neoplasms in both the groups. The total incidence of adverse events (AEs) was the percentage of these events in the total number of cases in the group.

2.4. Statistical Processing. The data was visualized by GraphPad Prism 6 (GraphPad Software, San Diego, USA). Counting data were expressed by case number/percentage (n (%)), and the chi-square test was used for comparison between groups. Mean ± standard deviation (mean ± SD) was used to represent the measurement data. The methods for
intergroup and intragroup (before and after treatment) comparisons of measurement data were the independent sample t-test and paired t-test, respectively. Statistically significant differences were assumed at $P$ values less than 0.05.

### 3. Results

#### 3.1. Baseline Data of HPV-Infected Patients
The two cohorts differed insignificantly in age, mean age, course of disease, pathological classification, HPV genotyping, residence, family history, and other baseline data ($P > 0.05$), as given in Table 1.

#### 3.2. Efficacy in HPV-Infected Patients
The NCR and ORR of RG were 57.27% and 90.90%, respectively, while those of CG were 47.78% and 72.22%, respectively. The above data revealed statistically higher NCR and ORR in RG compared with CG ($P < 0.05$), as given in Table 2.

#### 3.3. Vaginal Microecology in Patients with HPV Infection
Significant differences were present in catalase-positive, sialidase-positive, abnormal microbial density, and abnormal microbial diversity between RG and CG ($P < 0.05$); while the two cohorts of patients showed no statistical significance in Trichomonas vaginalis-positive and Candida-positive ($P < 0.05$), as given in Table 3.

#### 3.4. Microecological Recovery of HPV-Infected Patients
The vaginal microecology recovery rate in RG was significantly higher than that in CG (90.00% vs. 65.56%), while the pH and Nugent scores of vaginal secretions were significantly lower ($P < 0.05$), as shown in Figure 1.

#### 3.5. Safety of Treatment in HPV-Infected Patients
The corresponding cases of vaginal redness and swelling, vaginal tingling, vaginal bleeding, and cervix or vaginal neoplasms were 6, 4, 4, and 0 in RG, and 4, 2, 4, and 2 in CG, respectively. RG and CG presented no statistical difference in the incidence of AEs (12.73% vs. 13.33%, $P > 0.05$), as given in Table 4.

### 4. Discussion
HPV is a DNA tumor virus, which is small, double-stranded, and nonenveloped, with many subtypes [13, 14]. After infecting cervical basal epithelium, it can complete its life cycle by relying on host cell differentiation and can control the cell cycle and even cause carcinogenic lesions by building an environment that supports viral DNA amplification [15]. HPV can be sexually transmitted, which is the trigger of almost all CC lesions [16]. We found that lacidophilin vaginal capsules have beneficial effects on the curative effect and microecological restoration of HPV-infected patients and hereby report the findings in detail.
We enrolled 200 patients with HPV infection and grouped them into two groups, in which CG was treated with rh-IFN-α2b and RG was treated with lacidophilin vaginal capsules on the basis of CG. The results identified statistically higher NCR and ORR under the combined intervention of lacidophilin vaginal capsules plus rh-IFN-α2b compared with rh-IFN-α2b intervention alone. After being placed in the human cervix, lacidophilin vaginal capsules can induce the growth of LAB that generate lactic acid, bacteriocin, and biosurfactant to form an anti-infection barrier mucosa, so as to competitively check and balance and even inhibit the reproduction of harmful pathogenic bacteria and restore the balance of vaginal microecological flora, thus achieving the therapeutic purpose [17]. In the vaginal microecological evaluation, the incidence rates of catalase-positive, sialidase-positive, abnormal microbial density, and abnormal microbial diversity were found to be significantly lower in RG, while no significant differences were determined in Trichomonas vaginalis-positive and Candida-positive. It indicates that the vaginal microecology of patients with lacidophilin vaginal capsule intervention is generally better. Previous studies have shown that the dynamic balance mechanism of vaginal microecology can be affected by microbial diversity, density, reproduction rate, and host status, and once this balance is maladjusted, it is easy to induce microecological infectious diseases, such as trichomoni- asis vaginitis and bacterial vaginosis [18, 19]. Furthermore, the vaginal microecological recovery rate of patients additionally treated with lacidophilin vaginal capsules was found to be markedly higher, with statistically lower vaginal secretion pH and Nugent scores. Previous evidence has shown that lacidophilin vaginal capsules have the function of converting monosaccharides generated by glycogen into lactose in the vaginal microecological environment, which can effectively maintain the stability of vaginal acidic environment and correct the disorder of vaginal flora [20]. In terms of safety, we mainly recorded the cases of vaginal redness and swelling, vaginal tingling, vaginal bleeding, and cervical or vaginal neoplasms in HPV-infected patients. Although there is one more drug in RG, the incidence of AEs was no different from that in CG, suggesting a higher safety profile of the treatment implemented in RG.

