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Original Article

The Role of Interleukin-6 in Predicting the Development of Meconium Aspiration Syndrome in Infants Born with Meconium-Stained Amniotic Fluid; A Retrospective Analytical Study

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Abstract

Background: Since it is not always possible clinically and radiographically to predict the development of meconium aspiration syndrome (MAS) in infants born with meconium-stained amniotic fluid, there is a need for biomarkers that may predict the development of MAS in these infants. **Methods:** The study was planned in Ankara Zekai Tahir Burak Gynecology Hospital. Among term infants (>37 gestational weeks) born from mothers who had Meconium-Stained Amniotic Fluid (MSAF), the files of 60 patients who met the criteria for inclusion were retrospectively reviewed between January 2014 and May 2014. **Results:** There was no statistically significant difference between the characteristic features of infants who developed and did not develop MAS. Of the acute phase reactants, CRP, leukocyte count, platelet count, and thetotal neutrophil count did not show a statistically significant difference in both groups. We found that IL-6 was significantly higher in infants who developed MAS. The cut-off value for IL-6 was 51 with 62% sensitivity and 96% specificity. Morbidities such as pneumothorax and persistent pulmonary hypertension were observed more frequently in newborns who developed MAS and required longer mechanical ventilation, surfactant therapy, nasal CPAP support, inotropic support, and free oxygen therapy. **Conclusions:** We found that interleukin 6 is a good marker in predicting the development of meconium aspiration syndrome. We believe that this biomarker can be very useful when assessed with clinical and radiographic findings.

Key words: Newborn, meconium aspiration, meconium-stained, amniotic fluid, Interleukin-6

Introduction

Meconium-stained amniotic fluid occurs in approximately 8-25% of live births, and approximately 5% of which develop meconium aspiration syndrome. Approximately 30-50% of infants who develop meconium aspiration syndrome require intubation [1-6]. Tracheal aspiration of meconium may cause serious complications such as pneumothorax, atelectasis, chemical and secondary bacterial pneumonia, surfactant inhibition, and pulmonary hypertension, as well as complication-related morbidity and mortality [6-10].

In the early phase of meconium aspiration syndrome, non-specific findings such as increased ventilation in the radiography, flattening of the diaphragm, irregular linear or patchy areas of atelectasis are observed, whereas typical findings such as generalized, rough, homogeneous opacities due to pneumonia and interstitial edema may be delayed until 48-72 hours. Therefore, there is a need for markers that may predict which patient will develop meconium aspiration syndrome [6, 11, 12]. The important role of inflammation in MAS pathogenesis is acknowledged. Previous studies showed that cytokine levels in MAS increase *in vitro* and *in vivo* [13, 14].

To the best of our knowledge, no biomarker has been previously studied in the literature to predict MAS development in infants born with meconium; therefore, we carried out this study to determine whether the inflammation indicators that are routinely examined in the first 6 hours in our hospital are potential biomarkers that can predict the development of meconium aspiration syndrome.

Methods

The study was planned as a retrospective observational study in Ankara Zekai Tahir Burak Gynecology Hospital, which provides a level 3 neonatal intensive care service.

Among term infants (>37 gestational weeks) born from mothers who had

Meconium-Stained Amniotic Fluid (MSAF), the files of 60 patients who met the criteria for inclusion were retrospectively reviewed between January 2014 and May 2014.

Newborns with severe perinatal asphyxia (Stage 2 or stage 3 hypoxic-ischemic encephalopathy findings according to Sarnat and Sarnat) [15]. Infants born from mothers with suspected chorioamnionitis (fever in the mother, mother having leukocytosis, early membrane rupture (>18 hours), tachycardia in the mother or fetus, mother having foul-smelling discharge), those with reproductive blood culture and newborns with major congenital anomalies were excluded from the study.

Babies born with MSAF were intervened in line with the American Heart Association (AHA) guidelines 2010, the Eurepean resuscitation council and the international Liaision committee on resuscitation (AHA, ERC, ILCOR) recommendations.

A total of 60 newborns meeting the inclusion criteria were enrolled in the study. The groups were MAS (+) group which developed MAS (group 1, N: 19) and MAS (-) group which did not develop MAS (group 2, N: 41).

Leukocyte count, absolute neutrophil count, IL-6 (interleukin-6), CRP (C-reactive protein), platelet count, and blood culture results examined at 6thhour after delivery, as well as morbidity such as pneumothorax, persistent pulmonary hypertension and mortality in the neonatal period, were assessed.

