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Umbilical Cord Blood as an Alternative for Infant Blood in the Neonatal Sepsis Evaluation:

Evidence-Based Practice Literature Review Project

Teresa Baker

Dr. Janice Anderson
Nurs 6023
Philosophy of Nursing Science
August 11, 2009

Texas Woman's University
College of Nursing
Dallas Center

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Early onset bacterial sepsis, primarily with group-B streptococci (GBS) is a leading cause of potentially preventable neonatal morbidity and mortality in the United States (Hansen, Forbes & Buck, 2005; CDC 2002). According to the Centers for Disease Control and Prevention (CDC), GBS emerged as the leading infectious cause of neonatal morbidity and mortality in the United States in the 1970's. Initial case series reported case-fatality ratios as high as 50%. Prior to active prevention initiation, an estimated 7,500 cases of neonatal GBS disease occurred annually. After guidelines for prevention of perinatal group B streptococcal disease were published in 1996, data collection showed that despite striking declines in disease incidence, GBS remained a leading infectious cause of morbidity and mortality among newborns. These findings prompted the CDC to reevaluate prevention recommendations. In 2002, revised recommendations were published to include an algorithm for management of newborns. The recommendations were to screen all asymptomatic newborns that were at risk for sepsis. Part of this evaluation consists of drawing a complete blood count (CBC) with differential and blood culture (CDC, 2002). These changes have made sepsis evaluation the most common cause for triage admission to the nursery and account for one third of such admissions (Hansen, Forbes & Buck, 2005).

Providing there is a significant correlation of the laboratory results, the use of umbilical cord blood for the detection of neonatal bacteremia may prove to be a satisfactory alternative to infant phlebotomy. This method would spare trauma to infant and family and provide improved utilization of time and resources.

Purpose

The purpose of this evidence-based inquiry is to evaluate the current, best evidence-based literature related to methods for rapid and accurate detection of neonatal bacteremia to comply with the CDC guidelines for prevention of GBS disease. The clinical problem that will guide this review is: In the population of neonates <7 days of age, will the use of umbilical cord blood rather than infant blood be a reliable alternative for obtaining a CBC and blood culture for the detection of early onset neonatal bacteremia?

Justification

Incidence

Sepsis evaluation has become the most common cause for triage admission to the nursery and account for one third of such admissions. Between 324,000 and 608,000 newborns require a sepsis evaluation in the United States annually (Hansen, Forbes & Buck, 2005).

Health Risk

Early onset bacterial sepsis, primarily with group-B streptococci (GBS) is a leading cause of potentially preventable neonatal morbidity and mortality in the United States (Hansen, Forbes & Buck, 2005). Long term sequelae are frequently encountered in survivors of GBS sepsis (Polin et al, 1981). In 2002, CDC, the American College of Obstetricians and Gynecologists (ACOG), and the American Academy of Pediatrics (AAP) issued revised guidelines for the prevention of perinatal GBS disease. These guidelines recommend screening of pregnant women for GBS colonization and treatment with intrapartum antibiotic prophylaxis for GBS carriers (CDC, 2007). The recommendation for infants whose mothers were inadequately treated with two doses of antibiotics prior to delivery and are asymptomatic, is to obtain a CBC with differential and

blood culture. Following the institution of the universal screening protocol, rates of neonatal and pregnancy-associated GBS disease were examined. Based on surveillance data from the Active Bacterial Core surveillance (ABCs) system, the CDC analyzed the period from 2003-2005 and compared data from 2000-2001, the period immediately preceding the universal screening recommendations. The analysis indicated that the annual incidence of early onset GBS disease in infants aged 0-6 days was 33% lower during 2003-2005 than during 2000-2001. Based on the decreased incidence of GBS disease in neonates, the report on this analysis indicates the need for continued surveillance to monitor the impact of guidelines on perinatal GBS disease and to guide further interventions (CDC, 2007).

Optimal management of infants at high risk for developing GBS sepsis include earliest possible identification of infants at risk, rapid and accurate detection of neonatal bacteremia, and early initiation of antibiotic therapy according to guidelines to prevent the potentially fatal neonatal disease. As the clinical signs of sepsis are frequently nonspecific, subtle and difficult to diagnose, awaiting the clinical emergence of sepsis before beginning treatment diminishes the opportunity for a successful outcome (Polin et al, 1981).

