2013년 8월
석사학위논문

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지도교수 신 봉 석

이 논문을 의학 석사학위신청 논문으로 제출함

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조선대학교 대학원

의 학 과

최 훈

최 훈의 석사학위논문을 인준함

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ABSTRACT

The assessment of therapeutic effects for Measles, Mumps, and Rubella vaccine intralesional immunotherapy in patients with warts.

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배 경: 사마귀를 치료하는데 있어서 다양한 방법이 시도되고 있지만, 기존에 사용되던 파괴적인 치료법의 경우 통증이 심하거나 비효과적이며 치료 후 흉터를 유발할 가능성을 가지고 있다. 그렇기 때문에 치료효과가 더 뛰어나면서 앞서 언급한 부작용들을 최소화한 새로운 치료법이 필요한 실정이다.

목 적: 사마귀 환자를 대상으로 홍역, 볼거리, 풍진(Measles, Mumps, and Rubella, MMR) 백신을 이용한 병변내 면역 요법의 치료 효과와 이에 영향을 줄 수 있는 인자들을 확인해 보고자 하였다.

연구방법: 본 연구는 후향적 연구로 2011년 1월부터 2012년 12월까지 다양한 임상양상의 사마귀를 주소로 피부과에 내원하여 MMR 병변내 면역 요법을 시행한 136명의 환자를 대상으로 하였다. 환자들은 2주 간격으로 총 6회까지 치료를 시행하였으며, 치료반응을 매 방문시마다 사진촬영을 통해 확인하였다. 치료 반응은 사마귀의 크기와 수의 감소 정도에 따라 세 그룹(0-49%, 50-99%, 100%)으로 분류하였고, 완전 관해를 보인 환자군의 경우 6개월 뒤 재발여부를 확인하였다.

결 과: 치료한 사마귀 중 51.5%, 그리고 원위부 사마귀의 경우 46.7%에서 50% 이상의 호전을 보였다. 보통 사마귀의 경우 다른 임상양상의 사마귀에 비해 더 높은 치료반응을 나타내었으며, 이는 통계학적으로 유의하였다. 하지만 치료에 영향을 줄 것으로 생각되었던 다른 인자들(성별, 연령, 이환기간, 병변의 개수, 과거치료력 등)의 경우 통계학적인 연관성을 가지지 않았다. 모든 환자들이 병변내 주사시 약간의 통증을 호소하였지만 다른 부작용은 거의 없었으며, 완전 관해를 보인 환자 중 5.6%에서 6개월 후 재발하는 양상이었다.

결 론: 본 연구의 경우 사마귀에 대한 병변내 면역요법에 대한 기존 연구보다 다소 낮은 치료반응을 보였지만, 다수의 보통 사마귀를 가지면서 통증에 민감한 환자들에게 있

어 일차적인 치료법으로 고려해 볼 수 있을 것으로 생각된다. 그리고 부분 관해를 보인 환자를 대상으로 치료 횟수를 늘림으로써 더 높은 치료 반응율을 보일 것으로 예측되며, 추후 이에 대한 부분을 고려한 연구가 필요할 것으로 생각된다.

I. Introduction

Warts are common hyperkeratotic papillomas caused by multiple strains of the human papilloma virus (HPV), and may be located on any skin or mucosal surface[1,2]. Generally, although warts resolve spontaneously over several years, many persons look for treatments because they might be unsightly and often tender or painful[3]. Primary treatments for warts are destructive methods such as topical salicylic acid, cantharidine, bleomycin sulfate, cryotherapy, laser ablation, and surgical methods, but they can usually cause pain and scarring[2,3]. And many researches have shown that wart multiplication is affected by the immune system, especially cell-mediated immunity, so contact sensitizers(eg. squaric acid dibutylester, diphenylcyclopropenone), imiquimod, intralesional interferons, and oral drugs such as cimetidine have been used as immunotherapies[1,2].

Recently, studies with intralesional injection of Mumps or *Candida* skin test antigens for immunotherapy have been conducted, and Johnson *et al.*[4] experienced that 74% of subjects experienced improvement of treated warts and 78% of subjects with multiple warts experienced resolution of untreated distant warts. Intralesional immunotherapy induces a delayed-type hypersensitivity reaction for certain viral, bacterial, and fungal antigens, as well as for HPV, and then improves the ability of the immune system to recognize and treat HPV[1].

