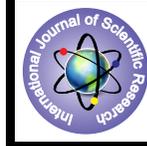


## Role of Serum Malondialdehyde in Detecting The Oxidative Stress in Newborn



### Medical Science

**KEYWORDS :** Oxidative stress, Malondialdehyde (MDA), Reactive Oxygen Species (ROS), Free radicals.

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### ABSTRACT

**INTRODUCTION:** Birth is, in itself, a hyperoxic challenge. The fetus transfers from an intrauterine hypoxic environment with a PO<sub>2</sub> of 20-25 mm Hg to an extra uterine normoxic yet relatively hyperoxic environment with a PO<sub>2</sub>

of 100 mm Hg.

Extrauterine aerobic existence requires efficient cellular electron transport systems to produce energy. In concert with energy-producing oxidative metabolism, biochemical defenses protect against oxidation of cellular constituents by oxygen radicals. When this balance is impaired, however, tissue damage may result. It is known that increasing free oxygen radicals in newborns damages the cell membrane by way of lipid peroxidation, and this damage may be associated with various pathologies recorded in newborns.

**OBJECTIVES:** In this study we aim to investigate the relationship between MDA levels and mother related, and newborn related factors, which may affect these levels and also compare the MDA levels between the various modes of delivery. We also measure biochemical values in the umbilical cord blood of newborn infants born via various modes of delivery.

**METHODOLOGY:** The study was conducted at A J Institute of Medical Sciences, between

January 2013 and November 2013 on 24 newborns born via elective CS, 24 newborns born via emergency CS, and 24 newborns born via normal vaginal delivery. Total bilirubin, uric acid, LDH and malondialdehyde (MDA) levels were measured in the umbilical cord blood.

**RESULTS:** Among the 72 (100%) newborns, 52.8% (n=38) were female and 47.2% (n=34) were male babies where p value was not significant. Among the 72 (100%),

6.9% (n=5) babies were born with meconium stained liquor and all these 5 babies were delivered by emergency cesarean section. The mean serum MDA level in babies born through normal vaginal delivery was of mean 0.584±0.596, while in babies born through elective cesarean section was of mean 0.313±0.301 and in those born by emergency cesarean section was 0.953±1.114. The p value between groups was estimated using Fishers test ANNOVA was <0.016 which was highly significant. In the emergency CS group, it was determined that the malondialdehyde level increased as there is either hypoxia or hyperoxia status in the umbilical cord blood. Similarly in these groups a positive correlation was detected between the total bilirubin, uric acid with malondialdehyde levels in the umbilical cord blood.

**CONCLUSION:** The babies born by emergency cesarean section have undergone more oxidative stress as compared to other modes of delivery. It is also proved in this study that serum malondialdehyde(MDA) levels in the cord blood is reliable marker to detect the oxidative stress during the immediate perinatal period in a term newborn baby.

### INTRODUCTION

Free radicals are highly reactive molecules containing one or more unpaired electrons. They donate or abstract electrons from other molecules in an attempt to pair their electrons from and generate a more stable species. Oxygen derived reactants collectively termed ROS and RNP are normally produced in living organisms. When produced in excess, they are important mediators of cell and tissue injury.(1)Birth is, in itself, a hyperoxic challenge. The fetus transfers from an intrauterine hypoxic environment with a PO<sub>2</sub> of 20-25 mm Hg to an extrauterine normoxic yet relatively hyperoxic environment with a PO<sub>2</sub> of 100 mm Hg.(2)Extrauterine aerobic existence requires efficient cellular electron transport systems to produce energy. In concert with energy-producing oxidative metabolism, biochemical defenses protect against oxidation of cellular constituents by oxygen radicals.(3-4). When this balance is impaired, however, tissue damage may result. It is known that increasing free oxygen radicals in newborns damages the cell membrane by way of lipid peroxidation, and this damage may be associated with various pathologies recorded in newborns, such as hypoxic-ischemic encephalopathy, intraventricular hemorrhage, necrotizing enterocolitis, and bronchopulmonary dysplasia.(5-6)

