Novel predictor markers for early differentiation between transient tachypnea of newborn and respiratory distress syndrome in neonates

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Abstract

Neonatal Respiratory Distress Syndrome (RDS) and Transient Tachypnea of newborn (TTN) are common similar neonatal respiratory diseases. Study the early predictor markers in differentiation between TTN and RDS in neonates. A prospective case control study which was done in Neonatal Intensive Care Unit (NICU) of Tanta University Hospital (TUH) from September 2016 to March 2018. Three groups of neonates were included in the study: RDS group (45 neonates), TTN group (45 neonates), and control group (45 healthy neonates). There were statistically significant difference (SSD) between our studied three groups as regard serum Malondialdehyde (MDA), Superoxide dismutase SOD, Lactate dehydrogenase (LDH), and blood PH and *P*-values were 0.001* for these comparative parameters. The ROC curve of RDS cases revealed that the serum MDA Cut off, sensitivity and specificity were 1.87 mmol/L, 98%, 96%, respectively which had the highest sensitivity and specificity followed by the serum SOD then the serum LDH and lastly the blood PH while in TTN cases, the serum MDA Cut off, sensitivity and specificity were 0.74 mmol/L, 96%, 93%, respectively then the serum SOD then the serum LDH and lastly the blood PH. Serum MDA, SOD, LDH, and PH had a beneficial role as early predictors in differentiation between TTN and RDS in neonates.

Introduction

Respiratory distress (RD) in neonates is manifested by tachypnea, retraction, grunting, and or cyanosis and represent the commonest cause of admission to neonatal intensive care unit (NICU).[1–4] RD is caused by respiratory or non-respiratory causes (which may be cardiac, neurological, metabolic, hematological, and others).[5,6] The most common respiratory causes of RD in neonates are respiratory distress syndrome (RDS) and transient tachypnea of newborn (TTN).[7,8]

Neonatal RDS is a common respiratory disease which occur in neonates due to deficiency of the surfactant which is secreted by type 2 pneumocyte which help the inflation of the alveoli during inspiration and prevent the atelectasis and collapse of the

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alveoli during expiration, surfactant is a lipoprotein material, neonatal RDS is mainly present in preterm neonates due to immature type 2 pneumocyte and affect the male more than female. Immature epithelial Na+ channel expression is one of the pathogenetic mechanisms leading to human neonatal RDS.[9,10]

TTN is an important neonatal disease which occur due to delayed resorption of lung fluid, so the retained fluid occupies the position of air with decrease in gas exchange and subsequent RD, it occurs mainly in cases of cesarean section (CS) due to improper squeezing of the lung to expel the lung fluid, it is mainly a transient benign disease as there is a spontaneous absorption of lung fluids by lung lymphatics, it is mainly occur in cases delivered by CS.[11–14]

Early differentiation between RDS and TTN is very important for early diagnosis and early management with better prognosis, but unfortunately both diseases are very common in incidence and very similar in their clinical manifestation but with completely different modes of management.[13,15,16]

Malondialdehyde (MDA) is the dialdehyde of malonic acid, and a biomarker of oxidative stress (OS) and lipid peroxidation, the OS is an imbalance between oxidants and antioxidants. OS cause cell death and tissue damage by apoptosis or necrosis. We have chosen MDA as it is the most common product of lipid peroxidation, in addition to it is easy to estimate and inexpensive.[17–21]

MDA is produced through the effect of the free radicals on the tissue cells which leads to lipid peroxidation. There is positive correlation between the rise in free radical production and the high levels of MDA. MDA level is commonly known as a marker of OS and the degree of lipid peroxidation can be estimated by the amount of MDA in the tissues.[22–26]

Superoxide dismutase (SOD) is an enzyme found in body cells. It helps break down free radicals (harmful O2 molecules) in the cells and this help in prevention of tissue damage. SOD is beneficial in the situations where free radicals (harmful O2 molecules) are thought to play a role in disease.[27–30]

SOD is an enzyme that cause breakdown of the superoxide oxygen radical (O2-) into molecular oxygen (O2) and H2O2. Superoxide is produced during oxygen metabolism and it causes tissue damage. H2O2 is degraded by catalase. Thus, SOD is considered an important antioxidant defense which is present tissue cells which exposed to O2. SOD has powerful anti-inflammatory activity.[31–33]

