Original Article

Evaluating the effectiveness of antibiotics in the treatment of aseptic meningitis caused by the MMR vaccine

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Abstract

Introduction: In some cases, MMR vaccine injection causes fever, seizures, parotitis, and aseptic meningitis in children. Since in patients suspected of having meningitis, antibiotics are initially started with a meningeal dose and considering that a group of patients receive antibiotics despite the diagnosis of aseptic meningitis, evaluation of the effectiveness of antibiotics in the treatment of aseptic meningitis caused by the MMR vaccine is necessary in order to prevent drug resistance, indiscriminate use of antibiotics, and additional costs.

Materials and methods: In this descriptive-analytical study, which was conducted from 2016 to 2019 at Hazrat Ali Asghar Hospital in Iran, the number of samples studied was 50 patients. The patients were included in the study after checking the children's vaccination cards and considering the inclusion and exclusion criteria. Cerebrospinal fluid samples were taken and sent to the laboratory for culture and analysis and latex agglutination test. Also, in order to ensure the viral origin of the studied meningitis patients, antibiotic effectiveness was evaluated using the disk diffusion method. The demographic and medical information of the patients was recorded in a researcher-made questionnaire, and finally, the data were analyzed using SPSS version 22 software.

Results: The mean and standard deviation of the children's age was 13.35±1.26 months. Also, 36.6% of the children were girls and 63.1% of them were boys. The youngest age was 1.2 and the oldest age was 2 years. Among the studied patients, 12 children did not receive antibiotics during hospitalization and 38 people received antibiotics during hospitalization. At first, ceftriaxone was started for 38 people and vancomycin for 36 people. Then, ceftriaxone was continued for 14 people, ceftriaxone and vancomycin for 6 people, cefotaxime for 14 people, and cefotaxime and vancomycin were continued for 4 people. Among the 12 children who did not receive secondary treatment with antibiotics, 10 children had initially received ceftriaxone and 8 children had received vancomycin. Examining the relationship between hospital symptoms and antibiotic prescription showed that the degree of fever was significantly different in both groups. There was no significant relationship between the duration of fever and the use of antibiotics, and also between the duration of hospitalization and the use of antibiotics.

Discussion and conclusion: Antibiotic use in children with aseptic meningitis caused by MMR vaccine injection, in addition to having no effect on the treatment, may cause the exacerbation of meningitis complications. Also, there was no significant difference between the duration of hospitalization in people who received antibiotics and patients who did not receive antibiotics.

Keywords: MMR vaccine, aseptic meningitis, seizure, fever.

INTRODUCTION

Central nervous system infection may be disseminated or focal. Meningitis and encephalitis are examples of disseminated infections (1). Meningitis is a disease of the central nervous system (CNS) that involves the meningeal membrane and is

characterized by fever, headache, nausea, vomiting, meningeal irritation, and cerebrospinal fluid (CSF) changes (2). Although it is possible to get meningitis at any age, it is more common in children under the age of five. Meningitis exists in various types, including viral, bacterial, fungal, etc., but viral infections are usually more common than other infections.

Bacterial meningitis is one of the most serious infections, which occurs in infants and older children (3). Viral meningitis is one of the most common types of meningitis in which the tissue covering the brain and spinal cord becomes inflamed, and this type is often less severe than bacterial meningitis (4). Non-polio enteroviruses are the most common cause of viral meningitis, especially from late spring to fall (when viruses are more prevalent). However, a small percentage of people infected with enteroviruses actually develop viral meningitis. Other viruses that can cause viral meningitis include Measles virus, rubella, herpes viruses, and arboviruses (4).

The MMR vaccine is recommended by the Advisory Committee on Immunization Principles, the American Congress of Obstetricians and Gynecologists (ACOG), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP) for routine use to prevent measles, mumps, and rubella (5). This vaccine contains weakened measles viruses (Edmonston-Ender's virus strain), mumps (Jeryl Lynn virus strain), and rubella (Wistar RA 23/7 virus strain) (6). But one of the most important issues regarding vaccination is the safety of the vaccine itself. Aseptic meningitis and meningoencephalitis, which are the most common complications of mumps, have been reported following the injection of MMR vaccines. The incidence of meningitis following Zagreb, Hoshino, and Urabe strains has been proven by molecular studies (7). Since the Zagreb strain vaccine is commonly used in Iran, it is necessary and important to study aseptic meningitis caused by the injection of this vaccine and the related aspects, including early diagnosis and proper and timely treatment. It seems that antibiotics are ineffective in the treatment of viral meningitis, and the treatment includes monitoring the patient to prevent complications of the disease. In general, it can be said that the diagnosis of the viral agent of meningitis is useful and reduces the prescription of antibiotics and the duration of hospital stay (8). In children under two years of age, before determining the cerebrospinal fluid culture results, the use of antibiotics is started with a meningeal dose, and after the diagnosis of aseptic meningitis, the antibiotic treatment dose is changed to a non-meningeal dose and continues with an antibiotic. Therefore, we decided to investigate the effectiveness of antibiotics in the treatment of aseptic meningitis caused by the MMR vaccine in order to prevent drug resistance, indiscriminate use of antibiotics, and additional costs, as well as provide more effective treatments and improve the quality of life of patients.