Newborns are prone to oxidative stress than children and young adults. There are some special reasons for this. These infants very often 1) are exposed to high oxygen concentration, 2) have infections or inflammation, 3) have reduced antioxidant defence, and 4) have free iron which enhances the Fenton reaction leading to production of highly toxic hydroxyl radicals.(7-8).Malondi-

aldehyde is one of the fairly reactive metabolite products resulting from the effect of free oxygen radicals on tissues and from a series of reactions during lipid peroxidation. The plasma MDA level is a sensitive indicator of lipid peroxidation and thus of oxidative stress.(8,9). The perinatal period is a significant period which affects the rest of the newborn's life. Although the relation between mother-related factors (the presence of systemic diseases such as preeclampsia, and hypertension), birth related factors (low gestational age, low Apgar score, presence of hypoxic-ischemic encephalopathy, etc),

and exposure of newborns to oxidative stress has been discussed in previous studies, there is an insufficient number of studies that have been conducted on this issue.(10) Here in this study we aim to investigate the relationship between MDA levels and mother related, and newborn related factors, which may affect these levels and also compare the MDA levels between the various modes of delivery. We also measure biochemical values in the umbilical cord blood of newborn infants born via various modes of delivery. We assume that the MDA level in cord blood is an anterograde significant.

### METHODS

It is a hospital based study. The research will involve asking a brief questionnaire, general examination & then 5ml of the cord blood of the newborn baby will be collected, and will be sent for estimation of serum malondialdehyde(MDA) levels, serum uric acid, serum bilirubin and serum LDH using ENZYME LINKED IMMUNOSORBENT ASSAY. No further follow ups will be re-

quired. Inclusion criteria all term newborn babies. Exclusion criteria preterm infants, infants with congenital anomalies, infants with umbilical cord abnormalities and pregnant women with DM, HTN, Chronic diseases.

Objectives of study : 1. To study the levels of serum Malondialdehyde levels in the cord blood of term newborn infants. 2. To compare serum Malondialdehyde levels in newborn infants born through various modes of delivery. 3. Study of relationship between serum Malondialdehyde levels with respect to serum total bilirubin levels, serum uric acid levels and lactate dehydrogenase of the cord blood.

All term newborns delivered in AJ Institute of Medical Sciences between January 2013 to November 2013 will be included in the study. This study was carried out on a set of 72 babies who were born by emergency cesarean section, elective cesarean section and normal vaginal delivery, 24 in each group. Serum MDA levels were assessed in the cord blood of all the babies to measure the oxidative stress in each of them. Serum uric acid, serum bilirubin and serum LDH were also measured to assess the oxidative stress.

Cord blood serum MDA levels were assessed by using OxiSelect™ MDA Adduct ELISA Kit which is an enzyme immunoassay.

**RESULTS**

This study was done to study the levels of serum MDA along with serum bilirubin, serum uric acid and lactate dehydrogenase as markers of oxidative stress in term newborn infants born in our hospital and compare their levels in various modes of delivery.

72 of the newborns were included in the study. 24 were born normal vaginal delivery, 24 were born by elective cesarean section and 24 were born by emergency cesarean section.

Among the 72 (100%) newborns, 52.8% (n=38) were female and 47.2% (n=34) were male babies. In the normal vaginal delivery group, 62.5% (n=15) were females and 37.5% (n=9) were males, in the elective cesarean section group 37.5% (n=9) were females and 62.5% (n=15) were males and in the emergency cesarean section group 58.3% (n=14) were females and 41.7% (n=10) males. The p value was 0.178 and was not significant. Among the 72 (100%), 6.9% (n=5) babies were born with meconium stained liquor and all these 5 babies were delivered by emergency cesarean section. The p value was 0.005 when compared to the other groups and was highly significant as shown in table .

