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EFFICACY OF CORTICOSTEROIDS IN NEONATES WITH MECONIUM ASPIRATION SYNDROME

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Abstract:
Objectives: *The objective of study was to know about effectiveness of corticosteroid therapy in neonates with meconium aspiration syndrome in comparison with control.*
Materials and Methods:
The study was conducted in pediatrics unit Punjab medical college Allied/ DHQ hospital Faisalabad in the duration of six months after the approval of synopsis.
Results: *Out of 92 cases (46 in each group) 46.67% (n=19) in A-Group and 56.67% (n=22) in other B-Group were between 1-3 hours of life, 36.67% which is (n=16) in A-Group and 30% which is (n=14) in B-Group were between 4-6 hours while only 16.67% which is (n=11) in A-Group and 13.33% which is (n=10) in B-Group were between 6-8 hours of life, mean and sd was calculated as 3.78+2.26 in A-Group and 4.12+2.77 years in B-Group, 63.33% (n=29) in A-Group and 56.67% (n=26) in B-Group were male while 36.67% (n=17) in A-Group and 43.33% (n=20) in B-Group were females, mean duration of stay in hospital was significantly reduced in children administered corticosteroid therapy.*
Conclusion: *Treatment with corticosteroid in neonates suffering from meconium aspiration syndrome is effective in terms of hospital stay duration while comparing with symptomatic treatment only.*
Key Words: *Meconium aspiration syndrome, neonates, corticosteroid therapy, Symptomatic*

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INTRODUCTION:

Meconium is the infant's earliest stool. It is found in the gastrointestinal tracts of fetuses as early as 14-16 weeks of gestation [1]. "Meconium aspiration syndrome (MAS) is when the newborn has respiratory distress and the only explanation for the distress is that the infant has swallowed meconium-stained amniotic fluid (MSAF). Meconium-stained amniotic fluid occurs when the fetus defecates prior to delivery and it occurs in approximately 10-15% of term (37 weeks of gestation) or post term pregnancies. MAS occurs in only 1-4% of newborns that are born with meconium-stained fluid" [2,3,4]. Meconium aspiration syndrome (MAS) is one of major causes of respiratory failure in the term and post-term neonates. Pathophysiology of MAS is complex and not understood completely. In the acute phase, aspiration of meconium causes mechanical airway obstruction. When reaches the alveoli, meconium evokes surfactant dysfunction, inflammation, vasoconstriction, and airway hyperreactivity [5]. Resulting leakage of proteinaceous fluid and cells with neutrophils into alveolar spaces further deteriorates the acute lung injury. "Hypoxia and higher levels of thromboxane A2, leukotrienes, prostaglandins, and endothelin-1 may result in pulmonary vasoconstriction, while Broncho active substances such as leukotrienes and platelet-activating factor may be responsible for airway hyperreactivity. Oxidative damage to lung tissue is further aggravated by ventilation with high oxygen concentrations, nitrogen species, and other biologically active substances."

In presence of these findings, administration of anti-inflammatory drugs, e.g., corticosteroids (CS) may reduce the inflammatory response, edema, vaso- and bronchoconstriction, and thereby improving the lung functions in MAS. In the previous studies, significant reduction was noted in duration of hospital stay and need for oxygen therapy. Moreover, treatment with intravenous dexamethasone has improved the gas exchange and has decreased pulmonary vascular resistance, lung edema, and number of lung neutrophils. Nebulized budesonide has improved lung function in chlorine gas injured piglets [5-9]. Pilot studies have shown that duration of stay in hospital (in days) was significantly reduced (19±3.75, 11±1.5 days) in those who were given corticosteroids and in those who were not given respectively. Since the information on the advantages of Corticosteroids administration in MAS is scant rationale of our study to evaluate the effectiveness of corticosteroids on the clinical course and outcome of neonates with MAS especially with reference to duration of stay in hospital in days.

FETAL STRESS

MSAF has also been attributed to a fetal response to intrauterine stress and hypoxia, with the passage of meconium occurring more frequently when umbilical vein oxygen saturations are below 30%. Furthermore, the degree of MSAF is related to the degree of hypoxia with "thick" stained MSAF being associated with lower oxygen concentrations than "light" stained MSAF. One theory to explain this is that of intestinal ischaemia, which is thought to result in relaxation of the fetal anal sphincter and increased gastrointestinal peristalsis, thereby, leading to the passage of meconium. It has been theorized, therefore, that during hypoxia, the fetal circulation shunts blood away from the bowel and directs it to the brain and heart, thereby contributing to intestinal ischaemia and subsequently MSAF. Conversely, in animal studies, term rabbits failed to pass meconium during a hypoxic insult, calling into question, whether this mechanism is a major cause for meconium passage in a hypoxic human fetus. Vagally mediated gastrointestinal peristalsis in response to head or cord compression (the same reflex which initiates variable decelerations) may also be associated with meconium passage in the absence of fetal distress."

MECONIUM GRADING

For many years' attempts have been made to correlate increased meconium thickness with a worse perinatal outcome, but due to the subjectivity of assessing meconium thickness, it makes it very difficult to compare studies with any scientific rigour. Indeed, it has been shown that inter- and intra-observer agreement on visual grading of MSAF thickness is poor illustrates a common grading system of meconium). However, there does appear to be a significant linear association between meconium thickness and abnormal fetal heart rate patterns during labour, low Apgar scores and risk for caesarean section delivery. There also appears to be a higher risk of neonatal intensive care admission in pregnancies with thick meconium as compared to those with clear amniotic fluid, suggesting that thick meconium, not thin, is associated with an increased risk for perinatal complications during labour and delivery. A system of measuring quantitative meconium concentrations using a "meconiumcrit" (percentage by volume of the solid component of meconium) was proposed in the 1990s, but this has

not been adopted clinically, as a study investigating the value of measuring meconium crit showed no significant correlation with umbilical artery pH or Apgar score and no clinical benefit. However, it should be noted that two cases of meconium aspiration syndrome occurred within this study, both of which were from the "thick" meconium group. Although there is limited good quality evidence suggesting that the use of a system to grade meconium has any significant impact on neonatal outcome, most obstetricians would consider thick meconium a more ominous sign than thin and the National Institute of Clinical Excellence (NICE) recommends a standardized scoring system for the degree of meconium staining and its association with neonatal outcome. Further to this, accurately estimating the degree of meconium thickness is of importance as it helps determine the intensity of monitoring required following birth."

