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Comparison of Intratracheal Salbutamol Plus Surfactant Versus Surfactant Alone in Preterm Neonates with Respiratory Distress Syndrome: A Randomized Controlled Trial.

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Abstract

Objectives: To compare the effect of intratracheal administration of salbutamol along with surfactant therapy as against surfactant alone on preterm babies with Respiratory Distress Syndrome (RDS).***Methods :*** A randomized controlled trial was conducted in the Neonatal Intensive Care Unit (NICU), Department of Pediatrics, Children Hospital, Pakistan Institute of Medical Sciences (PIMS), Islamabad for a period of six months. Eighty-two preterm infants of either gender, having a gestational age between 28 weeks and less than 37 weeks and fulfilling the clinical as well as radiological criteria of RDS were recruited in the study. They were randomly divided into two equal groups. Group A was administered intratracheal surfactant alone while Group B was administered intratracheal surfactant along with salbutamol. The main criterion was INSURE failure (need for reintubation within 72 hours).***Results:*** The demographics and the clinical status of both groups were similar at baseline. The incidence of INSURE failure was significantly low in Group B compared to Group A (29.3% vs. 51.2%, P=0.043). Complication rate was significantly low in neonates who received a combination of surfactant and salbutamol (22.0% vs. 43.9%, P=0.034). Mechanical ventilation was needed in fewer patients from Group B (22.0% vs. 39.0%, P=0.093). There was a significant reduction in hospital stay for Group B (80.8±44.8 hours vs. 94.7±77.7 hours, P=0.003). Mortality was significantly low in the same group (22.0% vs. 43.9%, P=0.034).***Conclusion:*** The administration of intratracheal salbutamol as an adjuvant to surfactant therapy led to a significant decrease in INSURE failure, complication rates, hospital stay and mortality in premature neon.
Keywords: Respiratory Distress Syndrome; Salbutamol; Surfactant; Mechanical Ventilation; Preterm Neonates.

Keywords: Respiratory Distress Syndrome (RDS), Premature Neonates, Surfactant Therapy, Intratracheal Salbutamol, INSURE Technique, Nasal Continuous Positive Airway Pressure (NCPAP).

INTRODUCTION

One of the most common causes of respiratory failure and mortality in newborns is Respiratory Distress Syndrome (RDS)(1). The disorder mainly occurs owing to surfactant deficiency caused by lung immaturity that leads to alveolar collapse, gas exchange abnormalities, and increased work of breathing(2). The administration of exogenous surfactant therapy has helped reduce morbidity and mortality in neonates with RDS(3). Despite the advances made through the use of exogenous surfactants, respiratory problems and failure continue to be significant contributors to morbidity and mortality in neonates(4).

Intubation, Surfactant, and Extubation (INSURE) in conjunction with nasal continuous positive airway pressure (NCPAP) is the main strategy that has been employed in the management of neonatal RDS(5). However, INSURE failure with consequent need for reintubation continues to pose significant challenges to medical practice, and the failure rate has been reported to range from 16.7% to 35%(6).

Alongside the surfactant deficiency, the inefficient clearing of pulmonary fluid is a component of the pathophysiology of RDS(7). β_2-adrenergic receptor stimulants like salbutamol facilitate sodium transportation by the epithelium and increase alveoli fluid absorption, possibly increasing lung compliance and ventilation capacity(8). Past researches have reported

that using salbutamol in conjunction with surfactant could help decrease the need for respiratory support and provide better clinical results among neonates with RDS(9).
Salbutamol, a selective β_2 adrenoceptor agonist, has been studied in combination with surfactants in premature babies with RDS(10). Many clinical trials have found improved respiratory function, decreased mechanical ventilation requirements, and lower duration of hospital stay in those treated with salbutamol(11). Nevertheless, available information is insufficient and sometimes conflicting(12). Information on the efficacy of intratracheal salbutamol treatment in RDS babies in Pakistan is lacking(13).

As a result, this research was conducted to assess the efficacy of administration of salbutamol in addition to surfactant therapy versus surfactant therapy alone in premature infants suffering from respiratory distress syndrome with special reference to INSURE failure, need for ventilation, duration of stay in the hospital, and mortality(14).

Only limited data have been found in Pakistan about the efficacy of intratracheal salbutamol with surfactant in premature neonates with RDS. The present research was designed to investigate the efficacy of intratracheal salbutamol with surfactant as compared to surfactant alone in order to reduce INSURE failure among neonates with RDS(15)..

