Clinical Research

Assessment of Side Effects of COVID-19 Vaccination in Child Patients Diagnosed with Type-1 Diabetes Mellitus

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ABSTRACT

Objective: COVID-19 has become a global pandemic since March 2020. Vaccination is essential as there is no cure for COVID-19 infection yet. Vaccination is important for individuals with Type-1 DM because Type-1 Diabetes Mellitus (DM) is also considered among the medical conditions that can increase the risk of severe illness in children. One of the most important reasons for vaccine refusal in parents of children with chronic diseases is anxiety about developing side effects after vaccination. With this study, we aimed to detect the side effects of the vaccination in children with Type-1 DM who are vaccinated against COVID-19 by comparing them with children who do not have any chronic diseases.

Material and Method: We compared the side effects of the vaccine in 34 children with type 1 DM who were vaccinated against COVID-19 and 34 children who were also vaccinated against COVID-19 without any chronic disease. The survey forms about the side effects that may occur after the COVID-19 vaccine, developed by the researcher in line with the literature, was filled out by the patient and/or their parents via the Google survey forms.

Results: The most common local side effect was pain at the injection site with 88.20%, while swelling was 26.50%, and redness was 17.60%. There was no statistical difference between the groups in the rate of occurrence of local side effects ($p > 0.05$).

Conclusion: Our results show that post-COVID-19 vaccine side effects are generally local, mild and, prevalent, as well as systemic/severe reactions are rare. Side effects related to the COVID-19 vaccine in patients with type-1 DM were similar to the control group. Our study could be useful in reducing anxiety about vaccine-related side effects in this group of patients and their parents.

Keywords: *COVID-19 Vaccination, Side Effects, Type-1 Diabetes Mellitus.*

ÖZ

Tip-1 Diabetes Mellitus Tanısı Alan Çocuk Hastalarda COVID-19 Aşısı Sonrası Görülen Yan Etkilerin Değerlendirilmesi

Amaç: COVID-19, Mart 2020'den beri küresel bir pandemidir. Henüz COVID-19 enfeksiyonu için bir tedavi bulunmadığından aşı şarttır. Tip-1 Diabetes Mellitus (DM) da çocuklarda ağır hastalık riskini artırabilecek tıbbi durumlar arasında sayıldığından Tip-1 DM'li bireyler için aşılama önemlidir. Kronik hastalığı olan çocukların ebeveynlerinde aşı reddinin en önemli nedenlerinden biri aşı sonrası yan etkiler geliştirme kaygısıdır. Bu çalışma ile COVID-19 aşısı olan Tip-1 DM'li hasta çocukları ile herhangi bir kronik hastalığı olmayan çocuklar arasında aşının yan etkilerini karşılaştırmayı amaçladık.

Gereç ve Yöntem: COVID-19 aşısı olan Tip-1 DM'li 34 çocuk ile COVID-19 aşısı olan ve herhangi bir kronik hastalığı olmayan 34 çocukta aşının yan etkilerini karşılaştırdık. Literatür doğrultusunda araştırmacı tarafından geliştirilen COVID-19 aşı sonrası oluşabilecek yan etkiler ile ilgili anket, Google anket formu aracılığıyla hasta ve/veya ebeveynleri tarafından dolduruldu.

Bulgular: En sık lokal yan etki enjeksiyon yerinde %88.20 ile ağrı, şişlik %26.50 ve kızarıklık %17.60 idi. Lokal yan etkilerin görülme oranında gruplar arasında istatistiksel fark yoktu ($p > 0.05$).

Sonuç: Sonuçlarımız, COVID-19 sonrası aşı yan etkilerinin genellikle lokal, hafif ve yaygın olduğunu ve sistemik/şiddetli reaksiyonların nadir olduğunu göstermektedir. Tip 1 DM'li hastalarda COVID-19 aşısına bağlı yan etkiler kontrol grubuna benzerdi. Çalışmamız bu hasta grubunda ve ebeveynlerinde aşıya bağlı yan etki kaygısını azaltmada faydalı olabilir.