MATERIALS AND METHODS

Type of research and the study population

In this study, which is a retrospective descriptive-analytical study, the study population included all children under two years of age who were referred to the emergency and infectious department with fever, symptoms of meningeal irritation, and sometimes parotitis, and were diagnosed with aseptic meningitis. The cases were admitted to Hazrat Ali Asghar Hospital between 2016 and 2019.

Sampling method and sample size

To determine the required sample size at the confidence level of 95%, the power of the test of 80%, and the accuracy of 0.1 after setting the value in the following formula, the sample size was calculated to be 50 people. It should be noted that the researcher could increase it to 60 people following a 10% drop.

$$n = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2 \times (s_1^2 + s_2^2)}{d^2}$$

$$z_{0,975} = 1,96$$

$$z_{0,8} = 0,86$$

$$d=0.1$$

$$s_1 = s_2 = 0,3$$

$$n = \frac{(1,96 + 1,28)^2 \times (2 \times 0,3^2)}{0,2^2} = 50$$

Inclusion and exclusion criteria

Inclusion criteria included full consent to participate in the study, being under 2 years of age, and a definitive diagnosis of

aseptic meningitis within one month after receiving the MMR vaccine. Exclusion criteria included unwillingness to continue participating in the study, the existence of underlying and chronic diseases in children, lack of consent to perform cerebrospinal fluid sampling, and the presence of defects in the medical records.

Data Collection tools

In this study, data collection was done using a researcher-made checklist, which was designed based on similar articles and the opinion of professors of Iran University of Medical Sciences. This questionnaire consisted of two parts, i.e., demographic information and clinical information. Also, the validity and reliability coefficient of the mentioned questionnaire was calculated to be 0.89 based on Cronbach's alpha, which indicated the appropriate validity of this questionnaire.

Method

This study, which used an analytical-observational method, was performed after the approval of the project in the research center of the educational and therapeutic hospital and the approval of the ethics committee in medical research with the code of ethics of 18969. After that, all children under two years of age with fever and symptoms of meningeal irritation and sometimes parotitis, who were diagnosed with aseptic meningitis and were admitted to the emergency and infectious department of Hazrat Ali Asghar Hospital during the years 2016 to 2019, were studied. The cases were questioned about receiving the MMR vaccine, and their vaccination card was checked to determine the exact date of vaccination, and if they had aseptic meningitis within one month after receiving the vaccine, they were included in the study. Then, by considering the inclusion and exclusion criteria of the study, the number of studied samples was considered to be 50 people. Cerebrospinal fluid samples were taken from the patients and sent to the laboratory for culture and analysis and latex agglutination test. Also, in order to ensure the viral origin of the studied meningitis patients, antibiotic effectiveness was evaluated using the disk diffusion method. Then, the demographic information, including age and gender, and medical information, including the status of the last vaccine, time of vaccine injection, the onset of fever, duration of fever, other associated symptoms, antibiotic treatment at home, degree of fever, time to see a doctor, the result of cerebrospinal fluid culture and the duration of hospitalization in people who received and did not receive antibiotics, were recorded in the relevant checklists. Lastly, the data were analyzed statistically.

Data analysis method

The obtained data were statistically analyzed using SPSS version 22 statistical software. The results for quantitative variables were expressed as mean and standard deviation (Mean ± SD) and for categorical qualitative variables as percentages. Comparison between quantitative variables was done by t-test, and in case of non-normal distribution, Mann-Whitney U test, Chi-Square Test, and Fisher's Exact Test were used to investigate the relationship between qualitative variables. A significance level of less than 0.05 was considered.

