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Transcutaneous electromyography of the diaphragm

Monitoring breathing and the effect of respiratory support in preterm infants

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Chapter 3

The effect of minimally invasive surfactant therapy on diaphragmatic activity

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Abstract

Background

Minimally invasive surfactant therapy (MIST) is increasingly used to treat preterm infants with respiratory distress syndrome (RDS). However, the effect of MIST on breathing effort is poorly studied.

Objectives

To describe the effect of MIST on neural breathing effort assessed with transcutaneous electromyography of the diaphragm (dEMG) in preterm infants with RDS.

Methods

Preterm infants with a gestational age < 37 weeks treated with MIST for RDS were included. dEMG measurements were done from 15 minutes before up to one hour after MIST. The percentage change in dEMG activity after MIST and the clinical response were analyzed.

Results

Twenty preterm infants (mean gestational age 29.3 (SD 2.1) weeks; mean birth weight 1,230 (SD 391) g) were included. Seventeen infants did complete the one hour measurement. Eleven (65%) infants had a decrease in their $peak_{dEMG}$ activity (median change -11.8% (IQR -26.8 to 5.8, p = 0.08)) one hour after MIST. $Tonic_{dEMG}$ activity decreased in 12 (71%) infants with a median reduction of 6.3% (IQR -29.2 to 9.0, p = 0.07). FiO_2 showed a rapid decrease following MIST (before 0.47 (IQR 0.38–0.84), one hour after 0.25 (IQR 0.21–0.30), p < 0.001).

Conclusion

In addition to improved oxygenation, MIST results in a decrease in neural breathing effort measured by dEMG activity in the majority of preterm infants with RDS.

Introduction

Neonatal respiratory distress syndrome (RDS) is common in preterm infants and the main cause of respiratory failure in the first days of life.[1] RDS is characterized by surfactant deficiency leading to atelectasis and low end-expiratory lung volume (EELV).[2] Furthermore, compliance of the respiratory system is decreased while airway resistance is increased.[2] This will result in impaired gas exchange and increased work of breathing.

The treatment of RDS consists of respiratory support and exogenous surfactant administration. This surfactant administration improves pulmonary function and, more importantly, results in less neonatal mortality and morbidity.[3] Traditionally, surfactant is administered via an endotracheal tube. However, to prevent adverse effects of intubation and mechanical ventilation, surfactant is increasingly administered while infants are breathing spontaneously with nasal continuous positive airway pressure (nCPAP) support. During this so-called minimally invasive surfactant therapy (MIST) procedure, surfactant is administered via a small catheter inserted through the vocal cords into the trachea.[4–6]

In contrast to endotracheal surfactant treatment, the effect of MIST on pulmonary function has been poorly studied. Although it has been established that MIST results in a rapid increase in EELV, thereby improving oxygenation[7], the effect on breathing effort is unknown.

Recently, transcutaneous electromyography of the diaphragm (dEMG) has been introduced as a noninvasive easy-to-use bedside monitoring tool in neonatal intensive care.[8] dEMG measures the electrical activity of the diaphragm, the main respiratory muscle in preterm infants. This electrical activity of the diaphragm is considered a noninvasive measure of neural drive and breathing effort.[9]

The primary aim of this study is to describe the effect of exogenous surfactant administration via the MIST procedure on neural breathing effort assessed by measuring the electrical activity of the diaphragm. We hypothesize that neural breathing effort will decrease after MIST.

Methods

Study population

This prospective observational cohort study was conducted in the neonatal intensive care unit (NICU) of the Academic Medical Center (Amsterdam, The Netherlands). Infants born between 26 and 37 weeks of gestation were eligible if diagnosed with RDS and treated with a first dose of exogenous surfactant via the MIST procedure. According to our department protocol, infants were candidates for MIST if they received nCPAP ≥ 6 cmH$_2$O with a FiO$_2 > 0.30$ and had an adequate respiratory drive and a postnatal age

< 72 hours. Based on these same criteria infants could be treated with a subsequent dose of surfactant, given either via MIST or via endotracheal intubation. Infants with major congenital anomalies of chest or abdomen were excluded. The study protocol was approved by the Medical Ethics Committee of the Academic Medical Center Amsterdam and informed consent was obtained from both parents before the start of the study.

