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Original article

Ischemia-modified albumin as a novel marker for diagnosis of necrotizing enterocolitis in newborn infants

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Abstract

Background: Necrotizing enterocolitis (NEC) is the most common neonatal gastrointestinal emergency. Ischemia-modified albumin (IMA) is a marker of oxidative stress and ischemia. Its role in early diagnosis of NEC has been little investigated so far.

Aim: The objective of our research was to study the role of serum IMA in diagnosis of NEC in newborn infants.

Material and methods: The study was carried out on 80 neonates; 40 with NEC and 40 controls, subjected to serum IMA dosage with ELISA.

Results: There was a highly statistically significant increase in IMA in both preterm (60.59 ± 34.97 U/ml) and full-term infants with NEC (60.50 ± 29.88 U/ml) compared to their controls (11.28 ± 3.09 U/ml; 5.34 ± 1.88 U/ml). The positive predictive value of IMA in preterm and full-term with NEC was 100% and 94.74%, while the negative predictive value was 80% and 90.48%, respectively. There was a statistically significant increase in serum level of IMA in stage II NEC compared to stage I NEC as well as in non-survivor cases. Significant positive correlation between serum IMA level and duration of recovery from NEC was detected.

Conclusions: IMA is a sensitive marker for diagnosis of NEC in full-term and preterm infants and can predict severity of NEC and death.

Keywords

Ischemia-modified albumin, necrotizing enterocolitis, newborn infants, full-term infants, preterm infants, neonatal gastrointestinal emergency.

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Introduction

Necrotizing enterocolitis (NEC) is one of the most important medical emergencies in the Neonatal Intensive Care Unit (NICU). It is the second most common cause of morbidity in premature infants [1]. The disease is burden with high mortality rate and can affect the quality of life because of its gastrointestinal complications (late colonic strictures, incisional hernias, adhesive bowel obstruction and short bowel syndrome) and neurological outcomes (significant neurodevelopment-mental delay, neurological deficits included auditory and visual impairment).

Some conditions are considered important for initiation of intestinal injury leading to development of inflammation, these include prematurity, imbalance in microvascular tone, formula feeding, abnormal microbial intestinal colonization and translocation, highly immune-reactive intestinal mucosa and ischemia due to decreased oxygen supply to intestinal cells with development of inflammation and coagulative necrosis, pneumatosis, and perforation [2].

Despite the adoption of preventive strategies as prenatal glucocorticoid, breastfeeding, use of donor milk and probiotic supplementation, NEC is still relatively common in most NICUs [3, 4].

Differential diagnosis with other conditions as sepsis, spontaneous intestinal perforation, bowel obstruction, and allergic enterocolitis is often difficult and it could be useful to identify a NEC-specific marker.

IMA (ischemia-modified albumin, i.e. albumin modified by the free radicals produced in ischemic tissue) [5] has been proposed as sensitive marker for the diagnosis of myocardial ischemia presenting with typical acute chest pain. IMA levels are also known to increase in other ischemic conditions, as well as being an indicator of oxidative stress [6].

The role of IMA in early diagnosis of NEC has been little investigated.

The main objective was measuring IMA levels in a group of newborn with NEC and controls to study its efficacy as a marker for early diagnosis of NEC. Secondary objective was to correlate IMA levels to identified risk factors.

Material and methods

Study design and patient data

This is a case control study carried out on 2 groups of newborns ≤ 28 days, 40 cases and 40 apparently healthy controls. Each group was divided in 2 subgroups, preterm and full-term babies, whose gestational age (GA) was assessed with the New Ballard Score [7]. They were admitted to the NICU of AL-Azhar University hospitals.

Exclusion criteria

Newborn infants with congenital anomalies, congenital heart disease, feeding intolerance, intestinal obstruction.

Methods

All the studied groups were subjected to full medical history taking and clinical general and local examinations. Bell's staging was carried out in NEC cases [8].

Duration of recovery from NEC was estimated from the day of diagnosis till the day of disappearance of NEC symptoms.

Laboratory investigations included complete blood count (CBC), serum electrolytes, urea, creatinine, C-reactive protein (CRP), and quantitative determination of serum IMA.

Anterior-posterior and left-lateral abdomen X-ray was performed.