Anahtar Sözcükler: *COVID-19 Aşısı, Yan Etkiler, Tip-1 Diabetes Mellitus.*

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The first case of coronavirus disease (COVID-19) was reported in Wuhan, China, in December 2019. On 11 March 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic (1). There is currently insufficient data for the exact treatment of COVID-19 infection. Therefore, the prevention of diseases and protection of them is extremely important (2). According to investigations, COVID-19 is known to cause mild symptoms in children, but Type-1 DM is also considered among the medical conditions that can increase the risk of severe disease in children (3). High blood sugar levels can affect immune responses, increase susceptibility to infections and lead to an increase in the rate of mortality. Vaccination is therefore

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critical for individuals with Type-1 DM (4).

Firstly, at the end of 2020, two COVID-19 vaccines based on the mRNA (Pfizer &Biontec and Moderna) received emergency use authorization from the American Food and Drug Administration (5). On January 13, 2021, the Turkish Medicines and Medical Devices Agency (TITCK) granted an emergency use for the Sinovac vaccine (6). Sinovac®, Pfizer &Biontech® and Turkovac® vaccines are still produced (7). In our country, vaccination started on August 18, 2021, for those over the age of 12 with a chronic disease and for those over the age of 15 without any chronic disease (8).

Vaccine hesitancy and/or refusal are present in many countries around the world, especially Turkey, and vaccine rejection cases are increasing (9). Anxiety about developing post-vaccine side effects is one of the major causes of vaccine refusal in parents of children with chronic diseases. There are few studies that assess the general side effects of vaccines in the childhood age group. Rash, induration, and sensitivity can be seen after almost all parenteral vaccine applications, and these responses are the result of an inflammatory response to a foreign substance (10). After the COVID-19 vaccines, redness, swelling, itching, and pain can generally be seen in the injection site. In addition, fatigue, headache, tremors, fever, axillary lymph node growth, and joint pain may occur. (11). In many studies, local reactions (rash, redness, swelling, and pain) are common at the injection site, followed by systemic reactions such as not feeling well (fatigue and weakness) and pain (joint, muscle, body) (12-14). Cardiovascular side effects, such as hypertension, bradycardia, tachycardia, atrial fibrillation, acute coronary syndrome, and pulmonary thromboembolism, had a frequency of less than 0.1% and were similar to vaccination with a placebo (15). Myocarditis and pericarditis are extremely rare after the COVID-19 vaccine. As of December 16, 2021, the Vaccine Adverse Event Reporting System has received 1,947 preliminary reports of myocarditis or pericarditis among people aged 30 and under who have been vaccinated against COVID-19 (16).

In this study, we aimed to compare the side effects of the vaccine between Type-1 DM patients under the age of 18 who were vaccinated against COVID-19 and children without any chronic disease.

MATERIAL AND METHOD

In the study, the minimum sample amount required to detect a significant difference was calculated to be at least 21, considering type I error (alfa) of 0.05, power (1-beta) of 0.8, and effect size of 0.62 (17). In this study, we planned to determine the side effects of the COVID-19 vaccine in 34 vaccinated children with Type-1 DM by comparing them with 34 healthy children who were also vaccinated. Inclusion criteria are as follows; To be under the age of 18, to be followed up with the diagnosis of Type 1 DM in the pediatric endocrinology department, and not to have any additional disease. Exclusion criteria are as follows; Any glucose value in the database above 126 mg/dl, having ever been diagnosed with type 1 DM and other hormone disorders (thyroid dysfunction, precocious puberty, congenital adrenal hyperplasia), as well as having a chronic disease.

The created survey form was filled out by children and their families through Google survey forms. This study was approved by the Ethics Committee of Inonu University (dated 30.11.2021, 24th meeting, numbered 2021/2573), and informed consent was received from all patients or their parents.

Statistical Analysis

The assumption of normal distribution for quantitative data was examined with the Kolmogorov-Smirnov test. Normally distributed quantitative data were presented as mean±standard deviation, and qualitative data were presented as number (percentage). In the analysis of the data, independent samples t-test and Chi-square tests were used if appropriate. The $p<0.05$ value was considered statistically significant. The American Psychological Association (APA) 6.0 style was used to report statistical differences (18). All analyses were performed using IBM SPSS Statistics for Windows v28.0 (New York; USA).

RESULTS

The study included a total of 34 Type-1 DM patients, 15 girls (44.10%) and 19 boys (55.90%), with an average age of 15.35±1.95 (years). In the control group, there were a total of 34 healthy children, 16 (47.10%) girls, and 18 (52.90%) boys, with an average age of 15.25±1.93 (years). No difference was detected between the groups in terms of average age and gender distribution (Table 1).

