Herpes zoster and post-herpetic neuralgia deteriorate the quality of life because of severe pain and complications, and cause considerable social and economic burden of disease. In 2012, herpes zoster vaccine was released in Korea. The efficacy of herpes zoster vaccine is known to be 51.3-66.5% among the aged over 60 and 69.8-72.4% among adults between 50 and 59. It is also known that preventive efficacy is maintained for at least 5 years. Although there can be local reactions such as redness, pain and swelling at the site of injection and systemic reaction such as headache and eruption after herpes zoster vaccination, most of the adverse reactions are minor and disappear within days by themselves. As it is a live vaccine, persons with severe immune-suppression and pregnant women should not be vaccinated with the vaccine. Currently, Korean Society of Infectious Diseases recommended for the aged over 60 to be vaccinated with herpes zoster vaccine by subcutaneous route. In this article, clinical aspects and burden of disease of herpes zoster, efficacy and effects of herpes zoster vaccine, and herpes zoster vaccine recommendation by Korean Society of Infectious Diseases are discussed.

Keywords: Herpes zoster, Neuralgia, Vaccines, Republic of Korea, Review

Introduction

Herpes zoster is the disease occurring with the reactivation of the varicella-zoster virus (VZV) which was in latent state in dorsal root ganglia after the primary infection as chickenpox. Herpes zoster does not threaten human life directly but the quality of life may be deteriorated because of acute and chronic pains caused by the disease. Additionally, although rare, it may accompany severe complications. In particular, as the incidence rate and complication occurrence rate of herpes zoster become higher among the aged, this disease can cause considerable healthcare, social and economic burden of disease to the aged [1].

Accordingly, in order to prevent the incidence and to reduce the burden of disease of herpes zoster, herpes zoster vaccine was developed and successful clinic test results were published in 2005 [2]. Based on the research results, US Food and Drug Administration authorized to use the vaccine for the aged over 60 in May, 2006 and US Advisory Committee on Immunization Practices (ACIP) recommended the aged over 60 to be vaccinated unless they are in severe immune-compromised state [3]. In Korea, herpes zoster vaccine was licensed in 2009 but it was not used in actual clinical situations.
It came to be vaccinated with the commercial release in 2012. In this article, clinical aspects and burden of disease of herpes zoster, efficacy and effects of herpes zoster vaccine, and herpes zoster vaccine recommendation by Korean Society of Infectious Diseases (KSID) are discussed [4].

Clinical Features of Herpes Zoster

The clinical course of herpes zoster can be divided into three stages such as pre-eruption, acute eruption, and chronic period. In pre-eruption period, 70-80% patients complain pains or reactions alongside the dermatome 2-3 days before skin lesions come to appear. In acute eruption period, there become erythematous macula-papule and vesicles are made very quickly. New vesicles are being created for 3-5 days and sometimes are fused together. The vesicles become ulcers after being broken and then dried after curst is made. Symptoms and lesions disappear in 10-15 days but some may persist more than a month. In some cases, pain becomes chronic. Herpes zoster usually invades only one dermatome but rarely does it invade adjacent dermatomes.

According to the location of herpes zoster, it can show herpes zoster ophthalmicus, Ramsay-Hunt syndrome, loss of taste at 2/3 of tongue, and ipsi-lateral facial palsy. It may develop complications such as encephalitis, myelitis, retinitis, acute retinal necrosis, and stroke, although rare. The relapse rate is estimated as 1-6% [5]. The most problematic complication of herpes zoster is neuralgia after herpes zoster (post-herpetic neuralgia [PHN]). It is known that the pains resulted from herpes zoster and PHN are severer than labor pain or pains by arthritis or chronic cancer [6]. Because of these severe pains, it may deteriorate the quality of life considerably.

Disease Burden of Herpes Zoster

The lifetime cumulative incidence rate of herpes zoster is known as 10-30% [7]. Although herpes zoster can occur in all the ages, it is much more common among the aged over 50, and the incidence rate becomes higher with age. According to a study result, while herpes zoster was shown in 18% of herpes zoster patients, it was shown in 33% of herpes zoster patients over 79, which confirms the higher incidence rate of PHN in the aged [13].

