Original Article

Safety and Reactogenicity of the Inactivated Poliomyelitis Vaccine (Poliorix™) in Korea (2006-2012)

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Objective: As per the requirement of Korean Food and Drug Administration, this post-marketing surveillance was conducted in Korea to evaluate the safety and reactogenicity of *Poliorix*™ following its introduction in 2006.

Methods: In this open, multicenter study, the vaccine was administered as per the current practice of Korean doctors and in reference to the guidebook by the Korean Pediatric Society and as indicated in the Korean label which was as follows – for primary vaccination three doses were given to infants at ages 2, 4 and 6 months whereas, for the booster dose a single dose was given to children aged 4-6 years. Safety data during this six year surveillance was collected using diary cards which were distributed to the parents to record adverse events.

Results: A total of 639 subjects were enrolled into the study. Of these, 617 subjects and 22 subjects received the vaccine as a primary and booster dose, respectively. At least one unsolicited symptom was reported in 11.4% (73/639) of the subjects during the 7-day follow-up period; upper respiratory tract infection (2.5%;16/639) was the most frequently reported unsolicited symptom. One subject reported at least one unsolicited symptom (gastroenteritis) of grade 3 intensity within the 31-day post-vaccination period. Approximately 1.7% (11/639) of subjects reported 13 serious adverse events (SAEs). All SAEs were resolved by the end of the study.

Conclusion: In Korea, primary and booster vaccination with *Poliorix*™ was well-tolerated in healthy subjects when administered according to the prescribing information as part of routine clinical practice. **(Korean J Pediatr Infect Dis 2013;20:139-146)**

Key Words : Poliomyelitis, Inactivated polio vaccine, Safety, Reactogenicity, Korea

Introduction

In 2011, poliomyelitis was associated with 650 cases worldwide which is a significant reduction from the reported 350,000 cases in 1988[1, 2]. This was largely due to concerted efforts to eradicate the disease in 1988, especially when the World

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Health Organization launched the Global Polio Eradication Initiative[1]. The use of both a live attenuated oral poliovirus vaccine (OPV) and the inactivated poliovirus vaccine (IPV) has contributed to a significant reduction in the incidence of worldwide poliomyelitis[1, 2]. However, several reports of a rare, but serious, complication; vaccine-associated paralytic poliomyelitis (VAPP) have been associated with the use of OPV[3]. The recommendation of an "all-IPV schedule", based on the Salk strain has been adopted by many countries worldwide[4, 5]. In Korea, similar recommendations have been made by the Korean National Immunization program[6] and in 2006, the inactivated polio vaccines including *Poliorix*™ (GlaxoSmithKline Vaccines, Belgium) were approved for use.

The present post-marketing surveillance study was conducted as a requirement of the Korean Food and Drugs Administration (KFDA) to ascertain the safety and reactogenicity of *Poliorix*™ in the Korean population when administered according to the prescribing information.

Material and methods

1. Study design

This open, non-comparative, multi-center post-marketing surveillance study was conducted in the Republic of Korea for a period of six years, following the approval of *Poliorix*™ in 2006. Eligible participants were healthy male or female children between two and six months of age (primary vaccination) or between four and six years of age (booster vaccination) at the time of vaccination and whose parent/guardian provided written informed consent. A child was excluded from the study if there were any contraindication or risks as described in the Korean label[7]. In this study, *Poliorix*™ was administered according to the current practice of Korean doctors in reference to the guidebook of the Korean Pediatric Society[8] and as indicated in the Korean label 7): For primary vaccination, three vaccine doses were given to infants at 2, 4 and 6 months of age and administered concomittently DTaP vaccine. All subjects were administered Hib (*Haemophilus influenzae* tybe b) vaccine and pneumococcal conjugate vacine within two weeks; for the booster vaccination schedule, a single dose was given to children aged 4-6 years with DTaP vaccine concomittently. The type of vaccines to administered concomittently were the same according to pre-determined protocol in all participating centers. The study design is outlined in Fig. 1. The inactivated polio vaccine *Poliorix*™ has been developed and manufactured by GlaxoSmithKline Vaccines, Belgium. Each dose of *Poliorix*™ contains 40D antigen units of type 1 (Mahoney), 8D antigen units of type 2 (MEF-1) and 32D antigen units of type 3 of the poliovirus[9]. Immediately after vaccination, the vaccines were observed for at least 30 minutes in case there was a rare anaphylactic reaction. Diary cards (DICA) were distributed and instructions were given to the parents/guardians on how to record adverse events. DICA was filled out by parents or guardians, be instructed to make a note and grading of any solicited local adverse events (pain, redness, swelling) and general adverse events (fever, irritability, drowsiness, gastrointestinal symptoms, loss of appetite). Children either whose DICA was returned after the last vaccination or whose case report form was completed through phone contact were considered to have completed the study. The