MIST procedure

The MIST procedure was based on the technique described by Göpel et al.[4] Briefly, infants were placed in supine position and the larynx was visualized by laryngoscopy while receiving nCPAP. Local anesthesia was induced with lidocaine spray, after which a 3.5- or 5-french catheter was placed 1-2 cm below the vocal cords using a Magill forceps. The surfactant (Curosurf 80 mg/ml; Chiesi Pharmaceuticals BV, Amsterdam, The Netherlands) was dosed by vial and administered slowly over 1-3 minutes.

Study procedure

The dEMG measurement started 15 minutes before the MIST procedure and was continued up to one hour after surfactant administration. Three skin electrodes (disposable Kendall H59P Electrodes, Covidien, Mansfield, MA, USA), i.e. 2 in the left and right nipple line at the costo-abdominal margin and 1 ground electrode on the sternum, were used. The electrodes were connected to a portable 16-channel physiological amplifier (Dipha-16, Demcon, Son, The Netherlands) which was wirelessly connected to a bedside computer. The raw, monopolar EMG signals were digitally transformed to a bipolar EMG signal and high-pass filtered in Polybench (Applied Biosignals, Weener, Germany). The electrical activity of the heart was removed from the EMG signal and the resulting gated EMG signal is filled with a running average as described by O'Brien et al.[10] This averaged dEMG signal was post processed and used for the data analyses. More information on the technical aspects of the signal processing are provided elsewhere.[10,11]

Standard monitoring of the heart rate and respiratory rate with chest impedance and oxygen saturation with pulse oximetry were continued during the measurement.

Data collection

The following characteristics were collected when infants were included in this study: gestational age, birth weight, Apgar score, administration of antenatal steroids, mode of delivery, and postnatal age at MIST (in hours). The settings of the respiratory support, including the FiO_2, were closely monitored during the measurement. During 3 days following the first MIST, data on changes in the respiratory support and the need for additional surfactant doses were collected.

Stable 30-seconds recordings without movement or technical artifacts were selected at baseline (time = -5 minutes) and one hour after MIST (time = +60 minutes). For each individual breath in these selected recordings, the following dEMG parameters were assessed: $peak_{dEMG}$ activity (µV), $tonic_{dEMG}$ activity (µV), and $amplitude_{dEMG}$ (µV). The $peak_{dEMG}$ activity was determined as the highest point in the signal, the $tonic_{dEMG}$ activity was determined as the lowest point in the signal, and the $amplitude_{dEMG}$ was calculated as the difference between the highest ($peak_{dEMG}$) and lowest ($tonic_{dEMG}$) points. These dEMG parameters were averaged over all breaths detected in the selected 30-seconds of recording for each individual infant. The percentage change (Δ %) in $peak_{dEMG}$ activity, $tonic_{dEMG}$ activity and $amplitude_{dEMG}$ was calculated compared to baseline. The inspiratory time (Ti_{dEMG}, s), expiratory time (Te_{dEMG}, s), the respiratory rate (breaths per minute) and the heart rate (beats per minute) were extracted from the dEMG signal as well. To be able to describe the change over time within the one hour measurement period, we also assessed these dEMG parameters 5 minutes (time = +5 minutes) and 30 minutes (time = +30 minutes) after MIST.

Statistical analysis

SPSS version 24.0 (IBM, Armonk, NY, USA) and GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA) were used for the statistical analysis. Data were expressed as mean ± SD or median (IQR), depending on their distribution.

The overall changes in diaphragmatic activity and clinical parameters were compared before and one hour after MIST by using a Wilcoxon signed-rank test. Based on the change in diaphragmatic activity one hour after MIST compared to baseline, infants were divided into a group showing a decrease in diaphragmatic activity and a group showing an increase in diaphragmatic activity. Patient and clinical characteristics were compared between these 2 groups. For normally distributed numerical data an unpaired *t* test and for non-normally distributed numerical data a Mann-Whitney *U* test was used. A $χ^2$ test was used for categorical data. $p < 0.05$ was considered statistically significant.