Herpes Zoster Vaccine

Efficacy and clinical effectiveness

In 2012, the herpes zoster vaccine (ZOSTAVAX, Merk & Co. Inc., Whitehouse Station, NJ, USA) was released for the first time in Korea. The vaccine strain used for the zoster vaccine is Oka/Merk strain which is the same strain used for varicella vaccine (VARIAX, Merk & Co. Inc.). In the herpes zoster vaccine, at least 19,400 plaque forming unit (4.29 log10) vaccine strains are contained per dose (0.65 mL), which is 14 times of VARIAX.

A Shingles Prevention Study (SPS) on ZOSTAVAX was executed for three years from 1998 to 2001 on 38,546 adults over 60 years old [2]. From the study, it was found that the herpes zoster vaccine showed clinical efficacy reducing herpes zoster incidence by 51.3% and PHN incidence by 66.5% among subjects over 60, and also reduced burden of disease caused by herpes zoster by 61.1%. Additionally, complications related to herpes zoster such as allodynia, bacterial superinfection, eye herpes zoster, disseminated zoster, peripheral nerve palsy, ptosis, scarring, and anesthesia were observed less in vaccine inoculation group.

In VZV specific immune response measurement performed on partial subjects out of subjects of SPS, immune reactions increased in vaccine inoculation group than placebo group in all three analysis methods such as glycoprotein enzyme-linked immunosorbent assay, responder cell frequency (RCF), and interferon-γ enzyme-linked immune-sorbent spot-forming cell (IFN-γ ELISPOT), and it was confirmed that the increase of immune reaction had negative correlation with the incidence of herpes zoster [14]. The preventive effect against herpes zoster was gradually decreasing during the
first year of vaccine inoculation but they were maintained stably for at least three years, and PHN showed similar aspects. The increase of RCF and IFN-r ELISPOT reaction was maintained for 3-6 years after vaccine inoculation. However, a later study reported that the efficacy after 5 years was not clearly known although the efficacy of the herpes zoster vaccine was maintained for 5 years without statistically significant difference [15].

In 2012, ZOSTAVAX Efficacy & Safety Trial (ZEST) evaluating the efficacy of ZOSTAVAX on the adults between 50-59 who did not have past history of herpes zoster was executed [16]. According to this study, ZOSTAVAX decreased the incidence of herpes zoster by 69.8-72.4%, which was better than the result of SPS. Although it showed a little higher reaction rate than SPS, there was not much difference in the incidence of major reactions.

**Recommendation of Korean Society of Infectious Diseases**

In 2012, KSID recommended to inoculate herpes zoster vaccine to adults over 60 without contraindication but the recommendation for adults at 50 through 59 was deferred, saying that they could be vaccinated [4]. It was because the clinical efficacy of the herpes zoster vaccine on the population from 50 to 59 could not be verified from the dimension of association as the result of ZEST study was not officially published, although Korea Food and Drug Administration lowered the age to use ZOSTAVAX to 50 in July, 2011.

In chronic disease patients and the immune-compromised, the risk of incidence of herpes zoster increases but herpes zoster vaccination is not recommended under the specific age even though they have an immune deficiency disease because the recommendation criteria were set by age. It is because there are not sufficient research results regarding the safety and usefulness of herpes zoster vaccine in the immune-compromised. If reliable results are made in the follow-up studies regarding the usefulness of herpes zoster vaccine in the immune-compromised, there is possibility that herpes zoster vaccine can be recommended to the population with lower age.

There are some different opinions regarding the necessity of herpes zoster vaccine to those who have past history of herpes zoster. US Center for Disease Control and Prevention (US CDC) recommended to inoculate herpes zoster vaccine regardless of past history of herpes zoster, because there is risk of recurrence although it is rare, because it is not clear up to when the incidence risk is reduced, and because there is possibility that the patient does not know about the past disease history. In a study which evaluated the safety and the immunogenicity of ZOSTAVAX on those who were over 50 in 2010, there were no major reactions when ZOSTAVAX was inoculated to those who had herpes zoster in the past, and other local or systemic reactions were similar to the results of SPS [17]. Additionally, the antibody titer measured 4 weeks after the vaccination, those who had ZOSTAVAX showed 2.1 times higher before the vaccination and 2.07 times higher than those who had placebo. It seems that the study results supported the recommendation of US CDC. In a cohort study performed on those who had herpes zoster within two years to evaluate the recurrence risk of herpes zoster, however, herpes zoster recurrence rate was low regardless of the inoculation of ZOSTAVAX, which can be interpreted that ZOSTAVAX vaccination may not be necessary for those who had past history of herpes zoster [18].