In our country, combination Measles, Mumps, and Rubella(MMR) vaccination was introduced in 1982, and recommended that it should be first administered at the age of 12-15 months and readministrated at the age of 4-6 years. In present, a new MMR vaccine, Priorix®(developed by GalaxoSmithKline in 1997), is being used ,and shows safety and excellent immunogenicity[5]. So, we used Priorix® for the treatment of warts, and have tried to evaluate the efficacy and safety of the immunotherapy through a retrospective study.

II. Patients and Methods

A. Patients

This study was a retrospective study that included patients diagnosed as warts from January 2011 to December 2012 who visited the department of dermatology of Chosun University Hospital in Gwangju, Korea and treated with MMR vaccine(Priorix®).

B. Methods

We obtained the databases through medical records, including age, sex, type of warts, disease duration, treatment number, previous treatment, side effects, and clinical photographs, and checked whether with distant warts(warts in different anatomic sites) or not. According to the type of warts, patients were classified into three groups(common wart, palmoplantar, and verruca plana), and periungual warts were included in common warts. Disease duration was also sorted into four categories; under six months, six months to one year, one year to two years, and over two years. We also evaluated other clinical variables affecting treatment response of MMR immunotherapy.

Before MMR vaccine treatment, patients who had prior allergic response to MMR vaccine, acute febrile illness, past history of asthma or allergic skin disorders, past history of meningitis or conclusions, pregnancy, lactation, and iatrogenic or primary immunosuppression were excluded. The patients were tested for existing immunity by intradermal injection of 0.1mL of MMR vaccine into the volar aspect of the forearm before treatment, and a positive reaction was defined as erythema and induration of at least 5mm in diameter within 48~72 hours. According to the method described by Johnson *et al.*[4], MMR vaccine was given to the patients who had a positive reaction, and injection volume was determined by the size of a positive reaction: 0.3mL with diameter of lesser than 20mm, 0.2mL with diameter of 21 to 40mm, and 0.1mL with diameter of greater than 40mm. Patients were injected into the same single wart or the largest wart in cases of multiple warts at 2-week intervals until complete response was accomplished or for a maximum of 6 treatments. Patients were evaluated for the response at one month after session to stop treatment. Depending of the decrease in size of warts, response to treatment was classified into 3 categories; complete response, partial response, and no response. Distant warts were also

classified in association with the decrease in size and number of warts. Complete response (100%) was adjudicated to have occurred when the clinical characteristics of the warts were no longer demonstrated. Partial response for warts was assessed as follows: 50-99%, and no response was defined with less than 50% of improvement. The authors judged what showed over partial response of immunotherapy as treatment responders. Patients were evaluated after each treatment session for the efficacy and safety of MMR, and follow-up was made after 6 months to detect any recurrence.

C. Statistical analysis

All date were checked and analysed using the SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as mean±SD for quantitative variables, and number and percentage for qualitative ones. ANOVA and Chi-square test were used as appropriate. P-values<0.05 were considered significant.

III. Results

There were 243 patients who visited to our hospital due to warts and were treated with MMR vaccine during the study period. Of these, 107 patients, who didn't show a positive reaction for existing immunity and have a combination therapy, fear to injection or failure to follow up, were excluded from this retrospective study, and total 136 patients were involved lastly. Eighty-four patients (61.8%) were men and 52 patients (38.2%) were women, and the mean age of patients was 17.7 years (3-64 years). Most patients had multiple warts, with an average of 6.99 warts per patient, and 90 patients (66.7%) had distant warts. Other clinical characteristics were summarized in Table 1.

36 patients (26.5%) experienced complete response (Fig. 1 and 2) of their treated warts, and the average number of treatments was 5.38. Partial response (Fig. 3 and 4) in 34 patients (25.0%) and no response in 66 patients (48.5%) were observed. As a result, responders to the treatment accounted for 51.5% of patients. Among patients who had distant warts, 22 patients (24.5%) showed complete response and 20 patients (22.2%) showed partial response, so response rate of distant warts are 46.7% (Table 2).

The average age of patients with complete response was 15.6 years and was lower than that of patients with no response, although there was no statistical difference ($p>0.05$). As regards the type of warts, common warts, including periungual warts, showed significantly higher clinical response than others ($p<0.05$), and other clinical variables, including sex, disease duration, number of warts, and previous treatment, showed no statistically significant association with the therapeutic response ($p>0.05$) (Table 3). Most patients who underwent MMR intralesional immunotherapy had painful sensation during injection, but they didn't feel any discomforts after injection. In five of patients who underwent treatment, mild side effects, such as mild pruritus, burning sensation or swelling on the injection site, were observed. Recurrence was observed in 2 patients out of the 36(5.6%) who showed complete response after the six month follow-up period.

