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ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA

Oseltamivir use for viral pneumonia in newborns

Yenidoğanlarda viral pnömonide oseltamivir kullanımı

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ABSTRACT

Objective: Viruses are demonstrated to be an uncommon etiologic agent of early and late pneumonia. In this study we aimed to investigate the safety and affectivity of oseltamivir use for viral pneumonia in newborns.

Methods: This was a retrospective study conducted in a single tertiary neonatal intensive care unit between September 2009 and April 2013. Demographic, clinical and laboratory data before and after treatment, duration of hospitalization, time of clinical improvement were recorded.

Results: During the study period, a total of 69 newborn cases who were treated by oseltamivir for H1N1 swine flu (n=12) or suspicious influenza (n=57) were evaluated. Mean birth weight and gestational age were 3100±601 grams and 37.9±1.8 weeks, respectively. On admission, median postnatal age was 20.6 (7-47) days. Oseltamivir, along with supportive care, was administered as 3.0 mg/kg/dose twice a day for 5 days according to the recommendations of Food and Drug Administration (FDA). The median time of initiation of oseltamivir was 2.3 days (1-4) after admission and the median hospitalization day was 10.4 days (5-22). No adverse effects associated with oseltamivir were observed and all patients were discharged after full recovery.

Conclusion: Oseltamivir use in addition to supportive therapy seems to be safe and effective in newborns with severe viral pneumonia.

Key words: Pneumonia, newborn, antiviral treatment

ÖZET

Amaç: Yenidoğanlarda en sık pnömoni etkenleri sıklıkla bakteriyel olmakla birlikte daha az sıklıkta viral etkenler de saptanabilmektedir.

Yöntemler: Bu çalışmada 2009-2013 yılları arasında Dr. Sami Ulus Kadın Doğum, Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi'nde oseltamivir verilen hastalar retrospektif olarak değerlendirilmiştir. Hastaların demografik ve klinik bulguları ile tedavinin kaçıncı gününde klinik iyileşmenin sağlandığı, hastanede yatış süresi dosyalardan kayıt edilmiştir.

Bulgular: Çalışma süresi boyunca kanıtlanmış H1N1 gribi (n=12) ve şüpheli vakalara (n=57) oseltamivir tedavisi verilen hastalar değerlendirilmeye alınmıştır. Ortalama doğum ağırlığı 3100±601 gram ve gestasyonel yaş 37.9±1.8 hafta; ortanca başvuru yaşı 20.6 (7-47) gün olarak bulunmuştur. Oseltamivir, bu vakalarda FDA'nın acil kullanım izni doğrultusunda oral 3.0 mg/kg/doz, günde iki kez 5 gün boyunca kullanılmıştır. Hastaneye yatışın ardından oseltamivir başlama zamanı 2.3 (1-4) gün olarak saptanmıştır; hastanede yatış süresi ise 10,4 (5-22) gün olarak bulunmuştur. Tedavi sırasında olguların hiçbirinde oseltamivir ilişkili yan etkiler gözlenmemiştir ve tüm vakalar sağlıklı olarak taburcu edilmiştir.

Sonuç: Ağır viral pnömoni düşünülen yenidoğan olgularda destek tedavilerinin yanı sıra oseltamivir verilmesi etkin ve güvenilir görülmektedir

Anahtar kelimeler: Pnömoni, yenidoğan, antiviral tedavi

INTRODUCTION

Pneumonia is an important cause of neonatal infection and accounts for significant morbidity and mortality, especially in developing countries. Due to the variability of pathogen agents according to the age, community and region, it is essential to estimate potential microorganisms for a rationalist management [1].

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Pneumonia is mainly caused by bacteria, viruses, and other organisms. Bacteria are the most common cause of pneumonia in infants. *Group B streptococcus* and gram negative enteric bacteria predominate up to postnatal day 20 which is acquired by vertical transmission during delivery. Pneumonia in infants aged 3 weeks to 3 months is primarily due to infections caused by bacteria and commonly caused by *Streptococcus pneumoniae*. In some instances, causative agent cannot be found especially in newborns [2].

