Post-Vaccination Adverse Events in Korean Children Reported by their Parents

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Abstract

This study purpose is to examine the types and patterns of post-vaccination adverse events perceived by parents with infants and young children ultimately in order to monitor adverse events suspected to be associated with vaccines and to provide basic information for developing measures against such adverse events. From June 2006 to June 2013, 415 cases reporting experiences of vaccine adverse events in infants and young children were extracted and data were analyzed through content analysis. Among the vaccines perceived by parents with infants and young children to cause adverse events, DTaP-IPV was most frequent as found in 317 cases, which was followed by PCV/Hib in 259 cases, and BCG in 136 cases. As to the type of adverse events, after the vaccination of DTaP, 55 cases of ‘skin reactions’, 51 cases of ‘fever of over 39°C’, and 45 cases of ‘digestive disorders’ including vomiting and diarrhea. After the vaccination of PCV/Hib, 62 cases of ‘fever’ happened, 54 cases of ‘skin reactions’, and 36 cases of ‘fretfulness or restlessness’. After the vaccination of BCG, ‘lymphadenitis over 1cm’ was most frequent as reported in 77 cases, and 21 cases of ‘skin reactions’ appeared. Finally, it is believed necessary to make efforts to reduce post-vaccination adverse events through the safe management of vaccine, thorough preliminary checkup of the child’s condition before vaccination, and careful observation after vaccination. And there should be continuous long-term follow-up and research on causality for post-vaccination adverse events.

Keywords: Adverse Events, Contents Analysis, Vaccination

1. Introduction

With the recent advance of science and medicine, various types of vaccine have been developed and they have made remarkable achievements in eliminating infectious diseases. Although vaccines have reduced the incidence of preventable diseases, however, unexpected adverse events have also appeared because of components added to the vaccines in the manufacturing process in order to improve immunogenicity and to prevent deterioration or contamination¹. Most of drugs are administered to sick people, but vaccine is administered to healthy people in order to prevent diseases. For this reason, high safety is required in the procedure.

Vaccine contains active components consisting of vaccine antigen for producing active immunity against specific antigen, adjuvants used to increase immune reaction, stabilizers for maintaining vaccine stably, preservatives for keeping vaccine from being contaminated, and trace components used in the manufacturing process². Therefore, apart from the primary purpose of vaccine, which is immune creation, adverse events of vaccine take place occasionally. The adverse reactions of vaccine are largely divided into three categories, namely, local reactions, systemic reactions, and allergic reactions. The most common post-vaccination adverse reactions are local reactions such as pain at the injection site, swelling, and erythema, and such reactions are observed commonly even up to about 80% after the injection of vaccines containing adjuvants such as DTaP vaccine. Systemic adverse reactions include fever, malaise, muscle pain, headache, and low appetite, and they are relatively common after

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the injection of DTP containing a whole-cell pertussis component. Moreover, a systemic reaction similar to a mild form of natural infection caused by the multiplication of virus can happen after the injection of live attenuated vaccine. In addition, severe allergic or anaphylactic reactions caused by vaccine antigen itself or other substances contained in the vaccine happen at a rate of 1/500,0003.

The Vaccine Adverse Event Reporting System (VAERS) in the US reports about 10,000 cases of adverse event each year, and this number exceeds the incidence of diseases preventable with vaccine4. The total number of cases reported as post-vaccination adverse events by the Korea Centers for Disease Control for the last five years (2008–2012) was 3,705 cases including 407 cases in 2008, 2,380 cases in 2009, 471 cases in 2010, 238 cases in 2011, and 209 cases in 20122, but considering the limitation of the system relying on voluntary reporting, the actual number of adverse events is expected to be much larger.

The side effects of drugs appearing in clinical situations are affected by various factors including individuals’ diseases. For the same side effect, moreover, the reporters’ sensitivity to the symptoms may be different and, as a result, the side effect may be reported in different ways5. Randomized controlled trial is accepted as the most objective evidence in assessing the safety and risk of drugs. For drug safety, however, the number of subjects is small, the period of observation is short, and the subjects are limited to patients in a specific area, and for these reasons, information needs to be reviewed extensively through the results of preclinical studies, clinical experiments before and after commercialization, voluntary reports of adverse events, medical and epidemiological data, etc6.