IV. Discussion

There has been many researches for therapeutic or protective response of warts through controlling the immune system, and interferon alfa-2b, topical imiquimod, topical contact sensitizers, and cimetidine served as treatment of various warts.[3,6-8] Since Harada[9] reported the efficacy of *Candida* vaccination in the treatment of warts in the Japanese literature in 1979, diverse skin test antigens has been used in intralesional immunotherapy. In 2001, Signore[10] performed the study using *Candida albicans* intralesional injection to plantar wart and verruca vulgaris. He reported that a significant difference in outcome was not identified between intralesional immunotherapy and traditional treatment groups, although it might be helpful for patients with multiple warts and difficult to treat lesions, and didn't leave scarring unlike traditional treatment. Since then, studies of intralesional immunotherapy using Mumps, *Candida*, tuberculin, killed *Mycobacterium w* vaccine, and MMR vaccine have been introduced, and a variety of therapeutic effects was reported (Table 4).[1-4,10-16] Among them, the study with MMR vaccine in Egypt showed that complete response was achieved in 80% and 84.6% of patients presenting with recalcitrant and multiple warts, respectively.[1] They explained that three synergistic viral antigens in MMR vaccine could be associated with higher stimulation of the immune systems compared with a single antigen, and a vaccine is more strongly immunogenic than skin test antigens.[1,13]

The exact action mechanisms of intralesional immunotherapy are still uncertain, although several explanations has been proposed. Intralesional injection to HPV-infected tissue probably induces strong non-specific pro-inflammatory signals and attract antigen presenting cells, which recognize and process low-profile HPV particles.[4,13] The trauma itself, or the bystander effect, can also cause wart clearance in previously sensitized individuals,[11] and various cytokines such as IL-2, IL-4, IL-5, IL-8, IFN-γ and TNF-α that stimulate an immune response against HPV are released.[3,13] Lastly, antigen injection is associated with multiplication of peripheral blood mononuclear cells, and they activate cytotoxic T cells and natural killer cells to eliminate HPV.[3]

The present study also used MMR vaccine for intralesional immunotherapy of warts, and responders to the treatment accounted for 51.5% in treated warts and 46.7% in distant warts. The criteria of clinical response in each study performed in the past varied, but the result of our study was similar or slightly lower

compared with the previously reported literatures.[10-16] We considered what influenced on the clinical response of immunotherapy in this study. First, two MMR vaccines, M-M-R II® from Merk & Co. and Priorix® from GlaxoSmithKline, have been currently used in our country, and showed good immunogenic responses.[17] However, two vaccines contain different strains respectively, and Priorix® was developed more recently. So, because antigenic polymporphism of each vaccine strain produced strain-specific immunity,[18] it might influence the clinical response in this study using Priorix® alone. Second, various types of warts are caused by different HPV types.[19] In our study, because diverse types were included, there was the potential for that to influence the clinical response.

Signore[10] have reported that a better response in younger age groups and a number of warts was a significant marker of outcome. We also made an evaluation about factors affecting the clinical response. There was no statistically significant association between the therapeutic response and different clinical variables, except that the response rate of common warts was significantly better than that of other types of warts. We thought that it was attributable to the susceptibility to specific HPV of wart types. In addition, it has been reported that individual immune response to the virus could affect the treatment response.[20]

Intralesional immunotherapy is generally associated with mild side effects such as flu like symptoms, edema, erythema, itching and pain at the site of injection[21]. In our study, most patients complained tolerable pain during injection, and didn't feel any pain after treatment. Flu like symptoms were not found in our study, and relatively rare side effects, including pruritus, swelling, and burning sensation at injection site were in five patients. However, they were not worthy of stopping treatments, and the patients didn't complain side effects at following treatments. More severe side effects(e.g. infection, wounding and scarring) were not observed in our patients similar to other studies, too.[10]

There are some limitations in our study. One of the limitations was the lack of comparison group. Another limitation is total treatment number. Through review of medical records, we evaluated the efficacy of the treatment in a month after a maximum of 6 treatment. However, judging by what we had been through, number and size of warts were decreased in whom were treated with continuos MMR intralesional immunotherapy in the partial response group. So, if we increase the total treatment number, we would get higher therapeutic efficacy than that of our study. And last limitation of our study is that patients sample with verruca

plana were too small.

