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Evaluation of a prescreening blood donor program for prevention of perinatal transfusion-acquired cytomegalovirus (CMV) infection[2]

Nasreen A. Bhumbra[2], Patricia Lewandowski[3], Peter Lau[1], Marasri Sererat[1], Malini Satish[3], and George A. Nankervis[1]

[1]American Red Cross Blood Services, Northwest Ohio Region, [2]The Medical College of Ohio, and [3]The Toledo Hospital, Toledo, Ohio, U.S.A.

1 Introduction

Transfusion-acquired CMV infection in premature infants has been associated with significant morbidity and mortality especially if the infant is ill [1, 3, 10]. Pneumonia, hepatitis, thrombocytopenia and anemia associated with CMV infection can compound the problem in infants who may already have pulmonary, hepatic and marrow dysfunction resulting from prematurity per se and/or superimposed diseases. The use of CMV seronegative blood for transfusion in infants has been shown to prevent transfusion acquired CMV infection, but the logistics of obtaining CMV seronegative blood products in a timely manner for neonatal transfusions can be difficult [1, 11]. The purpose of this study was to determine the efficacy of utilizing a prescreened CMV seronegative blood donor program in preventing transfusion acquired CMV infection in premature infants.

2 Materials and methods

2.1 Populations

In northwest Ohio, the Regional Red Cross Blood Center services three intensive care nurseries (ICN) having a total of 85 beds. The total weekly blood needs of the three ICN is twenty units of blood collected in quint blood paks. The site of the study was the ICN at The Toledo Hospital, a level III regional neonatal center with 60 beds and 660 admissions annually. This ICN received 10 units of blood every week for neonatal transfusions during the study period.

2.2 Blood donors

Beginning in April, 1983, selected group 0 blood donors who came to the Blood Center to donate were screened for CMV antibody. The seronegative donors were offered the opportunity to join the "Baby Donor Club", which required a donation at least every four months and the availability to come to the Blood Center when a donation was requested. Re-screening of the donors was performed every four months to validate their seronegative status.

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Curriculum vitae

NASREEN A. BHUMBRA *M.B., B.S., M.D., was born in Varanasi, India in 1947. From 1966 to 1971 she studied medicine at the Institute of Medical Sciences in Varanasi, India. Following pediatric training at the same Institute, she worked as a lecturer at the Christian Medical College and Brown Memorial Hospital in Ludhiana, India. Since 1981 she has been on the staff of the Medical College of Ohio at Toledo. As of 1985 she has been Director of the Clinical Virology Laboratory at the Medical College of Ohio. Her main fields of interest include pediatric infectious diseases and virology.*

2.3 Infants

The subjects of this study were infants with birth weights less than 2000 g who were born between July 1, 1983 and April 30, 1985 to CMV seronegative mothers and received blood transfusions. Proper informed consent was obtained from their parents/guardians. CMV antibody status of the infants was first determined by testing the cord blood. CMV serology of the infant was then repeated at the time of the first transfusion, and eight weeks after the first and last transfusions. Likewise, a urine specimen for CMV culture was also obtained at the time periods stated above.

As an environmental control, thirty term infants with birth weights of less than 2000 g born of CMV seronegative mothers, who resided in the same nursery but did not receive blood transfusions, were followed by urine cultures and serology during the first week of life and eight weeks after discharge.

2.4 Preparation of red blood cells

Blood was collected in a standard quint blood bag with citrate-phosphate-dextrose-adenine (CPDA-1) anticoagulant according to standard technique [2]. The red blood cells prepared from the blood had a hematocrit of 75%. A satellite bag was often shared by several infants each day.

Fresh frozen plasma from group AB donors used for the infants was obtained from random donors whose CMV seroreactivity was not determined.

2.5 Virus isolation

Urine specimens pretreated with antibiotics were cultured for CMV by inoculation into tubes of human embryonic lung fibroblasts [8]. All cultures were examined twice weekly for 4 weeks for the appearance of typical focal CMV induced cytophatic effect (CPE) and verified by specific immunofluorescence when applicable.

2.6 CMV antibody screening

Initially, blood samples were screened for CMV antibody using the Enzyme linked immuno-assay Bio-Enza Bead (Litton Bionetics, Charleston, SC). Beginning in January 1984, the interpretation of the results was modified to consider individual sample color variation. The changes were prompted by a disconcordance of results with parallel testing with the complement fixation (CF) method. The results of evaluation of serology techniques are published elsewhere [9].

Beginning in October 1984, the screening test was performed using the CMV total antibody EIA (Abbott Laboratories, Chicago, Ill.).

3 Results

Five hundred and eighteen group 0 Rh positive and 637 group 0 Rh negative donors were recruited into the "Baby Donor Club" during the study period. However, only 306 (26%) donors were still in the Club at the end of the study. The high attrition rate was due to relocation, loss of contact, or inability to comply with the requisite of availability and/or frequency of blood donation. During the study period, 16 donors seroconverted, a rate of 0.7% per annum.

