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The Role of Serum Interleukin-6 in Assessing Prognosis for Infants born with Meconium-Stained Amniotic Fluid

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Abstract
Meconium aspiration syndrome (MAS) is seen in 10% of neonates born with meconium-stained amniotic fluid (MSAF) with high mortality. Studies suggest proinflammatory cascade in progression to MAS with trials on dexamethasone use. An observational study, comprising of 40 term neonates born through MSAF. Cord serum IL-6 was measured by electro-chemiluminescence. The newborns were followed up for progression to MAS. We included 20 term appropriate for age newborns born with no fetal distress and clear amniotic fluid for IL-6 reference range. As the IL-6 values showed skewed distribution, comparison of median (MAS, no MAS, reference) was done by Kruskal-Wallis. Confounding variables were adjusted using regression. The median IL-6 values were 2297pg/mL in newborns with MAS, 2009.5pg/mL with no progression, and 49.8pg/mL in the reference group. The differences in IL-6 were significant (p=0.002) between the newborns with MSAF and the reference group, but comparable (p>0.05) between the MAS and the newborns with no progression. Factors like fetal distress and birth asphyxia did not influence IL-6 levels. Significant elevation of cord serum IL-6 was seen in newborns born with MSAF. However, it was not a predictive marker for progression.

Keywords: Serum interleukin-6, prognostic marker, meconium-stained amniotic fluid

Introduction
Meconium staining of amniotic fluid is seen in 4-22% of neonates [1]. It is seen when fetus passes meconium in-utero. About 3-12% of neonates progress to meconium aspiration syndrome (MAS) characterized by collapse of alveoli, air leak syndrome, and persistent pulmonary hypertension. Birth asphyxia and secondary bacterial infections, also complicate MAS. Though progression is more prevalent with thick meconium, MAS can occur in vigorous babies with thinly stained amniotic fluid. The disease usually has higher complications and death in term newborns. Newborns with a severe course require prolonged mechanical ventilation, high-frequency ventilation (HFOV), or inhaled nitric oxide. Mortality rate may be as high as 5 to 12% [2]. An Indian study reported mortality in 24% of MAS [3].

Meconium or the 'earliest stool' of the infant, consists of desquamated intestinal epithelial cells, gastrointestinal secretions, swallowed amniotic fluid, lanugo, and vernix. Fractional analysis has shown several hydrophobic and hydrophilic compounds in the meconium [4]. Pathogenesis of MAS is a complex interaction of mechanical obstruction of peripheral airways, chemical pneumonitis, meconium-induced surfactant deficiency, and meconium-induced systemic inflammation. The pro-inflammatory and pro-oxidative mechanisms, especially the interleukins (IL) induce programmed cell death of type II alveolar cells, aggravate surfactant deficiency, and damage the pulmonary alveolar-capillary membrane. In animal and in-vitro models, MSAF contains IL-6 and other cytokines [5, 6].

Clinical studies have investigated inflammatory indices in MAS. Hofer *et al.* [7] studied leukocyte count, neutrophil count, IT ratio, and CRP and relationship with severity. Maternal CRP is higher in the neonates born with MSAF in another study [8]. Lactate dehydrogenase has been studied as a marker in estimating neonatal intensive care unit stay and need for oxygen supplementation among MAS [9]. Okazaki *et al.* [10] found significantly elevated cytokine and chemokine profiles in newborns with MAS. Inhaled budesonide has shown promising results in two clinical trials substantiating the role of inflammation in pathogenesis [11, 12].

Hofer *et al.* [7] showed that inflammatory indices as predictor for illness severity in meconium aspiration syndrome. Authors evaluated leukocyte count, neutrophil count, IT ratio, and CRP in meconium aspiration syndrome in a retrospective data analysis.

Infants with positive blood cultures were excluded.

