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# Prognostic Markers of Neonatal Outcomes in Full Term Neonates Suffering from Perinatal Asphyxia

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## Abstract

### Objective

The aim of this study were, using only the score clinic of Sarnat and Sarnat, the blood markers of asphyxia that are routinely used in all hospitals of our country (Brazil) and the ultrasonography imaging method performed with 24 and 72 hours and 28 days of life, verify if these are sufficient to detect the neurological evolution of the patient.

### Methods

The study was conducted with a prospective cohort of term newborns that suffering perinatal asphyxia by Buonocore criteria (2002). These criteria identify the level of the pH in cord blood that was collected of all newborns and also the blood markers: glutamic oxaloacetic transaminase, glutamic pyruvate transaminase, lactate dehydrogenase and creatine kinase (CKMB).These testes were collected at birth, with 24, 48 and 72 hours of life. The score clinical of Sarnat and Sarnat was performed with 24 hours, 48 hours and 72 hours of life and the ultrasound skull with 24, 48, 72 hours of life and in the end of neonatal period with 28 days of life. The period of study was one year.

### Results

In the study´s period 2989 babies were born. The Buonocore criteria were found in 28 newborn showing a frequency of 1% of perinatal asphyxia. The marker of asphyxia were between the normal value of reference and only de iso-enzyme CKMB was a good marker, com value more than 5,10 ng/mL. The brain ultrasonography was altered with 72 hours of life, but one newborn presented alterations only with 28 days of life. The clinical examination using the clinical score of Sarnat and Sarnat demonstrated that 21,42% presented hypoxic-ischemic encephalopathy. In the ROC curve we observed sensitivity of 85,7%, specificity of 85,7% and accuracy of 85,7% correlated the value of CKMB and the brain ultrasonography of 72 hours of life.

### Conclusions

Perinatal asphyxia may be diagnosed in any hospital if the neonatologist or the neurologist apply the easy score clinical of Sarnat and Sarnat, the iso-enzime CKMB and the serial ultrasonography. In this study the worse alteration was with 72 hours of life, however we must be careful because in one neonate the alteration was present only with 28 days of life.

**Keywords:** Newborn; Blood; Infant; Hypoxic-ischemic; Chi-square; Maternal; Ultrasound; Perinatal

## Introduction

The perinatal asphyxia has been improvements in the last years due a medical knowledge and the care of the pregnant women and her newborn [1]. However in developing countries the perinatal asphyxia continue being the third cause of the neonatal mortality, responsible for 23% [2]. The hypoxic-ischemia encephalopathy (HIE) is a principal consequence with neurologic abnormalities [3,4].

Prevalence of perinatal asphyxia varies from 1 to 6 per 1000 live births. Its main complication is the HIE, with incidence of 0.3 to 2 per 1000 live births in term newborns [5]. Organic changes resulting from asphyxia can be detected through laboratorial markers that show

cellular necrosis. These markers are simples and are performed in all the hospitals. We cited the glutamic oxaloacetic transaminase (GOT), the glutamic pyruvic transaminase (GPT), the lactate dehydrogenase (LDH), and the creatine kinase (CKMB) [6]. Using only the umbilical cord pH and Apgar bulletin is not easy proving that perinatal asphyxia is present. We know that there are excellent markers for perinatal asphyxia and that the hypothermia is the ideal treatment in the first 6 hours of life. However we decide do these work with few and simples blood tests and one image test, ultrasound skull7 that is the reality in not tertiary centers. This test is considered appropriate for not being invasive; it can be performed the bedside with a satisfactory resolution when compared to other, more cost effective methods [7-9].

Then the aim of this study was, using only the simples blood test, the ultrasound skull and the score clinic of Sarnat and Sarnat [10] verify if it is possible detect perinatal asphyxia and neurological evolution of the patient only during the permanence in the hospital. After the discharge all the patients of the hospital return to the ambulatory.

