SPECIAL ARTICLE

# Transfusion in the Newborn

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**Abstract**

*Transfusion, either with whole blood or blood components is frequently needed in the neonatal intensive care. Certain aspects are very important to consider. Citrated blood is prefered to heparinized blood. Transfusion must be rational, either with whole blood or blood components. Whole blood is only indicated for repletion of blood volume, exchange transfusion and certain cases in which no blood component needed is available. To improve oxygen carrying capacity, to stop bleeding due to coagulation defect, thrombocytopenic bleeding due to depressed platelets production and to counter gram negative septicemia, blood component is indicated to obtain optimal effects with minimal side effects.*

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## Introduction

Recent advances in neonatal intensive care have permitted the survival of extremely premature infants. Especially in critically ill infants with birth weights < 1500 g overcoming the hematologic problems is an essential part of intensive care and blood transfusion is indispensable [1,2].

In the neonatal period there are many hematologic problems, e.g. bleeding, feto-maternal transfusion, hemolytic disease of the newborn, hydrops fetalis, neonatal thrombocytopenia, vitamin K depended factors deficiency, etc. Besides, conditions such as shock, sepsis, respiratory distress syndrome, anemia either physiologic or pathologic and the special characteristics of the neonatal erythrocytes result in inadequate tissue oxygenation. In all the conditions transfusion is considered necessary.

It is estimated that bleeding constitutes 15% of primary causes of neonatal deaths and 4% of secondary causes [2]. Vit K deficiency - due to deficiency in the mother, the low level of vit K in the breast-milk or other unknown mechanisms - commonly occurred in the newborn, especially in the preterm baby, and can result in serious bleeding in the first few days of life (hemorrhagic disease of the newborn).

HbF which constitutes nearly 100% of newborn Hb, has a high oxygen affinity so that oxygen release to the tissue is more difficult than that from adult Hb. Erythrocyte of the neonate is less deformable than that of the adult and therefore is more difficult to pass the narrow capillary lumen. The increased number of erythrocytes, 80% or more of the fetal type, and an elevation of plasma viscosity are factors that cause higher blood viscosity [3]. Serious neurologic and cardiorespiratory problems have been described in the presence of blood hyperviscosity in the neonatal period and transfusion may give benefit.

## Considerations on the blood

There is controversy on the relative merits of citrated and heparinized blood, a controversy which is particularly relevant to pediatrics. Table 1 summarizes the arguments.

In general the balance of advantage at all ages is seen in citrated blood [2,4]. Hypo and hyperglycemia in using citrated blood dextrose give practically no problems, although post transfusion the glucose concentration can reach 20-180 mg/dL [2]. It seems to have no serious effect and if this complication happens it can easily be controlled by insulin glucose.

Sodium concentration in 24-72 hours old citrated blood, which is often used, is of the order of 322 mg/dl or 168 mmol/L. Theoretically after two volume exchange transfusions (90% replacement) with citrated blood containing 168 mmol/L, the sodium concentration in the neonate blood will be 165 mmol/l. Practically the sodium concentration hardly changes during the transfusion, presumably due to the fact that the slowness with which the sodium load is added allows equilibrium effects to occur. Sodium (Na+) concentration increases from 138 ± 6 pre transfusion to 139 ± 4 mmol/L post transfusion.

In citrated blood ionized calcium is bound by citrate, so that massive transfusion has a hypocalcemic effect. But this has no long term effect, even if it causes convulsions, and it can be easily corrected by calcium gluconate. By giving 1 mL of

10% calcium gluconate pr 100 mL of blood exchanged in a series of 21 exchange transfusions, Forfar (1982) reported that babies pre transfusion serum calcium concentration had a mean value of 2.1 and a post transfusion value of 2.3 mmol/L [2].

Some neonatologists believed that the 'ultra fresh' blood maintains the hematocrit longer as fewer senescent cells are transfused. The study of Stevenson et al., (1982) doesn't support this concept. Citrated blood stored for 24-48 hours carries less risk of infection than heparinized blood which has to be used fresh, especially related to CMV infection [2,5]. CMV-seronegative blood is preferred. Saline washing of erythrocytes is not effective in preventing post transfusion CMV in neonates [6]. One must keep in mind that up to 75% of blood donors have CMV [6]. One must keep in mind that up to 75% of blood donors are seropositive, while of the CMV-seronegative neonates who are exposed to at least one seropositive donor or receive more than 50 ml PRC conventionally processed, 24% acquires CMV, and up to 50% of these infants may have severe illness or die [7].

