fortune Journals

JOURNAL OF PEDIATRICS, PERINATOLOGY AND CHILD HEALTH

ISSN: 2641-7405

Research Article

Surfactant Therapy's Impact on Meconium Aspiration Syndrome in Resource-Limited Settings: A Focus on India

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Abstract

Purpose: Meconium aspiration syndrome (MAS) is concerning for term infants, with surfactant therapy as an adjunct. However, its efficacy is varied, especially in resource-limited areas. This study addresses surfactant's impact on MAS mortality and morbidity rates in low-middle-income settings, aiming to optimize resource allocation and cost-effectiveness amidst challenges like expensive treatment and limited access to advanced interventions like ECMO and iNO therapy in India.

Methods: This hospital-based observational study examined surfactant bolus effects in the Neonatal Intensive Care Unit (NICU) at King George Hospital, Visakhapatnam, from January 2020 to July 2021. It involved 64 neonates divided into 32 cases and 32 controls. Control neonates were chosen from prior patients treated following established guidelines, including empirical antibiotics administration between January 2019 and December 2019.

Results: The mean duration of surfactant administration since birth is 13.67 hrs. (Range: 4.6 to 23), yielding reduction in oxygenation index (P=0.008) and pao2/pAo2 (P=0.005) at 24 hours Mortality rate: surfactant group 9.38% (3/32), standard care 15.63% (5/32), not statistically significant (P=0.449). Surfactant group showcased a remarkable 4.8-day reduction in hospital stay duration (P=0.0001). Similarly, surfactant-treated neonates demonstrated shorter mechanical ventilation by 3.3 days (P=0.0004), and oxygen therapy duration reduced by 1.7 days (P = 0.001).

Conclusion: Our study indicates that adjunctive surfactant administration can alleviate financial strain by notably shortening hospital stays, mechanical ventilation, and oxygen therapy in resource-limited settings. This suggests potential benefits for government policies in terms of cost reduction and healthcare burden. These findings also offer insights for future research, particularly regarding optimal timing of surfactant intervention in the context of Meconium Aspiration Syndrome (MAS).

Keywords: MAS; Surfactant; India; Healthcare policies; Observational

Introduction

Meconium aspiration syndrome (MAS) refers to respiratory distress in newborns delivered through meconium-stained amniotic fluid (MSAF) when no alternative explanations account for their symptoms [1]. MAS exhibit a spectrum of severity, ranging from mild respiratory distress to critical respiratory failure. Thick meconium can be inhaled during birth, causing respiratory distress. If meconium isn't cleared, it can block airways and cause

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Citation: Pratheek Choppala, Sai Sanjana Jalagadugula, Vivek Peddakota, Harikrishna Enapothula, Yashwanth Katlagunta, Siddharth Sai, Swamy Naidu. Surfactant Therapy's Impact on Meconium Aspiration Syndrome in Resource-Limited Settings: A Focus on India. Journal of Pediatrics, Perinatology and Child Health, Perinatology and Child Health. 8 (2024): 10-14.

Received: January 09, 2024
Accepted: January 23, 2024
Published: February 05, 2024

Choppala P, et al., J Pediatr Perinatol Child Health 2024
DOI:10.26502/jppch.74050174

lung problems like hyperinflation and atelectasis. Chemical inflammation follows, with risk of complications like pneumothorax. Meconium proteins and fatty acids deactivate surfactant, causing atelectasis and lung problems. Reduced surfactant production worsens issues like poor compliance contributing to respiratory failure in MAS [2]. Exogenous surfactant administration is believed to enhance lung function and oxygenation in infants with severe MAS [3]. While the effectiveness of antibiotic therapy for infants with MAS remains unclear, broad-spectrum antibiotics like ampicillin and gentamicin/amikacin are often given as a precaution [3-5]. This practice arises due to challenges in differentiating MAS from serious bacterial infections (like early-onset sepsis or bacterial pneumonia) through symptoms alone. Symptomatic infants with meconium-stained amniotic fluid (MSAF) might indicate intrauterine stress, potentially related to intraamniotic infection [4]. Current research suggests considering bolus surfactant therapy on a case-by-case basis in nurseries with high MAS-related mortality rates or limited access to other respiratory interventions like HFV or NO. This study aims to assess the combined use of antibiotics and surfactant therapy versus antibiotics alone. It focuses on a resource-limited country, aiming to potentially reduce costs for economically disadvantaged individuals. To our knowledge, very few established studies on surfactant bolus administration for MAS have been conducted in our country, despite strong evidence from global studies endorsing its potential as a therapeutic intervention. This investigation took place in a resource-constrained setting where options like ECMO, iNO therapy, liquid ventilation assistance, and high-frequency ventilation were not widely accessible due to inadequate infrastructure. Acquiring biological surfactant proved challenging due to financial limitations within this population.