SOD acts as a defense mechanism against the cell injury caused by OS through breakdown of O2- into O2 and decrease O2- level which damages the cells at excessive concentration.[34,35] Superoxide (oxygen with an extra electron), leak from the respiratory system and cause cells damage. This superoxide may cause damage in the cell DNA or affect the body enzymes.[36,37]

SOD is considered one of the antioxidant proteins which protect the cells through detoxification of superoxide anion to H2O2, which is further transformed to O2 and H2O by catalase.[38,39]

Lactate dehydrogenase (LDH) is an enzyme found in most of the cells of the body. Because it is released during tissue damage due to perinatal or neonatal asphyxia or other causes, it is a marker of common injuries and disease especially respiratory diseases like RDS which may leads to decrease the oxygen supply to the tissues.[40–43]

LDH has an important role in energy production. When these tissues are damaged by perinatal or neonatal hypoxia or other factors, they secrete LDH into the blood. High levels of LDH in the blood indicate tissue damage, so LDH test is used to find out and monitor tissue damage especially respiratory diseases. LDH is an enzyme required in energy production for our body.[44–47]

Blood gases is very important in detecting and monitoring of respiratory diseases in neonates especially RDS and used as a good follow up of the cases for the need of respiratory support either invasive or non-invasive ventilation.[48]

The aim of this study is to study the serum MDA, SOD, LDH, and blood PH as early predictor markers in differentiation between neonatal TTN, RDS, and healthy neonates matched in age and sex.

Patients and methods

Study design

A prospective case control study which was done in NICU at TUH from September 2016 to March 2018. This study was approved by the ethical committees of Faculty of Medicine, Tanta University, and Thai Clinical Trials Registry (TCTR), TCTR identification number is TCTR20201104005. Informed consents of the parents of the delivered admitted neonates after a complete description of

the study were obtained. After exclusion of neonates who suffered from RD from any causes other than RDS and TTN, also, we had excluded the neonates who had delivered vaginally or by assisted delivery to fix the mode of delivery to avoid its affection in the results of our parameters and we had finally included in the study 3 groups of neonates : group 1 (RDS group) which included 45 neonates suffered from RDS according the criteria of diagnosing them as RDS cases,[49–52] group 2(TTN group) which included 45 neonates suffered from TTN according the criteria of diagnosing them as TTN cases[53–57] after complete general and chest examination and chest X-ray finding and group 3 (control group) which included 45 healthy neonates matched in age and sex. RDS cases were further divided into noninvasive ventilated cases (who were the cases which needed only nasal canula or CPAP) and invasive ventilated cases (who were the cases which needed invasive MV). None of the classic TTN cases who included in the study were in need of CPAP or MV and they just needed oxygen supplementation through the nasal canula (2 L/min). The sample size and power analysis were calculated using Epi-Info software statistical package created by WHO and CDC & Prevention, Atlanta, Georgia, USA version 2002.[58] The criteria used for sample size calculation were as follows: 95% confidence limit, 80% power of the study. The sample size was found at $N = 45$ for each study group.

We have chosen MDA as it is the most common product of lipid peroxidation, in addition that MDA, SOD and LDH are easy to estimate and inexpensive.

Specimen collection and analyzing of the blood

One milliliter of capillary blood samples were collected from all neonates who included in the research and suffering from RD in the first 24 h after delivery. Blood samples were sent to do blood pH and the samples were centrifuged at 3000 rpm for 15 min at 4°C to separate serums for the determination of LDH, MDA, and SOD, samples were stored in different specimen containers at −20°C to −70°C till quantification of the measured parameters.

