



Monitoring of Regional Cerebral Oxygenation after Red Blood Cell Transfusion in the Preterm Infant

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Abstract

Background: Anemia is one of the most frequent complications of prematurity and it compromises the neurological development of the newborn. During hospitalization, more than 80% of premature infants need to be transfused with red blood cells (RBC) as part of the treatment. There are different opinions among experts about the hematocrit (Hct) and hemoglobin (Hb) threshold levels that would determine a transfusion, and this is closely related to the tissue's oxygen delivery. The use of near-infrared spectroscopy (NIRS) provides substantial data on oxygen kinetics, allows for the assessment of the regional O₂ saturation percentage (cerebral and somatic), and assessment regarding the need for RBC transfusion. The aim of the present study was to evaluate the effects of RBC transfusion in preterm cerebral oxygenation.

Method: This retrospective descriptive study included preterm infants from 27 to 35 weeks of gestational age with anemia requiring RBC transfusion, in which the regional cerebral saturation was measured by NIRS.

Results and conclusion: Ten RBC transfusions were studied in 5 patients. It was observed that after RBC transfusions, regional cerebral saturation increased significantly likely due to an increase in the oxygenated Hb level, although cerebral fractional oxygen extraction (FOE) decreased. This result could be related to the increase in oxygen availability after the transfusion procedure or because of a decrease in cerebral blood flow, both being probably transient phenomena. This work has allowed us to get to know the basics of using NIRS technology, and to highlight the role of this new technology in neonatal units.

Keywords: NIRS; Preterm, Red blood cell transfusion

Introduction

In Uruguay, there are about 47,000 births per year, of which approximately 10% are born before 37 weeks of gestational age [1]. Anemia is one of the most frequent complications of prematurity and it compromises the neurological development of the newborn. The factors responsible for anemia of prematurity, and its high RBC transfusion rate are linked to iatrogenic, physiological, and hematopoietic immaturity system factors. It has been stated that the amounts of blood withdrawn from preterm for laboratory testing are the main cause of anemia in this group of patients. All newborns experience a decline in hemoglobin (Hb) concentration during the first week of life.

This decline results from multiple physiological factors as well as additional factors in preterm neonates. Premature infants do not complete the third trimester of gestation and it is at this stage that occurs the highest iron transport through the placenta. On the other hand, at this stage of development erythropoiesis mainly occurs in the liver and in the bone marrow. The liver is less sensitive to anemia in the generation of an erythropoietin response; thus, it will be less intense. All mechanisms such as: rapid growth, multiple blood extractions and inadequate erythropoiesis contribute to anemia and its severity [2].

Moreover, symptoms of anemia are related to deficiency of tissue oxygenation because of a decrease in the oxygen supply. One of the most frequently used treatments for the correction of this deficiency is the RBC transfusion. Despite exposure to various risks related to this treatment, during hospitalization, 80% of preterm infants require RBC transfusion [3]. In addition, the indication of transfusion remains controversial [4], and its adverse effects are still under discussion [5]. However, the Hb and/or hematocrit (Hct) thresholds that determine a decrease in oxygen supply and demand by the tissues, mainly at brain level have not been systematically evaluated.

This is because the metabolic demands of oxygen vary in the different clinical situations, as well as in the different stages of postnatal development, and among individuals. Studies comparing restrictive versus liberal RBC transfusion which have been implemented have not yet demonstrated superiority of one type of criterion against the other, especially in neurological development [6-8]. Moreover, it has been shown that having an institutional policy for RBC transfusion and having a methodology to implement it reduces the number of RBC transfusions [9,10]. Therefore, the effort to find elements that collaborate in the development of an

institutional policy plays a key role in the optimization of the use of RBC transfusion, which is a critical concept for guiding our work.

The use of NIRS provides substantial data on the kinetics of oxygen at the brain and it reflects the physiological variability of each newborn. The NIRS allows us the assessment of the percentage of oxygenated Hb in the brain in relation to the total Hb, of which 70% corresponds to the venous bed, by measuring the regional brain or somatic O₂ saturation (rcSO₂ and rsSO₂ respectively). This non-invasive monitoring technology allows us to better understand cerebral oxygenation by means of calculating FOE which represents the balance between the amount of O₂ delivery and extraction. FOE gives us more information about cerebral O₂ metabolism. It also indirectly allows us the assessment of cerebral perfusion because rcSO₂ depends on the blood flow of the monitored region.

NIRS is a technology that helps determining if in the course of anemia there is a decrease in the O₂ delivery to the tissues, mainly to the brain, since it is one of the most vulnerable and sensitive organ in the face of increases and decreases of O₂ concentration [5]. Thus, this work aimed to study the variation of regional brain oxygenation in preterms that required RBC transfusion.

