JPPT | Single-Center Retrospective Study

Characterization of Neutropenia in Preterm Neonates Following Administration of Darbepoetin Alfa

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OBJECTIVE This study is to evaluate the effects of darbepoetin alfa (darbe) on neutrophil count in preterm neonates treated for anemia of prematurity.

METHODS This was a retrospective chart review comparing the absolute neutrophil counts (ANCs) of neonates administered 2 doses of subcutaneous darbe 10 mcg/kg to that of a randomly selected comparator group of neonates not administered the drug. Neonates <34 weeks gestational age, gestational age between 23w1d and 33w4d, born between July 2016 and June 2019, were included in the study.

RESULTS The ANCs of 45 darbe-treated neonates compared with those of 45 randomly selected comparator control neonates revealed no difference in the rate of occurrence of neutropenia (ANC ≤1000/μL) between the darbe-treated neonates (26.7%) and comparator neonates (24.4%) ($p > 0.99$). There was also no difference in the rate of occurrence of severe neutropenia (ANC ≤500/μL) between the darbe-treated neonates (11.1%) and comparator neonates (6.7%) ($p = 0.70$). Darbepoetin alfa did not lead to differences in rates of resolution of neutropenia or severe neutropenia.

CONCLUSIONS Short-term administration of darbe did not affect the ANCs of preterm neonates treated for anemia of prematurity. There was no difference in the rates of occurrence of neutropenia, severe neutropenia, or resolution of either between the darbe-treated neonates and comparator neonates.

ABBREVIATIONS ANC, absolute neutrophil count; CBC, complete blood cell count; darbe, darbepoetin alfa; ESA, erythrocyte-stimulating agent; NICU, neonatal intensive care unit; GA, gestational age; rHuEpo, recombinant human erythropoietin; UWMC, University of Washington Medical Center

KEYWORDS darbepoetin alfa; drug-induced abnormalities; neonatal anemia; neonatal intensive care units; neutropenia; neutrophils

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Introduction

Many hospitalized neonates experience significant anemia, due to causes such as a natural physiologic decrease in erythropoietin production after birth, rapid somatic growth, shorter erythrocyte lifespan, and frequent phlebotomy.[1–4] The consequent anemia most strongly affects critically ill preterm infants, leading to tachycardia, increased oxygen needs, poor weight gain, diminished activity, and increased length of hospital stay.[5] In order to treat anemia of prematurity, erythropoietin-stimulating agents (ESAs) have been used to increase erythrocyte production in anemic neonates. Although epoetin alfa is the most commonly used and robustly studied ESA in neonates, darbepoetin alfa (darbe) has been used at the University of Washington Medical Center (UWMC) neonatal intensive care unit (NICU) since 2013. The UWMC NICU uses darbe because of its longer duration of action, allowing for once-weekly administration rather than 3 times weekly administration for epoetin alfa. Although ESAs are used to improve erythrocyte production in neonates, the question remains as to whether ESAs, specifically darbe, can lead to neutropenia. In a few studies, neonates administered an ESA experienced a decrease in neutrophil count, occasionally developing neutropenia or severe neutropenia. Studies have demonstrated that an upregulation of erythropoiesis, such as in the setting of anemia with reticulocytosis or after ESA administration, may lead to a subsequent downregulation of granulopoiesis and a transient decline in absolute neutrophil count (ANC).[6–8]

A few observational studies have analyzed the use of recombinant human erythropoietin (rHuEpo) for the treatment of anemia of prematurity and found neonates administered the drug had a decline in ANC, with some neonates even experiencing neutropenia (ANC <1000/μL) or severe neutropenia (ANC <500/μL).[9–11] To date, of the few studies that have examined the use of darbe for the treatment of anemia of prematurity, neutrophil count was either not assessed or did not demonstrate declines

similar to those in the erythropoietin studies.[12,13] Because of the understudied nature of darbe compared with its counterpart agent epoetin alfa, the purpose of this study was to analyze the effects of darbe on neutrophil count in preterm neonates.