Only few patients that really need whole blood transfusion. In massive transfusion, e.g. exchange transfusion, long stored blood should be avoided, because the immaturity of baby's liver and kidneys should be protected from metabolic load occurring in the blood during long storage. Rapid transfusion with high concentration of patassium, ammonium and acid can disturb normal body function [8].

## Packed red cell transfusion in small amounts

Replacement of blood drawn during the intensive monitoring of pH, acid-base balance, gas analysis etc makes 90% of packed red cell (PRC) transfusion indicated in the neonatal period, although microtests are aplied. The blood loss can reach as much as 12,4 mL per day during the intersive care [9]. As a general rule, transfusion for replacement in indicated if as much as 10% of total blood is drawn, although the condition of the baby is stable and the hemotocrit is enough.

In the neonate with respiratory distress especially when oxygen and/or respiratory aid is needed, top up transfusion is necessary to maintain the Hb > 13 g/dL >40%). It is assumed that the HbA containing transfused blood can supply oxygen to the tissue better during the period of diminishing lung function. On this issue there is still a disagreement, especially concerning the optimal Hb to be reached and the risk, that need to be studied [1].

In neonates with congenital heart disease with cyanosis or heart failure, it seems logical to maintain the Ht at the level >40%. Physiologic decline of Hb concentration produces a fall in blood viscocity that results in decreased pulmonary vascular resistance and increased left-to-right shunting. Increasing Hb to > 13g/dL results in increased pulmonary vascular resistance and decreased both left-to-right shunting and pulmonary blood flow. These changes lowers heart rate and left ventricular stroke volume without compromising oxygen transport to the tissues.

Tachypnea, dyspnea and apnea can be exacerbated by anemia. Although this problem is fairly common, with up to 25% of premature neonates experiencing at least one apneic spell, repeated or prolonged



spells are alarming. Keeping the Ht >30% may dicrease the number of spells, presumably by improvement in oxygen delivery to the central nervous system. RBC transfusions have been shown to alleviate irregular breathing patterns and episodes of bradycardia in anemic preterm infants when the mean Ht is increased from 27% to 36% [1,10] or 41 41.5% ± 1.1% [11].

Some neonatologist consider poor weight gain to be an indication for RBC transfusion, particularly if the Hb is below 10 g/dL and other signs of distress (e.g. tachycardia, respiratory difficulty, weak suck, less vigorous cry and activity) are evident. Infants with lowest Hb concentrations before transfusion exhibit the greatest increase in weight. Some authors failed to demonstrate a value for routine, small-volume red blood cells (RBC) transfusions in stable, growing, premature infants who were otherwise healthy.

Table 1 : *Controversy on the relative merits of citrated and heparinized blood*

| Pro | Contra |
|---|---|
| **Heparinized Blood** | |
| Better preservation of-platelets and granulocytes | Has to be freshly obtained |
| No citrate effect | Anticoagulant effect |
| No acidotic effect | Clots tend to occur |
| No hyper-/hypo-glycemic effect | Higher rate of infection |
| No sodium load | Higher rate of infection |
| | Waste and expense |
| **Pro** | **Contra** |
| **Citrated Blood** | |
| More readily available | Citrate effect |
| No heparin effect | Acidotic effect |
| No clotting | Hyper-/hypo-glycemic-effect |
| No free fatty acid effect | Sodium load |
| Less risk of infection | Platelets and granulocytes less viable |

* Cited from Forfar, 1982 [2]

