Original Article

Lactate and S100 protein as early biochemical indicators of birth neonatal asphyxia caused by intrauterine umbilical cord strangulation: a medicolegal view

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ABSTRACT

Background: From a forensic pathologist's perspective, there are several aspects of the perinatal postmortem that are particularly important if the baby was born alive or dead. In cases of litigation for perinatal morbidities occurring in hospitals, access to the obstetric and neonatal notes if the baby is born alive and dies a few hours or days later is essential to reach a correct interpretation and conclusion. Hypoxic ischemic encephalopathy (HIE) after prenatal asphyxia is an important cause of neonatal morbidity and long-term neurological disability. It has many causes including intrauterine strangulation by umbilical cord (nuchal cord). Failure of early diagnosis of neonatal asphyxia and its treatment is considered a medicolegal negligence against the doctors. **Aim**: The present study aimed to use cord blood lactate & S100 protein levels as early markers of neonatal hypoxia caused by nuchal cord to minimize the risk of medicolegal liabilities against the doctors and hospitals. **Methods**: This is a comparative cross-sectional study conducted on 30 hypoxic neonates due to intrauterine cord strangulation. Lactate & S100 protein levels in the cord blood were measured. These were compared to 30 apparently healthy neonates matched in age, sex and body weight as a control group. **Results**: Lactate & S100 protein levels in cord blood were a higher significant difference in HIE neonates than control group. **In conclusion**: lactate & S100 protein levels in cord blood could be used as an early marker for diagnosis of neonatal HIE.

Key words: Hypoxic, ischemic, encephalopathy, Nuchal cord, Lactate, S100 protein.

I. INTRODUCTION

With a reported prevalence of 100-250/1000 live births in the poor countries, birth asphyxia is a major cause of infant illness and mortality (Lawn et al., 2009). Birth asphyxia is the leading cause of early newborn death in the world, accounting for 23% of all neonatal deaths. Every year, between 4 and 9 million babies are born, of which 1.2 million die and a similar number acquire serious neuro-disabilities such as cerebral palsy, epilepsy, and developmental delay (Manandhar and Basnet, 2019).

The umbilical cord encircling the neck which termed {nuchal cord} is a common umbilical abnormality in man. It has been found in 23-37 percent of human pregnancies, with the rate increasing as the pregnancy progresses. (Clapp et al., 2003). Nuchal cord can be single or multiple and tight or loose. [Type A] cord wraps around the neck in 360 degrees, wherein, the placental end crosses over the umbilical end, entangling the neck in an unlocked pattern whereas in [Type B] pattern the cord cannot be undone and ends up as a true knot. Here, the placental end crosses under the umbilical end, entangling the neck in a locked pattern (Collins, 2002).

Multi-organ damage and cardiovascular failure were major outcomes of perinatal hypoxia. Postnatal neurological impairment may be caused by myocardial injury, right ventricular dysfunction, abnormal circulatory transition, and defective autoregulation. As a result, adequate monitoring and specific therapy are required following an asphyxial insult (Kluckow, 2011).

Lactate is invariably produced in the event of hypoxia and poor tissue perfusion. When a clinical reduction of oxygen and substrate delivery occurs, aerobic metabolism through Krebs cycle cannot be sustained and tissues need anaerobic metabolism to meet the energy requirement. This leads to increased production and accumulation of blood lactate and reflects tissue hypoxia (Jin et al., 2013). Once produced prenatally, the placenta excretes it. During neonatal period liver and kidneys control its excretion. Many observational studies have shown that lactate analysis has similar or better predictive properties compared with pH in identification of short-term neonatal morbidity (Borruto et al., 2008).

The S-100 protein is a calcium binding protein found in high concentrations in astroglial cells. It regulates calcium-dependent signaling in neuronal differentiation, outgrowth, and apoptosis. It is considered as an indicator of glial activation and/or death in many disorders of the CNS (Sedaghat and Notopoulos, 2008).

