A Comparison of Once- and Thrice-Weekly Erythropoietin Dosing for the Treatment of Anaemia of Prematurity

Dear Editor,

Globally, 1 in 10 infants are born prematurely according to reports by the World Health Organisation (WHO).[1] Anaemia of prematurity (AOP) is a common complication in preterm very low birth weight (VLBW) infants. The need for multiple blood transfusions may expose these infants to increased risk of infections and related adverse reactions.

The Cochrane Systematic Review surmised that erythropoietin (EPO) given later in the postnatal period to stable growing preterm infants is effective therapy for AOP in reducing the number of blood transfusions.[2] However, significant variations were noted in the EPO dosing regimen and the duration of treatment in these studies.[3,4] EPO at a dose of 250 IU/kg thrice-weekly for 6 weeks is a commonly practised regimen based on previous larger trials and is the current treatment protocol for infants with AOP in our neonatal intensive care unit (NICU).

There were several recent studies reporting comparable effectiveness between once- and thrice-weekly EPO dosing with no significant differences in the frequency of adverse events.[5,6] Simplification of the dosing regimen is attractive and may help improve in the compliance with therapy with the reduction in the number of injections, therefore reducing the frequency of pain inflicted, and decreased hospital revisits, staff workload and risk of medication errors. Aiming towards service improvement, we studied whether once-weekly dosing of EPO was comparable to thrice-weekly dosing in treating AOP.

This is a non-randomised comparative study that used a non-inferiority analysis technique. This study was approved by the Universiti Kebangsaan Malaysia (UKM) Research Ethics Committee and registered in the Malaysian National Medical Research Trial Registry (NMRR-13-866-17373). Preterm infants included in this study were of gestational ages of <33 weeks; birthweight <1500 g; tolerating full enteral feeding of at least120 mL/kg/day and with haemoglobin (Hb) levels of <12 g/dL. Parental informed consent was obtained before enrolling the infants who met these study inclusion criteria. The determination of the non-inferiority margin was done based on the principle of the 95-95 approach.[7,8] Based on only one available study as reference,[9] the margin of non-inferiority was calculated to be -0.125 g/dL. The sample size thus comprised 35 patients per group by using -12.5% as the margin of non-inferiority, significance level of 0.05 and 0.8 as the power of the study.[10]

We compared 2 back-to-back periods of therapeutic intervention. A historical cohort group comprised infants receiving EPO at the conventional dose of 250 IU/kg thrice-weekly between October 2012 and March 2013. Several more infants were prospectively enrolled to receive this regimen when this study was commenced to make up the numbers required in this arm as determined by the sample size calculation followed by the comparison treatment group comprising prospectively enrolled infants who were given the new alternative regimen of 750 IU/kg/dose once-weekly (similar cumulative dose of 750 IU/kg weekly for both groups). Treatment with subcutaneous EPO with either of the assigned dosing regimen was administered for a period of 6 weeks as per unit protocol. All patients received Erythropoietin-beta (Recormon®) (Roche Diagnostics GMBH, Germany). In addition, patients in both groups received oral ferrous ammonium citrate at a treatment dose of 6 mg/kg/day upon initiation of EPO therapy. The Hb change from pre-therapy baseline level was the primary outcome measure. For the intention-to-treat (ITT) analysis, all infants who fulfilled the selection criteria were included, whereby any missing Hb readings were adjusted by the "Last Observation Carried Forward" method. The changes in absolute reticulocyte count (ARC) and serum ferritin levels were monitored following the commencement of EPO before the subjects were discharged home. Data were collected weekly until the first 2 months of post-discharge from the NICU.

