STUDY OF EARLY INHALED BUDESINIDE THERAPY IN MECONIUM ASPIRATION IN TERM AND POST TERM NEONATES

BY

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Dissertation submitted to

BLDE (Deemed to be University) Vijayapur, Karnataka

In partial fulfillment of the requirements for the degree of

DOCTOR OF MEDICINE

IN

PEDIATRICS

Under the guidance of

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KARNATAKA

2020

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PG IN PEDIATRICS

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MAS- Meconium aspiration syndrome

MSAF-Meconium stained amniotic fluid

MSL-Meconium stained liquor

ECMO- Extracorporeal membrane oxygenation

HFV-High frequency ventilation

i NO- Inhaled Nitric oxide

BPD- Broncho pulmonary dysplasia

CRP- C-Reactive Protein

INTRODUCTION

One of the most prevalent cause of respiratory distress in term and post-term newborns is Meconium aspiration syndrome. Incidence of Meconium-stained amniotic fluid is 5-25%[1]. A round 5 to 10 percent of infants born by MSAF have MAS. Compared to neonates born by clear amniotic fluid,respiratory distress is 100 times more likely to occur in babies with MSAF.

Meconium-containing amniotic fluid aspirated into the lungs causes meconium aspiration syndrome (MAS). The risk of surfactant inactivation and pulmonary inflammation, also known as chemical pneumonitis, may be brought on by the diverse chemical components of meconium. The small airways may become mechanically obstructed as a result of the aspirated meconium. The overextended lungs of newborns with partial airway obstruction will cause more air leakage complications.

As the severity of inflammation impacts the pathogenesis of MAS, reducing the inflammation may enhance clinical outcomes in newborns with MAS. Meconium passage in post-term pregnancies have been attributed to gastrointestinal maturation, but meconium passage in near-term or term foetus has been attributed to feto-maternal stress factors and/or infection.[2]

A mortality risk of 5% occurs in 5% to 20% of newborns with meconium-stained amniotic fluid (MSAF). With advancements in obstetric practices and perinatal care, the incidence of MAS is decreasing in industrialised nations; however, MAS continues to be a severe respiratory concern and a leading cause of newborn mortality in developing countries.

The primary goal of treating MAS is to prevent the development of more serious complications such as persistent pulmonary hypertension in newborns by providing supportive care to ensure proper oxygenation, ventilation, and stabilisation of the systemic circulation. This involves the use of extracorporeal membrane oxygenation (ECMO (HFV),exogenous surfactant,high frequency ventilation), and inhaled nitric oxide. Systemic parenteral corticosteroids have been studied for the treatment of MAS since 1975 due to the severe inflammation that follows meconium aspiration. In vitro, proinflammatory cytokine production can be reduced by steroids. Steroid therapy to reduce inflammation in newborns

with MAS may potentially be beneficial.

Gupta et al.[3] conducted studies to see whether inhaled beclomethasone medication can be utilised to prevent the development of BPD.

As there is only restricted data on the subject of the techniques, benefits, and drawbacks of local corticosteroids in meconium aspiration syndrome, and an absence of sufficient evidence to assess the potential merits and drawbacks of early nebulized steroids -Budesonide in the clinical course of neonates with MAS, a study was planned to examine the clinical spectrum of MAS babies.

AIMS AND OBJECTIVES

AIMS

To study the effects of early inhaled Budesonide therapy on meconium aspiration in term and postterm infants.

OBJECTIVES

To study the effects of Budesonide in Meconium aspiration neonates in terms of

1. the duration of NICU stay
2. the duration of oxygen requirement
3. the outcome at the end of NICU stay

REVIEW OF LITERATURE

The term "meconium" comes from the Greek word "mekoni," which is akin to opium or poppy juice. The comparison between the presence of this chemical in the amniotic fluid and the sleeping infant was popularized by Aristotle[4].

Meconium is first seen in the 5th month of gestation.[5] It consists of various products of secretion, excretion, and desquamation by the gastrointestinal tract, besides undigested debris from swallowed amniotic fluid, such as desquamated cells of skin and intestine, lanugo hair, and vernix caseosa[6].

The ingested amniotic fluid undergoes digestion and absorption and the residue mixes up with gastrointestinal tract secretion, desquamation, and exudates from the gut and finally transformed into a gelatinous dark green, semi-solid substance called meconium[7]. Its greenish-black color is due to the presence of biliverdin. The amount of production ranges from 60-200gms. It starts to build up in the distal small intestine during the fourth month of pregnancy, when the gastrointestinal system is fully developed with a patent lumen[8]. The meconium often proceeds to the colon as gestation progresses.

FORMATION OF MECONIUM

By day 14 following fertilization, the gastrointestinal tract is lined by undifferentiated cuboidal cells, which are derived from both endoderm and splanchnic mesoderm.

By week 7, intestinal villi are visible, and weeks 10 and 12 mark the beginning of active absorption of glucose and amino acids, respectively. By 12 weeks gestation, the development of Meissners and Auerbach's plexus within the intestinal wall coincides with the onset of peristalsis of the small intestine and colon.

From about 70 to 85 days after conception, meconium starts to develop in the foetal gut. Amniotic fluid has a high concentration of intestinal enzymes early in pregnancy; this concentration then declines, presumably due to the increased anal sphincter tone.

CONTENTS OF MECONIUM

Meconium is a semisolid viscous material formed by gradual dehydration by absorption of water in the intestine.

The constitution of meconium-

- Colour is dark green
- pH: 5.5 to 7
- Physical characteristics include thick, viscous, and odourless.
- 80% is made up of carbohydrates, there is no measurable protein with low lipid level.
- Electrolytes: Na, Ca, K, Mg, Zn, Cu
- Water: 70-80%
- Nitrogen: high

The green colour of meconium is caused by a high concentration of bile pigments excreted by

the biliary tract commencing in the fourth month.

There is intestinal bacteria in the fetus, which is cause for the differences in composition between meconium and adult stool.

Abnormal colour of Amniotic Fluid

The clinical importance of an amniotic fluid colour deviation is evident.

1. Green-colored meconium is indicative of foetal distress.

2. Amniotic fluid with a golden hue is indicative of Rh incompatibility and results from excessive foetal RBC hemolysis and bilirubin production.

3. In post-maturity, amniotic fluid is greenish yellow in colour.

4. Concealed accidental haemorrhages result in dark-colored amniotic fluid.

5. IUDs generate amniotic fluid that is tobacco-juice dark brown in colour. Old haemoglobin is typically present, accounting for the dark colour.

THEORIES OF MECONIUM PASSAGE

Maturation theory

Absence of meconium in the amniotic fluid in preterm neonates may indicate gastrointestinal maturity in late gestation[9,11.] When compared to preterm newborns with clear liquor, term infants who have passed meconium have higher umbilical cord concentrations of an intestinal peptide called motilin that is necessary for bowel peristalsis and defecation. Preterm pregnancy with MSAF is anominous sign of chorioamnionitis and in utero cord compression[10].

As gastrointestinal tract development and myelination advance throughout pregnancy, the neuronal regulation of meconium passage is similarly influenced by gestational age. The premature fetus's capacity to pass meconium into the amniotic fluid would be impaired by the bowel's immaturity of intrinsic and extrinsic innervation. Preterm neonates, as compared to term neonates, have fewer ganglion cells in the distal colon and more unmyelinated nerve trunks at autopsy.

With increasing gestation, the foetal small intestine transit time shortens.

The intestinal tract responds to sympathomimetic drugs more effectively as the foetus develops. After the foetal intestinal tract has fully developed after 34 weeks, parasympathetic stimulation commence the meconium passage. With increasing gestational age, the likelihood of meconium passage during labour rises to 30% at 40 weeks and 50% at 42 weeks, respectively.

THEORY OF FETAL DISTRESS.

It has long been considered over how intestinal peristalsis and foetal hypoxia correlate with one another. Walker[11] found that heavy meconium is more frequently associated with lower oxygen saturation than light meconium and that meconium was released more frequently when the umbilical vein's oxygen saturation was below 30%.

Hon hypothesised that meconium is expelled as a result of parasympathetic activation during cord compression, but Krebs and Associates[12] reported no difference in the frequency of varied decelerations

regardless of the presence of meconium.

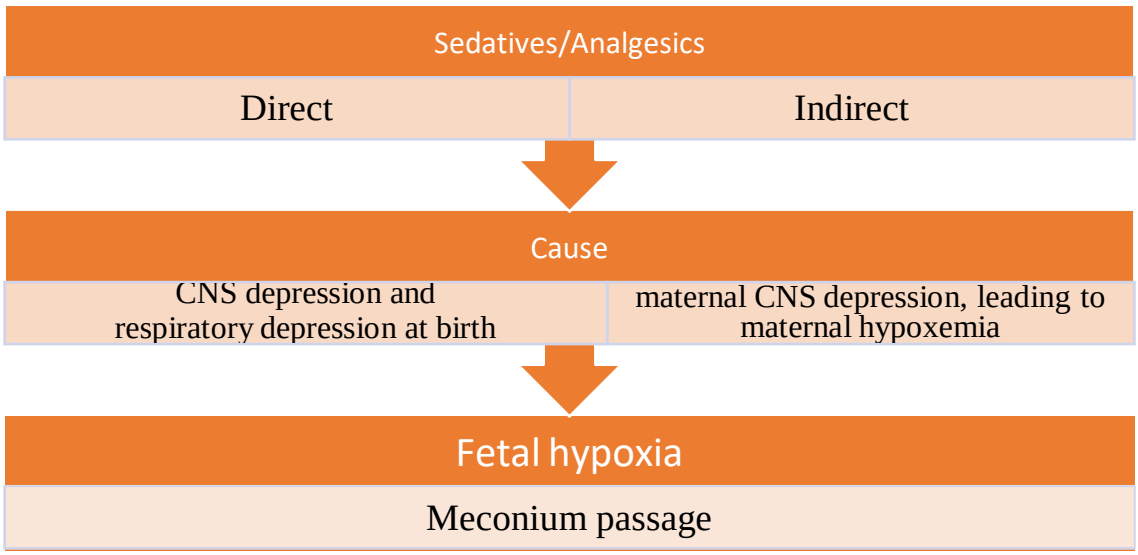
It was found that umbilical cord erythropoietin concentrations were higher in pregnancies complicated by meconium-stained amniotic fluid, indicating an association between chronic hypoxia and meconium passage[13,14].When the last biophysical profile score was abnormal, amniotic fluid was discovered more than twice as frequently, according to Manning and colleagues[15] (6 or less).

Meconium is frequently passed during foetal compromise, either acute or subacute.When a preterm infant develops foetal enteritis, meconium passage may occur (Listeria monocytogenes, ureaplasmaurealyticum, rotavirus). Amniotic fluid with thick meconium stains has a higher risk of peripartum infections. Based on certain studies, cholestasis of pregnancy may increase the likelihood of meconium passage.

Sedatives, Analgesics, and Anesthetics

Almost all the drugs of this category with few exceptions cross the placental membrane. Their effects on the fetus depend upon various factors e.g., dose, route of administration, the individual response of both mother and fetus to the drug, and time of administration before delivery. Huch described the mechanism of hypoxemia as follows.

Figure 1- Mechanism of Sedatives on Meconium aspiration



Cord Round the Neck, Knots of the Cord, and Cord Compression:

The cord frequently becomes coiled around parts of the fetus, usually the neck. The longer the cord, the greater the likelihood of coiling. The cord around the neck may create problems in labour, particularly a floating head and prolonged labour. Short cord around the neck interferes with the descent of head.

It may cause strangulated asphyxia and may be responsible for a high rate of meconium passage, morbidity, and mortality.

Cord stretching occurs during the descent of the head in labour and it causes the narrowing of the caliber of the umbilical vein. As a result, the fetus suffers from hypoxia and meconium passage.

OTHER THEORIES

It has been suggested that MSAF and maternal use of certain medicines and herbal treatments are associated. Meconium passage was reported to occur more frequently in women who had previously used castor oil and "sihlambezo" herbal supplements[16].

A 25µg intravaginal misoprostol decreases meconium passage, and MSAF was more prevalent in inductions with dinoprostone, according to Chitrakar[17].

Meconium-stained amniotic fluid in pregnant mothers is more common in cases of advanced gestation, early membrane rupture, obstructed labour, preeclampsia, and non- reassuring foetal heart rate[18].

INFLUENCE OF GRAVIDA, PARITY, AND MATERNAL AGE ON MECONIUM STAINING

Elderly primigravida and multigravida were found to have higher rates of MSAF.

According to Fitzgerald[19], incidence of primigravida was twice as high as that of multipara.

Walker showed that meconium staining increased from 2% in primigravida younger than 20 years old with a gestation age of 38 weeks to 42 weeks to 44% in primigravida at or above 35 years old with the same duration of gestation.

More gravid women had a lower incidence, according to Miller[20].

According to HariBhaskar[21], MSAF is more prevalent among primipara between the ages of 20 years and 35 years.

According to Rosario[22], there were no appreciable differences in terms of maternal age and parity between the meconium-stained group and the group with clear AF.

MECONIUM ASPIRATION SYNDROME

Meconium inhalation before, during, or immediately after delivery causes MAS[23].

According to Katz and Bowes[24] review, in the 1990s, it was estimated that between 7 and 22% of infants overall had meconium-stained amniotic fluid, but between 2000 and 2007, the frequency of MSAF was only 8%, and the incidence of severe MAS requiring respiratory support was only 0.067%. Meconium-stained liquid fluid increases the risk of MAS in newborns by 5%.[25].

The following characteristics are used to define MAS:

1. The presence of meconium below the voice chords.
2. Clinical respiratory distress within the first 24 hours of life.
3. An abnormal chest X-ray with aspiration pneumonitis.

In utero, the foetus shows breathing-like movements, but it is generally accepted that AF is routinely ingested and does not enter the trachea except during extreme hypoxia, hence a severe asphyxia episode is crucial in the development of MAS.

