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Comparison of complications of pentavalent and DTP vaccination in infants aged 2-6 months in Anzali, Iran

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ABSTRACT

***Background*:** Despite the efforts to enhance hygiene education and personal hygiene and use of antibiotics and vaccination, infectious diseases remain the second cause of mortality worldwide. Vaccination is one of the greatest medical achievements in the prevention of mortality and morbidity, which has decreased treatment costs. This study aimed to compare the complications caused by pentavalent and diphtheria-tetanus-pertussis (DTP) vaccination in infants aged 2-6 months.

***Methods*:** This analytical cross-sectional study was conducted on all the infants aged 2-6 months referred to the healthcare centers of Anzali, Iran. Demographic data and complications of vaccination were collected from all the samples. Data analysis was performed using descriptive statistics, Fisher's exact test, Chi-square, and Mann-Whitney U test, and logistic regression analysis in SPSS.

***Results*:** In total, 353 infants, including 163 female (46.2%) and 190 male (53.8%), were enrolled in this study. According to the results, 229 infants (64.9%) presented with vaccination complications. Fewer side effects were noted in infants receiving pentavalent vaccination compared to those receiving DTP vaccination (P=0.38). In order of occurrence, the most common complications of DTP vaccination were fever, excessive crying, and fussiness, respectively. Moreover, a significant correlation was observed between the used milk by infants and the extent of complications caused by vaccination in the pentavalent group (P=0.037).

Conclusion: According to the results of this study, application of pentavalent vaccination not only minimizes the local reactions, but it also diminishes local discomfort through reducing the number of injections. Therefore, infants receiving this type of vaccination encounter minimum local reactions. It is recommended that further investigation be conducted on larger sample sizes in multiple healthcare centers.

Keywords: Complication, DTP, Immunization, Pentavalent

Introduction

Despite the efforts to enhance hygiene education and personal hygiene and use of antibiotics and vaccination, infectious diseases remain the second cause of mortality and the most important reason for age-related disabilities around the world. Effects of infectious diseases may vary depending on the country or region (1, 2).

Infectious diseases are the second most common cause of morbidity worldwide (1), and vaccination is the most influential method in the prevention of disability and morbidity, as well as the reduction of treatment costs (2, 3). The World Health Organization (WHO) declared vaccination against diphtheria, tetanus, and pertussis mandatory in 1974. This was part of the pandemic vaccine program, which significantly decreased the mortality rate caused by the aforementioned life-threatening diseases in infants and newborns (4).

Previous studies have suggested that although diphtheria-tetanus-pertussis (DTP) vaccination could be effective, it might cause several neonatal complications, including fever, mild crankiness, tenderness, tiredness, loss of appetite, redness or swelling at the site of vaccination (7), excessive crying, nausea and vomiting (5), soreness, fussiness, need for incubation, and neurological disorders (6). In addition, some studies have reported drowsiness one or two days after vaccination, which gradually decreased during the first week of birth.

Hepatitis B is one of the most common viral diseases (8). Vaccination could significantly reduce the rate of viral diseases, such as hepatocellular carcinoma. According to WHO and UNICEF, DTP vaccination is normally associated with no complications (4). To date, these two

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vaccination methods have been routinely applied for infants aged 2-6 months.

Recent national protocol of immunization has suggested pentavalent vaccination for the prevention of hepatitis B, DTP, and H influenza type B (Hib), which must be injected at 2-6 months of age. Considering the presence of haemophilus B in the aforementioned diseases, this combined vaccination could increase immunization availability for various patients (9). Haemophilus B is a gram-negative bacterium, which leads to severe infections such as meningitis, pneumonia, septicemia, and even morbidity in infants. Neonates aged 4-12 months are more susceptible to this life-threatening disease compared to other infants.

According to the protocol suggested by UNICEF, injections at three different intervals have a protection rate of 95%. In addition, it is affirmed that complications such as redness, swelling, and hyperthermia might be observed at the injection site, and fever lower than 38°C might occur after vaccination (4). Based on previous studies on pentavalent vaccination, it has been concluded that complications caused by pentavalent vaccination were not greater than a single DTP vaccination (5).

