Original Article

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Evaluation of Efficacy of Varicella Vaccine in Pediatric Patients with Acute lymphoblastic Leukemia

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Abstract

Background: Varicella is a highly contagious and dangerous disease especially in immunocompromised patients. Children with cancer are at increased risk of severe illness and may fatal cases occur. Vaccination from VZV (varicella zoster vaccine) infection can be safe, immunogenic, and effective in children with leukemia who meet the criteria and are at the risk of serious disease or death. The aim of this study was investigate the efficacy of vaccines VZV on pediatric patients with Acute Lymphoblastic Leukemia

Materials and Methods: The study was performed on 46 ALL children aged between 1to15 years old who underwent chemotherapy. Considering the efficacy of vaccines on pediatric patients the title serum sample of IgG-anti-VZV avidity was determined using a test kit before and after the injection of vaccines VZV.

Results: A total of 46 patients were included analysis. Their title serum sample IgG were negative before the injection of vaccines VZV and after receiving VZV vaccine with respect to title serum sample IgG atatus, 31 (67.4%) patients were positive and 15 (32.6%) patients were negetive. No significant was observed association between either title of IgG-anti-VZV after receiving of VZV vaccine and gender (P = 1.0) title of IgG-anti-VZV and age groups (P =0.387).

Conclusion: Regarding the obtained results, it can be concluded that varicella vaccination can have an acceptable effectiveness on pediatric patients with ALL. Varicella vaccination can be recommended for protecting these patients against VZV in order to decrease the morbidity rate caused by this infection.

Key Words: ALL, children, Varicella Vaccine

Introduction

Varicella zoster virus (VZV) is usually self-limiting and a mild disease in healthy children (1). On the other hand, most children with cancer still seem to have a perfectly functioning immune system at the time of disease presentation (2),but immunocompromised children, especially those who cancer are receiving chemotherapy are at great risk of suffering from severe, , prolonged, and complicated varicella. It can be resulted in disseminated disease, hepatitis, encephalitis, pneumonia and even death (3). The most common pediatric malignancy is acute lymphoblastic leukemia (ALL) that accounts for nearly 75% of all newly diagnosed leukemia and 25% of all malignancies in childhood(4). However, treated ALL children can experience significant morbidity from VZV infection (5). Although primary VZV infection in these children has mortality rate of 7%–10% in the absence of antiviral treatment, mortality rate can be reduced given that

antiviral and appropriate supports are readily available (6). Some clinical trials declare that vaccination can be safe, immunogenic, and effective in children with leukemia who meet the criteria and are at risk of serious disease or death (5, 7) . Due to the risk of serious complications or death from varicella among patients with ALL, they suggest the use of vaccines for decreasing the rate of mortality caused by VZV infection (8). This study was designed to investigate the efficacy of vaccines VZV on pediatric patients with acute lymphoblastic leukemia

Materials and Methods

This study was performed on ALL children aged between 1-15 years old with who referred to hematology-oncology ward at Dr. Sheikh children's hospital, Mashhad. ALL of patients were in maintenance phase of chemotherapy. From 66 patients, 15 cases had positive serum title pre-vaccination and 6 patients were Lymphopenia (lym <1500). The records of these patients and entirely to the discretion of the treating physician and the patients who received the vaccine were selected 46 candidates, then one dose of vaccine-type VZV (OKA. Japan) injected subcutaneously into them. All study participants or their parents/legal guardian gave their written informed consent. The title serum sample IgG-anti-VZV avidity was determined using a test kit, which involved the removal of low-avidity antibodies via urea treatment and measurement of the remaining bound IgG by ELISA before and 6 week following the injection in order to explore the efficacy of vaccines VZV on pediatric patients. Results were reported as positive or negative, if IgG titer was less than 80 it was considered as negative and > 80 as positive.

