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Original Article

Comparison of Efficacy of Beractant and Poractant Treatment Performed with Minimal Invasive Technique

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ABSTRACT

Background: The literature review has demonstrated the short-term benefits of minimally invasive surfactant therapy (MIST) in spontaneously breathing preterm neonates. This study was conducted to compare the efficacy of beractant and poractant alfa treatments performed with the MIST method in newborns with respiratory distress syndrome (RDS) and its effect on preterm morbidity and mortality.

Methods: The patients diagnosed with RDS less than 35 weeks of gestational age and stabilized with nasal continuous positive airway pressure (nCPAP) in the delivery room were screened retrospectively. The cases were divided into two groups of beractant (BG) and poractant alfa (PG). While the BG (n=24) consisted of patients receiving beractant treatment with MIST during nCPAP, the PG (n=34) were those subjected to poractant alfa treatment.

Results: It was found out that in PG the scores of surfactant reflux to esophagus and desaturation during surfactant administration were significantly lower (P=0.012 and P=0.009, respectively). No significant difference was observed between the two groups regarding bronchopulmonary dysplasia, sepsis, patent ductus arteriosus, pneumothorax, intubation rate in postnatal 72 h, total period of intubation, nCPAP, duration of hospitalization, and mortality rate.

Conclusion: According to the results of this study, surfactant reflux to esophagus and desaturation during the intervention procedure were lower in the PG group, most probably due to a lower volume of poractant than beractant. However, since a small number of patients were included in this study, it is recommended to perform further studies consisting of a larger number of cases.

Keywords: Minimal invasive technique, Premature, Surfactant

Introduction

Respiratory distress syndrome (RDS) is one of the main causes of mortality in premature neonates with very low birth weight. The most important treatment stages of RDS consist of proper mechanical ventilation and surfactant administration. Since mechanical ventilation is known to have serious pulmonary side effects, noninvasive mechanical ventilation techniques are preferred currently (1-3).

Early nasal continuous positive airway pressure (nCPAP) and surfactant administration have been reported to reduce the incidence of bronchopulmonary dysplasia (BPD), need for mechanical ventilation, and air leakages (4). The INtubate, SURfactant, Extubate (INSURE) method, involving early nCPAP and surfactant administration, has been developed to combine the benefits of shorter duration of invasive ventilation and early surfactant treatment (5, 6). However, the INSURE technique requires intubation of the patient to deliver surfactant and positive pressure ventilation even for a short time. On the other hand, even short-term intubation has been reported to cause pulmonary damage (7).

Recently, attention has been directed to the minimally invasive surfactant therapy (MIST) method, which is performed on spontaneously breathing newborns and followed-up of nCPAP

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treatment. This technique has been introduced by Kribs et al. in Germany (8). The Literature review revealed that only limited studies have been devoted to examine the effectiveness and advantage of MIST method compared to the standard application (9-14). This study was conducted to evaluate premature newborns conditions receiving beractant and poractant alfa and to compare the efficacy and practicability of the MIST method.

Methods

The current study was carried out on premature newborns less than 35 weeks gestational age administered surfactant with the nasogastric tube under nCPAP without intubation within January 2014-December 2015. This retrospective study was conducted in the Neonatology Clinic of Zeynep Kamil Maternity and Children's Diseases Training and Research Hospital, Istanbul, Turkey. The necessary data regarding the patients' demographic information and clinical and laboratory data were obtained from the patients' documents. The patients intubated in the delivery room, having congenital anomalies, and diagnosed with asphyxia and hydrops fetalis were excluded from the study.

In the aforementioned neonatology clinic, newborns are stabilized in the delivery room, followed by being transported to the neonatal intensive care unit, under nCPAP with positive end-expiratory pressure of 6 cm H_2O and monitored through pulse oximetry. Short binasal prongs are applied during nCPAP treatment. Surfactant therapy is performed on patients with typical clinical and radiological findings of RDS, and oxygen saturation was required to maintain within 90-95% if the fraction of inspired oxygen (FiO_2) is higher than 0.35.