Materials and Methods

Study Design. This was a retrospective chart review of preterm neonates present in the UWMC NICU between July 1, 2016, and June 30, 2019. Neonates administered darbe were compared with a randomly selected comparator group of neonates not administered the drug. This study was approved by the University of Washington Institutional Review Board.

Patient Population. Neonates were included in the study if they were present in the UWMC NICU between July 1, 2016, and June 30, 2019, had a gestational age (GA) at birth of <34 weeks and a NICU length of stay of ≥30 days. Of these neonates meeting the minimum inclusion criteria, neonates were included in the darbe-treated group if they were administered 2 subcutaneous doses of darbe given 7 days apart per the UWMC protocol and had at least 1 complete blood count (CBC) with a differential prior to (baseline) and following the 2 doses. For the comparator group, neonates were included if they were not administered darbe but had at least 1 CBC with a differential after day of life 30. Neonates were excluded from the study if they were administered darbe via a route other than subcutaneous, or if they received any other ESA or filgrastim during their NICU stay. Neonates were also excluded if they received blood transfusions either during the darbe course or at any time during the NICU stay for the comparator neonates, received a diagnosis of anemia due to primary hemolytic disease, had evidence of congenital neutropenia, had severe renal or hepatic impairment, or had a symptomatic infection requiring antibiotics within a week of receiving darbe or within a week of baseline labs for the comparator neonates. To randomly select the comparator group, eligible neonates not administered darbe were assigned a subject number. Using a random number generator, patients were screened for inclusion criteria until a matching sample size to the darbe group was generated.

Darbe Dosing Protocol. In the UWMC NICU, iron status and anemia are assessed by hematocrit, hemoglobin, zinc protoporphyrin to heme ratio, ferritin, and reticulocyte count. Hemodynamically stable anemic neonates >7 days old are considered eligible to receive darbepoetin alfa if their hematocrit is ≤26% and their reticulocyte count is ≤6%. The decision to administer darbe is based on provider judgment. Darbepoetin alfa 10 mcg/kg, based on the neonate's total body weight at the time of the first dose, is administered subcutaneously every 7 days for 2 doses. Darbepoetin alfa is available in 3 concentrations (60, 100, and 200 mcg/mL) and dispensed for subcutaneous administration with a dose volume between 0.1 and 0.2 mL. Darbepoetin alfa dosing guidelines are used regardless of gestational, postnatal, or adjusted gestational age. At the UWMC NICU, neonates administered darbe receive supplemental iron either intravenously or orally depending on the neonate's enteral feeding status. Oral iron is initiated at a minimum dose of 6 mg/kg/day, with a maximum dose of 12 mg/kg/day. If neonates require intravenous supplemental iron, the dose is 1 mg/kg/day. Supplemental iron is continued for at least 2 weeks after the last dose of darbepoetin alfa, but it may be continued until signs of iron deficiency have corrected or the neonate discharges. For all neonates, regardless of darbe administration, CBCs and iron study labs are collected every 2 weeks, or more often if clinically indicated.

Data Collection. Birth labs and characteristics were collected for each neonate. Baseline labs for darbe-treated neonates were collected prior to the first dose of the drug and at follow-up 1 week after the second dose. For comparator neonates, baseline labs were collected between days of life 21 and 35 and then at follow-up approximately 2 weeks later, at least after day of life 30. This time frame for the comparator neonates was determined from preliminary data showing darbe-treated neonates received the drug at a mean postnatal age of 38 days. As aforementioned, iron study labs and CBCs were collected every 2 weeks, or more often if clinically indicated. From follow-up labs until discharge, ANC values reflecting neutropenia (ANC ≤1000/μL), severe neutropenia (ANC ≤500/μL), and the ANC nadir were recorded. Subsequent resolutions of any neutropenia (at least 1 ANC value >1500/μL) or severe neutropenia (at least 1 ANC value >500/μL) were recorded. Lab values after discharge were not collected. The ANC was lab reported based on only segmented neutrophils, or polys. Administration of corticosteroids prior to or during the darbe course or at any time during the NICU stay for the comparator neonates was recorded. If neonates were administered corticosteroids after ANC nadir, corticosteroid use was not collected. Data on the use of probiotics were not collected.

