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ORIGINAL ARTICLE

Efficacy of recombinant human granulocyte colony stimulating factor in very-low-birth-weight infants with early neutropenia

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Background/Purpose: Neutropenia is a risk factor for nosocomial infections (NI) in very-low-birth-weight (VLBW) infants. Although recombinant human granulocyte colony stimulating factor (rhG-CSF) increases the neutrophil counts in neutropenic VLBW infants, its long-term efficacy for early neutropenia (EN) remains unknown.
Methods: In this case-controlled study, charts of VLBW recipients of rhG-CSF for EN (total neutrophil count $<1.5 \times 10^9$/L during first 7 days) were reviewed and compared to gestational age, total neutrophil count, and birth weight matched infants unexposed to rhG-CSF.
Results: Twenty-seven infants were identified in each group. Mortality and morbidity did not differ between the two groups. Rate of NI (16/27 vs. 4/27, $p = 0.002$, odds ratio = 8.36) as well as the total number of episodes of NI (22 vs. 4, $p = 0.007$) were higher in rhG-CSF (+) group than in the rhG-CSF (−) group.
Conclusion: Our experience does not show benefit in empirical use of rhG-CSF in preventing NI in VLBW infants with EN.
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Introduction

Neutrophils play an important role in host defense against infections. Neutropenia is common in premature infants and neutrophil function is impaired[1] in this group. Neutropenia usually develops in the first week of life, affects 5–68% of premature infants, and is normally transient.[2–4] Manroe et al

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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first identified neutropenia as an important predictor of infection in newborn infants.[5] Subsequent studies supported the contention that early neutropenia (EN) in premature infants may increase the incidence of nosocomial infection (NI) especially when it is associated with maternal hypertension.[6,7] It has been proposed that increasing the neutrophil count in neutropenic premature infants by either recombinant human granulocyte-colony-stimulating factor (rhG-CSF),[8–10] or granulocyte-macrophage-colony-stimulating factor (rhGM-CSF)[11] may prevent or decrease NI. There is one randomized controlled trial published in neonatal neutropenia, developed within 21 days (mean >4 days) of life, to study prophylactic rhG-CSF use in decreasing NI in premature infants which demonstrates efficacy for only 2 weeks.[12] The *Cochrane Review* finds no sufficient evidence to support the introduction of either G-CSF or GM-CSF into neonatal practice, either as treatment of established systemic infection to reduce mortality, or as prophylaxis to prevent systemic infection in high risk neonates.[13] Nonetheless, some neonatologists empirically administer rhG-CSF to premature infants with EN on the assumption that it reduces the risk of NI. This practice prompted us to review our own experience. We previously reported that EN, developed in the 1st week of life, is not associated with increased incidence of NI in very-low-birth-weight (VLBW) infants.[14] We now examine the efficacy of empirical use of rhG-CSF for EN in this group of infants.

Methods

Records of VLBW infants admitted to the neonatal intensive care unit of University of Florida Health Science Center at Jacksonville, between January 2002 and July 2004, were reviewed with the approval of the Institutional Review Board (UF-IRB3). There were totally 338 VLBW infants with gestational age <34 weeks that were admitted during this period. EN was defined as a total neutrophil count (TNC) $<1.5 \times 10^9$/L within the 1st week of life. Infants who developed neutropenia within 24 hours of a positive culture, or those who received rhG-CSF within 24 hours of a positive culture, were excluded. Empirical rhG-CSF (5–10 μg/kg/day for 3–5 days) for EN, once daily via intravenous lines, was prescribed at the discretion of the attending neonatologist(s). Our group determined as the unit policy to give rhG-CSF via the intravenous route after discussion with our pharmacists.

Total white cell counts were obtained using an automatic cell counter after correction for nucleated red blood cells. TNC were obtained by multiplying total white cell counts by the sum of percentages of segment, band, and metamyelocyte. NI was defined as a positive culture of a body fluid after 3 days of life. Two positive cultures obtained from two different sites on the same day were required to categorize coagulase-negative *Staphylococcus* as a true NI. The time of positive culture was defined as the time when it was drawn. Microbiology reports were obtained from the hospital mainframe computer system and cross-referenced with both medical record number and date of birth of the patient. The computerized database of hospital pharmacy was used to identify the dates and times of administration of all prescriptions of rhG-CSF.

VLBW infants who received empirical rhG-CSF for EN and fulfilled our predetermined criteria were included in rhG-CSF (+) group. During the same period, VLBW infants with EN but unexposed to rhG-CSF and matched for gestational age (±1 week), birth weight (±150 g), and the lowest TNC in the 1st week of life ($\pm 250 \times 10^6$/L) comprised the rhG-CSF (−) group.

Gestational age (GA) was determined either by the last menstrual period or prenatal ultrasound before 20 weeks' gestation. Birth weight below the 10th percentile of the corresponding gestational age was defined as small for dates. Maternal hypertension included pre-eclampsia/eclampsia, chronic hypertension, and HELLP syndrome. Central line was placed by a team of health professionals, used only for parenteral nutrition, and was considered as positive when NI occurred in the presence of central line(s). Oxygen requirement at 28 days was defined as bronchopulmonary dysplasia, whereas oxygen usage after post-conceptional age of 36 weeks was defined as chronic lung disease (CLD). Necrotizing enterocolitis (NEC) was defined using modified Bell's staging criteria[15] and included infants with Stage II or higher NEC. An outcome of patent *ductus arteriosus* was assigned if an infant was treated either with indomethacin or ibuprofen or by surgical ligation. Papile's classification[16] was used to grade intraventricular hemorrhage. Age of NI was determined by the date of positive culture(s).

Statistical analysis

Data were analyzed after de-identification. All continuous variables were analyzed by nonparametric test (paired and nonpaired) and expressed as median (interquartile range, IQR). Odds ratios (OR) with 95% confidence intervals (CI) were obtained for Fisher's exact test. In order to avoid inappropriate matching, data of all infants with EN were entered into multivariate logistic regression using NI as the dependent variable with GA, birth weight, sex, premature rupture of membranes, maternal hypertension, central line usage, total days on parenteral nutrition, small for date status, lowest TNC within the first 7 days, and prophylactic use of rhG-CSF for EN as independent variables. Log rank test was used to compare the probability of NI between rhG-CSF (+) and rhG-CSF (−) groups and hazard ratio (with 95% CI) was obtained. A p-value <0.05 for any independent variable was interpreted as significant. MedCalc version 12.2 was used for statistical analyses.

Results

Of 338 VLBW infants, 332 had hemogram data within the 1st week of life. Among these 332 infants, 113 (34.0%) developed EN and 31 received rhG-CSF. Eleven infants were excluded due to early infection (8 infants) or dying within 72 hours after birth (3 infants; Fig. 1). Of the remaining 102 VLBW infants with EN not associated with infection, 27 (26.5%) received empirical rhG-CSF within 5 days after birth (median = 1 days, IQR: 0–2 days). These infants comprised the rhG-CSF (+) group. We selected 27 infants in the rhG-CSF (−) group who matched infants in the rhG-CSF (+) group. These two groups were compatible with the

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