Studies have shown associations between the severity of neuronal injury and the concentration of S100 which has led to special interest in S100 in asphyxiated newborns. However, there have only been a few studies investigating brain injury biomarkers from umbilical cord blood sampled at birth (Wirds et al., 2003; Gazzolo et al., 2009; Michetti et al., 2012).

Pregnant women are worried about the occurrence of nuchal cord. The concern depends on their education status, but in general, mothers suspect that nuchal cord can be accountable for poor adverse effect of the newborn and its further development. Thus, mothers who have had their newborn showing nuchal cord and a retarded development blame midwifes and obstetricians and search for a legal dispute claiming a broad spectrum from

compensation to an occupational ban (Kong et al., 2015).

For this medicolegal aspect, the current study was designed to use cord blood lactate & S100 protein levels as early markers of neonatal hypoxia caused by nuchal cord to reduce the risk of medicolegal negligence & liability against the doctors.

II. PATIENTS AND METHODS:

2.1 Type of study:

The current study is a cross- sectional study that was conducted after obtaining ethical approval from the ethical committee, Faculty of Medicine, Benha University. All participants received detailed information concerning the aims of this research work, and informed consent was obtained from the parents of each of them before the beginning of the study.

2.2 Patients:

This study was conducted on 30 asphyxiated full-term neonates delivered either vaginally or by cesarean section at Gynecology & Obstetric department, Faculty of Medicine, Benha University Hospitals, Egypt. The study was carried out at the period between beginnings of June till the end of September 2021, so we chose the sample size of the study matching the inclusion and exclusion criteria. These were compared with 30 age-matched apparently healthy full-term neonates with no obstetrical problems as a control group.

- Inclusion criteria

1.Full-term neonates delivered with wrapped umbilical cord around his neck one or more times.

2.Newborns were considered to be hypoxic when they fulfill the criteria guided by the American Academy of Pediatrics (AAP) (Blackmon et al., 2006):

Persistence of an expanded Apgar score of 0-3 for longer than 5 minutes, neonatal neurologic complications (e.g., seizures, coma, and hypotonia), base deficit > 10 and multiple organ involvement (e.g., kidney, lungs, liver, heart, intestines).

- Exclusion Criteria:

1.Preterm neonates delivered before 36 weeks gestation.

2.Newborn delivered with major congenital anomalies or chromosomal abnormality.

3.Traumatic brain injuries.

4.Maternal drug addiction.

5.Intrauterine infection, and general anesthesia during birth process.

All patients and controls were subjected to full maternal history taking, full detailed history of resuscitation, Apgar score at 1 and 5 minutes, thorough physical examination by a pediatrician. System examination with special emphasis on neurological examination with assessment of severity of hypoxic ischemic encephalopathy using Sarnat and Sarnat staging.For both groups the following data wascollected:

- Socio-demographic data of cases: age, gender and residence.
- Medico-legal aspects of cases: cause, pattern, site, type and outcome of
- injuries. Causative instruments, types of treatment (surgical or conservative) provided, and condition of the case at discharge time.

2.3 Sample collection:

The umbilical cord blood was extracted immediately after birth from double-clamped segment of the umbilical cord into 3 ml plastic syringes flushed with a heparin solution. Upon arrival of the samples in the laboratory, blood gas, lactate, and glucose levels were measured. From all neonates included in the study, 1mL of umbilical cord blood samples was collected then centrifuged at 2500 rpm for 5 min and frozen at -80°C. S100 protein level was measured in these samples.

2.4 Determination of umbilical cord blood lactate:

The lactate is changed into pyruvate and hydrogen peroxide by lactate oxidase. The hydrogen peroxide reacts in the presence of peroxidase with chromogen precursors giving a purple compound. The intensity of the color is proportional to concentration of lactate in the tested sample. The DXC-800 Automated Chemistry Analyser (Beckman Coulter) was used for lactate assays.