## Methods

It is a transversal study that was performed with a prospective cohort of 28 term newborns with diagnosis of perinatal asphyxia by Buonocore criteria. The patients were born in the Santa Helena Hospital, located in the city of São Paulo, after approval of the Ethics Committee of the related hospital and Science Ethics Committee of the Instituto da Criança do Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo (Brazil) and the signing of informed consent by parents or legal guardians. The study period was one year.

The Buonocore criteria is characterized by the presence, at birth, at least two of the following clinical and laboratory conditions: metabolic acidosis with pH ≤ 7.20 in blood collected from the umbilical vein, Apgar bulletin in the fifth minute of life < 6, need for fraction inspired of oxygen ≥ 40% to maintain an oxygen saturation ≥ 86%. In this study were excluded anyone newborn who presented neurological, cardiac, congenital gastrointestinal malformations, genetic syndromes and metabolic diseases that alone could change the neurological condition of the newborn.

After delivery were collected of the newborn cord blood to dose pH and also the enzymes: glutamic oxaloacetic transaminase (GOT), glutamic pyruvate transaminase (GPT), lactate dehydrogenase and the iso-enzyme creatina kinase- CKMB).The enzymes were collected at birth, with 24, 48 and 72 hours of life. The score clinical of Sarnat and Sarnat [10] was performed in the first 24 hours, with 48 and 72 hours of life and the ultrasound skull with 24,48,72 hours of life and at the final of neonatal period with 28 days of life.

The enzymes GOT, GPT and lactate dehydrogenase were performed at the Siemens unit Dimension RxLMax and CKMB in appliance “Vidas Bi Méneux”. The blood sample of the umbilical vein was collected in heparinized syringe, suitable for realization of the gasometry in the appliance of Radiometer-ABL 500.

The clinical examination according to the criteria of Sarnat and Sarnat [10] was performed on all neonates of the study by the researcher accompanied by the neurologist, with 24, 72 hours and 28 days of life and Doppler ultrasound skull was held with 24,72 hours and 28 days of life by a radiologist of the service, beside the bed, using portable equipment, General Electric brand, with neonatal transducer C721 number, specific for the newborn fontanel.

The clinical criteria of Sarnat and Sarnat [10] measure the severity of neurological impairment of the neonates, which evolved with HIE, classifying the patient in three stages according to level of consciousness, muscle tone, posture, tendinous reflexes, presence or absence of myoclonus and change of autonomic functions.

The calculation of sample was based on the proportion of perinatal asphyxia obtained in the literature, which varies in most studies of 1 to 6 per 1000 live births and hypoxic-ischemic encephalopathy, which varies from 0.3 to 2 per 1000 live births. Considering that this rate in Brazil could be up to 12 times higher, based on study of Lansky and collaborators of 2002, data relating to 28 term neonates [8].

## Statistical Analysis

For the comparison between the results obtained in the ultrasound skull with the blood test was used the McNemar's Chi-square Test. The relation between qualitative variables was evaluated by the Pearson Chi-square test or Fisher’s exact test. For the quantitative variable was used the Student T test or Mann Whitney test. ROC curve was used (Receiver Operating Characteristics) and calculated the AUC (area under the curve) to identify which point of cut would be better to differentiate patient with abnormal ultrasound skull of patients with normal ultrasound skull. For this reason, it has been calculated the sensitivity, specificity and accuracy of different cut-off points. In all statistical analysis was adopted a significance level of 5%. These calculations were performed using the software SPSS 16.0 for Windows.

## Results

Of 2989 live births during the period of study, 28 neonates, presented perinatal asphyxia (1% of the total of births) and the hypoxic-ischemic encephalopathy (HIE) was evidenced in 21,42%.

In relation to the maternal antecedents and of the neonates noted that maternal age ranged from 19 to 40 years, had a bigger number of mothers for the first time (64%), caesarean section (60.7%), and incomplete prenatal follow-up (67.9%) and of neonates of the masculine sex (57.2%).