Current guidelines do not recommend routine endotracheal suctioning even in a 'non-vigorous' baby as it does not influence the progression. The role of inflammatory indices and the rationale for steroid use needs validation. Among pro-inflammatory Interleukins, serum IL-6 assay is validated in clinical studies. By linkage of innate and acquired immunity there is enhanced differentiation of CD4 cells to mature forms. There is a paucity of studies as the role of interleukins in progression to MAS. We intend to look into the umbilical cord serum IL-6 as a prognostic marker in infants born through MSAF for the neonatal outcomes.

Methodology

Type of study	:	**Observational**
Study design	:	Cross-sectional, analytical
Study unit	:	Neonatal Intensive Care Unit, Department of Pediatrics,

Sampling Method: Convenience Sampling

Inclusion criteria

Singleton, term newborns born through MSAF.

Exclusion criteria

1. Preterm (gestational age <37 completed weeks)
2. Multiple gestation
3. Neonatal respiratory distress due to hemodynamically significant structural heart disease, structural malformations like diaphragmatic hernia
4. Major congenital malformations influencing the neonatal outcome

Control group

Inclusion criteria

1. Term, Singleton
2. Appropriate for gestational age born with clear amniotic fluid
3. Matched for maternal age and parity

Exclusion criteria

1. Meconium-stained amniotic fluid
2. Maternal chorioamnionitis
3. Fetal distress
4. Premature rupture of membranes
5. Preterm (gestational age <37 completed weeks)
6. Multiple gestation
7. Small and large for gestational age
8. Neonatal respiratory distress due to hemodynamically significant structural heart disease, structural malformations like diaphragmatic hernia
9. Major congenital malformations influencing the neonatal outcome

Sample size

All newborns born through MSAF were included. We expect to enroll a minimum of 60 newborns, of whom 8-10 (20-25%) may develop MAS.

Twenty normal newborns were recruited as control group for cord blood estimation of Interleukin-6

Data collection

Clinical: Demographic data include maternal age, parity, pregnancy-related illnesses like gestational hypertension and gestational diabetes mellitus. Sonographic data was looked into for fetal growth restriction, amniotic fluid volume, fetal Doppler indices, and biophysical profile. Gestational week, type of labor, whether artificial rupture of membrane showed meconium, the grade of meconium, duration of the second stage, and mode of delivery was recorded. Newborn resuscitation (if any), assessment of gestational age, and anthropometry was captured. The newborn was observed for 24 hours for the development of respiratory distress and progression using the Downe respiratory score [25]. The neonatal course of infants who develop MAS was recorded for the outcome.

Lab: Three milliliter of cord blood was collected in a plain vacutainer in all newborns with MSAF. Measurement of IL-6 was done by Electro-chemiluminescence Immunoassay. The value is expressed in picogram/ml. Other inflammatory markers like Leukocyte count, neutrophil to lymphocyte ratio, CRP, and procalcitonin was documented if done as part of standard care. Cord arterial blood gas was noted. When done as part of routine care, we noted the findings in the chest radiographs and echocardiogram.

Results

4(10%) had Birth Asphyxia and Encephalopathy. 9(22.5%) needed free flow oxygen, 5(12.5%) required High flow nasal canula, 3(7.5%) needed mechanical ventilation.

3(7.5%) of cases had pulmonary hypertension. 6(15%) of cases had metabolic complications

3(7.5%) of cases had Multiorgan dysfunction. No Air leak syndromes in my study population

All were discharged. No deaths noted.

Table 1: Neonatal Outcomes

Outcomes	**Symptomatic n=22(%)**
Birth Asphyxia and Encephalopathy	4(36.3)
Escalation of respiratory support	5(22.7)
Pulmonary Hypertension	3(13.6)
Metabolic complications	6(27.3)
Multi organ dysfunction syndrome	3(13.6)

The central tendencies of cord serum IL-6 is shown in Figure 1 and Table 2.

