SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Examination of clinical and technical factors affecting the success of less invasive surfactant therapy in premature infants

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The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, at 1 p.m., on 20.02.2024.

Introduction and literature review

Epidemiology of Respiratory Distress Syndrome

Respiratory distress syndrome (RDS), also known as hyaline membrane disease, which develops due to the immaturity of the lungs and the associated surfactant deficiency, is one of the most common complications of prematurity. RDS develops in case of about 5% of those born after the 34th gestational week, 30% of those born between the 28th and 34th gestational weeks, and approximately 60% of those born before the 28th week of pregnancy, i.e. the incidence of the disease increases with decreasing gestational age. RDS is the main cause of morbidity and mortality in premature babies, in connection with which the vast majority of extremely premature babies (born before the 28th week of gestation) require some respiratory therapy modality (oxygen supplementation, non-invasive respiratory support, invasive ventilation, surfactant therapy).

Pathogenesis of RDS

In the absence of an adequate surfactant pool, the alveolar surface tension rises to a critical level. The consequent decrease in compliance, progressive atelectasis, and – especially in the case of non-invasive respiratory support or invasive ventilation with inadequate end-expiratory pressure – the hyperinflation of the less affected lung areas leads to a deterioration of the ventilation-perfusion ratio. Alveolar hypoventilation causes hypoxia, hypercapnia and respiratory acidosis, which together result in deterioration of systemic and pulmonary perfusion (intra- and extrapulmonary right-left shunt), which, in the absence or failure of appropriate therapeutic interventions, may lead to circulus vitiosus multiple-organ insufficiency that is irreversible and incompatible with life.

Surfactant therapy in RDS

The dilemma of treating RDS: CPAP or surfactant?

Even today, exogenous surfactant replacement forms the basis of the treatment of RDS, the application of which was only possible with invasive ventilation for decades. The potential dangers of mechanical ventilation - even for a short time - are well known, while the use of prophylactic continuous positive airway pressure (CPAP) and the avoidance of endotracheal intubation are associated with significantly better outcomes in premature infants. However, early CPAP alone was not sufficient in about 40-65% of cases, and the need for mechanical ventilation in the first 72 hours (CPAP failure) was associated with significantly higher mortality and lower complication-free survival. In light of this, many neonatologists, considering the consequences of delaying adequate therapy and ensuring the benefits of early exogenous surfactant administration, still decided to perform endotracheal intubation. Providing the benefits of early prophylactic CPAP and early surfactant administration together is a serious dilemma: Which is more beneficial? Treat premature babies with non-invasive respiratory support, risking the risk of CPAP failure, or perhaps accept the potential complications of invasive ventilation required for early surfactant therapy? Is it possible to implement the two procedures together? The solution to the latter question was the use of less invasive surfactant administration (LISA).

Less invasive surfactant therapy

In 1992, Verder and his colleagues first used a thin catheter technique to administer surfactant in premature infants with RDS. Rediscovering the method about a decade later, Kribs and his team perfected it in Cologne. In the course of the LISA procedure, surfactant is administered during laryngoscopy in spontaneously breathing premature infants with nCPAP, through a thin catheter inserted into the trachea between the vocal cords.

The main advantage of the procedure compared to the administration of surfactant through an endotracheal tube lies in the avoidance of mechanical ventilation. While LISA used to be just a single intervention, today it refers to a complex care strategy supporting the transition to extrauterine life, including antenatal steroid prophylaxis, elements of care in the delivery room, such as delayed or physiologically based umbilical cord care, "minimal handling" approach, tactile stimulation, early, prophylactic CPAP use, caffeine loading and starting kangaroo care as soon as possible.

Although there are still many unanswered questions about the procedure, based on the results of the available randomized controlled and observational studies, according to the current European recommendation, LISA is the preferred surfactant administration method in spontaneously breathing premature infants.