**MECONIUM STAINED LIQUOR**

	Mode of delivery			Total
	NVD	LSCS Elective	LSCS Emergency	
Present	Count 0	0	5	5
	% 0.0%	0.0%	20.8%	6.9%
Absent	Count 24	24	19	67
	% 100.0%	100.0%	79.2%	93.1%
Total	Count 24	24	24	72
	% 100.0%	100.0%	100.0%	100.0%

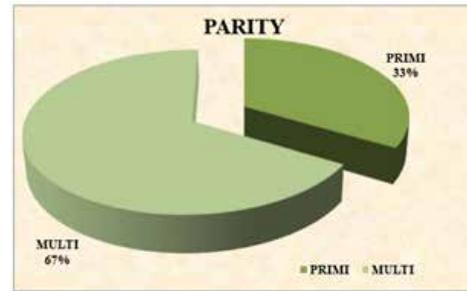
$\chi^2=10.746$  p=0.005 hs

When these 72 babies with various modes of delivery was compared by weight for gestational age, that is, small for gestational age appropriate for gestational age (SGA, AGA) p value was 0.03 and was significant as shown in table .

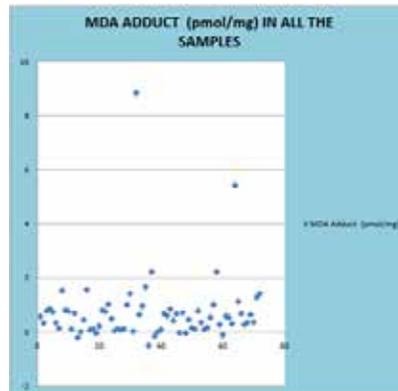
		MODE OF DELIVERY			Total
		NVD	LSCS Elective	LSCS Emergency	
AGA	Count 23	18	23	64	
	% 95.8%	75.0%	95.8%	88.9%	
SGA	Count 1	6	1	8	
	% 4.2%	25.0%	4.2%	11.1%	
Total	Count 24	24	24	72	
	% 100.0%	100.0%	100.0%	100.0%	

$\chi^2= 7.031$  p=0.03 sig

Other maternal factors like gravida-primipara or multipara mothers had no effect on the various modes of delivery with p value 0.087 not being significant as shown in graph .



The serum MDA level was estimated in all babies as plotted in graph



The serum MDA level compared between the three groups being various modes of delivery. The mean serum MDA level in babies born through normal vaginal delivery was of mean 0.584 with standard deviation of 0.596, while in babies born through elective cesarean section was of mean 0.313 with a standard deviation of 0.301 and in those born by emergency cesarean section was 0.953 with a standard deviation of 1.114. The p value between groups was estimated using Fishers test ANNOVA was <0.016 which was highly significant as shown in table .

**MDA, URIC ACID AND TOTAL BILIRUBIN IN VARIOUS MODES OF DELIVERY**

	N	Mean	Std deviation	F	p
MDA Adduct (pmol/mg)	NVD	584	596	4.4	0.016 sig
	LSCS Elective	313	301		
	LSCS Emergency	953	1.114		
Uric acid mg/dl	NVD	3.800	0.848	4.06	0.021 sig
	LSCS Elective	3.204	0.775		
	LSCS Emergency	3.896	0.909		
Total Bilirubin mg/dl	NVD	1.676	0.375	4.22	0.018 sig
	LSCS Elective	1.808	0.362		
	LSCS Emergency	2.187	0.588		

F : Fishers test ANNOVA  
p : p value

The serum bilirubin level was estimated in all babies and was compared between the three groups being various modes of delivery. The mean serum bilirubin level in babies born through normal vaginal delivery was 1.979 with standard deviation of 0.375, while in babies born through elective cesarean section was 1.808 with a standard deviation of 0.362 and in those born by emergency cesarean section was 2.187 with a standard deviation of 0.586. The p value between groups was estimated using Fishers test ANNOVA was <0.018 which was highly significant as shown in table .

The serum uric acid level was estimated in all babies and was compared between the three groups being the various modes of delivery. The mean uric acid level in babies born through normal vaginal delivery was 3.600 with standard deviation of 0.846, while in babies born through elective cesarean section was 3.204 with a standard deviation of 0.775 and in those born by emergency cesarean section was 3.896 with a standard deviation of 0.909. The p value between groups was estimated using Fishers test ANNOVA was <0.021 which was highly significant as shown in table .