2.5 Determination of S100 protein in umbilical cord blood:

The umbilical cord blood' S100 protein was measured by ELISA kit. The purified anti-S100 protein antibody was precoated onto 96-well plates, and the horseradish peroxidase-conjugated anti-S100 antibody was used as detection antibodies. The standards, test samples, and HRP-conjugated detection antibody were added to the wells, and mixed and incubated; thereafter, unbound conjugates were washed away with wash buffer. Tetramethyl benzidine (TMB) substrates (A and B) were used to visualize HRP enzymatic reaction. TMB was catalyzed by HRP to produce a blue color product that changed to yellow color after adding acidic stop solution. The density of the yellow product is proportional to the S100 amount of sample captured in plate. The optical density absorbance was read at 450 nm in a microplate reader, and then the concentration of S100 was calculated (Chongqing Biospes Co. Ltd Chongqing, China).

2.6 Sarnat & Sarnat staging:

All newborn delivered with hypoxia due to nuchal cord will be graded according to Sarnat & Sarnat staging (Gardiner et al., 2009).

- **Statistical analysis:**

Data were analyzed using SPSS software, version 22.0 (IBM, Armonk, NY, USA) for Windows. Categorical data were presented as number and percentages, Chi square ($\chi 2$) test was used to analyze them. Quantitative data were tested for normality using Shapiro-Wilks test assuming normality at $P>0.05$. Normally distributed variables were expressed as mean ±standard deviation and analyzed by Student "t" test and ANOVA for 2 and 3 independent groups respectively, while non parametric variables were presented as median and range, and analyzed by Mann Whitney U test (ZMWU) for 2 independent groups. Significant ANOVA was followed by post hoc multiple comparisons using Bonferroni adjusted tests to detect the significant pairs. ROC curves were constructed to assess the performance of the studied markers as early detection of NA. $P \leq 0.05$ was considered significant.

Table (1): Sarnat & Sarnat staging system

	Grade I Mild	Grade II Moderate	Grade III Severe
Alertness	Hyperalert	Lethargy	Coma
Muscle tone	Normal or increased	Hypotonic	Flaccid
Seizures	None	Frequent	Uncommon
Pupils	Dilated, reactive	Small, reactive	Variable, fixed
Respiration	Regular	Periodic	Apnoea
Duration	< 24 Hours	2 - 14 Days	Weeks

III. RESULTS

All children were examined by a pediatrician immediately after birth. All children have been born after the 38th week of gestation. Of all nuchal cords have been a single entanglement in 27 cases, 3 children presented a double umbilical cord entanglement.

Regarding the perinatal history, there was no statistically significant difference between study and control groups regarding gestational age, mode of delivery, sex, weight, head circumference and Length. However, there was a highly significant difference between studied groups according to Apgar score (1, 5 minutes) as illustrated in (Table 2).

Regarding to Sarnat & Sarnat stage of cases group, stage I and II represented 36.7% for each one while stage III represented 26.7% as shown in (Figure 1).

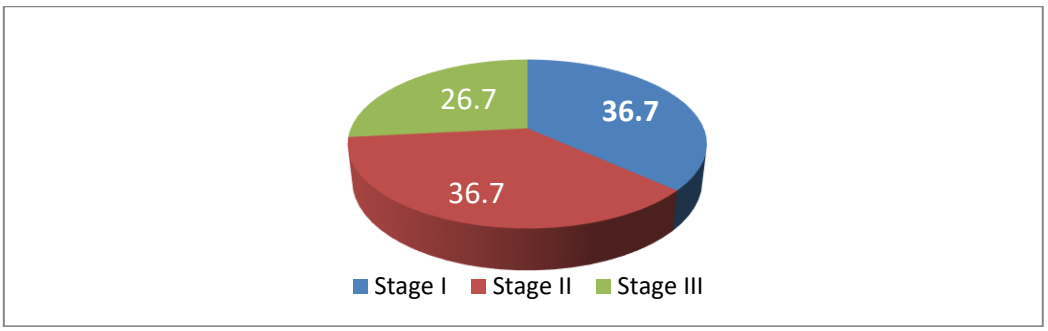

Figure (1): Sarnat& Sarnat stage of cases group.