CHARACTERISTICS AND COMPONENTS OF MECONIUM

Meconium is the intestinal content of the fetus and is variably composed of water (as much as 80%), mucopolysaccharides, bilirubin, intestinal enzymes, hair and squamous cells [12]. The characteristic green coloration is attributable to bile pigments, which are not released in significant amount until mid-pregnancy. Indeed, clear amniotic fluid has been retrieved by amniocentesis soon after 3-D ultrasonographic documentation of fetal defecation in utero [13]. The composition (and coloration) of meconium may not only change with advancing gestation, perhaps due to alterations in gut motility, but also depend upon the process underlying its passage (physiologic vs pathologic). Some have suggested that newborns exposed to birth asphyxia have a greater amount of bilirubin in meconium compared to those without [14]. The physical properties of meconium at term have been characterized by high adhesiveness with poor transportability by airflow, even when diluted [14].

INFLUENCE OF GESTATIONAL AGE ON MECONIUM PASSAGE

Although the intestinal contents may be released into the amniotic cavity as early as the mid-trimester, they are whitish in color at this point [13]. Therefore, the presence of a greenish discoloration in mid-trimester amniotic fluid should not be considered evidence of meconium passage. Indeed, cases of mid-trimester "meconium" –brown or green tinged amniotic fluid – reflect discoloration for other reasons, most commonly hemolysis of intra-amniotic bleeds, and do not represent intestinal passage. The presence of green or brown pigment in second trimester amniotic fluid is not an uncommon event, occurring in approximately 2% of amniotic fluid retrieved by genetic amniocenteses [18,19]. Spectrophotometric studies suggest that discoloration in such fluid is more likely due to hemolysis resulting from intra-amniotic hemorrhage antedating amniocentesis [20,21]. Regardless of the etiology, green or brown fluid is associated with a higher rate of spontaneous abortion or fetal death than clear fluid [21,22].

Passage of meconium in the preterm third trimester fetus has been reported to be a rare event, as typically it occurs near or post term [23]. "Reports of early meconium passage (ie, 26 weeks) are difficult to interpret because of the difficulty of identifying meconium with confidence. Alternative explanations for the finding of greenish stained membranes or fluid would include the presence of decomposed blood as a result of abruption. Staining for hemosiderin may help make the distinction" [23]. "On an experimental level, preterm fetal motilin levels are noted to be lower in the preterm than in term infants, suggesting that defecation in the preterm infant may not be secondary to physiologic peristalsis [24] though this finding has been disputed" [25].

MECONIUM RELEASE MECHANISM

The mechanism of meconium passage in the term and post-term fetus is hotly debated and probably there are variable and complex factors leading to the event. There are two prevailing and possibly compatible theories. One is that normal maturation of the gastrointestinal tract results in meconium passage. The alternate hypothesis is that pathologic processes, such as stress via hypoxia or infection, can trigger meconium passage. The issue is complicated by the observation that, independently from the factors leading to meconium passage, presence of meconium may subsequently cause complications, such as meconium-associated vascular necrosis of umbilical and placental chorionic vessels, [26-28] inhibition of neutrophil oxidative burst and phagocytosis [29] facilitating growth of pathogens within the amniotic fluid and subsequent intrauterine infection, [30] and vasoconstrictive activity on the placental vasculature" [31].

MECONIUM - RESULT OF GASTROINTESTINAL MATURATION

"Clinical observations suggest that normal maturation

of the gastrointestinal system may be implicated in a sizable proportion of cases of in utero meconium passage. Traditionally it was thought that passage of meconium in the amniotic fluid was related to release of fetal motilin, a 22-amino-acid polypeptide which promotes peristalsis. Indeed, cord blood motilin levels are higher in term infants passing meconium in utero compared with those who do not [32]. The low level of cord blood motilin in the extremely preterm (ie, mid trimester) fetus thus was interpreted as to militate against the hypothesis of in utero defecation in the mid-trimester [32]. The issue has been recently challenged by 3-D documentation of fetal defecation throughout the second and early third trimester in physiologic pregnancies, suggesting that motilin may not be a hormone indispensable for fetal defecation." "Using animal experimentation, researchers have sought to demonstrate that meconium passage may reflect normal physiology in some cases. In one study, a non-hydrosoluble contrast medium was introduced via nasogastric tube to fetal goat and its passage over time to the gastrointestinal tract and into the amniotic cavity was monitored [33-35].

MECONIUM PASSAGE-CONSEQUENCE OF FETAL HYPOXIA

"The relationship between meconium passage in utero, as evidenced by meconium-stained amniotic fluid, and fetal acidosis at birth is controversial. Some authors [36] have reported no association between meconium passage in utero and either mean umbilical artery pH or frequency of acidosis, whereas others [37] have found a relationship between meconium-stained amniotic fluid and lower fetal blood gas values. In part the discrepancy among reports can be explained by the low frequency of indicators of fetal hypoxemia associated with meconium passage. In a series of over 19,000 pregnancies at term (37 weeks or beyond) those with meconium-stained amniotic fluid had a non-reassuring FHR in less than 14% of cases, 5-minute Apgar score below 7 in less than 3.2% of cases, and umbilical artery pH<7.10 in less than 3.6% of cases, [38] suggesting that hypoxia is not a common cause of meconium passage.