Criteria of RDS: Evrim et al.,[49] Liu,[50] Downes et al.,[51] and Kero and Mäkinen[52]

RDS cases were diagnosed based on clinical and radiological diagnosis of RDS in the form of the presence of manifestation of RD according to the criteria of Downe's score combined with chest X-ray findings which include multiple diffuse mainly fine granular densities (Grade 1), air bronchograms (Grade 2), the characteristic ground-glass appearance (Grade 3), or white lungs (Grade 4). The patient group was clinically suffered from RD: tachypnea only (Grade 1), tachypnea and retraction (Grade 2), Grade 3 was tachypnea, retraction and Grunting (Grade 3), or tachypnea, retraction, grunting, and cyanosis (Grade 4).

Severity of RDS was based on Downe's Clinical Scoring System and chest X-ray findings.

Criteria of classic TTN: Haliday et al.,[53] Guglani et al.,[54] Hermansend and Lorah,[55] Liem et al.,[56] and Salama et al.[57]

Antenatal history: Absence of PROM, chorioamnionitis, maternal infection, meconium. Risk factors: CS, IDM, earlier sibling with TTN.

Clinical signs: No advanced resuscitation, Tachypnea shortly after birth, Persistent beyond 4 h of age, Rate up to 120 breath per minute, Mild increase in work of breath ± grunting, Needs ≤40% FIO2 nasal canula, Neurologically and hemodynamically: normal, PCO2: not more than 60 mmHg.

Radiological Signs: Normal or increased lung volume ± mild cardiomegaly, Prominent lung markings, Fluid in interlobar fissure, Mild pulmonary edema, No consolidations, Normal complete blood count (CBC), and C reactive protein (CRP).

Data collections

History taking, chest and systemic examination, respiratory examination were done for the diagnose RDS and TTN. Chest X-ray was done for all studied neonates CRP.

Estimation of serum MDA levels as an oxidative stress marker

Principle: The concentration of MDA in serum sample was determined by colorimetric method using a kit from Biodiagnostics, Egypt, and through a method described by Satoh[59] and Ohkawa et al.[60] In the protocol, thiobarbituric acid (TBA) reacts with MDA present in the sample (in acidic medium, at 95°C for 30 min) to form TBA-reactive products (TBARS). The absorbance of these pink products was then measured at 534 nm in the spectrophotometer. Detection of the serum levels were done

Table 1. Demographic data, APGAR score and time of sampling for the studied groups.

		RDS group (group 1) (N = 45)		TTN group (group 2) (N = 45)		Control group (group 3) (N = 45)		f. test	P-value
		N	%	N	%	N	%	X^2	P-value
Weight (kg)	Mean ± SD	2.43 ± 0.21		2.57 ± 0.22		2.5 ± 0.21		1.357	0.185
Gestational age (Week)	Mean ± SD	35.9 ± 1.3		37.1 ± 1.1		37.2 ± 1.1		1.658	0.102
APGAR score at 5 min	Median (IQR)	7 (5–9)		7 (5–9)		9 (7–11)		KWχ2: 15.631	0.001*
Time of sampling (h)	Mean ± SD	18.1 ± 3.1		18.1 ± 3.15		18.05 ± 3.05		0.652	0.864
Sex	Male	27	60	26	57.8	27	60	0.063	0.970
	Female	18	40	19	42.1	18	40		

*P-value is significant if <0.05, f: ANOVA, KWχ2: Chi square for Kruskal Wallis test.

and calculated using a kit-provided formula and presented as mmol/L.[61]

Estimation of serum SOD as an antioxidant enzyme activity

Principle: This measurement depends on the enzyme inhibition to the phenazine methosulfate–mediated reduction of nitro blue tetrazolium dye. The color which originates was measured at 560 nm. SOD activity was then calculated and presented as U/mL.[62]

Assessment of serum LDH activity

LDH activity was measured by the method of Babson and Babson.[63] It catalyzes the conversion pyruvate to lactate, NADH is oxidized to NAD in the process. The rate of decrease in NADH at wave length 340 nm is directly proportional to the LDH activity and determined spectrophotometrically.[63]

Statistical analysis

Data were processed using SPSS statistical package version 21.0, IBM Corporation Software Group, USA. Qualitative data was presented as frequency and percentage, whereas normal quantitative data was expressed as mean ± SD and abnormal data quantitative data was expressed as median (interquartile range). Comparison of the studied groups was done using Chi-square for qualitative data, ANOVA f-test for comparing between more than two means, Chi square for Kruskal Wallis test for comparing between median (IQR) and student's t-test for comparing between two means in quantitative data. All P values were two-tailed and $P \leq 0.05$ was considered statistically significant. Receiver operating characteristic

(ROC) curve was used. The optimal cut-off value of each marker was determined based on the Youden index.