Definitions. For this study, neutropenia was defined as having at least 1 ANC value of ≤1000/μL after the administration of darbe for the darbe-treated neonates or after baseline labs for the comparator neonates. Severe neutropenia was defined as having at least 1 ANC value of ≤500/μL for the same aforementioned time frames. For outcomes, neonates who experienced neutropenia without severe neutropenia were separated from neonates who experienced severe neutropenia. Resolution of neutropenia was defined as having at least 1 ANC value of >1500/μL after having experienced neutropenia. Resolution of severe neutropenia was defined as having at least 1 ANC

Table 1. Summary of Birth Characteristics and Selected Laboratory Values

	Darbe-Treated Neonates (n = 45)	Comparator Neonates (n = 45)	p value
Gestational age, mean ± SD, wk and day	30w0d ± 3w0d	30w1d ± 2w1d	0.79
Male, n (%)	20 (44.4)	18 (40)	0.67
Birth weight, mean ± SD, kg	1.3 ± 0.5	1.3 ± 0.3	0.69
NICU length of stay, mean ± SD, days	77 ± 26.6	69 ± 23	0.13
Maternal hypertension, n (%)	16 (35.6)	20 (44.4)	0.51
Maternal infection, n (%)	12 (26.7)	15 (33.3)	0.65
Cesarean delivery, n (%)	9 (20)	8 (17.8)	>0.99
Neonatal corticosteroid use, n (%)	6 (13.3)	4 (8.9)	0.74
Duration of corticosteroid use, median (IQR), days*	23.5 (13.8–39.3)	9 (6.8–12)	0.17
Neonatal mortality, n (%)	0 (0)	0 (0)	>0.99
Selected laboratory values at birth			
White blood cell count, median (IQR), thousand/μL	9.5 (3.2–31.5)	8 (2–24.9)	0.40
Red blood cell count, mean ± SD, million/μL	3.7 ± 0.7	4.5 ± 0.7	<0.01
Hemoglobin, mean ± SD, g/dL	14.5 ± 2.8	17 ± 2.7	<0.01
Hematocrit, mean ± SD, %	42.1 ± 7.5	48.1 ± 9.4	<0.01
Platelet count, mean ± SD, thousand/μL	232.4 ± 63.7	219 ± 78.1	0.37
Neutrophil percent, mean ± SD, %	38.2 ± 14.8	38.5 ± 14.3	0.92
ANC, mean ± SD, thousand/μL	4.7 ± 4	3.9 ± 3.2	0.29

ANC, absolute neutrophil count; darbe, darbepoetin alfa; NICU, neonatal intensive care unit

* Calculation only includes neonates administered steroids.

Table 2. Participant Characteristics and Selected Laboratory Values Just Prior to Darbepoetin Alfa (Darbe) Administration

	Darbe-Treated Neonates (n = 45)	Comparator Neonates (n = 45)	p value
Gestational age, mean ± SD, wk and day	34w6d ± 3w0d	34w1d ± 2w2d	0.16
Postnatal age, median (IQR), days	30 (14–99)	27 (21–40)	0.03
Body weight, mean ± SD, kg	2.2 ± 0.8	1.9 ± 0.5	0.09
White blood cell count, median (IQR), thousand/μL	8.2 (4.5–30.7)	9.8 (3–30.4)	0.14
Red blood cell count, mean ± SD, million/μL	2.7 ± 0.2	3.2 ± 0.4	<0.01
Hemoglobin, mean ± SD, g/dL	8.9 ± 0.6	11.1 ± 1.4	<0.01
Platelet count, mean ± SD, thousand/μL	392.4 ± 125.3	391.8 ± 123.2	0.98
Neutrophil percent, median (IQR), %	26 (9–74)	27 (13–64)	0.92
ANC, median (IQR), thousand/μL	2 (0.7–15.6)	2.6 (1–14)	0.28

ANC, absolute neutrophil count

value of >500/μL after having experienced severe neutropenia.