Table (3) revealed that there was a statistical high significant decrease of the level of umbilical cord PH, base excess among cases group. Moreover, there was statistically significant increase regarding lactate and S100 protein levels.

Analysis of receiver operating characteristics (ROC) curve of the studied markers for neonatal asphyxia caused by intrauterine umbilical cord strangulation was demonstrated in tables (4 & 5) and figure (2). As regards the studied markers in all studied groups, serum S100 protein level had a sensitivity of 100%and specificity of 96.7%, PPV of 96.8%, and NPV of 100%, which is superior to other markers such as lactate.

There were no significant statistical differences between the studied markers umbilical cord PH, base excess, umbilical lactate and umbilical S100 protein regarding the mode of delivery as showed in table 6, while table (7) revealed that S100 protein level was significantly higher in grade III HIE according to Sarnat & Sarnat stage.

Table (2): Comparison between the study and control groups regarding perinatal history.

Variable		Cases (n=30)		Controls (n=30)		Test of significance	P
Gestational age (week)	Mean±SD	38.3±1.1		38.5±0.7		St.”t= 0.61	0.54 (NS)
		No.	**%**	**No.**	**%**	**χ2**	**P**
Mode of delivery	CS	15	50.0	18	60.0	0.61	0.43 (NS)
	NVD	15	50.0	12	40.0		
Sex	Male	15	50.0	15	50.0	0.0	1.0 (NS)
	Female	15	50.0	15	50.0		
Weight (gm)	Mean±SD	3736.7±298.7		3689±408.4		0.52	0.6 (NS)
Head circumference (cm)	Mean±SD	35.4±2.7		35.1±0.97		0.71	0.47 (NS)
Length (cm)	Mean±SD	48.4±1.18		49.0±0.96		1.85	0.069 (NS)
APGAR 1 min	Median (range)	2.0 (0-4)		8.0 (7-9)		ZMWU= 6.7	<0.001 (HS)
APGAR 5 min	Median (range)	4.0 (1-6)		9.0 (8-10)		ZMWU= 6.83	<0.001 (HS)

SD: standard deviation, St.”t: Student “t” test; n: number, cm: centimeter, mg: milligram, CS: cesarean section, NVD: normal vaginal delivery, ZMWU= Z value of Mann Whitney U test, NS: non-significant, HS: Highly significant.

Table (3): Comparison between the study and control groups regarding umbilical cord PH, lactate and S100 protein.

Variables	Patients (n=30)			Controls (n=30)			St. "t"	P value
	Mean	± SD	Range	Mean	± SD	Range		
Umbilical cord PH	6.99	0.12	6.68-7.2	7.24	0.03	7.2-7.32	10.3	<0.001 (HS)
Umbilical cord base excess	-15.16	2.37	-19-(-11)	-2.00	3.62	-8.0 - 4	16.6	<0.001 (HS)
umbilical lactate (mmol/l)	7.50	3.12	3.1-14.1	3.16	1.05	1.9-5.1	7.19	<0.001 (HS)
12-24 hr lactate (mmol/l)	3.64	1.90	0.8-7.1	1.20	0.38	0.8-2.1	6.9	<0.001 (HS)
umbilical S100 protein (ug/l)	4.56	1.06	3.01-6.8	1.39	0.45	1.02-3.24	14.9	<0.001 (HS)

SD: standard deviation, n: number, St."t: Student "t" test, hr: hour, HS: Highly significant.

Table (4): The performance of the studied markers as early indicators of neonatal asphyxia caused by intrauterine umbilical cord strangulation.

