JOURNAL OF IRANIAN CLINICAL RESEARCH

ORIGINAL ARTICLE

Adverse Events Associated with Measles-mumps-rubella Vaccines in Arak

Fatemeh Dorreh[1]*, Masoumeh Heidary[2]

[1] Department of Pediatric, Arak University of Medical Sciences, Arak, Iran
[2] General Practitioner, Arak University of Medical Sciences, Arak, Iran

ABSTRACT

Background: Epidemiological study of adverse events following vaccination is not easy, and numerous countries do not have any reliable data in this regard. The aim of this study was to identify the adverse events following measles-mumps-rubella (MMR) vaccination in Arak, Iran.
Materials and Methods: This descriptive study was performed on 310 vaccinated children (12m-6y) at vaccination centers of Arak, Markazi Province, Iran. The parents were educated to use a daily diary to record symptoms during a 43-day period following immunization.
Results: In this study, 54.5% of the children (50.2% vaccinated with Razi vaccine and 62.1% with Indian vaccine) experienced at least one adverse event. Adverse events were fever (40.9%), pain (17.9%), erythema at injection site (9.6%), rash (14.5%), arthralgia (6.7%), parotitis (5%), headache with vomiting (4.5%), and febrile convulsions (1.6%). Seven children were hospitalized for the severity of symptoms. Two cases of aseptic meningitis were detected among the children in the study group.
Conclusion: The incidence of common and serious adverse events following the injection of both strains of MMR vaccine is relatively high in Iran.

Key Words: Adverse effects, Aseptic meningitis, MMR vaccine

➢ How to cite this paper:
Dorreh F, Heidary M. Adverse Events Associated with Measles-mumps-rubella Vaccines in Arak. Journal of Iranian Clinical Research. 2015; 1(1): 6-10.

INTRODUCTION

Preliminary prevention of infectious diseases through vaccination is one of the major accomplishments of medical sciences. Despite the great effectiveness of vaccines, they may still be accompanied with adverse effects and consequences. Measles-mumps-rubella (MMR) vaccine is a routine vaccination schedule in Iran, which has been introduced to the immunization program since 2004. According to the new national immunization program (2008), the vaccine should be administered in two doses, i.e., the first one at 12 and the second one at 18 months of age.

About 5-15% of sensitive individuals who receive MMR vaccine, then develop fever within 6-12 days post-vaccination, 10% suffer from local reactions (such as pain and erythema at the injection site), 5% experience transient rash within 7-10 days post-injection, and one per 25.000 to 200.000 cases experience transient thrombocytopenia [1, 2].

Other side effects, such as neurologic complications, febrile seizures, deafness, swelling of the parotid glands, joint pain, and transient paresthesia, are rarely reported [1]. The incidence of side effects varies depending on the different vaccine strains applied [3].

Epidemiological study of adverse effects following vaccination is not an easy task. Nonetheless, several studies on serious side effects of different MMR strains were carried out. In a study in Brazil, following a widespread MMR vaccination (using Urabe strain), the prevalence of aseptic meningitis was reported as one in 14000 cases [4]. In a study in the UK using Priorix strain, no increase in the risk of aseptic meningitis was reported; however, convulsion was reported following vaccination [5]. In another study conducted in Brazil using Leningrad-Zagreb strain, the prevalence of aseptic meningitis was reported as one case per 3390 [6]. In a series of studies in Netherlands and Finland, no correlation was reported between MMR vaccine and aseptic meningitis, encephalitis, and autism [7, 8].

Two strains of this vaccine are used in Iran (one Hoshino strain made by Razi Serum Institute and the other one Leningrad-Zagreb

* *Corresponding author:* Fatemeh Dorreh, Pediatric Ward, Amirkabir Hospital, Arak, Iran. Tel: 09181611123; Fax: 08633132510; Email: doreh.f@arakmu.ac.ir

strain produced by Serum Institute of India). In Iran, MMR vaccines have been manufactured for decades at Razi Vaccine and Serum Research Institute. These vaccines contain Hoshino strain for mumps, which may cause some adverse events just as other strains. However, there is a scarcity of comprehensive studies on these side effects.