The enzyme CKMB proved to be a good marker of asphyxia; therefore, all values were superior to 5.10 µg/mL and positively correlated with the alterations presented in the clinical examination (Tables 1-3) and with cranial ultrasonography (Table 4). The values of other enzymes, such as GOT (24 h), GOT and GPT (72 h) positively correlated with ultrasonography changes, which showed changes in 3.5% of patients within 24h of life, within 72 h and 28.6% within 28 days.

Ultrasound skull within 28 days showed statistically significant increase in the percentage of abnormal results when compared with the observed with 24 h ($p = 0.039$), although the stages of Sarnat [10] have improved, with the largest number of patients in stage I over the 28 days (Tables 2 and 3).

For the McNemar Chi-square test, it was found that there was statistical significant difference in the results of normal ultrasound skull with 24 hours (96.4%), when compared with 28 days (71.4%) ($p=0.039$).

In this research, with the objective to evaluate if the CKMB collected 24 hours after the birth differentiates patients with normal ultrasound skull of 72 hours from abnormal, had examined some points of cut to determine that one that presented biggest sensitivity, however it has been observed the value of the specify and accuracy. This evaluation was performed generating the ROC curve, calculating the area under the AUC (Figure 1), where it is possible to note sensitivity of 85.7%, specifity of 85.7%, and accuracy of 85.7%.

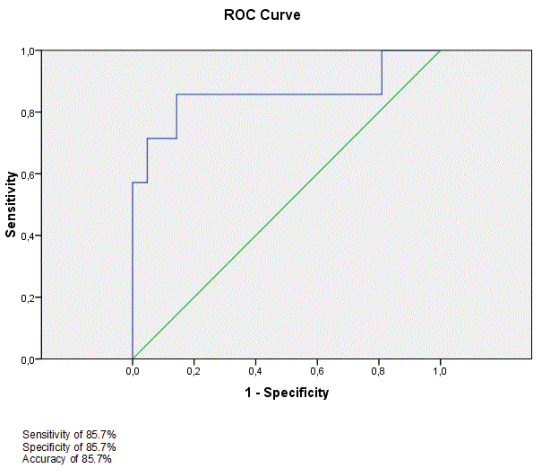


**Figure 1:** Curve ROC (Receiver Operating Characteristics) indicating the area under the curve in patients with normal and abnormal cranial ultrasonography with 72 hours correlating with values of creatina kinase (CKMB) 24-hour.

In the comparison of the evaluation of Sarnat [10] with 24 hours and 24-hour of ultrasound skull did not have statistical significant association, however, had statistical significant association between the evaluation of Sarnat [10] with ultrasound skull with 72 hours ($p<0,001$) and 28 days of life ($p<0,001$). The most frequent brain damage, detected by ultrasound skull, was ventricular dilatation, intracranial hemorrhage and different degrees of hypoxic ischemic encephalopathy.

In relation to the development of hypoxic ischemic encephalopathy it was noted 14 neonates with 24 hours of life that presented stage I of Sarnat [10], six neonates stage II and eight neonates stage III. With 72 hours, seven days and 28 days of life 21 neonates presented stage I, 2 neonates stage II, 5 neonates stage III and two presented convulsive crises in the first 24 hours of life (Tables 1-3).

The results showed that there was no statistically significant difference in median markers: GOT, GPT, LDH and CKMB collected with 24 hours of life and Sarnat 10 stages [10], evaluated in the same period ($p<0.05$) (Table 1). However, there was no statistical difference in median markers GPT and LDH collected with 24 hours of live, when compared with the stages of Sarnat to the 28 days of life ($p>0.05$) (Table 2); for the GOT markers and CKMB this difference was significant ($p < 0.05$).