Variable	Cutoff	Sensitivity %	Specificity %	PPV %	NPV %	AUC	SE	95%CI	P
umbilical lactate (mmol/l)	≥4.6	83.3%	90%	89.3%	84.4%	0.924	0.032	0.86-0.98	<0.001 (HS)
12-24 hr lactate (mmol/l)	≥1.45	86.7%	86.7%	86.7%	86.7%	0.897	0.045	0.81-0.98	<0.001 (HS)
umbilical S100 (ug/l)	≥2.54	100%	96.7%	96.8%	100%	0.994	0.006	0.98-1.0	<0.001 (HS)

HS: Highly significant, hr: hour

Table (5): Comparing the performance of the studied markers.

Paired-Sample Area Difference Under the ROC Curves				
Test Result Pair(s)	**Test and significance**		**AUC Difference**	**Std. Error Difference**
	Z	**P**		
Umbilical lactate – 12-24 hr lactate	0.735	0.462 (NS)	0.027	0.275
Umbilical lactate –umbilical S100	-2.249	0.025 (NS)	-0.071	0.195
12-24 hr lactate – umbilical S100	-2.229	0.026 (NS)	-0.097	0.226

NS: non-significant, hr: hour

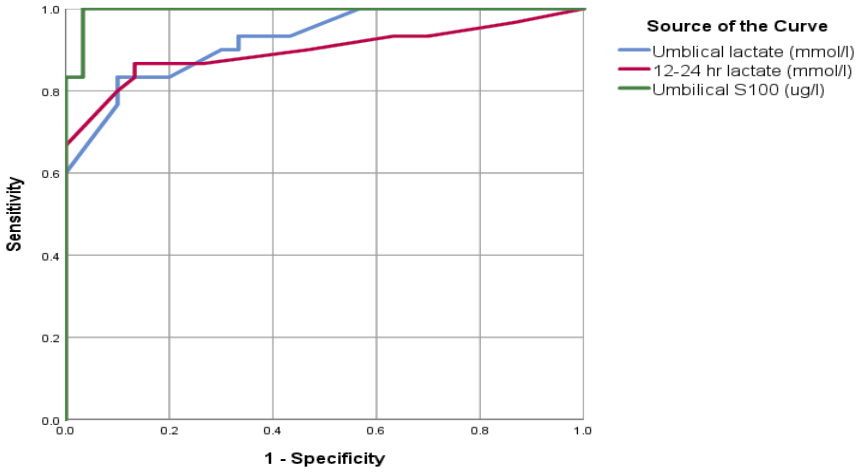

Figure (2): ROC curve for the performance of the studied markers as early indicators of neonatal asphyxia caused by intrauterine umbilical cord strangulation.

Table (6): Comparing the studied markers according to mode of delivery.

Variables	**NVD (n=15)**		**CS (n=15)**		**St."t"**	***P value***
	Mean	**± SD**	**Mean**	**± SD**		
Umbilical cord PH	7.03	0.11	6.96	0.13	1.5	0.14 (NS)
Umbilical cord base excess	-14.60	2.13	-15.73	2.54	1.32	0.19 (NS)
Umbilical lactate (mmol/l)	7.68	3.42	7.32	2.91	0.31	0.76 (NS)
12-24 hr lactate (mmol/l)	3.88	1.72	3.41	2.10	0.66	0.51(NS)
Umbilical S100 protein (ug/l)	4.76	1.00	4.36	1.12	1.03	0.31 (NS)

NVD: normal vaginal delivery, CS: cesarean section, n: number, St."t: Student "t" test, hr: hour, NS: non-significant

Table (7): Comparing the studied markers according to Sarnat & Sarnat stage.