Nonetheless, we have recently shown that the new appearance of meconium during labor or thickening of meconium during labor have a greater than 2-fold increased risk of umbilical artery pH<7.10 and 5-minute Apgar score<7 compared with presence of clear fluid or persistently thin meconium during labor [38] These findings suggest that if passage of meconium before labor may be a physiologic phenomenon related to the maturation of the gastroenteric nervous system, passage of fresh meconium during labor is more likely due to pathologic processes. In this context, the reported association between induction of labor with misoprostol and meconium passage is probably mediated by the significantly higher rates of uterine hyperstimulation with misoprostol" [39].

MECONIUM PASSAGE IN GESTATIONAL CHOLESTASIS

Passage of meconium is more prevalent in pregnancies complicated by gestational cholestasis. In one of the largest series on the topic, meconium passage before 37 weeks occurred in 18% of cases, a rate significantly higher than that of the general obstetric population at less than 37 weeks during the study period (3%; OR=7.3, 95% CI 3.3, 16.0) [41-48]. Moreover, at an average gestational age at delivery of 37.5+/−1.6 weeks, the rate of meconium-stained fluid was 12%, a rate usually reported in deliveries at or after 40 weeks. Finally, gestational cholestasis managed expectantly is associated with a stillbirth rate of 16.8% and such stillbirths are associated with meconium-stained fluid in 86% of cases, [49] a rate significantly higher than that commonly reported in large series of stillbirths. An understanding of the pathophysiology of meconium passage in the context of gestational cholestasis would also help to appropriately monitor at risk fetuses. Passage of meconium with obstetric cholestasis is not associated with evidence of placental dysfunction, as manifested by rates of fetal growth restriction or oligohydramnios [49] Instead, the rate of asphyxia is higher in cholestatic gestations than in the general pregnant population, [50] and it is independently correlated with the maternal serum bile acid level [50]. A significant and independent correlation has also been reported between maternal serum bile acid levels and probability of meconium-stained fluid. The frequency of meconium passage was 22% with maximum bile acid levels of<40μmol/L, and 44% when the levels were 40 or greater. Studies in animal models have shown that high maternal serum bile acid levels stimulate fetal colonic motility, causing passage of meconium. Less clear is the role of bile acids in fetal death. A recent histologic study of 49 placentas from patients with gestational cholestasis found no correlations between histopathology placental lesions and clinical or laboratory markers of gestational cholestasis; moreover, no pathognomonic lesions were detected

in such placentas. Experimental evidence has shown a dose-dependent vaso-constrictive effect of bile acids on placental chorionic veins. Recently, Serrano et al. reported abnormal microscopic placental findings in a rat model of cholestasis, including enhanced apoptosis and reduced trophoblastic tissue [51]. More studies are needed to establish whether fetal death is related to vasoconstriction of placental vessels and it is mediated by the maternal bile acid level.

MECONIUM IN THE PRE-TERM FETUS

The incidence of MSAF in the pre-term fetus is approximately 5% but is associated with a poorer neonatal outcome when compared to similar gestations with clear amniotic fluid, suggesting that meconium-stained amniotic fluid is a gestational age independent risk factor [52]. At term, only a relatively small amount of stress is required to result in the passage of meconium, however, in the pre-term fetus, the greater colonic distance over which the meconium has to travel, implies a greater severity and/or duration of stress, and may explain the increased perinatal morbidity and mortality seen in this group, particularly the increased incidence of cerebral palsy and intraventricular hemorrhage [53-54]. MSAF in the pre-term fetus, especially in the mid-trimester, may also be associated with acute ascending infections, and it has been speculated that intra-amniotic infections may cause fetal gastroenteritis and diarrhea. Women in pre-term labour with meconium-stained liquor have a higher incidence of clinical chorioamnionitis when compared to those with clear liquor [55].

COMPLICATIONS OF MECONIUM-STAINED AMNIOTIC FLUID

MSAF in the presence of fetal heart rate abnormalities is a strong indicator of fetal distress; however, it is also associated with complications in the newborn. Meconium directly alters the amniotic fluid, reducing its antibacterial activity, thereby; increasing the risk of perinatal bacterial infection, however, the most severe complication of MSAF is meconium aspiration syndrome [57].

MECONIUM ASPIRATION SYNDROME

Various components of meconium, in particular, bile salts and enzymes can cause complications if aspirated into the lungs of an infant prior to, during or immediately after birth, thereby, resulting in the Meconium Aspiration Syndrome. This occurs in approximately 5% of infants born with MSAF and has a mortality rate in the region of 3-5%. Meconium aspiration syndrome describes a wide spectrum of respiratory disease, ranging from mild respiratory distress to severe disease and death despite mechanical ventilation. Prior to the late 1970s it was thought that aspiration of amniotic fluid and meconium only occurred during the first few breaths after delivery, however, meconium has been found distally as far as the alveoli in stillborn infants [58].

Further to this, studies with radio-opaque contrast and Cr51 labelled erythrocytes injected into amniotic fluid have demonstrated that amniotic fluid enters the fetal lungs in the non-asphyxiated human fetus, suggesting that meconium aspiration occurs in utero. Animal studies have also shown that intrauterine gasping, resulting in greater aspiration of meconium, occurs in fetuses exposed to hypoxia, implying that fetal distress is a risk factor for development of meconium aspiration syndrome. Currently, there is no way to distinguish those who develop meconium aspiration from intrauterine gasping and those who develop it by inhalation at birth [59]. Perhaps the most significant risk factor for meconium aspiration syndrome is post-term delivery, due to the high prevalence of MSAF in this population and the increased incidence of oligohydramnios in these pregnancies. Oligohydramnios predisposes to cord compression which may help explain the higher frequency of meconium passage at this gestation, but more importantly, meconium passage in the presence of oligohydramnios results in a thicker meconium-stained amniotic fluid which can result in a more serious meconium aspiration syndrome and poorer neonatal outcome.