Moreover, it had statistical significant difference in the medium markers GOT, GPT, LDH and CKMB within 72 hours and the stages of Sarnat [10] evaluated with 28 days ($p<0.05$) (Table 3).

| Sarnat [10] 24 Hours | | | |
|---|---|---|---|
| | **Stage I (n=14)** | **Stage II (n=6)** | **Stage III (n=8)** |
| **GOT24 h** | 53 (47–75) | 74 (61–85) | 89 (78–107) |
| **GPT24 h** | 28 (23–31) | 30 (26–36) | 42 (32–60) |
| **LDH24 h** | 502 (377–712) | 638 (508–833) | 798 (689–900) |
| **CKMB24 h** | 22,10 (14,70-30,29) | 26,66 (20,50-52,35) | 70,35 (54,67-85,18) |
| GOT: glutamic oxaloacetic transaminase; GPT: glutamic pyruvate transaminase; LDH: lactate dehydrogenase; CKMB: creatine kinase | | | |

**Table 1:** Data of the sanguineous markers collected 24 hours after the birth of the 28 neonates suffering perinatal asphyxia diagnosis according to the criterion of Sarnat [10] with 24 hours.

| Sarnat [10] 28 days | | | | |
|---|---|---|---|---|
| | **Stage I (n=21)** | **Stage II (n=2)** | **Stage III (n=5)** | **p** |
| **GOT24 h** | 61 (47–77) | 102 (90–114) | 88 (80–100) | 0,016 |
| **GPT24 h** | 30 (26–34) | 40 (28–53) | 50 (34–68) | 0,060 |
| **LDH24 h** | 530 (460–712) | 896 (555–1237) | 807 (789–900) | 0,054 |
| **CKMB24 h** | 22,38 (15,10–14,19) | 54,67 (47,00 – 62,34) | 82,35 (72,20–88,01) | 0,001 |
| GOT: glutamic oxaloacetic transaminase; GPT: glutamic pyruvate transaminase; LDH: lactate dehydrogenase; CKMB: creatine kinase | | | | |

**Table 2:** Data of the sanguineous markers collected 24 hours after the birth of the 28 neonates suffering perinatal asphyxia diagnosis according to the criterion of Sarnat [10] with 28 days.

| Sarnat [10] 28 days | | | | |
|---|---|---|---|---|
| | **Stage I (n=21)** | **Stage II (n=2)** | **Stage III (n=5)** | **p** |
| **GOT24 h** | 43 (34–55) | 90 (62–118) | 84 (59–84) | 0,016 |
| **GPT24 h** | 26 (25–32) | 38 (30–47) | 48 (44–86) | 0,060 |
| **LDH24 h** | 486 (331–564) | 794 (577–1012) | 600 (562–625) | 0,054 |
| **CKMB24 h** | 12,39 (9,50–15,20) | 20,94 (11,57 – 30,32) | 41,23 (36,00–42,00) | 0,001 |
| GOT: glutamic oxaloacetic transaminase; GPT: glutamic pyruvate transaminase; LDH: lactate dehydrogenase; CKMB: creatine kinase | | | | |

**Table 3:** Data of the sanguineous markers collected 72 hours after the birth of the 28 neonates with perinatal asphyxia diagnosis according to the criterion of Sarnat [10] with 28 days.

It was observed that collected GOT and CKMB 24 hours after birth differed statistically patient with abnormal ultrasound skull to those with this normal examination to 28 days ($p<0.05$). Neonates with abnormal ultrasound skull with 72 hours presented the medians of

GOT, GPT and CKMB with 72 hours of life statistically larger, when compared with neonates with normal ultrasound (Tables 4 and 5). In addition, patients with abnormal ultrasound skull with 28 days presented medium of TOG, GPT, LDH and CKMB with 72 hours of life statistically larger than those with normal cranial ultrasonography with 28 days (Table 6).

## Discussion

Children with perinatal asphyxia may have a bad evolution with varying degrees of neurologic sequelae in the short, medium and long term. The present research conducted with the objective of recognizing precociously term neonates suffering perinatal asphyxia with simples blood test and one sequential neurologic score, and verifies those that have precociously neurological changes until hospital discharge or 28 days of life also with simple image test.

| **Cranial ultrasonography with 72 hours** | | | |
|---|---|---|---|
| | **Abnormal (n=7)** | **Normal (n=21)** | **P value** |
| **GOT24 h** | 90 (80–114) | 68 (49–77) | 0,020 |
| **GPT24 h** | 50 (28–68) | 30 (26–34) | 0,055 |
| **LDH24 h** | 789 (555–900) | 537 (460–736) | 0,140 |
| **CKMB24 h** | 72,20 (47,00–88,01) | 22,40 (15,21–34,97) | 0,004 |
| GOT: glutamic oxaloacetic transaminase<br>GPT: glutamic pyruvate transaminase<br>LDH: lactate dehydrogenase<br>CKMB: creatine kinase | | | |

**Table 4:** Data of the sanguineous markers collected 24 hours after the birth of the 28 neonates with perinatal asphyxia diagnosis according the cranial ultrasonography result with 72 hours.