Table 1. *Demographic characteristics.*

Variables		Groups						p-value*
		Patient			Control			
		n	%	Mean±SD	n	%	Mean±SD	
Gender	Girl	15	44.10	-	16	47.10	-	1.00
	Boy	19	55.90	-	18	52.90	-	
Age (years)		34	-	15.35±1.95	34	-	15.23±1.93	0.83

*SD: Standard deviation, *p <0.05 there is a statistically significant difference.*

The proportions of people with allergies to anything were not statistically different between the groups. The rate of being infected with COVID-19 was similar in both groups. The vast majority of those who were infected with COVID-19 in both groups had been infected before vaccination. No one had been infected with COVID-19 after the double-dose vaccine (Table 2).

Table 2. *COVID-19 and vaccination history.*

Variables		Groups				p-values*
		Patient		Control		
		n	%	n	%	
Presence of history of allergies to anything	No	4	11.80	8	23.50	0.34
	Yes	30	88.20	26	76.50	
Has he/she been infected with COVID-19?	Yes	9	26.50	11	32.40	0.58
	No	25	73.50	23	67.60	
If so, when he/she was infected with COVID-19?	Before vaccination	9	100.00	9	81.80	0.48
	After the 1st dose	0	0.00	2	18.20	
	After the 2nd dose	0	0.00	0.0	0.00	
Which vaccine was the first dose?	Biontech	28	82.40	29	85.30	1.00
	Sinovac	6	17.60	5	14.70	
Which vaccine was the second dose?	Biontech	19	55.90	14	41.20	0.32
	Sinovac	5	14.70	4	11.80	
	No	10	29.40	16	47.10	
Which vaccine was the third dose?	Biontech	1	3.00	0.0	0.00	0.37
	Sinovac	0	0.00	1	2.90	
	No	32	97.00	33	97.10	

**p <0.05 there is a statistically significant difference.*

In the patient group, the first dose vaccine rates of children were 28 (82.40%) Biontech, 6 (17.60%) Sinovac, while in the second dose, there were 19 (79.20%) Biontech, 5 (20.80%) Sinovac, a total of 24 children getting the second dose. In the control group, the first dose vaccine rates of children were 29 (85.30%) Biontech, 5 (14.70%) Sinovac, while in the second dose, there were 14 (77.80%) Biontech, 4 (22.20%) Sinovac, a total of 18 children getting the second dose. Biontech vaccine was the most preferred vaccine in both groups.

According to the assessed side effects of vaccines, there was no difference between groups in the rate of pain formation at the injection site (11.80% in every 2 groups, p =1.00), while there was a statistically significant difference in the description of the severity of pain (p =0.01).

At the injection site, 13 (38.20%) children in the patient group described the pain as low severity, while 2 (70.60%) children in the control group described it as low severity (p =0.007). In the patient group, 12 (35.30%) children described the pain as medium severity, while 6 (17.60%) children in the control group defined it as medium severity (p =0.09). In the patient group, 5 (14.70%) children defined the pain as high severity, while there were no children defining it as high severity in the control group (p =0.02). Pain severity at the injection site was described as low, medium, and high severity in the patient group, while low and medium in the control group (Table 3).