The mixed outcomes observed in various studies regarding the role of surfactant in relation to mortality, coupled with the limited number of research endeavors conducted in India, spurred our interest in this investigation. Therefore, our institution initiated a study comparing surfactant bolus infusion to standard therapy including empirical antibiotics among newborns with severe MAS.

Methods

The study's inclusion criteria encompass neonates with a gestational age surpassing 34 weeks, enrollment within the first 24 hours following birth, a confirmed diagnosis of Meconium Aspiration Syndrome (MAS) as per working definitions of the National Neonatal-Perinatal Database of India 2002-03, and a requirement for mechanical ventilation. Conversely, exclusion criteria involve neonates with congenital heart defects present at birth, severe congenital abnormalities, and instances of birth asphyxia (APGAR SCORE of 3 at 5 minutes or less).

In this study, a hospital observational approach was employed to investigate the effects of surfactant bolus administration in neonates with clinical indications of MAS. The study was conducted at the Neonatal Intensive Care Unit (NICU) of King George Hospital in Visakhapatnam, spanning from January 2020 to July 2021. The authors were not actively involved in the treating team decisions. A total of 64 neonates were included in the research, divided into two groups: 32 cases and 32 controls. The selection of cases was based on judgmental sampling, utilizing the average monthly admissions to the NICU. Control neonates were selected from a pool of previous patients treated in accordance with established guidelines which includes giving empirical antibiotics from January 2019 to December 2019.

Following the acquisition of informed written consent from the parent or guardian, pertinent data obtained from the medical history, physical examination, and investigation outcomes were meticulously documented using a predefined proforma which also includes maternal characteristics. The study conducted a comprehensive array of investigations. These included assessments such as complete blood counts, C-reactive protein (CRP) levels, blood cultures and sensitivity tests, chest X-rays, arterial blood gas analyses (ABG), and 2D echocardiography (2D ECHO)to detect the complications.

The fundamental care strategies for managing Meconium Aspiration Syndrome (MAS) remain consistent across both groups. These strategies encompass minimizing neonatal handling, providing a warm and comforting environment, closely observing color, crying, movement, and posture, as well as conducting blood tests to assess sepsis and glucose levels (GRBS). Initiation of antibiotics and vigilant monitoring of vital signs, including temperature, heart rate, respiration rate, spo2, blood pressure, and urine output, are fundamental aspects of care.

Regular assessments encompass evaluating respiratory severity using Downe's score, ABG, and chest X-ray (AP view), as well as continuous monitoring of glucose levels (GRBS).

Oxygen administration is initiated under specific criteria, such as respiratory distress, circulatory insufficiency, worsening Downe's score, spo2<92% at room air, and specific ABG parameters. Timely ABG measurements are crucial, performed on admission for all MAS cases, and subsequently repeated based on impending respiratory failure, clinical deterioration, or confirming ABG correction. Conducting echocardiography aids in ruling out congenital cardiac diseases and persistent pulmonary hypertension of the newborn (PPHN). Inotropes are introduced as necessary for circulatory insufficiency, hypotension, indications of PPHN, or oliguria. Gradual initiation of tube feeds, following stabilization of respiratory distress, ensures comprehensive care for infants in both groups.

Our ventilation approach focused on maintaining optimal oxygen (60-90mmHg) and carbon dioxide (35-40mmHg) levels. Strategies to prevent barotrauma and volutrauma were employed. The Oxygenation Index (OI = FIO2 * MAP * 100 / PaO2) defined severity, response, and intervention need (OI>15 indicates severe compromise). Arterial/Alveolar Oxygen Ratio (a/A ratio) was used to assess severity.

In the surfactant group, survanta was administered at a dosage of 100mg/kg. This formulation is mixed with 3 to 5 mL of saline per kilogram and is administered into the airway via an endotracheal tube using split aliquots in bolus fashion. The delivery of surfactant was carried out through endotracheal tube instillation, facilitated by a side hole adapter.