With regard to post-vaccination adverse events monitoring systems, the US has been operating the Vaccine Adverse Event Reporting System (VAERS) under the supervision of CDC and FDA since 1990, and the organization is monitoring the safety of vaccines by collecting all important adverse events of vaccines. In Korea, the post-vaccination adverse event monitoring system was introduced in 1994 when a series of mortal cases took place due to adverse events after vaccination for Japanese encephalitis7, and the system was computerized in 2000. In addition, doctors became obliged to report post-vaccination adverse events from 2001, and the monitoring system through Web-based (http://is.cdc.go.kr) integrated management was established in 2005.

Nevertheless, post-vaccination adverse events are not reported systematically because of medical care workers’ failure to report due to the limitation of the voluntary reporting system and difficulty in epidemiological investigation of post-vaccination adverse events in the whole population. Particularly for rare or slowly progressing post-vaccination adverse events, medical staff’s reports are not made properly. Thus, many parents with infants and young children often refuse vaccination for their children out of distrust of vaccines and anxiety about unknown adverse events rather than known ones8–10.

The association between vaccines and adverse events and wrong perception of the risk can induce people to distrust vaccination and result in a low vaccination rate and the outbreak of diseases. On the contrary, denying the association despite ample evidence may ruin people’s trust in vaccination and bring a negative effect on the government’s public health policies. In order to compare the benefits and risk of vaccination and to adjust vaccination policies appropriately, accordingly, it is important to monitor the safety of vaccination. Because patients participating in clinical experiments are different from the ordinary population11, it is almost impossible to carry out pharmacovigilance over post-vaccination adverse events with such information alone. Particularly for rarely happening side effects, post-commercialization reports for several years play an important role and they are the most valuable information for finding new side effects5. In this sense, it is keenly required to explore the types and patterns of post-vaccination adverse events perceived by parents reporting that they had experienced post-vaccination adverse event in their children.

Thus, for adequate pharmacovigilance over vaccines used to infants and young children, this study purposed to examine the types and patterns of post-vaccination adverse events perceived by parents with infants and young children ultimately in order to monitor thoroughly adverse events suspected to be associated with vaccines and to provide basic information for developing measures against such adverse events.

2. Research Methods

2.1 Design

This study was conducted as descriptive research for identifying the types and patterns of post-vaccination adverse events perceived by parents with infants and young children.
2.2 Subjects
Cases for this study were sampled out of 2,230 some postings about experiences of post-vaccination adverse events on the bulletin board for vaccine side effects in ‘Safe Vaccine Society’, an online site related to vaccination, during the period from June 2006 to June 2013. Of the postings, those about the posters’ own or their parents’, relatives’, and neighbors’ experiences were excluded and 415 cases reported by parents with infants and young reported on their children’s post-vaccination adverse events were selected as data for this study.

2.3 Data Collection Method
For collecting data of this study, the researcher met the site operator of ‘Safe Vaccine Society’ (www.selfcare.or.kr), a major online site for parents with infants and young children to share their experiences of vaccine side effects in their children, explained the purpose of research and data collection procedure, and got the members’ consents by email. From 2,230 some postings on the bulletin board for vaccine side effects during the period from June 2006 to June 2013, 415 cases reporting experiences of vaccine adverse events in infants and young children were extracted. Each case in the extracted data was recorded in a coding sheet, its contents were read thoroughly, and the type and pattern of post-vaccination adverse events were classified. In case the meaning of data was ambiguous or uncertain, the accurate meaning was inquired by email or phone. The period of data collection was from July 2 to August 15, 2014, and for ethical consideration of the subjects, this study was approved by the Institutional Review Board of W University Oriental Medicine Hospital where the researcher belonged before it was started (WSOH IRB 1211-01).

2.4 Data Analysis Methods
Because this study focused on exploring symptoms that parents with infants and young children regarded as post-vaccination adverse events, data were analyzed through content analysis, which is effective for this type of research. Content analysis, which aims to analyze contents themselves, is a systematic and objective method invented to investigate the contents of recorded information by describing contents and categorizing them systematically\(^{12}\). That is, this method focuses on the meaning of data\(^{13}\), and searches for meanings and derives themes from actual data through inductive analysis\(^{14}\). Data analysis in this study categorized using raw data obtained from bulletin board postings that described post-vaccination adverse events in children, and the specific analysis processes were as follows.

2.4.1 Setting Analysis Categories
In order to identify the types and patterns of adverse events by vaccine, this study used as basic framework ‘The Scope of Post-vaccination Adverse events To Be Reported’ in ‘Enforcement Regulations of the Infectious Disease Control and Prevention Act’\(^3\). That is, ‘type of vaccination with which adverse events appeared,’ ‘adverse event (clinical symptom),’ and ‘period until the appearance of post-vaccination adverse events (clinical symptoms) appear’ were set as analysis categories.