ETIOLOGY OF MECONIUM PASSAGE

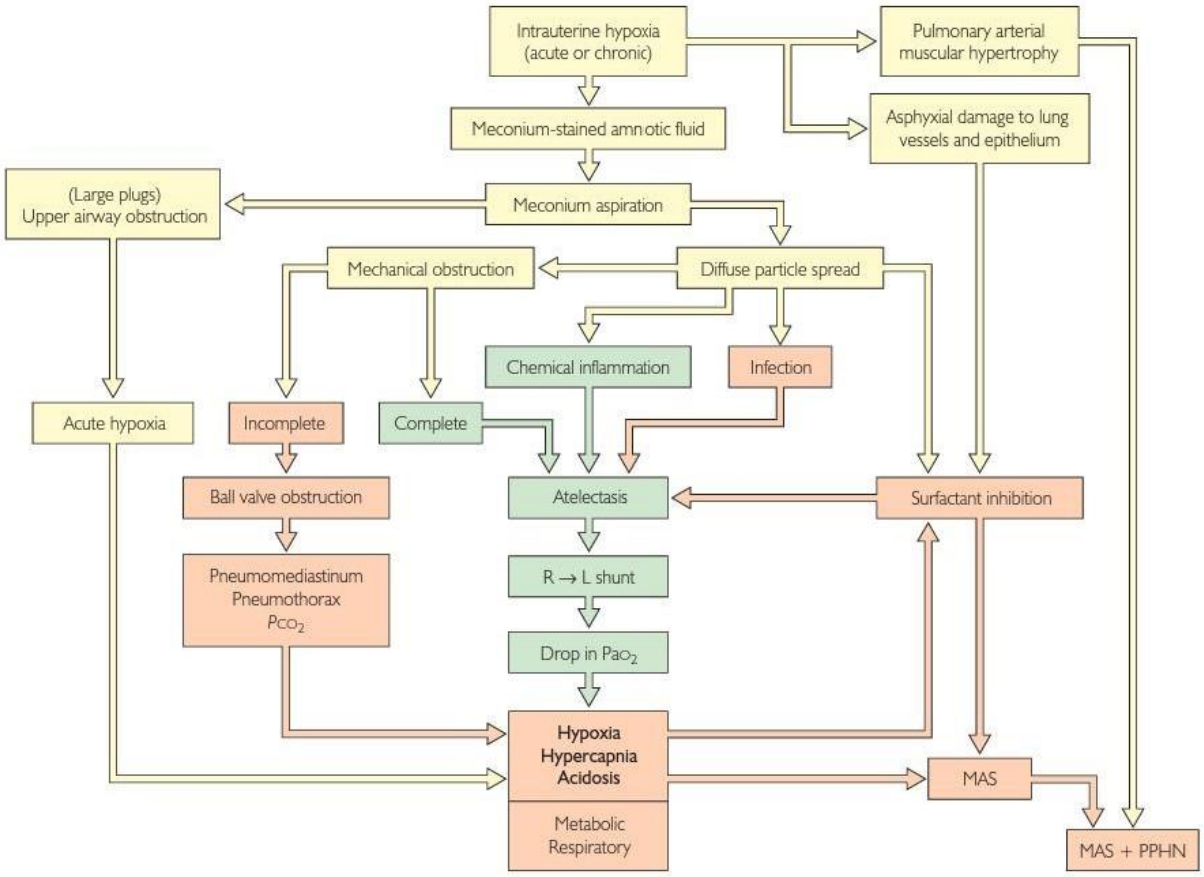


Figure 2- Pathophysiology of MAS[23]

Meconium, which is is a sticky substance is made up of inspissated foetal intestinal secretions.

1. As a result of physiological maturational events.

2. A response to chronic intrauterine hypoxia and

3. A response to acute hypoxic event

It probably has four deleterious, interrelated impacts on neonatal lung when inhaled.

1. It develops a ball valve mechanism in the airways, allowing air to enter past the

obstruction but prevents it from exiting. This causes air trapping, pulmonary overdistension, and pneumothorax by increasing airway resistance, particularly during expiration.

2.Meconium has irritant chemical nature. Released inflammatory cells and mediators injure the lung parenchyma, disrupt vascular contractility, and result in capillary leakage. Airway and alveolar epithelial necrosis are caused by the cytokines[26]. Meconium contains large amounts of phospholipase A2, which may cause apoptosis and damage[27].

After 24 to 48 hours of inhalation, the outcome is an acute exudative and inflammatory pneumonitis with alveolar collapse and cellular necrosis.

3. Despite the fact that meconium is initially sterile, the organic nature of the material that is inhaled puts the newborn at risk for lung infection, especially if Escherichia coli is present. In MSAF, phagocytosis and the neutrophil oxidative burst may be inhibited[28], allowing bacteria to proliferate.

Meconium inhibits polymorph function[28], and presence of meconium in amniotic fluid may indicate chorioamnionitis, which increases the risk of congenital pneumonia.

4.The production of surfactant is inhibited by meconium in a concentration-dependent manner[29,30,31]. In addition to its chloroform-soluble phase, the water/methanol-soluble phase of meconium (bilirubin and proteins) inhibits surfactant[32](triglycerides, free fatty acids and cholesterol).

Meconium modifies the morphological ultrastructure of a surfactant, reducing its capacity to reduce surface tension. Phosphatidylcholine levels have been found to be

lower in infants with severe MAS, or those who require ECMO[33].

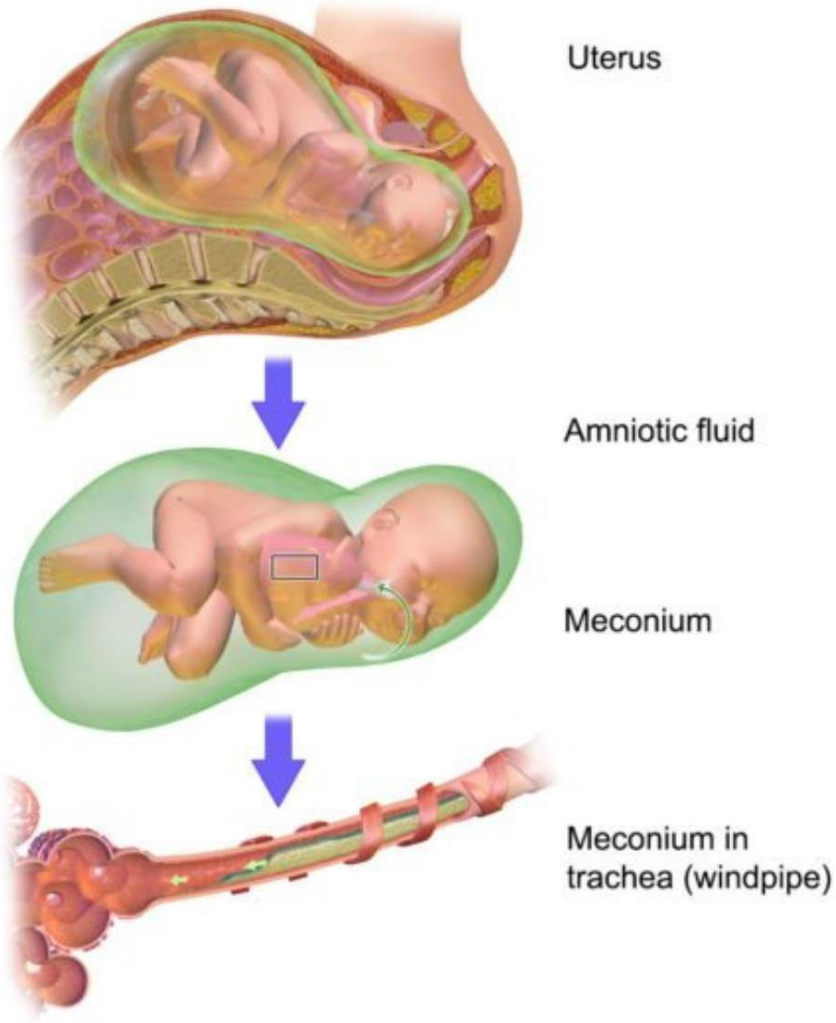


Figure 3 – Mechanism of Meconium passage

DIAGNOSIS

High-risk neonates may exhibit foetal bradycardia, tachycardia or absent foetal accelerations on in utero CTG. They may also present with cachexia at birth and have yellowish meconium staining on their skin, nails, and umbilical cord and typically develop Infant Respiratory Distress Syndrome within 4 hours of birth.

Any infant born through MSAF who develops signs of respiratory distress must be assessed for MAS. Although diffuse asymmetric patchy infiltrates are the typical radiographic findings in MAS, other radiographic features may also be present due to the heterogeneous aetiology.

Over airation is frequent which results in air leak syndromes such as pneumothorax, pneumomediastinum, or pulmonary interstitial emphysema. A series of 80 patients revealed a correlation between the severity of MAS and the degree of radiographic abnormalities, with consolidation or atelectasis being the most predictive of a poor outcome.

Arterial desaturation is the most important and frequent finding in MAS, which is due to right to left shunts. It occurs both the pulmonary and cardiac levels. These shunts occur through both foramen ovale and patent ductus arteriosus, according to studies using cardiac catheterization.

The neonates that develop MAS are typically hypoxic at delivery and have irregular or gasping breathing. Respiratory distress may appear immediately after birth or may take many hours to manifest. Infants that experience progressive respiratory distress within a few hours may have aspirated thin meconium following birth, which progresses gradually with breathing, finally reaching the periphery of lungs, and when the symptoms appear.

Infants with MAS usually have tachypnea, which may last for a few days to few weeks and sometimes it persists after complete recovery. Severely affected neonates have a respiratory rate of more than 100 cycles/minute and noticeable cyanosis. As a result of air trapping, there is a marked overdistension of the chest.

The vasoconstrictive effect of hypoxia on peripheral vessels may result in paleness in severe cases. The neurological symptoms of cerebral irritation, such as jitteriness, jerking, and convulsions due to cerebral oedema or haemorrhage caused by hypoxia, or both, may exacerbate the respiratory distress earlier or later.

Tachypnea, cyanosis, and cardiomegaly may mimic congenital heart disease. Initially, there is metabolic acidosis, followed by respiratory acidosis. Lactic acid production and tissue hypoxia lead to metabolic acidosis.

INVESTIGATIONS

Hematological

The white blood cells and nucleated red blood cell counts are frequently increased. White cell function is decreased[34]. Neonates with MAS who have PPHN, are ventilated, or may develop DIC as a result of severe hypoxia is due to thrombocytopenia.

Biochemical

There may be inappropriate ADH production and hyponatremia if there is coexisting severe birth asphyxia. Hyperkalemia and a raised urea can result from renal failure secondary to acute tubular necrosis. As with any critically ill infant, hypocalcemia is common.

Blood gases

Although hypoxia is prevalent, ventilation is not a concern in healthy neonates with mild and moderate MAS, and an efficient respiratory pump, and the PaCO2 may even be normal, lowor only slightly raised. In neonates with severe MAS, who require ventilation, PaCO2 >8 kPa (60 mmHg) is measured.

The metabolic acidemia of intrapartum asphyxia is initially reflected in pH changes; healthy babies typically correct acidemia spontaneously from pH in the 7.10–7.15 range with base deficiency values of 10-15 mmol/l[35]. Persistent metabolic acidaemia after first two hours points to an underlying issue, such as sepsis or hypotension, or renal failure, which need to be recognized and treated.

Urine analysis.

Infants with meconium aspiration syndrome have elevated urine 2-microglobulin levels, which suggest they have incurred some degree of renal damage[36]. As meconium pigments are absorbed through pulmonary epithelium and excreted in urine, the urine may have a greenish-brown colour.

Echocardiography

ECG and echocardiography may be normal in uncomplicated MAS. If there has been severe intrapartum hypoxia, the echocardiography will demonstrate diminished cardiac contractility and ECG abnormalities that indicate subendocardial ischemia. Righttoleft shunts at the ductal and atrial levels, as well as tricuspid insufficiency, which indicates elevated RV pressures, are seen in PPHN patients.

Chest X-ray

Widespread patchy infiltration occur in 20–30% of babies with MAS, and are typical early changes. At this early stage, overexpansion is also typical. The abnormalities diminish in mild to moderate cases after 48 hours.

Within 72 hours of age, in severe cases as the disease progresses, the appearance frequently changes to that of homogeneous and diffuse opacification of the lung fields as a result of interstitial oedema and pneumonitis secondary to the irritant effect of the inhaled meconium.

Although it is rare, in severe situations the X-ray may still be abnormal at 14 days and may coalesce into the pattern seen in BPD.

Most often airleaks in MAS are pneumothorax and pneumomediastinum.

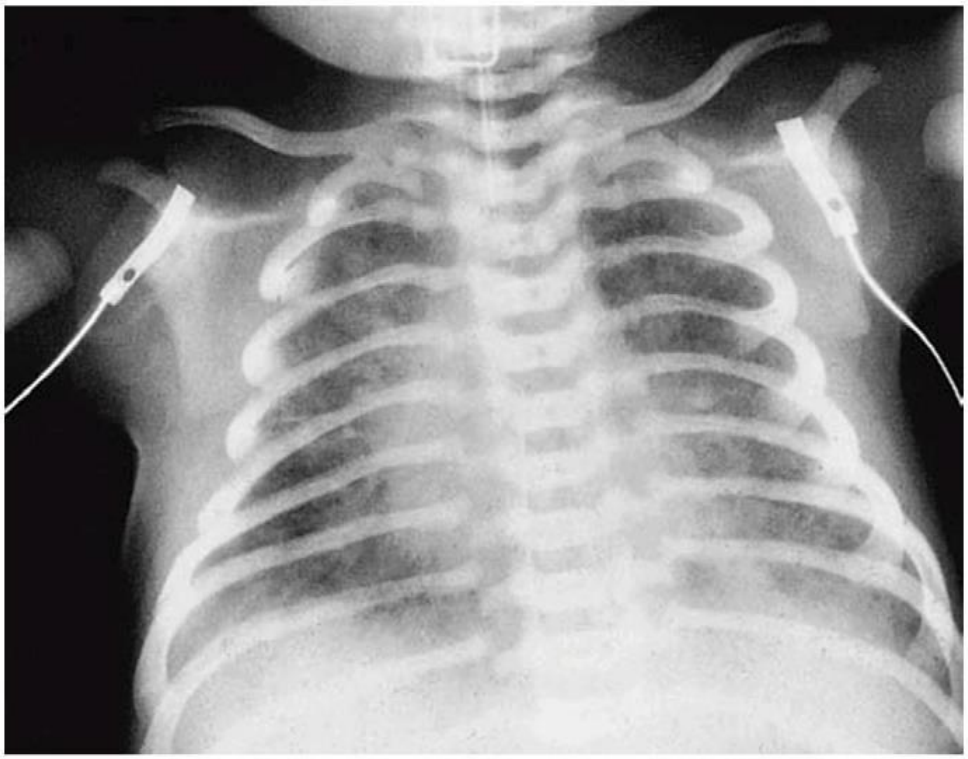


Figure 4- Chest X-ray in a baby with Meconium aspiration syndrome[23]

Microbiology.

An infection screen for infants with MAS must be done on being admitted in the NICU. As full-term babies with MAS frequently appear pink and vigorous despite having severe tachypnea and an abnormal chest x-ray appearance, there is a tendency to undermonitor them. In addition to the need for an early diagnosis of blood gas abnormalities, hypotension or electrolyte abnormalities, these babies with meconium aspiration syndrome also have a high risk of sudden deterioration due to a tension pneumothorax.

GRADING OF MECONIUM ASPIRATION SYNDROME

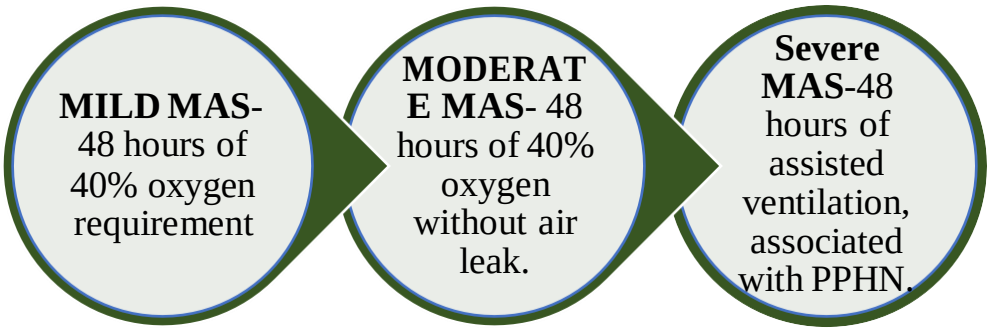


Figure 5- Grading of MAS

TREATMENT

The objective is to support the infant until the alveolar macrophages clear the debris and the baby's lungs function normally.

Oxygen therapy

Giving an appropriate concentration of warmed humidified oxygen up to 80–90% can benefit babies with MAS. During the acute stage of the illness, the oxygen saturation should be kept at 95% or at a PaO2 greater than 10 kPa. PaO2 in room air is normal by 48 hours of age, and in many minor cases, oxygen therapy at 40% or less for 24-48 hours is necessary.