General management of neonatal pneumonia consists of supportive therapy along with antibiotics since the etiology is accepted as bacterial unless another agent is proved. Antiviral agents are recommended for selected cases since the viral pneumonias can be life threatening in newborns. However indications are very limited for specific antiviral therapy. It is recommended to use acyclovir for herpes simplex virus (HSV) pneumonia and gancyclovir for *cytomegalovirus* (CMV) pneumonia [3,4]. Ribavirin is the only viral agent effective against respiratory syncytial virus (RSV) infections and especially recommended for infants with congenital heart diseases, chronic pulmonary disease and premature babies [5]. Due to high cost and lack of evidence of effectiveness in infants without co-morbidities, antiviral treatment is not routinely recommended for those infants. Although previous studies showed that oseltamivir was safe and beneficial in selected infants, there are no adequate data on this issue in newborns [6,7]. In this retrospective study, newborns treated by oseltamivir for H1N1 swine flu or suspicious influenza were assessed mainly for clinical improvement and possible adverse effects.

METHODS

It was a retrospective case study conducted in a single tertiary neonatal intensive care unit (NICU) of Dr Sami Ulus Maternity and Children Training and Research Hospital between September 2009 and April 2013.

During the study period, 69 newborn cases were diagnosed as viral pneumonia and treated with oseltamivir. Viral pneumonia was diagnosed by clinic and/or laboratory data. Hemogram, biochemical analyses, serum C-reactive protein level, blood culture, and chest radiography were obtained for all patients. The diagnosis of H1N1swine flu was confirmed by H1N1 influenza specific real-time polymerase chain reaction (PCR) assay from respiratory samples (nasopharyngeal and pharyngeal swabs). Oseltamivir was also given to the rest of the cases while waiting for PCR results, since severe viral pneumonia was suspected because of the worse clinical condition of the patients (i.e. hypoxia, tachypnea, severe respiratory distress requiring mechanical ventilation). The use of oseltamivir was decided according to the recommendations of World Health Organization (WHO).

Demographic, clinical and laboratory data including sex, gestational age, birth weight, age on admission, arterial blood gases at the time of hospitalization, need of mechanical ventilation, need of oxygen and intravenous fluid support, time of oseltamivir initiation, complete blood count, liver and kidney function tests before and after treatment, duration of hospitalization, time of clinical improvement were recorded to previously prepared forms. Possible adverse effects of oseltamivir were considered as wheezing, vomitting, rash, swelling of face and tongue, toxic epidermal necrosis, arrhythmia, convulsion and confusion according to the FDA data [8].

Statistical analysis

In statistical analyses of the data, the software package called SPSS (version 16.0) was used. The Kolmogorov-Smirnov test was performed to determine the shapes of the distribution of variables. In summarizing the data, mean ± SD or median values (interquartile range, IQR) were used, as appropriate. Pearson or Spearman test was used for correlation analyses. Group comparisons were analyzed by student t-test or Mann-Whitney U-test. Paired test or Wilcoxon test was used for paired samples. A two-tailed p value <0.05 was considered to be statistically significant.

RESULTS

During the study period, 287 newborns with suspicion of pneumonia were admitted to NICU. Sixty nine of these patients (%24) received oseltamivir in addition to supportive treatment. Thirty-nine

(%56.5) of them were boys. Mean birth weight and gestational age were 3100±601 grams and 37.9±1.8 weeks, respectively. On admission, median postnatal age was 20.6 (7-47) days. Major complaints were cough and feeding intolerance in all patients. Nearly all cases had a house contact with an adult suggesting upper respiratory tract infection.

H1N1-PCR was positive in 12 patients (17%). Oseltamivir was also given to other 57 patients while waiting PCR results since viral pneumonia was suspected due to clinical condition or severe respiratory distress requiring mechanical ventilation. The median time of initiation of oseltamivir was 2.3 days (1-4) after admission and the median hospitalization day was 10,4 days (5-22). Oseltamivir was administered as 3.0 mg/kg/dose twice a day for 5 days according to the recommendations of FDA for infants younger than 3 months [9,10].

Laboratory values including hemoglobin, platelet, alanine amino transferase (ALT), aspartate amino transferase (AST), blood-urea nitrogen (BUN), creatinine and glucose levels did not change statistically before and after oseltamivir treatment (Table 1). During the treatment period, no side effects including wheezing, vomiting, rash, swelling of face and tongue, toxic epidermal necrosis, arrhythmia, convulsion and confusion were observed. All patients were discharged uneventfully. Nine of the patients (45%) needed mechanical ventilation. In patients requiring oxygen support, oxygen was ceased on the median 6th day (2-9) of oseltamivir use.

