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A randomized, double-blind, placebo-controlled trial evaluating the safety of early oseltamivir treatment among children 0–9 years of age hospitalized with influenza in El Salvador and Panama

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ABSTRACT

Background: Oseltamivir reduces symptom duration among children with uncomplicated influenza, but few data exist on treatment efficacy and tolerability among hospitalized children, particularly among infants aged <1 year. We evaluated tolerability and efficacy of oseltamivir treatment of children aged 0–9 years hospitalized with influenza.

Methods: We conducted a double-blind, randomized, placebo-controlled trial at tertiary care hospitals in El Salvador and Panama. Primary outcomes were length of hospitalization and increased work of breathing. Children were eligible if hospitalized <7 days after symptom onset with cough or sore throat plus tachypnea. Children were randomized 1:1 to receive oseltamivir or placebo; had swabs collected at enrollment for influenza RT-PCR testing; were assessed at enrollment and every 12 h for work of breathing; and were followed for adverse events through 7 days after discharge. Analyses were intention-to-treat.

Results: Overall, 683 children were randomized (oseltamivir, n = 341, placebo n = 342). Fifty-three percent were aged <1 year and 30 had influenza (oseltamivir, n = 19; placebo, n = 11). The study was terminated early after enrollment of 21% of the sample size due to lower than anticipated participant accrual. Using Kaplan-Meier analysis, there was no significant difference in median length of hospitalization (3 days, IQR 2–4 vs. 5 days, IQR 3–7, p = 0.22) and increased work of breathing (36 h, IQR 24–72 vs. 96 h, IQR 13–108, p = 0.14) between oseltamivir versus placebo recipients. There was no difference in adverse events between groups.

Conclusion: Oseltamivir treatment was well tolerated among hospitalized children, including among infants aged <1 year.

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1. Introduction

Children aged <5 years and those with underlying medical conditions are at increased risk of influenza-associated hospitalization (Dawood et al., 2010; Poehling et al., 2006; Chiu et al., 2009; Neuzil et al., 2000a; Keren et al., 2005). Currently, oseltamivir is the only licensed medication for treatment of both influenza A and B viruses that is available as an oral suspension or as a capsule that can be compounded into a suspension for treatment of young children. Three randomized controlled trials have evaluated oseltamivir efficacy in children aged 1 year and older with uncomplicated influenza (Fry et al., 2014; Heinonen et al., 2010; Whitley et al., 2001), but efficacy has not been evaluated among hospitalized children in randomized trials. In addition, oseltamivir tolerability in children aged <1 year has not been evaluated by randomized trial because oseltamivir was licensed for influenza treatment only in children aged ≥1 year until December 2012. The availability of safe and effective influenza treatment options among children aged <1 year is critical because children in this age group have the highest rates of influenza-associated hospitalization of all pediatric age groups (Dawood et al., 2010; Poehling et al., 2006; Griffin et al., 2004; Neuzil et al., 2000b) and children aged <6 months are not eligible for influenza vaccination (Grohskopf et al., 2014).

During the 2009 influenza A/H1N1 pandemic, use of oseltamivir increased in many countries globally as the World Health Organization (WHO) recommended antiviral treatment for patients with severe influenza (WHO,), and some middle-income countries that previously lacked influenza treatment guidelines, such as El Salvador and Panama, developed national treatment guidelines for the pandemic (Ministerio de Salud Pública y Asistencia Social-El Salvador, 2009; Ministerio de Salud-Caja de Seguro Social, 2009). However, many middle-income countries lack guidelines for treatment of seasonal influenza. In El Salvador and Panama, since the 2009 pandemic, only limited supplies of influenza antiviral medication have been provided by the ministries of health for use in public hospitals and influenza antiviral treatment in hospitalized patients has been sparse and inconsistent across hospitals. To provide data to inform the development of seasonal influenza treatment guidelines in countries considering influenza antiviral medication use, we conducted a randomized, placebo-controlled trial to evaluate the tolerability and efficacy of early oseltamivir treatment at hospital admission to reduce severity of illness among children aged ≤9 years hospitalized with influenza in El Salvador and Panama.

2. Methods

2.1. Trial design and participants

This study was a multi-site, double-blind, randomized, placebo-controlled trial conducted during 2012 and 2013. Study sites included three hospitals in Panama and two in El Salvador that provided specialized pediatric care with intensive care units and capacity to provide mechanical ventilation. Children were enrolled during September–October 2012 (partial season) and April–October 2013 (full season), coinciding with periods of influenza virus circulation based on surveillance data from preceding years.

Guardians of children with respiratory illness were approached by study staff in the emergency departments of participating hospitals. After informed consent was obtained (and assent from children when specified by national law), children were screened for eligibility. To be eligible for enrollment, children had to be aged ≤9 years and hospitalized <7 days after symptom onset with symptoms meeting a modified version of the World Health Organization criteria for severe acute respiratory infection (cough or sore throat plus age-specific tachypnea); see Supplemental materials for exclusion criteria. Enrolled children whose admission orders included oseltamivir treatment as part of routine clinical care were included in an observational group, and the remaining children were eligible for randomization to active study drug or placebo. Use of placebo was considered acceptable because oseltamivir is not widely used among hospitalized children in Panama and El Salvador in part because data from randomized trials are not available on oseltamivir treatment efficacy in these settings and because trial participation did not preclude treatment with oseltamivir as part of clinical care at enrollment or at any point during trial participation (see Study procedures).

2.2. Randomization and blinding

Enrolled children eligible for randomization were assigned 1:1 to receive oseltamivir or placebo using site-stratified randomization sheets with randomly permuted blocks of 10 four digit numbers paired with treatment assignments (5 oseltamivir and 5 placebo per block). Randomization sheets were generated by a statistician without other study involvement. Prior to study unblinding, only study pharmacists and the CDC statistician who performed safety analyses for a data safety and monitoring board had access to treatment assignments which were kept in locked cabinets in the study pharmacies. Pharmacists prepared active study drug and placebo in identical storage containers marked only with randomization numbers. At the time of randomization, study physicians consulted randomization number lists without treatment assignment and assigned the first unused number and the corresponding medication bottle. An unblinded clinical monitor visited study sites periodically to evaluate for breaches in blinding.

2.3. Intervention

Randomized children received either active drug or placebo every 12 h for 10 doses. The first dose was given within 2 h of enrollment. For children aged 0–11 months, study drug was dosed at 3 mg/kg/dose. For children aged ≥12 months, study drug was dosed based on standard unit dosing: 30 mg/dose for children ≤15 kg, 45 mg for children >15–23 kg, 60 mg for children >23–40 kg, and 75 mg for children >40 kg. Oseltamivir was prepared according to package insert guidelines for emergency compounding of an oral suspension from 75 mg TAMIFLU® capsules modified to yield a concentration of 15mg/5 mL. Placebo was prepared using corn starch and suspension vehicle to produce a suspension with the appearance and taste of the active suspension.[1]

2.4. Study procedures

At enrollment, study physicians conducted a standardized baseline clinical assessment of oxygen saturation by pulse oximetry, supplemental oxygen or respiratory support requirement, and signs of increased work of breathing (i.e. grunting, nasal flaring, or intercostal/subcostal retractions) (see Supplemental materials for details). Study physicians also administered a questionnaire on participant demographics, medical history, and history of illness and collected information from children's medical charts on treatment plan. Throughout hospitalization, study physicians

[1] Due to an error in ordering, OraSweet® was used for compounding active study drug and placebo for the first 19 children in the efficacy population and 275 children in the safety population, after which OraSweet®Sugar Free was used per the TAMIFLU package insert.