Early Human Development 115 (2017) 71–76

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Effects of the early administration of sivelestat sodium on bronchopulmonary dysplasia in infants: A retrospective cohort study

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ARTICLE INFO

Keywords:
Bronchopulmonary dysplasia
Neutrophil elastase inhibitor
Chorioamnionitis

ABSTRACT

Background: Chorioamnionitis, or infiltration of the chorioamnion by neutrophils, is a risk factor associated with the development of bronchopulmonary dysplasia. Increased neutrophil elastase levels are observed in the tracheal aspirates of these patients.

Aims: To examine the effects of early administration of the selective neutrophil elastase inhibitor sivelestat, which is used to treat acute lung injury in adults, on bronchopulmonary dysplasia in extremely premature infants.

Study design: Retrospective cohort study.

Subjects: This study included extremely low-birth-weight infants born at a gestational age < 28 weeks. Patients were divided into groups based on the receipt of sivelestat.

Outcome measures: The primary outcome was the rate of bronchopulmonary dysplasia-free survival at a postmenstrual age of 36 weeks, and the secondary outcomes included various clinically significant factors of neonatal mortality and morbidity and adverse events.

Results: Of the 1031 included neonates, 124 (12.0%) were treated with sivelestat. Significant differences between the groups were noted for gestational age, delivery method, fetal number, the frequency of chorioamnionitis, immunoglobulin M levels, and WBC counts. No differences were identified concerning the bronchopulmonary dysplasia-free survival rate at a postmenstrual age of 36 weeks (adjusted odds ratio for sivelestat to control, 0.83; 95% confidence interval = 0.53–1.30). Secondary outcomes did not significantly differ between the groups.

Conclusions: In extremely premature infants, early sivelestat use was not associated with an improved rate of survival without bronchopulmonary dysplasia at a postmenstrual age of 36 weeks.

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http://dx.doi.org/10.1016/j.earlhumdev.2017.09.016
Received 6 March 2017; Received in revised form 18 September 2017; Accepted 18 September 2017

1. Introduction

Bronchopulmonary dysplasia (BPD) is the most prevalent long-term morbidity in extremely low-birth-weight-infants (ELBWIs), and it is linked to increased risks of reactive airways disease, pulmonary hypertension, post-neonatal mortality, and adverse neurodevelopmental outcomes [1]. Although multiple drugs are routinely used to prevent and treat BPD [2], no single therapy has been confirmed to significantly reduce the incidence or severity of BPD. In recent years, chorioamnionitis (CAM) has attracted attention as an important cause of BPD [3]. CAM is histologically defined by the infiltration of inflammatory cells, mostly neutrophils, into the chorion, amnion, and placenta [4,5]. High levels of interleukin (IL)-8, a neutrophil migration factor, in tracheal aspirates obtained from infants intubated soon after birth were associated with the development of BPD and a need of prolonged mechanical ventilation [6]. IL-8 levels in gastric aspirates from very premature infants shortly after birth were associated with risks of moderate or severe BPD [7]. Other reports indicated that neutrophils counts and neutrophil elastase–alpha 1-proteinase inhibitor complex levels were elevated in tracheal aspirates from newborns who developed neonatal pulmonary emphysema, one of the BPD phenotypes [8,9].

Neutrophil elastase release is considered an important mechanism by which neutrophils cause lung interstitial and alveolar damage [10], and sivelestat, a selective neutrophil elastase inhibitor, has been indicated as a potential treatment for patients at risk of acute lung injury (ALI) [11,12]. In addition, high doses of sivelestat significantly inhibited IL-8 mRNA expression in alveolar epithelial type II cells [13]. Studies have reported that sivelestat can prevent changes in neutrophil pliability induced by both inflammatory mediators and dysfunctional pulmonary microcirculation [14,15]. Nomura and colleagues reported in their randomized controlled trial that treatment with sivelestat during bypass surgery prevented pulmonary damage and inhibited proinflammatory cytokine activity [16]. The results from these studies suggested that sivelestat can suppress neutrophil recruitment to lung capillaries and thus prevent the development of ALI. Therefore, in the current study, we hypothesized that treatment with sivelestat would suppress the development or severity of BPD. To test our hypothesis, we conducted a retrospective clinical study of ELBWIs who were born at a gestational age (GA) of < 28 weeks.