Continuous positive airway pressure.

Although CPAP can promote oxygenation, it may cause pneumothorax. Additionally, term neonates who utilise nasal prongs typically become irritable with a drop in PaO2.

Intermittent positivepressure ventilation.

Theoretically, low PEEP andlong expiratory time are the best settings in MAS. Increasingthe PEEP will improve the oxygenation, but at the cost of risk of pneumothorax.

Improvement of blood gases can help in rapid weaning. Decrease in the requirement of FiO2 to less than 50%-60% can then be followed by weaning the peak pressures. The baby can then be extubated to hood oxygen.

High frequency. ventilation

HFJV used along with surfactant was reported to improve oxygenation in MAS[37]. A retrospective review showed no significant difference in the outcome of MAS babies supported by HFJV. HFOV used along with Nitric Oxide showed improvement in oxygenation and outcome in infants with MAS and PPHN[38].

Extracorporeal. membrane oxygenation

Arandomised trial showed that ECMO had improved the survival rates of meconium aspiratedbabies with an oxygenation index of>40 by 50%.Around 94% of infants with meconium aspiration who received ECMO survive with no apparent increase in the likelihood of impairment of neurological outcomes.

Pulmonary vasodilators

Phosphodiesterases are enzymes that catalyse the hydrolytic lysis of the 3' PDE bond of the cyclic nucleotides- cGMP and AMP, which are crucial for the relaxation of the smooth muscles of the pulmonary arteries. PDE inhibitors, such as Milrinone, a PDE3 inhibitor, Dipyridamole, a non-specific PDE5 inhibitor and Sildenafil- an inhibitor of PDE5 have been used to treat newborns with pulmonary hypertension.

In human and animal studies, Sildenafil selectively lowers pulmonary vascular resistance. It causes vasodilation by raising cGMP and blocking the PDE which is responsible for cGMP's conversion to guanosine monophosphate. Infants with an oxygen index >25 wereallocated randomly to receive either oral sildenafil (1 mg/kg every 6hourly) or placebo in a small trial. The infants who received sildenafil demonstrated improved oxygenation. Compared to only one of the six controls, six out of seven newborns receiving sidenafil survival.

Milrinone results in an improvement in oxygenation in newborns who are nonresponsive to iNO, although some of the infants suffered severe ICH.

Inhaled Nitric oxide.

Nitric Oxide is a vasodilator that aids in relaxation of the smooth muscle of the blood vessels. Synthesis is from the endothelial cells from oxygen and L-arginine. Low levels of arginine have been reported in neonates with PPHN, but this is not a widely accepted finding.NO permeates the smoothmuscle cells and activates guanylate-cyclase, which increases 3,5GMP and causes the smooth muscles relaxation.

NO activates guanylate-cyclase in the smooth muscles of pulmonary arteriolar wall when it is inhaled because it diffuses over the alveolar-capillary membrane. The resultant increase in cGMP relaxes the

smooth muscles. Subsequently, NO attaches to haemoglobin rapidly; after binding, it is inactivated and has no systemic effects.

HFJV or HFOV can be used along with inhaled nitric oxide. The combination of inhaled nitric oxide and HFOV is superior to HFOV or inhaled nitric oxide alone in infants with severe lung disease and PPHN[39].

A poor response to inhaled nitric acid has been observed in babies with systemic hypotension , severe parenchymal disease, myocardial dysfunction, structural pulmonary abnormalities such as pulmonary hypoplasia or dysplasia and can develop a sustained dependence on iNO.

Surfactant

Babies who received surfactant within 6 hours of birth had fewer air leaks, required oxygen and IPPV for a shorter amount of time, according to a randomised prospective research.

In a randomised experiment, term infants with respiratory failure of which half had MAS and needed up to four doses of surfactant to reduce their requirement for ECMO, but no other significant changes in outcome were seen. Surfactant treatment decreased the probability of needing ECMO, but not death, according to a meta-analysis of the findings of four randomised trials[40,41].

Surfactant lavage may be an efficient way to improve gas exchange since it helps to wash out meconium and the byproducts of inflammation and dilution of the meconium. Large aliquots (15 ml/kg) of surfactant were administered during a study without causing any adverse acute effects, and at 48 hours, oxygenation was better than it was with the controls[41].

COMPLICATIONS

Airway obstruction

Atelectasis is the result of meconium completely blocking the airways. The ball-valve effect, which is the result of air being trapped and the alveoli becoming hyperdistended is caused by partial occlusion. The gas which is trapped hyperinflates the lungs may rupture and enter the mediastinum, pleura or pericardium causing pneumomediastinum, pneumothorax or pneumopericardium respectively**.**

Surfactant dysfunction

Meconium inhibits surfactant synthesis and deactivates surfactant. Diffuse atelectasis is caused when components of meconium, particularly the free fatty acids (such as palmitic, stearic, and oleic), which have a higher minimal surface tension than surfactant.

Persistent pulmonary hypertension of the newborn

Due to chronic intrauterine stress and thickening of the pulmonary vessels, neonates with meconium aspiration syndrome (MAS) suffer primary or secondary persistent pulmonary hypertension. PPHN additionally contributes to the hypoxemia caused by MAS. Presence of meconium in the airway may put a newborn at risk for pulmonary infection**.**

PREVENTION OF MAS

Antenatal

Amnioinfusion did not show a reduced risk of MASorperinatal deaths accordingto a randomized trial which included 1998 pregnant women with thick meconium stained amniotic fluid at 36 weeks gestation.

Intrapartum fetal heart rate monitoring

FHR monitoring is now considered to be standard of care, especially in pregnancies where there is thought to be a higher risk of intrapartum foetal hypoxemia (eg, post-term pregnancy, intrauterine growth restriction, preeclampsia).

The main objective is to evaluate how effectively the foetus is being oxygenated during labour. Evaluation and interventions are utilised in patients with abnormal tracings suggestive of foetal stress to lower the risk of prenatal asphyxia. Although the combination of a non reassuring FHR tracing and thick meconium in amniotic fluid has been associated to an increased risk of MAS, the benefit of intrapartum foetal monitoring in preventing MAS has not been proven.

As neonates with a gestational age of more over 41 weeks have the highest chance of developing MAS, preventing deliveries beyond that point minimises the incidence of MAS. In an effort to reduce the number of post-term births, women who are well-dated and have no contraindications to induction can be offered induction of labour at 39 weeks gestation..

Intrapartum/Postpartum

Mode of delivery

Caesarean sections are usually performed on infants with foetal distress, a risk factor for MAS, which may explain why MAS is generally considered to be more common in caesarean section babies than vaginal babies.

Airway suctioning.

Despite the fact that it is evident that some meconium can be inhaled prior to labour, it is thought that many cases of MAS are brought on by inhaling meconium in the few minutes before delivery. Randomized trials that looked at the issue of whether tracheal suctioning and intrapartum intubation are necessary have now been reported.

The incidence of MAS did not significantly differ between babies who were randomly assigned to undergo naso or oropharyngeal suctioning before delivery of the shoulders or to receive no suctioning at all.

The incidence of MAS or other respiratory difficulties was not significantly different between seemingly healthy newborns who were randomly assigned to receive regular delivery room care, intubation, and tracheal suctioning.

In comparison to routine resuscitation, including oropharyngeal suction, routine endotracheal intubation at birth did not show a significant benefit in terms of mortality, MAS, or hypoxic-ischaemic encephalopathy (HIE), according to a metaanalysis of the results of four randomised trials that included vigorous term meconiumstained babies .

IPPV.

The criteria for IPPV resuscitation are unaffected by the presence of meconium, however it

is always essential to clear the airway of as much of the obstruction before beginning positive-pressure ventilation.

Bronchial lavage

It is disputed whether or not to inject water or saline into the lower respiratory tract because doing so has been linked to an increase in wet lung , and bronchial lavage on a routine basis can be harmful. However, one study discovered that tracheal suction mixed with saline lavage lowered airway resistance by 35% after beginning IPPV.

Postnatal gastric aspiration

Because it is assumed that the baby will have swallowed the meconium during delivery, many medical professionals regularly aspirate the stomach of a newborn who has swallowed meconium during delivery. This prevents a further meconium inhalation after vomiting or reflux.

ENHANCING HEALTHCARE OUTCOMES

It is essential for the early detection of risk factors contributing to MAS. This enables early planning via communication and interprofessional relationships.The obstetrician can aid in identifying patients with infants that are vulnerable to MAS. A specialised facility with access to a neonatal critical care unit should be used for delivery. This will enable qualified staff, such as a nurse, paediatrician or neonatologist, and respiratory therapist, to be present for the delivery and prepared in the event that respiratory support is eventually required. Formation of an interprofessional working group to address these patients will have a good effect on care and result in better care.

Studies in the past on similar topic

RCTs were analysed by **Phattraprayoon, N. et al**[42]. to assess the effectiveness, safety, and adverse effects of various steroids in infants with MAS. Their findings demonstrated the advantages of both IV methylprednisolone and nebulized budesonide on the duration of respiratory distress, the requirement for oxygen, and hospitalisation, including ICU admission.

Evidence also suggests that nebulized budesonide reduces the time it takes to reach full feeding without statistically significantly raising infection and complication rates. Regardless of the steroid type used, there was no decrease in mortality. It has been demonstrated that budesonide instillation with surfactant improves.

Infants with MAS were primarily treated with supportive respiratory and cardiovascular care, along with additional modalities like surfactants. A Cochrane meta-analysis only included papers by Yeh et al. and Wu et al., but it investigated the impact of steroids on infant MAS.

Due to a lack of data, this meta-analysis found no relationship between steroids and the length of oxygen therapy or mortality rate. Between newborns with MAS and those who did not receive steroids, there was no discernible difference in the frequency of PPHN. Neonates with or without budesonide did not differ in terms of pneumothorax. There was no discernible rise in hypertension or hyperglycemia among newborns receiving steroids.

Neelmani Garg et al[43]. compared case and control groups for factors such as birth weight, sex distribution, mode of delivery, HIE staging, and Apgar scores at 1, 5, and 10 minutes.

In comparison to the controls(3.461 ± 1.148) the intervention group's dependency on oxygen which was measured in mean days was significantly lower (p value 0.001) in the intervention group (1.794 ± 0.950).

For all cases, mean oxygen need lasted 2.62 days.This decrease in oxygen dependence was attributed to steroids antiinflammatory effects, which reduce lung inflammatory alterations and shorten the duration of oxygen dependence.

A study by **Goswami JN et al**[44]. on neonates born with thick Meconium stained liquor revealed that Group A (which was nebulized with budesonide) required considerably less oxygen supplementation (p value- 0.05) than Group B. (nebulized with normal saline).

Additionally, **Basu et al**[45]. discovered the steroidtreated groups had considerably shorter periods of oxygen dependency (p value-0.05).

The duration of oxygen dependence was observed to differ in a statistically significant way by **Tripathi et al**[46]. when they assessed the function of budesonide in the treatment of MAS.

METHODOLOGY

SOURCE OF DATA

Place of study: NICU Of Shri B M Patil Medical College Hospital and Research Centre, BLDE (Deemed University), Vijayapura, Karnataka

Duration of study: January 2021 to August 2022

Study design: Prospective Comparative Study

Inclusion criteria:

All term and postterm neonates with a history of meconium aspiration admitted in NICU will be included.

Exclusion criteria:

Neonates with a history of meconium aspiration, with congenital anomalies of the respiratory tract.

Neonates with a history of meconium aspiration on a conventional ventilator as the primary mode of respiratory support

Neonates with a history of meconium aspiration with congenital pneumonia

METHOD OF COLLECTION OF DATA

Term and postterm neonates with a history of meconium aspiration are given Budesonide nebulization at 2 hours and 12 hours of admission. The neonates are observed for the duration of oxygen requirement, the period of stay in NICU and the outcome at the end of NICU stay.

GROUP 1- Term and postterm neonates with a history of meconium aspiration will receive nebulization with 0.5mg budesonide dissolved in 2.5ml of sterile normal saline at 2 hours and 12 hours of admission

GROUP 2- Term and postterm neonates with a history of meconium aspiration will receive nebulization with 2.5ml Normal Saline at 2 hours and 12 hours of admission.

Random allocation will be done,i.e the first ten babies will receive budesonide nebulization, and the next ten babies will receive normal saline nebulization.Besides the above intervention, all the neonates' management was done according to the standard protocols of our NICU for MAS.

The required minimum sample size is 54 per group(i.e., a total sample size of 104, assuming equal group sizes)to achieve a power of 80% and a level of significance of 2% (two-sided), detecting a real difference in means between two groups.

$$N = 2\left[\frac{(Z_a + z_\beta) \times S}{d}\right]^2$$

Z_a Level of significance=98%

Z_β--the power of the study=80%

d=clinically significant difference between two parameters

S= Common standard deviation

STATISTICAL ANALYSIS

- The data obtained was entered in a Microsoft Excel sheet, and statistical analysis was performed using a statistical package for the social sciences (SPSS Version 20).
- Results were presented as Mean±SD, counts and percentages, and diagrams.
- For normally distributed continuous variables between the two groups were compared using an independent t-test. For not normally distributed variables, the Mann-Whitney U test was used. Categorical variables between the two groups were compared using the Chi-square test.
- $p<0.05$ is considered statistically significant.

RESULTS

Table 1: Distribution of Gender

Gender	Frequency	Percent
Female	45	41.3
Male	64	58.7
Total	109	100.0

A total of 109 babies were enrolled for the prospective comparative study. Out of 109 babies, 45(41.3%) were females and 64(58.7%) were males.

Figure6- Distribution of Gender

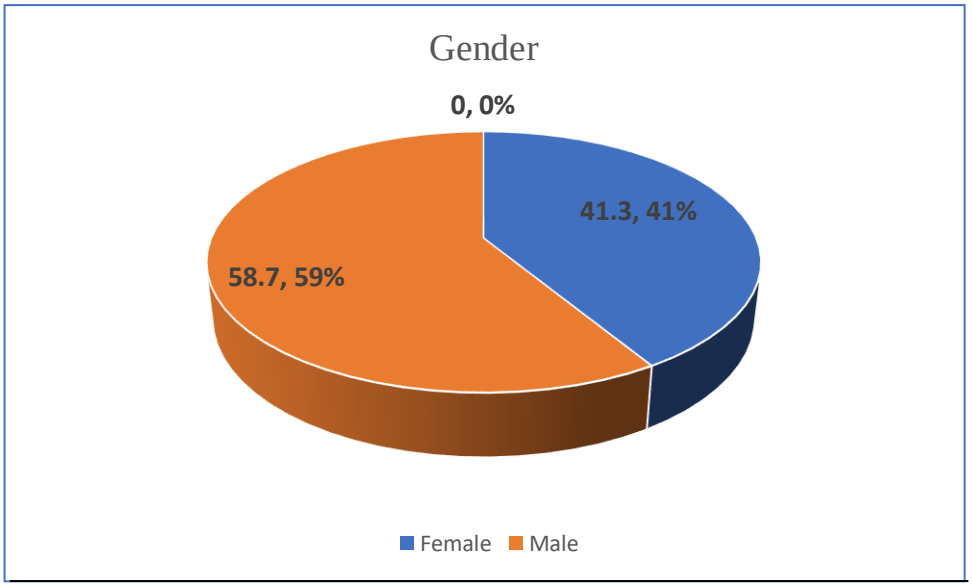


Table 2: Distribution of Type of MAS

Type of MAS	Frequency	Percent
Mild	56	51.4
Moderate	53	48.6
Total	109	100.0

A total of 109 babies were enrolled for the prospective comparative study. Out of 109 babies, 56(51.4%) babies had mild MAS, while 53(48.6%) babies had moderate MAS.