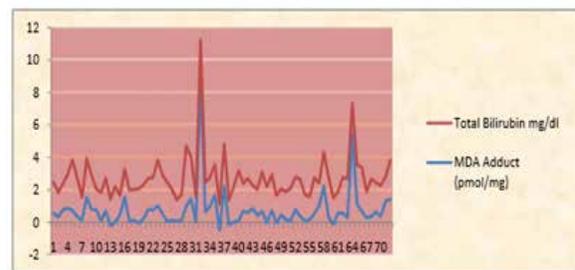
MDA, URIC ACID AND TOTAL BILIRUBIN IN VARIOUS MODES OF DELIVERY

	N	Mean	Std deviation	F	p	
MDA Adduct NVD (pmol/mg)	24	584	596	4.4	0.016 sig	
	LSCS Elective	24	313			301
	LSCS Emergency	24	953			1.114
Uric acid mg/dl	NVD	24	3.800	0.846	4.05	0.021 sig
	LSCS Elective	24	3.204	0.775		
	LSCS Emergency	24	3.896	0.909		
Total Bilirubin mg/dl	NVD	24	1.979	0.375	4.22	0.018 sig
	LSCS Elective	24	1.808	0.362		
	LSCS Emergency	24	2.187	0.586		

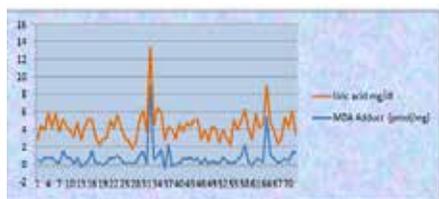
F : Fishers test ANNOVA

p : p value

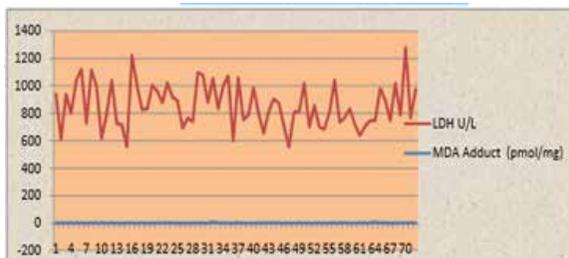
In multiple comparisons between the serum MDA, serum bilirubin, serum uric acid with various modes of delivery using the Turkey HSD, it was noted that serum MDA was statistically significant between elective cesarean section and emergency cesarean section and similar results were noted for serum bilirubin and serum uric acid with p value of 0.012, 0.016 and 0.014 respectively as shown in table and graphs .



SERUM MDA WITH SERUM BILIRUBIN



SERUM MDA WITH SERUM URIC ACID



SERUM MDA WITH SERUM LDH

Anthropometric measurements like head circumference, weight and length of the neonates were not affected by the various modes of delivery. Similar result was noted between the respiratory rate and the various modes of delivery .

APGAR scores of these babies at 1 and 5 minutes were also statistically analysed between the various modes of delivery and was noted that at 1 minute APGAR was minimum score of 5 in 2.8% (n=2) and both babies delivered by emergency caesarean section, maximum score of 10 in 18.1% (n=13) in which 6 babies delivered by elective cesarean section with significant p value of 0.01 as measured by Pearson Chi-Square test as shown in table .

APGAR AT 1 MIN

		MODE OF DELIVERY			Total
		NVD	LSCS Elective	LSCS Emergency	
5.00	Score	0	0	2	2
	%	0%	0%	8.3%	2.8%
6.00	Score	1	1	9	11
	%	4.2%	4.2%	37.5%	15.3%
7.00	Score	4	2	7	13
	%	16.7%	8.3%	29.2%	18.1%
8.00	Score	13	12	1	26
	%	54.2%	50.0%	4.2%	36.1%
9.00	Score	2	3	2	7
	%	8.3%	12.5%	8.3%	9.7%
10.00	Score	4	6	3	13
	%	16.7%	25.0%	12.5%	18.1%
Total	Score	24	24	24	72
	%	100.0%	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	30.153	10	.001

Similarly at 5 minutes APGAR was minimum score of 6 in 1.4% (n=1), delivered by emergency cesarean section, maximum score of 10 in 62.5% (n=45) in which 20 babies delivered by elective cesarean section showing a significant p value of 0.01 as measured by Pearson Chi-Square test as shown in table .