MECONIUM-INDUCED LUNG INJURY AND DEVELOPMENT OF THE MECONIUM ASPIRATION SYNDROME

The pathophysiology of meconium aspiration is a complex series of events, superimposed on the normal switch that occurs when (intrauterine) fluid-filled lungs are changed into an air-filled organ, required for adequate gas exchange. Perinatal aspiration of meconium may interfere with this normal transitional process, causing airway obstruction, direct toxic damage of lung tissue, surfactant inactivation, meconium associated pulmonary inflammation (‘chemical pneumonitis’) and decreased arterial oxygen tension [58,59] Furthermore, immediate changes in pulmonary vasoreactivity lead to a rise in pulmonary vasomotor

tone and subsequently to persistent pulmonary hypertension and prolonged (severe) hypoxaemia.

MECHANICAL EFFECTS

Aspirated meconium may partially or completely obstruct smaller airways. Partial obstruction (ball valve phenomenon) will lead to air trapping and hyperinflation of certain lung fields and pneumothorax may occur. Tyler et al. showed in adult rabbit lungs that small airway obstruction by meconium is followed by a transitional period leading to (partial) alveolar collapse and cellular necrosis within 48 h. Due to (partial) alveolar obstruction (with relatively good perfusion) a ventilation–perfusion mismatch develops, resulting in a fall in PaO2. Complete obstruction of the smaller airways by meconium, causes the air to be absorbed and atelectasis ensues. Furthermore, a direct damaging effect on alveolar cells has been reported by Zagariya et al., who demonstrated several morphological changes following meconium exposure in rabbit lungs. The major features were detachment of airway epithelium from stroma and shedding of epithelial cells into the airway, indicating a direct deleterious effect of meconium on lung alveolar cells [59]. The lung areas which do not or only partially participate in ventilation (because of obstruction and/or destruction) will become hypoxic and subsequently, an inflammatory response may follow. In addition, a rise in FRC leads to an increase in pulmonary vascular resistance. Together with a patent ductus arteriosus and foramen ovale (due to postnatal cardiovascular changes), elevations of pulmonary artery pressure cause right-to left shunting across the duct or foramen, resulting in a further deterioration of the PaO2 and an increase in hypoxaemia. Chronic hypoxia will lead to an increase in pulmonary vascular smooth muscle tone and persistent pulmonary hypertension causing respiratory and circulatory failure [60]

CHEMICAL EFFECTS

Another mechanism contributing to meconium-induced neonatal respiratory distress is surfactant inactivation (functional deficiency). Surfactant reduces alveolar surface tension to facilitate lung expansion, preventing alveolar collapse after (the onset of) breathing. In 1987, Clark et al. postulated that, in dog lungs, free fatty acids present in meconium replaced surfactant phospholipids, possibly changing lung compliance in MAS [61]. Sun et al. likewise demonstrated in 1993 that meconium itself seems to interfere with the surface tension lowering capacity of surfactant [62] It was suggested that surfactant inhibition leads to decreased lung–thorax compliance, increased paCO2, and histological evidence of atelectasis. This effect could be (partially) counter-acted by administration of large doses of natural surfactant in animals with experimentally induced meconium aspiration syndrome, resulting in improved compliance and ventilation. In 2007, El Shahed et al. reported that surfactant administration in neonates with MAS leading to moderate or severe respiratory failure, will decrease the number of infants needed to treat with extracorporeal membrane oxygenation (ECMO). However, treatment with surfactant did not significantly affect mortality in infants with respiratory disorders like MAS [63]. Further research is needed to compare surfactant therapy and other currently used treatment strategies.

INFLAMMATORY RESPONSES

Aspirated meconium has long been associated with pneumonitis in neonates [64]. Many recent studies illustrate the involvement of inflammatory mediators and reactive oxygen species in the pathophysiology of MAS, eventually leading to local injury and interference with surfactant function. Given the current understanding of the pathophysiology, the term "meconium associated pulmonary inflammation" (MAPI) is probably more accurate than 'chemical pneumonitis'.

CYTOKINE AND CHEMOKINE ACTIVATION

Intrapulmonary meconium may trigger lung inflammatory cells to express inflammatory cytokines and oxygen radicals, resulting in lung airway epithelial cell injury and death through apoptosis. For instance, Zagariya et al. demonstrated that in saline-treated rabbit lungs, 94% of the cells were macrophages and 1% neutrophils, whereas in meconium-instilled rabbit lungs the proportion of neutrophils increased up to 7%, implying that meconium provokes a chemotactic reaction. In the rabbit lung cells meconium stimulated the production of pro-inflammatory cytokines, such as IL-1β, IL-6, IL-8 and TNFα. No differences were seen in the level of IL-10, a non-inflammatory cytokine, usually associated with decreased inflammation and inactivation of inflammatory cytokines [59]. Thus, changes in these cytokine levels may regulate the susceptibility for meconium-induced inflammatory responses and lung injury. Monoclonal human anti-IL- 8 inhibits human meconium-induced neutrophil chemotaxis in vitro in a dose-dependent way.

Possibly, IL-8 from meconium itself, causes a neutrophil influx characteristic of pneumonitis in MAS. Meconium is an extrinsic source of other proinflammatory cyto- and chemokines, such as IL-1β, IL-6, GM-CSF, INF-γ and TNF-α, as well [58]. These mediators may contribute in vivo to local pulmonary inflammation with influx of leucocytes, T-lymphocytes, monocytes and macrophages, leading to parenchymal injury and remodeling of lung tissue.

