Umbilical blood biomarkers for predicting early-onset neonatal sepsis

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Background: Since the 1990s, finding the most efficient markers or combinations as predictors of early-onset neonatal sepsis has been the hot topic of studies. But there is no review of such biomarkers detected in umbilical blood at birth. By comparing clinical values of common inflammatory markers detected in cord blood shortly after birth, in this study we tried to find the most performing one or the most efficient combination that might be potentially used in birth room, as the earliest predictor of early-onset neonatal sepsis.

Data sources: We searched PubMed and Elsevier's Web of Science for studies evaluating cord blood inflammatory markers in relation to early-onset neonatal sepsis.

Results: Among C-reactive protein (CRP), procalcitonin (PCT), IL-6, IL-8, TNF-α and IL-1β, none of them could be used individually to establish or exclude the diagnosis of early-onset neonatal sepsis, but PCT, IL-6 and IL-8 have great superiority to CRP, TNF-α and IL-1β. When combined with other hematological markers and clinical observation, the clinical reliability of PCT, IL-6 and IL-8 could be improved. Prolonging the sample collection time window seems to have a positive effect on the clinical utility of IL-6 and IL-8.

Conclusions: More researches focusing on the combination of different umbilical cord biomarkers in different clinical settings are needed to achieve clearer conclusions. Multi-center, large-sized analysis, especially examining groups of cytokines, is also expected.

Key words: C-reactive protein; interleukins; neonatal sepsis; procalcitonin

Introduction

According to the 2002 International Pediatric Sepsis Consensus Conference, pediatric sepsis is defined as systemic inflammatory response syndrome in the presence of or as a result of suspected or proven infection.[1] But so far, a worldwide agreement on the definition of early-onset neonatal sepsis (EONS) has not been reached. In this review, we aim to integrate the previous literatures investigating biomarkers in cord blood at birth for the immediate diagnosis of EONS. Cord blood is the earliest hematologic sample from the object, which could guide the clinicians to carry out effective therapeutic strategy as soon as possible. Besides, a painless and non-invasive manipulation avoids iatrogenic stress source to vulnerable newborns, which could cause deterioration and possible anemia.

Theoretically, the ideal markers for detecting EONS should have the highest sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and optimal likelihood ratio (LR), which means a LR(+) >10 and LR(-) <0.1, but these requests cannot be met at the same time. In consideration of the possible devastating sequele of missed diagnosis, a maximum sensitivity and NPV should be considered prior to meeting high specificity and PPV. But in terms of the value of performing a diagnostic test, the likelihood ratios, independent of prevalence, are recognized as the best index to determine whether a test result changes the probability that a condition (here, infection) exists.

For each biomarker, we described its kinetic features in response to infection, origin cells, relationship between its initial cord blood concentration and gestational age, its permeable ability to cross the placenta, as well as the statistical value. We also evaluated possible combination of different umbilical blood markers.
**Blood biomarkers**

**C-reactive protein (CRP)**

This acute phase protein is often used as a routine infectious marker in the past decade.\(^2,^3\) Serum CRP level increases within 6-10 hours in neonates after exposure to infection and peaks at 2-3 days followed by a decrease with favorable evolution.\(^2,^4,^5\) It is suggested that fetal CRP independent production.\(^6\) Gestational age has a positive effect on CRP concentration at birth and its response extents after birth.\(^7\)

When investigating inflammatory mediators in umbilical plasma drawn immediately after delivery, Døllner et al\(^5\) found that CRP levels were undetectable in nearly all of the neonates, both in infectious and control groups. In another similar investigation, Santana et al.\(^4\) using a more sensitive method allowing a detection limit of 1 mg/dL, found that cord blood CRP levels were low (0.076-0.63 mg/dL) and of no significant difference among infected, non-infectious and healthy groups.

But in a prospective test run by 197 samples, Joram et al\(^8\) reported the limitation of cord blood CRP as a diagnostic marker for EONS. Irrespective of gestational age, with the cut-off value of 5 mg/L, they received a performance as follows: sensitivity 50%, specificity 97%, PPV 67%, NPV 94%, LR(+) 16.7, and LR(-) 0.51.