The prevalence of fever and convulsion, swelling of the parotid glands, stiff neck, and aseptic meningitis within one month after MMR vaccination motivated the researchers to conduct this study. Herein, we aimed to investigate serious and common side effects of MMR vaccine by monitoring vaccinated children.

MATERIALS AND METHODS

In this descriptive study performed in 2008, 460 MMR-vaccinated children (regarding the need for a sample size of 300 subjects and probability of exclusion or subject attrition) were selected through convenience sampling method. The vaccines were administered at vaccination centers in Arak. The subjects were recruited over a course of four months of sampling.

Based on the latest national immunization program, 12 months old, 18 months old, and 18 months to 6 year-old children were included in the study. After obtaining informed consent from their parents, data collection forms were given to the participants, which included age, sex, history of any specific diseases, history of hospitalization, vaccination schedule and any adverse event following it, and eight major MMR vaccine side effects, comprising of erythema and pain at the injection site, fever, convulsion, arthralgia, swelling of the parotid glands, skin rash, and headache with vomiting. Information including the vaccine strain received, injection date, and contact number were also recorded. After 43 days, the desired data was gathered from the completed forms or through telephone calls.

Parents of the children receiving MMR and diphtheria, pertussis, and tetanus (DTP) vaccines at the same time were informed about the erythema and pain at different injection sites.

Samples with incomplete forms or vaccine side effects such as diarrhea, cough, and cold were excluded from the study. Finally, the required data was extracted from 310 remaining forms.

Of the two hospitalized children with suspected meningitis, three samples of cerebrospinal fluid (CSF) were prepared for smear-culture and titer for mumps IgM antibody (using ELISA method) and delivered to the laboratory.

Research data was analyzed by SPSS, version 11.5.

In all stages of the study, the ethical principles of Helsinki Declaration were observed. The patients were included in the study after informed consent was obtained from their parents. Confidentiality of the data was ensured. No cost was imposed on the families by the research.

RESULTS

Of the total of 310 participants, 50.3% were females. In total, 36.5%, 37.4%, and 26.1% were 12 months, 18 months, and 18-72 months old, respectively.

A total of 64.2% of the children were vaccinated with Hoshino vaccine strain made by Razi Serum Institute and 35.8% by Leningrad-Zagreb vaccine strain produced by Serum Institute of India.

In the study population, 169 (54.5%) subjects (24.5% male and 30% female) suffered from at least one MMR vaccine side effect, but there was no statistical difference between the boys and girls (P=0.044).

Based on vaccine strains, of the children who were vaccinated with the Razi and Indian vaccines, 50.2% and 62.1% experienced at least one side effect, respectively. The frequencies of the side effects based on the used vaccine strain are presented in Table 1. Considering

Table 1. Frequency of different adverse events of measles-mumps-rubella vaccines in 310 vaccinated children at immunization centers in Arak, 2008

Vaccine adverse events	Indian vaccine n(%)	Razi vaccine n(%)	Total n(%)	P-Value*
Pain at the injection site	25(22.5)	28(14.07)	53(17.09)	0.042
Erythema at the injection site	14(12.6)	16(8)	30(9.6)	0.135
Fever	65(58.5)	62(31.1)	127(40.9)	<0.001
Convulsion	3(2.7)	2(1)	5(1.6)	0.246
Parotitis	6(5.4)	10(5)	16(5.1)	0.539
Skin rash	15(13.5)	30(15.07)	45(14.5)	0.423
Arthralgia	4(3.6)	17(8.5)	21(6.7)	0.073
Headache and vomiting	4(3.6)	10(5)	14(4.5)	0.395

* P-value less than 0.05 was considered statistically significant

sex, there was only significant difference between the 21 subjects (7 males and 14 females) with arthralgia (P<0.001). Seven children required hospitalization during the study period.

The cerebrospinal fluid (CFS) test results of the two-hospitalized meningitis-suspected subjects (both males), who were admitted 43 days after vaccination, determined them positive for aseptic meningitis. Nevertheless, their mumps IgM antibody titers were negative.

DISCUSSION

In this study, more than half of the children experienced at least one side effect following MMR vaccination. The incidence of side effects was higher in girls compared to boys. In a study in Tabriz, in which the relationship between aseptic meningitis and history of MMR vaccine was investigated, 75% of subjects were male [9].