Infants without respiratory distress were monitored at the side of the mother. Infants with mild tachypnea (respiration rate: 60-80/min) or mild subcostal retractions were proceeded to free oxygen monitoring (by a hood to ensure approximately 30% oxygen concentration).

Infants with pronounced subcostal retraction and/or moaning were taken to nasal CPAP (continuous positive airway pressure) support. Infants with nasal CPAP deficiency were intubated and

taken to mechanical ventilator monitoring.

Mechanical ventilator monitoring: the maintenance of respiration with an artificial respiratory device with the help of intubation. MV requirement: Patients were intubated and taken to MV in case the moaning and retractions continued on nasal CPAP, pH value was below 7.2 in blood gas, apnea was present requiring positive pressure ventilation and pCO_2 value was above 65 mmHg despite NCPAP [16].

The diagnosis of persistent pulmonary hypertension (PPHT) was made by detecting right to left shunt with ECHO in infants having pre-ductal oxygen saturation>5% compared to post-ductal oxygen saturation and by excluding other congenital heart diseases [17].

Surfactant treatment: Applied according to Canadian Pediatric Association recommendations [18].

Among infants diagnosed with meconium aspiration, intubated infants with fractionated oxygen requirement of >50% were given 100-200 mg/kg via endotracheal tube.

Inotropic support: Infants with hypotension (defined as mean blood pressure below the week of gestation) initial dopamine dose was started 5 μg/kg/min and increased to 15-20 μg/kg/min based on hemodynamic response [19].

Definition of MAS: It was defined as being born with meconium, developing respiratory distress, having respiratory distress not attributable to other reasons, having increased radiographic ventilation, and accompanying generalized roughness density [4].

Definition of Meconium-Stained Amniotic Fluid (MSAF): It was defined as the transition of meconium into amniotic fluid due to causes such as fetal distress or chorioamnionitis causing an increase in intestinal peristalsis before or during birth [11].

High sensitivity immunoturbidimetric assay on CRP (latex) Roche Modular P analyzer was used. (CRP latex HS,

Roche kit, Roche Diagnostics®, Mannheim, Germany). Results were reported in mg/dl.

Hematological parameters were measured with an automatic cell counter.

Serum IL-6 levels were measured with IMMULITE 1000 analyzer (Siemens Diagnostic Product Corporation®, Los Angeles, CA). Results were reported in pg/ml. Cut off values İL-6: 75pg/ml

The data were analyzed with SPSS® version 20 for Windows ®. The comparison was made with the Student's t-test. Correlation between IL-6 and white blood cell levels was performed by Pearson correlation test. A p-value of <0.05 was considered significant. ROC curve analysis was performed for IL-6. Cut off values: 5 mg/dl

Ethics approval and consent to participate: The study protocol was approved by the Ethics Committee of Ankara Zekai Tahir Burak Gynecology Hospital. Date: 02.06.2014, ID: 518

Informed written consents were obtained from all individual participants included in the study.

Statistical analysis

The data were recorded and analyzed with the SPSS v20. Categorical data were represented by frequency and percentage, while continuous data were represented by mean standard deviation and median (lowest-highest). Compatibility of continuous data to normal distribution was tested with the Kolmogorov-Smirnov test.

The T-test or the Mann-Whitney U test was used in the comparison of the means according to their suitability for normal distribution. A Chi-square test was used in comparing the categorical data. Correlation between IL-6 and other parameters was performed by Pearson correlation test. The $p<0.05$ value was accepted as the limit of significance. ROC curve analysis was performed for IL-6 cut off values 5 mg/dl

Results

During the study period, it was determined that 72 patients were born with meconium-stained amniotic fluid.

Five patients were excluded from the study due to moderate or severe perinatal asphyxia, two patients due to insufficient laboratory data, and 5 patients due to suspected chorioamnionitis findings.

There was no statistically significant difference between the characteristic features of infants who developed and did not develop MAS (Table 1). Of the acute phase reactants, CRP, leukocyte count, platelet count, and the total neutrophil count did not show a statistically significant difference in both groups (Table 2). It was found that IL-6 was significantly higher in infants who developed MAS (Figure 2). When analyzed with the ROC curve, the cut-off value was 51 for IL-6 (Sensitivity 62%, Specificity: 96%). Morbidities such as pneumothorax and persistent pulmonary hypertension were observed more frequently in newborns who developed MAS and required longer mechanical ventilation, surfactant therapy, nasal CPAP support, inotropic support, and free oxygen therapy ($p < 0.05$) (Table 3).