COMPLEMENT ACTIVATION

Recently, it has been hypothesized that meconium is a potent activator of complement, a key mediator of inflammation, and may thus contribute to the inflammatory response in MAS. Lindenskov et al. showed in both in vitro and in vivo models of MAS that meconium locally activates the alternative pathway of complement. They found increased concentrations of the terminal SC 5b-9 complex and subsequent cytokine release in newborn pigs and suggested that this local inflammatory reaction may be mirrored by a systemic inflammatory response as well [65]. The combined inhibition of complement and CD14 nearly completely abolishes meconium-induced formation of multiple inflammatory cytokines and chemokines and strongly reduces the formation of growth factors in human adult and umbilical cord blood. The same group suggested an important role for the lectin pathway of complement as well. In vitro, C1-INH, a serine protease inhibitor, inhibits the activation of the classical and lectin pathway of complement in meconium-induced inflammation in human umbilical cord blood. In summary, complement appears to play an important role in MAS-related inflammation and lung injury.

PHOSPHOLIPASE A2

Phospholipase A2 (PLA2) is a potent pro-inflammatory enzyme, triggering pro-inflammatory cells to produce cytokines and possibly leading to surfactant dysfunction and cellular destruction with tissue necrosis and, presumably, apoptosis. PLA2 activity has been detected in human meconium and in meconium-contaminated lungs, indicating that meconium itself is a source of this enzyme. Possibly, bile acids present in meconium raise PLA2 activity even more, as was found in vitro in human neonates. Kääpä et al. suggested that aspiration of meconium might also have systemic inflammatory and injurious effects through phospholipase activation. They demonstrated the presence of elevated levels of human PLA2- concentrations in plasma during the first hours after intratracheal meconium administration in newborn piglets [66]. These findings suggest a significant role for PLA2 in the pathogenesis of functional and structural changes in neonatal lungs and MAS development.

MECONIUM-INDUCED APOPTOSIS

Apoptosis, programmed cell death, is an important mechanism in the clearance of injured cells and in tissue repair, however too much apoptosis may cause harm. Increased apoptosis may also play a role in acute lung injury, leading to damage and detachment of lung airway or alveolar cells [58]. Vidyasagar and Zagariya recently postulated that cytokine expression following meconium exposure leads to an angiotensin II-induced apoptosis in lung cells [67]. Others also reported a role for the pulmonary renin–angiotensin system (RAS) in the cellular response to MAS through angiotensin II-mediated cell death. Several pulmonary cell types in newborn rabbit's express angiotensin II-receptors (type 1) abundantly after instillation of human meconium. Increases in angiotensin II-receptors (type 1) were associated with dose-related increases in cell death. Possibly, pulmonary RAS contributes to the pathophysiology of MAS and receptor blockade or ACE inhibition may be useful as new treatment strategies for preventing the cellular responses to MAS.

WHY DO SOME NEONATES DEVELOP MAS, WHEREAS OTHERS DO NOT: RISK FACTORS FOR MAS DEVELOPMENT?

The incidence of MAS in children born through meconium-stained amniotic fluid has decreased over the years, mainly due to improved healthcare and changing obstetric practices [68]. However, around 5% of the meconium-stained infants still develop meconium aspiration syndrome [68]. In view of the current knowledge of MAS pathophysiology, the question remains why some neonates born through meconium-stained amniotic fluid develop MAS and (many) others do not. Many pre-disposing factors remain to be elucidated, even though much effort has been done to identify risk factors for MAS development. For example, the risk of MSAF is higher in black mothers compared to mothers from other ethnic groups [69]. Similarly, Sriram et al. concluded that the offspring of non-Hispanic black mothers was at a significantly greater risk for MSAF and MAS development than offspring of non-Hispanic white mothers [70]. Furthermore, advanced gestational age [69] and (often subsequently) high birth weight have been linked to MAS development [69]. Cheng et al. demonstrated a higher risk of MAS

for neonates delivered at 40 (adjusted OR 1.55; 95%CI 1.43–1.69) and 41 (adjusted OR 2.12; 95%CI 1.91–2.35) weeks of gestation [70-71]. Zhang et al. reported that a birth weight greater than 4500 g and particularly greater than 5000 g, is associated with increased risks of perinatal and infant mortality and morbidity, including MAS [72]. Oligohydramnios, male gender or thick versus thin meconium has been suggested to increase the incidence of MAS [73]. However, these findings could not be reproduced in other studies [74].

Meconium below the vocal cords has long been considered to be associated with an increased risk of MAS [74]. However, current International Neonatal Resuscitation Guidelines do not recommend intrapartum or postnatal endotracheal suctioning of vigorous infants born through MSAF, based on the studies by Wiswell et al. and Vain et al [73-74]. They demonstrated that expectant management compared to intubation and suctioning of apparent vigorous meconium-stained newborns did not result in a decreased incidence of MAS. Subsequently, only for non-vigorous meconium-stained infants endotracheal suctioning is still recommended, despite lack of evidence. Foetal compromise (e.g. abnormal foetal heart rate tracings and/or low Apgar scores) and the association with MSAF and MAS have been extensively studied [73]. In a large Australian study Dargaville et al. showed a strong relation between a 5-minute Apgar score of less than 7 and MAS development, with an overall odds ratio of 52. Wiswell et al. found that 1-minute and 5-minute Apgar scores≤6 were independently related to respiratory disorders, like MAS (OR8.10; CI 5.18–12.64 and OR 17.70; CI 7.34–42.62, respectively) [73].

PERINATAL MANAGEMENT

Management of the 'post dates' pregnancy:

There is a clear association between advancing gestation and the incidence of MAS, particularly beyond 40 weeks' gestation. This may partly explain the variations in incidence of MAS as management of 'post dates' delivery varies. MAS is reduced after induction of labor postdates in comparison with expectant management [75]. The relative risk of MAS after induction versus expectant management is 0.29 (95% CI 0.12–0.68) at 41 weeks and 0.66 (95% CI 0.24–1.81) at 42 weeks (not significant). However, the absolute risk is small and this in isolation is not considered an indication for induction of labor beyond term.