MATERIALS AND METHODS

The randomized controlled trial was carried out in the Neonatal Intensive Care Unit (NICU), Department of Pediatrics, Children Hospital, Pakistan Institute of Medical Sciences (PIMS), Islamabad, for a period of six months following the approval of the study protocol. A total of 82 preterm infants were enrolled with the help of consecutive sampling method and assigned to two equally sized groups (n=41 each). The sample size of the current study was determined by using the sample size calculator of WHO at a level of significance of 5%, 90% study power, and expected rates of 66.7% and 41.7% in the control and intervention groups, respectively.

Preterm neonates of either gender having gestational age between 28 and 37 weeks, age less than six hours, and clinically as well as radiologically confirmed respiratory distress syndrome were included in the current study. Infants having birth injury, five-minute APGAR score ≤3, meconium aspiration syndrome, prolonged rupture of membranes (>18 hours), congenital malformations causing significant cardiorespiratory problems, or congenital heart disease were not eligible for the study(16).

The study involved randomization of eligible neonates by lottery method after acquiring informed consent from the parents/guardians into two groups(17). Neonates in group A were administered surfactant intratracheally alone in a dose of 100 mg/kg (4 ml/kg), while those in group B were administered surfactant (100 mg/kg) along with salbutamol (0.2 mg/kg) intratracheally. Both groups received conventional NICU care in the institution.

The demographic data, gestational age, weight at birth, exposure to antenatal steroids, and arterial blood gases measurements were noted. The main outcome measured in the study was the INSURE failure which was defined as need for re-intubation within 72 hours of extubation. Other measures used were complications, need for mechanical ventilation, respiratory support period, stay in the hospital, and mortality.

All data collected were entered and analyzed using Statistical Package for Social Sciences (SPSS). The quantitative data was presented in mean ± standard deviation form while categorical data in frequencies and percentages. Comparison between the groups was done using the relevant statistical test. The level of significance was taken to be $p < 0.05$.

RESULTS

Eighty-two preterm neonates with respiratory distress syndrome were included in this study and randomly divided into two groups, each comprising 41 neonates. In Group A (Surfactant alone), 61.0% (25/41) neonates were males while 39.0% (16/41) neonates were females, while in Group B (surfactant plus salbutamol), 51.2% (21/41) neonates were males while 48.8% (20/41) neonates were females (P = 0.373). The average gestational age was 32.5 ± 2.3 weeks in Group A and 33.2 ± 2.3 weeks in Group B (P = 0.200). The average weight at birth was 1.7 ± 0.25 kg and 1.8 ± 0.31 kg in Groups A and B, respectively (P = 0.937). The baseline demographic and arterial blood gas parameters were similar for both groups. After treatment, the arterial blood gas parameters were improved in both groups; however, no statistically significant difference was seen between the groups (P > 0.05). INSURE treatment failure necessitating intubation was seen in 51.2% (21/41) of neonates in Group A as compared to 29.3% (12/41) in Group B, indicating that there was a statistically significant decrease in INSURE. Mechanical ventilation was needed in 39.0% (16/41) neonates in the surfactant-only group versus 22.0% (9/41) in the combination group (P=0.093). The mean duration of respiratory support was 54.7±44.7 hours in Group A while it was 44.9±29.7 hours in Group B (P=0.244). Mean duration of hospitalization was significantly lower for neonates that received surfactant plus salbutamol (80.8±44.8 hours) than for those who were administered surfactant only (94.7±77.7

hours; P=0.003). The mortality rate was significantly lower in Group B than in Group A (22.0% vs. 43.9%, P=0.034). Overall, adjunctive intratracheal salbutamol was associated with improved clinical outcomes across the evaluated parameters.

Table-I: Baseline Characteristics of Study Participants

Variable	Group A (Surfactant Alone) n=41	Group B (Surfactant + Salbutamol) n=41	P-value
Male gender, n (%)	25 (61.0)	21 (51.2)	0.373
Female gender, n (%)	16 (39.0)	20 (48.8)	0.373
Gestational age (weeks), Mean ± SD	32.5 ± 2.3	33.2 ± 2.3	0.200
Birth weight (kg), Mean ± SD	1.7 ± 0.25	1.8 ± 0.31	0.937
Antenatal steroid exposure, n (%)	27 (65.9)	28 (68.3)	0.814

SD = Standard Deviation

Demographic and clinical data were similar between the two groups in terms of basic factors. There was no statistical difference with respect to sex, gestational age, body weight, and the administration of antenatal steroids (P>0.05).