## Plasma tranfusion

A neonate is capable to synthesize factor II, VII, IX and X, but due to the relative vit K deficiency, the activity of the vit K dependent factors is decreased, so that preterm infants are more endangered. Prothrombin precursor (PIVKA-II) - a protein induced by vitamin K absence or antagonist-II, which is not yet active as coagulation factor - can be detected either in the term or preterm infant [12]. The defective coagulation factor results in bleeding episodes characterized by increasing prothrombin time (PT) and activated partial thromboplastin time (APTT) [13,14]. Hemorrhagic disease of the newborn occurs on the second to fourth day of life, while deficiency of maternal vit K due to administration of anticonsulvants or anticoagulants in the mother causes bleeding in the first 24 hours of life [9,14]. The American Academic of Pediatrics has recommended to give all newborns 0,5 - 1 mg vit K1 at birth. If this procedure is not done and a hemorrhagic disease of the newborn occurs, 1 mg vit K1 administration will stop the bleeding and improve the PT and APTT in 4 to 6 hours. In a premature baby, however, the respons may be suboptimal due to the inability of the liver to synthesize prothrombin complex and in some cases free frozen plasma (FFP) transfusion 20 cc/kg body weight is needed [9]. If the tests are available, low normotest level with negative PIVKA-II is the indication for transfusion [12].

Another indication for plasma transfusion is the neonatal polycythemia-hyperviscosity syndrome. Goldberg et al (1982) and Black et al., (1982) in a long term follow up showed that infants with neonatal hyperviscosity who had received partial plasma exchange transfusion revealed a significantly lower incidence of motor and neurologic abnormalities than who had not, although the difference was not statistically significant [15,16].

## Thrombocytes

Thrombocytopenia in the neonate may be due to disturbances in distribution, production or destruction or combination of the causes. Castle et al., (1986) reported that thrombocytopenia developed in 22% of the infants studied [17]. The potential causes were : 52% had elevated levels of PAIgG (autoimmune thrombocytopenia), 21% had laboratory evidence of disseminated intravascular coagulation (DIC), and 12% had had exchange transfusions. Transient destructive thrombocytopenia develops in a large proportion (22%) of infants admitted to a neonatal intensive care unit, and birth asphyxia is an important risk factor. Mechanical ventilation in newborn infants can induce reduction of platelet count [18]. Platelets destruction may be caused by immune - isoimmune neonatal thrombocytopenia, autoimmune thrombocytopenia - or non immune - sepsis, shock, severe hypoxia, DIC. Sepsis is one of the most common causes of thrombocytopenia in neonates.

Thrombocytopenia bleeding due to decreased production is the most rational for platelets transfusion. Another indication is bleeding due to congenital functional defect of the platelets. If there is no increased destruction of platelets one unit/5 kg body weight will increase the platelets count from 5000 to 10000/ul and this level will decrease gradually in 4 to 6 days. If the platelets count doesn't increase after transfusion of platelets concentrate, increased destruction must be suspected, due to antibody, DIC or sepsis. Every platelets transfusion should be followed by a platelets count the morning after transfused platelets are quickly destroyed. $30.000/mm^3$, all subsequent platelet transfusions should be followed by two platelet counts - the first count is 1 hour after the end of platelet transfusion and the second is the morning after transfusion. If the 1 - and 24 - hours counts indicate lack of response, the patient's theraphy must be changed [19]. In this condition the transfused platelets are quickly destroyed. In neonatal isoimmune thrombocytopenia, in which the destruction of platelets is caused by platelet antibody originated from the mother, transfusion with the mother's platelets is the right choice. Platelets from random donors will be destroyed, because 98% of coagulation has P1A1 antigen, and the antibody in the mother's blood developed by fetal maternal transfusion is usually anti-P1A1.



## Exchange transfusion

In the neonatal period exchange transfusion is needed in hydrops fetalis, septicemia and hyperbilirubinemia. Exchange transfusion in 8 hours after birth has been proved to increase the survival rate of low birth weight infants with septicemia and respiratory distress syndrome [9]. The mechanism is not clear, presumably due to the improvement of the oxygen supply because the transfused HbA has oxygen affinity less than HbF, decreasing bilirubin level, elimination of toxic substances, improvement of coagulation pattern and better carbonic anhydrase of the transfused blood. Where the removal of bilirubin is the primary object, optimal dose is 2 volume exchange (200 ml/kg)/12 hours, which will replace approxymately 90% of the recipient's blood and the rate is 1.8 ml/kg/minute [20]. Exchange transfusion of 100 ml/kg will replace 70% and 50 ml/kg replace 45%.

HDN is the most important indication of exchange transfusion. The goals of transfusion are :

1. To eliminate the sensitized erythrocytes, which form the source of bilirubin if further destroyed by immune mechanism, and replace them with erythrocyte compatible with the mother antibody.
2. To eliminate the bilirubin.
3. To eliminate the antibody which will be attached to the newly produced by the neonate erythropoesis.
4. To improve the anemia.