Results

Three groups of neonates were included in this study: group 1 (RDS group) which included 45 neonates suffered from RDS, group 2(TTN group) which included 45 neonates suffered from TTN and group 3 (control group) which included 45 healthy neonates matched in age and sex.

Table 1 showed Comparison between the studied groups, which revealed non-SSD between the 3 groups as regard gestational age, weight, sampling time, and sex while there was SSD in APGAR score (P-value = 0.001*).

Table 2 showed comparison between the studied groups, there were SSD between the three groups as regard serum MDA, SOD, LDH, and blood PH and the P-values were 0.001* for these comparative parameters

Table 3 showed comparison between the invasive and noninvasive ventilated cases in group 1, there were SSD between both cases in group 1 as regard serum MDA, SOD, LDH, and blood PH and the P-values were 0.001* for these comparative parameters

Table 4 showed correlation between serum MDA, SOD, and LDH and blood PH levels in neonates of group 1 and 2 which revealed in group 1 that there was SSD between serum MDA, SOD, and LDH and blood PH where the P values are 0.002, 0.001, and 0.001, respectively while in group 2 there were SSD between serum MDA, SOD, LDH, and blood PH where the P values were 0.001* for these comparative parameters

Table 5 and Figure 1(a, b) showed Cut off value, AUC, sensitivity, specificity, PPV, NPV, and

Table 2. Serum LDH, MDA, and SOD and blood PH levels for the studied groups.

		RDS group (group 1) (N = 45)	TTN group (group 2) (N = 45)	Control group (group 3) (N = 45)	f-test	P-value
Blood PH	Mean ± SD	7.25 ± 0.06	7.32 ± 0.06	7.39 ± 0.05	11.527	0.001*
Serum LDH (IU/L)	Mean ± SD	1112 ± 162	820 ± 121	424 ± 65	13.529	0.001*
Serum MDA (mmol/L)	Mean ± SD	2.3 ± 0.5	1.3 ± 0.4	0.56 ± 0.2	9.834	0.001*
Serum SOD (U/ml)	Mean ± SD	197.2 ± 21.1	234.7 ± 9.5	254.8 ± 18	8.691	0.001*

*P-value is significant if <0.05.

Table 3. Blood PH and serum LDH, MDA, and SOD levels in neonates of group 1 according to the received treatment.

		Noninvasive ventilated cases (N = 40)	Invasive ventilated cases (N = 5)	T-test	P-value
Blood PH	Mean ± SD	7.27 ± 0.04	7.18 ± 0.01	4.958	0.001*
Serum LDH (IU/L)	Mean ± SD	1050 ± 90	1220 ± 54	4.108	0.001*
Serum MDA (mmol/L)	Mean ± SD	2.1 ± 0.2	2.55 ± 0.15	4.843	0.001*
Serum SOD (U/ml)	Mean ± SD	213.4 ± 15	182.3 ± 7.1	4.537	0.001*

*P-value is significant if <0.05.

Table 4. Correlation between serum MDA, SOD, and LDH and blood PH levels in neonates of group 1 and 2.

	Serum MDA (mmol/L)			
	Group 1		Group 2	
	r	P	r	P
Serum SOD (U/ml)	−0.444	0.002*	−0.595	0.001*
Serum LDH (IU/L)	0.743	0.001*	0.743	0.001*
Blood PH	−0.702	0.001*	−0.702	0.001*

*P-value is significant if <0.05.

accuracy of serum MDA, SOD and LDH, and blood PH levels in neonates of group 1 and 2. In group 1, the serum MDA Cut off, sensitivityand specificity were 1.87 mmol/L, 98%, and 96%, respectively then the serum SOD Cut off, sensitivityand specificity were 226 U/ml, 96% and 94%, respectively then the serum LDH Cut off, sensitivity and specificity were 935 IU/L, 93% and 89%, respectively and lastly the blood PH Cut off, sensitivity and specificity were 7.29, 90%, and 88%, respectively. In group 2, the serum MDA Cut off, sensitivity and specificity were 0.74 mmol/L, 96%, 93%, respectively then the serum SOD Cut off, sensitivity and specificity were 240 U/ml, 93%, and 90%, respectively then the serum LDH Cut off, sensitivity and specificity were 483 IU/L, 90% and 88%, respectively and lastly the blood PH Cut off, sensitivity and specificity were 7.36, 88%, and 84%, respectively.