Study Outcomes. The primary outcome of this study was the rate of occurrence of neutropenia (ANC ≤1000/μL), without severe neutropenia, between the darbe-treated neonates and comparator neonates. The secondary outcome of this study compared the rate of occurrence of severe neutropenia (ANC ≤500/μL) between the 2 groups. Additional secondary outcomes assessed the rates of resolution of neutropenia (at least 1 ANC value >1500/μL) and severe neutropenia (at least 1 ANC value >500/μL).

Table 3. Summary of Follow-Up Participant Characteristics and Laboratory Values

	Darbe-Treated Neonates (n = 45)	Comparator Neonates (n = 45)	p value
Gestational age, mean ± SD, wk and day	37w3d ± 3w0d	38w2d ± 7w5d	0.97
Postnatal age, mean ± SD, days	48.6 ± 15	43.3 ± 6.3	0.03
White blood cell count, median (IQR), thousand/μL	8.4 (4–19.3)	9.5 (5.4–14.5)	0.55
Red blood cell count, mean ± SD, million/μL	3.5 ± 0.4	3.1 ± 0.4	< 0.01
Hemoglobin, mean ± SD, g/dL	11 ± 1.1	10.3 ± 1.4	0.01
Platelet count, mean ± SD, thousand/μL	279.5 ± 99.4	396.4 ± 121.1	<0.01
Neutrophil percent, median (IQR), %	18 (4–67)	22 (8–47)	0.01
ANC, median (IQR), thousand/μL	1.4 (0.3–13)	1.9 (0.8–5.8)	0.03

ANC, absolute neutrophil count; darbe, darbepoetin alfa

Table 4. Primary and Secondary Outcomes

	Darbe-Treated Neonates (n = 45)	Comparator Neonates (n = 45)	p value
Primary Outcome: neutropenia, n (%)	12 (26.7)	11 (24.4)	>0.99
Resolution of neutropenia, n (%)	3 (20)	5 (31.3)	0.69
Severe neutropenia, n (%)	5 (11.1)	3 (6.7)	0.70
Resolution of severe neutropenia, n (%)	3 (60)	2 (66.7)	>0.99

Statistical Analyses. The primary outcome comparing the rate of occurrence of neutropenia was analyzed using a χ^2 test. Secondary outcomes were analyzed using a χ^2 test or Fisher exact test. A 95% CI was used with a significance level of $p < 0.05$. A power calculation was not performed. All analyses were performed using Stata version 14 (StataCorp, College Station, Texas) and PRISM 9 (GraphPad Software, San Diego, California).

Results

Patient Population. A total of 856 neonates were present in the UWMC NICU between July 1, 2016, and June 30, 2019. Of the 856 neonates, 91 were administered darbe, but only 45 met inclusion criteria (see Supplemental Figure). Of the 765 comparator neonates not administered darbe with a NICU length of stay ≥30 days, 114 were screened at random until 45 neonates met inclusion criteria. The most common reason for exclusion among both groups was lack of follow-up labs.

At birth, there was no difference in GA and weight between the 2 groups (Table 1). There was no difference in maternal characteristics of hypertension, infection, or delivery method. At birth, darbe-treated neonates had a significantly lower red blood cell count ($p < 0.01$) and hemoglobin ($p < 0.01$) values. There was no difference in neutrophil percent (38.2% ± 14.8% vs 38.5% ± 14.3%; $p = 0.92$) or ANC (4.7 ± 4 thousand/μL vs 3.9 ± 3.2 thousand/μL; $p = 0.29$; Table 1).