2.4.2 Analysis Criteria and Coding Method
In analyzing collected data, having contents related to the purpose of this study, two coders (researchers A and B) recorded in a coding sheet by case, read the contents thoroughly, and classified the type and pattern of adverse events according to vaccine. For any ambiguity or problem in the process of coding, it was discussed and resolved under the supervision of the principal researcher.

2.4.3 Reliability and Validity
The researchers of this study, who were all experienced in qualitative research, drew understanding and agreement upon analysis categories through a number of discussions. Each coder extracted contents fit for the purpose of this study according to analysis category, and after recording, intercoder reliability was calculated by Holst’s method\(^{12}\) (Holst’s method = \(2M/N1+N2\), \(N1+N2\): the total number of cases coded by the researchers; \(2M\): the number of cases coded consistently between the coders). When Holst’s method is used in content analysis, a reliability coefficient of about 90% is considered acceptable\(^{15}\), and the reliability coefficient in this study was 94%, showing a high degree of agreement. The validity of this study was tested by two nursing professors and two pediatric nursing professors who were highly experienced in content analysis.

3. Results
‘Appendix 3 of Enforcement Regulations of the Infectious Disease Control and Prevention Act’ suggests adverse events of vaccines for DTaP, Japanese encephalitis,
and hemorrhagic fever, and time for the appearance of post-vaccination symptoms, and adverse events to be reported after vaccination of poliovirus (for injection) hepatitis B, chickenpox, influenza or typhoid follow the criteria of DTaP except for cases designated by the Minister of Health and Welfare through the Korea Advisory Committee on Immunization Practices according to Paragraph 1 of Clause 1 of Article 7 of the regulations. Thus, this study also sorted out adverse events based on the categories and presented the results in Table 1.

In addition, clinical symptoms and time for the appearance of post-vaccination symptoms were presented for each of MMR, oral poliovirus vaccine, and tuberculosis vaccine (BCG), and for other vaccines, clinical symptoms and time for the appearance of symptoms were not presented. Table 2 shows adverse events for these vaccines.

Among the vaccines perceived by parents with infants and young children to cause adverse events, Diphtheria/Tetanus/Pertussis-PolioVirus (DTaP-IPV) was most frequent as found in 317 cases. Pneumococcus/Haemophilus

| The Types of Adverse Events | DTaP-IPV** | Japanese Encephalitis vaccine | Hepatitis B vaccine | Varicella vaccine |
|-----------------------------|------------|-------------------------------|---------------------|------------------|
| Time (day) | Frequency (people) | Time (day) | Frequency (people) | Time (day) | Frequency (people) | Time (day) | Frequency (people) |
| Anaphylactic reaction | - | 1 | - | - | 0 | 1 | - | - |
| Encephalitis, encephalopathy | - | 1 | - | - | - | - | - | - |
| CNS(central nervous system) reaction: hypotonic hypo-responsiveness, seizure, convulsion, etc. | 1–4 | 20 | - | - | 0–21 | 7 | - | 1 |
| Severe swelling with pain | 0–30 | 23 | 0–1 | 1 | 4 | 2 | - | - |
| Fever of over 39°C | 0–3 | 51 | 0–1 | 1 | 1–14 | 9 | 0–1 | 3 |
| Skin reactions | 0–7 | 55 | - | - | - | 16 | 0–1 | 2 |
| Digestive disorders: anorexia, diarrhea, jaundice, vomiting, etc. | 0–7 | 45 | - | - | 0–20 | 16 | 0–1 | 4 |
| Irritability, fidget, continuous loud shriek | 0–4 | 38 | - | - | 0–2 | 4 | 0–1 | 2 |
| Continuous sleeping exhausted, without responding to calls | 0–60 | 34 | - | - | 0–2 | 5 | 0–1 | 1 |
| Upper respiratory tract infection | 0–3 | 17 | 0–1 | 1 | - | 3 | - | - |
| Orbital edema or teardrop | 0–1 | 4 | - | - | - | 2 | - | - |
| Poor growth | 0–60 | 3 | - | - | - | 1 | - | - |
| Cold sweat or night sweat | 0–1 | 3 | - | - | - | 4 | - | - |
| Severe respiratory reactions: dyspnea, cyanosis, pneumonia, etc. | 0–2 | 3 | - | - | 0–8 | 4 | - | - |
| Urinary tract infection | - | 1 | - | - | - | 1 | - | - |
| Death | 1 | 1 | - | - | 0–20 | 1 | - | - |
| Others: Kawasaki disease, chicken pox, lymphadenitis, hypoglycemia, thrombocytopenia, leukocytosis, etc. | 1–5 | 4 | - | - | - | 1 | - | 2 |
| Developmental disorder: stop of coo and gurgle, sensitive or unresponsive to voice calls, eye contact is lost, etc. | 0–7 | 13 | - | - | - | 1 | - | - |
| Total | 0–60 | 317 | 0–1 | 3 | 0–21 | 78 | 0–1 | 15 |