Patients receiving surfactant with 5 or 6 F nasogastric tube under CPAP without intubation were divided into two groups of beractant and poractant (i.e., BG and PG). The initial dose of surfactant therapy was administered as 100 mg/kg/dose of beractant (Survanta®, Abbott, United States) or 200 mg/kg/dose of poractant alfa (Curosurf®, Chiesi Farmaceutici, Parma, Italy). The decision for the administration of the second and third surfactant therapies was based on the existing protocols of the clinic. The doses were repeated in 100 mg/kg both in beractant and poractant groups. However, it was applied through the endotracheal tube if the newborn required intubation before the repetition of the dose. The criteria for intubation within the first 72 h of life included more than 3 apnea episodes per hour or apnea episode requiring more than one positive ventilation within 6 h and pH < 7.20, PCO_2 > 60 mmHg in blood gas, and the need for FiO_2 > 0.50 to keep oxygen saturation within 90-95%.

The surfactant administration process was carried out by at least two physicians (i.e., an attendant neonatologist or neonatology fellow and a nurse). While one of the physicians inserted the catheter and managed the operation, the other one administered surfactant, provided oxygen support, and observed the patient. After surfactant was brought to room temperature, the calculated amount of it was drawn up into the syringe under sterile conditions. The tip of a 5 or 6 F feeding tube was inserted 1 cm beyond the vocal cords with direct visualization and the help of a direct laryngoscopy without the interruption of nCPAP ventilation. Afterward, the orogastric tube was inserted and fixed. The use of forceps was not needed to direct the feeding tube toward the trachea; therefore, it was fixed with hands.

During this process, the laryngoscope and blade were not withdrawn in order to monitor whether there was surfactant reflux or tube displacement. Surfactant was delivered by the physician holding surfactant syringe with a slow push in 1-2 min at one time, while the patient was in the supine position. After surfactant administration, the catheter and subsequently laryngoscope and blade were retracted. Aspiration was made through the orogastric tube inserted in the stomach to detect the existence of surfactant in the stomach and determine the amount (if any) of it.

The patients were observed for the incidence of desaturation, bradycardia, respiratory arrest, cough, bronchospasm, surfactant reflux from the trachea, and vomiting. An oxygen saturation value of 10% less than the previous level was defined as desaturation. The surfactant administration was repeated twice or thrice in case that the procedure failed on the first attempt. If the number of attempts for surfactant administration with catheter exceeded three times, the procedure was considered a failure. In this regard, the surfactant delivery was carried out with an endotracheal tube. Chest X-ray was ordered 2-4 h after surfactant administration. Blood gas and ventilation values were recorded at the baseline and the 2nd and 6th h following the procedure.

This retrospective study was approved by the Institutional Review Board of Zeynep Kamil Maternity and Children's Diseases Training and Research Hospital, and strictly followed the

institution's ethical guidelines. The collected data were analyzed in SPSS software (version 16) using descriptive statistics. Fisher's exact test or Chi-square test was used for categorical variables. A p-value of less than 0.05 was considered significant.

Results

A total of 58 premature neonates, who clinically and radiologically needed surfactant therapy, were included in the study. The subjects were divided into two groups of poractant alfa (n=34) and beractant (n=24). The patients and their parents' demographic information were similar in both groups (Table 1). The scores of bradycardia and reflux during surfactant administration were significantly higher in the beractant group (P=0.009 and P=0.012, respectively). The need for the second administration of surfactant was found in 17.6% of the cases in the PG, while none of the patients in BG required the second dose. Moreover, a significant difference was observed between the two groups in this regard (P=0.045). The patients' demographic characteristics, including intubation rate in 72 h of life, BPD, necrotizing enterocolitis (NEC), mortality rate, and duration of intubation, nCPAP, and hospitalization were similar in both groups (Table 2).

