

Interpretation of the Experts' Consensus on the criteria for the diagnosis and grading of neonatal asphyxia in China

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Neonatal asphyxia (NA) refers to a critically ill condition in which there is an acute interruption of gas exchange between mother and fetus via placental blood flow, causing severe fetal hypoxia and acidosis, which can be followed by the depression of respiratory, circulatory and central nervous systems. As a result, the neonates can not promptly gain and maintain normal breathing. However, there is still no relatively objective and scientifically rigorous assessment criteria for NA. Based on the research advances and real conditions in China and following the basic principles of evidence-based medicine, the Neonatal Professional Committee of Chinese Medical Doctor Association summoned a working panel to develop the diagnostic and grading criteria of NA to further standardize its clinical diagnosis and treatment (1). We hereby write this article to help the doctors further understand this Expert Consensus and apply it correctly in their clinical practices.

Apgar score often results in a high false positive rate of NA

Apgar score has been widely applied for the diagnosis of NA and the assessment of asphyxia degree in the past decades. However, it has many limitations (2); particularly, it has high sensitivity and low specificity, and the false positive rate of Apgar scoring can be up to 50-80% (3-5). Such a high misdiagnosis rate is resulted from the poorly defined diagnostic criteria, and can cause a series of medical, ethical and social issues. Other limitations of Apgar score in diagnosing NA include: (I) Although the Apgar score is useful for identifying the presence of respiratory depression

in neonates, it can not indentify its pathophysiological nature and etiology; (II) the Apgar score does not emphasize the role of respiratory depression; rather, it equally assigns the scores to five components with different importance degree; (III) its accuracy in assessing NA is affected by the gestational age; and (IV) it is not feasible for neonates upon endotracheal intubation and positive-pressure ventilation (ETI/PPV). However, since Apgar score can generally reflect the clinical manifestations of neonates with respiration, circulation, and CNS depression, the current Expert Consensus still includes it as a major indicator for assessing NA; together with umbilical arterial pH, the Apgar score can be useful for the diagnosis of NA.

During the panel meetings, the experts discussed why Apgar scores ≤ 7 at 1 minute after birth should be applied. Several international documents have proposed the use of 1-min Apgar scores ≤ 6 or 3, or 5-min Apgar score ≤ 7 , 6, or 3. However, no clinical evidence has demonstrated that the modification of Apgar scores can improve its specificity without lowering its sensitivity. As we all know, a normal fetus takes the first breath within 2 seconds after delivery, cries within 5 seconds, and establishes the regular respiration within 10 s to 1 min. If an infant fails to establish spontaneous and effective respirations 1 min after birth, the situation can be problematic. Also, a study (3) has shown that 40% of infants with the Apgar scores ≤ 7 at 1 minute after birth had hypoxic organ injury. To avoid misdiagnosis, the Expert Consensus still uses failure to establish regular and effective respirations 1 min after birth (respiratory depression and Apgar score ≤ 7) as one of the diagnostic criteria of NA, including those failure to establish

regular and effective respirations 5 min after birth and Apgar score ≤ 7 , or relatively high 1-min Apgar score but the infant experiences respiratory dysfunction with an 5-min Apgar score ≤ 7 .

In addition, for infants without spontaneous respiration or severe respiratory depression (e.g., without spontaneous breathing or with sobbing breaths), active and proper resuscitation may raise the 1-min Apgar score to 7 or higher. However, if the infants meet the other several criteria, they can still be diagnosed as with NA.

High rate of missed NA remains problematic in the United States

In the history, diagnosis of NA based on Apgar score alone had dramatically increased the diagnosis of NA. Therefore, many developed countries and regions have already ceased the application of Apgar score alone for NA diagnosis since 1990s. The diagnostic criteria (6) jointly released by American College of Obstetricians and Gynecologists (ACOG) and American Academy of Pediatrics (AAP) were once widely accepted. The criteria include (6): (I) umbilical arterial pH < 7.00 ; (II) an Apgar score of 0 to 3 for longer than 5 minutes; (III) neurologic manifestation, e.g., seizure, coma, or hypotonia, and (IV) evidence of multiorgan dysfunction. In fact, diagnoses based on these criteria not only include asphyxia but also hypoxic-ischemic encephalopathy (HIE) and multiorgan dysfunction. However, clinical practices have shown that the rate of missed diagnosis reached 79-88% (7,8). Obviously, the above criteria is not feasible for clinical application.