### Table 3: Vaginal microecology of HPV-infected patients (n (%)).

| Category                              | Control group (n = 90) | Research group (n = 110) | χ² value | P value |
|---------------------------------------|------------------------|--------------------------|----------|---------|
| Catalase-positive                     | 11 (12.22)             | 3 (2.73)                 | 6.855    | 0.009   |
| Sialidase-positive                    | 11 (12.22)             | 4 (3.64)                 | 5.260    | 0.022   |
| Trichomonas vaginalis-positive        | 10 (11.11)             | 5 (4.55)                 | 3.076    | 0.080   |
| Candida-positive                      | 7 (7.78)               | 3 (2.73)                 | 2.658    | 0.103   |
| Abnormal microbial density           | 20 (22.22)             | 7 (6.36)                 | 10.661   | 0.001   |
| Abnormal microbial diversity         | 15 (16.67)             | 6 (5.45)                 | 6.622    | 0.010   |

G *P < 0.01.

We enrolled 200 patients with HPV infection and grouped them into two groups, in which CG was treated with rh-IFN-α2b and RG was treated with lacidophilin vaginal capsules on the basis of CG. The results identified statistically higher NCR and ORR under the combined intervention of lacidophilin vaginal capsules plus rh-IFN-α2b compared with rh-IFN-α2b intervention alone. After being placed in the human cervix, lacidophilin vaginal capsules can induce the growth of LAB that generate lactic acid, bacteriocin, and biosurfactant to form an anti-infection barrier mucosa, so as to competitively check and balance and even inhibit the reproduction of harmful pathogenic bacteria and restore the balance of vaginal microecological flora, thus achieving the therapeutic purpose [17]. In the vaginal microecological evaluation, the incidence rates of catalase-positive, sialidase-positive, abnormal microbial density, and abnormal microbial diversity were found to be significantly lower in RG, while no significant differences were determined in Trichomonas vaginalis-positive and Candida-positive. It indicates that the vaginal microecology of patients with lacidophilin vaginal capsule intervention is generally better. Previous studies have shown that the dynamic balance mechanism of vaginal microecology can be affected by microbial diversity, density, reproduction rate, and host status, and once this balance is maladjusted, it is easy to induce microecological infectious diseases, such as trichomoni- asis vaginitis and bacterial vaginosis [18, 19]. Furthermore, the vaginal microecological recovery rate of patients additionally treated with lacidophilin vaginal capsules was found to be markedly higher, with statistically lower vaginal secretion pH and Nugent scores. Previous evidence has shown that lacidophilin vaginal capsules have the function of converting monosaccharides generated by glycogen into lactose in the vaginal microecological environment, which can effectively maintain the stability of vaginal acidic environment and correct the disorder of vaginal flora [20]. In terms of safety, we mainly recorded the cases of vaginal redness and swelling, vaginal tingling, vaginal bleeding, and cervical or vaginal neoplasms in HPV-infected patients. Although there is one more drug in RG, the incidence of AEs was no different from that in CG, suggesting a higher safety profile of the treatment implemented in RG.