Implications for Alternative Use of Cord Blood

To understand the impact of using cord blood as an alternative to using infant blood, one must understand the disadvantages of current practice. Shortly after delivery, well infants at risk for GBS sepsis are removed from their family, thus interrupting the bonding process. This is distressing to the family, knowing that their newborn infant is about to have a painful procedure out of their presence and comfort. Often an infant will be admitted into a triage bed for evaluation. If the venipuncture is unsuccessful, it may need to be repeated multiple times. At

times an arterial puncture is required and this procedure may require individuals with an increased skill level, distracting them from higher acuity tasks. In some settings, a nurse practitioner or physician may need to be called in from office or home to obtain the necessary blood (Hansen, Forbes & Buck, 2005). Often it is difficult to obtain an adequate volume of blood from a newborn which may cause a delay in bacterial growth or may be difficult to interpret (Polin et al, 1981). The volume of blood obtainable from the umbilical cord is usually more than adequate.

The use of umbilical cord blood would allow the entire evaluation to be performed in the labor or delivery room. The specimen would be attained at the earliest possible time, allowing rapid institution of antibiotic therapy. The method is noninvasive and nontraumatic and may be performed by a less skilled member of the health care team, and an adequate volume of blood could be easily obtained (Polin et al, 1981). “Reduction of these painful procedures, inconveniences and expenses is desirable for the infants, parents and the health care system. With the constant drive to improve efficiency and family-centered care, health care providers and parents alike will welcome these minor procedural changes” (Hansen, Forbes & Buck, 2005).

Definition of Terms

For the purpose of this project, the following terms were defined.

Umbilical cord blood

Cord blood is blood that is drawn either from a vein or an artery of a segment of umbilical cord that has been clamped on both ends, separated from the placenta and the infant.

Infant blood

Infant blood is a specimen of blood that has been obtained by either venipuncture or

arterial puncture from an infant.

Sepsis

“Sepsis is a toxic condition due to spread of bacteria or their products in the body”

(Merriam-Webster, 1994, p. 662).

Group B Streptococci

Group B Streptococci (GBS) is an organism that may colonize in a woman’s vagina.

During pregnancy, women can contract infections caused by GBS. Infants can become infected with GBS during passage through the birth canal. GBS causes severe invasive disease in young infants, which usually present with sepsis, pneumonia, meningitis, osteomyelitis, or septic arthritis (CDC, 2002).

Risk Factors for Perinatal GBS Disease

“In addition to colonization with GBS, other factors increase the risk for early-onset disease. These include gestational age <37 completed weeks, longer duration of membrane rupture, intraamniotic infection, young maternal age, black race, Hispanic ethnicity. Previous delivery of an infant with invasive GBS disease may increase the risk of early-onset disease in subsequent deliveries” (CDC, 2002).

I:T Ratio

The I:T ration is calculated on the CBC differential white count. It is a ratio of the immature (I) to total (T) granulocytes. The I:T ratio is sensitive to infection in neonates. If the I:T ratio is > or = to 0.2, it is significant for possible infection. The current standard of care is to base the decision to initiate antibiotics on whether or not the I:T ratio is normal or elevated (Hansen, Forbes & Buck, 2005).

Methodology

A review of the literature was performed using a meta-database via Texas Woman's University library and Scott and White Hospital medical library. Databases searched included the following: Cochrane Library (OVID), MeSH, DARE, PubMed, TRIP database, Google, and CDC. Search terms included "umbilical cord blood", "cord blood", "group B streptococci", and "neonatal sepsis evaluation". Using these search terms, only two articles were found that directly addressed the use of umbilical cord blood for detection of neonatal group B streptococcal bacteremia. Articles not included in the review of literature were those that focused on the use of umbilical cord blood for unrelated laboratory tests. Of interest, the two available articles were found using PubMed. *Clinical Evidence*, a computerized decision support system through the British Medical Journal, was also accessed but returned no results. Although several articles addressed using blood obtained from umbilical catheters, only two were found that directly addressed using the blood obtained from a segment of umbilical cord. There was one unrated article that was found relating to the possible use of cord blood investigating specific protein levels that may correlate with early onset neonatal sepsis. This article did not relate to the original evidence-based question. Although no new and little recent literature was located, evidence-based journals, synopses, syntheses and studies were incorporated into this literature review.