Risk factors of NA

Many risk factors can result in NA: (I) Maternal factors: primiparous women aged > 35 years or < 16 years; hypertensive disorders of pregnancy (including pre-eclampsia and eclampsia); severe lung disease, asthma, heart disease, primary hypertension, kidney disease, epilepsy, diabetes, or thyroid disease; low urinary estriol; anemia (Hb < 100 g/L); isoimmunization; placenta previa or placental abruption; hypotension; premature rupture of membranes; previous history of fetal death/stillbirth, or neonatal death. (II) Delivery-related factors: malposition; assisted deliveries (forceps, vacuum extractor, and internal podalic version); epidural anesthesia; prolonged labor; abnormal uterine contractions; use of oxytocin; or use of morphine-like analgesics and magnesium sulfate. (III)

Fetal factors: umbilical cord problems; cephalopelvic disproportion; premature birth; post-term birth; twins & multiple births; abnormality in fetal heart rate or rhythm; decreased fetal movement; amniotic fluid volume abnormalities; meconium stained amniotic fluid; intrauterine growth restriction; macrosomia fetus; fetal acidosis; or fetal anemia (Hb < 100 g/L). Research has identified 11 most significant risk factors: abnormal findings of fetal heart monitoring, fetal acidosis, placental abruption, placenta previa, abnormal fetal position, meconium stained amniotic fluid, forceps delivery, prolonged labor, abnormal uterine contraction, premature birth, and maternal asthma (9).

Inclusion of the risk factors in the diagnostic criteria helps the doctors to be more alert about NE and take necessary measures to prevent its occurrence and development. For diagnosis, a risk factor just indicates that there is a possibility of NA and do not mean that NA will be unavoidable. In fact, the presence of a risk factor is not a direct evidence of asphyxia. A domestic prospective study involving tens of thousands of subjects showed that although all the NA infants had risk factors, only 1.37% of infants with risk factors suffered from asphyxia (9). Therefore, these risk factors are just used as a minor criterion for explaining the etiology.

Umbilical cord arterial blood gas analysis

Clinical significance of arterial blood gases

In essence, asphyxia is the damaging hypoxemia and metabolic acidosis. Therefore, the diagnosis of NA should be based on more objective indicators to increase its accuracy and reliability. Among these indicators, umbilical cord arterial blood gas analysis provides a simple, accurate, and reliable tool. The results of umbilical cord arterial blood gas analysis at birth is a gold standard that reflects the blood gas and acid-base status immediately before birth (5), meanwhile it provides key evidences for analyzing the perinatal adverse events and neonatal status (5,10,11). Therefore, it has been widely accepted that umbilical cord arterial blood gas analysis should be added for neonates with low Apgar score to increase the accuracy of an NA diagnosis (12-15). The normal findings of umbilical cord arterial blood gas analysis is helpful to rule out the possibility of intrapartum asphyxia and its association with cerebral palsy (5,10,11), so as to avoid misdiagnoses and unnecessary legal disputes. Therefore, this Experts' Consensus emphasizes the importance of umbilical cord arterial blood gas analysis

in NA diagnosis.

Umbilical blood gas determination and Apgar scoring complement each other

Umbilical blood gas determination alone also has its limitations and can not be used as the only indicator for NA diagnosis. As shown in several large-scale domestic studies, except those with low Apgar scores, about 87% of neonates with umbilical arterial pH <7.00 did not have NA. On the contrary, the combination of umbilical arterial pH and Apgar score can overcome their shortcomings (3,4).

Clinical significance and pathological threshold values of umbilical arterial blood gas parameters

Among the umbilical arterial blood gas parameters, pH is most important. After the influence of maternal acidosis is ruled out, a decreased pH value can reflect the severity of neonatal hypoxia and acidosis. BE and PaCO₂ are helpful to identify the nature of acidosis. PaO₂ is least important, because the levels of PaCO₂ and PaO₂ fluctuate rapidly and dramatically, and can only reflect a transient condition at sampling. On the contrary, pH and BE reflect the outcomes of hypoxia and are more stable. Therefore, pH and/or BE have widely adopted for NA assessment.

As shown in a domestic study (4) with an ultra-large sample size, due to the individual differences, the pH values in NA neonates were not at a fixed “point” but vary within a certain range. The combination of 1-min Apgar score with umbilical arterial pH <7.20 had a sensitivity of 100% for NA diagnosis, but its specificity was only 64.4%. As the pH value declines, its specificity for NA diagnosis gradually increases but the sensitivity decreases. A low 1-min Apgar score with umbilical arterial pH <7.00 yielded a specificity of 99% for diagnosing NA, while the sensitivity was only 41%. In contrast, a low 1-min Apgar score with umbilical arterial pH <7.15 had a sensitivity and specificity of about 80% for NA diagnosis (4). After balancing the sensitivity and specificity, the expert group decided to use pH <7.15 as the umbilical arterial blood gas parameter for NA diagnosis. In NA neonates, the distribution of BE values are more diffuse than that of pH values; thus, pH is superior to BE as an indicator for diagnosing NA.