Figure 7- Distribution of Type of MAS

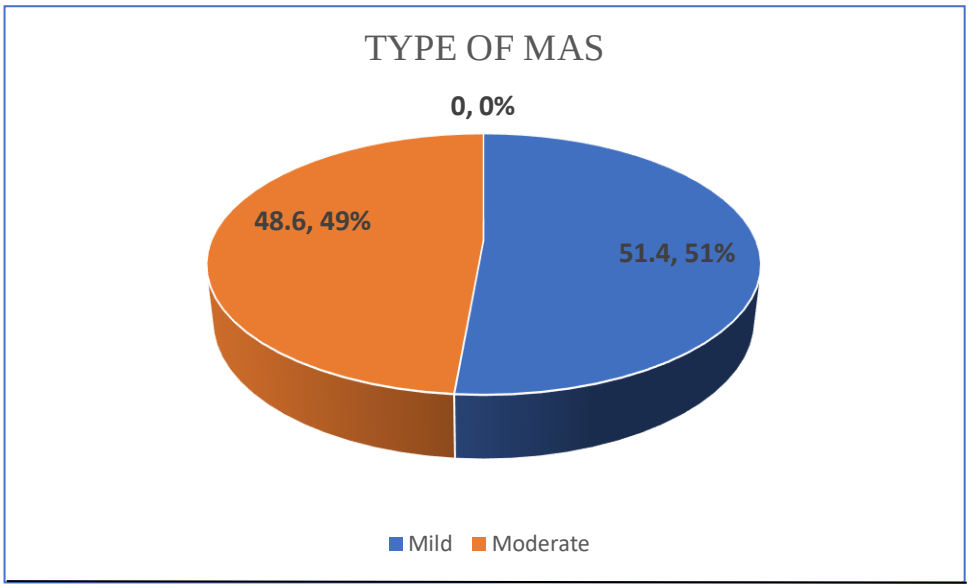


Table 3- Distribution of Downe's score

Downe's score	Frequency	Percent
1	26	23.9
2	76	69.7
3	7	6.4
Total	109	100.0

A total of 109 babies were enrolled for the prospective comparative study. Out of 109 babies, 26(23.9%) babies had downe's score 1/10, 76(69.7%) babies had downe's score 2/10 and 7(6.4%)babies had a downe's score of 3/10.

Figure 8- Distribution of Downe's score

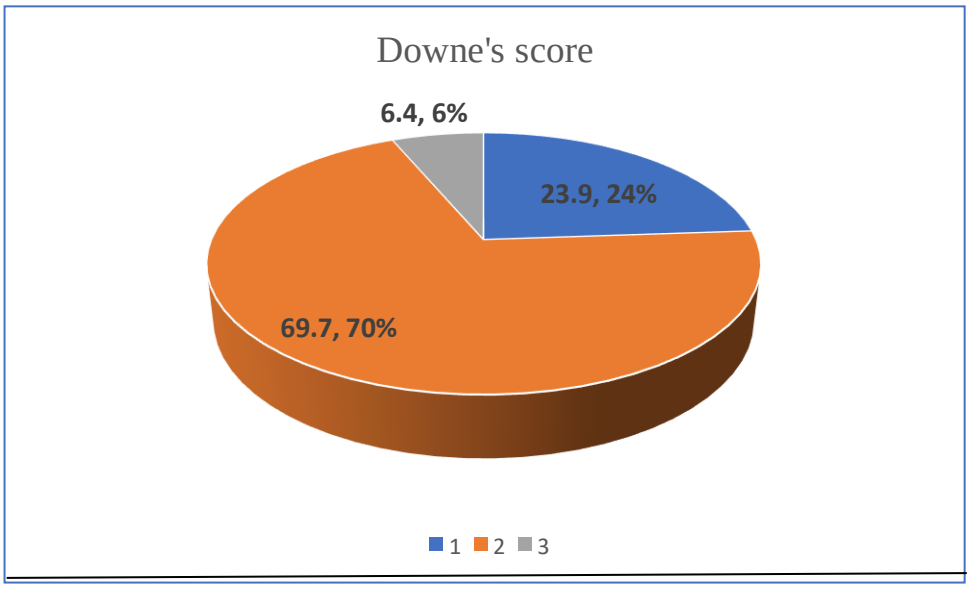


Table 4: Distribution of Primary mode of respiratory support

Primary mode of respiratory support	Frequency	Percent
HFNC	37	33.9
Hood O2	72	66.1
Total	109	100.0

A total of 109 babies were enrolled for the prospective comparative study. Out of 109 babies, 37(33.9%) babies were put on Hfnc as the primary mode of respiratory support and 72(66.1%) babies were kept on hood oxygen as primary mode of respiratory support.

Figure 9- Distribution of Primary mode of respiratory support

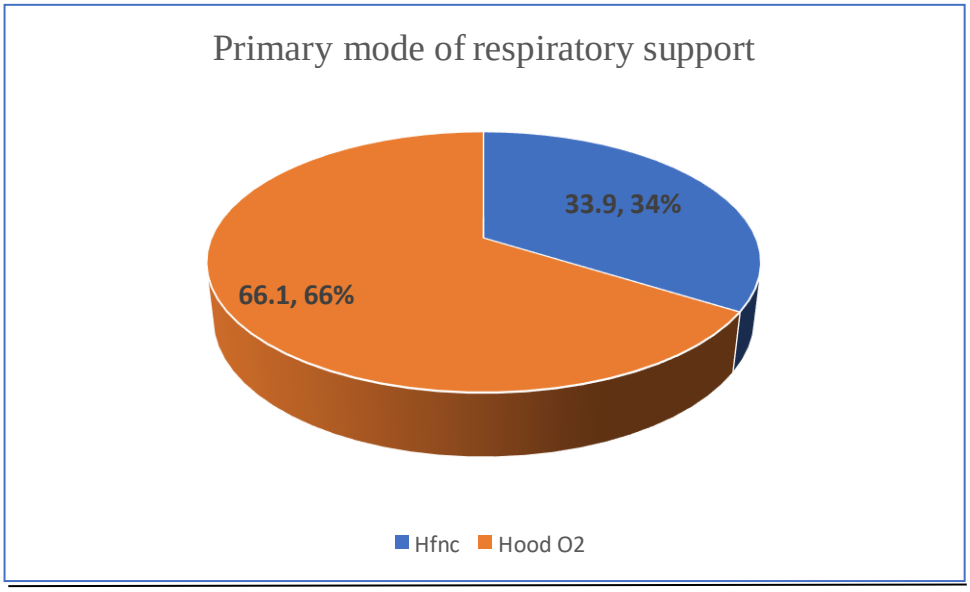


Table 5- Distribution of C-Reactive Protein(CRP)

CRP	Number of cases	Percentage
Negative	52	48%
Positive	57	52%
Total	109	100%

A total of 109 babies were enrolled for the prospective comparative study. Out of 109 babies with mild and moderate MAS, in 52(48%) babies CRP was negative and 57(52%) babies CRP was positive.

Figure 10- Distribution of CRP

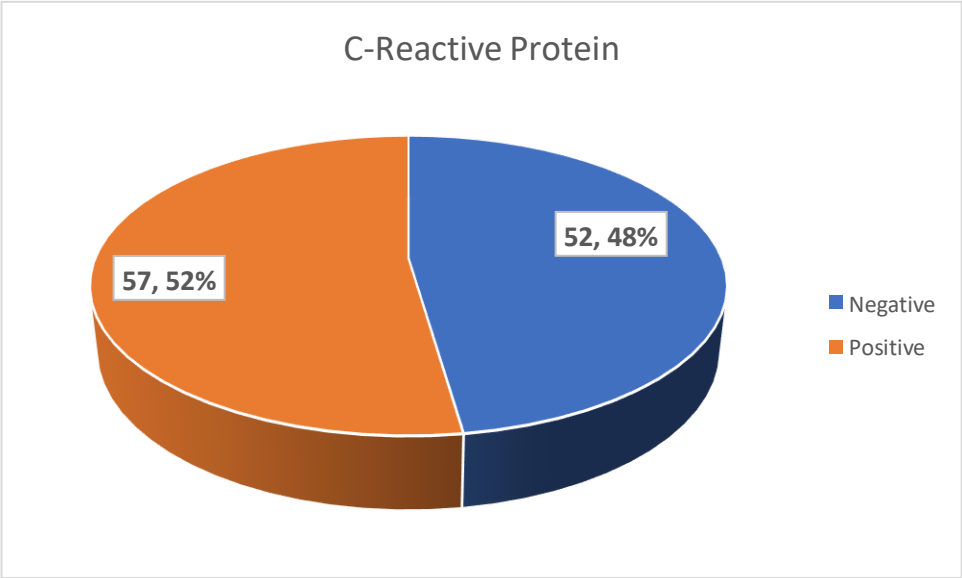


Table 6- Data based on Antibiotics usage

ANTIBIOTICS	No of cases	Percentage
Nil	30	27.5%
Given	79	72.5%
Total	109	100%

A total of 109 babies were enrolled for the prospective comparative study. Out of 109 babies with mild and moderate MAS,79(72.5%) babies needed antibiotics and 30(27.5%) babies did not require antibiotics.

Figure 11- Data based on Antibiotics usage

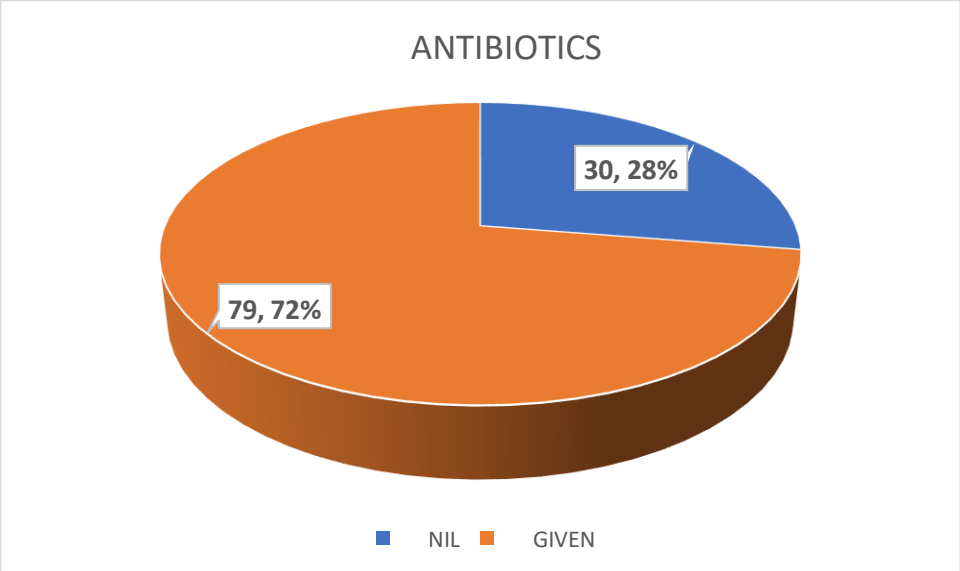


Table 7- Distribution of mode of delivery

MODE OF DELIVERY	Number of cases	Percentage
LSCS	85	77.9%
NVD	24	22.1%
Total	109	100%

A total of 109 babies were enrolled for the prospective comparative study. Out of 109 babies, 85 babies were delivered via LSCS(77.9%) and 24(22.1%) babies were delivered via NVD.

Figure 12- Distribution of type of delivery

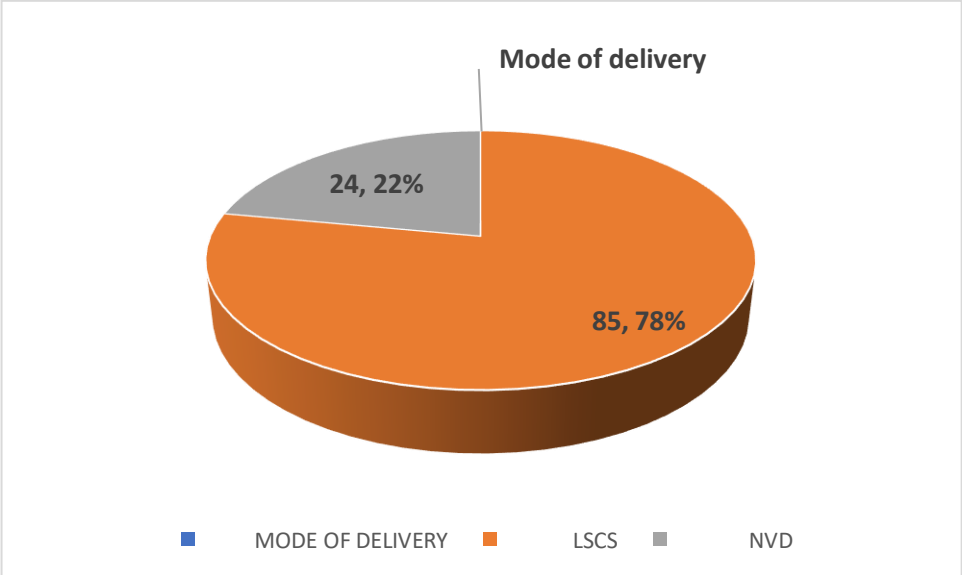


Table 8- Distribution of outcome

Outcome	Frequency	Percent
No ventilator	106	97.2
Needed ventilator	3	2.8
Total	109	100.0

A total of 109 babies were enrolled for the prospective comparative study. Out of 109 babies, 3(2.8%) babies needed ventilator during the course of the hospital stay, while 106(97.2%) babies did not need ventilator.

Figure 13 - Distribution of outcome

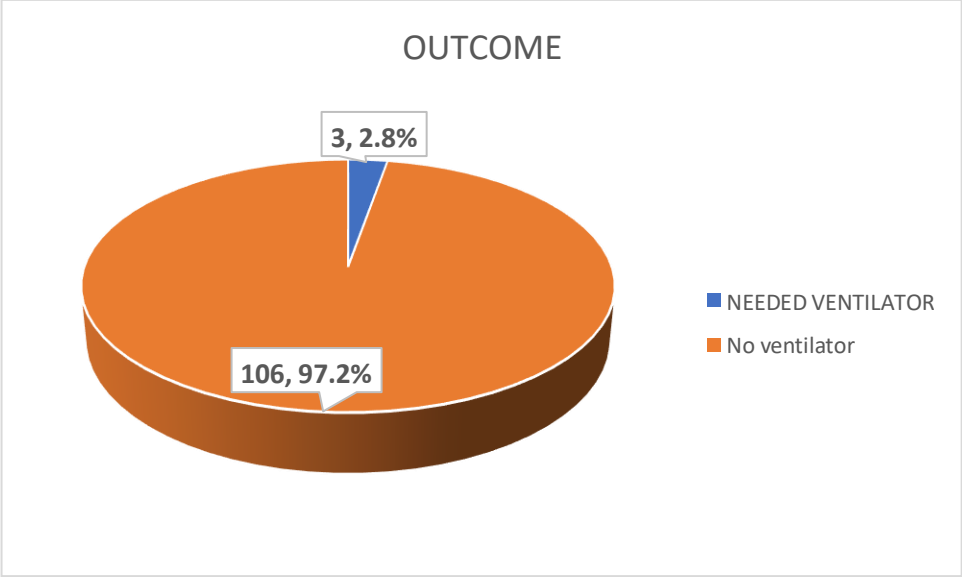


Table 9- Distribution of Mode of delivery and type of MAS

Mode of delivery	TYPE OF MAS		Chi square test value	p value
	MILD MAS	MODERATE MAS		
C-section	42 75%	43 81.1%	0.596	0.440
Normal vaginal delivery	14 25%	10 18.9%		
	56	53		

The association between mode of delivery and type was MAS was evaluated. Out of 85 babies delivered via LSCS, with, 42(75%) babies had mild MAS and 43(81.1%) babies had moderate MAS.