Ethical considerations

Informed consent was obtained from the patients before entering the study. The participation of patients in the study did not lead to the exclusion of them from standard treatment and did not involve additional costs for them. All necessary permissions to conduct this study were obtained from the ethics committees before the start of the study, and all patient information would remain completely confidential with the researcher, and the researcher is committed to preserving their information.

RESULTS

All 50 participants were diagnosed with meningitis and initially received appropriate antibiotics with meningeal dosage, and then the continuation of treatment was decided based on the laboratory results of the cerebrospinal fluid analysis. Then, despite being aseptic, antibiotics were continued for 38 children according to the doctor's opinion, and 12 children were discharged without receiving antibiotics after being diagnosed with aseptic meningitis. The mean and standard deviation of the age of children in the group receiving antibiotics was 13.35±0.26 months and in the group not receiving antibiotics was 13.63±0.71 months. In the group receiving antibiotics, 14 (36.6%) were girls and 24 (63.1%) were boys, and in the group not receiving antibiotics, 2 (16.7%) were girls and 10 (83.3%) were boys. The youngest age was 12 months and the oldest age was 20 months, which was the same between both groups (Table 1).

Table 1: Distribution of age and gender of children

Variables		**Received antibiotics**	**Did not receive antibiotics**
		Frequency (percentage)	**Frequency (percentage)**
Gender	Boy	24 (63.1 %)	10 (83.3 %)
	Girl	14 (36.6 %)	2 (16.7 %)
Age	Mean (standard deviation)	13.35(0.26 %)	13.63(0.71 %)

Among the cases, 12 children did not receive antibiotics during hospitalization and 38 people received antibiotics during hospitalization. At first, ceftriaxone was started for 38 people and vancomycin for 36 people. Then, ceftriaxone was continued for 14 people, ceftriaxone and vancomycin for 6 people, cefotaxime for 14 people, and cefotaxime and vancomycin were continued for 4 people. Among the 12 children who did not receive secondary treatment with antibiotics, 10 children had initially received ceftriaxone and 8 children had received vancomycin.

Also, 10 children (20%) had received antibiotics at home before going to the hospital. Antibiotics included azithromycin, cefixime, co-amoxiclav, amoxicillin, and ceftriaxone.

Table 2: Distribution of antibiotic prescription in children

		Received		Did not received	
Antibiotics		38	70.2	12	29.8
Prescribed Antibiotics	Ceftriaxone	38	100	10	55.7
	Vancomycin	36	94.7	8	44.3
Continued treatment		**Number**		**Percentage**	
Prescribed Antibiotics	Ceftriaxone	14		36.84	
	Ceftriaxone and Vancomycin	6		15.78	
	Cefotaxime	14		36.84	
	cefotaxime and Vancomycin	4		10.54	
At home		**Number**		**Percentage**	
Antibiotic Use	Type of antibiotics	2		0.2	
	Azithromycin	4		0.4	
	Cefixime	2		0.2	
	co-amoxiclav	1		0.1	
	Amoxicillin	1		0.1	
	Ceftriaxone	2		0.2	

In the group receiving antibiotics, the average injection time was 20.18 days. The duration of the fever was about 12.3 days. The average degree of fever was 38.89 and the mean duration of hospitalization was 5.44 days. (Table 3). But in the group that did not receive antibiotics, the average injection time was 18.45 days and the duration of fever was about 2.00 days. The average degree of fever was 38.86 and the mean duration of hospitalization was 3.73 days (Table 3). Examining the relationship between hospital symptoms and antibiotic prescription in children with aseptic meningitis caused by the MMR vaccine showed that there was a significant difference between the two groups in terms of the degree of fever ($P<0.05$). There was no significant relationship between the duration of fever and the use of antibiotics. Also, the relationship between the duration of hospitalization and the use of antibiotics was not statistically significant ($P>0.05$).

Table 3: Distribution of hospital parameters

	Received antibiotics		**Did not receive antibiotics**		**p**
Variables	**Mean**	**Standard Deviation**	**Mean**	**Standard Deviation**	
Injection time (days)	20.18	1.17	18.45	1.08	--
Fever duration (days)	3.12	0.41	2.00	0.35	0.55
Degree of fever	38.89	0.10	38.36	0.29	0.023
Duration of hospitalization (days)	5.44	0.33	3.73	0.44	0.22

The study of the distribution of clinical symptoms of meningitis showed that all 50 cases had a fever, 31 cases had vomiting, 7 cases had diarrhea, 5 cases had seizures, and 4 cases had restlessness. (Table 4). The comparison of the symptoms and complications of aseptic meningitis caused by the MMR vaccine in children who received antibiotics and those who did not receive antibiotics showed that the two groups were very similar in terms of clinical symptoms and no statistically significant difference was seen between the two groups. (p=0.99)