Clinical stages Sarnat [10] were related with the laboratory results of some enzymes (TOG, GPT, LDH, CKMB) collected at birth, at 24 hours and 72 hours and with the cranial ultrasonography findings, performed at 24 and 72 hours and in the 28th day of life.

Traditionally only the note of the bulletin of Apgar described in 1953 provided a definition of perinatal asphyxia [11]. The values of this test were questioned by several studies, such as Pereira and colleagues, held in the city of Porto Alegre, in 1996, with 76 term neonates, with the objective to relate the value of the Apgar bulletin with the pH of the umbilical artery and vein. The authors had found low correlation between clinical and laboratories parameters, with pH values to define asphyxia [11]. The same authors, in 1999, in research involving term neonates, also concluded that the Apgar bulletin less than 7 in the fifth minute, associated with the cord blood were not good indicators of evolution of organic failure [12].

Sato et al. [13], observed that term neonates with sagittal brain damage developed serious neurological changes in the long term, despite performing a few clinical manifestations at the beginning. This suggests that the use of the criterion of Buonocore et al. [9], which was used in this research, is more comprehensive than others, since it considers too neonates with moderate and not just serious asphyxia.

The criteria of ACOG used value of pH collected in umbilical vessels <7.0. We agreed that this criterion is more reliable in neonates with severe asphyxia, but those with moderate asphyxia that can have long-term neurological abnormalities may not be diagnosed.

The prevalence of perinatal asphyxia in this study was of 0.93 per 1000 live births, lower level than quoted in the literature, which is 1 to 6 per 1000 live births. This low level may be associated to the characteristics of the place of the study, for a population of a better socioeconomic level, beyond of the inclusion of term neonates. Prevalence of perinatal asphyxia studies conducted in Brazil, analyzing the declarations of live births, showed in 1991, a prevalence of 4.68 per 1000 live births in the city of Ribeirão Preto. In 1999, the prevalence in Brazil was of 2.1% and 1.4% in the South and Southeast and 6.2% in northeast [14]. These results have relation with the economic situation between different regions of the country.

The prevalence of hypoxic-ischemic encephalopathy in this survey was 0.2 per 1000 live births, also inferior to the cited one in the literature, that is of 0.3 the 1.2 for 1000 live births. However, among the 28 neonates, we observed by the score of Sarnat [10] moderate HIE in six neonates and severe in eight neonates. Research carried out in a public hospital in the city of São Paulo, by Cruz and Ceccon [15], in 2010, showed a much bigger frequency of 3. 2 for 1000 live births in relation to the hypoxic-ischemic encephalopathy. We think that this occurs because this hospital receives a large number of pregnant women without prenatal.

| | **USG skull with 72 hours of life** | | |
|---|---|---|---|
| | **Abnormal** | **Normal** | **p-value** |
| | (n=7) | (n=21) | |
| **TGO72 h** | 92,3 ± 52,6 | 47,1 ± 16,3 | 0,064 |
| **TGP72 h** | 61,3 ± 43,4 | 28,0 ± 7,4 | 0,088 |
| **DHL72 h** | 767,7 ± 490,1 | 472,5 ± 194,6 | 0,167 |
| **CKMB72 h** | 30,32 (13,00–41,23) | 12,79 (9,5–19,18) | 0,014 |

**Table 5:** Blood markers data collected in 72 hours according to the result of USG skull 72 hours of the 28 newborns with perinatal asphyxia diagnosis.