Variables	Stage I (n=11)		Stage II (n=11)		Stage III (n=8)		*ANOVA*	*P value*
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**		
Umbilical cord PH	7.09	0.075	7.01	0.085	6.84*†	0.094	19.7	<0.001 (HS)
Umbilical cord base excess	-13.0	1.09	-15.1*	1.37	-18.2*†	0.88	47.3	<0.001 (HS)
Umbilical lactate (mmol/l)	4.75	1.19	8.77*	1.91	9.52*	3.77	11.98	<0.001 (HS)
12-24 hr lactate (mmol/l)	1.78	.75	4.31*	1.40	5.28*	1.45	21.7	<0.001 (HS)
Umbilical S100 protein (ug/l)	3.75	.63	4.76*	.89	5.39*	1.04	9.05	=0.001 (HS)

*significant in comparison with stage I, †significant in comparison with stage II, n: number, hr: hour, HS: Highly significant.

IV. DISCUSSION

Umbilical cord is the connecting link between the foetus and the placenta through which foetal blood flows to and from the placenta. It extends from the foetal umbilicus to the foetal surface of the placenta. Excessively long cords are linked with cord entanglement. Cord compression is one of the postulated factors for birth asphyxia (Verma et al., 2020).

Hypoxic ischemic encephalopathy (HIE) after prenatal asphyxia is an important cause of neonatal morbidity, neurological disability and mortality and its early prediction is particularly important because of the brief therapeutic window and possible side effects of neuro protective interventions (Guan et al., 2017; Graham et al., 2018).

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In the present study, there was no statistically significant difference between the HIE group due to strangulation by umbilical cord and control group as regards gestational age, sex, head circumference, weight, length, and mode of delivery. While as regard Apgar score, the median of Apgar score at 1 and 5 minutes was significantly lower than the control which had normal Apgar score (7 - 9 at 1 and 5 minutes), these results were in agreement with Leybovitz-Haleluya et al., 2019 who illustrated that low Apgar score was associated with many problems in the newborns.

The results of the current study revealed that umbilical cord blood lactate and S100 protein level in HIE group due to umbilical cord strangulation were statistically significantly higher than control group, and the umbilical cord blood lactate level was detected in grade III HIE according to Sarnat & Sarnat staging.

These results were in line with some studies which found that serum lactate level was higher in hypoxic neonatal group than healthy one (Gasparović et al., 2012; Simovic et al., 2015). Also, the study of Chiang et al. (2016) revealed that higher serum lactate in hypoxic neonates and higher level was found in grade III HIE.

The current work showed that S100 protein levels were significantly higher in hypoxic neonates due to cord strangulation than control. This is in accordance with the findings of Beharier et al. (2012) and Douglas-Escobar et al. (2012).

The present study compared S100 protein results with the different clinical stages of the Sarnat & Sarnat clinical classification for HIE diagnosis and showed that S100 protein level was higher in grade III HIE. This is in accordance with the findings of Qian et al. (2009).

According to the ROC curve, the present study revealed that cord blood can be used to diagnose neonatal hypoxia caused by intrauterine strangulation by umbilical cord with sensitivity 83.3% and specificity 90%. This is in agreement with studies which illustrated that umbilical lactate level can be used in a middle-low resource setting as a measurement of intrapartum hypoxia, with reasonable sensitivity and specificity (Haiju et al., 2008; Allanson et al., 2018).

Also, the current study showed that S100 protein can be used for diagnosis of neonatal hypoxia due to intrauterine cord strangulation with higher sensitivity and specificity (100% & 96.7% respectively) than

cord blood lactate. These results were in line with the study which stated that serum S100 protein level had a sensitivity of 97% and specificity of 91%, with a diagnostic accuracy of 94%, which is superior to other markers such as lactate, which showed a sensitivity of 94% and specificity of 87% (Beken et al., 2014). Moreover, S100 protein is superior to other markers such as NRBCs, which showed a sensitivity of 83.4% and specificity of 73.5% (Boskabad et al., 2010).

V. CONCLUSION

This study concluded that both umbilical blood lactate and S100 protein could be used as early predictors in diagnosis of hypoxic ischemic encephalopathy caused by intrauterine cord strangulation which is very easy, cheap and non-invasive measures.

