Serum Cystatin C as Marker for Renal Function in Neonatal Asphyxia

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Abstract: Background: Despite advances in neonatal resuscitation, perinatal asphyxia remains a common problem, with serious effects on all body systems. Acute kidney injury (AKI) is a common consequence of perinatal asphyxia. Early diagnosis of AKI may help improving outcome. Cystatin C is a new marker of renal function that may aid in early diagnosis of AKI. **Objective:** To evaluate the diagnostic value of cystatin C for early detection of AKI among term infants with perinatal asphyxia. **Patients and methods:** A prospective case control study included 45 term neonates with HIE and 45 healthy controls. Serum cystatin c was measured within 24 hours after birth. AKI was defined using a serum creatinine based modification of the acute kidney injury network criteria. ***Results:*** Among the 45 neonates with perinatal asphyxia, 24 (53%) had AKI. Mean serum cystatin C value was significantly higher among HIE neonates than controls and higher amonh AKI-neonates. The incidence of AKI Stages 1, 2 and 3 was 12 (50 %), 7 (29 %) and 5(21 %) respectively. The trend in change in serum cystatin C values among different stages of AKI was found to be statistically significant and increased. ROC curve showed that a serum cystatin C cut off value of 1.495mg/l had 91.7% sensitivity and 85.7% specificity in predicting AKI with AUC of 0.965 [(95%CI): 0.92–1]. **Conclusions:** Serum cystatin C seems to be a promising marker for early diagnosis of acute kidney injury, further studies are recommended to validate these results.

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1. Introduction

Hypoxic ischemic encephalopathy (HIE) following severe perinatal asphyxia has an incidence of 1 to 2 per 1000 live births in the western world, and is far more common in developing countries **(Groenendaal and de Vries, 2015).**

Acute kidney injury (AKI) is a common consequence of perinatal asphyxia, a complex disorder with clinical manifestations ranging from mild dysfunction to complete anuric kidney failure **(Durkan and Alexander, 2011).** Acute kidney injury is defined as a sudden, severe derangement of glomerular filtration and tubular function. On the basis of serum creatinine (Cr) values, it is diagnosed with rise in serum creatinine from baseline by 0.3 mg/dL, an increase of 150% from baseline, or any value ≥2.5 mg/dL **(Chock et al., 2018).**

Using Cr as the most common method to monitor renal function and to diagnose AKI is not ideal for many reasons; serum Cr (SCr) concentration is affected by volume status. There is a likely variability in SCr generation associated with gestational age, muscle mass, and nutrition. In addition, it is unknown whether SCr-based AKI definition criteria should differ depending on gestational or postnatal age **(Zappitelli et al., 2017).**

Cystatin C (CysC) is a non-glycosylated protein that has been considered as a new marker of renal function. It is a proteinase inhibitor involved in normal intracellular protein turnover. Consequently, CysC is produced at a constant rate by any nucleated cell, and is eliminated exclusively through glomerular filtration. After ultrafiltration through the glomerular basal membrane, CysC is metabolized in the proximal renal tubular cell following endocytosis at the apical brush border of the renal tubular cell **(Levey et al., 2014).** Consequently, serum CysC reflects glomerular filtration rate (GFR), while urinary CysC reflects renal tubular dysfunction **(Allegaert et al., 2015).** Moreover, its concentration is not influenced much by age, gender, muscle mass, infections, and inflammatory or liver diseases **(Shlipak et al., 2013).**

Cystatin C does not cross the placental barrier and, as a result of this, does not reflect maternal values. Serum cystatin C remains a functional biomarker that has shown promise in neonates but warrants further study **(Askenazi et al., 2018).** As a functional biomarker serum, cystatin C has been shown to provide more accurate assessments of neonatal renal function than SCr. Studies evaluating the potential role of cystatin C in neonates have been recently extensively reviewed **(Filler and Lepage, 2013).**

The objective of this study was toevaluate the sensitivity of cystatin C for early detection of AKI among term infants with perinatal asphyxia.

2. Materials and Methods

The present case control study included 45 newborns with hypoxic ischemic encephalopathy, and another 45 apparently healthy newborns (controls). Subjects were selected from Neonatal intensive care unit at Al-Azhar university hospital (New Damietta) during the period from June 2015 to June 2018.

Indicators of acute perinatal asphyxia included: 1) the presence of a hypoxic event immediately prior or during delivery, 2) history of fetal distress (bradycardia, late decelerations), 3) metabolic acidosis (base deficit ≥ -12 mmol/l) within the first hour of life, 4) five minutes Apgar score ≤ 6, 5) clinical evidence of HIE and multiple organ involvement, and 6) need for advanced neonatal resuscitation at delivery **(Sarafidis et al., 2012)**.