In this regard, satisfactory results in the health promotion of infants could be obtained through the high coverage of neonatal immunization. Moreover, vaccination is required for other target groups accounting for 95% of the populations in different cities of our country. Combination of pentavalent vaccination in immunization programs leads to decreased incident of pneumonia, Hib, and meningitis, which promotes neonatal health. Furthermore, pentavalent vaccination protects infants against five major life-threatening diseases, including diphtheria, whooping cough, tetanus, hepatitis B, and Hib.

In this regard, diphtheria, tetanus, whooping cough (DTP), and hepatitis B have already been part of the immunization program of infants, with Hib vaccination as the fifth and newest part of the program. Therefore, these five combined vaccinations are identified as pentavalent vaccination.

According to the national vaccination protocol, pentavalent vaccination must be administrated at three different intervals. The first vaccination is performed in the second month of infancy, while the second and third vaccinations are conducted in the fourth and sixth months, respectively. While pentavalent vaccination is not associated with severe reactions, a few complications might be observed following the vaccination (similar to DTP vaccination), including redness and swelling, tenderness of the injection site, and fever. These symptoms are usually observed on the day of vaccination, followed by a gradual recovery within 1-3 days. Accordingly, a protocol similar to DTP vaccination has been proposed to reduce these symptoms.

Severe reaction to pentavalent vaccination rarely occurs. However, the process of vaccination should be terminated in the second interval in case of extreme sensitivity to vaccination in previous vaccinations among neonates (similar to DTP vaccination). If next dosages of vaccination are prohibited for an infant, administration of hepatitis B and Hib vaccination could be separately performed during the same intervals (except in case of complications associated with whooping coughs).

Pentavalent vaccination is available in two liquid and lyophilized forms. Simplicity of application and performance of the liquid form have made it the only method used in Iran (6). Pentavalent vaccination started on November 22, 2014, and infants who had received DTP (vaccination in the second month) prior to this time interval were administered the next two doses by the end of the sixth month of birth (7).

Some of the main advantages of pentavalent vaccination compared to other methods include decreased number of injection sites, acceptable effectiveness, and non-interference with hepatitis B, Hib, and DTP prevention (8). In addition, pentavalent vaccination is a new technique with fewer complications, compared to other immunization methods studied in Iran. With this background in mind, this study aimed to compare the complications of pentavalent and DTP vaccination in infants aged 2-6 months (7, 9).

Methods

This analytical cross-sectional study was conducted on all the infants aged 2-6 months, referred to the healthcare centers of Anzali, Iran. The pentavalent vaccination group received three doses of vaccination, i.e., primary vaccination, followed by immunization at four and sixth months following birth. Meanwhile, the DTP vaccination group received two doses of immunization within two- and four-month intervals following birth.

Sample collection was performed via census sampling. All the infants (aged 2-6 months), referred to the healthcare centers of Anzali, were enrolled in the study in the second half of 2014 and received vaccinations. In 2015, all the infants received pentavalent vaccine in healthcare centers; however, the immunization of infants was only allowed in the second half of 2015.

Study group

All the healthy infants (male and female; age: 2-6 months), who were referred to healthcare centers of Anzali and received pentavalent or DTP vaccination from June 2014 to December 2015, enrolled in the study. The inclusion criteria were as follows: 1) age range of 2-6 months; 2) lack of allergic reactions to previous vaccinations; and 3) no prior history of seizure.

Meanwhile, the exclusion criteria were as follows: 1) severe or mild illness; 2) immunodeficiency; 3) immunosuppressant therapy; 4) neurological dysfunctions (e.g., seizure); and 5) prior allergic reactions to vaccination methods. Finally, 259 infants were excluded from the study due to parents' unwillingness to cooperate with the researchers. Moreover, some of these infants were eliminated from the study since they were guests or foreigners or suffered from congenital anomalies.