Review of the Literature

Prevention and Guidelines for Treatment

Two of the articles were recommendations and reports from the Centers for Disease Control and Prevention, published in the Morbidity Mortality Weekly Report (MMWR),

prepared by the National Center for Infectious Diseases (CDC, 2002; CDC, 2007). The article published in 2002 presented the revised guidelines from the CDC for prevention of perinatal group B streptococcal disease. Key changes from the 1996 guidelines were highlighted, with differences and similarities in guidelines addressed. This article also reported the impact and implementation of the 1996 guidelines and the evidence for changes. Future prevention technology was addressed and updated recommendations were made based on critical appraisal of multistate population-based observational data and several studies from individual institutions that had been completed since the previous CDC recommendations. These recommendations were rated for strength and quality. Strength of evidence = Ia.

The article published in 2007 describes the results of an analysis performed by CDC utilizing surveillance data from the Active Bacterial Core surveillance (ABCs) from the period 2003-2005, comparing them with data from 2000-2001, the period prior to the universal screening recommendations. The results of this analysis indicated the incidence of early onset GBS disease, in infants 0-6 days of age, was 33% lower during 2003-2005 than during 2000-2001. Continued surveillance was emphasized to monitor the impact of the guidelines on perinatal GBS disease and trends and to guide future interventions. This continued surveillance will also aid in the detection of specific antibiotic resistant organisms that may develop. Strength of evidence = Ia.

Potential Use of Umbilical Cord Blood

There were little recently published articles on this subject, however, two original studies examined the use of umbilical cord blood as a substitute for infant blood for the detection of neonatal bacteremia.

Polin, Knox, Baumgart, Campman, Mennuti & Polin (1981) conducted a study comparing the incidence of positive umbilical cord blood cultures (UCBCs) to the incidence of positive peripheral venous cultures and determined whether a meticulous UCBC technique prevented contamination of culture specimens. Selected for the study were 196 women in labor and their 200 newborns. An attempt was made to include as many patients as possible with premature rupture of membranes (rupture of the membranes before the onset of labor), prolonged rupture of membranes (membranes ruptured more than 24 hours prior to delivery), and intrapartum fever (oral temperature $>38^{\circ}\text{C}$ during labor). In addition, as many patients as possible without complications were included in the study to serve as controls. UCBCs were drawn using a specific sterile technique. Peripheral blood cultures were drawn from 29 infants. Six specimens (3%) were reported as having bacterial growth. For analysis, the positive UCBCs were divided into those exhibiting growth within 48 hours and those with delayed growth (more than 48 hours). Three specimens exhibited bacterial growth on the second day of incubation. One case yielded an alpha-hemolytic streptococcus. The other two cases yielded organisms regarded as contaminants. This study demonstrates that contamination of UCBC specimens can be avoided by meticulous attention to sterile technique. The incidence of clinically significant false-positive UCBCs was 0.5%. In addition, the single case of true bacteremia was detected in both the UCBC and peripheral venous blood culture. The authors conclude from this study that meticulous and fastidious collection of UCBCs can prevent contamination of culture specimens. The single case of true neonatal bacteremia was identified in a UCBC specimen; however, a larger prospective study to document the sensitivity and specificity will be required to determine suitability of this method. Umbilical cord blood culture may prove a satisfactory alternative to the postnatal

peripheral venous blood culture for detection of neonatal bacteremia (Polin, et al, 1981).

Strength of evidence = 2a.