Table 3. *Side effects of the vaccine.*

Variables		Groups				p-value*
		Patient		Control		
		n	%	n	%	
Swelling at the site of the vaccine injection	Low Severity 2-5 Cm	9	26.50	8	23.50	0.56
	Medium Severity 5-10 Cm	1	2.90	0	0.00	
	High Severity >10 Cm	0	0.00	0	0.00	
	No	24	70.60	26	76.50	
Redness at the site of the vaccine	Low Severity 2-5 Cm	9	26.50	3	8.80	0.11
	Medium Severity 5-10 Cm	0	0.00	0	0.00	
	High Severity >10 Cm	0	0.00	0	0.00	
	No	25	73.50	31	91.20	
Pain at the injection site	Low	13	38.20	24	70.60	**0.016**
	Medium	12	35.30	6	17.60	
	High	5	14.70	0	0.00	
	No	4	11.80	4	11.80	
Fever	38-38.4	4	11.80	2	5.90	0.23
	38.4-38.9	1	2.90	2	5.90	
	38.9-40	3	8.80	0	0.00	
	No	26	76.50	30	88.20	
Headache	Low	9	26.50	3	8.80	**0.026**
	Medium	4	11.80	1	2.90	
	High	2	5.90	0	0.00	
	No	19	55.90	30	88.30	
Chill tremors	Low	3	8.80	4	11.80	0.68
	Medium	1	2.90	0	0.00	
	High	2	5.90	1	2.90	
	No	28	82.40	29	85.30	
Vomiting	Low	2	5.90	0	0.00	0.20
	Medium	1	2.90	0	0.00	
	High	0	0.00	0	0.00	
	No	31	91.20	34	100.00	
Diarrhea	Low	3	8.80	0	0.00	0.23
	Medium	0	0.00	0	0.00	
	High	0	0.00	0	0.00	
	No	31	91.20	34	100.00	
Muscle pain	Low	5	14.70	4	11.80	0.98
	Medium	2	5.90	2	5.90	
	High	2	5.90	2	5.90	
	No	25	73.50	26	76.50	
Joint pain	Low	4	11.80	2	5.90	0.40
	Medium	2	5.90	0	0.00	
	High	1	2.90	1	2.90	
	No	27	79.40	31	91.20	
Signs of cardiac involvement	Chest Pain	1	2.90	0	0.00	0.23
	Tachycardia	2	5.90	0	0.00	
	Dyspnea	1	2.90	0	0.00	
	No	30	88.20	34	100.00	

**p<0.05 there is a statistically significant difference.*

The rate of headache occurrence was significantly higher in the patient group (n =15, 44.10%) compared to the control group (n =4, 11.70%) (p =0.007). Nine (26.50%) children in the patient group described headache as low severity, while 3 (8.80%) children in the control group described it as low severity (p =0.05). In the patient group, 4 (11.80%) children described headache as medium severity, while 1 child (2.90%) defined it as medium severity (p =0.16) in the control group. In the patient group, 2 (5.90%) children defined headache as high severity, while there were no children defining it as high severity in the control group (p =0.15). The severity of the headache was defined as low, medium, and high severity in the patient group, while it was defined as low and medium in the control group. There was no statistically significant difference between the other side effects (Table 3).

In all 2 groups, there was no person who reported a severe allergic reaction after the vaccine. Just 4 people (11.80%) from the patient group described a cardiac involvement symptom that did not require treatment. Those who used painkillers or antipyretics after the vaccine were 17 people (50.00%) in the patient group and 15 people in the control group (p =0.80). Post-vaccination side effects were more commonly seen in the patient group after the first dose, and in the control group after the second dose, but no difference was detected between the groups. Side effects mostly occurred in the first 3 days in both groups, with no difference between the groups (Table 4).

Table 4. *Doses and days in which side effects occur.*

Variable		Group		p-value*
		Patient	Control	
		%	%	
If there was a side effect which dose did it occur in?	1st dose	62.21	44.02	0.07
	2nd dose	37.79	55.98	
If there was a side effect which day did it occur in?	First 3 days	93.28	100.00	
	3-5 days	2.84	0.00	0.20
	After day 5	3.88	0.00	

**p<0.05 there is a statistically significant difference.*

DISCUSSION

In this study, we compared the side effects of vaccination in children with Type-1 DM and healthy children without any disease. There was no difference in vaccination side effects in Type-1 DM patients compared to healthy children. Only the severity of pain at the injection site and the frequency and severity of headaches were greater in patients with Type 1 DM diagnoses.

Children and adolescents with T1DM should be vaccinated according to the recommended immunization program for healthy children. Pneumococcal vaccines may also be needed, and flu vaccines should be administered rigorously each year (19).

The COVID-19 pandemic, which has gripped the entire world for nearly 2 years, is particularly heavy-handed in people with chronic illnesses (20). Several recent studies have shown that both poorly controlled patients with Type-2 diabetes and Type-1diabetes are more vulnerable to serious diseases following COVID-19 compared with people without diabetes (21-23).

Vaccination of children/adolescents is seen as important for ending the pandemic by helping the world make significant progress to gain herd immunity (24). Vaccination has been recommended by the American Academy of Paediatrics as the benefits of COVID-19 vaccination in children between the ages of 12 and 17 are greater than the risks of possible side effects (25).