Vaccine

The pentavalent and DTP vaccines used in this study were made in India. According to the results, 0.5 mg of the pentavalent vaccine was injected in the anterolateral part of the left quadriceps muscle. Post-vaccination instructions, including the time of injection site compression and usage of acetaminophen (two drops per weight every 4 h) to prevent fever, were provided for mothers by trained personnel of the healthcare centers (6). Moreover, DTP vaccination was administrated based on the routine national protocol of vaccination.

Study design

In this study, a vaccination report card was completed by the parents after each immunization process. The gathered data included demographics (e.g., age, gender, birth weight, gestational age, and breastfeeding technique) and complications caused by vaccination (e.g., fever, redness, scars, seizures, excessive crying over 3 h, nausea and vomiting, rashes, swelling, and loss of appetite). Data sheets were completed in each healthcare center.

In addition, a contact number was obtained from the parents in order to inquire about neonatal complications one week after injection. In case of any noted side-effects, the parents were asked to visit the center for physician's assessment of the complications. Finally, the confirmed information was documented in the data sheets.

Ethics

At first, objectives of the study were explained to the parents and they were assured of the safety of vaccination process. This study was conducted in accordance with the guidelines of the Ethics Committee of Guilan University of Medical Sciences.

Statistical analysis

Finally, the data (i.e., prevalence, percentage, mean, and standard deviation) was reported through discretionary analysis and then analyzed, using Fisher's exact test, Chi-square, Mann-Whitney U test, and logistic regression analysis. Current household records in healthcare centers were used to complete the information; furthermore, interviews were conducted with the parents. In total, among 353 infants in the study, 163 (46.2%) were female and 190 (53.8%) were male. Based on the protocol, all the two-month-old infants received their DTP vaccines before November 22, 2014. After reaching six months of age, the infants were enlisted to receive pentavalent vaccination.

Results

Demographics of the first group of infants in this study are shown in Table 1.

Table1. Demographic characteristics of the studied infants

Demographics		Pentavalent vaccination	DTP vaccination	Total
Gender	Male	83 (48%)	80 (44.4%)	163 (46.2%)
	Female	90 (52%)	100 (55.6%)	190 (53.8%)
Vaccination	2nd month	129 (74.1%)	0	129 (36.5%)
	4th month	44 (25.3%)	65 (36.3%)	109 (30.9%)
	6th month	0	115 (63.9%)	115 (32.6%)
Nutrition	Breast milk	133 (76.9%)	134 (74.4%)	267 (75.6%)
	Powdered milk	21 (12.1%)	28 (15.6%)	49 (13.9%)
	Combined	19 (11%)	18 (10%)	37(10.5%)
Gestational age	Term	163 (94.2%)	165 (91.7%)	328 (92.9%)
	Pre-term	10 (5.8%)	15 (8.3%)	25 (7.1%)
Birth weight (gr) mean±SD		3268±451	3272±464	3270±457

Table 2. The frequency of reported post-vaccination complications

Type of complication	DTP vaccination		Pentavalent vaccination		P-value
	N	%	N	%	
Fever	109	60.9	94	54	0.19
Redness	17	9.5	10	5.7	0.185
Seizure	1	0.6	0	0	0.323
Excessive crying	20	11.2	20	11.5	0.92
Scars	0	0	0	0	---
Nausea and vomiting	5	2.8	4	2.3	0.76
Feeling of warmth	1	0.6	0	0	0.32
Swelling	6	3.4	12	6.9	0.13
Poor feeding	14	7.8	8	4.6	0.21
Diarrhea	6	3.4	8	4.6	0.54
Restlessness	16	8.9	21	12.1	0.92
Drowsiness	5	2.8	5	2.9	0.96
Urticaria and rash	1	0.6	2	1.1	0.54

In this study, no significant difference was observed in the demographic variables of the two groups. In total, 229 infants (69.9%) manifested post-vaccination complications, 109 of whom received pentavalent vaccination (47.5%), and 120 cases (59.4%) had DTP vaccination. However, no statistically significant difference was observed between the two groups in this regard (P=0.38). Moreover, most of the complications were observed within the first 24 h after vaccination (n=121, 34.3%). Although the infants of the DTP group showed more complications in less than 48 h, and pentavalent immunization recipients had fewer side effects, no significant difference was observed between the two groups regarding the time of complication incidence (P=0.031).