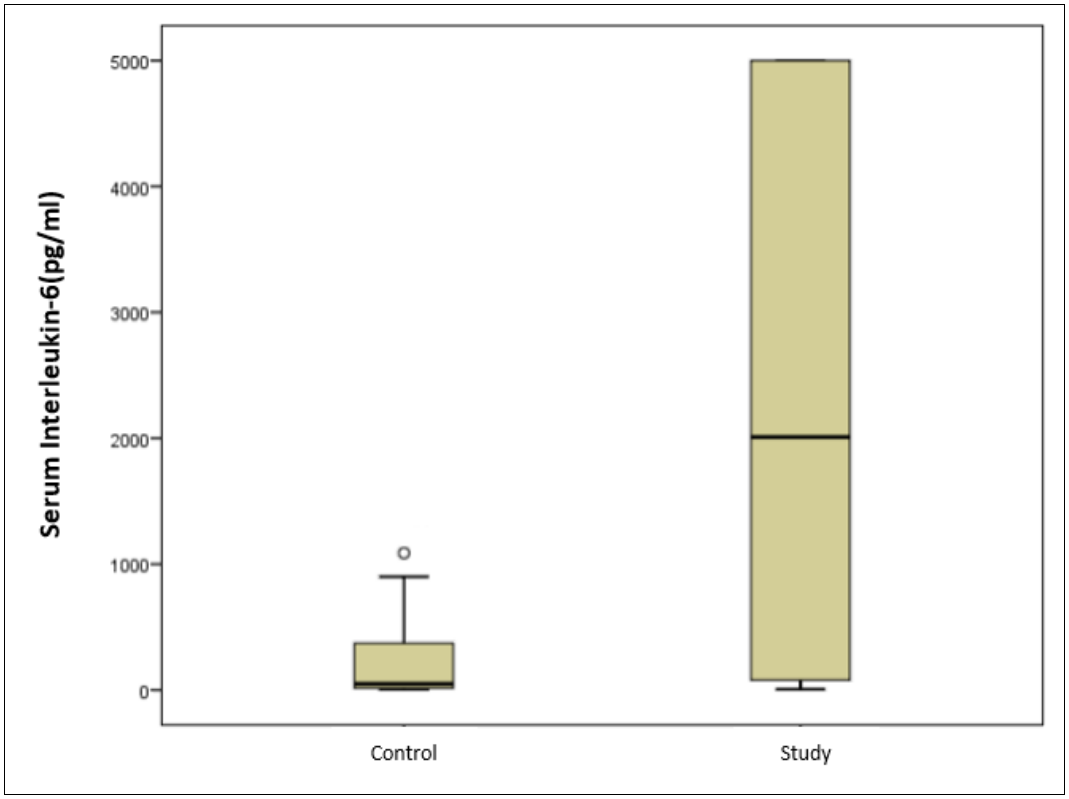

Fig 1: Interleukin 6 levels

There was one outlier with value of 1088pg/ml in the control group.

Table 2: Central tendencies of cord serum IL-6 among study and control group

Cord serum IL-6 (pg/ml)	Study group	Control group
Mean (SD)	2413.8 (2231.1)	235.2 (330.1)
Median (IQR)	2009.5 (4924)	49.8 (385)
Minimum	7	3
Maximum	5000	1088

The cord Serum IL-6 values showed a skewed distribution.

Table 3 and Figure 2 shows the central tendencies of cord serum IL-6 in 3 groups namely MAS, no MAS, control group

Table 3: Central tendencies of cord serum IL-6 among MAS, no MAS, control group

	Symptomatic (pg/ml)	Asymptomatic (pg/ml)	Control (pg/ml)
Median Serum IL-6	2297	2009	49.81
IQR	4857	4961	385
Maximum	5000	5000	1088
Minimum	13	7	3
Mean(SD)	2523.0(2307.0)	2280.5(2193.4)	235.3(330.2)

The median difference in IL-6 between newborns born with MSAF and the reference group was significant (Test statistics=12.3, p=0.002).