Materials and Methods

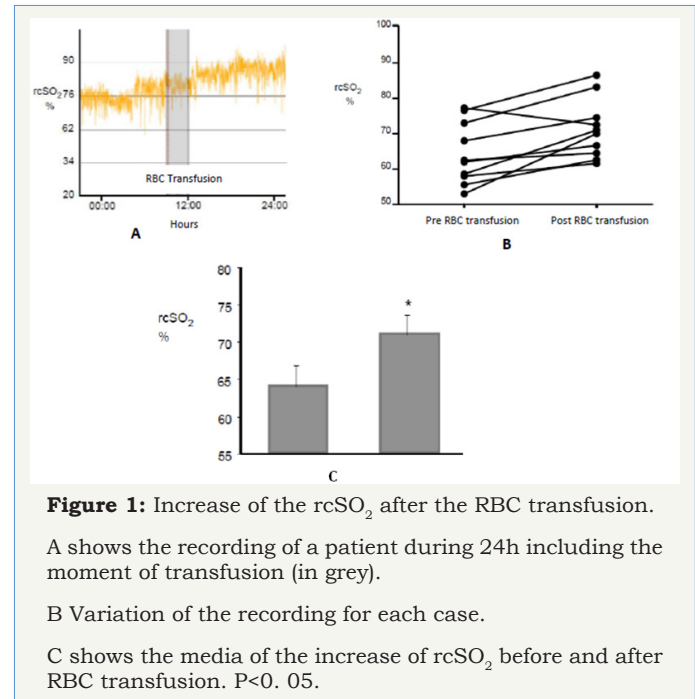
This work was carried out after the approval of the Bioethics Committee of Hospital de Clínicas of the Facultad de Medicina, Universidad de la República. A retrospective descriptive study was performed. This study enrolled patients admitted to the intensive care unit of the Neonatology Department of the Hospital de Clínicas from January 1st, 2014 to October 31st, 2016. The inclusion criteria were: newborns with anemia of prematurity requiring RBC transfusion with a gestational age, at the time of RBC transfusion, between 27 and 35 completed weeks. The indication of RBC transfusion was according to the following criteria: Ventilated patients with FiO₂ requirement >0.4 and an Hct ≤30%; Patients ventilated with a FiO₂ requirement <0.4 and an Hct ≤25%; Patients with supplemental O₂ requirement, who have an Hct ≤20% and tachycardia for more than 24 hours or decrease in the growth rate or increased O₂ requirements in the last 48 hours [11].

Exclusion criteria for this study were: all patients older than 35 weeks of gestational age, presence of malformations in the central nervous system, previous diagnosis of hemoglobinopathies and patients undergoing a generalized infection. The variables analyzed were rcSO₂, pulse saturation by pulse oximetry (SatO₂), anthropometric data of weight, height, days of life, type of ventilation-in case of mechanical ventilation or noninvasive ventilation- and clinical symptoms of anemia.

Data collection

Data collection was performed by analyzing the medical records of patients enrolled in this study. Patients who met the inclusion criteria were monitored by NIRS (INVOSTM 5100) for a period of 12 hours before the beginning of transfusion up to 12 hours after ending it, as shown in (Figure 1A). With the patient in the supine position a NIRS sensor was placed on the skin of the frontoparietal

side of the neonatal skull, adjusting its position according to the characteristics of the cephalic convexity of each patient, in order to obtain the best signal/noise ratio in the record. With regard to the region where the sensor was positioned, several studies showed that there are no differences in rcSO₂ values between the frontal and temporol-occipital regions [12].



Since the patients were preterm, including some very immature whose skin is fragile, the self-adhesive sector of each sensor was protected with a hydrocolloid compound based on carboxymethylcellulose sodium, pectin and gelatin, to avoid the direct fixation of the sensor to the skin. In this way the sensor was placed on each region with an elastic headband avoiding skin lesions. NIRS enable real time measurement of the rcSO₂ by emitting near infrared light from sensors with LED lights. Each set of sensors has two detectors of different depth range from the LED emitter, allowing the measurement of two depths. The records obtained by this technology are stored in digital format in the database of the unit.

The data of the transfused patients obtained by the NIRS began to register 12hours before the transfusion (t0) and then every 3 hs: t1, t2, t3, etc. The total duration of the registry varied depending on the clinical situation of each patient.

Data analysis

The NIRS recorders were analyzed with the COVIDIEN INVOS Analytics Tool - Version 1.2. program, as well as transferred to a computer and analyzed with OpenOffice, Text Document and Spreadsheet programs.