Darbepoietin alfa–treated neonates were administered the drug at a mean GA of 34w6d ± 3w0d and median postnatal age of 30 days (IQR, 14–99), with baseline labs collected immediately prior to this time (Table 2). Comparator neonates had baseline labs collected at a mean GA of 34w1d ± 2w2d and a median postnatal age of 27 days (IQR, 21–40). The postnatal age for baseline lab collection was significantly different ($p = 0.03$). At baseline, darbe-treated neonates had significantly lower red blood cell count ($p < 0.01$) and hemoglobin ($p < 0.01$) values. The 2 groups had similar ANCs (2000/μL [IQR, 0.7–15.6] vs 2600/μL [IQR, 1–14]; $p = 0.28$). Six darbe-treated neonates were administered corticosteroids at a mean GA of 28w4d ± 3w6d for a median duration of 23.5 days (IQR, 13.8–39.3). Four comparator neonates were administered corticosteroids at a mean GA of 32w3d ± 3w6d for a median duration of 9 days (IQR, 6.8–12). There was no difference in the GA of corticosteroid administration ($p = 0.21$) or duration of corticosteroid administration ($p = 0.17$).

Darbepoietin alfa–treated neonates had follow-up labs collected at a mean GA of 37w3d ± 3w0d and mean postnatal age of 48.6 ± 15 days (Table 3). Comparator neonates had follow-up labs collected at

Figure 1. Neutrophil count trend for neutropenic neonates. (a) Darbepoietin alfa–treated neonates from drug administration until discharge (n = 12). (b) Comparator neonates from baseline labs until discharge (n = 11).

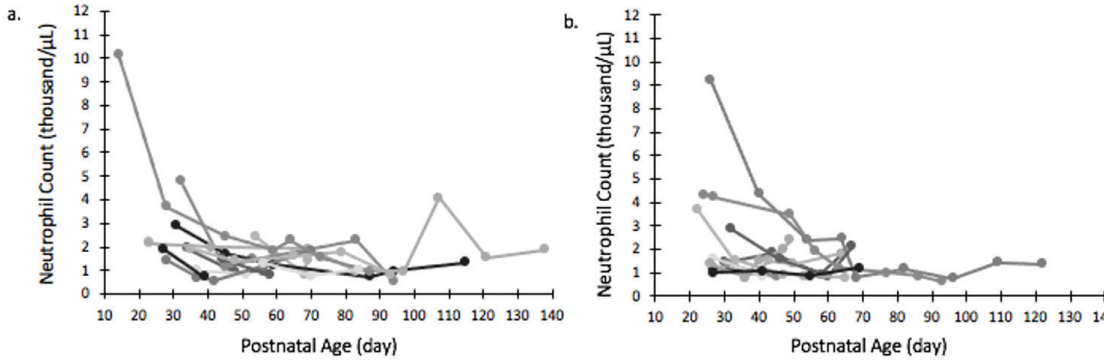
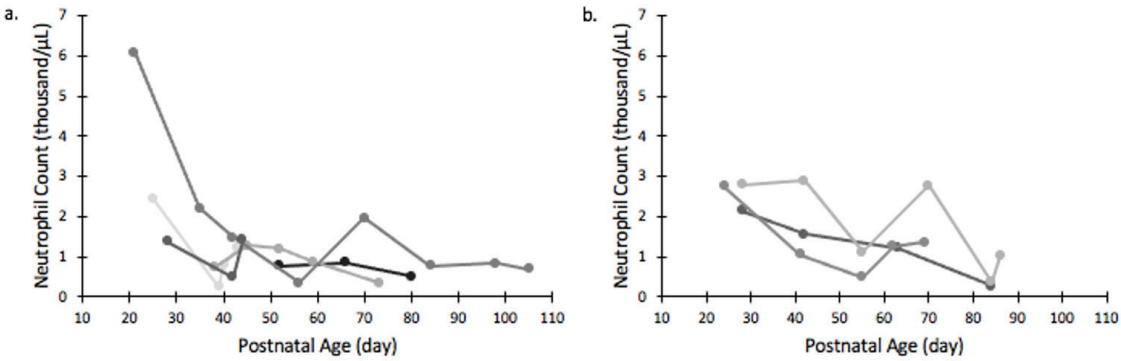


Figure 2. Neutrophil count trend for severely neutropenic neonates. (a) Darbepoietin alfa–treated neonates from drug administration until discharge (n = 5). (b) Comparator neonates from baseline labs until discharge (n = 3).