Among the studied infants, complications caused by DTP vaccination were fever, excessive crying, and fussiness, respectively. Meanwhile, side effects of pentavalent vaccination (high fever, fussiness, and excessive crying) were observed in 15 infants, and 94 cases had fever only. Therefore, no significant difference was observed between the groups in terms of vaccine type and high fever (P>0.05) (Table 2).

According to our findings, there was no significant correlation between the breastfeeding technique and severity of complications caused by DTP vaccination (P=0.35). However, there was a significant difference between the infants of pentavalent group in this regard (P=0.037) since breast-fed infants showed more extreme complications compared to bottle-fed infants or the group that used both.

Furthermore, no significant relationship was observed between maternal age and gender of the infant with the type of vaccination (P>0.05). Assessment of post-vaccination complications was performed using logistic regression analysis indicating no significant effects regarding the effect of maternal age, type of vaccination, and breastfeeding technique.

Discussion

Pentavalent vaccination has been widely used in over 100 countries in recent years for the prevention of DTP, hepatitis B and Hib. In this regard, countries alongside the Persian Gulf, such as UAE, Saudi Arabia, and Oman, have been using this vaccination method in their all-inclusive immunization program since 2008 (10, 11).

All around the world, immunization has been known to have a significant effect on public health (12), and numerous studies have been conducted in different countries to highlight the preventive effect of vaccination on several diseases.

The immune system of fetus is partly immature at birth, which could result in humoral and cellular immunodeficiency (13, 14). As a result, infant immunization might not lead to rapid antibody response, while it could provoke the immune system to act as the foundation of such responses in the future (15). According to the literature, immune system response to Hib, combined with other vaccines, is of paramount importance for the promotion of public health.

In total, 353 infants were enrolled in the present study, among which 163 (46.2%) were female and 190 (53.8%) were male. The infants were randomly divided into two groups of DTP vaccination (n=180) and pentavalent vaccination (n=173). According to the obtained results, no statistically significant difference was observed between demographic characteristics of the two groups (P>0.05).

In a study conducted by Faingezcht et al. in Costa Rica, among 207 infants, 103 were female and 104 were male. These two groups randomly received monovalent Hib vaccine and pentavalent vaccination. After the evaluation of the results, no significant difference was reported between the demographic characteristics of the studied newborns (9).

According to the findings of the present study, 229 infants (64.9%) showed post-vaccination complications. Despite the fewer complications observed in the infants of the pentavalent group compared to the DTP group, no statistically significant difference was noted between the groups (P=0.38). The results of the current study indicated that the highest rate of complications occurred in the first 24 h. However, no significant difference was observed in the occurrence of

complications in both groups in terms of vaccination time intervals.

In the current study, the most common complications in the DTP group were respectively as follows: fever, excessive crying, and fussiness, whereas the complications observed in the pentavalent group were fever, fussiness, and excessive crying, respectively. In addition, hyperpyrexia was reported in 15 cases, and mild fever was observed in 188 neonates.

Findings of the present study were indicative of no significant difference between the two groups in terms of vaccination complications within 24-48 h after vaccination (P>0.05). In the study by Faingezicht et al., the pentavalent group had no systemic or localized complications compared to the monovalent Hib group. Nevertheless, it should be noted that their samples received only one vaccination during the study. The results obtained by Faingezicht et al. revealed three major complications, the most significant of which was seizure in the pentavalent group a few hours after the first vaccination. However, spontaneous remission of the seizure occurred in the infants.