A total of 68 VLBW infants had sufficiently available data for comparative analysis; n = 35 in the control group (conventional thrice-weekly regimen) and n = 33 in the treatment group (alternative once-weekly regimen), as shown in Figure 1. The characteristics of infants before EPO therapy were comparable except for a significantly lower pre-treatment Hb in the once-weekly than thrice-weekly (10.5 ± 1.06 g/dL vs 11.5 ± 1.76 g/dL, respectively; P = 0.01) group (Table 1). The mean corrected gestational age when EPO was commenced was similar, 32.3 ± 2.3 weeks vs 32.6 ± 2.6 weeks (P = 0.64), which translated to an average postnatal age of 25.1 ± 6.5 days vs 23.3 ± 10.4 days in the once-weekly and thrice-weekly group, respectively. There was no difference in the respiratory status of the infants in

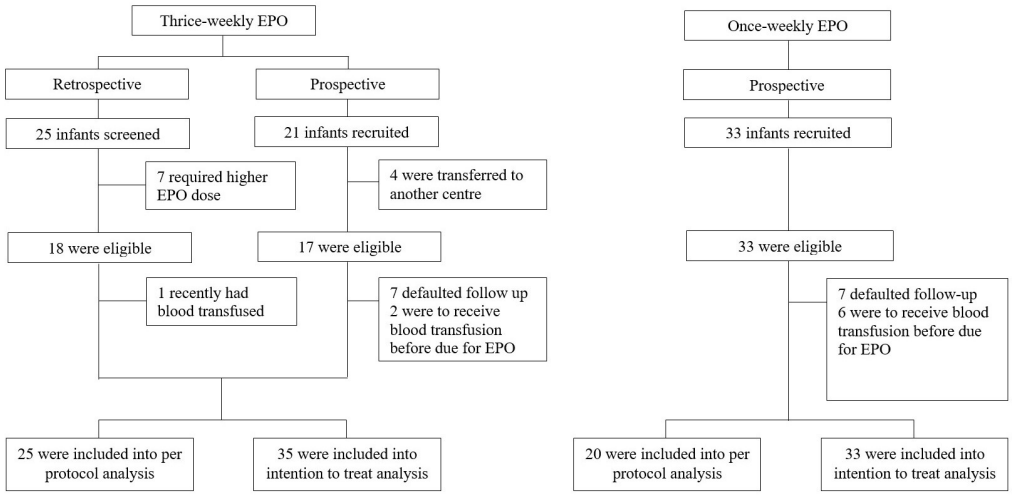

Fig. 1. Charts showing enrolment and outcomes.

Table 1. Subject Characteristics and Treatment Outcomes

Variables	**Thrice-Weekly EPO n = 35**	**Once-Weekly EPO n = 33**	***P* Value**
Gender, male, n (%)	16 (45.7)	15 (45.5)	0.90
Gestational age, weeks	29.3 (2.31)	28.7 (2.14)	0.27
Corrected gestational age at the commencement of EPO, weeks	32.6 (2.6)	32.3 (2.3)	0.64
Birth weight, kg	1.2 (0.27)	1.1 (0.26)	0.06
Body weight at the commencement of EPO, kg	1.4 (0.31)	1.3 (0.32)	0.31
Hb level, g/dL	11.5 (1.76)	10.5 (1.06)	0.01*
Serum ferritin at entry, µmol/L	370 (280)	415 (445)	0.71
Body weight at 5th week, kg	2.2 (0.50)	2.0 (0.49)	0.02*
†Hb level at 5th week, g/dL	11.0 (1.71)	10.0 (1.73)	0.02*
†Hb increment from baseline by 5th week, %	-2.1 (17.3)	-4.3 (14.7)	0.57
†ARC at 5th week, $\times 10^9$/L	247 (109)	174 (77)	<0.01*
†Serum ferritin at 5th week of EPO, µmol/L	169 (117)	170 (119)	0.96
Mechanical ventilator support, median [IQR] (day)	0.0 [0.00 – 0.00]	0.0 [0.00 – 0.00]	0.08
CPAP support, median [IQR] (day)	5.0 [0.00 – 27.00]	1.0 [0.0 – 17.88]	0.30
Highest FiO_2, median [IQR] (%)	21.0 [21.0 – 25.0]	21.0 [21.0 – 25.0]	0.92
Infants requiring blood transfusion, n (%)	3 (8.6)	6 (18.2)	0.30‡
Pre-transfusion Hb level, g/dL	8.3 (0.35)	8.4 (0.65)	0.75
Cumulative EPO dose received prior to blood transfusion, IU/kg	1500.0 (1561.25)	2125.0 (876.78)	0.20
IVH and resolution on cranial ultrasound, n (%)	23 (88.5)	18 (100.0)	0.12§
Chronic lung disease, n (%)	8 (22.9)	5 (15.6)	0.45‖
Retinopathy of prematurity, n (%)	2 (5.9)	3 (10.0)	0.66¶

