Early Biochemical markers of hypoxic ischemic encephalopathy in neonates

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ABSTRACT

Objectives: The aim of this study is to evaluate some biochemical parameters including serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) in newborns with birth asphyxia.

Methods: This retrospective study was conducted in King Hussein medical center over two year period. Fifty seven patients were enrolled in this study who fulfills the inclusion criteria (group A), another sixty patients were enrolled as control (group B). Biochemical parameters as CPK and LDH were measured in both groups.

Results: Forty seven patients out of fifty (82%) showed liver involvement indicated by the elevation of LDH and CPK, done in the first three days of life. Most of the patients were in the grade one of HIE according to sarnat and sarnat classification. Statistical analysis was done for the available data and showed significant elevation of both CPK and LDH in asphyxiated babies.

Conclusion: Measurement of both CPK and LDH in babies with high risk and who are suspected to have birth asphyxia, can help in predicting those who are candidate for neuroprotective measures as hypothermia, which might lead to significant improvement In neurodevelopment abilities of neonate later on.

Key words: Asphyxia, CPK, Encephalopathy, Hypoxia ,LDH .

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Introduction

Birth asphyxia and its well-known sequalea, hypoxic ischemic encephalopathy is an important cause of permanent brain damage leading to neonatal death or Manifested later as cerebral palsy or mental retardation. Cerebral palsy is one of the most costly neurological disabilities because of its frequency (2/1000 birth), and its persistence over life span.[1,2] The neonatal brain can be damaged very easily when the cause is profound hypoxia and ischemic insult. In these circumstances, which are potentially damaging, rapid recognition and appropriate response is essential.[3] Multiorgan dysfunction becomes apparent in asphyxiated babies including renal failure, necrotizing enterocolitis, persistent pulmonary hypertension and different metabolic abnormalities.[4]brain damage is of most concern because it is the least likely to heal completely. Cholestasis in infancy is a non specific response to several hepatic injury which includes hypoxia that results in ischemic hepatitis.[5] Evaluation of some liver biochemical markers as CPK and LDH can help us to predict neonates with asphyxia early in order to initiate hypothermia therapy

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Methods

This study was conducted in King Hussein medical center over two year's period between July 2012-July 2014. It was approved by the ethical committee of the Royal Medical Journal. Fifty seven patients (group A), 14 females and 43 males, were recruited in this study that fulfill the inclusion criteria according to the American College Of Obstetricians And Gynaecologist[4] which includes:

1. Profound metabolic or mixed academia (pH<7) on an umbilical arterial blood sample.
2. Persistence of an A pgar score of 0-3 for longer than 3 minutes.
3. Evidence of neonatal neurological sequalea (e.g. seizure, coma, hypotonia).
4. Multiple organ involvement (e.g. kidney, lungs, liver, heart, intestine)

Babies who are premature or had severe sepsis or congenital abnormalities or patients with neonatal jaundice were excluded.

The patients with HIE were divided into three groups (stage 1: mild, stage 2: moderate, stage 3: severe) according to sarnat and sarnat staging system which depends on constellation of neurological findings that includes: any combination of altered muscle tone, altered sensorium, altered deep tendon reflexes, absent primitive neonatal reflexes, dilated pupils and seizures. Another sixty newborns (group B) were recruited as controlled group, most of them were admitted either due to rule out sepsis or respiratory distress as transient tachypnea of newborn Blood samples for assessing both CPK and LDH were withdrawn within the first few hours of life and usually in the first two hours in both groups.

Data were recorded using the Statistical software Minitab Release 13.1.

Mean (standard deviation) values were given according to distribution of the data. P <0.05 was considered statistically significant.