Importance of ruling out other causes

The fourth criterion of NA diagnosis urges that other

causes of low Apgar score must be ruled out. This has not been seen in other criteria or recommendations on NA diagnosis. These causes include (2-4): (I) congenital malformations of the respiratory system; (II) congenital malformations of the circulation system; (III) congenital malformations of the central nervous system; (IV) neuromuscular disorders; (V) fetal hemorrhagic shock; (VI) fetal hydrops; or (VII) fetal passive drug toxicity from intrapartum high-dosage use of magnesium sulfate or anesthetic/analgesic agents to the mother. In fact, NA remains a major cause of medical disputes in China. All the above mentioned causes, particularly the congenital malformations, can mimic the clinical manifestations of NA. However, the maternal-fetal gas exchange through the placenta shows no disorder, the umbilical cord arterial blood gas remains normal, and there is no relationship with the measures taken by the medical staff during the labor. Therefore, these conditions should be properly diagnosed according to their specific etiologies and should not be misdiagnosed as NA. Therefore, the “differential diagnosis” added in the Experts’ Consensus can enhance the scientific rigor and accuracy of NA diagnosis, improve the doctor’s understanding and management of NA, and avoid or minimize the misdiagnoses and their related medical disputes.

Grading of NA

Clinical experiences have shown that NA neonates (even without respiration or heart beating at birth) will not necessarily suffer from organ injury if they can gain timely and proper neonatal resuscitation. In recent years, unfortunately, NA-associated deaths in neonates are mainly resulted from various severe complications of NA. Therefore, after a neonate is transferred to the intensive care unit after resuscitation, any potential organ injury (and its severity) must be carefully examined. The grading of NA is helpful to guide the post-resuscitation management for NA infants. The care, monitoring, and treatment should be properly adjusted for infants with or without organ injury and its severity, it has been shown that the incidence of organ injury is closely related with the severity of acidosis. As the umbilical cord arterial pH value decreased from 7.20 to <7.00, the organ injury rate gradually rose from 0.39% to 13.62%; in contrast, with the BE value dropped from ≥ -10 mmol/L to <-20 mmol/L, the organ injury rate gradually increased from 1.24% to 9.05% (4). The vital organs are often protected by some physiological

mechanisms such as diving reflex in case of hypoxia. While brain is often the last damaged organ, brain injury is often associated with multiple organ dysfunction. However, in a neonate with acute total asphyxia, the body can not provide timely compensation; then, the brain can be damaged first (without multiple organ dysfunction) due to its high oxygen consumption rate and metabolism rate. Hypoxic-ischemic organ injury is a marker of decompensation during the pathophysiologic process of asphyxia, indicating that the persistent, severe hypoxia has developed from the physiological stress compensation to pathological decompensation. Therefore, it can be used for grading the severity of asphyxia. In the presence of other NA criteria, asphyxia cases without organ injury can be diagnosed as mild and those with organ injury as severe. The diagnosis of organ injury can be based on the criteria proposed by the Subspecialty Group of Neonatology, Pediatric Society, Chinese Medical Association and in the monograph Practical Neonatology (16,17).

Key points

During the clinical application of the Experts' Consensus, the medical staff must pay attention to the following key points: (I) Among these NA diagnostic criteria, the first one is a minor criterion and the others are the major criteria; (II) Once a neonate at high risk of asphyxia is born in the delivery room or operating room, clamp a segment of umbilical cord (near the fetal side) with two sterile hemostats immediately, cut off the umbilical cord from the outer side of the hemostats, and sampling the umbilical cord arterial blood from the cut down umbilical cord for blood gas analysis; (III) For neonates without spontaneous respiration or with severe respiratory depression at birth and/or with low Apgar scores 1 min or longer after birth, umbilical cord arterial blood gas analysis must be conducted; if no such abnormality is found, the cut down umbilical cord specimen can be discarded; (IV) Non-vigorous neonates with low Apgar score at birth should be timely transferred to neonatal intensive care unit after proper resuscitation, in which they should undergo further examinations for the presence of organ injury and differential diagnosis and receive appropriate medical care.

In summary, the Experts' Consensus on the Criteria for the Diagnosis and Grading of Neonatal Asphyxia in China developed by the Neonatal Professional Committee of Chinese Medical Doctor Association will play an active role in standardize the diagnosis and treatment of NA and

avoid/minimize medical disputes. However, since the nature of NA is still poorly understood and the development of medical sciences still has many limitations, this Experts' Consensus is still far from perfect and warrants further revisions in the coming years.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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