Results

Study population

Twenty-one preterm infants were included in the study. One infant did not receive MIST because it was technically not possible to insert the catheter in this extremely low birth weight infant weighing 465 g. This infant was therefore not included in the analysis. The basic characteristics of the remaining 20 infants are shown in Table 1. The median surfactant dose was 200 mg/kg (IQR 159–210). In 3 infants the measurement

was stopped early due to respiratory failure and the need for endotracheal intubation and ventilation. Nine (45%) infants needed a subsequent dose of surfactant after the first MIST procedure and 7 (35%) infants needed mechanical ventilation in the first 72 hours after birth.

Table 1. Baseline characteristics of the study population

Characteristic	Value
Gestational age at birth, weeks	29.3 ± 2.1
Birth weight, g	$1,230 \pm 391$
Male	11 (55%)
Complete course of antenatal steroids	6 (30%)
Caesarean section	11 (55%)
Apgar score at 5 min	8 (7 - 9)
Postnatal age at measurement, h	5 (4 - 14)
nCPAP level, cmH_2O	6 (6 - 7)
FiO_2	0.47 (0.38 - 0.84)

The total number of patients is 20. Values are presented as mean $\pm$ SD, number (%), or median (IQR). nCPAP, nasal continuous positive airway pressure; FiO_2, fraction of inspired oxygen.

The effect of MIST on diaphragmatic activity

One hour after MIST, 11 (65%) infants showed a decrease in $peak_{dEMG}$ activity and 12 (71%) infants showed a decrease in $tonic_{dEMG}$ activity. The median percentage change in $peak_{dEMG}$ activity and $tonic_{dEMG}$ activity was -11.8% (IQR -26.8 to 5.8, $p = 0.08$) and -6.3% (IQR -29.2 to 9.0, $p = 0.07$), respectively, one hour after MIST (Table 2).

The percentage change in $peak_{dEMG}$ activity over time per infant is shown in Figure 1. The $peak_{dEMG}$ activity tended to increase in the first 5 minutes after MIST, followed by a gradual decrease at time = +30 and time = +60 minutes in the majority of the infants. A similar pattern was seen for $tonic_{dEMG}$ activity and the $amplitude_{dEMG}$ (Table 2).

Comparison of the group of infants who showed a decrease in $peak_{dEMG}$ activity one hour after MIST to those who showed an increase revealed no significant differences in gestational age, birth weight, postnatal age at measurement, baseline FiO_2, the change in FiO_2 one hour after MIST, or the need for an additional dose of surfactant (Table 3).

The effect of MIST on clinical parameters

FiO_2 showed a significant, rapid and persistent decrease following MIST (baseline 0.47 (IQR 0.38–0.84); +5 minutes, 0.30 (IQR 0.28–0.55); +60 minutes 0.25 (IQR 0.21–0.30), $p < 0.001$). Ti_{dEMG}, Te_{dEMG}, respiratory rate, and heart rate did not change in the first hour after MIST (Table 2).
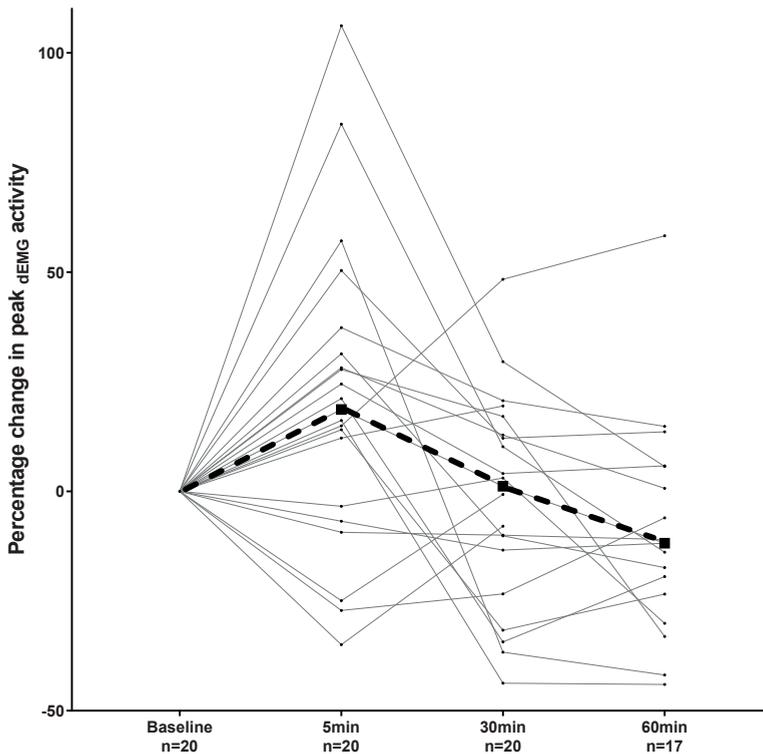
Figure 1. Percentage change in peak$_{dEMG}$ activity over time compared to baseline. Every line represents an infant. The bold, dashed line represents the median change over time in the first hour after minimally invasive surfactant therapy. dEMG, electromyography of the diaphragm.