Clinical studies related to the short-term outcome of LISA

Despite the fact that LISA has significantly improved the success rate of early CPAP, according to the literature, endotracheal intubation or mechanical ventilation is required in the first 72 hours in a significant part of premature babies who underwent LISA, around 23-62%, which is associated with significantly lower complication-free survival, higher IVH, severe IVH, BPD, severe BPD, severe ROP, air leak incidence, and longer mechanical ventilation and hospitalization time. In their retrospective study, Janssen et al. identified four independent predictors of LISA failure: gestational age below 28 weeks, elevated CRP value measured 24 hours after birth, lack of antenatal corticosteroid prophylaxis, and poractant-alpha dose below 200mg/kg. During the post hoc analysis of the cohort study by Kruczek and his team, the highest FiO_2 before surfactant administration was identified as an independent risk factor for CPAP failure after LISA. In connection with this, the authors themselves noted that the median FiO_2 before the intervention was significantly higher (0.4) than the treatment threshold of the current recommendation (0.3). Ramos-Navarro and his colleagues also investigated the prediction of the outcome of LISA. According to their observation, the change in FiO_2 need after intervention is a reliable predictor of therapeutic response (avoidance of CPAP failure).

Research related to various devices and device selection

Since the release of the first publications, many versions of the method have been published, and in recent years the range of available tools has also expanded rapidly. According to the results of surveys conducted so far, the preference for using a nasogastric tube shows significant differences worldwide (7-83.1%). During a simulation study carried out by Rigo et al., the neonatologists performing the intervention found it easier to use devices with semi-rigid or guide wires compared to the traditional gastric tube. During another simulation study, among the various semi-rigid catheters, the LISAcath, specially developed for surfactant administration, was preferred over the AngioCath (Becton, Dickinson and Company, New Jersey, USA).

Objectives

Prevention of CPAP failure after LISA is essential to improve the outcome in premature infants with RDS. The focus of our work was the examination of clinical and technical factors influencing the success of LISA.

1. According to our hypothesis, the outcome of LISA can be predicted based on the clinical variables available before the intervention. Our primary goal was to investigate the success rate of LISA and to identify outcome predictors, which can help in clarifying the target population and the treatment indication.
2. In addition to the clinical parameters, the technical implementation also plays a significant role in the outcome of the LISA. Since October 2014, LISA performed at the Division of Neonatology of the Department of Pediatrics of the University of Debrecen using a flexible gastric tube has been part of the care of premature babies suffering from RDS. The semi-rigid catheter (LISACath), which has been available since September 2019, quickly became the first device of choice. Our objective was to test the hypothesis that switching to LISAcath was beneficial in terms of the technical outcome of the intervention.

Materials and methods

Study populations

Determination of LISA success rate and identification of predictors

We performed a retrospective study of premature babies cared for between January 1, 2014 and December 31, 2019 at the Division of Neonatology of the Department of Pediatrics of the University of Debrecen. Patients born before the 33rd gestational week, stabilized with early CPAP and then treated with LISA were selected for the study. Premature infants who required primary intubation during stabilization in the delivery room or after NIC admission, as well as those born prematurely with congenital anomalies potentially affecting standard care and respiratory outcomes were excluded.

Comparison of nasogastric tube and semi-rigid catheter use during LISA

Within the framework of a quality improvement study, we performed a post hoc analysis of data collected prospectively between December 2019 and September 2021. During the examination, we processed the data of premature babies who were born locally between the 24th and 34th gestational weeks, and who were stabilized with early CPAP, and then received LISA. For each patient, only the completion of the first LISA was evaluated. Premature babies who had previously undergone endotracheal intubation for any reason or those born with the malformations detailed above were excluded from the study.

Prenatal and early postnatal care

Due to the occurrence of possible preterm births during the two studies, the pregnant women received antenatal steroid prophylaxis (32 mg dexamethasone in two doses, a single repeat after 1-2 weeks) and magnesium sulfate treatment for neonatal neuroprotection. If possible, delayed umbilical cord care (30-60 seconds) was performed. The milking of the umbilical cord was not part of the routine care, it was done only in selected cases.

After completing the initial steps (preventing hypothermia, positioning, pharyngeal suction if warranted, then repositioning) in the delivery room, we started with early CPAP (NeopuffTM, Fisher & Paykel, Auckland, New Zealand), with a target value of 6-9 cm of water. The initial FiO_2 value in those born before the 28th week was 0.3, while in the case of those born between the 28th and 31st weeks, it was 0.21-0.3, and it was 0.21 over this age, which was titrated based on the measurement of preductal SpO_2 values (GE Dash 3000 Patient Monitor, GE Healthcare, Chicago, USA or Masimo Root Monitor with Radical 7 Handheld Pulse Oximeter sensor, Masimo Corporation, Irvine , USA). Careful tactile stimuli were used to stimulate spontaneous breathing. In addition to the above, in case of persistent apnea, insufficient spontaneous breathing or bradycardia, masked IPPV ventilation was performed, and endotracheal intubation was limited to IPPV-refractory cases. After successful stabilization, the premature babies were transported to the NIC in a preheated transport incubator with CPAP respiratory support provided via a face mask.