Results

A total of fifty seven patients (group A) were enrolled in this study, forty three males (43), and fourteen females (14). Their birth weights ranges from 1.35 kg to 4.77 kg, twenty six were delivered normally (45.6%), fourteen were delivered by caesarean section (24.5%), and seventeen patients were delivered by vacuum delivery (29.8%). According to sarnat and sarnat classification, most of the patients, 35 patients (61.5%) were grade one I, eighteen patients (31.5%) were grade two II and four patients were grade three III (7%). Among the biochemical parameters, CPK values in the asphyxiated babies were significantly higher than the control, see figures 1, 2 and 3 which reveal this significant difference. Same observation is noted in regard to LDH values, where values in the asphyxiated babies were significantly higher than the control; see figures 4,5,6,7. Statistical inference for two samples (T-test) was conducted for the CPK values of normal and asphyxiated new born and results are shown in Table I (Outliers values (6 values as revealed in figure 1) were removed : 6204, 5649,5432,4798,4638 and 4532 prior conducting this test): T-Test of difference = 0 (vs not =): T-Value = 8.47 P-Value = 0.000**.** DF (degree of freedom) = 52. At the 0.05 level (α= 0.05) p value is less than 0.05 (0.000 <0.05), the null hypothesis is rejected and we conclude that we have strong evidence that CPK is significantly higher in patients with asphyxia than normal. T test was also conducted for LDH values as well and indicates that it was significantly higher in patients with asphyxia, where p value <0.05 (An outlier value revealed in figure 2 was removed : 4450 prior performing this test)see Table II. T-Test of difference = 0 (vs not =): T-Value = 13.52 P-Value = 0.000 DF (degree of freedom) = 55 At the 0.05 level (α= 0.05) p value is less than 0.05 (0.000 <0.05), the null hypothesis is rejected and we conclude that we have strong evidence that LDH is significantly higher in patients with asphyxia than normal. Surprisingly, two patients of those who were grade three HIE showed normal CPK and LDH. Brain ultrasound was done to all patients routinely and all were normal. Brain CT was done to those who showed abnormal CNS examination. They were seven patients, two of them showed subgaleal hematoma in brain CT scan, and

one showed occipital hematoma. Abdominal ultrasound as well was not done routinely to all patients. But was performed in 4 patients, who showed abdominal distension and increasing abdominal girth, and all were normal.

Upon follow up at the clinic, all patients with elevated liver enzymes were back to normal even those who sustained neurological sequalea.

Table (1): Two-sample T test for CPK vs CPK-N

	N	Mean	StDev	SE Mean
CPK	51	1562	881	123
CPK-N	60	504	149	19

Table (2): Two-sample T for LDH vs LDH-N

	N	Mean	StDev	SE Mean
LDH	56	1473	688	92
LDH-N	60	226.1	59.2	7.6

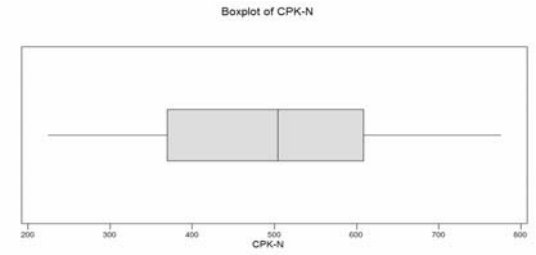

Fig. 1: Box plot for CPK values in normal new borns.

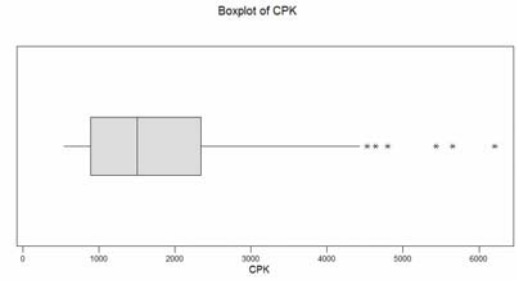

Fig. 2: Box plot for CPK values in asphyxiated new borns.

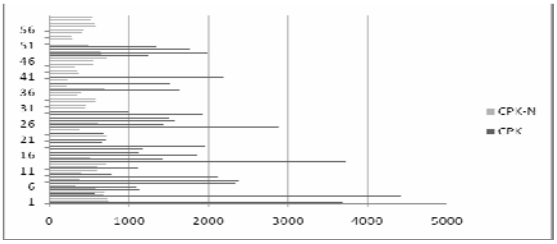

Fig. 3: comparison between CPK values in normal neonate CPK-N and asphyxiated babies.