Table 1. Laboratory values before and after oseltamivir treatment (mean ± standard deviation)

	Before treatment	After treatment	p
Hemoglobin (g/dl)	12.6±2.5	11.8±2.4	0.06
Leukocyte, (cell/mm^3)	9100±3716	10180±4159	0.5
Platelet, (x10^3/mm^3)	396±17	421±20	0.6
BUN, (mg/dl)	8±5.2	11.8±11.2	0.4
Creatinin, (mg/dl)	0.38±0.13	0.31±0.13	0.6
AST, (mg/dl)	35.6±11.1	43.6±29.5	0.4
ALT, (mg/dl)	18.4±7.3	24±10	0.1
Glucose, (mg/dl)	120±22	111±24	0.07

DISCUSSION

Although bacteria account for the largest proportion of neonatal pneumonia, viruses are demonstrated to be an uncommon etiologic agent of early and late pneumonia. Because viral pneumonia may be severe in infants, antiviral treatment is recommended in selected cases in addition to supportive treatment. However indications for antiviral therapy are very limited [3,4,5]. There are rare data on administration of oseltamivir for selected influenza pneumonia cases in newborns [11,12].

Oseltamivir is an antiviral agent that selectively inhibits the neuraminidase of both influenza A and B viruses. Influenza virus neuraminidase enzyme (NA) plays an essential role in release and spread of progeny virions, following the intracellular viral replication cycle. Causing virion aggregation on host cell oseltamivir confines the spread of infection in mucosal secretions [13,14].

Oseltamivir is indicated for the prevention and treatment of acute uncomplicated infections due to influenza A and B viruses among children older than 1 year. The use of oseltamivir is not recommended among children younger than 1 year [9]. Toxic effects of oseltamivir are reported in a study on baby rats however there very limited data on newborns and infants [15].

FDA urgently approved the use of oseltamivir among infants younger than 3 months during 2009 H1N1 pandemia [9,10]. In literature, there are only a few case series and retrospective studies regarding safety, efficacy and adverse effects of oseltamivir administered to newborns during H1N1 pandemia. Our previous research, including ten common cases with this study, showed no adverse effects in patients who received oseltamivir for H1N1 swine flu [16].

One retrospective cohort study found no evidence of an association between oseltamivir use during pregnancy and a variety of adverse events, including preterm birth, premature rupture of membranes, and increased duration of hospital stay for mother or neonate, malformations, or low fetal weight [17]. Another study, including 86 pregnant women administered oseltamivir and 860 controls,

showed that babies whose mothers used oseltamivir had higher risk for transient hypoglycemia in late term, but no difference were detected between two group in terms of low apgar score, prematurity, congenital malformation and still birth [18].

A study in which oseltamivir was used for the treatment of pneumonia in two premature infants requiring assisted ventilation and third full-term newborn without complicated disease during H1N1 pandemia showed good tolerability and efficacy [19]. In another study, oseltamivir was used in four preterm infants infected with H1N1 and 13 preterm infants who were in contact with H1N1 and reported no side effect [20]. In a study, three out of six infants experienced H1N1 infection received oseltamivir and no adverse effects were detected [11]. In a retrospective study conducted during H1N1 outbreak, five infants received oseltamivir for treatment and four infants for prophylaxis. Respiratory functions were improved in infants who were treated for infection and did not deteriorate in prophylaxis group. Conjunctivitis occurred in an infant and improved without treatment. One infant developed necrotizing enterocolitis (NEC) three days after completing oseltamivir treatment [21]. As far as we know, our study is the largest case report in literature which evaluates oseltamivir use in newborns.

Most frequent side effects reported in literature are vomiting and nausea among adults. Generally it is mild to moderate and occurs in the first two days of treatment. Other side effects are rash, swelling of tongue, toxic epidermal necrosis, hepatitis, abnormal liver tests, arrhythmia, convulsion, confusion and aggravation of diabetes mellitus [22]. Among newborns, all data regarding side effects of oseltamivir is obtained from clinical observational studies. In a study, newborns administered oseltamivir developed conjunctivitis and NEC, where as in another study, newborns had different side effects including rash, gastrointestinal symptoms and elevated liver enzymes which improved after ceasing the treatment [6, 21]. In our study no adverse effects mentioned above were observed among the treated infants.

In conclusion the use of oseltamivir, along with the supportive therapy, is demonstrated to be safe and effective in newborns with severe viral pneumonia. However, randomized clinical trials are required to evaluate oseltamivir overall benefit.

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