Outcomes

The primary outcomes involved investigating mortality benefits, along with evaluating the durations of hospital stay and mechanical ventilation. Additionally, the secondary objectives encompassed understanding how surfactant administration influenced the total duration of oxygen therapy and relevant ventilation indices, such as oxygenation index (OI) and pao2/pAo2 at the 24-hour mark. Alongside these aspects, the study also considered associated complications.

Statistical analysis and Ethics

The data were presented using various statistical measures depending on their distribution. Numbers, frequencies (%), mean with standard deviation (SD), or median with 1st and 3rd quartiles (interquartile range, Q1 - Q3) were used to represent the data. To compare outcomes, the chi-square test was employed for categorical data, while the student's t-test was utilized for continuous data. A significance level of P-value less than 0.05 was used in all statistical tests. The statistical analysis was performed using SPSS version 29.0.0.0. To mitigate potential data analysis bias, this study employed blinding of the data analyst to the groups and ensured their non-involvement in the data collection process. This study was conducted following ethical approval granted by Dr. N.T.R University of Health Sciences, Vijayawada, with registration number M190302006.

Results

Table 1 presents the selected demographic and baseline characteristics of the entire population. Notably, no differences were observed between the groups concerning factors such as gestational age, gender, mode of delivery, APGAR scores at birth, and respiratory distress indicators (Downes score) or ventilation indices (OI and pao2/pAo2) at admission.

Outcomes: Significant differences were observed between the two groups in terms of the duration of ventilation, oxygen therapy, and hospital stay. Out of a total of 8 deaths, one in each group resulted from hypoxic-ischemic encephalopathy, while all other deaths were attributed to hypoxic respiratory failure. The mortality rate in the surfactant group was 9.38% (3/32), compared to 15.63% (5/32) in the standard care group. However, this difference did not reach statistical significance.

The mean duration of surfactant administration was 13.67 (Range: 4.6 to 23), resulting in a notable reduction in oxygenation index and pao2/pAo2 at 24 hours. In the surfactant group, there was a notable reduction in the duration of hospital stay by 4.8 days. Similarly, neonates who received surfactant exhibited shorter periods of mechanical ventilation, as evidenced by a mean reduction of 3.3 days. Additionally, the total duration of oxygen therapy was decreased by 1.7 days in this group (Table 2).

Table 1: Baseline variables.

Parameters	Surfactant (n=32)	No surfactant (n=32)	P value
Male sex, n (%)	18 (56.25%)	21 (65.63%)	0.44
Gestational Age, Mean (Range)	39.68 (35-42)	39.34 (35-42)	0.38
Birth weight{kg}, Mean (Range)	2.90 (2.5 - 3.5)	2.88 (2.5 - 3.5)	0.8
Mode of delivery			
Vaginal	10 (31.25%)	22 (68.75%)	0.2
LSCS	15 (46.88%)	17 (53.13%)	
APGAR score, mean(S.D)			
1min	6.15 (0.36)	6.25 (0.43)	0.35
5 min	8.46 (0.50)	8.56 (0.50)	0.46
Downes score at admission, Mean(S.D)	8.57 (0.98)	8.59 (0.94)	0.69
Mean duration of surfactant administration since birth {Hrs}, (S.D)	13.67 (5.47)		
Oxygenation index at admission, Mean	13.94 (6.6)	15.71 (6.7)	0.296
pao2/pAo2 at Admission, Mean	0.13 (0.08)	0.11 (0.03)	0.1
S.D = Standard deviation , LSCS - Cesarean delivery			

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DOI:10.26502/jppch.74050174

Table 2: Outcomes

Outcome	Case	Control	P value
Mortality	3 (9.38%)	5 (15.63%)	0.449
Oxygenation index, At 24 hours	6.13 (5.4)	9.76 (5.1)	0.008
pao2/pAo2, Mean at 24 hours	0.29 (0.13)	0.20 (0.11)	0.005
Duration of Ventilation, Mean (S.D)	2.87 (1.25)	6.18 (4.35)	0.0001
Duration of o2 therapy, Mean (S.D)	3.0 (1.56)	4.71 (2.12)	0.0004
Duration of hospital stay, Mean (S.D)	6.56 (2.46)	11.3 (5.7)	0.001

Discussion

MAS is a serious newborn respiratory disorder for which there is a frustrating lack of specific therapy. Our study wants to emphasize the impact of surfactant in the disease outcome which could help in allocation of resources in a resource-limited setting. A Cochrane review focused on bolus surfactant administration reported findings from four trials involving 326 infants. The analysis showed no statistically significant impact on mortality (typical risk ratio 0.98, 95% CI 0.41 to 2.39; typical risk difference -0.00, 95% CI -0.05 to 0.05). One trial (n = 40) demonstrated a significant reduction in hospital stay duration (mean difference -8 days, 95% CI -14 to -3 days). However, no other statistically significant reductions were observed in other outcomes studied, such as assisted ventilation duration and supplemental oxygen duration [6].