One hundred twenty-seven of 183 (69%) of the ICN admissions during the study period were recruited into the study. These patients received an average of 145 ml of blood from six donors in eight transfusions. None of the CMV seronegative infants who received CMV seronegative blood or the control newborns showed clinical or laboratory evidence of CMV infection. However, six units of CMV seropositive blood were given to 22 infants during the study period. These units were mistakenly identified as CMV seronegative due to technical errors or poor sensitivity of the test kit in the initial phase of the study. Fifteen of these 22 infants were among the participants of our study. One infant in the study group who was born at 30 weeks gestation with a birth weight of 530 gm died at 4 weeks of age following complications of prematurity, gram negative sepsis, necrotizing enterocolitis and hyaline membrane disease. This infant is not included in the statistical analysis. Two of the remaining 14 infants developed CMV infection as evidenced by seroconversion and viruria after each received 15 ml of CMV seropositive blood. However, six of these 14 infants who also received aliquots of 10 to 24 ml from the same units showed no serological or culture evidence of CMV infection. During the study period, another infant in the study group acquired CMV infection through granulocyte transfusions.

Comparing the infected and the uninfected infants who received CMV seropositive RBC, there was no significant difference with regard to age at

transfusion, the number and amount of CMV seropositive blood transfusions, the number of seropositive donors, or the survival of the infants. However, the birth weight of the uninfected group (946 ± 312 gm) was significantly lower than the infected infants (1337 ± 222 gm) ($p < 0.03$).

In further analysis of the transfusion characteristics of the three infants with transfusion acquired CMV infection, we noted that two premature babies who required transfusions for anemia of immaturity had a single exposure to CMV seropositive RBC. One baby also received 103 ml of RBC from six CMV seronegative donors, but each received 15 ml of RBC from donors whose CF titers of the CMV antibody were 8 and 32 respectively. Seroconversion and viruria were noted eight weeks after the last transfusion. Neither infant had any symptoms attributable to CMV infection. The third infant weighed 910 gm at birth and had neutropenia and probable sepsis at 2 weeks of age. In addition to 313 ml of RBC from 25 CMV seronegative donors, he received four granulocyte concentrations from three CMV seropositive donors. CMV infection was noted eight weeks later with interstitial pneumonia, deterioration of pulmonary function, hepatitis and thrombocytopenia. The baby recovered without sequelae, but had persistent viruria until the last urine culture 13 months after the granulocyte transfusions. The CF titers of the granulocyte donors were 16, 32 and 32.

Sixteen units of blood were collected from seroconverted donors. Fifteen units were not used for infant transfusions as seroconversion was found either before their release to the hospitals or they were retrieved before use. One unit was given to three infants in one to six transfusions. Two infants were CMV seropositive on the cord blood serology and were not included in the follow-up. The third was a 1 kg premature twin baby whose cord blood was CMV seronegative. He received 14 ml of RBC from the seroconverted donor. On follow-up studies at four and eight weeks post-transfusion, the infant remained CMV seronegative and no viruria was detected.

During the study period, thirteen infants also received fresh frozen plasma from as many donors with an average of 64.8 ml (6–235 ml). The CMV antibody status was available in six donors and three of them were seropositive. None of the thirteen infants showed evidence of CMV infection.

4 Discussion

Our study indicates that the use of seronegative red blood cells is highly successful in the prevention of primary CMV infection in this susceptible population. All CMV negative babies given CMV seronegative blood remained uninfected. However, transfusion of CMV seropositive blood resulted in CMV infection in 3 of 14 (21%) CMV seronegative infants. As little as 15 ml of RBC given in a single transfusion resulted in infection in two of the babies. However, six babies who received aliquots of blood from the same seropositive units did not develop clinical or laboratory evidence of CMV infection. In reviewing the factors such as age, body weight, amount and the number of CMV seropositive blood donors exposed, which might have influenced the CMV infectivity, only the body weight was statistically different between the two groups. This finding suggests that birth weight alone is not necessarily a reliable indicator for susceptibility of CMV infection.

Previous studies have emphasized the use of CMV seronegative blood to prevent CMV infection [1, 11]. Results of other studies document the infectivity of granulocyte concentrates as well [6, 10]. In contrast at least three of the infants who received fresh frozen plasma obtained from CMV seropositive donors showed no evidence of CMV transmission in this study.

While availability and freshness are two prerequisites of blood needs in neonatal transfusion, it is a special challenge to the blood collecting agency to meet these goals in an economical and efficient manner. This study was designed to test a prescreening donor pool concept. During the study period an adequate supply of less than five-day-old blood was available for all three ICN. An annual donor seroconversion rate of 0.7% is consistent with other studies [4, 7]. While all 127 premature babies who participated in the study received multiple blood transfusions, three infants were exposed to CMV seropositive blood due to seroconversion of a donor. One of these three infants developed CMV infection which lead to serious morbidity. A recent study suggested that recently infected donors may transmit CMV more efficiently than latent infected donors [5]. We find it prudent that the prescreened blood be retested before its use. Recently, a rapid latex agglutination test has become available. Such testing allows us

to recheck the CMV seronegative status of the blood in a timely fashion prior to its release. This test further expedites the availability of CMV seronegative blood with minimal cost and delay. This study indicates that a prescreened donor pool is a sound medical and economical approach to provide blood for premature infants for prevention of transfusion-associated CMV infection.

