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Short communication

A randomized open-label clinical trial of an anti-HPV biological dressing (JB01-BD) administered intravaginally to treat high-risk HPV infection

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Abstract

Currently, there is no specific antiviral therapy for HPV infection. We conducted a randomized open-label clinical trial of JB01-BD, an anti-HPV biological dressing from Shanxi Jinbo Pharmaceutical Co., Ltd., China, for treatment of HPV infection. Seventy-seven women with cervical infection by high-risk HPV were randomly divided into a treatment group and a non-treatment group. After treatment, about 60.5% (23/38) of HPV-positive women in the treatment group became HPV-negative compared with 13.5% (5/37) of women in the non-treatment group becoming HPV-negative ($P < 0.001$). These data suggest that JB01-BD is an effective topical biological agent for the treatment of cervical HPV infection.

Keywords: Cervical cancer; Human papilloma virus (HPV); Antiviral therapy; Clinical trial

1. Introduction

As the fourth most common cancer in women worldwide, cervical cancer has caused more than 266,000 deaths each year [1]. About 80% of cervical cancer occurs in developing countries, where it has become the second leading cause of cancer mortality in women between 15 and 44 years of age [2]. Each year in China, about 135,000 women develop cervical cancer, and 50,000 die from it [3]. This statistic indicates a rapid increase in the incidence of cervical cancer with a correspondingly increased threat to women's health. This calls for the development of effective and safe biological agents to prevent cervical cancer.

The induction of cervical cancer by infection with high-risk human papillomavirus (HPV) is well established [4]. As a

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double-stranded DNA, non-enveloped virus, HPV has a genome consisting of three regions: E (early genes E1-E7), L (late genes L1 and L2) and LCR (long control region). HPV have been divided into high-risk and low-risk subsets [5]. HPV always infects epithelial cells or mucosal tissues, mainly around the mouth, hands, feet and genitals. When the skin or mucosa is injured, HPV particles can penetrate the human barrier, exposing the target tissue cells to direct contact. At the same time, however, this process also affords the best opportunity for blocking HPV infection and preventing cervical cancer. So far, there has been no specific antiviral therapy for treatment of HPV infection. Although HPV vaccines have been licensed in many countries, they are not available in some developing countries, such as China, and their application is still limited by high cost and the large number of HPV subtypes [6,7], making it necessary to find a specific and effective agent to treat and prevent HPV infection.

It has been reported that anhydride-modified proteins have broad-spectrum inhibitory activities against several viruses [8–12]. In particular, the 3-hydroxyphthalic anhydride-modified bovine beta-lactoglobulin has exhibited potent antiviral activity against infection by high-risk and low-risk HPV subtypes [11]. It is inexpensive and highly stable in aqueous solution, thus being able to be easily formulated into a topical gel [8,11,12].

Recently, this chemically modified protein, desingated JB01, was formulated into biological dressing (JB01-BD) by the technologists at the Shanxi Jinbo Pharmaceutical Co., Ltd., Taiyuan, China. Here, we conducted a randomized open-label clinical trial of JB01-BD in women infected with HPV of high-risk types to evaluate the efficacy of JB01-BD in treatment of HPV infection.

2. Materials and methods

2.1. Materials

JB01-BD, which contains 0.01% (w/w) JB01, the chemically modified bovine beta-lactoglobulin [11], in a biological dressing, was obtained from Shanxi Jinbo Pharmaceutical Co., Ltd., JB01-BD was produced under GMP conditions. The main ingredients of the biological dressing are 2% (w/w) carbomer and 2.5% (w/w) glycerol. Both are generally recognized as safe (GRAS) excipients under U.S. FDA guidelines, and both have been used as inactive pharmaceutical additives. According to the treatment guidelines of HPV infection in China, there is no corresponding drug for control group. Moreover, producing a placebo biological dressing without JB01, but with the same look and feel as JB01-BD, proved impractical; therefore, the subjects in the control group received no treatment in this trial.

2.2. Participants

The study was approved by the Ethics Committees of the participating hospitals. All enrolled subjects signed a written informed consent. The inclusion criteria are as follows: women aged 25–65 years old infected by high-risk HPV, such as HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 [13], but without a high level of cervical lesions (Thinprep cytologic test). The exclusion criteria included the following: allergic reaction to product components, liver or kidney dysfunction, tumor malignancy, immunodeficiency, active vaginal inflammation (trichomoniasis, mold, bacteria), as well as subjects presenting with an STD or other disease which, in the clinical experience of the doctor, would disallow participation in this study. Clinical trials were scheduled to avoid the menstrual period, pregnancy and lactation. Subjects volunteered to participate in this clinical trial and signed an informed consent form before testing.

2.3. Study design

A randomized open-label phase I/IIa clinical trial was conducted at two hospitals in China to evaluate the efficacy of JB01-BD as a topical treatment of cervical infection specifically derived from high-risk HPV types. The trial was registered with the Clinical Trial Registry (ChiCTR-TRC-12002016). The study participants were randomly divided into a treatment group and a control group by using a computer-generated randomized numbering system to achieve equal sample size in both groups. Before treatment, each participant was tested for HPV-DNA loads in accordance with the manufacturer's instructions (Digene Hybrid Capture 2 High-Risk HPV DNA Test, Digene Corporation, USA). The signal from liquid-based cervicovaginal specimens was measured in relative light units (RLU) and compared with the average signal of positive controls provided by the manufacturer. The RLU/cutoff (RLU/CO) ratio value is considered positive when greater than, or equal to, 1, corresponding to a concentration of 1 pg/mL [14]. For participants in the treatment group, JB01-BD (3 g per dose) was administered intravaginally every other day for 3 months, except during the menstrual period. Those in the non-treatment group received no treatment in this trial. All participants were followed up monthly. After 3 months, HPV-DNA loads were tested again.

2.4. Data analysis

All subjects enrolled and randomized were described using medians and frequency counts. All statistical analyses were performed using SPSS version 13.0. The between-group differences were compared using Rank Sum test or Chi-square test. A p-value of less than 0.05 was considered to be statistically significant.

3. Results

3.1. Enrollment

The total enrollment was 77 participants, including 38 women receiving JB01-BD and 39 women without treatment (Table 1). Thirty-eight participants completed the trial in the treatment group, while 37 participants completed the trial in