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Research Article

Does Prophylaxis Against Respiratory Syncytial Virus Infection Affect the Weight Percentiles of Infants with Hemodynamically Significant Congenital Heart Disease?

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Respiratuvar Sinsityal Virüs Profilaksisi, Hemodinamik Olarak Önemli Konjenital Kalp Hastalığı Olan Bebeklerin Ağırlık Persentillerini Etkiler mi?

ABSTRACT

Objective: *The risk of severe respiratory syncytial virus (RSV) infection with significant morbidity and mortality is greatest in patients with hemodynamically significant congenital heart disease (hs-CHD). The humanized monoclonal antibody, palivizumab, was used as prophylaxis for RSV infection in children <24 months of age suffering from hs-CHD. We performed this study to evaluate the effects of RSV prophylaxis with palivizumab on the weight percentiles of infants with hs-CHD.*
Methods: *During the RSV seasons between 2013 and 2017, children <24 months of age with hs-CHD who received ≥3 doses of palivizumab prophylaxis were included in this study. All patients were evaluated according to their weight percentiles examined at birth, at the first, and the last dose of palivizumab prophylaxis. The third percentile was accepted as the cut-off value of the lower weight percentile, and values below the 25th percentile were accepted as poorly controlled hs-CHD.*
Results: *Sixty-one infants aged between 10 days and 15 months were included in the study. The infants received the first dose of palivizumab at the age of 5 months, and all infants received 4.56±0.78 injections on an average. The number of patients weighing lower than the 25th percentile at the first, and the last dose of palivizumab were 36 (59 %) and 29 (47.5 %), respectively. A statistically significant difference was found between weight percentiles of infants at the first and the last dose of palivizumab (p<0.05).*
Discussion and conclusion: *RSV prophylaxis with palivizumab affects weight percentiles positively, and it may help to reduce the hospitalization rate due to RSV infections in infants with hs-CHD.*

Keywords: *Congenital heart disease, RSV, palivizumab, weight percentile, infant*

ÖZ

Amaç: *Solunum Sinsityal Virüs (RSV) enfeksiyonu, hemodinamik olarak önemli konjenital kalp hastalığı (hö-KKH) olan bebeklerde önemli morbidite ve mortaliteye neden olabilir. Bir monoklonal antikor olan palivizumab, hö-KKH tanılı, 24 aydan küçük çocuklarda RSV enfeksiyonu profilaksi için kullanılmaktadır. Bu çalışmada, RSV profilaksisinin hö-KKH'li bebeklerin ağırlık yüzdelikleri üzerindeki etkilerini değerlendirmeyi amaçladık.*
Yöntem: *2013-2017 yılları arasındaki RSV mevsiminde ≥3 doz palivizumab profilaksisi alan 24 aydan küçük hö-KKH'lı çocuklar retrospetif olarak değerlendirildi. Prematüre doğan olgular, genetik sendrom tanısı, kronik akciğer hastalığı veya ek hastalığı olan hastalar çalışma dışı bırakıldı. Tüm hastalar doğumda, palivizumabın başlangıç ve son dozunda ölçülen vücut ağırlık persentiline göre değerlendirildi.*
Bulgular: *Çalışmaya 10 gün ile 15 ay arasındaki 61 olgu dahil edildi. Olguların 25'i (%41) erkek ve 36'sı (%59) kızdı. Olguların ilk palivizumab dozu uygulandığındaki ortanca yaşı 5 ay, ortalama uygulanan palivizumab dozu sayısı 4,56±0,78 idi. Vücut ağırlığı 25 percantil altı olan hasta sayısı Palivizumab ilk dozu uygulamasında 36 olgu/61 (59 %) olup son doz uygulamada ise 29/61 (% 47,5) idi. Palivizumabın ilk ve son dozlarında bebeklerin ağırlık yüzdelikleri arasında istatistiksel olarak anlamlı bir fark bulundu (p<0,05). 19 (%31,1) hastanın vücut ağılığı persantillerinde en az bir persentile ilerleme oldugu görülürken, 33 olgunun (%54) vucut ağırlığı persantilini koruduğu görüldü.*
Sonuç: *Bu çalışmada RSV profilaksi alan hastaların yaklaşık 1/3'ünün vucut ağılığı percantillerinde en az bir percentile ilerleme olduğu görülürken, hastaların yaklaşık yarısının vücut ağırlığı persantilini koruduğu gösterildi. RSV profilaksisi hö-KKH'lı bebeklerde RSV enfeksiyonlarına bağlı hastanede yatış oranını azaltmaya ve ağırlık persentillerini olumlu etkilemeye yardımcı olabilir.*