**Adverse events**

In SPS, the safety was evaluated on 21,000 people and a sub-study was performed that asked 3,345 vaccine group and 3,271 placebo group to record reactions on vaccination report card (VRC) up to 42 days after vaccination [2]. In the study, both groups showed major reaction rate as 1.4%, while in the evaluation through VRC, vaccine group showed relatively higher major reaction rate (1.9% vs. 4.9%). Major reactions which were judged to be related with herpes zoster vaccine were found in 2 subjects, which were attack of asthma and poly-myalgia rheumatic respectively. The most common reaction after the vaccination was redness, pain, swelling, pruritus, and hematoma in the injection site, and headache was the most common systemic reaction. Most of reactions were minor and slight and they disappeared within days automatically. Although there were a few reports regarding zoster-like eruption after vaccination, only wild type VZV was identified and no case was diagnosed as eruption by Oka/Merk strain. When varicella-like eruption occurs after vaccination, they are sensitive to VZV and virus can be spread through them. Therefore, it is necessary to take care not to contact those who do not have of varicella immunity if they have skin lesions such as eruption after vaccination. The aspects and frequency of reactions reported in ZEST study were similar to the results of SPS [16].
Precautions to vaccination

The aged tend to be in immune deficiency because of diseases such as cancers or to have anti-cancer drugs or immune-suppressants. As the currently licensed herpes zoster vaccine is a live-attenuated vaccine, those who have severe immune deficiency diseases or use immune-suppressants should not have herpes zoster vaccination. However, those who have not had anti-cancer treatment or radiotherapy for at least 3 months because of leukemia in the state of remission, those who have local/inhaled steroid or low does systemic steroid, those who have steroid as an alternative medicine for adrenal insufficiency, and those who have low dose immunosuppressant (less than 0.4 mg/kg/wk of methotrexate, 3.0 mg/kg/day of azathioprine, and 1.5 mg/kg/day of 6-mercaptopurine) are exempted from the contraindication.

As materials regarding the safety and efficacy of herpes zoster vaccination while recombinant human immune control agents (adalimumab, infliximab oretanercept) were being used, it is desirable to be vaccinated before the administration of these drugs or 1 month after the completion of the administration. It is desirable for those who use antiviral agents such as acyclovir, famciclovir, valacyclovir to have herpes zoster vaccination at least 24 hours after the completion of the administration, as such agents can affect the proliferation of virus.

Like most other vaccines, herpes zoster vaccine does not show significant difference in effects or reactions even when it is vaccinated with other vaccines such as influenza vaccine. However, in the product manual of herpes zoster vaccine, it is recommended to have 23-valent pneumococcal polysaccharide vaccine (PPV23) vaccination to have 1 month interval. It is because there was a report that concurrent vaccination of herpes zoster vaccine and PPV23 may reduce immunogenicity [19]. However, in later study results, it was reported that there was no difference in efficacy even when herpes zoster vaccine and PPV23 were vaccinated at the same time [20] and US CDC announced that there would be no problem even they were inoculated concurrently.

Future Perspectives

Herpes zoster vaccine was proved to be relatively effective and safe through large scale clinical studies. However, there are not sufficient materials regarding if the effects of vaccine could be maintained for a long time or whether revaccination would be effective if long-term effects of vaccine was shorter than expected. There are some different opinions regarding the interval of revaccination for those who have past history of herpes zoster. Additionally, there are controversies about cost-effectiveness of herpes zoster vaccine among regions and nations. In particular, there are no studies on the usefulness of herpes zoster vaccine among Korean population and have not been any materials on cost-effects. Therefore, there is possibility to change the recommendation on herpes zoster vaccine according to the results of further studies.

Recently a new inactivated herpes zoster vaccine in addition to ZOSTAVAX has been developed and is under the clinical test. As ZOSTAVAX is live-attenuated vaccine, it has limitation that it is difficult to use the vaccine to the immune-compromised. The new inactivated herpes zoster vaccine can have an advantage that even immune-compromised who were contraindicated to the use of live-attenuated herpes zoster vaccine can be vaccinated. Therefore, it is possible to change the recommendations of herpes zoster vaccine according to the study results. However, as the new inactivated herpes zoster vaccine is still under clinical test, it needs to pay attention to the study results that will be reported in the future regarding the preventive effects and adverse reactions.

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