Table 2. Change in dEMG derived parameters and clinical parameters over time

	Baseline (n = 20)	5 min (n = 20)	30 min (n = 20)	60 min (n = 17)
dEMG derived parameters				
Δ Peak$_{dEMG}$ activity (%)	0.0 (0.0 to 0.0)	18.7 (-6.0 to 35.9)	1.2 (-20.9 to 16.1)	-11.8 (-26.8 to 5.8)
Δ Tonic$_{dEMG}$ activity (%)	0.0 (0.0 to 0.0)	2.5 (-10.0 to 34.2)	1.7 (-25.4 to 9.4)	-6.3 (-29.2 to 9.0)
Δ Amplitude$_{dEMG}$ (%)	0.0 (0.0 to 0.0)	34.3 (-4.0 to 49.8)	1.2 (-16.1 to 22.5)	-5.8 (-21.0 to 7.4)
Absolute parameters				
Ti$_{dEMG,}$ s	0.5 (0.4 to 0.5)	0.5 (0.4 to 0.5)	0.4 (0.4 to 0.5)	0.4 (0.4 to 0.5)
Te$_{dEMG,}$ s	0.5 (0.4 to 0.6)	0.6 (0.4 to 0.6)	0.5 (0.4 to 0.6)	0.5 (0.4 to 0.5)
Respiratory rate, breaths/min	65 (53 to 73)	58 (53 to 71)	65 (56 to 77)	69 (62 to 77)
Heart rate, beats/min	144 (138 to 158)	150 (137 to 160)	147 (132 to 157)	144 (132 to 157)
FiO$_2$	0.47 (0.38 to 0.84)	0.30 (0.28 to 0.55)	0.27 (0.21 to 0.38)	0.25 (0.21 to 0.30)

dEMG derived parameters are presented as a percentage change compared to baseline. Data are expressed as median (IQR). dEMG, electromyography of the diaphragm; Ti$_{dEMG,}$ inspiratory time; Te$_{dEMG,}$ expiratory time.

Table 3. Comparison of infants showing a decrease versus an increase in $peak_{dEMG}$ activity 1 h after MIST

	Decrease (n = 11)	Increase (n = 6)	*p* value
Gestational age, weeks	29.8 ± 2.1	29.4 ± 2.5	0.75
Birth weight, g	1,328 ± 421	1,079 ± 414	0.26
Postnatal age at measurement, h	6 (5 to 20)	9 (4 to 16)	0.59
Cases in which surfactant was needed a second time	4 (36.4%)	2 (33.3%)	0.90
Baseline FiO_2	0.46 (0.31 to 0.80)	0.45 (0.40 to 0.59)	0.81
Δ FiO_2 at 60 min compared to baseline, %	-46 (-60 to -30)	-49 (-57 to -35)	0.88

Normally distributed numerical data are presented as mean ± SD (unpaired t test). Categorical data are presented as numbers (%) (χ2 test). Non-normally distributed numerical data are presented as median (IQR) (Mann-Whitney U test). dEMG, electromyography of the diaphragm. MIST, minimally invasive surfactant therapy.

Discussion

This study explores for the first time the effect of exogenous surfactant administration via the MIST procedure on neural breathing effort measured by electrical activity of the diaphragm in preterm infants with RDS. Compared to baseline, the peak and tonic diaphragmatic activity decreased one hour after the MIST procedure in the majority of infants, with a trend toward an average reduction of, respectively, 11.8% and 6.3%.