#### Figure 1: Microecological recovery of HPV-infected patients. (a) The vaginal microecological recovery rate of patients in the two groups. (b) The pH of vaginal secretions in the two groups. (c) Nugent scores of patients in the two groups. ** *P < 0.01.

### Table 4: Safety analysis of patients with HPV infection (n (%)).

| Category                                | Control group (n = 90) | Research group (n = 110) | χ² value | P value |
|-----------------------------------------|------------------------|--------------------------|----------|---------|
| Vaginal redness and swelling            | 4 (4.44)               | 6 (5.45)                 | —        | —       |
| Vaginal tingling                        | 2 (2.22)               | 4 (3.64)                 | —        | —       |
| Vaginal bleeding                        | 4 (4.44)               | 4 (3.64)                 | —        | —       |
| Cervical or vaginal neoplasms           | 2 (2.22)               | 0 (0.00)                 | —        | —       |
| Total                                   | 12 (13.33)             | 14 (12.73)               | 0.016    | 0.899   |
research of Verdenelli et al. [21], probiotic suppositories containing LAB not only restored and maintained normal vaginal microflora but were also well tolerated and beneficial to promote women’s vaginal health, which has certain similarities with the results of this study.

The main contribution of this study to the drug treatment of HPV-infected patients is to confirm the effectiveness of lacidophilin vaginal capsules in such a patient population, which can play a therapeutic role in promoting microecological recovery, inhibiting serum inflammatory factors, and reducing the incidence of grade III-IV AEs, providing a reliable basis for drug selection and prevention of CC in patients with HPV infection. There are still some limitations that need to be taken into consideration. First of all, long-term follow-up has not been carried out, which if supplemented for prognostic analysis, can help further understand the impacts of the two treatments on the prognosis of HPV-infected patients; second, conducting animal experiments for basic research can help further understand the therapeutic mechanism of lacidophilin vaginal capsules in HPV-infected patients; finally, the sample size should be increased to further improve the accuracy of experimental results.

Taken together, with certain safety, lacidophilin vaginal capsules can significantly improve the curative effect of HPV-infected patients, maintain their vaginal microecological balance, and inhibit inflammation, which is worthy of clinical promotion.

Data Availability
The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest
The authors declare that there are no conflicts of interest.

Acknowledgments
This work was supported by Wuxi Science and Technology Bureau-Research and Development of Medical and Public Health Technology Project (WX03-02B0105-071800-60).