Statistical analysis

Data collected were analyzed by computer program SPSS® "Statistical Package for Social Science 1993" version 16.

Independent (unpaired) student t-test was used to determine significance for numeric variables between the two groups. Chi-square test was performed to determine significance between non-parametric variables. Person's correlation was used in each group for numeric variables.

A receiver operating characteristic (ROC) curve analysis was done to determine sensitivity, specificity, cut-off point, positive and negative predictive values of IMA.

The p-value was considered significant when < 0.05.

Ethical consideration

An informed written consent was obtained from the parents of all the subjects included in the study before their involvement. Aim, steps of the study, potential benefits and hazards of the study were also discussed. Confidentiality of all data was ensured. The Ethical Committee of Faculty of Medicine for Girls, AL-Azhar University approved the study.

Results

The results are shown in **Tables 1-7**.

Patient characteristics

There were no significant differences between control and NEC preterm infants regarding GA, length, head circumference, gender and Apgar score, but birth weight was significantly lower in the NEC group compared to the control group.

Apgar score was significantly lower at 1 and 5 minutes in full-term NEC patients compared to their controls (**Tab. 1**).

As expected, there was higher incidence of neonatal risk factors (respiratory distress, sepsis, blood transfusions, H2 blocker administration, enteral feeding and respiratory support) in full-term and preterm with NEC compared to their controls. Maternal risk factors as premature rupture of membranes (PROM), chorioamnionitis and pregnancy-induced hypertension (PIH) was increased among NEC groups (**Tab. 2**).

The incidence of perinatal asphyxia, meconium aspiration and hypoxic-ischemic encephalopathy (HIE) was increased in full-term with NEC compared to preterm with NEC (**Tab. 3**).

Diagnostic value of IMA

Serum levels of IMA were statistically higher in preterm and full-term infants with NEC compared to their controls. Also there was significant increase in IMA serum level in stage II compared to stage I NEC patients (**Tab. 4**).

The best cut-off point of IMA serum level was > 13.87 U/ml between all NEC patients and their controls with sensitivity of 82.50% and specificity of 92.50%. The best cut-off point was > 18.55 U/ml between preterm with NEC and their controls with sensitivity of 70.00% and specificity of 100.00%. The best cut-off point was > 12.66 U/ml between full-term with NEC and their controls with sensitivity of 90.00% and specificity of 95.00% (**Tab. 5**).

A ROC curve showed that IMA is an ideal marker for diagnosis of all cases of NEC, it has high sensitivity to detect diseased cases and high specificity that can eliminate non-diseased cases.

Between risk factors considered, perinatal asphyxia, formula feeding and blood transfusions were significantly positive correlated with IMA levels (**Tab. 6**).

IMA and survival of NEC cases

IMA was significantly increased among non-survivor preterm and full-term NEC cases compared to survivors (**Tab. 7**).

Table 1. Patient characteristics.

Variable		Preterm infants		Preterm Chi-square test/ Independent t-test/ Mann-Whitney test		Full-term infants		Full-term Chi-square test/ Independent t-test/ Mann-Whitney test	
		Control group	NEC group	X^2/t/Z	p-value	Control group	NEC group	X^2/t/Z	p-value
Gestational age (weeks)		35.05 ± 0.83	34.01 ± 2.40	3.776	0.072	38.30 ± 1.17	38.15 ± 1.23	0.395	0.695
Weight (g)		2,125.00 ± 355.96	1,527.50 ± 595.26	4.326	0.000	3,302.50 ± 454.07	3,095.00 ± 681.70	-1.133	0.264
Length (cm)		48.75 ± 1.62	47.45 ± 4.22	3.234	0.0512	50.35 ± 1.04	50.05 ± 1.91	-0.618	0.540
Head circumference (cm)		31.70 ± 0.57	31.10 ± 2.08	1.247	0.220	33.35 ± 0.99	33.60 ± 0.50	-1.009	0.320
Gender	Male, n (%)	9 (45%)	10 (50%)	0.100	0.752	10 (50%)	9 (45%)	0.100	0.752
	Female, n (%)	11 (55%)	10 (50%)			10 (50%)	11 (55%)		
Apgar score at 1 min		6.50 ± 1.00	6.15 ± 0.67	1.715	0.201	6.70 ± 0.86	4.55 ± 2.11	-4.416	0.000
Apgar score at 5 min		8.15 ± 0.81	7.95 ± 0.76	0.805	0.426	8.50 ± 0.61	6.40 ± 2.16	-4.184	0.000

Data are presented as mean ± SD, if not otherwise indicated.
NEC: necrotizing enterocolitis.