Table 4: Distribution of clinical symptoms

Clinical Symptoms	**Antibiotics**				**p**
	Received		**Did not receive**		
	Quantity	**Percentage**	**Quantity**	**Percentage**	
Vomiting	31	63.2	8	61.5	0.99
Restlessness	4	8.1	1	7.7	
Diarrhea	7	14.2	2	15.4	
Seizure	5	10.2	2	15.4	
Skin lesions	1	2	0	0.0	
Abdominal pain	1	2	0	0.0	
Cough	1	2	0	0.0	
Total	49	100	13	100	

The study of the relationship between hospital symptoms and antibiotic prescription in children with aseptic meningitis caused by the MMR vaccine showed that the degree of fever was significantly different in the two groups (P<0.05). There was no significant relationship between the duration of fever and the use of antibiotics and between the duration of hospitalization and the use of antibiotics (P>0.05).

Table 5: Relationship between symptoms and antibiotic prescription

	Received antibiotics		**Did not receive antibiotics**		**p**
Variables	**Mean**	**Standard Deviation**	**Mean**	**Standard Deviation**	
Injection time (days)	20.18	1.17	18.45	1.08	--
Fever duration (days)	3.12	0.41	2.00	0.35	0.55
Degree of fever	38.89	0.10	38.36	0.29	0.023
Duration of hospitalization (days)	5.44	0.33	3.73	0.44	0.22

The laboratory findings among the studied children showed that the average white blood cell count was equal to 741.50, of which 81.17% were lymphocytes. (Table 6). Also, among the 38 patients, 16 people were subjected to a secondary cerebrospinal fluid analysis, which again confirmed aseptic meningitis.

Table 6: Distribution of laboratory findings in the studied children

	Variables	**Average**	**Standard Deviation**
Primary CSF analysis	White blood cells	741.50	829.236
	Lymphocytes	81.17	11.45
Secondary CSF analysis	White blood cells	286.50	330.92
	Lymphocytes	80.0	14.14

There was no statistically significant difference between the study and control groups in terms of the average white blood cells, lymphocytes, red blood cells, and any of the laboratory results (P>0.05).

Table 7: Examining the relationship between laboratory findings and antibiotic prescription

Hematological variables	Antibiotics				p
	Received		Did not receive		
	Average	Standard Deviation	Number	Percentage	
White blood cells	450.54	117.54	286.50	330.92	0.60
Lymphocytes	80.0	14.16	80.0	14.14	0.97
Red blood cell	130.00	-	165.00	219.20	0.91

DISCUSSION

In the few years that have passed since the MMR vaccination in Iran, several cases of meningitis have been observed, which usually occur within the weeks after receiving the vaccine (9). Complications caused by the MMR vaccine occur at three time points after vaccination. First, local side effects caused by the injection in the form of pain and swelling at the injection site, which is related to the first 1-2 days. Second, the fever caused by the measles component, which occurs at an average frequency of 5-15% one week (6-12 days) after MMR and can be accompanied by seizures and encephalopathy, but does not cause meningitis (10). Third, the complications caused by the mumps component, which occur on average 9 to 25 days after vaccination based on the period of mumps incubation, and include fever, parotitis, and meningitis in the order of prevalence (11). In our study of children under 2 years of age who received the MMR vaccine, the average injection time was 20.18 days. The mean duration of the fever was about 3.12 days and the average degree of fever was 38.89ºc. Also, the mean duration of hospitalization was determined to be 5.44 days. The distribution of clinical symptoms of meningitis in children showed that 39 children (78%) had vomiting, 9 people had symptoms of diarrhea (18%), 7 people had fever and seizures (14%), and 5 people had restlessness (10%). In a study by Geier DA et al., which was conducted in 2021, the MMR vaccination was investigated in American children. In this study, the frequency of children who had convulsions after the MMR vaccine was reported to be 30.9%, which was higher than our study (12). Also, in a study by Azarkar et al. that was conducted in 2003, seizures ranked fourth among the symptoms, but in Rahmani et al.'s study in 2020, nausea and vomiting with 74% frequency and then fever with 66% frequency ranked first and second among the symptoms after vaccination, and this difference can be due to the difference in the number of samples studied, the time to refer to medical centers according to the specific conditions, and cultural characteristics of each region. But in general, the results of this study and previous studies showed that nausea and vomiting are the most common symptoms in children with aseptic meningitis following vaccination, and the next most common symptom is fever (13.14).

