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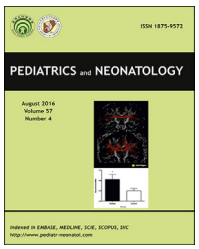

ORIGINAL ARTICLE

Determination of tissue hypoxia by physicochemical approach in premature anemia

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Key Words
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tissue hypoxia

Background: Anemia is a common problem in premature infants and its most rapid and effective therapy is erythrocyte transfusion. However, owing to inherent risks of transfusion in this population, transfusions should be administered only when adequate oxygen delivery to tissues is impaired. The aim of this study was to determine tissue acid levels using Stewart method in an attempt to evaluate the tissue oxygenation level and thereby the accuracy of transfusion timing.
Methods: This study included 47 infants delivered at gestational age below 34 weeks who required erythrocyte transfusion for premature anemia. Strong ion gap (SIG), unmeasurable anions (UMA), tissue acid levels (TA), and Cl/Na ratios were calculated before and after transfusion.
Results: The mean birth weight and gestational age of the study population were 1210 $\pm$ 365 g and 29.2 $\pm$ 2.7 weeks, respectively. Tissue acid levels were increased (TA $\geq$ 4) and tissue hypoxia developed in 10 (16.6%) of 60 erythrocyte transfusions administered according to the restrictive transfusion approach. The patients were divided into two groups according to tissue acid levels as low ($<$4) and high ($\geq$4) tissue acid groups. The group with tissue hypoxia (TA $\geq$ 4) had significantly higher UMA levels but a significantly lower Cl/Na ratio; and UMA levels decreased and Cl/Na ratio increased after transfusion in this group. Tissue hypoxia secondary to anemia was shown to be improved by erythrocyte transfusion.
Conclusion: The results of the present study suggest that the determination of the level of tissue hypoxia by the Stewart approach may be an alternative to restrictive transfusion guidelines for timing of transfusion in premature anemia. It also showed that a low Cl/Na ratio can be used as a simple marker of tissue hypoxia.

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1. Introduction

Anemia is a common problem in premature infants and its most rapid and effective therapy is erythrocyte transfusion. However, owing to the inherent risks of transfusion in this population, many centers have introduced more restrictive policies. Erythrocyte transfusion is performed when the level of anemia becomes symptomatic or is thought to compromise adequate oxygen delivery to tissues. Nevertheless, diagnosis of tissue hypoxia in newborns is difficult and controversial. The aim of this study was to determine tissue acid levels (TA) by the Stewart method before and after transfusion in an attempt to evaluate the state of tissue oxygenation and therefore the adequacy of transfusion timing in preterm infants.

The Stewart physiochemical method was described in 1981 and, unlike the Henderson–Hasselbach method it is based on the theory that HCO3 does not determine plasma pH.[1–4] Independent variables responsible for plasma pH are arterial partial carbon dioxide pressure (PaCO2), strong ion difference (SID), and nonvolatile weak acids (Atots). SID is the difference between strong cations and strong anions dissolved in plasma, and calculated with the formula SID = (Na + K + Ca + Mg) − (Cl + lactate). Atots are the sum of bound or dissolved acids in plasma; it consists of albumin and phosphate (P) concentrations and it is equal to anion gap under normal conditions. SID is elevated in pathological conditions where unmeasurable anions (UMA) such as lactate, ketoacids, and sulfate are increased. In that case, effective SID (SIDe) is calculated with the formula SIDe = HCO3 + (0.28 × Albumin) + (1.8 × P). The difference between SID and SIDe is equal to strong ion gap (SIG) and reflects UMA. TA are equal to the sum of lactate and UMA levels.

The Stewart method accurately quantifies the individual components of acid–base balance and allows the clinician to understand the pathogenesis of acid–base alterations in critically ill patients.[3,5–8] Respiratory disorders are induced as a consequence of a change in PaCO2, whereas metabolic disorders are always due to an alteration in either SID or Atot. When SID narrows, either by a relative decrease in cations (e.g., hyponatremia) or a relative increase in anions (e.g., hyperchloremia), metabolic acidosis develops. A relative increase in cations or a relative decrease in anions widens SID and causes metabolic alkalosis. For example, furosamide causes greater renal loss of Cl than Na, leading to increased SID and metabolic alkalosis. Likewise, increased Atot concentration (e.g., hyperphosphatemia) leads to metabolic acidosis and decreased Atot concentration (e.g., hypoalbuminemia) leads to metabolic alkalosis. In addition, various UMA generated in pathologic conditions can change SID. For example, tissue acids generated in peripheral tissues during hypoxia lead to metabolic acidosis. The potential advantage of the Stewart method is direct quantification of SIG, UMA, and TA.[3,5–8] However, the analysis of acid–base equilibrium by Stewart method requires multiple arithmetic calculations. Cl/Na ratio is a simpler method used to assess the presence of tissue acidosis.[6,8–12] It is based on the hypothesis that, because SIG ions are negatively charged, other plasma anions (Cl and albumin) must fall during tissue acidosis to maintain electroneutrality if the cations (Na and K) remain constant. Therefore, metabolic acidosis and a low Cl/Na ratio (<0.75) indicate SIG elevation, whereas a high Cl/Na ratio (>0.79) indicates acidosis caused by hyperchloremia. A normal Cl/Na ratio (0.75–0.79) in conjunction with metabolic acidosis suggests mixed type metabolic acidosis where hyperchloremia and SIG increases occur simultaneously.

2. Materials and methods

This study was conducted at Başkent University, Faculty of Medicine, Neonatal Intensive Care Unit between February 1, 2010 and July 31, 2012. This study was approved by our University Institutional Review Board (Project no: KA11/124). Forty-seven infants with a gestational age below 34 weeks who needed erythrocyte transfusion for anemia were enrolled. Infants with sepsis, patent ductus arteriosus, necrotizing enterocolitis, or major congenital anomalies were excluded. Erythrocyte transfusions were given according to restrictive transfusion guidelines used in our neonatal intensive care unit (Table 1). Transfusions consisted of packed red blood cells with a storage life of less than 10 days which were passed through leukocyte removal filter and irradiated. Erythrocyte transfusions were administered at a volume of 15 mL/kg and infusions lasted at least 2 hours.

In the present study, blood samples of 2.5 mL were obtained before and 12 hours after erythrocyte transfusion. Samples were analyzed for complete blood count, complete blood chemistry, and blood gas analysis. Concentrations of Na, K, Cl, Mg, and P were measured by an

Table 1 Transfusion guidelines.

Transfusions based upon hemoglobin or hematocrit triggers can be considered for the following clinical settings:
(1) infants connected to a conventional ventilator who require mechanical ventilatory support and have a hematocrit level less than 35%;
(2) infants who do not require mechanical ventilatory support but have a hematocrit level less than 30% and one or more of the following criteria: tachycardia lasting for more than 24 hours (peak heart rate >180 bpm), tachypnea lasting for more than 24 hours (respiratory rate > 60 breaths/min), twofold increase in oxygen requirement in the past 48 hours, metabolic acidosis as evidenced by pH: 7.20, weight increase less than 10 g/kg per day despite being fed on a 120 kcal/kg per day diet in the previous 4 days;
(3) preterm infants who have a hematocrit level less than 30% and required a serious surgical procedure in the past 72 hours;
(4) asymptomatic preterm infants who have a hematocrit level less than 25%.

bpm = beats per minute.

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