Table 2. Comparison between necrotizing enterocolitis (NEC) groups and their controls regarding the risk factors.

Variable			Preterm control group (n = 20)		Preterm NEC group (n = 20)		Preterm Chi-square test		Full-term control group (n = 20)		Full-term NEC group (n = 20)		Full-term Chi-square test	
			No.	%	No.	%	X^2	p-value	No.	%	No.	%	X^2	p-value
PROM > 18 h		No	20	100	15	75	5.714	0.017	19	95	4	20	4.190	0.001
		Yes	0	0	2	25			1	5	16	80		
Respiratory distress		No	20	100	0	0	40.000	0.000	20	100	1	5	36.190	0.000
		Yes	0	0	20	100.			0	0	19	95		
Sepsis	EOS	No	20	100	1	5	36.190	0.000	20	100	1	5	36.190	0.000
		Yes	0	0	19	95			0	0	19	95		
	LOS	No	20	100	7	35	19.259	0.000	20	100	11	55	11.613	0.001
		Yes	0	0	13	65			0	0	9	45		
Blood transfusion		No	20	100	5	25	24.000	0.000	20	100	9	45	15.172	0.000
		Yes	0	0	15	75			0	0	11	55		
H2 blocker		No	20	100	13	65	2.913	0.004	20	100	15	75	2.390	0.017
		Yes	0	0	7	35			0	0	5	25		
Enteral feeding		No	20	100	3	15	5.085	0.000	20	100	6	30	4.245	0.000
		Yes	0	0	17	85			0	0	14	70		
Respiratory support	SIMV	No	20	100	1	5	36.190	0.000	20	100	1	5	36.190	0.000
		Yes	0	0	19	95			0	0	19	95		
	CPAP	No	20	100	5	25	24.000	0.000	20	100	4	20	4.987	0.001
		Yes	0	0	15	75			0	0	16	80		
Chorioamnionitis		No	20	100	15	75	5.714	0.017	20	100	15	75	5.714	0.017
		Yes	0	0	5	25			0	0	5	25		
PIH		No	20	100	16	80	4.444	0.035	20	100	15	75	24.000	0.000
		Yes	0	0	4	20			0	0	5	25		

CPAP: continuous positive pressure ventilation; EOS: early-onset sepsis; HIE: hypoxic-ischemic encephalopathy; IUGR: intrauterine growth retardation; LOS: late-onset sepsis; NEC: necrotizing enterocolitis; PIH: pregnancy-induced hypertension; PROM: premature rupture of membranes; SIMV: synchronized intermittent mandatory ventilation.

Table 3. Comparison between preterm and full-term infants with necrotizing enterocolitis (NEC) regarding neonatal risk factors.

Variable			Preterm NEC group (n = 20)		Full-term NEC group (n = 20)		Chi-square test	
			No	%	No	%	X^2	p-value
IUGR		No	17	85	19	95	1.111	0.292
		Yes	3	15	1	5		
Respiratory distress		No	0	0	1	5	1.026	0.311
		Yes	20	100	19	95		
Perinatal asphyxia		No	20	100	9	45	15.172	0.000
		Yes	0	0	11	55		
Meconium aspiration		No	20	100	14	70	7.059	0.008
		Yes	0	0	6	30		
HIE		No	19	95	9	45	12.571	0.006
		Yes	1	5	11	55		
Sepsis	EOS	No	1	5	1	5	0.000	1.000
		Yes	19	95	19	95		
	LOS	No	7	35	11	55	1.616	0.204
		Yes	13	65	9	45		
Blood transfusion		No	5	25	9	45	1.758	0.185
		Yes	15	75	11	55		
H2 blockers		No	13	65	15	75	1.654	0.234
		Yes	7	35	5	25		
Enteral feeding		No	3	15	6	30	0.690	0.051
		Yes	17	85	14	70		
Oxygen therapy	SIMV	No	1	5	1	5	0.000	1.000
		Yes	19	95	19	95		
	CPAP	No	5	25	4	20	0.378	0.704
		Yes	15	75	16	80		

CPAP: continuous positive pressure ventilation; EOS: early-onset sepsis; HIE: hypoxic-ischemic encephalopathy; IUGR: intrauterine growth retardation; LOS: late-onset sepsis; NEC: necrotizing enterocolitis; SIMV: synchronized intermittent mandatory ventilation.