Razi vaccine was associated with significantly fewer local adverse events such as pain at injection site and fever. The incidence of other adverse effects of Razi and Indian vaccines was similar. No study was previously conducted on the differences between two vaccine strains in Iran.

A fever of 39.4˚C or higher was reported in approximately 5% to 15% of vaccine recipients, usually between 6-12 days after MMR vaccination, which generally lasts 1-2 days, but may continue for as long as five days [1, 2]. In our study, fever was the most common side effect with an incidence of 40.9%. In a study in Singapore, where RIT 4385 mumps strain was used, 42.8% of the patients developed fever [10]. Therefore, the incidence of this side effect may vary depending on the strain used.

In this study, the rate of pain at injection site with the Indian strain was higher than other reports. However, no difference was found regarding erythema at injection site [1, 2, 10].

Skin rash was reported in approximately 5% of vaccine recipients [1]. We found a three-fold increase in the risk of skin rash in our study. The incidence of arthralgia was comparable with those reported by reference books. Although fever, pain at injection site, and skin rash occurred more frequently in our study, these side effects are generally not serious ones.

Although swelling of the parotid glands is rarely reported in other studies, 5% of our subjects contracted this side effect. This usually happens 2-3 weeks after vaccination and is a harmless and mild side effect, but it could concern families and might result in misdiagnosis.

Barlow *et al.* in a prospective cohort study confirmed a significant increase in the risk of febrile seizure within 8-14 days after MMR vaccination (25-32 cases per 100000 injections) [11]. Miler et al. reported a frequency of one febrile seizure per 1150 MMR vaccinations [5].

Compared to other studies, in the current study the risk and incidence rate of febrile convulsion were higher and occurred 11-14 days post-vaccination.

Mumps vaccine virus strains are associated with aseptic meningitis, with widely varying estimates of risk. These discrepancies in estimated rates may be due to differences in study design or case ascertainment, as well as vaccine strains. Accordingly, our findings highlighted the need for further efforts to determine the rate of adverse events following immunization associated with different mumps vaccine.

The U.S. Center for Disease Control and Prevention characterized vaccine-associated aseptic meningitis by the onset of fever, with pleocytosis of 10–1500 leukocytes/ml occurring within 15–35 days after vaccination, as well as signs and symptoms of meningeal clinical involvement [12]. The incidence rates of aseptic meningitis induced by Jeryl-Lynn and Leningrad-Zagreb vaccine strains were reported to be 1 in 1.8 million and 1 in 1000 million cases, respectively [12].

In a study by Nagai et al. in Japan, the incidence of aseptic meningitis was 13/1051 (1.24%) in the patients with symptomatic natural mumps infection and was estimated to be 0.7-1.1% when considering asymptomatic infections. In comparison with natural mumps infection, aseptic meningitis only occurred in 10/21,465 (0.05%) vaccine recipients. The prevalence rates of fever, swelling of the parotid glands, vomiting, headache, and convulsion were reported 37.5%, 26.1%, 3.5%, 12%, 4.8%, and 0.3%, respectively [13].

In a study conducted in Tabriz, of 65 cases of aseptic meningitis who were hospitalized in 2005, 67.7% had received MMR vaccine less than a month earlier. Half of the patients had fever and convulsion, and one-thirds of them presented with swelling of the parotid glands [9].

In the present study, two out of 310 subjects experienced aseptic meningitis, which is considered a high incidence.

One of rare adverse effects associated with MMR vaccine are third and sixth nerve palsies.

Menzoti et al. reported one case of third nerve palsy with systemic symptoms that did not recover completely [14]. Fortunately, no nerve palsy was observed in our study.

In a systematic review, Demicheli et al. reviewed 64 studies that included 14700000 children and evaluated the impact and side effects of MMR vaccination. The highest risk of aseptic meningitis was within the third week after immunization with Urabe-containing MMR (risk ratio [RR] 14.28; 95% confidence interval [CI] from 7.93 to 25.71) and within the third (RR [relative risk]: 22.5; 95% CI[confidence interval]: 11.8 to 42.9) or fifth (RR: 15.6; 95% CI: 10.3 to 24.2) weeks after immunization with the vaccine prepared with the Leningrad-Zagreb strain. A significant risk of MMR exposure during the two weeks before febrile seizure (RR: 1.10; 95% CI: 1.05 to 1.15) was reported in a large cohort study involving 537,171 childrenaged between three months and five years old [15].