The second case of complication was acute bronchiolitis observed in the pentavalent group within two weeks of vaccination, followed by respiratory distress, which could be associated with the type of vaccination. Meanwhile, the third case of complication was syncytial virus infection in the monovalent group within three days of the first vaccination. However, no allergic or hypotonic reactions were reported in the groups (9).

Pentavalent vaccination was first introduced in Vietnam in 2010, followed by 43 cases of post-immunization complications with pentavalent vaccine. Moreover, 12 morbidities and 9 cases of severe complications were reported after pentavalent vaccination during October 2012-March 2013 in this country (16). Mortality rate due to pentavalent vaccination has been reported at 1.8 per one million vaccinations (11).

In a study conducted in USA, complications of pentavalent vaccination were as follows: 1) fever (25.8%); 2) tenderness of the injection site (15.8%); 3) edema of the injection site (10.8%); and 4) vasodilation (10.5%). According to the results of the aforementioned study, 0.3% of complications accounted for the incidence of abscess at the injection site (n=426), which showed the risk of 3 to 4 cases per ten million immunized population (9).

In another research, Cunha et al. stated that the most common systemic complications of DTP and pentavalent vaccination might be hypotonic-hyporesponsive episode (HHE), fever higher than 39.5°C, seizure due to fever, and generalized exanthema. These side effects indicated that HHE was almost exclusively correlated with DTP (30.4%) and pentavalent vaccination (41.6%).

These vaccination methods were associated with absence seizures and fever in 75% of the cases, and fever under 39°C in 69.5%. In addition, these methods could result in localized reactions such as redness and pain. These reactions were mostly observed 6 h after vaccination of infants under 12 months of age (18).

In one study, Karami et al. reported the occurrence of inflammation and swelling within 48 h after DTP vaccination. Moreover, other symptoms associated with vaccination were observed in the studied samples as follows: redness (40.7%), fever of 38°C or higher (46.4%), drowsiness (31.5%), excessive crying (over 3 h) (3.1%), and seizure and muscle weakness (0.057%) (19).

On the other hand, another study conducted in Kashan (Iran) (20) reported pain at the injection site in 44.7% of the samples, whereas swelling was observed in 31.4% of the cases, and other symptoms (e.g., redness, fever, and drowsiness) were seen in 27.7%, 54.5%, and 4.9% of the cases, respectively. Another study by Mahdi et al. marked that pentavalent vaccination had a higher immunicity for antigens in infants in weeks 6, 10, and 14 (post-vaccination period) compared to monovalent vaccine (21).

Diversity of reactions and complications in various studies has suggested that different components might be used in the production of a vaccine. The first experiment of Sauer et al. on different vaccines elaborated mild reactions and common complications of diphtheria vaccine. In addition, Suser reported that localized pain, redness, swelling, and low fever were the most common complications observed several days after DTP vaccination. There were significantly different types of reactions reported in various studies, which seem to be due to the presence of diverge components of the vaccines and method of data analysis (i.e., semblance analysis) (22).

Although Iran has been importing pentavalent vaccination in recent years, no studies have been conducted regarding the associated complications. In the present study, we aimed to confirm that pentavalent vaccination could be followed by fewer local reactions. Moreover, use of this vaccination method might lead to reduced number of injections, fewer post-immunization complications, and minor local reactions in infants.

Our results suggested that pentavalent vaccination has fewer complications, compared to isolated immunization, and could be considered as a beneficial and safe immunization protocol. Furthermore, our findings suggested that rate of pentavalent vaccination complications was significantly higher in infants who were exclusively breast-fed. As a result, parents must be essentially advised prior to vaccination process.

Therefore, it is recommended that further studies be conducted on larger sample sizes in multiple medical centers in order to confirm the accuracy of the obtained results of the present study. Moreover, future studies must evaluate the complications caused by different types of vaccination, as well as plasma antibody levels after immunization. On the other hand, investigation of the immunogenicity of vaccines and their protective efficacy is of paramount importance in the Iranian population.

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