The Serum IL-6 values showed a skewed deviation among the three groups.

Comparison of median cord serum IL-6 between the 3 groups was significant. Bonferroni post-hoc tests showed significant differences between newborns who developed meconium aspiration syndrome and controls, and also between newborns born through MAS but not progressed to MAS and controls. The difference was not significant between who progressed and did not progress to MAS.

Table 4: Pair-wise comparison of sub groups

Pair-wise comparison	Test Statistics	Standard Error	Standard test Statistics	Significance	Adjusted Significance
MAS-Control	14.6	5.6	2.5	0.009	0.028
No MAS- control	17.9	5.3	3.3	0.001	0.002
MAS-no MAS	-3.28	5.5	-5.9	0.550	1.00

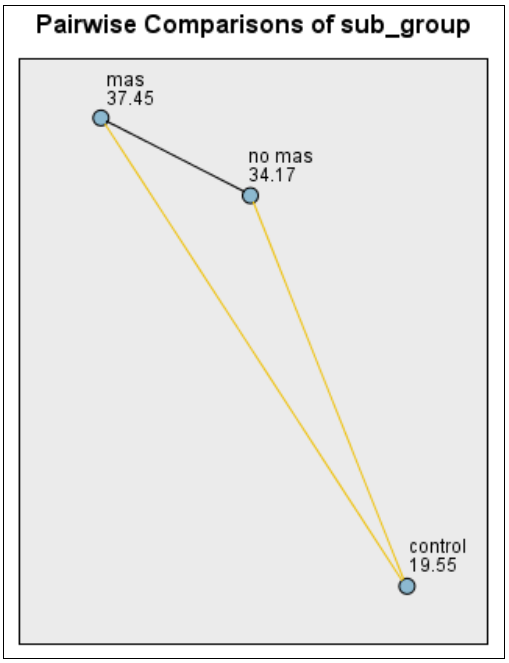

Fig 2: Bonferroni post-hoc: Pair-wise comparison of sub groups

The differences in IL-6 were comparable (p>0.05) between newborns with progression to MAS and newborns with no

progression.
Serum IL-6 showed no significant correlation with meconium grade, need for oxygen, ventilation, and development of PPHN. There was no air leak syndrome and death in our study.
Regression statistics did not show a maternal or natal variable significantly influencing cord serum IL-6 values in the newborns.
We found that birth weight was a significant determinant for progression to MAS (B=1.003(95%CI 1.000-1.006); p-0.032) irrespective of grade of meconium.
Our study results showed that there is IL-6 surge in the presence of MSAF. Thus, cord serum IL-6 was not useful as a marker for progression to MAS in newborns born through MSAF.