V. Conclusions

Intralesional immunotherapy of MMR vaccine has much less painful and safe than the traditional destructive modalities, so we think it has a high level of tolerability, Besides, patients treated with intralesional immunotherapy as well as who with distant warts showed similar clinical response. We evaluated the treatment response depending of the types of warts that have not previously been reported, and our results demonstrated that common warts had good therapeutic effect. Therefore, it could be considered as a primary remedy for whom have multiple common warts and are sensitive to pain. In addition, for improving the therapeutic effects of intralesional immunotherapy, it is necessary to increase the number of treatment in the group that showed a partial response. In the future, we think that randomized controlled trials to find clinical factors affecting the efficacy will be needed.

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Table 1. Clinical characteristic of the patients

Characteristics	
Age	
Mean(range)	17.7(3-64 years)
Sex	
Male	84 (61.8%)
Female	52 (38.2%)
Disease duration	
< 6months	36 (26.5%)
6months~1year	11 (8.1%)
1year~2years	36 (26.5%)
>2years	53 (39%)
Number	
Single	13 (9.6%)
Multiple	123 (90.4%)
Distant warts	90(66.7%)
Type of warts	
Common wart	65 (47.8%)
Palmoplantar wart	64 (47.1%)
Verruca plana	7 (5.1%)
Previous treatment	
No treatment	54 (39.7%)
Previous treatment	82 (60.3%)

Table 2. Intralesional immunotherapy response rate and distant response rate

	No response	Partial response	Complete response
Immunotherapy (total : 136)	66 (48.5%)	34 (25%)	36 (26.5%)
Distant wart (total : 90)	48 (53.3%)	20 (22.2%)	22 (24.5%)

Table 3. Comparison of the groups' response to the therapy

Characteristics	No response (N=66)	Partial response (N=34)	Complete response (N=36)	P-value
Age	18.9(3-64)	17.3(5-41)	15.6(3-47)	>.05*
Sex				
Male	40 (47.6%)	23 (27.4%)	21 (25.0%)	>.05†
Female	26 (50.0%)	11 (21.2%)	15 (28.8%)	
Disease duration				
< 6months	16 (44.4%)	6 (16.7%)	14 (38.9%)	>.05†
6months ~ 1year	5 (45.5%)	4 (36.4%)	2 (18.2%)	
1year ~ 2years	17 (47.2%)	8 (22.2%)	11 (30.6%)	
> 2years	28 (52.8%)	16 (30.2%)	9 (17%)	
Number				
Single	8 (61.5%)	2 (15.4%)	3 (23.1%)	>.05†
Multiple	58 (47.2%)	32 (26%)	33 (26.8%)	
Morphology				
Common wart	27 (41.5%)	15 (23.1%)	23 (35.4%)	<.05†
Palmoplantar wart	34 (53.1%)	17 (26.6%)	13 (20.3%)	
Verruca plana	5 (71.4%)	2 (28.6%)	0 (0%)	
Previous treatment				
No treatment	27 (50%)	13 (24.1%)	14 (25.9%)	>.05†
Previous treatment	39 (47.6%)	21 (25.6%)	22 (26.8%)	

*Statistical analysis performed using ANOVA test,

†Statistical analysis performed using Chi-square test.

Table 4. Previous published literatures for intralesional immunotherapy of warts

Study	Case No.	Mean age (yrs)	Subjects	Used antigen or vaccine	Note
Johnson *et al.*[4]	55	31.3(mumps) 22.1(*candida*)	Periungual or palmoplantar wart	Mumps and *Candidia* test antigen	49% and 70% experienced complete response in mumps and *candida* group, respectively.
Signore *et al.*[10]	87	23.7	Common and plantar wart	*Candida albicans*	51% had complete clearing of warts. Intralesional immunotherapy is a simple, effective, and well-tolerated modality in selected patients.
Clifton *et al.*[2]	47	12.9	Recalcitrant wart	Mumps or *Candida* antigen	47% experienced 100% resolution of treated warts, and distant wart response rate were 34%. It might be considered a first-line therapy in children with large or multiple warts.
Horn *et al.*[3]	54	37	Wart(unmentioned)	Mumps, *Candida*, or *Trichophyton* skin test antigen	The responder of treated wart and distant warts was 54% and 41%, respectively. Intralesional immunotherapy for common warts is effective and safe.
Gupta *et al.*[13]	10	28.9	Anogenital wart	Killed *Mycobacterium w* vaccine	80% had complete clearance of warts, and the results are likely to be better than those in published studies.
Maronn *et al.*[14]	170	10.14	Wart(unmentioned)	*Candidia* antigen	87% had complete resolution, but over the half with complete resolution had treated other concurrent therapy.
Nofal *et al.*[1]	135	32.4	Common warts	Mumps, measles, and rubella vaccine	Complete response was achieved in 80%, and intralesional immunotherapy is a effective and safe therapy for common warts(particularly multiple).