Results

A total of 46 patients were included in this analysis (25 boys, 21 girls). Their title serum sample IgG were negative before the injection of vaccines VZV, and 45 (97.8%) patients received one dose of VZV vaccine and only one patient (2.2%) received two doses of VZV vaccine. According to the tables 1 and 2, only one female patient received two doses of VZV vaccine, who was at the age group 10 to 15 years old. There was no significant association between doses of VZV vaccine and gender (P = 0.457) and also there was no significant association between doses of VZV vaccine and age groups (P = 0.370). After VZV vaccine receiving, 31 (67.4%) patients had positive title serum sample IgG and 15 (32.6%) patients had negative title serum sample IgG. According to Table 3, 68% of boys and 66.7% of girls had positive title serum sample IgG after receiving VZV vaccine. No significant association was found between title of IgG-anti-VZV and gender (P = 1.0). Moreover, 42.9% of children aged 1 to 5 years old, 72.4% of children aged 5 to 10 years old, and 70% of children aged 10 to 15 years old had positive title serum sample IgG (Table 4) and there was no significant association between title of IgG-anti-VZV and age groups (P = 0.387).

Table I: Distribution of the number of doses of vaccine according to gender

Dose vaccine	Gender				P-value
	Boy		Girl		
	Count	Percent	Count	Percent	
One dose	25	100	20	95.2	0.457
Two doses	0	0	1	4.8	
Total	25	100	21	100	

Table II: Distribution of the number of doses of vaccine according to age group

Dose vaccine	Age group						P-value
	1to 5 years		5 to 10 years		10 to 15 years		
	Count	Percent	Count	Percent	Count	Percent	
One dose	7	100	29	100	9	90	0.37
Two doses	0	0	0	0	1	10	
Total	7	100	29	100	10	100	

Table III: Distribution of title serum sample IgG after received of VZV vaccine according to gender

Title of IgG	Gender				P-value
	Boy		Girl		
	Count	Percent	Count	Percent	
Positive	17	68	14	66.7	1.0
Negative	8	32	7	33.3	
Total	25	100	21	100	

Table IV: Distribution of title serum sample IgG after received of VZV vaccine according to age group

Title of IgG	Age group						P-value
	1to 5 years		5 to 10 years		10 to 15 years		
	Count	Percent	Count	Percent	Count	Percent	
Positive	3	42.9	21	72.4	7	70.0	0.387
Negative	4	57.1	8	27.6	3	30.0	
Total	7	100	29	100	10	100	

Discussion

Immunocompromised patients are threatened by severe infections, in part by infectious agents which rarely cause complications in non-immunosuppressed children. VZV infections in this patient cohort have an increased risk of serious morbidity and even death (9). Caniza et al., conducted a large retrospective study and suggest that VZV vaccination should not be undertaken in children with ALL. They found that only 0.057% of children, enrolled on ALL protocols during the modern era (after 1984), died by VZV infection (5). Before the era of antiviral therapy, disseminated VZV infections have been described in children with cancer under chemotherapy, especially in acute lymphoblastic leukemia (10). In the United States, VZV vaccination coverage was 89% among US children aged 19 to 35 months in 2006, where universal VZV vaccination was introduced in 1995 (11). Marin et al., (12), Asano et al., (13), and Seward et al., (14) demonstrated that risk of VZV infection can be reduced in countries where susceptible children aged 1 year and older in the general population are routinely vaccinated. Recently, an increasing general awareness of varicella-related complications has led to the assumption that hospitalization with subsequent severe complications occurs in approximately 20% of VZV-infected, immunocompromised patients (9). Pourakbari et al., showed the seroprevalence rate of VZV was about 65% in population when IgG antibodies were used against VZV in serum sample of them (15). Socan et al., reported that VZV IgG was positive in 85.6% individuals at Slovenia (16) and accordingly, this study applied the title serum sample IgG to determine the seropositive for VZV before and after the injection. The results of this study revealed positivity of title serum sample IgG in 15 patients and its negativity in 46 patients before the injection of vaccines VZV. While after the injection of vaccines, 31 patients (67.4%) had positive and 15 patients (32.6%) had negative title serum sample IgG. The efficacy of this vaccine depends on the number of doses and the interval since the last dose. Cenoz et al., suggested that the second dose of vaccine increases the effectiveness with respect to the first dose; they reported Vaccine effectiveness was 87% for one dose and 97% for two doses (17). In a literature review, Seward et al., found a mean effectiveness for one dose of vaccine about 84.5%; with a range of 44% to 100% (18). Shapiro et al., estimated