Discussion

The purpose of present study was to estimate cord serum IL6 levels in newborns born with MSAF, and compare the serum IL6 levels of newborns who develop MAS and those who do not. We found that cord serum IL6 was highly elevated in newborns born through MSAF. Meconium is potent stimulator of inflammatory cascade [12]. Animal studies revealed elevated inflammatory mediators' concentration in lavage of meconium instilled lungs.
Our study results showed that the overall comparison of median cord IL-6 levels between the groups, namely newborns born with MSAF but no progression, newborns with progression to MAS, and normal newborns was significant. Bonferroni post-hoc tests showed significant differences between newborns who developed MAS and controls, as well as newborns born through MSAF but no progression (no MAS) and controls. However, cord serum IL6 born through MSAF with and without progression was similar.
Meconium is a neutrophil chemoattractant. TNFα is also detected. Addition of meconium to amniotic fluid makes it a good culture medium for microorganism growth. Lee *et al*. and Romero *et al*. found elevated inflammatory markers in amniotic fluid stained with meconium. Alghazali *et al*. [8] demonstrated elevated maternal CRP in women with MSAF in labor. Yokoi *et al*. studied association of meconium aspiration syndrome with clinical variables, histopathology of placenta, inflammatory markers. Among 1336 newborns with meconium-stained amniotic fluid, 6.6% progressed to meconium aspiration syndrome. They concluded that lower APGAR score at one minute and five minute, reduced pH in blood of umbilical cord, cord inflammation, increased levels of α_1-acid glycoprotein, haptoglobin is associated with progression to meconium aspiration syndrome concluding that inflammation in-utero can be independent variable assessing progression to meconium aspiration syndrome.
Hofer *et al*. [7] found that elevated IT-ratio, CRP, low leukocyte, and neutrophil counts were positive predictors for progression to MAS. Kamath *et al*. [9] in an Indian study found elevated LDH to be good prognostic marker for neonatal outcome in MSAF. Karabayir *et al*. and Rodriguez *et al*. found elevated blood lactate a good predictor for MAS and disease severity.
There are only two studies on serum IL-6 in MAS by Okazaki *et al*. [10] and Ekmen *et al*., both international.
Okazaki *et al*. [10] estimated 17 serum chemokines and cytokines in 36 neonates, of which 11 had MAS,16 born through MAS but with no progression to MAS, and nine healthy children. The samples were drawn within six hours of life. Eight of the 11 infants with MAS received assisted ventilation. Seen elevated were IL-6, IL-8, GMCSF, GCSF, INF-ɤ and TNF-α. C-reactive protein was elevated but not significant. The mean (SD) serum IL-6 levels in the newborns with MAS, newborns born through MSAF but with no MAS, and healthy newborns were 909.5 (268.1), 213.4 (69.4), and 13.1 (7.2) pg/mL respectively. They found mean IL-6 of 909.5±268.1pg/ml among MAS and those who born with MSAF but did not progress had mean of 213.4±69.4 pg/ml and among controls is 13.1±7.2 pg/ml. The mean difference between the groups born through MSAF with and without MAS is 696.1 picogram/ml (p=0.005). The mean difference between those progressed to MAS and healthy group is 886.4 picogram/ml (p=0.002). The mean difference of born through MSAF but no MAS and healthy newborns was 200.3 pg/ml with no significance. There was no association with the oxygenation index and, therefore, the severity of lung disease.
Ekmen *et al*. from Turkey, retrospectively analyzed data of 60 term newborns from mothers who had MSAF. They included 19 newborns with MAS and 41 newborns with MSAF who did not progress to MAS. They found that acute phase reactants, CRP, leukocyte count, platelet count, and the total neutrophil count was similar in both groups. But IL-6 was significantly higher with mean of 516pg/ml (15-2250 pg/ml) ($p< 0.005$) in infants who developed MAS in comparison with mean of 116 pg/mL (5-2247 pg/mL) in those who did not progress. They found IL-6 cut-off value of 51pg/ml to be 62% sensitive and 96% specific for progression to MAS.
Both Okazaki *et al*. [10], Ekmen *et al*. determined serum IL6 levels at six hours of life and found the mean difference to be significant. Both the authors did not find CRP to be a useful marker for to MAS.
Our study estimated serum Interleukin-6 in cord blood. We found cord serum IL6 to have a mean (SD) of 2413.8 (2231.1) pg/ml and median (IQR) of 2009.5 (4924) pg/ml. As the cord serum IL6 value was not normally distributed, we used the median value for comparison. The serum IL6 in the Ekmen study has a range between 5 and 2250 pg/mL; however, the authors have used mean for comparison. Also, the suggested cut-off 51pg/mL by the authors is much lower than the mean value of serum IL6 in the newborns who did not progress to MAS.

Conclusion

- Significant difference in cord serum interleukin 6 was noted between newborns born through MSAF and reference group.
- Cord serum interleukin 6 was comparable between neonates who developed MAS and who did not progress to MAS.
- Serum Interleukin 6 did not show significant correlation with grade, need for oxygen, development of persistent pulmonary hypertension.

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Author's Contribution

Not available.

Conflict of Interest

Not available.

Financial Support

Not available.

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