It has been reported that COVID-19 vaccine hesitancy in Turkey is at a high level, with 31% of vaccine hesitancy (26). The concerns about the COVID-19 vaccine are the safety of the vaccine, lack of trust in vaccines and/or pharmaceutical companies, inadequate knowledge of a new vaccine, and especially long-term potential side effects (27, 28). Although about 60.40% of the U.S.A adult population has been fully vaccinated by the end of July 2021, only 33% of 12-17-year-olds were vaccinated against COVID-19 in the same period, and 25% of parents said they would definitely not get their children vaccinated (29, 30). One study reported a 40% vaccine hesitancy rate against the COVID-19 vaccines in parents of children and adolescents younger than 18 (31). Another study reported that 21.30% of parents of young adolescents with chronic illnesses had vaccine hesitancy (32). In the study of Akarsu B. (33), the proportion of people who say they will not get vaccinated because of the side effects of vaccines is 27.70%, while the proportion who say they will not get their children vaccinated due to side effects falls to 11.90%.

Although allergic reactions to vaccination are a common concern, rates of vaccine-related allergic reactions are not high and many of them are not serious. In fact, the risk of anaphylaxis for many vaccines is very low (1 in 1,000,000 doses) (34). Overall, FDA and CDC reports note that the risk of serious side effects involving organs is balanced between placebo and vaccine groups (35). Our study results are in line with the literature which reports that there are no cases of serious adverse effects related to vaccination in both doses.

Local reactions such as pain at the injection site are responsible for most of the complaints, while systemic/severe reactions are rare (36). Reactions are often self-limiting and reported more often after 2nd dose compared to the 1st dose (37, 38). In the study of See ML, among all vaccinated people between the ages of 12 and 15, 90.90% reported at least one local injection site reaction within 7 days of vaccination. Pain at the injection site was the most frequent local reaction in this study and was a little more prevalent after the 2nd dose (39). In our study, the most common side effect among all participants was pain at the injection site with 88.20%, while swelling was 26.50% and redness was 17.60%. The side effects were more common in the patient group after 1st dose and in the control group after 2nd dose, although causing no statistically significant difference (p =0.07). It's worth noting that most observed reactions are low or medium in severity, which coincides with reports on vaccine safety (36).

Headache, which occurs relatively frequently after vaccination, has been reported as a notable systemic side effect in the range of 23.80-55% (12, 13, 36). In our study, it was the 2nd most common (27.90%) side effect (44.10% of the patient group and 11.70% of the control group).

The severity of the pain at the injection site and the frequency and severity of the headache complaint were higher in the patient group, while the rates of post-vaccine painkiller use were similar in both groups. It did not cause further analgesic use, which suggested that differences between them might be associated with the relative defining and that it had little clinical significance.

Fever is reported to have a frequency of 18-48% and is generally responsive to antipyretics (37, 40). In our study, 17.60% of all participants reported fever, which was compatible with the literature.

It's worth noting that participants were asked to identify past negative events. Because there may be side

effects that they forget or misidentify. A community-based survey would also be more appropriate for this type of study. However, as social distance is still highly recommended, we preferred to conduct this study as web-based research to ensure the safety of all our study participants. There are no other studies reporting the occurrence of adverse reactions related to the COVID-19 vaccination in the population of children with Type-1 DM in Turkey. Studies with wider participation will continue to contribute to this issue.

The limitation of our study is that our number of patients was low. The side effects seen in the patients are not based on the observation and examination of the doctor. Because it is a retrospective study, the accuracy of the answers to the questions is based on the statements of the patients and their parents.

Conclusions

Our results show that side effects following the COVID-19 vaccine are relatively common, albeit often mild and self-limiting. Local reactions, such as pain at the injection site, are responsible for the majority of events, while systemic/severe reactions are rare. In patients diagnosed with Type-1 DM, the side effects of the COVID-19 vaccine were similar to the control group, except for the severity of the pain at the injection site and the higher frequency and severity of the headache. Our study could be useful in reducing vaccine-related side-effect anxiety in this group of patients. However, a follow-up study on a wider population is needed to assess the long-term side effects and efficiency of COVID-19 vaccines in children with Type-1 DM.

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