Table 1. Comparison of demographic and perinatal characteristics of the subjects

	Poractant alfa group (n=34)	Beractant group (n=24)	P-value
Gestational age * (week)	31 (24-35)	31.5 (27-35)	0.224
Birth weight* (g)	1505 (695-2930)	1667 (1190-3000)	0.051
Male gender (n%)	20 (58.8%)	14 (58.3%)	0.97
Cesarean delivery (n%)	31 (91.2%)	22 (91.7%)	0.94
Premature rupture of membranes (n%)	9 (26.5%)	7 (29.2%)	0.821
Preeclampsia (n%)	9 (26.5%)	6 (25%)	0.90
Antenatal steroid (n%)	20 (58.8%)	15 (62.5%)	0.766
APGAR scores at 5th min*	8 (4-9)	8 (6-9)	0.821

* Values given as median (minimum–maximum)

Table 2. Comparison of short term pulmonary and postnatal outcomes

	Poractant alfa group (n=34)	Beractant alfa group (n=24)	P-value
Time of first surfactant dose (hour*)	1 (0.5-20)	3 (0.25-27)	0.098
Adverse events during surfactant administration			
Bradycardia	4 (11.8%)	10 (41.7%)	0.009
Surfactant reflux during procedure	10 (29.4%)	15 (62.5%)	0.012
Second dose of surfactant	6 (17.6%)	0 (0%)	0.045
Intubation in 72 h of life	20 (58.8%)	16 (66.7%)	0.544
Pneumothorax (n%)	5 (14.7%)	1 (4.2%)	0.194
PDA required medical treatment (n%)	9 (26.5%)	7 (29.1%)	0.786
ROP requiring intervention (n%)	1 (3.3%)	3 (13.6%)	0.168
IVH (all grades)	5 (14.7%)	3 (12.5%)	0.810
NEC≥ Grade 2	2 (5.8%)	0(0%)	0.140
BPD (n%)	5 (14.7%)	3 (12.5%)	0.810
Duration of invasive mechanical ventilation (days*)	1 (0-30)	1 (0-4)	0.190
Duration of nCPAP (days*)	1 (0-18)	3.5 (0-15)	0.190
Duration of hospitalization (days*)	30 (1-127)	21.5 (7-79)	0.580
Death (n%)	4 (11.8%)	0 (0%)	0.145

BPD: bronchopulmonary dysplasia, ROP: retinopathy of prematurity, PDA: patent ductus arteriosus, IVH:Intraventricular hemorrhage, NEC: necrotizing enterocolitis, n-CPAP:nasal continuous positive airway pressure

* values given as median (minimum–maximum).

Discussion

In the present study, the evaluation of beractant and poractant alfa treatments was performed using the MIST method. Based on the results, surfactant reflux and desaturation were lower in the PG group during the procedure. Furthermore, no difference was observed in terms of outcomes, including intubation in 72 h of life, BPD, NEC, mortality rate, and duration of intubation, nCPAP, and hospitalization. Since there are some harmful effects of intubation and positive pressure ventilation on the immature lungs, different methods have become a current issue for surfactant administration for RDS treatment. Although these methods are in experimental stages, nebulized surfactant application and surfactant administration using a laryngeal mask are not common in clinical

practice (15, 16).

Today, surfactant administration via thin catheters under nCPAP in newborns with spontaneous breathing is the most preferred method. In this regard, the MIST or less invasive surfactant administration (LISA) methods is performed since 2001. Since this method is more difficult to perform, compared to the standard procedure, it requires more experience. However, the proper gestational week, at which premature neonates are eligible for receiving this type of treatment, is still a matter of clarification (17, 18). In the current study, surfactant was administered using the MIST method in premature newborns born between 24 and 35 gestational weeks.

Several complications may be observed during the application, such as bradycardia, tachycardia, apnea, cough, and surfactant reflux. The results of a study performed by Mohammadizadeh et al. (19) revealed the complication rate of 31.6%. There is no consensus about the application of premedication before surfactant administration. In this respect, Kanmaz et al. (20) reported that they did not administer any premedication and obtained the rate of bradycardia and desaturation as 17%. In a study conducted by Kribs et al. (8), atropine was used as premedication resulting in the incidence rate of bradycardia as 7.4%.