98.3% effectiveness for two doses of vaccine in preventing laboratory confirmed cases (19). Vaccine effectiveness of 67.4% was demonstrated for one dose of vaccine in the current study. The results of this study were in line to other published investigations. The effectiveness of a single dose of varicella vaccine was very high during the first three years (> 90%) and fell in children who had been vaccinated more than three years previously (61%), which supports the role of waning immunity as an explanation of the suboptimal effectiveness of a single dose of varicella vaccine (20, 21). The results of this study showed that 42.9% of children aged 1 to 5 years old, 72.4% of children aged 5 to 10 years old, and 70% of children aged 10 to 15 years old had positive title serum sample IgG following varicella vaccine (Table 4). Thus according to obtained results, the effectiveness of a single dose of varicella vaccine can be achieved in age range of 5 to 15 years old for pediatric ALL patients. Although official recommendations and guidelines (22) suggest that individuals with ALL could be vaccinated, pediatric oncologists avoided VZV vaccination to prevent transmission of vaccine-type VZV to susceptible patients (23) and to avoid withholding chemotherapy for two weeks. Furthermore, a case of progression to severe VZV disease and death after vaccination was recently reported by Caniza et al., (5). Overall, the rate of early mortality from infection is declining. Prucker et al., reported only 21 infectious deaths, and no deaths from VZV, in a population of 896 children with ALL (24). IgG antibody avidity may serve as a marker to evaluate long-term aspects of humoral immunity, although the clinical relevance and association with protection against VZV re-infection and reactivation has to be awaited. Cellular immunity against VZV is significantly diminished in ALL patients who have to be considered when evaluating immunity against VZV (25). Regarding immunisation in children with cancer, for some vaccines there is enough evidence to design good recommendations for protecting these patients against vaccine-preventable diseases without any risk of poor immune response or adverse events.

In the current study,13% of patient experienced vaccination side effects ; that is 3 patients experienced maculopapular rash , 1 headache, 1 fever and 1 thrombocytopenia.

Conclusion

Most children with cancer still seem to have a perfectly functioning immune system at the time of disease presentation. The concentrations of total immunoglobulins and antibodies against specific vaccine antigens are usually in the normal range. Routine vaccination against varicella has a great potential to significantly reduce the burden of this disease, given that sufficiently high coverage reach in the target population. Regarding the results, it can be concluded that varicella vaccination can have an acceptable effectiveness on pediatric patients. Furthermore, varicella vaccination is recommended for protecting these patients against VZV in order to decrease morbidity of this infection in these patients.

Conflict of interest statement

We also confirm that there is no conflict of interest to disclosure.

References

1. Heininger U, Seward JF. Varicella Lancet 2006; 368(9544):1365-76.

2. Ercan TE, Soycan LY, Apak H, Celkan T, Ozkan A, Akdenizli E, et al. Antibody titers and immune response to diphtheria-tetanus-pertussis and measles mumpsrubella vaccination in children treated for acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2005; 27:273–7.