Gonzales de Dios [16] evaluated the repercussions in neonates suffering perinatal asphyxia using also enzymes and GOT and GPT. He noted that these enzymes increased by 33% of neonates suffering severe perinatal asphyxia, considering this as a transitory repercussion of perinatal asphyxia than as a marker of neurological development.

Karlsson et al. [17], in Sweden, conducted a prospective study with term neonates suffering perinatal asphyxia to verify that there was no elevation of liver enzymes and if this elevation associated with the presence of neurological changes. This study showed that 12 of the 26 neonates studied showed elevation of GOT and GPT, similar result to the present casuistry, showing that perinatal asphyxia may induce hepatic lesions secondary to hypoxia.

In relation to myocardial lesion markers, chose it enzyme CKMB and observed that this proved useful as high values correlated positively with the presence of neurological and ultrasonography changes. The CKMB in the umbilical cord blood showed values of 62.95 ng/ml; with 24 hours of life these values had reached 326.31

ng/ml and with 72 hours of life they had decreased for 63.91 ng/ml. Cruz and Ceccon [14], observed in 28 term neonates that the elevation of CKMB correlated with severe metabolic acidosis and greater degree of neurological deficiency.

Kanik et al. [18] evaluated if the myocardial dysfunction in neonates suffering hypoxic-ischemic encephalopathy is a significant predictor of morbidity. For this they included in study 34 term neonates suffering hypoxic-ischemic encephalopathy and performed the dosage of serum CKMB with 24, 48 and 72 hours of life, showing a significant correlation between the elevation of this enzyme and the occurrence of hypoxic-ischemic encephalopathy the same that occurs in our study.

| Skull USG with 28 Days | | | |
|---|---|---|---|
| | **Abnormal (n=8)** | **Normal (n=20)** | **p- value** |
| **TGO72 h** | 73 (52–101) | 44 (34–57) | 0,013 |
| **TGP72 h** | 46 (28–67) | 26 (24–32) | 0,021 |
| **DHL72 h** | 588 (528–818) | 490 (324–564) | 0,028 |
| **CK-MB72 h** | 33,16 (21,46–41,61) | 12,34 (9,48–17,19) | 0,002 |

**Table 6:** Blood markers of data collected after 72 hours of birth of 28 infants with diagnosis of perinatal asphyxia according to the result of USG skull 28 days.

In this present research, patients with abnormal ultrasound skull, with 72 hours of life, presented the medians of GOT and CKMB, collected 24 hours after birth, statistically higher than those presented by patients with normal ultrasound skull (Table 4). The choice of ultrasound skull was due to examination be made at person's beside and does not need sedation for their achievement [19].

Brain lesions observed on ultrasound of neonates suffering perinatal asphyxia are varied, being the peri/intraventricular hemorrhage the most prevalent [20], which also occurred in this casuistry, with frequency of 21.4%; the most frequent brain lesions were ventricular dilatation, intracranial haemorrhage of varying degrees and HIE.

Garcia et al. [7] emphasizes the importance of the ultrasound skull does not inhabit only in the diagnosis of acute pathologies, but also in the fact of being a useful examination to define neurological groups of risk for neurological sequelae in long-term follow-up.

Concluding, the criteria of Buonocore et al. [9] remain suitable for the definition of asphyxia but are included neonates not only with severe asphyxia but also with moderate, and the clinical score of Sarnat [10] continues being sufficiently useful for evaluating of neurological evolution of neonates suffering perinatal asphyxia. Optimum blood marker of perinatal asphyxia in this casuistry was the enzyme CKMB, which correlated with the clinical second Sarnat [10] and with changes in cranial ultrasonography. Curve ROC showed that the 24-hour values of CKMB in relation to the cranial ultrasonography of 72 hours presented sensitivity of 85.7%, specifity of 85.7% and accuracy of 85.7% (Figure 1).

Therefore, it is necessary the precocious identification of children at risk of neurologic sequelae asphyxiated and precocious selection of those who could benefit from neuroprotective therapeutic.

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