Comparisons between groups are on intention-to-treat basis; Values are expressed as mean (SD) unless specified otherwise.
ARC: Absolute reticulocyte count; CPAP: Continuous positive airway pressure; EPO: Erythropoietin; FiO_2: Fractional inspired oxygen; Hb: Haemoglobin; IVH: Intraventricular haemorrhage
*Statistically significant at $P < 0.05$.
†Missing values handled using the "Last Observation Carried Forward" method. Refer to Figure 2 for the available data for each variable and time-point.
‡RR (95% CI) = 0.47 (0.13-1.73).
§RR (95% CI) = 0.89 (0.77-1.02).
‖RR (95% CI) = 1.46 (0.53-4.01).
¶RR (95% CI) = 0.59 (0.11-3.30).

both groups at and after EPO treatment. Specifically, the duration of mechanical ventilation support, continuous positive airway pressure (CPAP) therapy and the highest FiO_2 required were not different between the groups. These implied that the 2 groups of infants were comparable in terms of baseline characteristics. The severity of intraventricular haemorrhage (IVH) and rates of resolution were similar between groups.

There was no significant difference in the percentage of Hb increment from pre-treatment baseline between the groups (-4.3 ± 14.7 % vs -2.1 ± 17.3 %; $P = 0.57$). The mean in ARC peaked after 3 weeks of EPO treatment in both groups (Fig. 2) and it was significantly higher in the thrice-weekly ($247 \pm 109 \times 10^9$/L) than once-weekly ($174 \pm 77 \times 10^9$/L) group with $P < 0.01$ when analysed under ITT (Table 1). However, there were many missing data after the initial 4-week period and based on per protocol (PP) analysis, mean ARC was not significantly different between EPO once- and thrice-weekly at the 5th week of treatment ($196 \pm 90 \times 10^9$/L vs $253 \pm 80 \times 10^9$/L, respectively; $P = 0.20$). There was also no significant difference in serum ferritin of infants who received once-weekly EPO compared to those who received the thrice-weekly regimen (170 ± 119 μmol/L vs 169 ± 117 μmol/L; $P = 0.96$) (Table 1).

In clinical outcomes, the increment in weight was significantly lower resulting in a lower mean body weight in the once-weekly group (2.0 ± 0.49 kg) as compared to the thrice-weekly group (2.2 ± 0.50 kg) ($P = 0.02$). The need for blood transfusion when on EPO, although was twice more frequent in the once-weekly group, was not statistically significant (RR = 0.47, 95% CI [0.13 to 1.73]; $P = 0.30$). In all these infants, blood transfusion was administered after 3 weeks of EPO therapy (mean cumulative dose of 2125 ± 877 IU/kg) and when the mean Hb had decreased by 2.4 ± 1.13 g/dL. Hence, there was no significant difference between the groups and the indications were in abiding with the unit transfusion guideline which involves transfusing growing VLBW infants only when the Hb level is below 8 g/dL, or higher if the infant is symptomatic with increased oxygen supplementation or elevated baseline heart rate and poor weight gain. The trend in weekly changes of Hb and ARC for the 2 groups are shown in Figure 2.

Although several studies have associated exogenous EPO therapy with the incidence and severity of retinopathy of prematurity (ROP), a recent meta-analysis indicated insufficient evidence for such a relationship.[11-14] Our study did not show a significant difference in the ROP rates between groups and these cases were all non-threshold diseases. The incidence of ROP in our unit has remained low despite an active EPO use policy for AOP when benchmarked against most of the centres in the Vermont-Oxford Neonatal Network.