*DTaP : Diphtheria, tetanus, and Pertussis, "IPV: Inactivated poliovirus vaccine
Influenza Type b (PCV/Hib) was found in 259 cases and Bacillus Calmette-Guerin (BCG) was found in 136 cases. As to the type of adverse events and time for the appearance of symptoms, after the vaccination of diphtheria/tetanus/pertussis (DTaP), 55 cases of ‘skin reactions’ such as urticaria and rash happened between the day of vaccination and day 7, 51 cases of ‘fever of over 39℃’ between the day of vaccination and day 3, and 45 cases of ‘digestive disorders’ including vomiting and diarrhea between the day of vaccination and day 7.

After the vaccination of pneumococcus/haemophilus influenza type b (PCV/Hib), 62 cases of ‘fever’ happened between the day of vaccination and day 3, 54 cases of ‘skin reactions’ between the day of vaccination and day 7, and 36 cases of ‘fretfulness or restlessness’ between the day of vaccination and day 8.

After the vaccination of tuberculosis (BCG), ‘lymphadenitis of over 1cm’ was most frequent as reported in 77 cases, and time for the appearance of the symptom was varied from 3 days to 30 months. Next, 21 cases of ‘skin reactions’ appeared between the day of vaccination and 3 months.

4. Discussion

This study was conducted in order to identify the types and patterns of post-vaccination adverse events perceived by parents with infants and young children, and to provide basic information for assuring the safety of vaccination in infants and young children through pharmacovigilance over adverse events suspected to be associated with vaccines.
First, DTaP was the vaccine for which parents reported adverse events in their infants and young children most frequently (317 cases). Among the reactions, 55 cases were skin reactions such as atopy, rash, urticaria, and eruption, 51 cases fever of over 39°C, 45 cases digestive disorders such as vomiting, diarrhea, diarrheic stool, constipation, nursing refusal, and low appetite, 38 cases continuous fretfulness, continuous crying without sleeping, continuous loud shrieky screaming, etc., 34 cases continuous sleeping exhausted without responding to calls, 20 cases central nervous reactions such as seizure and convulsion, 17 cases upper respiratory infections, and 13 cases developmental disorder such as regression.

Besides, there were severe adverse events including 3 cases of severe respiratory reactions such as dyspnea, cyanosis, and pneumonia, 1 cases of anaphylactic reaction, and 1 cases of death.

DTaP vaccine is for preventing diphtheria, tetanus, and pertussis, and its primary vaccination is done in 2, 4 and 6 months of birth, and booster injection is given in 15–18 months and 4–6 years. Then, Td/Tdap vaccine is injected at the age of 11–12, and afterward vaccination is made once in every 10 years. In addition to diphtheria, tetanus, and pertussis toxoid, DTaP vaccine components include adjuvants such as aluminum hydroxide, preservatives such as phenoxyethanol and thimerosal, stabilizers such as polysorbate80, antibiotics such as neomycin and polymixin B, and trace components used in the manufacturing process such as glutaraldehyde and formaldehyde. Because of these components, vaccination may cause adverse events apart from its primary purpose, which is immune creation. According to¹, there can be local reactions such as erythema, callus, pain, and tenderness, systemic symptoms such as dizziness, low appetite, vomiting, and fever, and rarely but severe adverse events such as anaphylactic reaction, spasm, hypotonic hypo-responsiveness, continuous high fever, and encephalosis. In the contents reported by the parents were found upper respiratory infection, urinary tract infection, and Kawasaki infection, which are not in the list of adverse events suggested by⁴. They are believed to have happened because the vaccinated children became vulnerable to infection temporarily after vaccination, but there were 38 cases of continuous loud crying without sleeping for 2–3 days, 34 cases of continuous sleeping exhausted without responding to calls, and 13 cases of behavioral or developmental abnormalities. Considering the reports of seizure or spasm, hypotonic hypo-responsiveness, dyspnea and cyanosis, anaphylactic reaction, and even death, what is more, we should not exclude them as irrelevant to vaccination but need to conduct extensive examination and long-term observation on their causal relation with vaccination through epidemiological investigations.