In the present study, no premedication was given to the study participants. According to the findings of this study, surfactant reflux from the trachea and bradycardia were found as the complications during the surfactant administration. The rates of surfactant reflux and bradycardia were significantly higher in the BG than in the PG, the reason for which could be attributable to the need for a greater administration volume of beractant than of poractant alfa. In a study carried out by Kribs et al. (11), despite the patients administered surfactant with MIST method had lower birth weight and were smaller for gestational age than their counterparts administered surfactant with the standard procedure, the rates of mechanical ventilation support, BPD, and mortality were reported to be lower in the MIST group.

Surfactant plays a peculiar role in the development of pulmonary functions, especially in small premature neonates; moreover, it is administered earlier and as prophylactic in patients received surfactant via a thin catheter. Accordingly, less common chronic pulmonary disease in small premature neonates might be attributed to surfactant itself rather than a novel method. Additionally, as the use of caffeine and theophylline was higher in the group administered surfactant via a thin catheter, it can be concluded that it has enhanced the pulmonary function effectively, protecting against chronic pulmonary disease.

In their multicenter, prospective, randomized controlled study, Göpel et al. (21) reported that the need for mechanical ventilator was less in patients who were followed-up under nCPAP, had spontaneous breathing, and administered surfactant via a thin catheter, compared to those administered standard procedure. Nonetheless, no significant difference was found between these two groups regarding the rates of BPD and mortality. In a randomized controlled study performed by Kanmaz et al. (20), the administration of surfactant via catheters was reported to decrease the need for a mechanical ventilator, duration of mechanical ventilation, and the incidence of BPD. The results of a study conducted by Bao et al. (22) were indicative of the need for mechanical ventilator and shorter nCPAP duration in the group administered surfactant with MIST method; however, no significant difference was found in the incidence of BPD. Klebermass et al. (23) administered surfactant with the LISA method in premature neonates between 23 and 27 weeks of gestational age. According to the results of the aforementioned research, 95% of newborns tolerated the administered surfactant and 68% of the cases were still followed-up under CPAP on the third day. In the same study, the rates of mortality, intraventricular hemorrhage, and periventricular leukomalacia were lower, while the rates of patent ductus arteriosus and premature retinopathy were higher in the LISA group, compared to those in the standard procedure group.

Tomar et al. (24) administered surfactant with a modified MIST method in premature newborns between 24 and 34 weeks of gestational age. They reported that there were no differences in the requirement of intubation and mechanical ventilation in the first 72 h; however, the duration of mechanical ventilation and continuous positive airway pressure were significantly lower in the modified MIST group. In the same study, the authors stated that the modified MIST technique was an effective method for RDS treatment in preterms resulting in better clinical efficacy and comparable outcomes than the more invasive INSURE procedure, which deserves further evaluation. In our study, no significant difference was observed between the groups administered beractant and poractant alfa with the MIST method, regarding intubation in 72 h of life, BPD,

NEC, mortality rate, and duration of intubation, nCPAP, and hospitalization.

In the first 72 h of life, the rate of intubation following surfactant administration via thin catheter was reported to be 30% to 42% (20, 24); nonetheless, in the present study, this value was obtained as 66.7% and 58.8% in the beractant and poractant alfa groups, respectively. This discrepancy may be related to the different applications in clinics. This finding also suggests that surfactant administration with MIST cannot be appropriate for every patient. In addition, the researchers of this study believe that complications during the procedure and the rate of intubation in the first 72 h of life would decrease with the increase of experience over time.

The limitations of this study were its retrospective design, small sample size, and single-center trial. In conclusion, in the present study, the efficacy and reliability of beractant and poractant administrations with the MIST method were compared. This method is increasingly gaining importance and is recognized as an invasive method. The patients' demographic characteristics, including intubation in 72 h of life, BPD, NEC, mortality rate, and duration of intubation, nCPAP, and hospitalization were similar between the two groups. Since the MIST method is considered to be more noninvasive, it seems to have a more important role in daily practice.

Conclusion

According to the results of this study, surfactant reflux to esophagus and desaturation during the intervention procedure were lower in the PG group, most probably due to a lower volume of poractant to beractant. However, since a small number of patients were included in this study, it is recommended to perform further studies consisting of a larger number of cases.

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Conflicts of interest

The authors declare that there is no conflict of interest regarding this study.

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