An original paper was published by Hansen, Forbes & Buck (2005) addressing the potential substitution of cord blood for infant blood in the neonatal sepsis evaluation. They conducted a prospective cohort study comparing CBC/differential and blood culture results of paired samples of umbilical cord and infant blood from term newborns. Inclusion criteria was any term infant whose blood was to be obtained for CBC/differential and blood culture for sepsis based on clinical indications. Otherwise, eligible infants were excluded only if unable to obtain cord blood for technical reasons. An umbilical cord blood culture (UCBC) and a peripheral venous blood culture were drawn from each infant enrolled in the study. All 113 umbilical cord and infant blood cultures were negative. Therefore, the false-positive blood culture rate was zero. The false-negative blood culture rate is not measurable as there were no positive cultures. Spearman's correlation of the I:T ratio between cord and infant blood was 0.32 ($p=0.001$). The 0% false-positive blood culture result is consistent with the only other published study on the subject (Polin et al, 1981) and strongly contradicts the impression that UCBCs have an unacceptably high false-positive rate. The limitations of this study are that there were no positive cultures to assess the cord blood for false-negative results, but this was not the goal of the study because it was not the concern raised by clinicians who were skeptical of cord blood testing. Also, the study was limited to term infants. The conclusion of the authors was that cord blood can be safely substituted for infant blood in routine sepsis evaluations of asymptomatic, term infants based on both the low false positive cord blood culture rate and the significant association between high I:T ratios in cord and infant blood. Strength of evidence= 2a.

Of interest, the Polin, et al study was mentioned in this study as the only other published study on this subject.

Conclusions

Perinatal group B streptococcus (GBS) remains a leading cause of neonatal morbidity and mortality in the United States. Despite the steady decrease of incidence with revised guidelines by CDC for prevention of GBS disease, continued surveillance is needed to monitor the impact of the guidelines on perinatal GBS disease and trends and to guide future interventions. Continued surveillance will also aid in detecting future antibiotic resistant strains of bacteria (CDC, 2007).

The CDC has issued universal guidelines that recommend obtaining a complete blood count (CBC) with differential and blood culture from any infant who has risk factors for GBS sepsis (CDC, 2002). These changes have made sepsis evaluation the most common cause for triage admission to the nursery and account for one third of such admissions. Between 324,000 and 608,000 newborns require a sepsis evaluation in the United States annually (Hansen, Forbes & Buck, 2005). Optimal management of infants at high risk for developing GBS sepsis include earliest possible identification of infants at risk, rapid and accurate detection of neonatal bacteremia, and early initiation of antibiotic therapy according to guidelines to prevent the potentially fatal neonatal disease (Polin et al, 1981).

Although published literature on this subject were scarce, two published studies clearly indicate the use of umbilical cord blood for sepsis evaluation may be a reliable alternative to obtaining blood from the infant via venipuncture. Both studies showed a strong correlation between blood cultures obtained from a segment of umbilical cord, using sterile technique,

and blood cultures obtained peripherally from an infant. The incidence of clinically significant false-positive cord cultures was 0-0.5% (Hansen, Forbes & Buck, 2005; Polin et al, 1981). The single case of true bacteremia was detected from both the cord blood culture and the peripheral venous blood culture (Polin et al, 1981). These studies were unbiased, as infants were enrolled randomly and treatment was initiated per established guidelines prior to return of the laboratory results. Both studies included infants with premature rupture of membranes, prolonged rupture of membranes and intrapartum fever. In addition patients without complications were included in the studies. The limitations of the Hansen and colleagues (2005) study was that there were no positive cultures to assess false negatives and only term infants were enrolled. Further studies are warranted which would substantiate the evidence that umbilical cord blood can be substituted for infant blood in the sepsis evaluation.

Providing there is a significant correlation of the laboratory results, the use of umbilical cord blood for the detection of neonatal bacteremia may prove to be a satisfactory alternative to infant phlebotomy. The use of umbilical cord blood would allow the entire sepsis evaluation to be performed in the labor or delivery room. It would not be necessary to remove the infant from the parents' presence, and bonding would not be interrupted. The specimen would be attained at the earliest possible time, allowing rapid institution of antibiotic therapy. The method is noninvasive and nontraumatic for the infant and may be performed by a less skilled member of the health care team. An adequate volume of blood could be easily obtained (Polin et al, 1981). With the constant drive to improve efficiency and family-centered care, health care providers and parents alike will welcome these minor procedural changes in order to reduce painful procedures, inconveniences and expenses (Hansen, Forbes & Buck, 2005).

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