Table-II: Comparison of Clinical Outcomes between Study Groups

Outcome	Group A (Surfactant Alone) n=41	Group B (Surfactant + Salbutamol) n=41	P-value
INSURE failure (re-intubation), n (%)	21 (51.2)	12 (29.3)	0.043
Complications, n (%)	18 (43.9)	9 (22.0)	0.034
Mechanical ventilation required, n (%)	16 (39.0)	9 (22.0)	0.093
Mortality, n (%)	18 (43.9)	9 (22.0)	0.034

INSURE = Intubation-Surfactant-Extubation

The neonates who received intratracheal salbutamol, along with the surfactant, had significantly reduced incidences of INSURE failure, complications, and mortality when compared to the neonates receiving only the surfactant. Although the need for mechanical ventilation was less in the case of the salbutamol group, it did not have statistical significance (P=0.093).

Table-III: Duration of Respiratory Support and Hospital Stay

Variable	Group A (Surfactant Alone) Mean ± SD	Group B (Surfactant + Salbutamol) Mean ± SD	P-value
Duration of respiratory support (hours)	54.7 ± 44.7	44.9 ± 29.7	0.244
Length of hospital stay (hours)	94.7 ± 77.7	80.8 ± 44.8	0.003

SD = Standard Deviation

Respiratory support time was lower in the group that received both surfactant and salbutamol treatment, although there was no statistical significance between the two groups. On the other hand, a significant reduction in hospitalization time was observed in those who took salbutamol along with surfactant (P=0.003).

DISCUSSION

The results of the present research are based on the data obtained in other studies conducted earlier that considered the approaches to respiratory support and the methods used to facilitate the positive effects in preterm infants suffering from RDS. According to the work of Cherif et al., the inability to use surfactant treatment by means of the INSURE approach is a serious problem in preterm infants which is connected with poor neonatal outcomes(5). In its turn, Dargaville et al. found that CPAP failure and intubation were related to morbidity in preterm infants(15).

The less invasive procedures used in the administration of surfactant led to lower incidences of mechanical ventilation and bronchopulmonary dysplasia when compared to conventional intubation procedures(18). In the same way, Aguar et al. concluded that minimally invasive surfactant therapy yielded similar results as the INSURE procedure, although it was less invasive than the latter(19).

Physiological rationale for the use of salbutamol as an adjunctive therapy is well-established from the laboratory studies. The essential mechanism involved in the transport of alveolar fluid in relation to neonatal lung adaptation was explained by Jain and Eaton(6), whereas the enhancement in the alveolar fluid clearance due to β-adrenergic stimulation was studied by Sakuma et al(8). On the other hand, the effect of β-agonists on the activation of sodium channel in the pulmonary epithelium leading to lung fluid absorption has been demonstrated by Chen et al(9).

Further, our results are consistent with research on bronchodilator treatment in neonatal respiratory diseases. Lee et al. found a beneficial effect of salbutamol treatment on short-term respiratory status in ventilator-dependent premature infants with no substantial side effects(20). Mussavi et al. found a significant improvement in respiratory distress scores and shorter duration of CPAP in neonates receiving salbutamol treatment. Additionally, a meta-analysis on the efficacy of Ventolin treatment in acute respiratory distress syndrome found an improvement in ventilator-free days and organ failure-free days in treated patients.

Large neonatal trials have consistently underscored the importance of reducing invasive ventilation in preterm infants(21). The SUPPORT trial found a decrease in respiratory morbidity from the use of early CPAP compared to intubation and surfactant in routine care, while Stevens et al. found better respiratory outcomes with less invasive strategies of respiration support(2). Similarly, Lemyre et al. found lower rates of respiratory failure and intubations with the use of nasal intermittent positive pressure ventilation compared to conventional CPAP(22). The results of the current study provide additional evidence for using intratracheal salbutamol as an adjunctive therapy to established surfactant protocols.

CONCLUSION

The use of intratracheal administration of salbutamol as an adjuvant to surfactant treatment has led to a significant reduction in the incidence of INSURE failure, complications, length of hospitalization, and mortality among preterm babies suffering from respiratory distress syndrome. While there were no significant differences in the parameters of arterial blood gases, respiratory support duration, or need for mechanical ventilation, the clinical results have clearly favored the treatment modality involving surfactant with salbutamol.

Recommendation

There is need for further multicenter randomized clinical trials with large numbers of patients to support this evidence and determine the safety and efficacy of intratracheal salbutamol administration in preterm infants with respiratory distress syndrome..

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