Anahtar kelimeler: *Konjenital kalp hastalığı, RSV, palivizumab, ağırlık persentili, infant*

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INTRODUCTION

Respiratory syncytial virus (RSV) is the common pathogen of lower respiratory tract infections in childhood and causes up to 200.000 infant deaths per year worldwide [1]. It is reported that RSV-related hospitalizations lead to increased morbidity and mortality rates in children with hemodynamically significant congenital heart disease (hs-CHD) compared with healthy children [1,2]. The prevention of RSV infections in infants with hs-CHD has been an important goal in the follow-up of these patients [2,3].

RSV infections in infants with CHD increase the rates of hospitalizations, intensive care unit stays, and the requirement for supportive treatments, as well as causing malnutrition by reducing infant's ability to benefit from sufficient amount of breast milk. These disadvantages may cause weight loss, and growth retardation and developmental delay [4,5]. Corrective cardiac surgery may be delayed because of poor nutritional status of the patient.[4-6]. Although studies conducted in developed countries have reported that growth returns to normal after early corrective surgery, it has been shown that malnutrition problems can persist at a high rate in children even after surgery in developing countries [4,5]. Protecting against RSV infection allows for surgery to be performed at the scheduled time and prevents development of these negative consequences as well [5,6].

Palivizumab (Synagis®, Abbvie, Turkey), a monoclonal antibody against the RSV fusion (F) protein, was approved by the United States Food and Drug Administration in 1998 for immunoprophylaxis against RSV in "high-risk pediatric patients." In 2006, the American Academy of Pediatrics (AAP) released a clinical practice guideline recommending palivizumab prophylaxis against RSV for those children identified as high risk based on available data. Updated guidelines, published in July 2014, has recommended palivizumab immunoprophylaxis for all children with hs-CHD [1,3]. Several randomized controlled trials have reported that palivizumab which is also a cost-effective prophylactic modality, reduced RSV-related hospitalizations in children with hs-CHD [2,7-9]. However, no studies have so far been published on the assessment of the weight status of patients, which would suggest good clinical outcomes. The aim of this study was to evaluate the effects of RSV prophylaxis with palivizumab on weight percentiles of infants with hs-CHD.

MATERIAL and METHOD

Study design and population

We retrospectively evaluated the effects of RSV prophylaxis with palivizumab on the weight percentiles of infants with hs-CHD at our Pediatric Cardiology Department between October 1st, 2013, and March 31st, 2017. The study involved children with hs-CHD aged <24 months who received ≥3 doses of palivizumab prophylaxis during the RSV season.

The diagnosis of hs-CHD was provided based on uncorrected or palliated cyanotic or acyanotic disease associated with documented pulmonary hypertension (more than 50% higher than the age-adjusted systemic pressure) and/or requirement for daily medication to manage congestive heart failure. Patients with a genetic syndrome, prematurity, chronic lung disease, or additional disease were excluded from the study.

The medical records of the patients were evaluated retrospectively in terms of patient demographics (age, sex), baseline clinical characteristics (weight, weight percentile, type of CHD and related medical/surgical treatments, heart failure, comorbidities), the age of the patients at the first dose of palivizumab, the duration, and frequency of hospital stays, intensive care unit (ICU) admissions, length of ICU stay, requirement for mechanical ventilation, and mortality.

Palivizumab prophylaxis

The time interval between October 1st and March 31st was accepted as the RSV season. Palivizumab was administered intramuscularly for RSV prophylaxis at monthly doses of 15 mg/kg between October and March. The patients were divided into two groups

according to age of the patients at the first dose of palivizumab as Group 1 (0-6 months) and Group 2 (>6 months), and the two groups were compared and statistically analyzed.

Evaluation of weight percentiles

The recorded weight measurements of patients on each following visit were evaluated, and weight percentiles were calculated according to weight percentile values for Turkish children [10]. All patients were evaluated according to their weight percentiles at birth and at the time when they received the first and last doses of palivizumab. The third percentile was accepted as the cut-off value of the lower weight percentile [10]. In addition, values below the 25th percentile were accepted as an indication of a poorly controlled disease. Thus, weight percentile changes during the palivizumab administration period were evaluated and grouped as consistent, and increased or decreased weight percentiles.