Amnio infusion:

The infusion of fluid transcervically during a labor complicated by meconium-stained liquor has been considered to be of possible benefit in reducing MAS, either by diluting thick meconium or by providing support to the umbilical cord and so reducing the risk of hypoxia–ischaemia due to cord obstruction. In a systematic review of published studies, Xu et al. concluded that the practice may be of benefit in settings where close electronic intrapartum monitoring is not available, but does not prevent MAS in settings where close monitoring could be achieved.[76] These findings have been questioned, with discussion around the inclusion of trials in the analysis,10 but the practice of amnio infusion has not been widely adopted.

Pharyngeal suction before delivery of the shoulders:

Until recently it was common practice to recommend intrapartum suctioning of the fetal oropharynx at the maternal perineum, before delivery of the fetal shoulders, with the aim of removing meconium from the upper airway before the onset of breathing. A large multi-center randomized trial has shown that this is not effective in reducing the incidence of MAS, the need for mechanical ventilation or the risk of mortality. This practice is no longer recommended in neonatal resuscitation guidelines. Other practices aimed at promoting effective upper airway suction, such as chest splinting to prevent breathing before suction has been carried out, have not been studied properly and are not recommended.

POSTPARTUM MANAGEMENT

Tracheal suction:

There is still some uncertainty about the value of attempting to suction meconium directly from the trachea. The practice of suctioning the trachea immediately after birth was previously believed to reduce the incidence of MAS. However, another large multi-center trial has shown that in *vigorous* infants (defined as having a heart rate more than 100 beats/min, as well as presence of spontaneous respirations and reasonable tone), there is no benefit from routine suction of the trachea. It is still recommended that infants who are not vigorous at delivery undergo laryngoscopy and tracheal suction before the use of positive pressure ventilation, but the value of this practice has not been established with a definitive randomized study.

Nasal continuous positive airway pressure

(nCPAP) is often used as an intermediate level of support in infants with impaired respiratory function. Although its use has been described in MAS, [77] it has not been studied systematically and shown to be of benefit. As MAS is associated with gas trapping and air leaks due to airway obstruction, some would consider nCPAP to be contraindicated. The use of nCPAP in MAS should be considered experimental until better evidence defines whether it has a role.

VENTILATION:

Conventional – ventilating infants with MAS can be difficult and the indications for commencing ventilation are not established. As there can be different disease patterns, with some infants having very patchy disease and others a more homogenous problem, no single approach to ventilation is optimal. The most commonly described pattern is to use a low level of positive end expiratory pressure (PEEP) and a long expiratory time, to avoid worsening any gas trapping, though this approach may well need to be adapted depending on the response of the infant. Pulmonary flow graphics can be of use in tailoring the expiratory time to the mechanics of a particular infant's lungs to ensure that expiration is complete. Infants with MAS are often severely ill, with a requirement for a high FiO2 and airway pressures, and it is common for both sedation and paralysis to be used to optimize infant–ventilator interaction.

High frequency oscillatory ventilation (HFOV) – because the disease can be severe and high pressures are often required when conventional ventilation is used, HFOV is also a commonly used mode [77-78]. Again, the role of HFOV in MAS has not been defined through good quality trials, though in a sub-group of a larger trial, the use of HFOV lead to short-term improvements in gas exchange.

SURFACTANT:

Replacement – meconium is a potent inhibitor of surfactant function.20 Clinical trials have not demonstrated a reduction in mortality with the use of surfactant replacement, but in a meta-analysis of two trials which enrolled 208 infants, the need for extracorporeal life support (ECLS) was significantly reduced (RR 0.64, 95% CI 0.46–0.91; NNT 6, 95% CI 3–25). The mortality of infants with MAS when treated with ECLS is now so low that it is unlikely that controlled trials of surfactant therapy in this condition could use mortality as an outcome. Most would now consider surfactant treatment to be an integral part of the treatment of MAS [79]. The response to a single dose of surfactant can be blunt and several doses can be required before the desired response is seen. It is not uncommon for treatment to be followed by a mild deterioration in condition for a few minutes, with reduced saturations and a mild increase in pCO2, but this is usually short lived.

Lavage – an alternative to surfactant replacement therapy is to use lavage with relatively large volumes of diluted surfactant to facilitate removal of meconium from the lungs, whilst maintaining sufficient surfactant function. This technique has shown promise in small preliminary studies but some infants do not tolerate it well. Experimental work is ongoing to establish the most effective treatment schedules and preparations. Larger clinical trials will be required to establish the place of this treatment. Given the evidence from controlled trials for the efficacy of 'conventional' surfactant therapy in MAS, lavage should probably not be compared to no surfactant treatment in future trials.

Nitric oxide

Many infants with MAS have a degree of persistent pulmonary hypertension of the newborn (PPHN) and consequently have disproportionate difficulty with oxygenation in relation to their apparent degree of lung disease. Close attention to basic homeostasis, including maintenance of a generous systemic blood pressure, control of acidosis and avoidance of hypercarbia, should help to minimize this problem. Inhaled nitric oxide (iNO) has emerged as the treatment of choice for PPHN in term or near-term infants due to its efficacy in reducing the number of infants who go on to require ECLS and its relatively selective action on the pulmonary vasculature. As iNO is delivered as an inhaled gas, good alveolar recruitment is required to maximize its effectiveness and it may be more effective in combination with HFOV if the lung disease is severe. As a sub-group within larger studies of iNO in term and near-term infants with severe respiratory failure and or PPHN, infants with MAS represent a large proportion of the infants studied but they have not been studied in isolation or reported separately in sufficient numbers to enable definitive conclusions about the relative efficacy of iNO in MAS. A review did not show any reduction in mortality with the use of iNO, but did demonstrate a reduction in the need for ECLS, a technique discussed below. Avoidance of the need for this invasive and not universally available technique is viewed as a benefit of iNO therapy, so it has been widely adopted in the treatment of MAS-related PPHN.