a mean GA of 38w2d ± 7w5d and a mean postnatal age of 43.3 ± 6.3 days. The postnatal age for follow-up lab collection was significantly different (p = 0.03). At follow-up labs, darbe-treated neonates had significantly lower neutrophil percent (18% [IQR, 4–67] vs 22% [IQR, 8–47]; p = 0.01) and ANC (1400/µL [IQR, 0.3–13] vs 1900/µL [IQR, 0.8–5.8]; p = 0.03). Darbepoietin alfa–treated neonates also had significantly lower platelet counts (279.5 ± 99.4 vs 396.4 ± 121.1 thousand/µL; p < 0.01).

Primary Outcome. There was no difference in the rate of occurrence of neutropenia between darbe-treated neonates and comparator neonates (Table 4). Twelve darbe-treated neonates (26.7%) versus 11 comparator neonates (24.4%) experienced neutropenia, without severe neutropenia (p > 0.99).

Secondary Outcomes. There was no difference in the rate of occurrence of severe neutropenia between darbe-treated neonates and comparator neonates (Table 4). Severe neutropenia occurred in 5 darbe-treated neonates (11.1%) and 3 comparator neonates (6.7%; p = 0.70).

Neutropenia resolved in 3 darbe-treated neonates (20%) and 5 comparator neonates (31.3%; p = 0.69). If neutropenia resolved after the neonate was discharged it was not recorded. Figure 1 shows the ANC trend for neutropenic neonates from baseline lab collection until discharge. Severe neutropenia resolved in 3 darbe-treated neonates (60%) and 2 comparator neonates (66.7%; p > 0.99). If severe neutropenia resolved after the neonate discharged it was not recorded. Figure 2 shows the neutrophil count trend for severely neutropenic neonates from baseline labs until discharge.

Discussion

In this retrospective chart review neonates treated with short-term darbe did not experience higher rates of neutropenia or severe neutropenia compared with a randomly selected comparator group of neonates not administered the drug. Additionally, there was also no difference in the rates of resolution of neutropenia or severe neutropenia. Interestingly, although there was no observed difference in the rate of occurrence

of neutropenia or severe neutropenia, darbe-treated neonates vs comparator neonates had significantly lower ANC and platelet count at follow-up labs immediately after drug administration.

In this study, both darbe-treated neonates and comparator neonates experienced neutropenia at similar rates of occurrence, 26.7% and 24.4%, respectively. Darbepoietin alfa–treated neonates experienced neutropenia at a postnatal age of 69.6 days, which resolved after 28.3 ± 3.7 days. Comparator neonates experienced neutropenia at a postnatal age of 56.9 days, which resolved after 17 ± 14 days. Although neutropenia occurs in roughly 8% of all neonates sometime during their NICU stay, most neutropenic episodes are early onset and occur in the first week of life and resolve within 5 to 7 days.[1] In a study of 225 neonates by Omar et al,[7] the incidence of late-onset neutropenia in very low birth weight neonates was 10% and occurred at 3 to 10 weeks of life with a duration of 1 to 3 weeks. Similarly to Omar et al, both darbe-treated neonates and comparator neonates experienced late-onset neutropenia with extended durations. However, in this study the rate of occurrence of late-onset neutropenia was much higher than that reported by Omar et al. The increased rate of neutropenia and the fact that both groups of neonates experienced neutropenia in this study are most likely due to the much smaller sample size compared with that of Omar et al. Additionally, the rate, onset, and duration of neutropenia observed in this study may be specific to the UWMC NICU patient population, leading to the differences in our characterization of neutropenia compared with prior literature.