Ethical considerations

Ethics approval was obtained from the Ethics Committee (No: 2018-102, Date: 06.25.2018). The procedures undertaken by participants were performed after obtaining informed consent from the parents.

Statistical analysis

Statistical analyses were performed using the SPSS version 16.0 software package (SPSS, Inc., Chicago, IL, USA). Qualitative and quantitative (continuous) variables are shown as the number of cases (n), percentages (%), and mean±standard deviations (SD), respectively. Freidman test was used to analyse the consecutive body weights. Wilcoxon's signed-ranks test was used for the comparison of weight percentiles at the first and last doses of palivizumab, and the Kruskal-Wallis test was used for the comparison of weight percentiles according to the number of doses. Pearson's correlation analysis was used to examine the relationship between variables of interest. A p-value of <0.05 was accepted as statistically significant.

RESULTS

This study involved 61 infants aged between 10 days and 15 months. The demographic features of the patients are given in Table I. There was a female predominance [25 males (41%) and 36 females (59%)]. The median gestational age was 38 weeks and ranged between 37 and 41 weeks. All patients were fed orally. No patient was given protein or calorie supplements during follow-up period.

Table 1. Demographic features of the patients.

	Median	Range (min-max)
Gestational age (week)	38	37-41
Age	5 months	10 days-15 months
Birth Weight (gr)	3000	2130-4000
	Number	**(%)**
Age at the first palivizumab dose		
0-6 months	40	65
>6 months	21	35
Number of palivizumab administrations		
3 doses	9	13
4 doses	9	13
5 doses	43	74

The most common cardiovascular diagnosis was ventricular septal defect (VSD) (n=29, 47.5%), followed by atrial septal defect (ASD) (n=21, 34%), tetralogy of Fallot (n=6, 9.8%), patent ductus arteriosus (n=3, 4.9%), and atrioventricular septal defect (AVSD) (n=2, 3.2%).

The median age of the infants at the first dose of palivizumab was 5 months (range, 10 days-15 months). Most of the patients (n=40, 65.6%) were aged under 6 months when they received their first dose of palivizumab. The number of palivizumab doses ranged between 3 and 5 (mean±SD: 4.56±0.78). Most of the patients (n=43, 70.5%) received five doses of palivizumab. A total of 278 doses of palivizumab were injected.

The birth weights of the patients ranged between 3rd and 50-75th percentiles (median: 10-25th percentile). The distributions of the weight percentiles of the patients at birth, and at the first and the last doses of palivizumab are shown in Figure 1. At birth,

9 (14.7%), patients had weight percentiles <3rd, and weight percentiles of 31 (50.8%) patients were lower than the 25th percentile. At the first dose of palivizumab, 5 (8.2%), patients had weight percentiles <3rd, and weight percentiles of 36 (59%) patients were lower than the 25th percentile. At the last dose of palivizumab, 8 (13.1%), patients had weight percentiles <3rd and weight percentiles of 29 (47.5%) patients were lower than the 25th percentile.

The changes of the weight percentiles of the patients at the birth, the first and the last doses of palivizumab are shown in Figure 2. The weight percentiles at the last dose of palivizumab in 19 (31.1%) patients showed at least one level improvement and 33 (33/61:54%) patients maintained their percentile value. There was a decline in the weight percentile at least one level of nine patients. A statistically significant difference was found between the weight percentiles at the first and last doses of palivizumab (p=0.03). There was no statistically significant difference for weight percentile change according to age at the first dose of palivizumab between Group 1 (0-6 months) and Group 2 (>6 months) (p>0.05). There was no statistically significant difference between the group given five (n=43), and three or four doses (n=18) of palivizumab in terms of weight percentiles (p>0.05).