CORTICOSTEROIDS

Corticosteroids are a class of chemicals that includes steroid hormones naturally produced in the adrenal cortex of vertebrates and analogues of these hormones that are synthesized in laboratories. Corticosteroids are involved in a wide range of physiological processes, including stress response, immune response, and regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behavior.

BIOSYNTHESIS

The corticosteroids are synthesized from cholesterol within the adrenal cortex. Most steroidogenic reactions are catalyzed by enzymes of the cytochrome P450 family. They are located within the mitochondria and require adrenodoxin as a cofactor (except 21-hydroxylase and 17α-hydroxylase). Aldosterone and corticosterone share the first part of their biosynthetic pathway. The last part is mediated either by the aldosterone synthase (for aldosterone) or by the 11β-hydroxylase (for corticosterone). These enzymes are nearly identical (they share 11β-hydroxylation and 18-hydroxylation functions), but aldosterone synthase is also able to perform an 18-oxidation. Moreover, aldosterone synthase is found within the zona glomerulosa at the outer edge of the adrenal cortex; 11β-hydroxylase is found in the fasciculata and zona glomerulosa.

CORTICOSTEROIDS FOR MECONIUM ASPIRATION SYNDROME

Meconium produces chemical pneumonitis as a major part of MAS. Despite this, a Cochrane review of two small studies of corticosteroids in MAS showed no benefit from steroid therapy. Infants treated with steroids remained oxygen dependent for longer. A further two small studies have since contradicted this finding [81]. Infants treated with steroids showed a reduction in the duration of oxygen dependence and improved X-ray appearances. Further studies are required and, with the concerns that have arisen from the use of steroids to treat bronchopulmonary dysplasia about the possible effects of high dose steroids on infant growth and development, speculative treatment should best be avoided in the interim. Given the complexity and expense of some of the other treatment modalities, it would be helpful to determine more reliably whether steroids have any role, particularly in settings where resources are more limited.

ROLE OF ANTIBIOTICS

The presence of meconium increases the chances of positive cultures from amniotic fluid in preterm and term infants. However, studies evaluating the development of sepsis in infants with MSAF failed to demonstrate that relationship [87]. Three randomized control studies reported that routine antibiotic prophylaxis is not recommended in the management of MAS for those without perinatal risk factors [88-90]. Antibiotic therapy did not affect the clinical course and outcome related to infection in MAS without perinatal risk factors for infection and without ventilator use. The role of antibiotics in the management of MAS may need to be reevaluated in well-designed trials. Unless there is definite risk for infection, prophylactic use of antibiotics in MAS did not reduce infection. If antibiotics are started for suspected infection due to perinatal risk factors, consider discontinuing antibiotics once the blood culture results are negative.

NITRIC OXIDE

Severe MAS is often associated with PPHN, resulting in severe hypoxemia. Randomized clinical trials have demonstrated that iNO therapy decreases the need for ECMO in addition to mortality in full-term and near-term neonates with hypoxic respiratory failure and PPHN. For hypoxic respiratory failure due to MAS, infants responded well to combined iNO and HFV as compared to either treatment alone. The response to combined treatment with HFV and iNO reflects both decreased intrapulmonary shunt and augmented nitric oxide delivery to its site of action.

EXTRACORPOREAL MEMBRANE OXYGENATION

ECMO has been used as a final rescue therapy in infants with severe and refractory hypoxemia associated with MAS. Use of ECMO has been decreased significantly in developed countries with the availability of iNO and HFV. Infants with MAS make up approximately 35% of the infant population who require ECMO. The survival rate has approached 95% of infants with MAS who underwent ECMO [91]. In the ECMO registry, the highest survival rates (>90%) were seen in the patients with MAS who qualified for ECMO

ADJUNCTIVE THERAPIES

All infants with MAS should be monitored using noninvasive monitors (pulse oximeter, transcutaneous O_2/CO_2 methods) and blood gas sampling should

preferably be done with an indwelling arterial line. Sedation and analgesia are used frequently in infants with MAS and PPHN to alleviate pain and discomfort that may lead to hypoxia and right-to-left shunting. Opioids, particularly morphine or fentanyl, are frequently used to optimize gas exchange and also to avoid asynchrony, reflex catecholamine release, and aggravation of pulmonary vascular resistance. Depolarizing muscle relaxants (pancuronium, vecuronium) were widely used in the past along with opioids to decrease agitation and subsequent hypoxic episodes in ventilated infants. The benefits of neuromuscular blockade include improved oxygenation, decreased oxygen consumption, and decreased accidental extubations. However, the use of neuromuscular blockade remains controversial and is reserved for the infant who cannot be treated with sedatives alone. Neuromuscular blockage can promote atelectasis of dependent lung regions and ventilation perfusion mismatch and may also be associated with increased risk of death [92]. Nearly 30–50% of infants with PPHN do not respond to iNO therapy. Infants who do not show initial response to iNO and those that deteriorate subsequently while on iNO therapy continue to have significant PPHN and need other alternative therapy [93]. Alternatives available include (a) phosphodiesterase-5 inhibitors like Sildenafil, Zaprinast, Milrinone, dipyridamole, (b) prostaglandins like Prostacyclin or PGE1, (c) tolazoline, Magnesium sulfate, (d) NO precursor L-Arginine, (e) free radical scavengers like Superoxide dismutase, (f) experimental agents like Bosenthan (endothelin antagonist).

DATA COLLECTION

Approval of ethical committee was obtained. Risks and benefits of corticosteroids were discussed with the parents to take the informed consent. Neonates with above selection criteria were taken in the study. Meconium aspiration syndrome was confirmed by detailed history, clinical examination and chest X-ray. Children were divided into two groups using random number table. A-Group neonates given i/v corticosteroids in a dose of 0.5mg/kg/24hrs in 3 divided doses and symptomatic treatment (oxygen inhalation via nasal canula, antibiotics, calcium, glucose and IV fluids). B-Group neonates given symptomatic treatment only. Excluding the patients mentioned in exclusion criteria on the basis of history, examination and relevant investigations-controlled confounders. Performa was filled on admission and follow up was carried out weekly for 4-week period by me. Duration of stay in hospital (in days) was noted in each group. Adherence was enforced by telephone contact to family.