Out of 24 babies delivered via NVD, 14(25%) babies had mild MAS and 10(18.9%) babies had moderate MAS. There was no statistical significance between type of MAS and mode of delivery.

Figure 14: Distribution of Mode of delivery and type of MAS

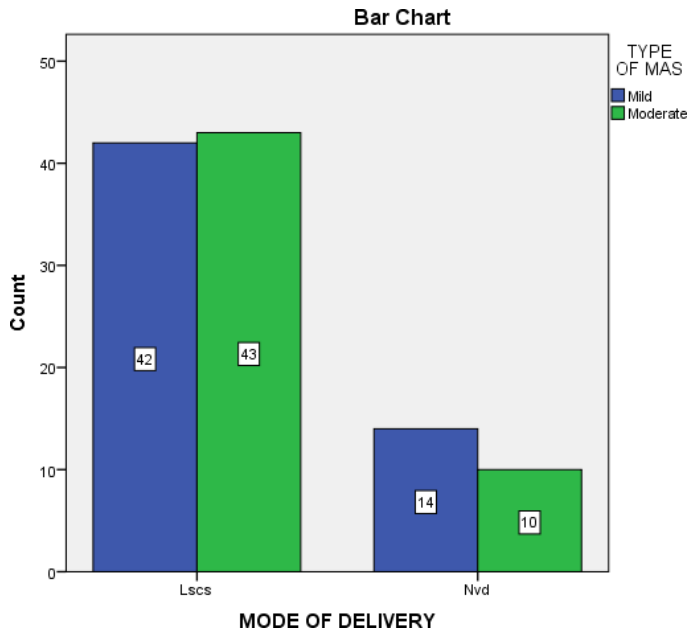


Table 10: Distribution of Birth weight and type of MAS

BIRTH WEIGHT		TYPE OF MAS				Chi square test value	p value
		Mild MAS		Moderate			
BIRTH WEIGHT	2000-2999	16	28.6%	21	39.6%	2.004	0.367
	3000-3999	38	67.9%	29	54.7%		
	4000-4999	2	3.6%	3	5.7%		
Total		56		53			

association between birth weight and type of MAS was evaluated.Out of 51.3% babies with mild MAS, 28.6% had birth weight between 2000gms-2999gms, 67.9% had birth weight between 3000gms-3999gms and 3.6% had birth weight between 4000gms to 4999gms.

Out of 48.6% babies having moderate MAS, 39.6% babies had birth weight between 2000gms-2999gms, 54.7% had birth weight between 3000gms-3999gms and 5.7% had birth weight between 4000gms to 4999gms There was no statistical significance between the two groups.

Figure 15: Distribution of Birth weight and type of MAS

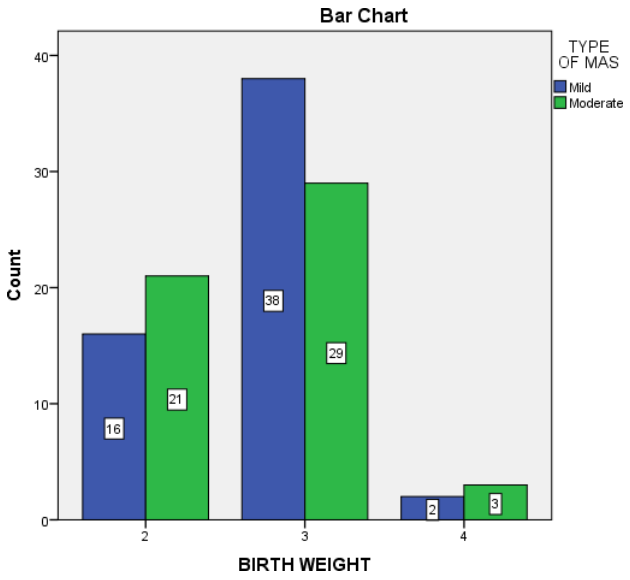


Table 11: Distribution of type of MAS and Intervention

		BUDESONIDE	NORMAL SALINE	Chi square test value	p value
TYPE OF MAS	Mild	31 55.4%	25 44.6%	1.105	0.293
	Moderate	24 45.3%	29 54.7%		
Total		55	54		

Out of 109 babies, 56 babies had mild MAS and 53 babies had moderate MAS. 31(55.4%) babies with mild MAS were given budesonide nebulization and 25(44.6%) babies were given normal saline nebulization. 24(45.3%) babies with moderate MAS were given budesonide nebulization and 29(54.7%) were given normal saline nebulization. The groups were randomly allocated.

Figure 16: Distribution of type of MAS and Intervention

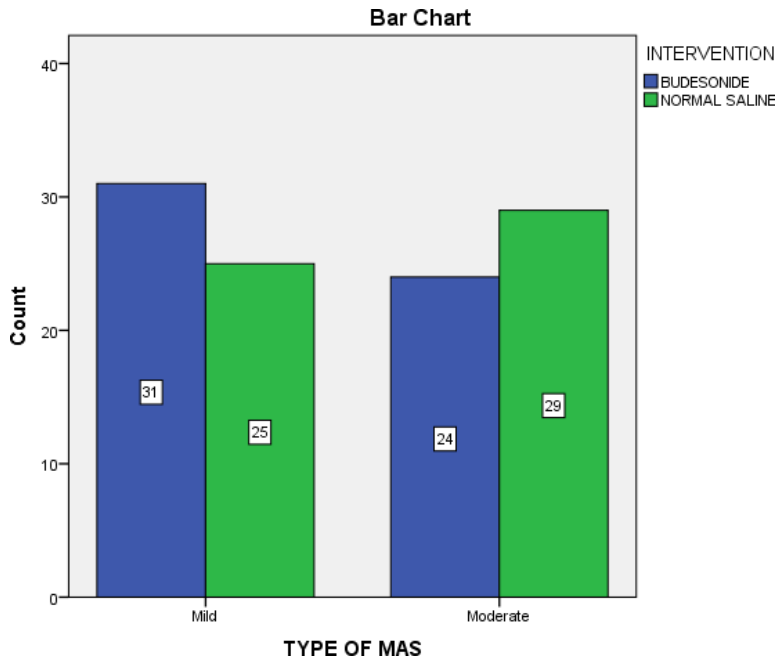


Table12: Distribution of Number of days on oxygen support and Intervention

NUMBER OF DAYS ON OXYGEN SUPPORT		INTERVENTION		Chi square test value	p value
		BUDESONIDE	NORMAL SALINE		
NUMBER OF DAYS ON OXYGEN SUPPORT	2-4	34 61.8%	22 40.7%	9.095	0.028
	5-7	21 38.2%	26 48.1%		
	8-10	0 0.0%	5 9.3%		
	11-13	0 0.0%	1 1.9%		
Total		55 100.0%	54 100.0%		

Out of 109 babies, 55 babies were given budesonide nebulization, out of which, 34(61.8%) babies had oxygen dependency of 2-4 days and 21(38.2%) babies had oxygen dependency of 5-7 days.54 babies were given normal saline nebulization,22(40.7%) babies has oxygen dependency of 2-4 days, 26(48.1%) babies had oxygen dependency of 5-7 days,5(9.3%) babies had oxygen dependency of 8-10 days and 1(1.9%) baby had oxygen dependency for around 11-13 days.

Figure 17: Distribution of Number of days on oxygen support and Intervention

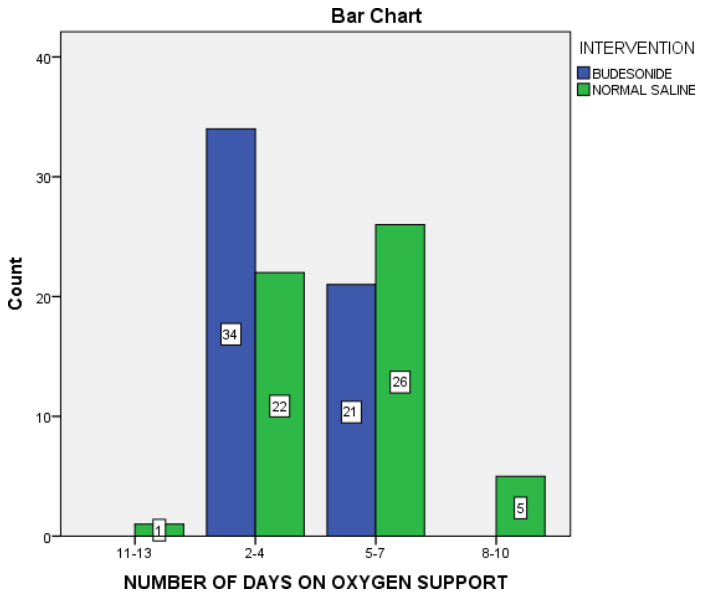


Table 13: Distribution of Outcome and Intervention

OUTCOME		INTERVENTION		Chi square test value	p value
		BUDESONIDE	NORMAL SALINE		
OUTCOME	No ventilator	55 51.9%	51 48.1%	3.142	0.076
	Needed ventilator	0 0.0%	3 100.0%		
Total		55	54		

Out of 109 babies with mild and moderate MAS, 106 babies did not need ventilator in the course of their hospital stay, 3(2.7%) babies who were given normal saline nebulization needed ventilator. There was no statistical significance between the two groups.

Figure 18: Distribution of Outcome and Intervention

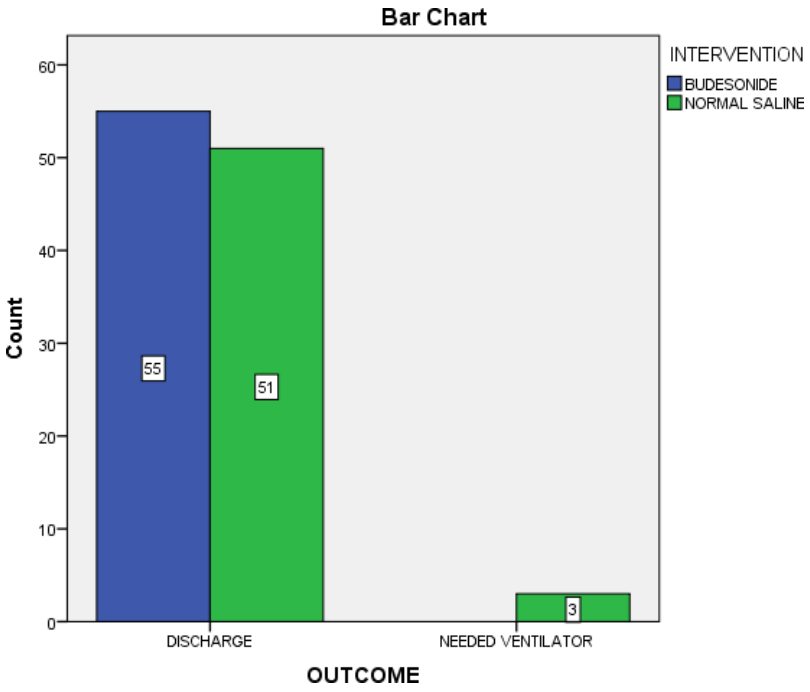


Table 14: Independent Samples Mann-Whitney U–Test

Variables	Group	Mean	SD	Mann-Whitney U–Test value	p-value
GESTATIONAL AGE	BUDESONIDE	38.636	0.91	1556.5	0.650
	NORMAL SALINE	38.537	0.966		
CRP	BUDESONIDE	11.689	9.087	1144	0.038
	NORMAL SALINE	16.161	12.619		
DOWNE'S SCORE AT ADMISSION	BUDESONIDE	1.782	0.534	1367	0.376
	NORMAL SALINE	1.87	0.516		
NUMBER OF DAYS ON OXYGEN SUPPORT	BUDESONIDE	4.036	1.49	1030.5	0.005
	NORMAL SALINE	5.185	2.19		
NUMBER OF DAYS ADMITTED IN NICU	BUDESONIDE	4.891	1.641	1093	0.016
	NORMAL SALINE	6.093	2.421		

Out of 109 babies with mild and moderate MAS, Number of days of oxygen support was 4.036 ± 1.49 days in Budesonide group, 5.185 ± 2.19 days in Normal saline group. There was statistical significance between the two groups (p value-0.005). Number of days admitted in NICU was 4.891 ± 1.641 days in Budesonide group, and 6.093 ± 2.421 days in Normal saline group. There was statistical significance between two groups (p value 0.016).

DISCUSSION

Distribution in gender

A total of 109 babies were enrolled for the prospective comparative study. Out of 109 babies, 45(41.3%) were females and 64(58.7%) were males.

In a study by Neelmani et al[44], male and females were in equal number in their study.

Distribution of Downe's score

In our study, 23.9% neonates had Downe's score 1/10,

69.7% neonates had Downe's score 2/10 and 6.4% had Downe's score of 3/10.

Neelmani et al[44] revealed that the mean Downes' score was lower in the nebulized budesonide group (over 5 days) than in the control group (p 0.05). Rana et al[47] revealed that the nebulized budesonide with IV methylprednisolone group had a lower median Downes' score (days 2-7) than the control group (p 0.05).

According to Neelmani et al. study[44], the difference between the mean Downe's Scores for the intervention group and the controls, which was 2.978 ± 2.122, was statistically significant.

Distribution of Primary mode of respiratory support

In our study, the primary mode of respiratory support was HFNC in 33.9% neonates and hood oxygen in 66.1% newborns.

Distribution of CRP and antibiotics

Out of 109 babies with mild and moderate MAS, in 52(48%) babies CRP was negative and 57(52%) babies CRP was positive.

Out of 109 babies with mild and moderate MAS,79(72.5%) babies needed antibiotics and 30(27.5%) babies did not require antibiotics.

Distribution of Outcome

97.2% babies did not need ventilator while 2.8% neonates needed ventilator during the course of hospital stay. Six RCTs[43,44,45] determined the effect of steroids on the need for mechanical ventilation. Two studies[48,49] showed no significant difference in the need for mechanical ventilation when using IV dexamethasone versus the control with very low-quality evidence.

Distribution of Birth weight and type of MAS

Out of 51.3% babies with mild MAS, 28.6% had birth weight between 2000gms-2999gms, 67.9% had birth weight between 3000gms-3999gms and 3.6% had birth weight between 4000gms to 4999gms. Out of 48.6% babies having moderate MAS, 39.6% babies had birth weight between 2000gms-2999gms, 54.7% had birth weight between 3000gms-3999gms and 5.7% had birth weight between 4000gms to 4999gms. There was no statistical significance between the two groups.

Distribution of Mode of delivery and type of MAS

Out of 109 babies, 85 babies were delivered via LSCS(77.9%) and 24(22.1%) babies were delivered via NVD. There was no statistical significance between the two groups.

Caesarean sections are usually performed on infants with foetal distress, a risk factor for MAS, which may explain why MAS is generally considered to be more common in caesarean section babies than vaginal babies.