Adverse events for the vaccines of PCV/Hib, hepatitis B, Japanese encephalitis, and chickenpox showed patterns similar to those for DTaP vaccine, but with regard to BCG vaccine, lymphadenitis of over 1cm in diameter was reported most frequently (77 cases), and with regard to MMR, skin reactions such as atopy and urticaria were most frequent (14 cases).

BCG vaccine is for preventing vaccine, and currently in Korea, Danish strain is used as intradermal BCG vaccine and Tokyo strain as percutaneous BCG vaccine. BCG vaccine is injected once within a month from birth. In this study, lymphadenitis was reported as the most frequent adverse event of BCG vaccine (77 cases), which was followed by skin manifestations (21 cases) and local lesions at the injection site (11 cases). This result is consistent with the report of¹⁶ that half of the adverse events of BCG vaccine were local lesions at the injection site and the other half were regional lymphadenitis, and the report of¹⁷ that 773 of 1559 cases of BCG vaccine adverse events were local complications and 647 were lymphadenitis. Bacillus Calmette-Guerin (BCG) lymphadenitis is the most common complication of BCG vaccination¹⁸. For ordinary people not familiar with these adverse events of BCG vaccine, post-vaccination lymphadenitis may lead them to distrust the government’s vaccination policies and even to refuse childhood vaccination. Thus, it is necessary to oblige medical staff to give explanations not only about the effects of vaccination but also about its adverse events before injecting vaccine. What is more¹⁹, reported severe adverse events of BCG vaccine such as clinical manifestations of bone and joint in 27 cases, abnormalities in chest X-ray in 13 cases, skin manifestations in 17 cases, diseases in other sites or organs in 8 cases, and death in 6 cases¹⁹, and also reported serious adverse events including osteomyelitis, BCG abscesses and lymphadenitis in 2 cases and death in 5 cases. In this study, granuloma in 3 cases, sepsis or shock in 2 cases, and seizure in 1 case were reported as severe adverse events. Because severe adverse events are usually caused by defects in BCG strain itself or the host’s immunodeficient state¹¹,¹⁶,¹⁹, it is believed necessary to make efforts to
reduce post-vaccination adverse events through the safe management of vaccine, thorough preliminary checkup of the child’s condition before vaccination, and careful observation after vaccination.

MMR vaccine is prepared by attenuating MMR virus cultured in chick embryo tissue, so vaccine components such as ovalbumin, which is major allergy antigen protein in eggs, and gelatin, which is collagen from cow or pig and used as stabilizer, may induce severe allergic reactions in egg allergy patients or atopy patients, and this is consistent with the reports of parents with atop children and young children that atopy skin reaction grew worse after MMR vaccination. When post-vaccination adverse events are expected, it is necessary for the medical workers to search for a safer alternative vaccine and to explain actively the method and procedure to reduce adverse events.

As presented above, this study examined the types and patterns of post-vaccination adverse events in children perceived by Korean parents with infants and young children. Cases of adverse event reported by parents included harmful reactions actually induced by vaccine including reactions to additives in the vaccine, adverse events aggravated by the subject’s immunodeficiency, and accidental cases not related to vaccination. Accordingly, it is hard to say that all of post-vaccination adverse events reported by the parents are in a causal relation with vaccine, but rather than excluding symptoms seemingly irrelevant to vaccination, we need to conduct research and long-term follow-up on causal relations with vaccination including the subjects’ immunodeficiency and responses to vaccine additives. In order to reduce post-vaccination adverse events and promote safe vaccination, furthermore, we need to make it obligatory to give detailed explanations about post-vaccination adverse events of vaccine and additives and to take history of allergy or immunologically diseases, and there should be continuous long-term follow-up and research on causality for post-vaccination adverse events.

As this study collected data from a website for exploring parents’ perception of post-vaccination adverse events in their infants and young children, the sample may have a limitation in representing the whole population. Because of difficulty in conducting a national epidemiological investigation of parents who have experienced in post-vaccination adverse events, the government needs to provide national support for such research.

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6. References

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