definitions of safety and reactogenicity parameters have been provided in Table 1 and Table 2.

The study was conducted according to the regulations of Koreran Food and Drug Association (KFDA) and Declaration of Helsinki, 1996. All protocols were submitted and got approval of each Institutional Review Board (IJUPH IRB No 07-127).

2. Analysis

Analysis of safety was performed on the total vaccinated cohort which included all children for whom data was available following at least one dose of administered vaccine.

The percentages of children with any solicited symptom and specifically, local (pain, redness and swelling) and general symptoms (fever, axillary; irritability, drowsiness, loss of appetite and gastrointestinal condition) during the 7-day follow-up period were reported with 95% confidence interval (CI). Occurrences of unsolicited adverse events

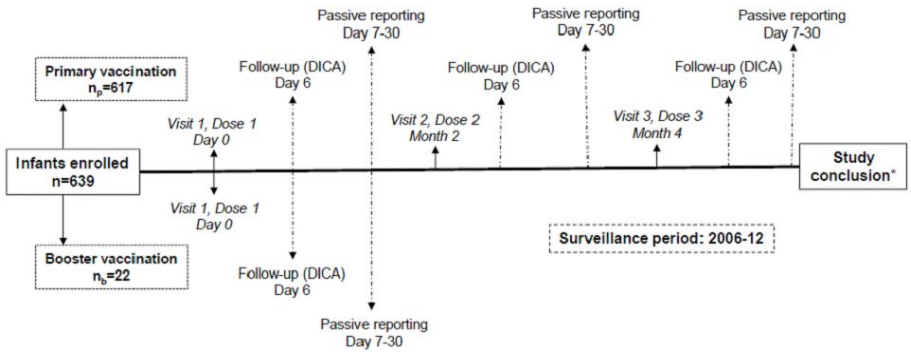

Fig. 1. Study design.

Table 1. Definition of Parameters for the Assessment of Safety and Reactogenicity

Symptom	Intensity Grade	Definition
Solicited local AE		-
-Pain	Grade 0	Absent
	1	Minor reaction to touch
	2	Cries/protest on touch
	3	Cries when limb is moved/spontaneously painful
-Redness/Swelling		
	Grade 0	Absent
	1	Record greatest surface diameter in mm *Primary vaccination: ≤5 mm; Booster vaccination: ≤20 mm*
	2	*Primary vaccination: >5 to 20 mm; Booster vaccination: >20 to 50 mm*
	3	*Primary vaccination: >20 mm; Booster vaccination: >50 mm*
Unsolicited AE and SAE		
	1 (mild)	-An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities
	2 (moderate)	-An AE which is sufficiently discomforting to interfere with normal everyday activities
	3 (severe)	-An AE which prevents normal, everyday activities and would cause the parents/guardians to seek medical advice

Table 2. Definition of Parameters for the Assessment of Safety and Reactogenicity: Solicited General AE

Symptom	Intensity Grade	Definition
Solicited general AE		
Drowsiness	Grade 0	Behavior as usual
	1	Drowsiness easily tolerated
	2	Drowsiness that interferes normal activity
	3	Drowsiness that prevent normal activity
Gastrointestinal	Grade 0	Gastrointestinal symptoms (nausea, vomiting, diarrhea and/or abdominal pain): normal
	1	Gastrointestinal symptoms tolerated
	2	Gastrointestinal symptoms that interfere with normal activity
	3	Gastrointestinal symptoms that prevent with normal activity
Irritability	Grade 0	Behavior as usual
	1	Crying more than usual/no effect on normal activity
	2	Crying more than usual/interferes with normal activity
	3	Crying that cannot be comforted/prevents normal activity
Loss of appetite	Grade 0	Appetite as usual
	1	Eating less than usual/no effect on normal activity
	2	Eating less than usual/interferes with normal activity
	3	Not eating at all
Fever		Record temperature
	Grade 3	Temperature >39.0℃, Axillary

(classified by the Medical Dictionary for Regulatory Activities Primary System Organ Class and Preferred Term) (AEs) during the 7-day follow-up period and 31-day follow-up period were reported. Occurrence of serious AEs (SAEs) during the entire study period was also reported. All statistical analyses were performed using Statistical Analysis System (SAS) version 9.2.