The pulmonary effects of surfactant administration via an endotracheal tube have been extensively studied in animal models and preterm infants with RDS.[12–16] A study in preterm infants showed that MIST improved oxygenation and EELV, similarly to endotracheal administration.[7] Up to now the effect of surfactant administration on neural breathing effort has not been studied, either in intubated or in spontaneous breathing preterm infants. Previous studies have shown that transcutaneous dEMG is able to detect changes in neural breathing effort caused by treatment interventions in preterm infants.[17,18]

The decrease in electrical activity of the diaphragm that was seen in the majority of the preterm infants is consistent with our hypothesis. The reduction in $peak_{dEMG}$ activity is probably best explained by the improved compliance of the respiratory system, which is one of the main variables impacting breathing effort. Improved compliance following surfactant treatment via an endotracheal tube has been reported in previous studies in preterm infants.[16,19] The reduction in $tonic_{dEMG}$ activity can be explained by the increased and more stable EELV after surfactant treatment as reported during both invasive and noninvasive surfactant treatment.[7,13] Increased tonic diaphragmatic activity is one of the mechanisms by which preterm infants can increase their EELV in case of surfactant deficiency.[20,21]

An interesting finding was the individual variability in response to MIST, showing that diaphragmatic activity did not decrease in all infants. We can only speculate on the reasons for this. First, the effect of surfactant on compliance of the respiratory system and EELV may vary between infants due to differences in surfactant deposition or surfactant inactivation by alveolar proteins.[22] Second, it could be that the effect of surfactant on compliance of the respiratory system may take longer than the first hour after the procedure as shown in some physiological studies.[15,23] Finally, the improvement in EELV following MIST might result in relative overdistention of the lung. This would place breathing on the less compliant part of the pressure-volume relationship of the lung as nCPAP pressure was not reduced in the first hour after MIST.

Furthermore, it was interesting to observe an increase in diaphragmatic activity 5 minutes after the MIST procedure in the majority of infants. Again, we can only speculate on possible explanations. First, opening of the mouth during the MIST procedure might reduce the positive airway pressure of the nCPAP. This could lead to a loss of EELV and a decrease in compliance resulting in an increased breathing effort. Second, there might be increased airway resistance due to the surfactant deposition, which will increase the breathing effort. Third, the infants might be still aroused at this time point due to the MIST procedure which might also affect diaphragmatic activity.

An explorative analysis was done to investigate whether the diaphragmatic response to MIST was influenced by patient and clinical characteristics. The selected characteristics were considered factors that might explain the variability of the response to surfactant administration via MIST on diaphragmatic activity. None of these variables were different between infants who had a decrease in diaphragmatic peak activity and those infants showing an increase. In addition, no difference was seen in FiO_2 in the 2 groups of infants. Therefore, the variability of diaphragmatic response to MIST seems not to influence the clinical response to surfactant administration.

This study has several limitations that need to be addressed. First, this study did not simultaneously measure changes in compliance and resistance of the respiratory system with diaphragmatic activity. Information on these variables would have allowed us to explain some of the findings in our study. However, compliance and resistance of the respiratory system are difficult to measure in infants on noninvasive support. Our findings may be different when administering surfactant prophylactically. Finally, the diaphragmatic activity was only measured up to one hour after MIST. It might be that the new balance of the respiratory system after MIST is not yet established in the first hour after surfactant administration and a longer measurement time might change our findings.

In conclusion, this study shows that, in addition to improved oxygenation, the neural breathing effort measured by diaphragmatic activity decreases in the majority of preterm infants in the first hour following surfactant administration via the MIST

procedure. However, there is considerable variation in this response, with some infants showing no change or even an increase in neural breathing effort. This explorative study adds important new knowledge on the physiological changes following MIST in preterm infants with RDS. It also provides valuable information for clinicians, i.e., that manifestation of the positive effect of MIST on the respiratory system may take more than one hour and is variable between infants. Further research is needed to identify factors that impact the effect of MIST on breathing effort. Such a study would require a large sample size and a longer measurement time. In addition, it would be of interest to compare the effect on neural breathing effort of surfactant administered via an endotracheal tube and MIST.

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