There is no correlation between IL-6 and CRP and White blood cell levels, and p-values are 0.58 and 0.869 respectively (Table 4),(Figure 1). A comparison was made between ventilated MAS positive and MAS negative newborns in terms of IL-6 levels. mean IL-6 in MAS (+) ventilated babies: 541, mean of IL-6 in babies ventilated with MAS (-): 60. ($p<0.05$). No growth was detected in the blood culture of any patient. Tracheal aspirate culture was not taken from the patients.

Discussion

IL-6 is a strong inflammatory mediator, and plasma concentration has been tested as a prognostic factor in several studies. It tops the list as one of the most important predictors of perinatal inflammation.

Elevated levels of IL-6 are also affected in infectious and many non-infectious

inflammatory and stressful conditions [20,21].

As a result of a systemic review and meta-analysis conducted by Tieying Hou et al., the authors emphasized that IL-6 and CRP frequently increase in non-infectious diseases and may function as useful prognostic tools in these infants, consisting of both infected and non-infected patients [22].

Reinhart et al. showed that septic patients with IL-6 > 1000 pg/ml had higher mortality [23]. The strategy with regard to starting antibiotics in infants with meconium aspiration syndrome is uncertain [24,25]. When Mahendiran et al. examined the procalcitonin levels as a marker that could predict the accompaniment of neonatal sepsis in infants with MAS, the authors detected elevated procalcitonin levels in all infants with meconium aspiration syndrome, whether or not having an accompanying bacterial infection.

Therefore, they concluded that it should not be used as a marker predicting bacterial infection in infants with meconium aspiration syndrome [26].

Lindenskov et al. have shown a close relationship between complement activation and meconium aspiration syndrome and impaired lung function in the animal mode [27].

Cayabyab et al. reported that patients who were monitored in a mechanical ventilator due to meconium aspiration syndrome differed in terms of cell count in the tracheal aspirate fluid and cytokine levels by the change on airway pressure [28].

Okazaki et al. compared 17 types of cytokine and chemokine levels, including Interleukin-6, which they thought tobe involved in the pathogenesis of meconium aspiration syndrome, between infants with meconium aspiration syndrome, neonates without meconium aspiration syndrome and older healthy children, and they found that 8 of these pro-inflammatory mediators (interleukin-1, interleukin-6, interleukin-8, granulocyte-macrophage colony-

stimulating factor, granulocyte colony-stimulating factor, interferon-gamma, macrophage inflammatory protein-1, and tumor necrosis factor) were significantly higher than healthy children and 6 of them than infants without meconium aspiration syndrome [14].

They concluded that these pro-inflammatory mediators cause lung damage and are involved in MAS pathogenesis.

Hofer et al. showed that there is a relationship between severe MAS and elevated CRP, low leukocyte count, and low absolute neutrophil count, and reported that these results can be used in clinical practice to determine the course of patients with MAS [13].

To the best of our knowledge, the current study is the first study in which CRP, il-6 and hematological inflammation parameters were evaluated to predict MAS development in infants born with meconium.

In this study, we determined that interleukin 6 is a good marker in predicting the development of meconium aspiration syndrome. For the development of MAS, we found the IL-6 cut-off value of 51 with 62% sensitivity and 96% specificity.

Since there was no growth in the blood culture of our patients, and other acute phase reactants did not increase, the high IL-6 level was not considered to be associated with bacterial infection.

Blood samples for IL-6 were taken 6 hours after birth. This duration is short for development of lung injury and inflammatory response against it in the ventilator. Therefore, we did not high IL-6 levels was not attributed to lung injury.

However, in future studies, we suggest the investigation of IL-6 level in cord blood to rule out the possibility of being affected by ventilator-induced lung injury [6].

Our study partially overlaps with an important study in which it has concluded that fetal systemic inflammation plays a role in the pathogenesis of MAS.

The authors of this study suggest that biomarkers including chemokines, acute phase reactants and cytokines, or pathological findings should be investigated to predict the development of MAS[6].

We found that the levels of other inflammatory markers did not increase in infants who developed meconium aspiration syndrome, which supported the thesis that il-6 was involved in the pathogenesis of MAS.