Although there was no difference in the rates of occurrence of neutropenia or severe neutropenia between the 2 groups, it is still of interest that overall darbe-treated neonates had a significant decrease in ANC after drug administration at follow-up labs. Although this is one of the few studies to demonstrate a decline in neutrophil count after darbe administration, Halperin et al[9] reported a similar ANC decline in neonates immediately after administration of rHuEpo. All 7 infants in the Halperin et al study experienced an ANC of <1 thousand/μL, whereas 5 infants experienced an ANC of <500/μL. A similar decline in neutrophil count after rHuEpo administration was also exhibited by Christensen et al[11] and Ohls and Christensen.[14] The results of this study along with prior literature add to the thought that an upregulation of erythropoiesis may lead to a subsequent downregulation of granulopoiesis and a transient decline in neutrophil count.[7,8] As this study observed, a downregulation of granulopoiesis may be a class effect of ESAs that is short term and does not necessarily lead to neutropenia. However, further investigation into the true incidence and clinical significance of darbe-induced neutrophil decline needs to be performed.

In addition to the immediate decrease in neutrophil count after drug administration, darbe-treated neonates also experienced a significant decline in platelet count at follow-up labs. Compared with this study, other neonatal studies show conflicting effects on platelet count after ESA administration.[12,15,16] Although the upregulation of erythropoiesis by ESAs is thought to downregulate granulopoiesis, there is scarce evidence to show ESAs downregulate thrombopoiesis. Additional research regarding the effect of darbe on platelet count and any clinical significance should be considered in order to better characterize the effects of this drug in preterm neonates.

There are limitations to this study that should be considered. Despite reviewing neonates for inclusion in the study during a 3-year period, the limited use of darbepoetin at the UWMC NICU only provided a small sample size. This study was a retrospective chart review, leading to challenges in laboratory collection and thorough assessment for neutropenia resolution after discharge. In addition, although the exclusion criteria attempted to control for confounding factors associated with preterm neutropenia, not all factors could be accounted for. Factors associated with preterm neutropenia not evaluated in this study include, but are not limited to, neonatal intrauterine growth restriction, neonatal asphyxiation at birth, and inherited metabolic errors. This study attempted to address idiopathic neutropenia as a confounding variable through the use of a randomly selected comparator group. Additionally, although there was no difference between groups in neonatal use of corticosteroids, GA of administration, or duration of use, the effect of corticosteroids on neutrophil count and neutropenia was not assessed. Corticosteroids are widely known to increase white blood cell count but more specifically neutrophils, so it would be challenging to say if corticosteroid use affected the rate of neutropenia in this study. Furthermore, based on the UWMC NICU darbe protocol and inclusion criteria neonates received exactly 2 doses of darbe. It is not possible to say if long-term use of darbe or additional doses would have affected neutropenia outcomes. Ohls et al[12] administered neonates epoetin alfa and darbe until a gestational age of 36 weeks and reported no incidences of neutropenia (ANC ≤500/μL). Although it is in contrast to the study by Ohls et al, this study followed neonates past 36 weeks, at which time point neutropenia and severe neutropenia occurred. Lastly, based on the purpose of this study, the safety outcomes of darbe-induced neutropenia, such as infection or sepsis, were not assessed. Although this study found no difference in mortality between the 2 groups and darbe has been used safely at UWMC since 2013, further investigations into the clinical effects of darbe on neutrophil count and safety outcomes must be considered.

There are strengths of the study that should be highlighted. Although erythropoietin has been extensively studied in preterm neonates, to our knowledge this is one of the few studies assessing short-term darbepoetin

alfa use in preterm neonates. Even more so, this is one of the few retrospective studies that will add to the less characterized effects of darbe on neutrophil count. Additional research into the effects of darbe on neonatal neutrophil count and platelet count is recommended.

Conclusion

In conclusion, short-term use of darbe did not lead to higher rates of occurrence of neutropenia or severe neutropenia in preterm neonates treated for anemia of prematurity. Additionally, darbepoetin alfa did not lead to decreased rates of resolution of neutropenia or severe neutropenia. Although neonates administered darbepoetin alfa experienced transient declines in neutrophil count and platelet count immediately after drug administration, additional studies regarding the clinical significance of these findings should be performed. Darbepoetin alfa continues to be used safely and effectively for the treatment of anemia of prematurity at the UWMC NICU.

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