Table 4. Ischemia-modified albumin (IMA) among the studied groups.

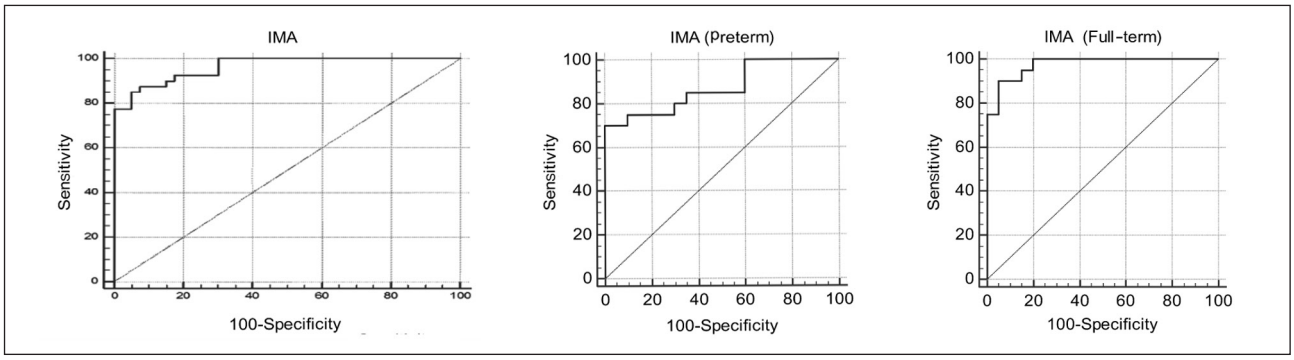
Variable	Control group		NEC group		Independent t-test	
	Mean ± SD	Range	Mean ± SD	Range	t	p-value
Preterm IMA (U/ml)	11.28 ± 3.09	(7.02-18.55)	60.59 ± 34.97	(9.98-101.21)	6.282	0.000
Full-term IMA (U/ml)	5.34 ± 1.88	(2.34-7.98)	60.50 ± 29.88	(9.98-92.8)	28.180	0.000
Stage of NEC	**Stage I**		**Stage II**		**t**	**p-value**
Preterm IMA (U/ml)	51.11 ± 33.79		89.01 ± 21.57		2.331	0.032
Full-term IMA (U/ml)	50.92 ± 25.72		93.43 ± 0.79		2.281	0.034

IMA: ischemia modified albumin; NEC: necrotizing enterocolitis.

Table 5. Sensitivity, specificity and cut-off point of ischemia-modified albumin (IMA) in diagnosis of necrotizing enterocolitis (NEC).

Cut-off point	AUC	Sensitivity	Specificity	PPV	NPV
All NEC cases > 13.87 U/ml	94.9	82.50	92.50	94.4	84.1
Preterm > 18.55 U/ml	87.2	70.00	100.00	100.00	80.00
Full-term > 12.66 U/ml	97.5	90.00	95.00	94.74	90.48

NEC: necrotizing enterocolitis; NPV: negative predictive value; PPV: positive predictive value.



ROC curve, cut-off point, sensitivity and specificity for detection of NEC cases, preterm and full-term.

Table 6. Correlation between ischemia-modified albumin (IMA) serum level in preterm and full-term infants with necrotizing enterocolitis (NEC) and the studied risk factors.