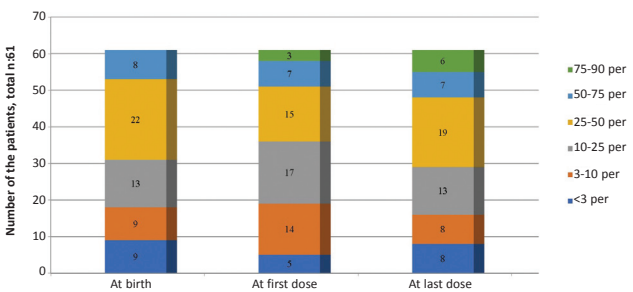

Figure 1. The distributions of the weight percentiles of patients at birth, and the first and the last dose of palivizumab.

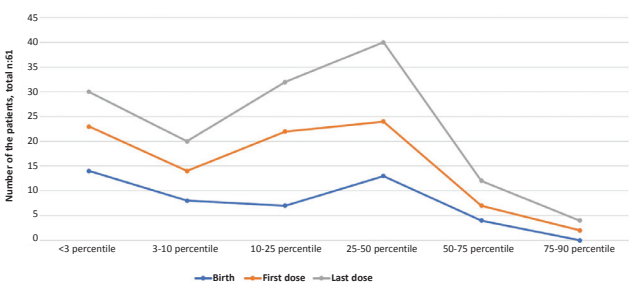

Figure 2. The changes of the patient's weight percentiles of patients at birth, the first and the last dose of palivizumab.

Six (9.8%) patients including 3 cases with VSD, and 3 cases with ASD were hospitalized due to lower respiratory tract infection. Five of the six patients were younger than 6 months (Group 1), the other patient (ASD) was 12 months old. The median hospitalization period was 6 (range, 3-10) days. Only one 2-month-old infant with VSD needed hospitalization in the intensive care unit for 4 days. None of the patients required mechanical ventilation support or exited. Five of the six patients who were five had lower weight percentiles <10th hospitalized, percentile.

DISCUSSION

Children with hs-CHD are at major risk for hospitalization due to respiratory diseases, particularly acute bronchitis and bronchiolitis [1,2]. RSV-related hospitalization has led to increased morbidity and mortality rates in children with hs-CHD [11,12]. RSV is a common pathogen in respiratory tract infections in childhood. Patients with hs-CHD are at risk for RSV-associated lower respiratory tract infections, changes in respiratory mechanisms, pulmonary hypertension, and cyanosis, and ventilation-perfusion mismatch can worsen the effects of respiratory illness with higher morbidity rates than in the general pediatric population [7,12]. Therefore, prevention of RSV in patients with hs-CHD has been an important goal. Although the relevant literature involves several studies that evaluated the cost-effectiveness of RSV prophylaxis, no studies have so far directly evaluated the weight trend of infants with hs-CHD under RSV prophylaxis [2,8,9]. The present study has showed that RSV prophylaxis with palivizumab had positive effects on weight percentiles in infants with hs-CHD.

Children with CHD can experience nutritional deficiencies during follow-up due to many factors such as low energy intake, hypermetabolism, prenatal factors, and infections [4,13]. Chromosomal anomalies or genetic diseases and additional acute-chronic diseases that accompany CHD may contribute to

growth retardation. In the present study, patients with a genetic syndrome, prematurity, chronic lung disease or comorbidities were excluded from the study to avoid bias. In addition, all patients were fed orally and no patients were given caloric support during follow-up. Many studies have emphasized that growth retardation with varying degrees of severity can be seen in different types of congenital heart defects [14,15]. In fact, malnutrition, additional infections, and hospitalization cause infants with hs-CHD to lose weight, which may affect the clinical course and the planned surgery time [14,16]. In the present study, when the weight percentiles were evaluated at the last dose of palivizumab, more than half of the patients maintained their percentile values and one-third of all patients showed at least one level improvement of their weight percentiles. In addition; at the first dose of palivizumab 36 (36/61: 59%), and at its last dose decreased number of patients (n=29: 47.5%) had weight percentiles lower than the 25th percentile A decline in weight percentiles over time was seen only in nine (14.7%) patients. Therefore, RSV prophylaxis with palivizumab may positively affect weight percentiles in children with CHD.