Categorization of the enrolled asphyxiated neonates intosubgroups (AKI, no-AKI) was based on to the most recent criteria of NIDDK, using the change in serum creatinine and urine output. AKI is defined as persistently elevated serum creatinine >1.5 mg/dl, rise of serum creatinine ≥0.3 mg/dL within 48 h or serum creatinine rise ≥ 1.5 to 1.9 × reference (lowest prior) serum creatinine measurement within 7 days, or urine output ≤ 1 mL/kg/hour **(Zappitelli et al., 2017).**

Preterm neonates, neonates with congenital abnormalities or chromosomal anomalies, newborns of mothers suffering from diabetes mellitus, hypertension, pre-eclampsia, and children of multiplepregnancies and metabolic disorders were excluded from the study.

The statistical analysis was performed using an IBM compatible computer and statistics for SPSS 22 statistical package. For qualitative data, frequency and percent distributions were calculated and for comparison between groups, the Chi square (X^2) test was used. For quantitative data, mean, standard deviation (SD) were calculated and for comparison between two groups, the independent samples (t) test was used. Sensitivity was calculated from the equation (true positive/ true positive + false negative). Specificity was calculated from the equation (true negative/true negative + false positive). For interpretation of results, p value < 0.05 was considered significant.

3. Results

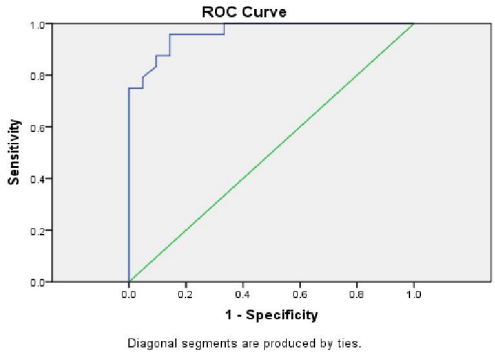

Fig. (1): ROC curve – serum cystatin C for predicting AKI in neonatal asphyxia

Table (1): demographic, perinatal and laboratory results of studied cases

	Asphyxia	Control	P	AKI	No-AKI	P
Age (hours)	6.36±4.98	7.9±4.97	0.148	6.46±5.47	6.24±4.5	0.88
Gestational age (weeks)	38.6±1.05	38.5±0.99	0.47	38.83±1.1	38.4±1.08	0.2
Males/Females	23/22	24/21	1	13/11	10/11	0.66
Cesarean delivery	32 (71%)	27 (60%)	0.27	18 (75%)	14 (67%)	0.27
1-minute Apgar score	2.71±1.44	8.58±0.62	**<0.001***	2.17±1.49	3.33±1.11	**0.005***
5-minute Apgar score	5.13±1.47	9.64±0.49	**<0.001***	4.63±1.44	5.71±1.31	**0.011***
MAP (mmHg)	46.8±6.09	56.8±4.4	**<0.001***	43.96±4.8	50.05±5.9	**<0.001***
PH	7.03±0.11	7.31±0.04	**<0.001***	6.99±0.09	7.08±0.11	**0.006***
Pco_2(mmHg)	60.95±12.3	37.4±3.24	**<0.001***	65.1±11.8	56.2±11.4	**0.015***
Po_2(mmHg)	63.07±14.7	97.8±1.31	**<0.001***	57.9±15.2	69±12.03	**0.009***
HCO3(meq/l)	12.11±4.24	19.46±2.2	**<0.001***	10.9±4.1	13.5±4.06	**0.042***
Base excess	-12.84±4.2	2.86±1.15	**<0.001***	-14.1±4.2	-11.4±3.8	**0.027***
Sodium (meq/l)	138.5±7.07	140.7±5.6	0.105	137.0±8.1	140.3±5.3	0.12
Potassium (meq/l)	4.39±0.73	4.17±0.67	0.133	4.55±0.79	4.22±0.63	0.14
RBG (mg/dl)	56.84±12.9	66.4±11.1	**<0.001***	54.2±13.5	59.9±11.8	0.14
Creatinine (mg/dl)	1.24±0.44	0.82±0.32	**<0.001***	1.37±0.52	1.1±0.28	**0.032***
BUN (mg/dl)	27.11±10.4	14.8±9.75	**<0.001***	29.5±11.5	24.33±8.4	**0.088**

*** = significant.**

The baseline parameters ofthe study participants are mentioned in table (1). Among the 45 neonates with perinatal asphyxia, 24 (53%) had AKI. Mean serum cystatin C value was significantly higher among HIE neonates than controls and higher amonh AKI-neonates. The incidence of AKI Stages 1, 2 and 3 was 12 (50 %), 7 (29 %) and 5(21 %) respectively. The trend in change in serumcystatin C values among different stages of AKI was found to be statistically significant and increased (table 2).