VI. LIMITATIONS

One of the limitations of the current study could be related to the small sample size as it is being a single-center study. Hence, we suggest future larger multicenter studies.

VII. RECOMMENDATIONS

On the light of the results of the present study, we recommend using S100 protein and lactate in umbilical cord blood as early markers of neonatal asphyxia caused by nuchal cord because they are simple, non-invasive and cheap. Also, further studies on another useful biomarker for early detection of neonatal asphyxia should be done.

VIII. CONFLICTS OF INTEREST:

The authors of the study declared that there are no conflicts of interest.

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الملخص العربي

اللاكتات وبروتين اس100 كمؤشر بيوكيميائي مبكر لاختناق الأطفال حديثي الولادة عن طريق خنق الحبل السري داخل الرحم: وجهة نظر طبية قانونية

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مقدمة البحث: من وجهة نظر إختصاصي الطب الشرعي ، هناك العديد من الجوانب ذات أهمية عن الوفاة خاصة في الفترة المحيطة بالولادة إذا ولد الطفل حياً أو ميتاً. في حالات التقاضي بشأن أمراض الفترة المحيطة بالولادة التي تحدث في المستشفيات ، من الضروري الوصول إلى ملاحظات التوليد وحديثي الولادة إذا ولد الطفل على قيد الحياة وتوفي بعد بضع ساعات أو أيام للوصول إلى تفسير واستنتاج صحيحين. ولقد يعد اعتلال الدماغ الإقفاري بنقص الأكسجين ما قبل الولادة سببًا هاما لأمراض الأطفال حديثي الولادة والإعاقة العصبية طويلة الأمد. و له العديد من الأسباب بما في ذلك الخنق داخل الرحم بواسطة الحبل السري. ويعتبر عدم التشخيص المبكر للاختناق الوليدي وعلاجه إهمالاً طبياً قانونياً تجاه الأطباء. **الهدف من البحث**: هدفت الدراسة الحالية إلى استخدام قياس مستويات بروتين اس 100واللاكتات داخل دم الحبل السري و كدلائل مبكرة لنقص الأكسجين فى الاطفال حديثي الولادة الناجم عن الحبل القفوي لتقليل مخاطر المسؤوليات الطبية القانونية ضد الأطباء والمستشفيات. .**طريقة البحث:** وتم اجراء هذه الدراسة على ثلاثون من الاطفال حديثي الولادة الذين يعانون من نقص الأكسجة بسبب خنق الحبل السري لقياس مستويات بروتين اس 100 واللاكتات في دم الحبل السري. تمت مقارنة هؤلاء مع ثلاثين حديثي الولادة الذين يتمتعون بصحة جيدة على ما يبدو متطابقين في العمر والجنس ووزن الجسم كمجموعة ضابطة. **النتائج:** وقد وجدت هذه الدراسه انه يوجد ارتفاع ذو دلالة احصائية في مستوي بروتين اس 100 و اللاكتات داخل دم الحبل السري فى حديثي الولادة الذين يعانون من نقص الاكسجين نتيجة خنق الحبل السري بالمقارنة مع المجموعة الضابطة. **الخلاصة**: خلصت هذه الدراسة إلي أنه من الممكن استخدام نسبة بروتين اس 100 و اللاكتات داخل دم الحبل السري كمؤشر حيوي مبكر لتشخيص الاعتلال الدماغي لنقص الاكسجين في حديثي الولادة. **التوصيات**: في ضوء نتائج الدراسة الحالية ، نوصي باستخدام بروتين اس 100 واللاكتات في دم الحبل السري كعلامات مبكرة للاختناق الوليدي الناجم عن الحبل القفوي لأنها بسيطة وغير جراحية ورخيصة. كذلك ، ينبغي إجراء مزيد من الدراسات حول مؤشر حيوي مفيد آخر للكشف المبكر عن الاختناق الوليدي.