Subcutaneous EPO has a relatively short half-life, ranging from10 to 22 hours at a steady state in premature infants.[15]As such, the pharmacokinetics of EPO in preterm infants may necessitate a more frequent dosing. Our study which showed that once-weekly EPO did not result in a more rapid rise in the reticulocyte count compared to the thrice-weekly is supportive of a more frequent dosing. We speculate that a more constant steady state EPO receptor saturation or stimulation may be required for an increased and more sustained bone marrow response for a Hb rise. Higher erythropoietic activity with the thrice-weekly dosing regimen has also been reported in previous studies.[5,6] There was no significant difference in ferritin level between the groups, similar to other reports.[5,6] In comparing the 2 dosing regimen, our study showed that EPO dosing of 750 IU/kg once-weekly was inferior to EPO 250 IU/kg thrice-

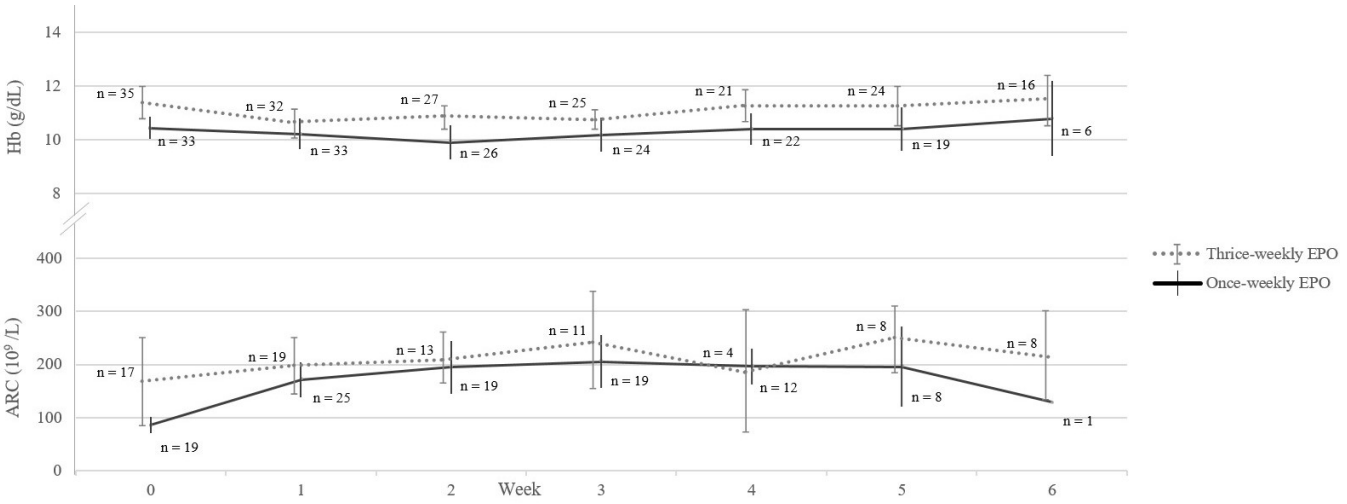

Fig. 2. Graphs showing weekly changes of haematological parameters for thrice-weekly versus once-weekly erythropoietin dosing.

weekly, based on the crossing below of the predetermined non-inferiority margin of -0.125 and the lower bounds of the 95% CI for both PP (d = -0.24; lower bound 95% CI = -1.27) as well as ITT analyses (d = -0.05; lower bound 95% CI = -0.93).

There were several limitations in this study such as phlebotomy blood losses that were not recorded, missing data due to patient lost to follow-up after discharge and the study design was not a true randomised trial, with infants recruited from 2 different periods and they were not matched in characteristics. These may be improved together with the inclusion of pain scores or local site reactions relating to the dosing frequency in future larger controlled trials in determining the optimal use and dosage of EPO in the treatment of AOP.