Indication to perform transfusion is usually based on the level of bilirubin or hemoglobin, although it is difficult to determine at what exact level the transfusion is really imperative. There are cases with indirect bilirubin 20 mg/dL without any signs of kernicterus, on the other hand there are low birth weight infants showing kernicterus at autopsy with bilirubin less than 15 mg/dL. Exchange transfusion is needed by low birth weight infants at lower level of bilirubin than normal infants [21]. The American Academy of Pediatrics has recommended the maximal unconjugated bilirubin level be lowered to 18,0 mg/dL [22]. Roberton (1982) recommended the bilirubin level to perform exchange transfusion as follows (Table 2) [21].

Exchange transfusion should be carried out at levels 2-3 mg less than the above values if the infant is seriously ill with acidemia, hypoxia, septicemia etc. Serial 2-4 hoursly measurements may be necessary as indicated. If the unconjugated bilirubin is rising at more than 0.5-1.0 mg/hr then plans should be made in advance on the basis of the rise of bilirubin to carry out the exchange transfusion

Table 2 : *Recommendation of the bilirubin level to perform exchange transfusion*

| Birth weight | Unconjucated bilirubin |
|---|---|
| - 1250 g | 13 mg/dL |
| 1250 - 1499 g | 15 mg/dL |
| 1500 - 1999 g | 17 mg/dL |
| 2000 - 2499 g | 18 mg/dL |
| 2500 g | 20 mg/dL |

* Cited from Roberton (1982) [21].

before the danger level is reached [21]. Many other criteria have gained acceptance as indications for exchange transfusion in HDN. Cord hemoglobin levels less than 11-13.0 g/dL are felt by some to indicate the necessity for early exchange based on the severity of the hemolytic process at the time of birth. Likewise, a level of serum unconjugated bilirubin in cord blood of highes than 4 mg/dL can be used to predict an extreme course of the hemolytic process [22]. The blood used for Rh HDN is group O rhesus negative, and more than 24 hours but less than 3 days stored to prevent CMV infection and potassium load. In Indonesia where the frequency of Rh(D) negative blood is only 0.023% the Rh HDN incidence is extremely rare [5]. ABO HDN which prevalence is several times than Rh HDN, is fortunately milder. Phototherapy plays an important role in the more slowly developing jaundice associated with ABO incompatibility. It reduces significantly the the need for exchange transfusion, in ABO incomptability but doesn't wholly remove the need of exchange transfusion, i.e. if the level of bilirubin is quickly rising [20]. Another indication of exchange transfusion is neonatal polycytemia [23]. The goal is to reduce Ht to less than 60%. Setzer et al. (1984) demonstrated an effective method for the treatment of severe hyperkalemia in the neonate, using exchange transfusion with blood units prepared by washing stored red blood cells with saline and reconstituted with blood-group specific or compatible fresh frozen plasma [24].

Hydrops fetalis is an indication for partial exchange transfusion. Transfusion can be carried out with fresh PRC, heparinized blood is better and usually needs one volume of exchange transfusion.

## Granulocyte transfusion

Newborns with gram negative bacterial septicemia usually suffered from neutropenia. The band/segment ratio is increased, up to 0.5 or more and in the bone marrow there is a depletion of post mitotic neutrophils, i.e. segment, band and metamyelocytes [1,25,26]. Besides, the granulocytes show decreased chemotaxis and bactericidal respons [23,27]. Postnatal development of chemotaxis proficiency is delayed in preterm infants and the delay is more pronounced in infants born at less than 34 weeks of gestational age [28]. It has been proven that septic cases with better post mitotic neutrophil storage pool in the bone marrow have better prognosis than that with neutrophil depletion. In the later cases antibiotic sometimes failed to induce recovery, and in these cases the survival of cases given granulocyte transfusion is better than those without [9,23,29,30]. Due to the discovery of potent antibiotics recently, it is still a question whether granulocyte, it is still a question whether granulocyte transfusion has still a place in the treatment of septicemia, considering that granulocyte therapy is not without disadvantages. Generally, in the early stage of sepsis, massive and potent antibiotic is considered enough, but if antibiotic therapy fails and especially if neutrophil depletion occurs, granulocyte transfusion is indicated.



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