Limitations: This is a retrospective analytical study, Although we excluded conditions predisposing to sepsis development in newborns and infants with neonatal sepsis with culture positivity, we could not exclude that the increase in inflammatory indicators is not related to sepsis, since we know that blood culture positivity is at the rate of 50% in neonatal bacterial sepsis even under the best conditions. Besides, we know that it is difficult to evaluate inflammatory indices in mechanical ventilation monitoring.

Conclusions

We conclude that interleukin 6 can be used as a biomarker to predict the development of meconium aspiration syndrome (MAS) in infants born with meconium stained amniotic fluid (MSAF). However, there is a need for larger randomized controlled studies to say this more clearly.

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Author's contributions

Sadrettin E: Conceptualization; Investigation; Writing - original draft; Writing - review & editing. Turan D: Data curation; Validation; Software; Writing - review & editing. Halil D: Supervision; Visualization. Fuat E: Formal analysis, Methodology. Nurdan U: Project administration; Software. All authors have read and approved the final manuscript.

Conflict of interest

Authors declare they have no conflict of interest

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Table 1. Comparison of basic clinical features in infants with and without MAS

Variables	**Group 1 (n : 19)**	**Group 2 (n : 41)**	**p-value**
Mother's age, in years	28.53 (18-38)	27.76 (17-39)	0.66
Delivery Method, % (NSVR/C/S)	42	46	0.76
Birth Week, in weeks	38.9 (37-41)	39.2 (38-41)	0.33
Birth Weight, in grams	3270.2 (2700-3990)	3331.7 (2500-4250)	0.61
Gender (M/F), %	53	54	>0.05

NSVR: Normal Spontaneous Vaginal Route, C/S: C: Section. M: Male F: Female

Table 2. Comparison of laboratory values between two groups

Variables	**Group 1** **(n : 19)**	**Group 2** **(n : 41)**	**p-value**
CRP (mg/dl)	7.26 (0.02-79)	6.17 (0.06-114)	>0.05
IL-6 (pg/ml)	516 (15-2250)	116 (5-2247)	<0.05
White Blood Cell	25004 (6200-42000)	21098 (9400-35000)	>0.05
Neutrophil	15368 (3800-23600)	14104 (4300-22200)	>0.05
Platelet	230789 (6300-449 000)	257951 (106 000-650 000)	>0.05

CRP: C-reactive protein, IL-6: Interleukin-6

Table 3. Comparison of clinical variables in the neonatal period

Variables	**Group 1 (n : 19)**	**Group 2 (n : 41)**	**p-value**
Surfactant, n(%)	17	0	0.00
Pulmonary hypertension	13	0	0.00
Pneumothorax, n(%)	6	0	0.00
Time on mechanical ventilation (day)	4.63 (1-15)	0.87 (0-1)	0.001
Inotropic support, n (%)	19	7	0.00
Exitus, n(%)	3	0	0.00

Table 4: Correlations between IL-6 and other acute phase reactant

Item		CRP	IL-6	White blood cell	Neutrophil
CRP	PearsonCorrelation	1	0,072	0,013	-0,029
	Sig. (2-tailed)	--------	0,585	0,919	0,826
	N	60	60	60	60
IL-6	PearsonCorrelation	0,072	1	-0,022	-0,026
	Sig. (2-tailed)	0,585	---------	0,869	0,841
	N	60	60	60	60
White blood cell	PearsonCorrelation	0,013	-0,022	1	0,596**
	Sig. (2-tailed)	0,919	0,869	---------	0,000
	N	60	60	60	60
Neutrophil	PearsonCorrelation	-0,029	-0,026	0,596**	1
	Sig. (2-tailed)	0,826	0,841	0,000	----------
	N	60	60	60	60