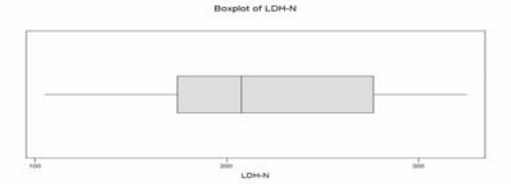

Fig. 4: Box plot for LDH values in normal new borns.

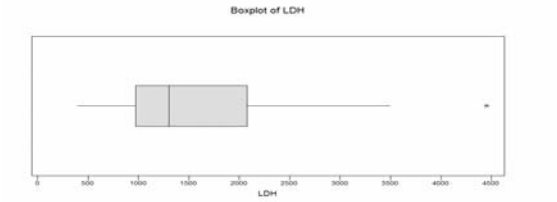

Fig. 5: Box plot for LDH values in asphyxiated new borns.

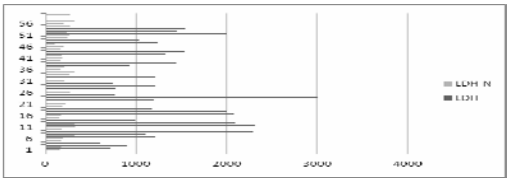

Fig. 6: comparison between LDH value in normal and aspyxiated babies.

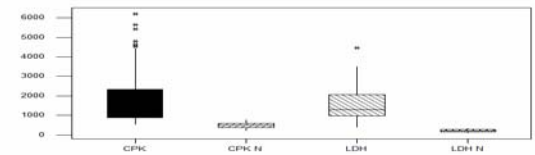

Fig. 7: Bar graphs for CPK and LDH values in normal and asphyxiated babies.

Discussion

Cerebral hypoxia and its complications is a major problem in neonate that needs careful observation. Possible predictive factors that might help in initiating preventive measures are main concern for researchers all over the world. Perinatal asphyxia and its outcome HIE, is graded into three groups according to different factors.[6] Some reports described early, moderate and transient elevation of liver enzymes following the hypoxic insult[5]. Pathogenesis might be related to biliary canilicular post hypoxic injury, or decrease in hepatocytes ATP which in turn leads to a decrease in bile flow rate.[7] In our study, the percentage of liver involvement was high reaching 82% of hypoxic patients. This exceeds most of the other studies.[8-10]

This could be justified by the fact that most of these studies considered more specific enzymes like ALT and AST than CPK and LDH to detect liver involvement. The aim of

this study was accomplished by the fact that both enzymes were significantly elevated in asphyxiated infants. LDH and CPK were higher in neonates with asphyxia than controlled neonates according to our laboratory reference points. This was statistically significant since both values had a p value <0,05, see the below charts. This is similar to various different studies showed the same results.[11-17] Many reports suggested that elevation of these biochemical markers especially LDH, is going parallel with the severity of the asphyxia. The greater the degree of the asphyxia, the greater the value of the enzymes elevation.[6,11-13] This was not statistically studied in our data, but upon observational basis, we found two patients with severe form of HIE (grade 3) with normal CPK and LDH. Such result is not unique to our study, some other studies showed similar pattern of involvement.[14,15] Regarding brain imaging , it is well-known that brain MRI is the best tool for evaluating hypoxic patients especially between 4th and 8th day after hypoxia. Brain ultrasound is not satisfactory and its specificity in children is unacceptably low.[17,18] nevertheless, ultrasound was the preferred tool in our institution due to its accuracy in detecting intravntricular bleeding rather than estimating the degree of birth asphyxia.

Hypothermia as a neuroprotective measure is the only proved mechanism in improving the neurodevelopment outcome.[19,20] Early assessment of CPK and LDH in high risk patients, can predict those who might benefit from hypothermia therapy.

Conclusion

As hypothermia is only effective in the first few hours of hypoxia, it is essential to detect these cases as early as possible. Elevated LDH and CPK can help in recognizing such cases to initiate therapy at an appropriate time. Whether to rely only on such simple measure or use a more sophisticated data is an issue to be discussed.

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