Another systematic meta-analysis published in Nature encompassed six RCTs employing bolus surfactant. The analysis indicated that the use of surfactant as either Slow Lung Lavage (SLL) or bolus surfactant (BS) did not lead to a reduction in neonatal mortality among those with established MAS. However, both SLL and BS led to a reduction in hospital stay duration by 2 days and 4.7 days, respectively. Similarly, neonates who received surfactant through either SLL or BS demonstrated shorter mechanical ventilation periods. The duration of oxygen therapy, however, did not show statistically significant differences [3].

Our findings align with the systematic review, revealing no difference in mortality but notable distinctions in the duration of hospital stay, mechanical ventilation, and even oxygen therapy. Notably, our study stands out as we administered surfactant to neonates within 24 hours of birth, with a mean duration of administration of 13.67 hours. In contrast, previous trials often included moderately ill neonates and administered interventions at a later stage.

The early administration of surfactant in our study could account for the observed reduction in the duration of oxygen therapy. Unlike several previous studies that administered surfactant only in severe MAS after a minimum of 48 hours of oxygen therapy, we administered it promptly. This strategy may have contributed to the reduction in oxygen therapy duration.

The observed benefits in hospital stay and ventilation durations potentially translate to reduced neonatal care costs, particularly significant in resource limited settings. Nonetheless, these benefits need to be balanced against the often prohibitive cost of surfactant in neonatal units. The elevated cost consideration in MAS compared to respiratory distress syndrome (RDS), due to higher dosage requirements, should be carefully weighed before recommending surfactant replacement therapy (SRT) modes in MAS cases [3].

The importance of timing in surfactant administration was highlighted in a systematic meta review on respiratory distress syndrome but not in MAS, which demonstrated significant reductions in neonatal mortality (typical risk ratio (RR) 0.84; 95% confidence interval (CI) 0.74 to 0.95) [7]. While our study didn't uncover mortality benefits, delving further into the timing of surfactant therapy in meconium aspiration syndrome could provide valuable insights to expand our understanding.

In resource-constrained environments such as India, where alternative therapies may be unavailable, government initiatives could play a pivotal role in facilitating access to treatments like surfactant at reduced or even no cost for individuals facing financial constraints. This approach not only benefits the patients directly but also alleviates the burden on healthcare facilities. By ensuring that resources are effectively allocated, such measures can significantly enhance the overall healthcare landscape.

Our study has certain limitations that should be acknowledged. Firstly, it was conducted at a single center, which might impact the generalizability of the findings. The sample size was determined using judgmental sampling based on the available MAS cases during the specific year 2020-2021, a period affected by the influence of the COVID-19 pandemic. To mitigate bias the authors maintained a degree of separation from the active management of patients, aiming to minimize potential clinician bias. Additionally, the data analyst responsible for analysis was blinded to the groups, thereby reducing the potential for analysis bias.

Conclusion

In conclusion, our study suggests that the adjunctive administration of surfactant could alleviate the financial burden by significantly reducing the duration of hospital stay, mechanical ventilation, and oxygen therapy in a resource limited setting. So the government policies could provide surfactant which could be beneficial and also reduce the healthcare burden. These findings have implications for

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DOI:10.26502/jppch.74050174

potential cost savings. Moreover, our study provides valuable insights that could guide further research, particularly focusing on the timing of surfactant intervention in the context of Meconium Aspiration Syndrome (MAS).

Author contributions: Dr. Sanjana was instrumental in refining the study protocol, overseeing data entry, and enriching the discussion section. On the other hand, Dr. Pratheek took the lead in the data analysis and results segment. Dr. Pratheek also made substantial contributions to the writing process and played a pivotal role in the article's publication. Protocol development and Excel entry by Dr. Vivek, Dr. Hari Krishna, Dr. Yaswanth and Dr. Siddharth.

Competing interests: The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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