ROC curve showed that a serum cystatin C cut off value of 1.495mg/l had 91.7% sensitivity and 85.7% specificity in predicting AKI with AUC of 0.965[(95%CI): 0.92–1] as shown in Fig. (1).

Table (2): Serum cystatin C among studied neonates

Condition	No. (%)	Serum cysC	P value
Asphyxia **Controls**	45 45	2.01±1.504 1.101±0.282	**<0.001***
AKI **No AKI**	24 (53.3%) 21 (46.7%)	2.79±1.7 1.12±0.31	**<0.001***
AKI stage **1** **2** **3**	 12 (50%) 7 (29%) 5 (21%)	 1.86±0.38 2.68±0.15 5.17±2.14	**<0.001***

* = significant.

4. Discussion

PA is one of the most common causes of neonatal AKI. Redistribution of cardiac output occurs post an asphyxial insult and in order to maintain cerebral, cardiac and adrenal perfusion, renal blood flow decreases. Hypoperfusion results in a prerenal failure stage which can progress to acute tubular necrosis and parenchymal injury **(Sweetman, 2017)**. Furthermore, hypoxia-ischaemia can release reactive oxygen species into the circulation and this free radical storm can further damage presensitised renal tissue **(Jetton and Askenazi, 2014; Liu et al., 2008).** Application of the new neonatal modification of the KDIGO/AKIN criteria by three recent studies, gives an incidence of AKI in 38–41.7% of PA infants **(Selewski et al., 2013; Sarkar et al., 2014; Kaur et al., 2011).**

It is very important to recognize AKI as earlier as possible, hours after an insult occurred in comparison with days it may take serum creatinine to rise. However, validation of novel AKI biomarkers is impairedby the lack of a high quality, sensitive, and specific definition of AKI in neonates **(Sweetmann and Molloy, 2013).**

Several studies demonstrated that serum CysC levels have been shown to be significantly higher in severely asphyxiated infants compared to mild-moderately asphyxiated newborns. Neurological follow-up during the first year of life found that more severe neurodevelopmental deficits were associated with significantly higher sCysC levels at third day of life (DOL) **(Kaur et al., 2011).** Furthermore, both umbilical and DOL 3 sCysC levels were shown to be significantly higher in infants exposed to PA (n = 50) compared to controls (n = 50). Area under the receiver operating characteristic curve (AUROC) for prediction of AKI was excellent for both umbilical and DOL 3 samples (0.92 and 0.7) **(Treiber et al., 2014).** However in a smaller study conducted by **Sarafidis et al. (2012)**, sCysC levels were significantly higher in PA infants (n= 13) compared to controls (n = 22) only on DOL 1 and not at later time points (DOL 3 and 10). In contrast, PA infants had significantly higher urinary CysC (uCysC) levels at all-time points compared to controls, suggesting that uCysC may be a more sensitive marker of perinatal hypoxia-ischaemia. Although not a distinct term PA infant cohort, **Li et al. (2012)** and **Askenazi et al. (2012)** showed that uCysC was highly predictive of AKI in an unwell neonatal population with AUROC of 0.92 and 0.82 respectively.

A number of studies have found that cystatin C is a verygood indicator and a useful tool for the early diagnosis of AKI. In pediatric patients admitted to the intensive care unit, cystatin C enables diagnosis of AKI up to 24–48 h before clinical diagnosis **(Krawczeski et al., 2010; Zaffanello et al., 2007). Askenazi et al. (2012)** found that the levels of urinary cystatin C were significantly higher in patients with AKI compared with the levels in those without AKI.

Elmas et al. (2013) found that serum cystatin C is an independent predictor of AKI in premature newborns with respiratory distress syndrome. **Kandasamy et al. (2013)** analyzed 10studies that assessed the sensitivity of cystatin C as an early biomarker of AKI in neonates and found that it can be successfully used for evaluation of renal function in sick neonates (sepsis-induced AKI and congenital renal anomalies). Their conclusion was that the number of studies that address this issue is small and that there are no studies linking cystatin Clevels with short- and long-term outcomes in sick neonates.

In summary, serum cystatin C is a sensitive marker for early renal injury among neonates with perinatal asphyxia, and is correlated with the severity of hypoxic ischemic encephalopathy.

Conclusions

Serum cystatin C seems to be a promising marker for early diagnosis of acute kidney injury, further studies are recommended to validate these results.

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