Our findings regarding the relationship between hospital symptoms and antibiotic prescription in children with aseptic meningitis caused by MMR vaccine showed that the degree of fever was significantly different in both antibiotic-consuming groups and patients who did not receive antibiotics. There was no significant relationship between the duration of fever and the use of antibiotics, and the relationship between the duration of hospitalization and the use of antibiotics was not statistically significant. Our findings also showed that the average white blood cell count was 741.50. Lymphocyte and red blood cell counts were 81.17 and 165.00, respectively. There was no difference between the two groups in terms of any of the laboratory results. In addition, the comparison of the symptoms and complications of aseptic meningitis in children who received antibiotics and those who did not receive antibiotics showed that the two groups were highly similar in terms of clinical symptoms and there was no statistically significant difference between the two groups. . In a study by Mac Donald et al., the average number of cerebrospinal cells in children with meningitis caused by MMR vaccine injection, preferring lymphocytes, was 51.3, and in 55% of the patients, the cerebrospinal fluid protein was more than 40 mg and in all of them, the ratio of Cerebrospinal fluid sugar to blood sugar was more than 0.4, which was consistent with the results of our study (15). In 2018, Yelehe et al. investigated the treatment of meningitis in children. In this study, the most prescribed antibiotics were ampicillin (24.82%) and gentamicin (24.34%). In our study, 12 children were not treated with antibiotics during hospitalization and 38 children received antibiotics during hospitalization. . At first, ceftriaxone was started for 38 people and vancomycin for 36 people. Then, ceftriaxone was continued for 14 people, ceftriaxone and vancomycin for 6 people, cefotaxime for 14 people, and cefotaxime and vancomycin were continued for 4 people. Among the 12 children who did not receive secondary treatment with antibiotics, 10 children had initially received ceftriaxone and 8 children had received vancomycin (16).

The results of our study showed that the efficacy of antibiotics on the investigated parameters in aseptic meningitis is low, and even in some cases, can lead to bacterial resistance and other tissue damage caused by meningitis. Additionally, in another study, it was found that the use of antibiotics caused meningitis. In this study, a 52-year-old female patient was investigated, who came to the emergency room on two different occasions with severe headache, neck pain, and dizziness. Initial cerebrospinal fluid (CSF) analysis revealed lymphocytic pleocytosis, and empiric intravenous acyclovir was initiated. The

result of the CSF bacterial and viral culture was negative. A second CSF analysis revealed neutrophilic pleocytosis, and empiric intravenous antibiotic and antiviral therapy was initiated, but CSF bacterial, fungal, and viral cultures were negative. The patient reported taking trimethoprim-sulfamethoxazole (TMP-SMX) for a right leg infection before and after the initial presentation. The patient's symptoms resolved without neurological complications after discontinuation of TMP-SMX. This case report shows the importance of paying attention to the reasonable use of antibiotics (17). Also, a study by Elmedani et al. showed that trimethoprim and sulfamethoxazole antibiotics can increase the incidence of aseptic meningitis. In fact, the inducers of meningitis in these antibiotics include the direct chemical stimulation of the drug or hypersensitivity reactions (type 3 or type 4) to the meninges (18). An immune complex reaction to this drug, which causes vasculitis of small vessels or delayed activation of T cells in the meninges, causes meningeal irritation. Also, considering that TMP-SMX crosses the blood-brain barrier, it can cause an inflammatory response in the central nervous system (meninges). Various studies have shown that in addition to TMP-SMX, other antibiotics such as amoxicillin, cephalosporins, rifampicin, valacyclovir, and ornidazole can play a role in causing or aggravating aseptic meningitis (19). Therefore, precautions should be taken before the use of antibiotics for the treatment of aseptic meningitis until the identification of the type of disease (bacterial or viral aseptic meningitis), in order to prevent the side effects of these drugs and the development and spread of antibiotic resistance.

CONCLUSION

Following the comparison of the symptoms and complications of aseptic meningitis caused by the MMR vaccine in children who received antibiotics and those who did not receive antibiotics, it was found that the two groups were very similar in terms of clinical symptoms, and no statistically significant difference was observed. Therefore, the use of antibiotics in children with aseptic meningitis caused by the MMR vaccine, in addition to having no effect on the treatment, may aggravate the complications of meningitis and cause drug resistance.

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