References
[1] L. Song, S. Liu, S. Zeng, L. Zhang, and X. Li, "miR-375 modulates radiosensitivity of HR-HPV-positive cervical cancer cells by targeting UBE3A through the p53 pathway," Medical Science Monitor, vol. 21, pp. 2210–2217, 2015.
[2] J. Kim, B. K. Kim, D. Jeon et al., "Type Specific Viral Load and Physical State of HPV Type 16, 18, and 58 as Diagnostic Biomarkers for High Grade Squamous Intraepithelial Lesions or Cervical Cancer. Cancer Res Treat," Cancer Research and Treatment, vol. 52, pp. 396–405, 2020.
[3] X. Wang, H. K. Wang, Y. Li et al., "microRNAs are biomarkers of oncogenic human papillomavirus infections," Proceedings of the National Academy of Sciences of the United States of America, vol. 111, no. 11, pp. 4262–4267, 2014.
[4] Q. Fan, Y. Wu, M. Li et al., "Lactobacillus spp. create a protective micro-ecological environment through regulating the core fucosylation of vaginal epithelial cells against cervical cancer," Cell Death & Disease, vol. 12, p. 1094, 2021.
[5] J. Ren, L. Li, B. Yu et al., "Extracellular vesicles mediated proinflammatory macrophage phenotype induced by radiotherapy in cervical cancer," BMC Cancer, vol. 22, no. 1, p. 88, 2022.
[6] H. Liu, Y. Zou, J. Zhu et al., "Preparation and evaluation of rhINF-alpha-2b sodium hyaluronate cross-linked porous microspheres: characterization, sustained-release properties, and antitumor activity," AAPS PharmSciTech, vol. 23, no. 1, p. 31, 2021.
[7] H. Liu, J. Zhu, P. Bao et al., "Construction and in vivo/in vitro evaluation of a nanoporous ion-responsive targeted drug delivery system for recombinant human interferon alpha-2b delivery," International Journal of Nanomedicine, vol. 14, pp. 5339–5353, 2019.
[8] S. Kaliki, S. Singh, S. Iram, and D. Tripuraneni, "Recombinant interferon alpha 2b for ocular surface squamous neoplasia: an efficient and cost-effective treatment modality in Asian Indian patients," Indian Journal of Ophthalmology, vol. 64, no. 10, pp. 702–709, 2016.
[9] M. Song, R. S. DiPaola, B. M. Cracchiolo et al., "Phase 2 trial of pacitaxel, 13-cis retinoic acid, and interferon alfa-2b in the treatment of advanced stage or recurrent cervical cancer," International Journal of Gynecological Cancer, vol. 24, no. 9, pp. 1636–1641, 2014.
[10] X. Y. Ang, U. M. Mageswaran, Y. L. F. Chung et al., "Probiotics reduce vaginal candidiasis in pregnant women via modulating abundance of Candida and Lactobacillus in vaginal and cervicovaginal regions," Microorganisms, vol. 10, no. 2, p. 285, 2022.
[11] A. Lebeau, D. Bruyere, P. Roncarati et al., "HPV infection alters vaginal microbiome through down-regulating host mucosal innate peptides used by Lactobacilli as amino acid sources," Nature Communications, vol. 13, no. 1, p. 1076, 2022.
[12] E. M. Lokken, C. Jisuvei, B. Oyaro et al., "Nugent score, amsex’s criteria, and a point-of-care rapid test for diagnosis of bacterial vaginosis: performance in a cohort of Kenyan women," Sexually Transmitted Diseases, vol. 49, no. 1, pp. e22–e25, 2022.
[13] H. Liu, J. Xu, Y. Yang et al., "Oncogenic HPV promotes the expression of the long noncoding RNA Inc-FANCi-2 through E7 and YY1," Proceedings of the National Academy of Sciences of the United States of America, vol. 118, Article ID e2014195118, 2021.
[14] K. Van Doorslaer, Q. Tan, S. Xirasagar et al., "The Papillomavirus Episteme: a central resource for papillomavirus sequence data and analysis," Nucleic Acids Research, vol. 41, no. D1, pp. D571–D578, 2012.
[18] Y. Zhang, T. Liu, J. Lin, F. Yu, and Z. Hu, “STROBE-sequencing analysis of the vaginal microecology of 4- to 6-year-old girls in Southwest China,” Medicine (Baltimore), vol. 100, no. 13, Article ID e25362, 2021.

[19] X. Wu, L. Wang, and Z. Xing, “Impact of HPV infection on vaginal microecology and maternal and neonatal outcomes,” Zhong Nan Da Xue Xue Bao Yi Xue Ban, vol. 46, no. 5, pp. 497–502, 2021.

[20] T. Sadahira, K. Wada, M. Araki et al., “Efficacy of Lactobacillus vaginal suppositories for the prevention of recurrent cystitis: a phase II clinical trial,” International Journal of Urology, vol. 28, no. 10, pp. 1026–1031, 2021.

[21] M. C. Verdenelli, C. Cecchini, M. M. Coman et al., “Impact of probiotic SYNBIO® administered by vaginal suppositories in promoting vaginal health of apparently healthy women,” Current Microbiology, vol. 73, no. 4, pp. 483–490, 2016.