Distribution of Type of MAS and Intervention

In our study, 51.3% neonates had mild MAS and 48.6% neonates had moderate MAS. 55.4% newborns having mild MAS were given budesonide nebulization, and 44.6% were given normal saline nebulization.

45.3% newborns having moderate MAS were given budesonide nebulization, and 54.7% were given normal saline nebulization.

Distribution of Primary mode of respiratory support and Intervention

In our study, 28.6% neonates were put on HFNC as the primary mode of respiratory support. 59.5% neonates on HFNC were given budesonide nebulization and 40.5% neonates were given normal saline nebulization.

66% neonates were put on hood oxygen as the primary mode of respiratory support, out of which 45.8% neonates were given budesonide nebulization and 54.2% were given normal saline nebulization.

Distribution of Number of days on oxygen support and Intervention

In our study, the requirement for oxygen was significantly lesser (p value-0.028) in neonates who received budesonide nebulization, than in neonates who received normal saline nebulization.

Out of 109 babies with mild and moderate MAS, Number of days of oxygen support was 4.036 ± 1.49 days in Budesonide group, 5.185 ± 2.19 in Normal saline group.

Data on the period of time of oxygen consumption was provided by **Neelmani et al**[44]. Both IV methylprednisolone and nebulized budesonide appeared to shorten the time requiring oxygen.

When evaluating the role of budesonide in the treatment of MAS, **Tripathi et al**[46]. found that the duration of oxygen dependence varied in a statistically significant way.

In comparison to the controls (3.461 ± 1.148), the intervention group's requirement (dependency) on oxygen (measured in mean days) was significantly lower (p value 0.001) in the intervention group (1.794± 0.950).

Additionally, **Basu et al**[45]. found that the steroid-treated groups experienced oxygen dependency for considerably shorter time periods (p value 0.05).

Goswami JN et al. studied neonates with thick Meconium-stained liquid and the results showed that

Group A, which received budesonide nebulization, required much less oxygen supplementation than Group B who received nebulized normal saline(p value 0.05).

For all individuals, the average oxygen need lasted 2.62 days. This decrease in oxygen dependence can be attributed to steroids' anti-inflammatory effects, which reduce lung inflammatory alterations and shorten the duration of oxygen dependence.

Distribution of Number of days admitted in NICU and Intervention

In our study, the number of days admitted in NICU was significantly lesser (p value-0.016) in neonates who received budesonide nebulization, than in neonates who received normal saline nebulization.

In our study, number of days admitted in NICU was 4.891 ± 1.641 days in Budesonide group, and 6.093 ± 2.421 days in Normal saline group. There was statistical significance between two groups (p value 0.016).

Four RCTs[43,44,45,46] reported evidence about the length of hospitalization, including admission to the intensive care unit (ICU). Their research revealed that the Budesonide group had decreased stay in NICU than the Normal saline group.

Nebulized budesonide may reduce the length of hospitalization, according to low-quality evidence from another four RCTs[47,48,49,50] (MD, 4.47 days; 95% CI, 8.64 to 0.30 days).

Study	Intervention	Our study	Neelmani garg et al	Basu et al	Tripathi et al
Number of days on oxygen support	Budesonide	4.036 ± 1.49	1.794± 0.950	4.59 ± 2.26	4.06± 1.52
	Normal saline	5.185 ± 2.19	3.461 ± 1.148	7.70 ± 1.63	7.00± 4.81
Number of days admitted in NICU	Budesonide	4.891 ± 1.641	3.055± 1.433	10.63 ± 1.56	12.18±6.22
	Normal saline	6.093 ± 2.421	5.085± 1.462	18.06±2.23	19.59± 12.77

LIMITATION

The limitation of our study was that the effect on severe MAS was not studied.

CONCLUSION

From the present study, it can be inferred that nebulization with budesonide in babies with meconium aspiration has significant effect on the oxygen dependency and NICU stay.

Budesonide nebulization reduces the number of days of requirement of oxygen and reduces the number of days admitted in NICU in mild and moderate MAS.

BIBLIOGRAPHY

1. Wiswell TE, Bent RC. Meconium staining and the meconium aspiration syndrome: Unresolved issues. Pediatr Clin North Am 1993; 40: 955-981.
2. Ahanya SN, Lakshmanan J, Morgan BL, Ross MG. Meconium passage in utero: mechanisms, consequences, and management. ObstetGynecolSurv. 2005 Jan;60(1):45-56; quiz 73-4. doi: 10.1097/01.ogx. 0000149659.89530. c2. PMID: 15618919.
3. Gupta GK, Cole CH, Abbasi S, Demmisse S, Njinimbam C, Nielson HC, et al: Effects of early inhaled beclomethasone therapy on tracheal aspirate inflammatory mediators IL-8 and IL-1ra in ventilated preterm infants at risk for bronchopulmonary dysplasia. PediatrPulmonol 2000; 30(4): 275-81.
4. Grand RJ, Watkins JB, Torti FM. Development of the human gastrointestinal tract: a review. Gastroenterology 1976;70:790-810
5. Jirasek JE, Uher J and Koldovsky O.A histochemical analysis of the development of small intestine of human fetuses. Acta Histochem 1965: 22:33
6. Fox WW, Berman LS,DownesJJ,Peckham C J. The therapeutic application of end expiratory pressure in the meconium aspiration syndrome. Pediatrics 1975; 56:214-217
7. Gooding CA, Gregory CA, Taber P and Wright RR. An experimental model for the study of meconium aspiration of the newborn. Pediatr Radiology 1971; 100:137-40
8. Schaffer AJ and Avery M. Diseases of the newborn. Philadelphia: W.B.Sounders Co.1971,p.267
9. Yurdakök M. Meconium aspiration syndrome: do we know? Turk J Pediatr. 2011 Mar-Apr;53(2):121-9.

10. Brabbing-Goldstein D, Nir D, Cohen D, Many A, Maslovitz S. Preterm meconium-stained amniotic fluid is an ominous sign for the development of chorioamnionitis and for in utero cord compression. J Matern Fetal Neonatal Med. 2017 Sep;30(17):2042-2045.

11. Walker J. Fetal distress. Am. J. Obestet. Gynecol. 1959: 77:94-107

12. Krebs H.B, Dunn L.J, Peters RE, Intrapartum fetal heart rate monitoring and association of meconium with abnormal fetal heart rate pattern. American Journal of obstetrics and Gynecology, 1980, August.

13. Sherrie D. Richey, Susan M. Ramin, Roger E. Bawdon, Scott W. Roberts, Jody Dax, Jodie Roberts, Larry C. Gilstrap,Markers of acute and chronic asphyxia in infants with meconium-stained amniotic fluid,American Journal of Obstetrics and Gynecology,Volume 172, Issue 4, Part 1,1995,Pages 1212-1215

14. AllahyarJazayeri, Mary K Jazayeri, Michelle Sahinler, Terry Sincich, Is meconium passage a risk factor for maternal infection in term pregnancies?,Obstetrics&Gynecology,Volume 99, Issue 4,2002,Pages 548-552

15. F.A. Manning, C.R. Harman, I. Morrison, S.M. Menticoglou, I.R. Lange, J.M. Johnson, Fetal assessment based on fetal biophysical profile scoring: IV. An analysis of perinatal morbidity and mortality, American Journal of Obstetrics and Gynecology, Volume 162, Issue 3,1990,Pages 703-709

16. Mitri F, Hofmeyr GJ, Van Gelderen CJ. Meconium during labour–self-medication and other associations. S Afr Med J 1987;71:431-3

17. Chitrakar NS. Comparison of Misoprostol versus Dinoprostone for preinduction cervical ripening at term. J Nepal Health Res Counc 2012:10:10-5

18. G/Silassie R, Gebretsadik W, Degefa N, Getahun D, Kassie N. Determinants of Meconium-Stained Amniotic Fluid at Hadiya Zone Hospitals, Southern Ethiopia; Unmatched Case-Control Study. Int J Womens Health. 2022 Sep 16;14:1351-1360.

19. FitzGerald TB, McFarlane CN. Foeatl distress and intrapartum Foetal death. British Medical Journal 1955: 2:358-361

20. Miller FC, Sacks DA, Yeh SY, Paul RH, Schifrin BS, Martin CB, Hon EH. Significance of meconium during labor. Am. J. Obstet. Gynecol. 1975: 122: 573-580

21. Hari Bhaskar S, Karthikeyan G, Vishnu Bhat B, Bhatia BD. Antenatal risk factors and neonatal outcomes in meconium aspiration syndrome. Indian J. Maternal and child Health 1997:8(1):9-12

22. Rosario MC, Seshadri L. Meconium staining of amniotic fluid in low risk parturients. Journal of Obstetrics and Gynaecology of India 1996; 46: 642-646

23. Rennie and Roberton's textbook of Neonatology,Meconium aspiration syndrome, 5th edition

24. Katz VL, Bowes WA. Meconium aspiration syndrome: Reflections on a murky subject. Am J ObstetGynecol 1992, 166; 71-83. Narang A. Definition of major illnesses as applicable at different levels of the health care delivery system. In: Neonatal Nomenclature and Data Collections. Eds. Singh M, Paul VK, Bhakoo ON. Delhi, Vani Press, 1989, pp 27-35

25. Cleary, J.M., Wiswell, T.E., 1998. Meconiumstained amniotic fluid and the meconium aspiration syndrome: an update. Pediatr Clin North Am 45, 511–529.

26. Zagariya, A., Bhat, R., Uhal, B., et al., 2000. Cell death and lung cell histology in meconium aspirated newborn rabbit lung. Eur J Pediatr 59, 819–826.

27. Holopainen, R.L., Aho, H., Laine, D.J., et al., 1999. Human meconium has high phospholipase A2 activity and induces cell injury and apoptosis in piglet lungs. Pediatr Res 46, 626–632.

28. Clark, D.A., Nieman, G.F., Thompson, J.E., et al., 1987. Surfactant displacement by meconium free fatty acids: an alternative explanation for atelectasis in meconium aspiration syndrome. Journal of Pediatrics 110, 765–770.

29. Wen, T.S., Eirksen, N.L., Blanco, J.D., et al., 1993. Association of clinical intra-amniotic infection

and meconium. Am J Perinatol 10, 438–440.

30. Moses, D., Holm, B.A., Spitale, P., et al., 1991. Inhibition of pulmonary surfactant function by meconium. Am J ObstetGynecol 164, 477–481.

31. Dargaville, P.A., South, M., McDougall, P.N., 2001. Surfactant and surfactant inhibitors in meconium aspiration syndrome. Journal of Pediatrics 138, 113–115.

32. Sun, B., Curstedt, T., Robertson, B., 1993. Surfactant inhibition in experimental meconium aspiration. Acta Paediatr 82, 182–189.

33. Janssen, D.J., Carnielli, V.P., Cogo, P., et al., 2006. Surfactant phosphatidylcholine metabolism in neonates with meconium aspiraton syndrome. Journal of Pediatrics 149, 634–639.

34. Dollberg, S., Livny, S., Mordecheyev, N., et al., 2001. Nucleated red blood cell counts in meconium aspiration syndrome. ObstetGynecol 97, 593–596.

35. J.A.D. Spencer, R.S. Wolton, P. Rolfe, P. Johnson,Mass spectrometer system for continuous skin-surface and intravascular blood gas measurement of maternal-fetal respiration in labour,Journal of Biomedical Engineering,Volume 9, Issue 2,1987,Pages 161-168

36. Cole, J.W., Portman, R.J., Lim, Y., et al., 1985. Urinary β2-microglobulin in full term newborns: evidence for proximal tubular dysfunction in infants with meconium stained amniotic fluid. Pediatrics 76, 958–964.

37. Dr. Jonathan M. Davis MD,Alan R. Spitzer MD,Christopher Cox PhD,William W. Fox MD. Predicting survival in infants with persistent pulmonary hypertension of the newborn.Pediatric Pulmonology Vol5,page 6-9

38. Kinsella et al- Kinsella JP, Truog WE, Walsh WF, Goldberg RN, Bancalari E, Mayock DE, Redding GJ, deLemos RA, Sardesai S, McCurnin DC, Moreland SG, Cutter GR, Abman SH. Randomized, multicenter trial of inhaled nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn. J Pediatr. 1997 Jul;131(1 Pt 1):55-62.

39. El Shahed, A.I., Dargaville, P.E., Ohlsson, A., et al., 2007. Surfactant for meconium aspiration

syndrome in full term/near term infants. Cochrane Database Systematic Reviews (3), CD002054.

40. Dargaville, P.A., Mills, J.H., Copnell, B., et al., 2007. Therapeutic lung lavage in meconium aspiration syndrome: a preliminary report. Journal of Pediatrics and Child Health 43, 539–545.

41. El Shahed, A.I.,Dargaville,P.E.,Ohlsson, A., et al., 2007. Surfactant for meconium aspiration syndrome in full term/near term infants.Cochrane Database Systematic Reviews(3), CD002054

42. Phattraprayoon N, Tangamornsuksan W, Ungtrakul T. Outcomes of endotracheal suctioning in non-vigorous neonates born through meconium-stained amniotic fluid: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2021 Jan;106(1):31-38.

43. Yeh TF, Harris V, Srinivasan G, Lilien L, Pyati S, Pildes RS. Roentgenographic findings in infants with meconium aspiration syndrome. *JAMA.* 1979 Jul 6;242(1):60–3.

44. Garg N, Choudhary M, Sharma D, Dabi D, Choudhary JS, Choudhary SK. The role of early inhaled budesonide therapy in meconium aspiration in term newborns: a randomized control study. J Matern Fetal Neonatal Med. 2016;29(1):36-40.

45. SriparnaBasu, Ashok Kumar & B. D. Bhatia (2007) Role of antibiotics in meconium aspiration syndrome, Annals of Tropical Paediatrics, 27:2, 107-113

46. Sandeep Tripathi, Arvind Saili, The Effect of Steroids on the Clinical Course and Outcome of Neonates with Meconium Aspiration Syndrome, *Journal of Tropical Pediatrics*, Volume 53, Issue 1, February 2007, Pages 8–12

47. Rana, K.S.; Konar, M.C.; Islam, K.; Barik, K.L.; Nayek, K.; Datta, A.K. Study on effects of steroid on clinical course, short-term and long-term outcomes in neonates with meconium aspiration syndrome. J. Neonat. Nurs. 2018, 24, 257–260

48. Sangeetha, T.; Ramanathan, R.; Yogavalli, S. Effectiveness of steroid therapy in newborns with meconium aspiration syndrome. J. Med. Sci. Clin. Res. 2017, 5, 22587–22590.

49. Patil, M.M.; Lakhkar, B.B.; Patil, S.V. Dexamethasone and outcome of meconium aspiration syndrome: Vijayapur, Karnataka experience. Sri Lanka J. Child Health 2018, 47, 21–26.

50. Wu, J.M.; Yeh, T.F.; Wang, J.Y.; Wang, J.N.; Lin, Y.J.; Hsieh, W.S.; Lin, C.H. The role of pulmonary inflammation in the development of pulmonary hypertension in newborn with meconium aspiration syndrome (MAS). Pediatri. Pulm. Suppl. 1999, 18, 205–208.

INFORMED CONSENT FORM

TITLE OF RESEARCH: STUDY OF EARLY INHALED BUDESONIDE THERAPY IN MECONIUM ASPIRATION IN TERM AND POST TERM NEONATES

GUIDE : DR S.S. KALYANSHETTAR

PG STUDENT : DR KONINKI SRAVANI

PURPOSE OF RESEARCH:

I have been informed that the purpose of this study is to assess the effect of early inhaled Budesonide therapy in meconium aspiration in term and post-term neonates.