2. Materials and methods

2.1. Design and study participants

Eleven tertiary neonatal intensive care units (NICUs) participated in this retrospective observational study. All ELBWIs (< 1000 g) who were born at a GA of < 28 weeks without major congenital anomalies, which were defined as defects that were present at birth and that had surgical, medical, or serious cosmetic significance, and who were admitted to participating NICUs between January 1, 2007 and December 31, 2013 were included. This study period was set because sivelestat was approved in 2002 in Japan, and it has been used to prevent or treat BPD since 2007. Neonates born outside the participating institutions, those who transferred to another hospital, and those who died within 48 h after birth were excluded from the study.

2.2. Data collection

Data were collected from the medical records of patients by attending doctors or trained research assistants at all participating sites until death or NICU discharge, transmitted electronically to our center, and stored. Patients were divided into the sivelestat (neonates who received sivelestat within the first 48 h after birth at a dose of 0.1–0.2 mg/kg/h for 7–14 days to prevent BPD) and control groups (neonates who did not receive sivelestat). Patients who received sivelestat in any other manner were excluded. The usual practice in most units is to administer 0.2 mg/kg/h sivelestat for 14 days because this dosage was described in the package insert for sivelestat administration. Although sivelestat is administered to patients with evidence of intrauterine inflammation, such as clinical CAM, funisitis, elevated WBC counts, or elevated immunoglobulin (Ig)M levels in most centers, the criteria used to decide which infants should be treated with sivelestat differed between units and varied over time.

2.3. Outcomes

The primary outcome of this study was BPD-free survival rate at a postmenstrual age (PMA) 36 weeks (BPD36). Secondary outcomes included BPD at 28 days of age (BPD28) and BPD36; death at discharge; oxygen-free survival at discharge; neonatal death; severe intraventricular hemorrhage (IVH) (grade 3 or 4); sepsis; patent ductus arteriosus (PDA); severe retinopathy of prematurity (ROP) (treated); gastrointestinal perforation; and adverse events, including increased transaminase levels, jaundice requiring exchange transfusion, leukopenia, thrombopenia, and elevated blood creatinine levels.

2.4. Definitions

GA was defined as the best estimate based on early prenatal ultrasound examination, the last menstrual period, and physical examination of the infants at birth. Neonatal death was defined as death within 28 days after birth. BPD was defined as supplemental oxygen use at 28 days old or a PMA of 36 weeks. PDA was diagnosed via echocardiography. IVH was diagnosed using cranial echography and classified using Papile's classification, with grades III and IV corresponding to severe IVH [17]. ROP was defined according to the international classification [18]. Small for gestational age (SGA) was defined as a birth weight less than the 10th percentile of the standard birth weight for GA published by the Japan Pediatric Society [19]. Gastrointestinal perforation was diagnosed if free air was detected in the abdominal cavity via radiograph examination regardless of the cause. Antenatal corticosteroid use was defined as the administration of at least one dose of a corticosteroid to the mother at any time before delivery to accelerate fetal lung maturity. The histologic criterion used for CAM was the presence of accumulated leukocytes extending through the fetal membranes using Blanc's classification [20], and funisitis was defined as migration of fetal inflammatory cells into or through the media of the umbilical arteries or veins. WBC counts and IgM levels were measured in the umbilical cord blood or blood taken from newborns soon after birth. Hyperleukocytosis was defined as a leukocyte count of > 40,000/mm^3 and hyper-IgM was defined as an IgM level of > 30 mg/dL. Neonatal sepsis was diagnosed in the presence of a positive blood culture result. Prophylactic indomethacin was administered to prevent IVH before 6 h of life. Exchange transfusions were performed when the serum total bilirubin level reached the exchange transfusion criterion of Kobe University [21]. Elevation of transaminases was defined as an AST level of > 140 U/L or ALT level of > 50 U/L. Leukopenia was defined as a leukocyte count of < 4000/mm^3. Thrombocytopenia was defined as a platelet count of < 150 × 10^9/L. Elevated creatinine levels were indicated by levels of ≥ 1.3 mg/dL.

2.5. Statistical analyses

Statistical analyses were performed using STATA/MP 13.1 for Windows. Maternal and infant demographic characteristics, perinatal risk factors, and the incidence of mortality and morbidity were compared between the sivelestat and control groups using Pearson's $\chi 2$ test for categorical variables and the *t*-test for continuous variables. The Wilcoxon signed-rank test was used when continuous data were not normally distributed. Multivariable logistic regression analysis was used to examine the effect of significant outcomes from the univariate