Discussion

This is the first research to the author's knowledge that had investigated the levels of MDA and SOD enzymes in the neonatal blood for the possibility of using it as an early predictor for early and proper differentiation between neonatal RDS and TTN with early diagnosis and early management which will lead to good prognosis and outcome for both diseases and avoid the complications of both diseases which may lead to persistent pulmonary hypertension, pneumonias and even respiratory failure which may lead to death or hypoxic permanent brain damage, so the early differentiation of both diseases with early management will lead to prevention of this hazardous sequalae.

Early and proper differentiation between RDS and TTN in the NICU is very important for early diagnosis and early management of both diseases. Unfortunately, both diseases are very common in incidence and very similar in their clinical manifestation but with completely different modes of management.[13,15,16]

The results of this study revealed that there were SSD between our studied three groups (RDS, TTN, and control groups) as regard serum LDH, MDA, SOD, and blood PH and the *P*-values were 0.001* for these comparative parameters, furthermore in cases of group 1 (RDS group) there were SSD between nonventilated and ventilated cases as regard serum MDA, SOD, LDH, and blood PH and

Table 5. Cut off value, sensitivity, specificity, PPV, NPV and accuracy of serum MDA, SOD and LDH, and blood PH levels in neonates of group 1 and 2.

	Cut off value	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy
Group 1							
Serum MDA (mmol/L)	1.87	0.991	98	96	97	95	97
Serum SOD (U/ml)	226	0.973	96	94	95	92	94
Serum LDH (IU/L)	935	0.943	93	89	91	90	91
Blood PH	7.29	0.917	90	88	89	91	90
Group 2							
Serum MDA (mmol/L)	0.74	0.983	96	93	95	92	94
Serum SOD (U/ml)	240	0.962	93	90	92	91	92
Serum LDH (IU/L)	483	0.920	90	88	89	90	90
PH	7.36	0.897	88	84	87	86	87
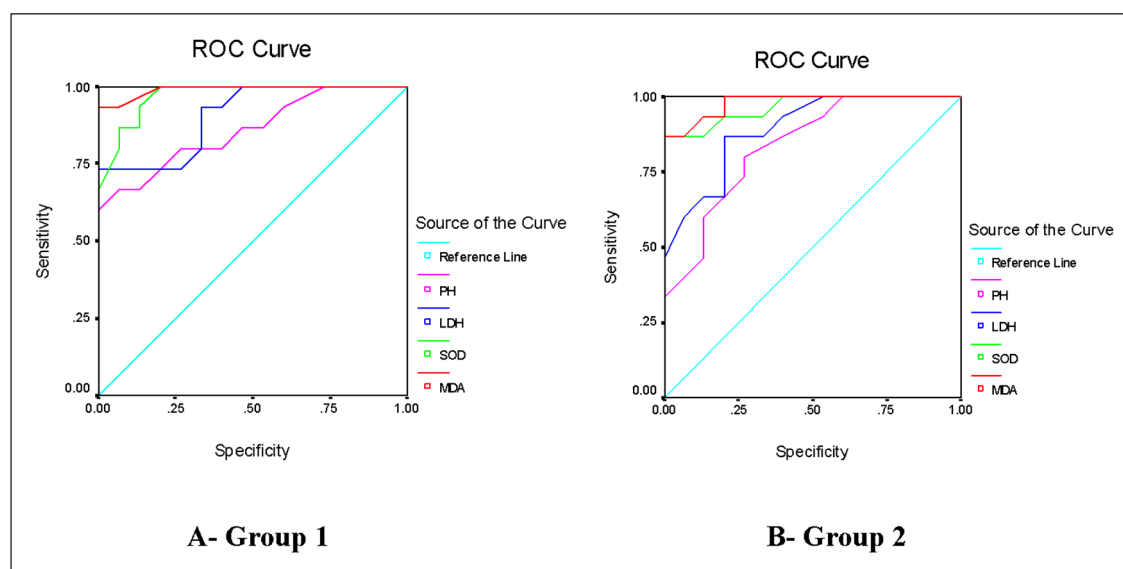
Figure 1. (a, b) Showed the ROC Curve in group 1 and 2.