PROCEDURE

After having obtained a detailed history and thorough a clinical examination, I understand that a final followup of the meconium aspiration neonates, and its outcome is planned.

RISKS AND DISCOMFORTS:

None

BENEFITS:

I understand that my baby's participation in this study will help to study the effect of early inhaled Budesonide therapy in meconium aspiration in term and post-term neonates.

CONFIDENTIALITY:

I understand that the study's medical information will become a part of hospital records and will be subjected to confidentiality and privacy regulations of the hospital. Information on sensitive personal nature will not be part of medical records but will be stored in the investigations research file.

If the data is used for publication, the identity will not be revealed; other identifiers such as photographs will be used only with special permission. I understand that I may see the photograph before giving my permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask for more information about the study at any time, and Dr. KoninkiSravaniat the Department of Pediatrics will be available to answer my questions and concerns. I understand that I will be informed of any new findings that are discovered during the study,
I will be informed of any new findings that are discovered during the study, which might influence my baby's continued participation. A copy of the consent form will be given to keep for careful reading.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my baby's participation is voluntary, and I may refuse to participate or withdraw the consent and discontinue participation in the study at any time without prejudice. I also understand that Dr.KoninkiSravani may terminate my participation in the study after explaining the reasons for doing so.

INJURY STATEMENT:

I understand that in the unlikely event of any injury to my baby, resulting directly from the participation in this study; if such injury were reported promptly, the appropriate treatment would be available to the baby. But, no further compensation would be provided by the hospital. I understand that my agreement to participate in this study and not waiving any of my legal rights.

I have explained to_____the purpose of the research, the procedures required and the possible risks to the best of my ability.

_____ _____

Dr.KoninkiSravani (Date)

(investigator)

PARENTS / GUARDIAN CONSENT STATEMENT:

We confirm that Dr.KoninkiSravani is conducting a study on "Study of early inhaled Budesonide therapy in meconium aspiration in term and post-term neonates. A Prospective study."

Dr.KoninkiSravani has explained to us the purpose of the research and the study procedure. We are willing to give as much information as required for the study and consent for interventions and the possible discomforts and benefits. We have been explained all the above in detail in our language, and we understand the same. Therefore we agree to give consent for our baby's participation as a subject in this research project.

_____ _____

(Parents / Guardian) Date

_____ _____

(Witness to signature) Date

10. SCHEME OF CASE TAKING- PROFORMA

Name

Ip No

Gender

Address

Contact number

Socio economic status

Gestational age

Obstetric history

Mode of delivery

Birth weight

Date of Birth

Downe’s score at admission

Date of Admission

Date of Discharge

Type of MAS

Intervention/ Non Intervention

Retractions at admission

Grunting at admission

Air entry at admission- Normal/ Mildly decreased/ Markedly decreased.

CRP

Antibiotics

The primary mode of respiratory support

The sequence of respiratory support

Number of days on Oxygen support

Number of days admitted in NICU

Outcome- Needed Ventilator/ Discharge/ Death

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
HR							
Spo2							
Mode of oxygen delivery							

ETHICAL CLEARANCE CERTIFICATE

IEC/NO-09/2021
Date-22/01/2021

B.L.D.E. (DEEMED TO BE UNIVERSITY)
(Declared vide notification No. F.9-37/2007-U.3 (A) Dated. 29-2-2008 of the MHRD, Government of India under Section 3 of the UGC Act, 1956)
The Constituent College
SHRI. B. M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Institutional ethical committee of this college met on 11-01-2021 at 11-00 am to scrutinize the synopsis of Postgraduate students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has been accorded Ethical Clearance

Title: Study of early inhaled budesonide therapy in meconium aspiration in term and post term neonates

Name of PG student: Dr Koninki Sravani, Department of Paediatrics

Name of Guide/Co-investigator: Dr S S Kalyanashettar, Professor & HOD of Paediatrics

DR S.V.PATIL
CHAIRMAN, IEC
Institutional Ethical Committee
B L D E (Deemed to be University)
Shri B.M. Patil Medical College,
VIJAYAPUR-586103 (Karnataka)

Following documents were placed before Ethical Committee for Scrutinization:

1. Copy of Synopsis / Research project
2. Copy of informed consent form
3. Any other relevant documents.

2

BIODATA

GUIDE

Name: DR. S.S KALYANSHETTAR

Date of birth: 17/1/1974

Education: MBBS, MD

Present Designation: PROFESSOR &

HEADOFDEPARTMENT

Dept of Pediatrics,BLDE (Deemed to be University) ShriB.M. Patil Medical College,

Vijayapura, Karnataka.

RegistrationNo:45576

Work experience: 18 years

Membership: Indian Academy of Pediatrics

BIODATA

CANDIDATE

Name	:	DR. KONINKI SRAVANI
DateofBirth	:	30/08/1994
Age	:	28 years
Qualification	:	MBBS
RegistrationNo	:	122530

Designation:Postgraduatestudent Department of pediatrics

ADDRESS:NRI PG hostel, Shri B MPatil Medical College
Hospital and Research
Centre, Vijayapura,
Karnataka- 586103

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
1	SOCIO ECONOMIC ST	GENDER	GESTATIONAL AGE	MODE OF DELIVERY	BIRTH WEIGHT	NICU ADMISSION IN H	INBORN/OUTBORN	DATE OF ADMISSION	DATE OF DISCHARGI	TYPE OF MAS	DOWNE'S SCORE AT	INTERVENTION	CRP	ANTIBIOTICS	PRIMARY MODE OF I	SEQUENCE OF RESP	NUMBER OF DAYS O	NUMBER OF DAYS A	OUTCOME
2	Lower middle	F	38	Lscs	2.8	1	Inborn	07-02-2021	07-02-2021	Mild	1	NORMAL SALINE	Negative	Nil	Hood o2	Hood-NIP-RA	2	3	No ventilator
3	Lower middle	M	38	Lscs	2.7	1	Inborn	06-04-2021	12-04-2021	Mild	2	NORMAL SALINE	Negative	given	Hood o2	Hood-RA	3	3	No ventilator
4	Lower middle	M	38	Lscs	2.9	1	Inborn	15-04-2021	23-04-2021	Mild	1	NORMAL SALINE	Negative	given	Hood o2	Hood-Hfnc-Hood-RA	5	6	No ventilator
5	Lower middle	F	39	Lscs	3.2	1	Inborn	23-04-2021	29-04-2021	Mild	2	NORMAL SALINE	Positive	given	Hood o2	Hood-Hfnc-Hood-RA	5	7	No ventilator
6	Lower middle	F	40	Nvd	2.9	1	Inborn	12-05-2021	17-05-2021	Mild	2	NORMAL SALINE	Positive	given	Hood o2	Hood-RA	4	4	No ventilator
7	Lower middle	M	40	Lscs	2.6	1	Inborn	16-05-2021	22-05-2021	Moderate	1	NORMAL SALINE	Positive	given	Hood o2	Hood-NIP-RA	4	5	No ventilator
8	Lower middle	F	37	Lscs	2.5	1	Inborn	16-05-2021	22-05-2021	Moderate	2	NORMAL SALINE	Positive	given	Hood o2	Hood-NIP-RA	5	5	No ventilator
9	Lower middle	M	40	Lscs	3.2	1	Inborn	30-05-2021	07-06-2021	Moderate	2	NORMAL SALINE	Positive	given	Hood o2	Hood-Hfnc-Hood-RA	7	7	No ventilator
10	Lower middle	F	39	Lscs	2.3	1	Inborn	08-06-2021	14-06-2021	Mild	2	NORMAL SALINE	Negative	given	Hood o2	Hood-Hfnc-Hood-RA	4	4	No ventilator
11	Lower middle	F	38	Nvd	2.5	1	Inborn	21-10-2021	24-10-2021	Mild	1	NORMAL SALINE	Positive	given	Hood o2	Hood-NIP-RA	2	3	No ventilator
12	Lower middle	M	38	Lscs	2.8	1	Inborn	30-10-2021	03-11-2021	Mild	2	BUDESONIDE	Negative	Nil	Hood o2	Hood-NIP-RA	3	4	No ventilator
13	Lower middle	F	39	Lscs	2.8	1	Inborn	31-10-2021	06-11-2021	Mild	2	BUDESONIDE	Negative	Nil	Hood o2	Hood-NIP-RA	3	4	No ventilator
14	Lower middle	M	39	Lscs	2.9	1	Inborn	01-11-2021	04-11-2021	Mild	2	BUDESONIDE	Negative	Nil	Hood o2	Hood-NIP-RA	2	2	No ventilator
15	Lower	M	38	Lscs	2.6	1	Inborn	02-11-2021	06-11-2021	Mild	2	BUDESONIDE	Negative	Nil	Hood o2	Hood-NIP-RA	4	4	No ventilator
16	Lower middle	F	40	Lscs	2.8	1	Inborn	03-11-2021	09-11-2021	Mild	2	BUDESONIDE	Negative	Nil	Hfnc	Hfnc-Hood-NIP-RA	6	6	No ventilator
17	Lower middle	M	39	Lscs	3	1	Inborn	04-11-2021	09-11-2021	Mild	2	BUDESONIDE	Negative	Nil	Hfnc	Hfnc-Hood-NIP-RA	4	5	No ventilator
18	Lower middle	M	38	Lscs	3	1	Inborn	09-11-2021	12-11-2021	Mild	1	BUDESONIDE	Negative	Nil	Hood o2	Hood-NIP-RA	2	3	No ventilator
19	Lower middle	M	38	Lscs	2.7	1	Inborn	09-11-2021	17-11-2021	Mild	1	BUDESONIDE	Positive	given	Hood o2	Hood-NIP-RA	6	7	No ventilator
20	Lower middle	F	40	Lscs	2.4	2	Inborn	11-11-2021	15-11-2021	Mild	2	BUDESONIDE	Positive	Nil	Hood o2	Hood-NIP-RA	3	4	No ventilator
21	Lower middle	F	38	Lscs	3	1	Inborn	13-11-2021	17-11-2021	Mild	2	BUDESONIDE	Positive	given	Hfnc	Hfnc-Hood-NIP-RA	4	5	No ventilator
22	Lower middle	M	37	Nvd	3	1	Inborn	16-11-2021	20-11-2021	Mild	2	NORMAL SALINE	Positive	given	Hood o2	Hood-NIP-RA	6	7	No ventilator
23	Lower	M	37	Nvd	2.6	1	Outborn	16-11-2021	20-11-2021	Mild	2	NORMAL SALINE	Positive	given	Hood o2	Hood-NIP-RA	5	7	No ventilator
24	Lower middle	F	39	Lscs	3.2	1	Outborn	21-11-2021	25-11-2021	Mild	2	NORMAL SALINE	Positive	given	Hood o2	Hood-NIP-RA	3	4	No ventilator
25	Lower middle	F	37	Lscs	1.9	1	Inborn	29-11-2021	03-12-2021	Mild	1	NORMAL SALINE	Negative	given	Hood o2	Hood-NIP-RA	3	4	No ventilator
26	Lower middle	M	37	Lscs	2.2	1	Inborn	29-11-2021	03-12-2021	Mild	1	NORMAL SALINE	Negative	given	Hfnc	HFNC-NIP- RA	3	4	No ventilator
27	Lower	F	39	Nvd	2.7	1	Inborn	02-12-2021	06-12-2021	Moderate	3	NORMAL SALINE	Positive	given	Hfnc	Hfnc-Hood-NIP-RA	4	5	No ventilator
28	Lower	M	37	Lscs	3.1	1	Inborn	06-12-2021	10-12-2021	Mild	2	NORMAL SALINE	Positive	given	Hood o2	Hood-NIP-RA	3	4	No ventilator
29	Lower	M	39	Nvd	2.9	1	Inborn	10-12-2021	17-12-2021	Moderate	2	NORMAL SALINE	Positive	given	Hood o2	Hood-Hfnc-Hood-RA	5	5	No ventilator
30	Lower	M	39	Lscs	2.9	1	Inborn	11-12-2021	18-12-2021	Moderate	2	NORMAL SALINE	Positive	Nil	Hfnc	Hfnc-Hood-NIP-RA	6	7	No ventilator
31	Lower middle	M	39	Nvd	3	1	Inborn	12-12-2021	18-12-2021	Moderate	3	NORMAL SALINE	Positive	given	Hfnc	Hfnc-Hood-NIP-RA	6	7	No ventilator
32	Upper middle	M	39	Lscs	2.8	1	Outborn	17-12-2021	23-12-2021	Moderate	3	BUDESONIDE	Positive	given	Hfnc	Hfnc-Hood-NIP-RA	5	6	No ventilator
33	Lower middle	F	39	Lscs	2.8	1	Outborn	20-12-2021	25-12-2021	Mild	2	BUDESONIDE	Positive	given	Hood o2	Hood-NIP-RA	5	5	No ventilator
34	Lower	M	40	Lscs	3.4	1	Inborn	24-12-2021	28-12-2021	Mild	2	BUDESONIDE	Negative	Nil	Hfnc	Hfnc-Hood-NIP-RA	4	5	No ventilator
35	Lower middle	M	41	Lscs	2	1	Inborn	05-01-2022	09-01-2022	Mild	3	BUDESONIDE	Negative	given	Hfnc	Hfnc-Hood-NIP-RA	4	5	No ventilator
36	Upper middle	M	39	Lscs	3.1	1	Inborn	11-01-2022	16-01-2022	Mild	1	BUDESONIDE	Negative	given	Hood o2	Hood-NIP-RA	3	4	No ventilator
37	Lower	M	37	Nvd	2.9	1	Inborn	14-01-2022	20-01-2022	Mild	2	BUDESONIDE	Positive	given	Hood o2	Hood-NIP-RA	3	5	No ventilator
38	Lower middle	M	39	Lscs	2.6	1	Inborn	20-01-2022	27-01-2022	Moderate	3	BUDESONIDE	Positive	given	Hfnc	Hfnc-Hood-NIP-RA	5	6	No ventilator
39	Upper lower	F	39	Lscs	2.9	1	Outborn	20-01-2022	24-01-2022	Mild	1	BUDESONIDE	Positive	given	Hood o2	Hood-NIP-RA	2	5	No ventilator
40	Lower middle	F	38	Lscs	1.8	1	Inborn	23-01-2022	27-01-2022	Mild	1	BUDESONIDE	Positive	given	Hood o2	Hood-NIP-RA	4	5	No ventilator
41	Lower	F	39	Lscs	1.8	1	Outborn	23-01-2022	27-01-2022	Mild	1	BUDESONIDE	Positive	given	Hood o2	Hood-NIP-RA	3	4	No ventilator
42	Lower middle	F	38	Lscs	2.9	1	Inborn	24-01-2022	01-02-2022	Moderate	3	NORMAL SALINE	Positive	given	Hfnc	Hfnc-Hood-NIP-RA	6	7	No ventilator
43	Lower middle	M	39	Lscs	2.7	1	Inborn	25-01-2022	02-02-2022	Mild	2	NORMAL SALINE	Positive	given	Hood o2	Hood-Hfnc-hood- NIP-	9	10	No ventilator
44	Lower middle	M	40	Lscs	2.5	1	Inborn	28-01-2022	09-02-2022	Moderate	2	NORMAL SALINE	Positive	given	Hfnc	Hfnc-Hood-NIP-RA	10	12	No ventilator
45	Lower middle	M	39	Lscs	3.8	1	Inborn	29-01-2022	09-02-2022	Moderate	3	NORMAL SALINE	Positive	given	Hood o2	Hood-Ventilator-Hfnc-I	10	11	NEEDED VENTILATO
46	Lower	F	39	Lscs	2.8	1	Outborn	30-01-2022	03-02-2022	Mild	2	NORMAL SALINE	Negative	Nil	Hfnc	Hfnc-Hood-NIP-RA	4	4	No ventilator
47	Lower middle	M	38	Lscs	2.9	1	Inborn	02-02-2022	06-02-2022	Mild	2	NORMAL SALINE	Negative	given	Hood o2	Hood-NIP-RA	3	5	No ventilator
48	Lower middle	M	38	Lscs	2.4	1	Inborn	03-02-2022	09-02-2022	Moderate	2	NORMAL SALINE	Positive	given	Hood o2	Hood-NIP-RA	5	6	No ventilator