CONCLUSION

The results of this study can be used to adopt cost-effective strains, with fewer side effects, in the National Immunization Program. The evidence of adverse events following immunization with MMR vaccine should be considered along with its role in preventing the target diseases.

The incidence of common and serious side effects following both strains of MMR vaccine is relatively high in Iran. Therefore, further extensive studies with larger sample size and concrete diagnosis of aseptic meningitis using polymerase-chain-reaction are suggested.

ACKNOWLEDGEMENTS

This study is the result of a student thesis. Hereby, we greatly appreciate the medical Research Committee of Faculty of Medicine, Arak University of Medical Sciences, Arak, Iran, for cooperating with this study.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Pickering L, Baker C, Long S. Red book: 2006 report of the Committee on Infectious Diseases. ELK Grove village (IL): American Academy of Pediatric; 2006.
2. Plotkin S, Orenstein W, Offit P. Vaccines. 5th ed. Philadelphia: Saunders; 2008.
3. Kliegman R, Behrman R, Jenson H. Nelson textbook of pediatrics, 18th ed. USA: Saunders; 2007.
4. Dourado I, Cunha S, da Gloria Teixeira M, Farrington CP, Melo A, Lucena R, et al. Outbreak of aseptic meningitis associated with mass vaccination with a urabe-containing measles-mumps-rubella vaccine: implications for immunization programs. American journal of epidemiology. 2000;151(5): 524-30.
5. Miller E, Andrews N, Stowe J, Grant A, Waight P, Taylor B. Risks of convulsion and aseptic meningitis following measles-mumps-rubella vaccination in the United Kingdom. American journal of epidemiology. 2007;165(6):704-9.
6. da Silveira CM, Kmetzsch CI, Mohrdieck R, Sperb AF, Prevots DR. The risk of aseptic meningitis associated with the Leningrad-Zagreb mumps vaccine strain following mass vaccination with measles-mumps-rubella vaccine, Rio Grande do Sul, Brazil, 1997. International journal of epidemiology. 2002;31(5):978-82.
7. Mäkelä A, Nuorti JP, Peltola H. Neurologic disorders after measles-mumps-rubella vaccination. Pediatrics. 2002;110(5):957-63.
8. Mrozek-Budzyn D, Kieltyka A, Majewska R. Lack of association between measles-mumps-rubella vaccination and autism in children: A case-control study. The Pediatric infectious disease journal. 2010;29(5):397-400.
9. Abdoli OS, Barzegar M, Malekian A. Relationship between aseptic meningitis and MMR vaccination. Medical Journal of Tabriz University of Medical Science. 2007;28(4):81-4.
10. Lim FS, Han HH, Bock HL. Safety, reactogenicity and immunogenicity of the live attenuated combined measles, mumps and rubella vaccine containing the RIT 4385 mumps strain in healthy Singaporean children. Annals-Academy of Medicine Singapore. 2007;36(12):969.
11. Barlow WE, Davis RL, Glasser JW, Rhodes PH, Thompson RS, Mullooly JP, et al. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. New England Journal of Medicine. 2001;345(9): 656-61.
12. Bonnet M-C, Dutta A, Weinberger C, Plotkin SA. Mumps vaccine virus strains and aseptic meningitis. Vaccine. 2006;24(49):7037-45.
13. Nagai T, Okafuji T, Miyazaki C, Ito Y, Kamada M, Kumagai T, et al. A comparative study of the incidence of aseptic meningitis in symptomatic natural mumps patients and monovalent mumps vaccine recipients in Japan. Vaccine. 2007;25(14):2742-7.
14. Manzotti F, Menozzi C, Porta MR, Orsoni JG. Partial third nerve palsy after Measles Mumps Rubella vaccination. Italian journal of pediatrics. 2010;36(1):59.
15. Demicheli V, Rivetti A, Debalini MG, Di Pietrantonj

C. Vaccines for measles, mumps and rubella in children. Evidence-Based Child Health: A Cochrane Review Journal. 2013;8(6): 2076-238.