To date palivizumab remains the only approved strategy to protect against RSV. The AAP released a clinical practice guideline recommending palivizumab prophylaxis against RSV for children identified as high risk based on available data and revised their guidelines in 2014, narrowing indications for palivizumab prophylaxis to children aged <12 months with hs-CHD [3]. In Turkey, palivizumab was licensed in 2010, and palivizumab prophylaxis is administered to children with hs-CHD aged <24 months. Studies are showing that RSV prophylaxis administered before 12 months of age is more effective compared with older infants. We administer palivizumab prophylaxis to patients with hs-CHD aged <24 months in our clinic. In the present study, 40 (65.6%) patients were younger than 6 months and only four were older than 12 months when they received their first dose of palivizumab. In the present study, improvements in the weight percentiles of the patients at the first dose of palivizumab were compared according to age and any statistically significant differences were not found between receivers of palivizumab prophylaxis aged 6 months or older in terms of improvements in their weight percentiles.

Palivizumab prophylaxis for RSV has been reported to reduce the risk of hospital admissions related to RSV infection in children with symptomatic cardiac disease [7,17,18]. The incidence rates of RSV-related hospitalizations in hs-CHD were 12% in infants aged <6 months, 7% between 6-12, and 4% between 12-24 months [19]. Although the related literature involves several studies that evaluated the cost-effectiveness of RSV prophylaxis, no studies have directly evaluated the weight trend of infants given RSV prophylaxis [8,9]. The study by Tavsu et al. included infants with gestational age less than 32 weeks, and they reported that palivizumab reduced incidence of RSV infections and hospitalization rates in both the prophylaxis season and the following year, but without any effect on infant development or anthropometric indices [20]. In our study, we found that RSV prophylaxis with palivizumab had positive effects on weight percentiles in infants with hs-CHD. The last dose of palivizumab showed at least one level improvement of weight percentiles in 19 patients, and 33 of 61 patients maintained their weight percentiles. The hospitalization rate in the present study was 9.8% (6/61), similar to those reported in the literature. Only one patient received intensive care treatment without mechanical ventilatory support and there was no exitus. However, five of the six patients who were hospitalized due to respiratory tract infection were aged younger than 6 months and five had weight percentiles <10th percentile. Therefore, it may be thought that improvement of nutritional status in patients with CHD can help to prevent hospitalization.

Study limitations

The present study has some important limitations because of its retrospective design and small sample size. First, there was no control group to compare the improvement in weight percentiles. We did not have a control group because palivizumab has been

given to all infants aged under 24 months with CHD in our clinic since 2010. Secondly, the sample of the present study consisted of patients with different ages and the etiology of CHD was heterogeneous. Although the use of palivizumab cannot be recommended for all patients with CHD, current guidelines about RSV prophylaxis recommend giving palivizumab to patients with hemodynamically significant CHD. The population of the present study was chosen according to this most recent guideline and all of them had hemodynamically significant CHD. Another limitation of the study is that not all patients received five doses of prophylaxis. It can be speculated that if all patients could receive five doses, their weight percentiles might have shown greater improvement. The last and the most important limitation is that the main factors affecting weight gain, such as daily energy intake and nutritional ingredients of infants, were not evaluated. Although other than the vaccine, many factors related to the infant and family can affect growth and weight gain, it was not possible to evaluate them in detail due to the retrospective design of our study. Nevertheless, most of the patients admitted to our hospital have a similar low-moderate socioeconomic status due to the location of our hospital. Therefore, it can be thought that the socioeconomic conditions that affected the growth of the patients were similar in our sample. Larger, multicentered, and well-designed future studies evaluating weight and growth parameters and nutritional condition are required to evaluate the effects of RSV prophylaxis with palivizumab on weight percentiles of children with CHD.

CONCLUSION

Pediatric patients with CHD tend to have malnutrition and growth retardation. Direct evaluation of the weight gain trend in these infants may better reflect clinical outcomes, which may be used as a predictor for the follow-up of these infants. Additionally, weight gain is accepted as an important factor for estimating the optimal timing of surgery. The weight gain trend of patients with CHD should be evaluated at each follow-up visit to the cardiology department. The present study showed that RSV prophylaxis with palivizumab effected weight percentiles positively in infants with CHD. Although our patient sample was too small to claim this absolutely, shorter hospitalization period and good weight gain may be considered to affect patients' general health state favorably with an advantage of faster recovery. Palivizumab prophylaxis for RSV is recommended to decrease morbidity and mortality rates of RSV in children with CHD.

Ethics Committee Approval: Ankara Pediatrics, Hematology Oncology Training and Research Hospital, Ethics approval was obtained from the Ethics Committee (06.25.2018-102).
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