Results

1. Study population

A total of 639 subjects were enrolled between August 2006 and February 2012 and were included in the total vaccinated cohort. Of these, 617 subjects received the vaccine as primary vaccination; the remaining subjects received the vaccine as a booster dose. The proportion of subjects who received one, two and three doses were 52.0% (321/617), 25.4 % (157/617) and 22.5% (139/617), respectively.

The mean age of subjects who received *Poliorix*™ as primary vaccination at each dose were: 8.8±2.1 weeks for the first dose, 18.2±2.3 weeks for the second dose and 27.7±3.0 weeks for the third dose. The mean age of the subjects who received *Poliorix*™ as the booster dose was 57.2±8.8 months.

2. Safety and Reactogenicity

1) General and local symptoms

(1) Primary vaccination

Any symptom was reported following 43.7% (460/1,052) of primary vaccination doses; symptoms after 2.9% (30/1,052) of doses were of Grade 3 intensity.

Occurrences of solicited local and general symptoms (including those of Grade 3 intensity) during the 7-day follow-up period are shown in Fig. 2. The most frequently reported solicited local symptom was injection site redness (11.3%; 119/1,052). Grade 3 redness and swelling were reported after 0.6%

(6/1,052) of doses each, and Grade 3 pain was reported following 0.4% (4/1,052) of doses. Irritability was the most frequently reported solicited general symptom which was reported after 29.4% (309/1,052) of doses.

(2) Booster vaccination

Any symptom was reported in 31.8% (7/22) of the subjects who received only the booster dose. Occurrences of solicited local and general symptoms (including those of Grade 3 intensity) during the 7-day follow-up period following administration of the booster dose are shown in Fig. 2. The most frequently reported solicited local symptom was injection site pain (31.8%; 7/22). Drowsiness (13.6%; 3/22) was the most frequently reported solicited general symptom. No Grade 3 or Grade 3-related solicited local and general symptoms were reported for any subjects following administration of the boo-