LEGENDS OF FIGURES

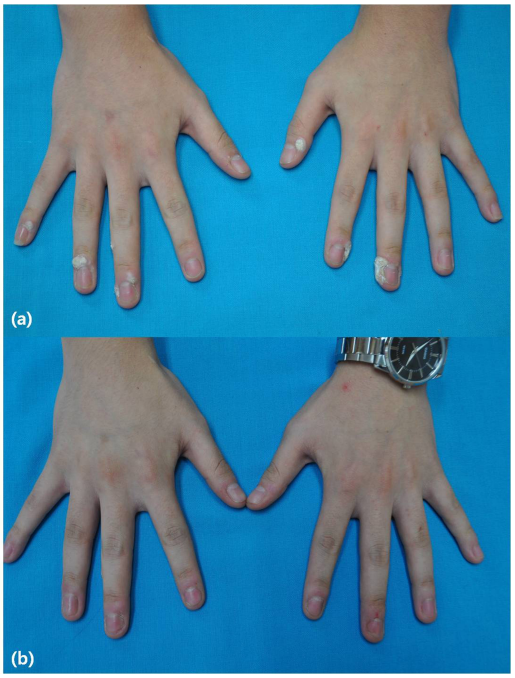

Fig. 1.

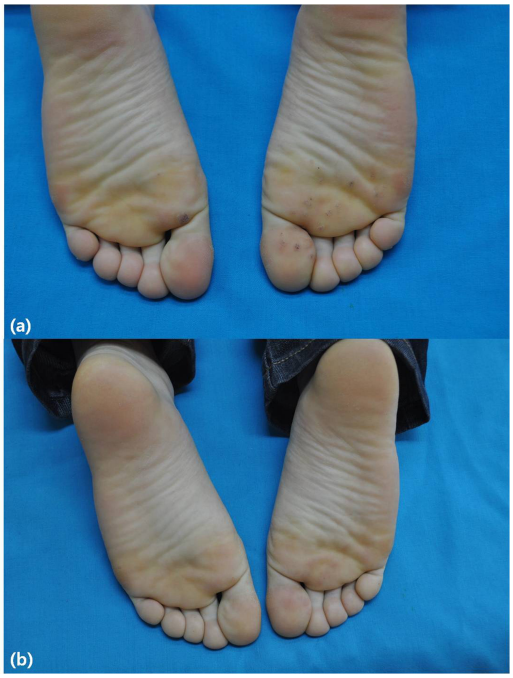

Fig. 2.

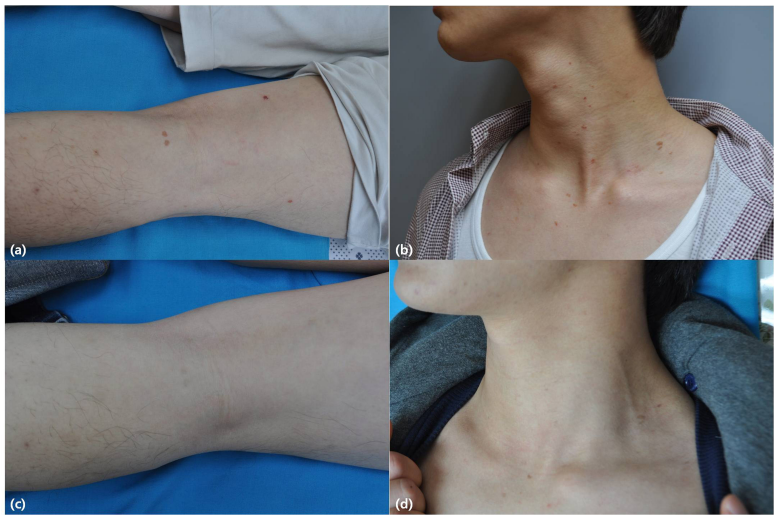

Fig. 3.

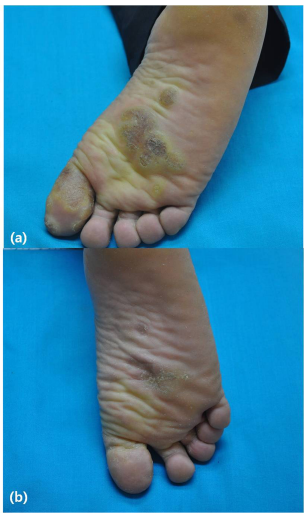

Fig. 4.