Acknowledgements

The authors would like to thank Professor Dr Shamsul Azhar Shah for his valuable statistical advice, as well as the nursing staff from the NICU, UKM Medical Centre for their assistance. This was a quality assurance based clinical study, assigned the UKM project code, NF-007- 2013, and was not funded by any specific research grant.

REFERENCES

1. World Health Organization. Preterm birth. Available at: http://www.who.int/mediacentre/factsheets/fs363/en/. Accessed on 13 March 2016.
2. Aher SM, Ohlsson A. Late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2012 Sep 12;(9):CD004868.
3. Rocha VLL, Benjamin AC, Procianoy RS. The effect of recombinant human erythropoietin on the treatment of anemia of prematurity. J Pediatr 2001;77:75-83.
4. Kotto-Kome AC, Garcia MG, Calhoun DA, Christensen RD. Effect of beginning recombinant erythropoietin treatment within the first week of life among very-low-birth-weight neonates, on "early" and "late" erythrocyte transfusions: a meta-analysis. J Perinatol 2004;24:24-9.
5. Ohls RK, Roohi M, Peceny HM, Schrader R, Bierer R. A randomized, masked study of weekly erythropoietin dosing in preterm infants. J Pediatr 2012;160:790-5.
6. Vazquez-Lopez MA, Llamas MA, Galera R, Sanchez AR, Lendinez F, Gonzalez-Ripoll M, et al. Comparison between one and three doses a week of recombinant erythropoietin in very low birth weight infants. J Perinatol 2011;31:118-24.
7. Schumi J, Wittes JT. Through the looking glass: understanding non-inferiority. Trials 2011;12:106.
8. Rothmann MD, Tsou HH. On non-inferiority analysis based on delta-method confidence intervals. J Biopharm Stat 2003;13:565-83.
9. Maier RF, Obladen M, Scigalla P, Linderkamp O, Duc G, Hieronimi G, et al. The effect of epoetin beta (recombinant human erythropoietin) on the need for transfusion in very-low-birth-weight infants. N Engl J Med 1994;330:1173-8.
10. Zhong B. How to calculate sample size in randomized controlled trial? J Thorac Dis 2009;1:51-4.
11. Brown MS, Baron AE, France EK, Hamman RF. Association between higher cumulative doses of recombinant erythropoietin and risk for retinopathy of prematurity. J AAPOS 2006;10:143-9.
12. Aher SM, Ohlsson A. Early versus late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database of Syst Rev 2012;10:CD004865.pub3.
13. Suk KK, Dunbar JA, Liu A, Daher NS, Leng CK, Leng JK, et al. Human recombinant erythropoietin and the incidence of retinopathy of prematurity: a multiple regression model. J AAPOS 2008;12:233-8.
14. Xu XJ, Huang HY, Chen HL. Erythropoietin and retinopathy of prematurity: a meta-analysis. Eur J Pediatr 2014;173:1355-64.
15. Ohls RK, Veerman MW, Christensen RDJ. Pharmacokinetics and effectiveness of recombinant erythropoietin administered to preterm infants by continuous infusion in total parenteral nutrition solution. Pediatr1996;128:518-23.

Chuan Poh Lim, [1]*MPharm*, Adyani Md-Redzuan, [2]*PhD*, Yin Key Lai, [3]*MPharm*, Boekhtiar Borhanuddin, [4]*MCHSc*, Fook Choe Cheah, [5]*MD, PhD*

[1]Department of Pharmacy, Singapore General Hospital, Singapore
[2]Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Malaysia
[3]Department of Pharmacy, Universiti Kebangsaan Malaysia Medical Centre, Malaysia
[4]Biostatistics Unit, The Malaysian Cohort Project, Universiti Kebangsaan Malaysia Molecular Biology Institute, Malaysia
[5]Department of Paediatrics, Universiti Kebangsaan Malaysia Medical Centre, Malaysia

Address for Correspondence: Prof Cheah Fook Choe, Department of Paediatrics, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, 56000 Cheras, Kuala Lumpur, Malaysia.
Email: cheahfc@ppukm.ukm.edu.my