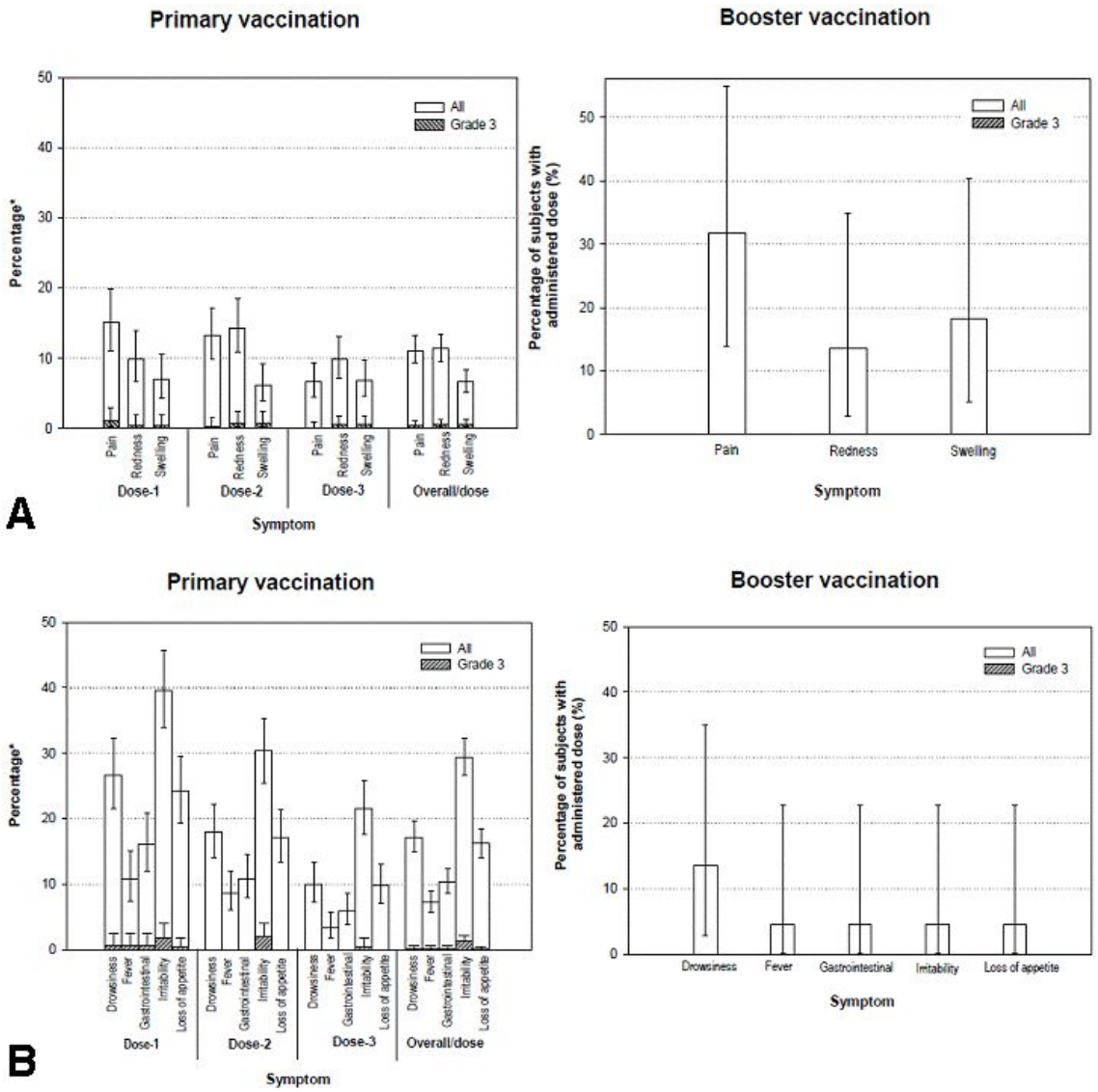

Fig. 2. Occurrence of each solicited symptom during the 7-day follow-up period for each dose of *Poliorix*™ (A) local symptoms (B) general symptoms (total vaccinated cohort).

ster dose.

2) Unsolicited adverse events

At least one unsolicited symptom was reported in 11.4% (73/639) of the subjects during the 7-day follow-up period; upper respiratory tract infection (2.5%; 16/639) was the most frequently reported unsolicited symptom. Most of the other unsolicited adverse events reported were common childhood diseases and not related to vaccination, including acute bronchiolitis (n=9), nasopharyngitis (n=9) and acute gastroenteritis (n=6). None of the subjects recorded unsolicited symptoms of Grade 3 intensity within the 7-day post-vaccination period. At least one unsolicited symptom was reported in 27.5% (176/639) of the subjects during the 31-day follow up period. Upper respiratory tract infection (7.2% [46/639]) was the most frequently reported unsolicited symptom during this time period. At least one grade 3 unsolicited symptom (acute gastroenteritis) was reported in 0.2% of subjects.

3) Serious adverse events

Approximately 1.7% (11/639) of subjects reported 13 SAEs after primary vaccination doses: pneumonia (n=3); acute bronchiolitis (n=4); infectious croup (n=1); aspiration pneumonia (n=1); viral infection (n=1); urinary tract infection (n=1); acute gastroenteritis (n=1); exanthem subitum (n=1). None of these SAEs were assessed as related to vaccination by the investigator. All SAEs recovered/resolved by the end of the trial. No SAEs were reported following the administration of the booster dose.

Discussion

The Republic of Korea was certified polio-free in 2000. Following global recommendations by the Advisory Committee on Immunization Practices for an "all-IPV schedule" or use of IPV, in conjunction with OPV, an "all-IPV schedule" was implemented in Korea in 2005[10]. Despite the polio-free status, one confirmed case of VAPP was reported in Korea in 2003. However, given the widespread use of OPV in Korea, it has been estimated that 0.5-2.0 cases of VAPP per year can be expected[11]. While the use of OPV may be critical to reach the common goal of global polio eradication, the risk of acquiring VAPP also needs to be considered. Additionally, due to the fact that the live vaccine virus can be shed by recipients and may subsequently circulate (circulating vaccine-derived polio virus); the risk of reintroduction of post-eradication polio into the population is significant[12]. A full IPV or an IPV-OPV sequential immunization schedule has been implemented in most high-income countries to prevent VAPP cases[13].