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
	SOCIO ECONOMIC ST	GENDER	GESTATIONAL AGE	MODE OF DELIVERY	BIRTH WEIGHT	NICU ADMISSION (H	INBORN/OUTBORN	DATE OF ADMISSION	DATE OF DISCHARGI	TYPE OF MAS	DOWNE'S SCORE AT	INTERVENTION	CPP	ANTIBIOTICS	PRIMARY MODE OF I	SEQUENCE OF RESP	NUMBER OF DAYS O	NUMBER OF DAYS A	OUTCOME
2	Lower middle	F	39	Lscs	3.2	1	Inborn	07-02-2022	10-02-2022	Mild	1	NORMAL SALINE	Negative	Nil	Hood o2	Hood-NP-RA	2	4	No ventilator
3	Lower middle	M	40	Lscs	3.5	1	Inborn	07-02-2022	16-02-2022	Mild	2	NORMAL SALINE	Positive	given	Hinc	Hinc-Hood-NP-RA	6	8	No ventilator
	Lower middle	F	38	Lscs	3.3	1	Inborn	13-02-2022	18-02-2022	Mild	2	NORMAL SALINE	Negative	given	Hood o2	Hood-NP-RA	5	6	No ventilator
2	Lower middle	M	40	Lscs	2.6	1	Inborn	15-02-2022	20-02-2022	Mild	2	BUDESONIDE	Negative	given	Hood o2	Hood-RA	2	2	No ventilator
3	Lower middle	F	37	Lscs	1.5	1	Inborn	05-03-2022	11-03-2022	Moderate	2	BUDESONIDE	Negative	Nil	Hinc	Hinc- Hood-NP-RA	5	6	No ventilator
4	Lower middle	M	38	Nvd	3	1	Inborn	07-03-2022	12-03-2022	Mild	2	BUDESONIDE	Negative	given	Hinc	Hinc- Hood-NP-RA	4	5	No ventilator
5	Lower	F	38	Lscs	2.6	1	Inborn	13-03-2022	17-03-2022	Mild	1	BUDESONIDE	Positive	given	Hood o2	Hood-NP-RA	3	4	No ventilator
6	Lower middle	F	39	Nvd	2.7	1	Inborn	29-03-2022	31-03-2022	Mild	1	BUDESONIDE	Negative	Nil	Hood o2	Hood-NP-RA	2	2	No ventilator
7	Lower middle	M	39	Lscs	2.5	1	Inborn	01-04-2022	04-04-2022	Mild	1	BUDESONIDE	Positive	given	Hinc	Hinc- Hood-NP-RA	5	6	No ventilator
8	Lower middle	F	37	Nvd	3.2	1	Inborn	03-04-2022	11-04-2022	Mild	2	BUDESONIDE	Positive	given	Hinc	Hinc - Hood -NP - RA	5	6	No ventilator
9	Lower middle	M	39	Nvd	2.6	1	Inborn	05-04-2022	11-04-2022	Moderate	2	BUDESONIDE	Positive	given	Hinc	Hinc- Hood-NP-RA	5	6	No ventilator
10	Lower middle	M	40	Nvd	2.7	1	Inborn	06-04-2022	08-04-2022	Mild	1	BUDESONIDE	Negative	given	Hood O2	Hood -NP - RA	2	2	No ventilator
	Lower middle	M	38	Lscs	3.3	1	Inborn	09-04-2022	15-04-2022	Moderate	2	BUDESONIDE	Negative	Nil	Hood o2	Hood-NP-RA	5	5	No ventilator
2	Lower middle	F	39	Lscs	2.8	1	Inborn	14-04-2022	18-04-2022	Moderate	2	NORMAL SALINE	Negative	given	Hood o2	Hood-NP-RA	4	5	No ventilator
3	Lower middle	M	39	Nvd	3	1	Inborn	15-04-2022	17-04-2022	Mild	2	NORMAL SALINE	Positive	given	Hood o2	Hood-NP-RA	2	2	No ventilator
4	Lower	F	38	Lscs	2.2	1	Inborn	16-04-2022	24-04-2022	Moderate	2	NORMAL SALINE	Positive	given	Hinc	Hinc-Hood-NP-RA	6	7	No ventilator
5	Lower middle	M	40	Lscs	3	1	Inborn	19-04-2022	26-04-2022	Moderate	2	NORMAL SALINE	Positive	given	Hood o2	Hood -NP-RA	6	7	No ventilator
6	Lower middle	M	39	Lscs	2.8	1	Inborn	25-04-2022	29-04-2022	Moderate	2	NORMAL SALINE	Negative	given	Hood o2	Hood-NP-RA	3	4	No ventilator
7	Lower	M	38	Lscs	1.9	1	Inborn	25-04-2022	01-05-2022	Mild	2	NORMAL SALINE	Positive	given	Hinc	Hinc-Hood-NP-RA	6	7	No ventilator
8	Lower middle	M	39	Lscs	3.1	1	Inborn	26-04-2022	03-05-2022	Moderate	2	NORMAL SALINE	Negative	given	Hood o2	Hood-Ventilator-Hinc-I	10	13	NEEDED VENTILATOR
9	Lower middle	M	38	Lscs	4	1	Inborn	26-04-2022	03-05-2022	Moderate	2	NORMAL SALINE	Positive	given	Hood	Hood -NP-RA	7	8	No ventilator
10	Lower middle	M	39	Lscs	3	1	Inborn	26-04-2022	01-05-2022	Moderate	2	NORMAL SALINE	Negative	Nil	Hood o2	Hood -NP-RA	4	5	No ventilator
	Lower middle	F	40	Nvd	2.6	1	Inborn	27-04-2022	03-05-2022	Moderate	2	NORMAL SALINE	Positive	given	Hood	Hood-HFNC-Hood-NI	6	7	No ventilator
2	Lower middle	M	38	Lscs	2.6	1	Inborn	28-04-2022	03-05-2022	Moderate	2	BUDESONIDE	Negative	Nil	Hinc	Hinc- Hood-NP-RA	5	6	No ventilator
3	Lower middle	M	39	Lscs	2.5	1	Inborn	28-04-2022	05-05-2022	Moderate	2	BUDESONIDE	Negative	given	Hinc	Hinc-Hood-NP-RA	7	8	No ventilator
4	Lower medical	M	38	Nvd	3.9	1	Inborn	29-04-2022	03-05-2022	Mild	2	BUDESONIDE	Negative	Nil	Hinc	Hinc- Hood-NP-RA	3	4	No ventilator
5	Lower middle	F	39	Lscs	2	1	Inborn	29-04-2022	06-05-2022	Mild	1	BUDESONIDE	Negative	Nil	Hood o2	Hood-NP-RA	3	4	No ventilator
6	Lower	Male	40	Lscs	3.8	1	Inborn	01-05-2022	09-05-2022	Moderate	1	BUDESONIDE	Negative	given	Hood O2	Hood -NP - RA	7	8	No ventilator
7	Lower	F	38	Nvd	2	1	Inborn	03-05-2022	10-05-2022	Moderate	2	BUDESONIDE	Negative	given	Hood O2	Hood -NP - RA	6	7	No ventilator
8	Lower middle	F	39	Lscs	2.8	1	Inborn	05-05-2022	10-05-2022	Moderate	2	BUDESONIDE	Negative	given	Hood o2	Hood-NP-RA	4	5	No ventilator
9	Lower middle	M	38	Lscs	2.2	1	Inborn	06-05-2022	12-05-2022	Moderate	2	BUDESONIDE	Negative	given	Hood O2	Hood - NP - RA	5	6	No ventilator
10	Lower	F	38	Nvd	3	1	Inborn	06-05-2022	08-05-2022	Mild	1	BUDESONIDE	Negative	given	Hood O2	Hood -NP - RA	2	2	No ventilator
	Lower middle	F	39	Lscs	3.2	1	Inborn	07-05-2022	13-05-2022	Moderate	2	BUDESONIDE	Positive	given	Hood o2	Hood- NP- RA	5	6	No ventilator
2	Lower middle	M	39	Lscs	3	1	Inborn	07-05-2022	16-05-2022	Moderate	2	NORMAL SALINE	Negative	Nil	Hinc	Hinc - hood - NP - RA	7	8	No ventilator
3	Upper lower	F	39	Nvd	2.5	1	Inborn	08-05-2022	12-05-2022	Mild	1	NORMAL SALINE	Negative	given	Hood o2	Hood- NP- RA	4	5	No ventilator
4	Lower middle	M	40	Lscs	2.1	1	Inborn	11-05-2022	16-05-2022	Mild	1	NORMAL SALINE	Positive	Nil	Hood o2	Hood-NP-RA	4	4	No ventilator
5	Upper class	F	37	Lscs	2.2	1	Inborn	12-05-2022	17-05-2022	Mild	1	NORMAL SALINE	Negative	given	Hood o2	Hood- NP- RA	4	4	No ventilator
6	Lower middle	F	38	Lscs	2.5	1	Inborn	13-05-2022	20-05-2022	Moderate	2	NORMAL SALINE	Positive	given	Hood o2	Hood-Hinc- NP- RA	5	5	No ventilator
7	Upper middle	M	37	Lscs	2.8	1	Inborn	14-05-2022	20-05-2022	Moderate	2	NORMAL SALINE	Negative	given	Hood o2	Hood-NP-RA	5	6	No ventilator
8	Lower	F	40	Lscs	2.2	1	Outborn	14-05-2022	22-05-2022	Moderate	2	NORMAL SALINE	Positive	given	Hinc	Hinc-hood- NP- RA	7	8	No ventilator
9	Lower	M	38	Nvd	2	1	Inborn	19-05-2022	27-05-2022	Moderate	2	NORMAL SALINE	Positive	given	Hood o2	Hood-Hinc-Hood-RA	8	9	No ventilator
10	Lower	F	38	Lscs	3.4	1	Inborn	19-05-2022	24-05-2022	Mild	1	NORMAL SALINE	Negative	given	Hood o2	Hood-NP-RA	5	6	No ventilator
	Upper middle	M	39	Nvd	2.6	1	Outborn	23-05-2022	05-06-2022	Moderate	2	NORMAL SALINE	Negative	given	Hinc	Hinc-ventilator -hinc-h	12	13	NEEDED VENTILATOR
2	Lower middle	M	39	Nvd	3.2	1	Inborn	25-05-2022	30-05-2022	Moderate	2	BUDESONIDE	Negative	given	Hood O2	Hood -NP - RA	4	5	No ventilator
3	Lower	F	39	Lscs	2.2	1	Inborn	01-06-2022	10-06-2022	Moderate	2	BUDESONIDE	Positive	given	Hinc	Hinc - hood- NP- RA	7	8	No ventilator
4	Lower middle	F	38	Nvd	3.2	1	Inborn	06-06-2022	09-06-2022	Mild	1	BUDESONIDE	Positive	given	Hood o2	Hood-NP-RA	2	2	No ventilator
5	Lower	M	38	Lscs	2.8	1	Inborn	11-06-2022	18-06-2022	Moderate	2	BUDESONIDE	Positive	given	Hinc	Hinc- Hood-NP-RA	6	7	No ventilator
6	Lower	M	37	Lscs	2.5	1	Inborn	13-06-2022	18-06-2022	Moderate	2	BUDESONIDE	Positive	given	Hood o2	Hood-NP-RA	4	5	No ventilator
7	Lower	M	37	Lscs	2.5	1	Inborn	17-06-2022	22-06-2022	Moderate	2	BUDESONIDE	Positive	given	Hinc	Hinc - hood- NP-RA	4	5	No ventilator
8	Lower middle	M	37	Lscs	2.1	1	Inborn	17-06-2022	21-06-2022	Moderate	2	BUDESONIDE	Positive	Nil	Hinc	Hinc-Hood-NP-RA	3	4	No ventilator
9	Upper middle	F	39	Lscs	2.4	1	Inborn	17-06-2022	20-06-2022	Mild	1	BUDESONIDE	Positive	given	Hood o2	Hood-NP-RA	2	3	No ventilator
10	Lower middle	F	39	Lscs	2	1	Inborn	18-06-2022	24-06-2022	Moderate	2	BUDESONIDE	Positive	given	Hood o2	Hood-NP-RA	5	6	No ventilator
	Lower	F	40	Lscs	1.8	1	Inborn	24-06-2022	29-06-2022	Moderate	2	BUDESONIDE	Negative	Nil	Hood o2	Hood -NP-RA	4	5	No ventilator
2	Lower middle	M	39	Lscs	2.2	1	Inborn	24-06-2022	28-06-2022	Moderate	2	NORMAL SALINE	Negative	Nil	Hood o2	Hood-NP-RA	3	4	No ventilator
3	Lower middle	F	37	Nvd	2.4	1	Inborn	25-06-2022	01-07-2022	Moderate	2	NORMAL SALINE	Positive	given	Hinc	Hinc-Hood-NP-RA	5	6	No ventilator
4	Lower middle	M	38	Lscs	2.7	1	Inborn	27-06-2022	03-07-2022	Moderate	2	NORMAL SALINE	Positive	given	Hood o2	Hood-Hinc-NP-RA	5	6	No ventilator
5	Lower middle	F	38	Lscs	2.9	1	Inborn	30-06-2022	09-07-2022	Moderate	2	NORMAL SALINE	Positive	given	Hinc	Hinc-Hood-NP-RA	7	8	No ventilator
6	Lower middle	M	39	Lscs	3	1	Inborn	06-07-2022	14-09-2022	Moderate	2	BUDESONIDE	Positive	Nil	Hinc	Hinc-Hood-NP-RA	7	8	No ventilator
7	Lower middle	M	39	Lscs	2.5	1	Inborn	06-07-2022	10-07-2022	Moderate	2	BUDESONIDE	Negative	Nil	Hinc	Hinc-Hood-NP-RA	3	4	No ventilator
8	Lower middle	M	39	Lscs	2.8	1	Inborn	06-07-2022	13-07-2022	Moderate	2	BUDESONIDE	Negative	Nil	Hinc	Hinc-Hood-NP-RA	6	7	No ventilator
9	Lower middle	M	38	Lscs	2.5	1	Inborn	08-07-2022	15-07-2022	Moderate	2	BUDESONIDE	Negative	Nil	Hood o2	Hood-NP-RA	3	4	No ventilator
	Lower middle	M	39	Lscs	2.4	2	Outborn	09-07-2022	11-07-2022	Mild	2	BUDESONIDE	Negative	Nil	Hood o2	Hood-NP-RA	2	2	No ventilator