**. Correlation is significant at the 0.01 level (2-tailed).

CRP: C-reactive protein, IL-6: Interleukin-6

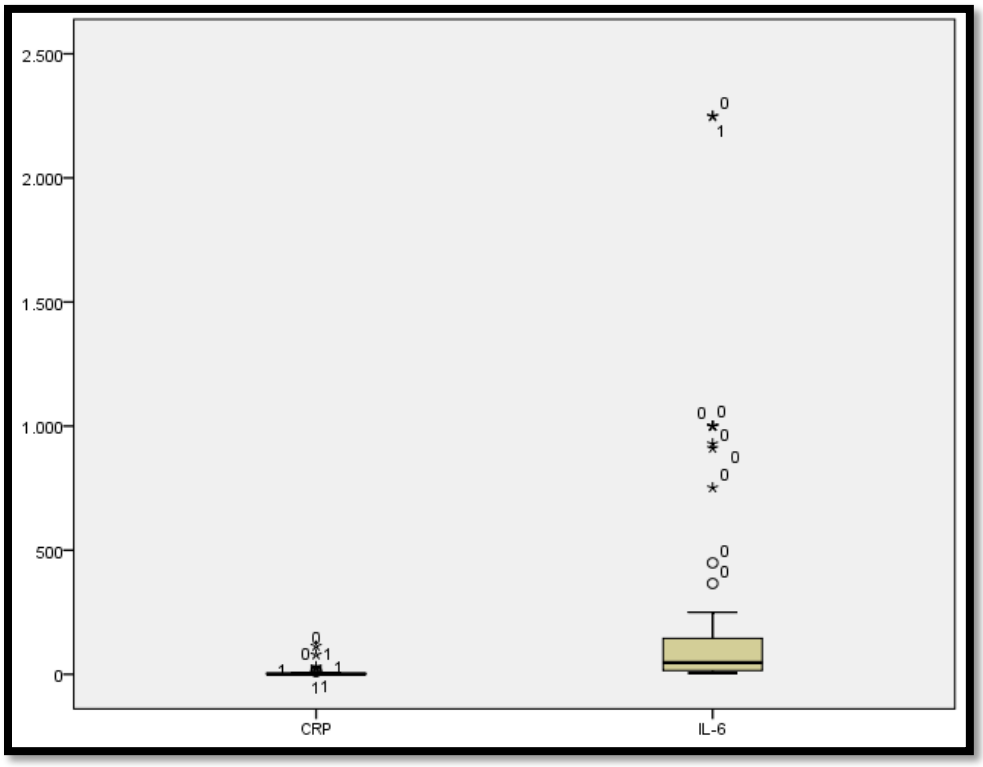

Figure (1): Serum levels of CRP: C-reactive protein, IL-6: Interleukin-6

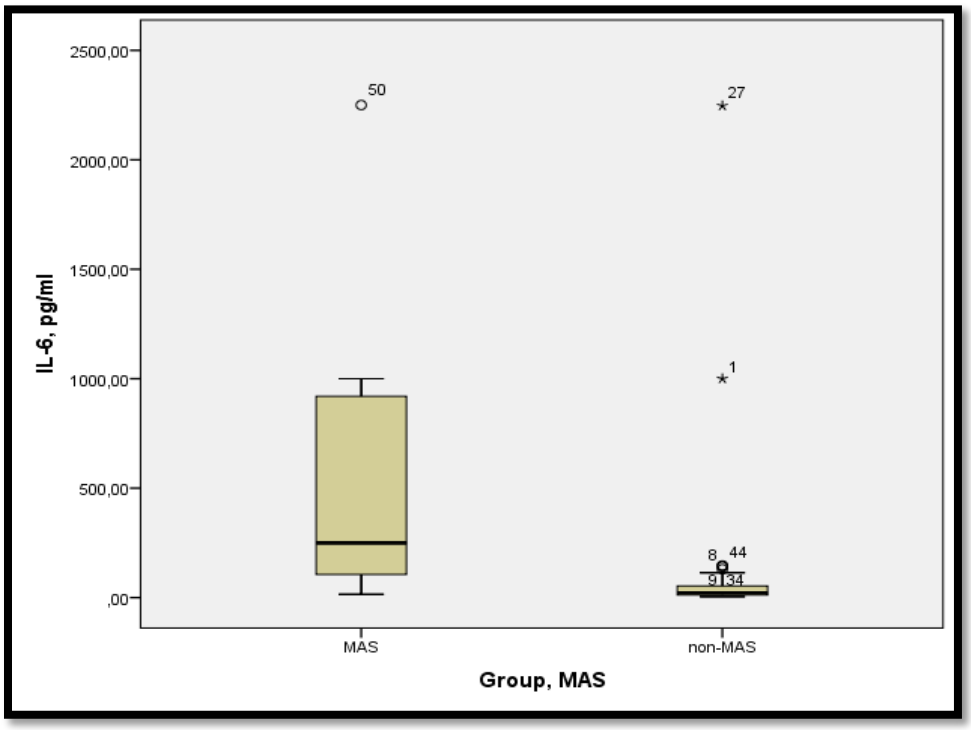

Figure (2): IL-6 levels in MAS and Non-MAS groups

MAS: Meconium aspiration syndrome, IL-6: Interleukin-6

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