This study was conducted to assess the safety profile of *Poliorix*™ which was approved for use in the Republic of Korea in late 2006. Data from this study indicate that *Poliorix*™ is well tolerated for both primary and booster administration by healthy Korean infants, when administered according to prescribing information as part of routine clinical practice. The incidence of adverse reactions (both solicited and unsolicited), especially of grade 3 intensity was low. No vaccine-related SAEs were reported throughout the study. The safety data of *Poliorix*™ reported in the present study are consistent with the existing safety profile of the vaccine[14, 15]. Additionally, no safety concerns were raised by any authority related to IPV. Given the safety and reactogenicity data from this post-marketing surveillance in Korea, the continued use of IPV appears to be an optimal solution to prevent the OPV-related risks

of VAPP and vaccine-derived poliovirus strains.

IPV is available either as a stand-alone vaccine or in combination with other vaccine antigens including diphtheria, tetanus, whole-cell or acellular pertussis, hepatitis B, *Haemophilus influenzae* type b (D, T, P, HBV, HiB)[5]. In clinical studies, *Poliorix*™ has been administered concomitantly with D, T, P, HBV and Hib antigens. Additionally, *Poliorix*™ can be given safely and effectively at the same time as measles, mumps, rubella, BCG and yellow fever vaccines and vitamin A supplementation. In this study, All subjects administered inactivated poliovaccine (*Poliorix*™) with DTaP vaccine in primary vaccination. And Hib vaccine and pneumococcal conjugate vaccine administered within two weeks concomittently. No safety concern reported and all subject well tolerated. Furthermore a recent study in Korea assessed that the combination vaccine DTaP-IPV was highly immunogenic, non-inferior to the commercially available standalone DTaP and IPV control vaccines and was well tolerated[15]. Offering IPV through combination vaccines in Korea may also offer practical advantages such as simplification of vaccine administration and higher probability of achieving greater vaccination coverage than if given separately.

In conclusion, this six year surveillance to monitor safety and reactogenicity of *Poliorix*™ in Korea reports an acceptable safety profile of the vaccine when administered according to the current practice of Korean doctors, as indicated in the guidebook of the Korean Pediatric Society and the Korean label.

한 글 요 약

우리나라 영아에서 주사용 소아마비 백신(*Poliorix*™)의 안전성 및 이상반응에 대한 연구

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목적: 한국은 2000년에 소아마비 무발생국가로 공인되었으며, WHO의 권고에 의해 2005년부터는 경구용소아마비 생백신 대신 주사용 사백신을 사용하기 시작했다. 본 연구는 2006년부터 국내에서 사용되기 시작한 주사용 소아마비 백신(*Poliorix*™)의 안전성 및 이상반응을 우리나라 영아들을 대상으로 알아보고자 한다.

방법: 2006년부터 2012년까지 6년 동안 다기관공동연구로 조사하였으며, 2, 4, 6개월의 기초접종과 4-6세의 추가 접종 후 7일 이내 및 31일 이내의 이상반응 및 안전성에 대해 조사하였다.

결과: 총 639명 중 등록대상자 중 617명은 기초접종, 22명은 추가접종을 실시하였으며, 639명 중 73명(11.4%)에서 명시되지 않은 이상반응을 보고하였으며, 이중 가장 많은 증상은 상기도 감염증상으로 접종 후 7일 이내에 639명 중 16명(2.5%)에서 보고되었다. 1명에서 grade 3 이상의 장염증상을 보고하였으며, 11명(1.7%)에서 중대한 이상반응을 보고하였으나, 이들은 모두 연구종료 이전에 호전되었다.

결론: 6년 동안의 시판 후 조사에서, 건강한 우리나라 영아들을 대상으로 한 주사용 소아마비 사백신(*Poliorix*™) 접종은 국내 건강한 소아에서 안전하고 내약성이 충분하였다.

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