3. Albrecht MA. Clinical features of varicella-zoster infection: chickenpox. Am Pediatr 2009; 17(2).
4. Javed F, Utreja A, Bello Correa FO, Al-Askar M, Hudieb M, Qayyum F, et al. Oral health status in children with acute lymphoblastic leukemia. Critical Rev Oncol Hemato 2012; 83 (2012):303–9.
5. Caniza MA, Hunger SP, Schrauder A, Valsecchi MG, Pui CH, Masera G, The Controversy of Varicella Vaccination in Children with Acute Lymphoblastic Leukemia. Pediatr Blood Cancer 2012; 58(1):12–6.
6. Feldman S, Lott L. Varicella in children with cancer: impact of antiviral therapy and prophylaxis. Pediatrics. 1987; 80(4):465–472.
7. LaRussa P, Steinberg S, Gershon AA. Varicella vaccine for immunocompromised children: results of collaborative studies in the United States and Canada. J Infect Dis. 1996; 174 (Suppl 3):S320–3.
8. Van Tilburg CM, Sanders EAM, Rovers MM, Wolfs TF, Bierings MB. Loss of antibodies and response to (re-)vaccination in children after treatment for acute lymphocytic leukemia: a systematic review. Leukemia 2006; 20:1717–22.
9. Liese JG, Grote V, Rosenfeld E, Fischer R, Belohradsky BH, v Kries R: The burden of varicella complications before the introduction of routine varicella vaccination in Germany. Pediatr Infect Dis J 2008; 27(2):119-24.
10. Feldman S, Hughes WT, Daniel CB: Varicella in children with cancer: Seventy-seven cases. Pediatrics 1975; 56(3):388-97.
11. National, state, and local area vaccination coverage among children aged 19–35 months-United States, 2006. MMWR 2007; 56(34):880–5.
12. Marin M, Meissner HC, Seward JF. Varicella prevention in the United States: a review of successes and challenges. Pediatrics 2008; 122(3):e744–51.
13. Asano Y, Suga S, Yoshikawa T, et al. Experience and reason: twenty-year follow-up of protective immunity of the Oka strain live varicella vaccine. Pediatrics 1994; 94:524–6.
14. Seward JF, Watson BM, Peterson CL, et al. Varicella disease after introduction of varicella vaccine in the United States, 1995–2000. JAMA 2002; 287:606–11.
15. Pourakbari B, Shahbaznezhad L, Parvaneh N, Nikkhah S, Mahmoudi S, Teymuri M, et al. Eroepidemiology of Varicella Zoster Virus among children, adolescents and medical students in a referral children medical center, Tehran, Iran, IRAN. J MICROBIOL 2012; 4 (3):136-8.
16. Socan M, Berginc N, Lajovic J. Varicella susceptibility and transmission dynamics in Slovenia. BMC Public Health 2010; 10:360.
17. Cenoz MG, Martínez-Artola V, Guevara M, ezpeleta C, Barricarte A, Castilla J. Effctiveness of one and two doses of varicella vaccine in preventing laboratory-confimed casesin children in Navarre, Spain. Human Vaccin Immunothera 2013; 9(5):1172–6.
18. Seward JF, Marin M, Vázquez M. Varicella vaccine effectiveness in the US vaccination program:a review. J Infect Dis 2008; 197(Suppl 2):S82-9.
19. Shapiro ED, Vazquez M, Esposito D, Holabird N, Steinberg SP, Dziura J, et al. Effectiveness of 2 doses of varicella vaccine in children. J Infect Dis 2011; 203(3):312-5.
20. Vázquez M, LaRussa PS, Gershon AA, Niccolai LM, Muehlenbein CE, Steinberg SP, et al. Effectiveness over time of varicella vaccine. JAMA 2004; 291(7):851-5.
21. Chaves SS, Gargiullo P, Zhang JX, Civen R, Guris D, Mascola L, et al. Loss of vaccine-induced immunity to varicella over time. N Engl J Med 2007; 356(11):1121-9.

22. American Academy of Pediatrics. Varicella-zoster infections. In: Pickering, LK, Baker, CJ, Kimberlin DW, Long SS, editors. Red Book: 2009 Report of the Committee on Infectious Diseases. Elk Grove Village, IL: American Academy of Pediatrics; 2009. p. 714-727.
23. Gershon AA, Steinberg SP, Gelb L. Live attenuated varicella vaccine use in immunocompromised children and adults. Pediatrics 1986; 78(4 pt 2):757–62.
24. Prucker C, Attarbaschi A, Peters C, et al. Induction death and treatment-related mortality in first remission of children with acute lymphoblastic leukemia: a population-based analysis of the Austrian Berlin-Frankfurt-Munster study group. Leukemia 2009; 23(7):1264–9.
25. Prelog M, Schönlaub J, Jeller V, Almanzar G, Höfner K, Gruber S, et al. Reduced varicella-zoster-virus (VZV)-specific lymphocytes and IgG antibody avidity in solid organ transplant recipients. Vaccine 2013; 31(20):2420–6.
26. Esposito S, Cecinati V, Brescia L, Principi N. Vaccinations in children with cancer. Vaccine 2010; 28(19):3278–84.