Abstract

The purpose of this study was to evaluate the efficacy of a prescreened CMV seronegative blood donor group in preventing transfusion-acquired CMV infection in premature infants in the perinatal period. Group 0 donors with known CMV seronegative status were recruited to supply blood to the neonatal intensive care nurseries. One hundred and twenty-seven low birth weight infants born of CMV seronegative mothers remained seronegative when blood for transfusion was screened for CMV antibody.
Twenty two infants shared six units of CMV seropositive blood due to technical errors or poor sensitivity of the test kit in the initial phase of the study. Fifteen of these patients were in the study group. One infant died of immaturity at four weeks of age and two of the remaining 14 showed asymptomatic CMV infection. Another infant who received granulocyte concentrates from CMV seropositive donors had symptomatic CMV infection.
Throughout the 24 month study period, blood supply to the ICN was adequate and timely. The donor seroconversion rate was 0.7% per annum. Only one infant was exposed to the risk of CMV infection due to donor seroconversion. We conclude that the prescreening donor program is a sensible and efficient approach for providing CMV seronegative blood in neonatal transfusion therapy.

Keywords: Cytomegalovirus infection, transfusion.

Zusammenfassung

Evaluierung eines Screenings auf Cytomegalievirus (CMV) bei Blutspendern zur Prävention perinataler transfusionsbedingter Infektionen
Untersucht wurde die Effizienz eines Screenings auf CMV bei Blutspendern zur Prävention transfusionsbedingter Infektionen bei Frühgeborenen in der Perinatalperiode. Neonatale Intensivstationen wurden mit Blut von Spendern mit der Blutgruppe 0 und bekanntem CMV-seronegativen Status versorgt. 127 untergewichtige Neugeborene von CMV-seronegativen Müttern blieben negativ, wenn die Transfundate auf CMV-Antikörper getestet worden waren.
22 Kinder erhielten CMV-seropositives Blut, was auf technische Fehler oder eine zu geringe Sensitivität des Test-Kits zu Beginn der Studie zurückzuführen war. 15 dieser Kinder waren in der Untersuchungsgruppe; davon starb eines wegen Unreife mit 4 Lebenswochen und bei 2 Kindern kam es zur asymptomatischen CMV-Infektion. Ein anderes Kind, das Granulozyten-Konzentrate von CMV-positiven Spendern erhalten hatte, entwickelte eine CMV-Infektion mit Symptomatik.
Während der 24monatigen Untersuchungsperiode gab es keine Engpässe oder zeitliche Verzögerungen bei der Versorgung der Intensivstationen mit Blut. Die Serokonversionsrate bei den Spendern betrug 0.7% pro Jahr. Lediglich ein Kind war wegen einer Konversion dem Risiko einer CMV-Infektion ausgesetzt. Wir glauben, daß das Screening der Spender auf CMV eine empfindliche und wirksame Methode ist, um für die neonatale Transfusionstherapie CMV-seronegatives Blut bereit zu haben.

Schlüsselwörter: Cytomegalievirus, Transfusion.

Résumé

Évaluation d'un programme de pré-dépistage chez les donneurs de sang dans le cadre de la prévention de l'infection à cytomegalovirus (CMV) acquise par transfusion périnatale
L'objectif de cette étude était d'évaluer l'efficacité d'une présélection d'un groupe de donneurs de sang CMV séronégatifs pour prévenir l'infection à CMV acquise par transfusion chez les prématurés en période périnatale. On a recruté des donneurs du groupe 0, ayant une CMV séronégative, pour les supplémentations sanguines des unités de soins intensifs néonataux (U. S. I. N.). Cent vingt sept enfants de faible poids de naissance nés de mère CMV séronégatives sont restés séronégatifs lorsque le sang des transfusions avait subi la recherche d'anticorps anti CMV.
Vingt deux enfants se sont partagés six unités de sang CMV séropositifs du fait d'erreurs techniques ou d'une faible sensibilité du kit dans la phase initiale de l'étude, quinze de ces patients étaient dans le groupe étudié. Un enfant est mort d'immaturité à quatre semaines d'âge et deux des 14 survivants ont présenté une infection à CMV asymptomatique. Un autre enfant qui avait reçu des

concentrés granulocytaires provenant de donneurs CMV séropositifs a présenté une infection à CMV symptomatique.
Tout au long des 24 mois de la période d'étude, l'apport sanguin à l'U. S. I. N. a été approprié et à temps. Le taux de séroconversion des donneurs est de 0,7% par an. Seul un enfant a été exposé au risque d'infection à CMV du fait d'une séroconversion d'un donneur. Nous en concluons qu'un programme de pré-dépistage des donneurs est une approche sensible et efficace pour que soit fourni du sang CMV séronégatif pour les transfusions néonatales.

Mots-clés: Infection à cytomegalovirus, transfusion.

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Peter Lau, M. D.
American Red Cross Blood Services
Northwest Ohio Region
2275 Collingwood Blvd.
Toledo, Ohio 43620, U. S. A.