Infection may be initiated relatively close to delivery, resulting in low levels of umbilical plasma CRP concentration. In infected infants born with extremely prematurity, CRP responses could be undetectable several days after birth.\(^9\) Cord blood CRP may not increase in presence of umbilical vasculitis which often reflects severe chorioamnionitis with neonatal diseases whereas many other inflammatory markers do.\(^10\)

In contrast, elevated cord blood CRP levels were observed in absence of infection with several intrapartum risk factors for infection,\(^11\) and in case of prenatal corticosteroid use,\(^7\) meconium inhalation syndrome and higher birth weight in preterm infants.\(^12\)

CRP has been proved as a "specific" but "late" marker of neonatal infection. Cord blood CRP concentration alone has little utility in EONS diagnosis.

**Procalcitonin (PCT)**

Firstly demonstrated to increase at the onset of bacterial infection and sepsis by Assicot et al\(^13\) in 1993, this acute phase reactant has the characters of acute phase proteins, hormones and cytokines.\(^14\) Serum PCT concentration raises 2-4 hours after endotoxin injection, reaches its peak level right after 6 hours, maintains a plateau through 8 to 24 hours\(^15\) and decreases to its normal level if the infection stimulus stops. Its half-life time is about 25-30 hours.\(^3\) In an investigation on postnatal physiological fluctuation of PCT in term and preterm cohorts, the serum PCT level increased rapidly after birth, peaked at 24 hours in term babies and a little earlier in preterm ones, decreased gradually by 48 hours until a minimum value appeared at about 80 hours for term ones and 5 days for preterm ones.\(^7\) However, this is contradictory to another investigation suggesting that PCT concentrations decreased with prematurity.\(^16\)

Antenatal inflammation, intracranial hemorrhage, birth asphyxia, respiratory distress syndrome, hypoxemia, hemodynamic failure, pneumothorax, neonatal resuscitation and gestational diabetes can also cause an increased circulating PCT concentration.\(^17-20\)

It was demonstrated that maternal venous PCT levels do not correlate with umbilical cord blood concentration in the infected neonates.\(^21\) But in non-infected babies, whether umbilical PCT levels are affected by maternal venous PCT levels remains controversial.\(^21,^22\)

Reference value in healthy neonates was established for the first time by time-resolved amplified cryptate emission (TRACE) technology in 2007, ranging from 0.04 to 0.43 mg/L.\(^23\) Considering that gestational age has a negative effect on PCT levels at delivery, clinical utility of PCT in the diagnosis of EONS requires the establishment of reference covering a range of both gestational and postnatal ages.\(^7\)

In 2006, Joram et al\(^8\) reported that umbilical blood PCT concentration could serve as a predictive marker for early diagnosis of very early onset neonatal sepsis. In this prospective study, the sample size was relatively small (197 neonates) and the result was inspiring. With the cut-off point being 0.5 μg/L, the sensitivity (0.875), specificity (0.987), PPV (0.875), NPV (0.987), LR(+) (67.3) and LR(-) (0.13) were all high.

However, in a recent report, a monocenter retrospective analysis\(^17\) has shown a different conclusion. This analysis was conducted on a large cohort of newborns with risk factors for EONS. When a cut-off value was 0.6 ng/mL, the sensitivity, specificity, NPV, LR(+) and LR(-) were all high while PPV was only 0.28. In the preterm subgroup, the sensitivity and NPV reached 1.0 but the PPV was still low. The authors verified the ability of PCT to detect non-infected patients among those presenting risk factors but a more certain conclusion claims prospective studies. Its low PPV was explained as the result of impact of perinatal asphyxia and antenatal inflammation which promoted PCT production. Indeed, in the former report, preterm babies occupied only 18% of the objects, but in the latter, premature babies' proportion was 38%. The increased proportion of premature neonates might enhance the bias caused by perinatal asphyxia and antenatal inflammation. Besides, the lower incidence of EONS in the latter study (1.2%) also influenced the