APGAR AT 5 MINS

		MODE OF DELIVERY			Total
		NVD	LSCS Elective	LSCS Emergency	
6.00	Count	0	0	1	1
	%	0%	0%	4.2%	1.4%
7.00	Count	1	0	8	9
	%	4.2%	0%	33.3%	12.5%
8.00	Count	3	2	7	12
	%	12.5%	8.3%	29.2%	16.7%
9.00	Count	3	2	0	5
	%	12.5%	8.3%	0%	6.9%
10.00	Count	17	20	8	45
	%	70.8%	83.3%	33.3%	62.5%
Total	Count	24	24	24	72
	%	100.0%	100.0%	100.0%	100.0%

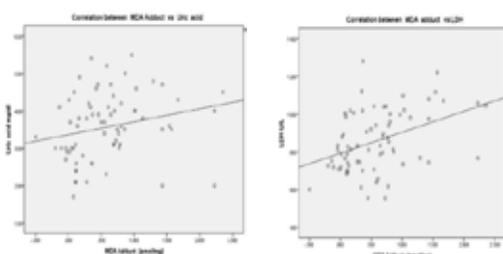
Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	26.167	6	.001

Serum MDA levels were correlated with serum uric acid, serum total bilirubin, LDH and weight of the baby and r values were 0.332, 0.407, 0.251, and 0.203 respectively showing positive correlation, and p values being 0.004, 0.001, 0.033, 0.087 respectively as shown in table and graphs .

CORRELATIONS

		Uric acid mg/dl	LDH U/L	Total Bilirubin mg/dl	Weight (gms)
MDA Adduct (pmol/mg)	r	.332	.407	.251	.203
	p	.004	.000	.033	.087
	N	72	72	72	72
Uric acid mg/dl	r		.154	.021	.026
	p		.196	.858	.831
	N		72	72	72
Spearman's rho	r			.488	.252
	p			.000	.033
	N			72	72
LDH U/L	r				.080
	p				.504
	N				72
Total Bilirubin mg/dl	r				.080
	p				.504
	N				72



That is serum MDA levels were increasing with increasing serum total bilirubin, serum uric acid and serum LDH.

Hence forth in this study it was proved that all the term babies born by emergency cesarean section have undergone more oxidative stress in comparison to the babies born through NVD and the least being in babies born through elective cesarean section which was effectively measured by serum MDA levels and also serum bilirubin and serum uric acid levels increase proportionately in these babies undergoing oxidative stress as an antioxidant response.

Discussion

The level of oxidative stress the term newborn babies are undergoing is difficult to determine clinically. Oxidative stress in biology and medicine occurs when generation of free radicals (oxidants) overwhelm the available antioxidants(11). Also it could be as a result of insufficient antioxidants in the system. This occurs even when there is minimal generation of free radicals. Majority of these free radicals like in the group reactive oxygen species have a damaging effect on cellular organelles like polyunsaturated membrane lipids(12). Free radical attack on membrane lipid produces MDA as one of the intermediate products of these dangerous reactions(12). Therefore, to measure oxidative capacity of these free radicals, MDA measurement from any biological sample is used(13).

This study was designed to assess the levels of serum MDA, serum bilirubin, serum uric acid and serum LDH levels in all the term babies born through various modes of delivery and also to study the correlation between serum MDA, serum bilirubin, serum uric acid and serum LDH levels. Data was collected from 72 term newborns and statistically analyzed.

For this SPSS software version 16.0 was used for statistical analysis of data. ANOVA was applied to statistically determine total number of patients. A Pearson chi Square test was applied to statistically determine significant difference between genders,

presence and absence of meconium stained liquor, small and appropriate for gestational age, gravida of the mother. Serum MDA levels, serum uric acid and serum bilirubin was compared in the various modes of delivery using Fisher test ANNOVA. Turkey HSD was applied to statistically determine multiple comparisons between groups.