FOE was calculated using the following equation:

$$FOE = VO_2 / DO_2$$

$$VO_2 \text{ (Consumption of } O_2) = \text{cardiac output} \times (\text{Hb} \times 1.39) \times (\text{sat } aO_2 - \text{sat } vO_2)$$

$$DO_2 \text{ (Delivery of } O_2) = \text{cardiac output} \times (\text{Hb} \times 1.39) \times \text{sat } aO_2$$

Then we can simplify the equation as follows:

$$FOE = \text{peripheral } \text{Sat}O_2 - \text{rcSO}_2$$

Peripheral $\text{Sat}O_2$

Statistical analysis

Descriptive statistics were computed for all variables. Data was summarized as mean \pm SD and Student's Test was performed to determine the statistical significance. It was considered statistically significant $p < 0.05$. Statistical correlation between different variables was performed.

Results

The study included 10 RBC transfusions in 5 patients. The patients' baseline characteristics are given in (Table 1). The mean of the gestational age at birth was 27 weeks (± 2), and birth weight was 985g (± 182 g); the Apgar test at the first minute was 3 to 9 and at 5 minutes from 6 to 10. For this group of patients the Hb at birth was 15.5g/dl (± 1.4) and the Hct was 37.6% (± 6.7). Patients' characteristics at the time of the RBC transfusion are shown in Table 2.

Table 1: Patient Characteristics.

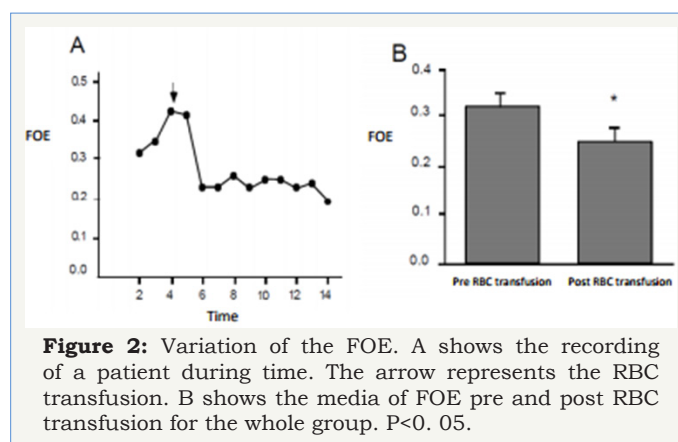
n = 5	
Gestational age (Wk), mean \pm SD	27 \pm 2
Birth weight (g), mean \pm SD	985 \pm 182
Delayed Cord clamping (%)	100
Apgar score at 1minute	3 to 9
Apgar score at 5minutes	6 to 9
Hemoglobin at birth (g/dl), mean \pm SD	12.5 \pm 1.4
Hematocrit at birth (%), mean \pm SD	37.6 \pm 6.7
Sex (%)	30% M 70% F

Table 2: Characteristics of patients at the time of transfusion.

(n= 10)	
Gestational age (Wk), mean \pm SD	30 \pm 6
Weight (g), mean \pm SD (n= 10)	1275 \pm 538
Hematocrit (%), mean \pm SD (n= 9)	25.0 \pm 4.5
Hemoglobin (g/dl), mean \pm SD (n= 9)	8.6 \pm 1.5
FIO ₂ , mean \pm SD (n= 10)	0.5
MV, RF(n=10)	0.1
CPAP, RF (n=10)	0.4

Patients were transfused at 31 (± 6) weeks of gestational age and their weight was 1275g (± 538). The value of Hb at the time

of RBC transfusion was 8.6 g/dl (± 1.6) and Hct 25.0% (± 4.5). Half the patients who participated in this study were receiving oxygen therapy at the time of RBC transfusion. Patients seldom required mechanical ventilation (MV). At the time of RBC transfusion only one patient required MV and 4 patients were receiving continuous positive airway pressure (CPAP). Regarding rcSO₂ records it can be said that no patient presented values lower than 55%; that is, all patients presented rcSO₂ values within the range considered the lowest limit of normality [13-15]. (Figure 1A) shows the recording of a patient during the RBC transfusion where it can be observed the increase of the rcSO₂ after the RBC transfusion. (Figure 1B) shows the variation of the rcSO₂ for each of the cases analyzed. A baseline value of 64% (± 2) and post-transfusion of 71% (± 2) was obtained for the total of the RBC transfusions, these variation was statistically significant ($p < 0.05$) as it is represented in the (Figure 1C).