Variable		No.	Preterm IMA	Independent t-test/ Mann Whitney test		No.	Full-term IMA	Independent t-test	
			Mean ± SD	t	p-value		Mean ± SD	t	p-value
IUGR	No	17	62.18 ± 35.83	1.297	0.211	16	75.01 ± 10.47	0.775	0.309
	Yes	3	89.75 ± 9.94			4	63.77 ± 0.00		
Perinatal asphyxia	No	19	78.87 ± 11.87	1.756	0.083	9	71.92 ± 7.39	2.243	0.038
	Yes	1	101.21 ± 0.00			11	82.52 ± 12.45		
Meconium aspiration	No	20	60.59 ± 34.97	-	-	14	75.06 ± 11.49	0.392	0.699
	Yes	0	-			6	73.01 ± 8.49		
Type of feeding	Mixed	7	35.71 ± 24.69	6.632	0.001	6	65.23 ± 3.75	3.485	0.005
	Formula	10	85.96 ± 12.65			8	81.90 ± 11.16		
Blood transfusion	No	5	23.99 ± 26.23	3.350	0.003	8	66.36 ± 3.47	4.342	0.004
	Yes	15	72.78 ± 28.74			12	81.07 ± 9.62		
H2 blocker	No	14	51.78 ± 35.55	1.596	0.128	15	56.12 ± 40.81	0.382	0.707
	Yes	6	76.94 ± 29.42			5	62.05 ± 26.22		

IMA: ischemia-modified albumin; IUGR: intrauterine growth retardation.

Table 7. Ischemia modified albumin (IMA) among survivors and non-survivors.

Variable	NEC group (survivors) (n = 9)	NEC group (non-survivors) (n = 11)	Independent t-test	
	Mean ± SD	Mean ± SD	t	p-value
Preterm IMA (U/ml)	37.95 ± 33.04	79.11 ± 24.74	3.188	0.005
Full-term IMA (U/ml)	48.29 ± 28.03	72.85 ± 22.94	2.144	0.035

IMA: ischemia modified albumin; NEC: necrotizing enterocolitis.

Discussion

This work highlights the possible role of IMA in early diagnosis of NEC among newborn infants. The mean values of serum IMA were significantly higher in preterm and full-term infants with NEC compared to their controls. Why IMA increases in NEC is not clear. It is possible that ischemia with subsequent cellular damage and activation of cascade of biochemical events and inflammatory mediators can be responsible [9], but IMA may also be generated from ischemia reperfusion injury and oxidative stress [10-12]. According to these considerations, some studies have concluded that serum IMA levels may be used in the early diagnosis of acute mesenteric ischemia [13, 14].

In our work IMA had the best cut-off point > 13.87 U/ml between NEC patients and their controls with sensitivity to detect neonates with NEC of 82.50% and specificity to exclude neonates without NEC of 92.50%. These diagnostic criteria were valid regardless of GA as in preterm infants the best cut-off point of IMA was > 18.55 U/ml with sensitivity to detect preterm infants with NEC of 70.00% and specificity to exclude preterm infants without NEC of 100.00%, while in full-term infants the best cut-off point was > 12.66 U/ml with sensitivity of 90.00% to detect full-term infants with NEC and specificity of 95.00% to exclude full-term infants without NEC.

IMA levels increased with the severity of NEC and were higher among preterm and full-term infants with stage II NEC compared to stage I. In stage II NEC the greater release of inflammatory mediators, such as platelet activating factor, could lead to an enhanced production of IMA due to ischemia of larger areas of mucosa. The same could explain the higher levels of IMA in non-survived subjects found in our work but already reported by other authors (Yakut et al.), and in infants with the longest hospitalization. These findings might aid in early diagnosis of severe cases before the progression of the disease [15].

We found significant positive correlation of IMA level with blood transfusions in both preterm and full-term with NEC. It could be explained by the fact that transfusions increase the production of new blood vessels, that are very sensitive to damage and ischemia [16].

Our study also revealed significant positive correlation between IMA and perinatal asphyxia in full-term infants with NEC. This is in agreement with the study of Biswas et al. reporting a series of events occurring during ischemia resulting in IMA molecule through a conformational change in the N-terminal of albumin [17].

Conclusion

This study highlights the value of IMA as novel marker in the diagnosis and follow-up of NEC in preterm and full-term infants. To our knowledge only one other report came to similar results [15] but only preterm infants were considered. In our study IMA was significantly increased in all NEC cases (full-term and preterm infants), and had high sensitivity and specificity for diagnosis of NEC.

Declaration of interest

The Authors declare that there is no conflict of interest and that they do not have any financial or personal relationships with others that could have inappropriately influenced this work. Funding source: there is no financial support.

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