Among the 72 (100%) newborns, 52.8% (n=38) were female and 47.2% (n=34) were male babies, so gender of the babies did not show any statistical significance. In their study, Macotta et al. 2004(14) found that cord blood MDA levels in babies delivered via elective cesarean section were lower compared to those of babies born via normal vaginal delivery. Yigit et al. 1998(15) also determined that cord blood MDA levels in babies born via spontaneous vaginal delivery were higher compared to those of babies born via cesarean section. However, in another study by Kirimi E et al.2010 (16), the role of perinatal distress on the production of oxygen radicals and on lipid peroxidation was demonstrated by an increased MDA level, regardless of gestational age, in babies delivered via cesarean section compared to babies born via spontaneous vaginal delivery. Mutlu et al. 2011(17) observed a lower lipid peroxidation in newborn delivered through CS than those delivered through vagina delivery. Mine et al. 2013(18) in their study observed oxidative stress to be more in babies delivered through vagina delivery than elective CS. In the study done by Lurie et al. 2007(19), it was shown that the MDA level in cord blood was increased in babies delivered via cesarean section compared to that of babies born via spontaneous vaginal delivery. It was asserted that this divergence from previous studies was due to the different caesarean indications of the cases.

In our study, mean cord blood MDA levels in the emergency cesarean and NVD groups were found to be statistically and significantly higher compared to that of the elective CS group. In their study, Kaya et al. 2000(20) evaluated the presence of oxidative stress in babies with presentation abnormality, compared cord blood MDA level and blood gas, and found that MDA level was a more sensitive indicator than blood gas.

In another study, Casey et al. 2001(21) attempted to reveal the status of the factors in the perinatal period and cord blood MDA level. The Apgar score was used to assess the physical condition of the newborn immediately after delivery. In our study, emergency cesarean section had low APGAR scores at 1 and 5 minutes in comparison to normal vaginal delivery and elective cesarean section. Bilgili et al. 2005(22) determined that the cord blood MDA level was higher in cases where the Apgar scores at the first and fifth minutes were lower than 7. In their study done by Lurie et al. 2007(19), it was indicated that, in evaluating oxidative stress, the determination of MDA in the cord blood was more significant than determining MDA in the plasma at the first hour.

In our study, in all the three groups, statistically significant correlation was determined between the Apgar scores at the first and fifth minutes and cord blood MDA level. Bolisetty et al. 2002(23)demonstrated that the short-term usage of multiple antioxidants by preterm pregnant women reduced the oxidative stress of the mother and baby at delivery. It has long been known that biliary pigments and biliverdin prevent cell membranes from experiencing lipid peroxidation. Bilirubin is an effective scavenger of oxidant radicals. Known as an antioxidant, bilirubin increases in case of oxidative stress(23). Yigit et al. 1998(15) found MDA concentrations in infants with hyperbilirubinemia to be remarkably high. This fact was seen as the response of babies to oxidative stress. As a result of Yigit et al study, the presence of a complex interaction between bilirubin and the level of MDA was emphasized. It was asserted that high bilirubin levels in newborns might play a defensive role against

oxidative stress because the antioxidant mechanisms are not fully developed(15). In our study, a positive correlation between the cord blood total bilirubin level and the MDA level was identified.

The MDA level was found to be statistically and significantly higher in newborns with a high total bilirubin level. In their study, Schrod et al. 1977(24)determined that among newborns with a gestational age between 22-42 weeks, the uric acid levels in the group with cord blood pH level below 7 were lower compared to that of the other group with no severe acidosis. It is thought that uric acid is the protective antioxidant of the mucosa, preserving the respiratory tracts of newborns in the initial weeks of life(24). In our study, the MDA level of infants in the emergency CS group was found to be statistically and significantly higher in newborns with a high level of uric acid in the cord blood. Uric acid is a major antioxidant in the human plasma. It correlates well with conditions associated with oxidative stress. It should be emphasized that uric acid may function either as an antioxidant mainly in the plasma or pro-oxidant mainly within the cell. Despite the damage that may be caused by oxidative stress in newborns delivered via emergency CS, it may be true that uric acid levels increase as a defense mechanism(25). If there are elective conditions at birth, oxidative stress is less. If there are emergency conditions at birth, it is higher. Thus, emergency births increase both risks and complications.

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