We observed a significant decrease in the cerebral FOE after the RBC transfusion. (Figure 2A) shows the variation of the cerebral FOE for one of the patients included in our study. This variation after the RBC transfusion was observed for the whole group as it is shown in (Figure 2B). The cerebral FOE decrease from 0.32 to 0.25 after the RBC transfusion, this result is statistically significant, which means that prior to the RBC transfusion the overall brain extraction approached 32%, falling to about 25%.

Discussion

NIRS technology has been used for several years in neonatal units. Continuous real time noninvasive monitoring can provide relevant information about the tissue oxygenation in function of the circulating O₂ [16]. In Uruguay, the first equipment available in intensive care, whether neonatal, pediatric, or adult, entered the Department of Neonatology, University Hospital, Universidad de la República, Montevideo in March 2013, as a donation by a former Professor of the Department, currently Professor Emeritus of the Faculty of Medicine, Universidad de la República, Montevideo, Dr. Martell. From that moment, the Department of Neonatology has had the opportunity to make the learning curve for the proper use of this equipment. One of the main topics that motivated the learning of this new technology was its usefulness in a very frequent pathology such as anemia of prematurity, making its utility indisputable in such situation.

In the whole group of patients, the NIRS has proved to be a non-invasive, useful and reproducible tool with the potential to provide elements that help to indicate a RBC transfusion and it is an excellent tool for monitoring the efficacy of this treatment. Continuous monitoring using NIRS did not interfere with patient care. As for the costs of using this equipment, the fungibles are focused on the consumption of sensors that are costly (approximately US\$ 140 each), not reusable, which is a limitation in patient monitoring. This study confirms statistically significant increase in the $rcSO_2$ after the RBC transfusion. This result agrees with others obtained in other neonatal units.

The increase in post-transfusion $rcSO_2$ is due to an increase in the oxygenated Hb level [15]. Such result is fundamental since it shows that the use of NIRS monitoring allows us the evaluation of the impact of the treatment of anemia by the RBC transfusion in the region studied, allowing to control the quality of the procedure and the expected response to the treatment. This fact shows that the NIRS constitutes an adequate tool to assess the efficacy of the RBC transfusion in the preterm newborn.

The cerebral FOE showed a statistically significant decrease 12 hours after the RBC transfusion. The decrease of the cerebral FOE can be transient after the RBC transfusion and it could be due to the abrupt increase of the concentration of oxygenated Hb. The increase in the availability of O_2 at the cerebral level, with constant O_2 consumption indicates a decrease in the FOE [17]. Some authors have stated that there is a negative correlation between FOE and Hb concentration, as well as an increase in FOE versus a decrease in $PaCO_2$ [18]. These authors have attributed the decrease in FOE, after transfusion, to a transient decrease in cerebral blood flow, in response to the increase in Hb concentration. In this work, the variations of the cerebral blood flow were not directly or indirectly explored, so it is not possible to relate the variation of the FOE to this regional hemodynamic parameter.

The usefulness of having NIRS for monitoring a preterm patient with anemia has been noted in some studies, even suggesting its incorporation as one of the decision criteria for a RBC transfusion in preterms. Recently, it has been shown that infants with initial $rcSO_2$ below 55% have a significant decrease of the apneas, after the transfusion, compared to those patients who have a level of $rcSO_2$ over 55% [14] prior to treatment.

The NIRS is used for the monitoring of different brain and somatic regions of patients, as has been pointed out [13,19] it has increased the number of utilities in different pathologies. A fundamental role of NIRS in the monitoring of the premature newborn is to avoid episodes of hypoxia and hyperoxia since it constitutes a complementary and very sensitive system of noninvasive monitoring of cerebral oxygenation. In these preterm patients avoiding these episodes is relevant since it has been stated that the damage that they produce at brain level has implications in neurodevelopment.

On the other hand, the NIRS has been used for the monitoring of $rcSO_2$ in premature patients with patent ductus arteriosus with

hemodynamic repercussion. In this group of patients it has played a key role in assessing treatment and preventing complications [20]. NIRS has been suggested as a noninvasive tool for detecting low splanchnic perfusion and therapeutic evaluation; its relation to different feeding techniques (bolus or continuous feeding) is currently subject of research [21]. These changes in regional saturation are presumed to be a potential splanchnic perfusion biomarker in preterm infants, useful in limiting local damage and avoiding morbidities.

This work has allowed us to know the basics of using NIRS technology as a useful tool for the monitoring of critical patients, reflecting situations of both pathophysiological stability and dynamic phenomena that need to be further studied, representing a kick for future research. On the other hand, we believe that our results provide evidence about the role of this new technology in the neonatal units, especially in Latin America.

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