the *P*-values were 0.001* for these comparative parameters. Our results also showed that the ROC curve of cases of group 1 (RDS cases) revealed that the serum MDA Cut off, sensitivity, and specificity were 1.87 mmol/L, 98%, 96%, respectively which had the highest sensitivity and specificity followed by the serum SOD then the serum LDH and lastly the blood PH while in cases of group 2 (TTN cases), the serum MDA Cut off, sensitivity and specificity were 0.74 mmol/L, 96%, 93%, respectively then the serum SOD then the serum LDH and lastly the blood PH.

Our results were in agreement with the researches which concluded that RDS neonates tend to have lower red cell SOD enzyme activity than those who did not develop RDS which may suggest that the possible cause of the oxidative injury to alveolar membranes in the developing of RDS itself and the levels were higher in neonates delivered by CS if compared to those who delivered by NVD and so we included the neonates delivered by CS only in our research to avoid any effect of the mode of delivery in our results.[64,65]

The results of this study were in agreement with the results of some studies which stated that lactate and LDH might be useful for predicting the severity of TTN patient[66] and our results agreed also with the results of some researches that had concluded that elevated LDH serum levels could be used as predictors for the severity of neonatal RDS.[41]

In agreement with our results, some studies indicated that the increased OS accompanied by reduced antioxidant defenses may play a significant role in the pathogenesis of RD in preterm newborns[67] and our results agreed with some studies revealed that there was an evidence of oxidative damage and diminished antioxidant defenses in newborns with RDS and the neonatal RDS is associated with certain damage of the cell lipids, proteins and DNA, due to the effect of oxidative stress.[68]

One study concluded that low blood pH at birth is associated with RDS in newborns and the blood gas analysis is important for early identification of newborns at high risk for RDS,[48] and another study showed that early blood gas analysis may be able to predict RD and both studies were agreed with the results of our study.[14]

In disagreement with our results, some studies stated that cord blood gases did not help in prediction of morbidity in neonates as RDS, and the values of cord blood gas did not predict the presence or severity of RDS,[69] while in agreement with our results, some researches showed that the elevated plasma LDH is strongly related to respiratory system affection in neonates which occur in first days of life especially neonatal RDS.[47]

Limitation of the study: the relatively limited number of cases in this study, so other researches needed to be done in the same point.

Conclusion: Serum MDA, SOD, LDH, and PH had a beneficial role as early predictors in differentiation between TTN and RDS in neonates.

Recommendation

Serum MDA, SOD, LDH, and blood PH could be used as early predictors in differentiation between TTN and RDS in neonates.

Declaration of conflicting interests

Funding

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Ethics approval

Response: My research title "Study of early predictor markers in differentiation between Transient Tachypnea of Newborn and Respiratory Distress Syndrome in neonates" had been reviewed by Thai Clinical Trials Registry (TCTR) Committee. My research had been approved for registration at TCTR. My TCTR identification number is TCTR20201104005.

This study was approved by the ethical committees of Faculty of Medicine, Tanta University.

Informed consent

Response: Written informed consent was obtained from legally authorized representatives (who are the parents of the studied neonates) before the study.

Trial registration

Response: My research title "Study of early predictor markers in differentiation between Transient Tachypnea of Newborn and Respiratory Distress Syndrome in neonates" had been reviewed by Thai Clinical Trials Registry (TCTR) Committee. My research deemed satisfactory for all items of Trial Registration Data Set required by World Health Organization. Therefore, my research had been approved for registration at TCTR. My TCTR identification number is TCTR20201104005.

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