DATA ANALYSIS

SPSS (Statistical Package for Social Sciences) version 10 was used to analyze data. Mean and standard deviation was calculated for quantitative variables like duration of stay in hospital in days. t-test was applied to compare two groups. P-value was less than 0.05, taken as statistically significant. Then Results were presented in tabulated and graphical forms.

RESULTS:

A total of 92 patients (46 in each group) were enrolled to determine effectiveness of corticosteroid therapy in neonates with meconium aspiration syndrome in comparison with control. We recorded age distribution and it was presented in Table No. 1, where 46.67% which is (n=19) in A-Group and 56.67% which is (n=22) in B-Group were between 1-3 hours of life, 36.67% (n=16) in A-Group and 30% (n=14) in B-Group were between 4-6 hours while only 16.67% (n=11) in A-Group and 13.33% (n=10) in B-Group were between 6-8 hours of life, mean and sd was calculated as 3.78+2.26 in A-Group and 4.12+2.77 years in B-Group. Distribution of gender of the patients show 63.33% (n=29) in A-Group and 56.67% (n=26) in B-Group were male while 36.67% (n=17) in A-Group and 43.33% (n=20) in B-Group were females. (Table No. 2) Comparison of mean duration of stay in hospital (in days) was done, where 8.2+0.90 days in A-Group and 10.6+0.88 days in B-Group was recorded. P value was calculated as 0.032 i.e. <0.05. (Table No. 3)

TABLE No. 1
AGE DISTRIBUTION OF THE SUBJECTS
(n=92)

Age (in hours)	A-Group (n=46)		B-Group (n=46)	
	No. of patients	%	No. of patients	%
1-3	19	46.67	22	56.67
4-6	16	36.67	14	30
6-8	11	16.66	10	13.33
Total	46	100	46	100
Mean and sd	3.78+2.26		4.12+2.77	

TABLE No. 2
GENDER DISTRIBUTION OF THE SUBJECTS
(n=92)

Gender	A-Group (n=46)		B-Group (n=46)	
	No. of patients	%	No. of patients	%
Male	29	63.33	26	56.67
Female	17	36.67	20	43.33
Total	46	100	46	100

TABLE No. 3
COMPARISON OF MEAN DURATION OF STAY IN HOSPITAL
(n=92)

Stay in Hospital (in days)	A-Group (n=46)	B-Group (n=46)
	8.2+0.90	10.6+0.88

P value=0.032

DISCUSSION:

Meconium aspiration syndrome (MAS) occurs in 2–22% of babies who born through meconium-stained amniotic fluid and carries significant mortality and morbidity. It is diagnosed when a baby delivered through meconium-stained amniotic fluid develops signs of respiratory distress in the presence of supportive chest X-ray. Appropriate intrapartum care is necessary with early detection and management of fetal hypoxia to minimize the risk from meconium staining of amniotic fluid [94]. A chemical pneumonitis occurs secondary to bile, bile acids and pancreatic secretions present in meconium. Therefore, it has been hypothesized that corticosteroids may be of benefit in the management of this condition because of their anti-inflammatory

properties. The findings of our study reveal a significant shorter duration of stay in hospital by comparing both groups, 8.2+0.90 days in A-Group and 10.6+0.88 days in B-Group were recorded which is significant as p value was 0.032 i.e. <0.05. Our study results are in agreement with pilot studies have shown that duration of stay in hospital (in days) was significantly reduced (3.5+0.97, 4.9+0.74 days) in those who were given corticosteroids and in those who were not given respectively [5-9].

Another double blinded randomized controlled trial study and a prospective Interventional Study over period of one-year in the neonatal unit of the Lady Hardinge Medical College and associated Kalawati Saran Children's hospital by Sandeep Tripathi and Arvind Saili [95] assessed infants in terms of duration of stay in hospital, oxygen dependency, X-ray clearances and also assessed for short term bad effects and recorded that there was a statistically remarkable difference in the duration of hospital stay, duration of oxygen dependence and radiological clearance. So concluded that steroids change course of Meconium Aspiration Syndrome and also affect the outcome. On the other hand, Triphati S[96] and Basu S[97] treated infants with steroids and remained oxygen dependent for longer, these findings are in contrast of the findings of our study, the reason for remaining on oxygen for longer may be due to any other complication i.e. respiratory distress syndrome.
However, on the basis of the results of the current study with support of other published studies and considering the fact that steroids, because of their anti-inflammatory properties, are potentially beneficial in Meconium aspiration syndrome, where pulmonary inflammation ('pneumonitis') is a prime component which justifies the hypothesis of the current study that "corticosteroids therapy is affective in meconium aspiration syndrome in terms of decrease in duration of hospital stay and need for oxygen therapy of neonates as compared to controls".

CONCLUSION:

We concluded that corticosteroid therapy in neonates with MAS is effective when compared with symptomatic treatment only

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EFFICACY OF COTICOSTEROIDS IN CLINICAL COURSE AND OUTCOME OF MECONIUM ASPIRATION SYNDROME IN TERTIARY CARE HOSPITAL IN FAISALABAD

PROFORMA

Case NO._____ Reg. NO._____ Date_____

Name: _____ Father's Name_____

Age/Sex_____ Tel. NO._____

Address_____

D.O.A._____ D.O.A._____

TREATMENT GIVEN

Group 1.Corticosteroids with antibiotics & fluids

Group 2.Only antibiotics with maintenance fluids

OUTCOME

1. Duration of hospital stay (in days)