After NIC admission, we switched to 5-9 cm H2O nasal CPAP (binasal fork or nasal mask, using Dräger Babylog VN500 or Care Fusion Infant Flow devices). Due to the risk of perinatal infection, empiric antibiotic treatment (ampicillin and gentamycin) was started in all cases, the continuation of which was decided at the age of 24-36 hours based on the clinic, available laboratory tests (blood count and CRP), and possible culture results. In order to prevent apnea, all premature babies received early (before 2 hours of age) caffeine citrate treatment (20 mg/kg saturation, then 5 mg/kg/day maintenance dose).

LISA procedure

Before 2017, exogenous surfactant treatment with poractant alfa (Curosurf, Chiesi Pharmaceuticals) was performed according to the current European RDS recommendation, while after that, according to the guidelines of the Hungarian Health Professional College, $FiO_2 \geq 0.3$ and/or Silverman-Anderson score ≥ 5 detected after initial stabilization was its indication. The recommended dose of poractant alfa was 200 mg/kg, but to optimize therapeutic costs and minimize drug loss, rounding to the "whole ampoule" was an accepted part of clinical practice. During the study period, LISA was the preferred method of

surfactant administration in spontaneously breathing premature infants, however, the attending neonatologist could deviate from this recommendation based on the given clinical situation. Contraindications to LISA were hemodynamic instability, severe RDS (FiO_2 >0.6 and/or pH <7.2 and/or severe extensive atelectasis on chest X-ray), clinically significant apnea despite caffeine saturation, any air leak syndrome, and history or current suspicion of pulmonary hypoplasia arising in connection with the situation.

In all cases, LISA was performed with continuous non-invasive monitoring of the premature infant, without interruption of respiratory support. The intervention was preceded by the insertion of an orogastric tube, positioning and non-pharmacological analgesia (supine position, neutral position of the head and neck, stabilization with a nest made of "comfort care" textile, buccal breast milk or sucrose, etc.), and the attending neonatologist could decide on an individual basis about the need for nalbuphine analgosedation. During LISA, a dedicated nurse positioned and observed the premature infant.

Between January 1, 2014 and December 31, 2019, interventions were performed exclusively using a 5Ch nasogastric tube (Sumi, Poland) (with or without Magill forceps). From September 2019, after preliminary preparation (reading the application specification, training videos, practicing on a premature manikin (Premature Anne Task trainer, Laerdal Medical AS, Stavanger, Norway), the LISAcath application was introduced. During the prospective data collection between December 2019 and September 2021, if both instruments were available, the choice was made based on the decision of the interventional neonatologist.

During the LISA, after carefully opening the mouth, a gentle laryngoscopy was performed, the identification of the anatomical structures was helped by the previously placed nasogastric tube. After introducing the flexible or semi-rigid device into the glottis at a depth of 1.5-2.0 cm, the neonatologist who performed the procedure fixed it with a finger at the corner of the mouth, then carefully removed the laryngoscope, taking care to avoid accidental catheter displacement, and kept the patient's mouth in a closed position throughout. The surfactant pre-absorbed into the dedicated syringe was then administered in small, approximately 0.2-0.4 mL fractions, in about 2-3 minutes. During the instillation

of the surfactant, an assistant checked the stomach contents by careful, fractional suction of the previously inserted orogastric tube, because the surfactant discharged from it can draw attention to the wrong introduction of the catheter or its displacement from the trachea. In case of desaturation, apnea, bradycardia occurring during the procedure, the use of tactile stimuli, increase of FiO_2 and PEEP, suspension of surfactant administration in refractory cases, masked IPPV, and endotracheal intubation in case of their ineffectiveness were recommended. At the end of the intervention, the device was removed, and then the premature babies were positioned according to nursing standards. In the first 72 hours, if LISA contraindications were not met, or other causes of respiratory failure other than RDS were excluded, in the case of 0.4> FiO_2 and/or 5> Silverman-Anderson score values, the local protocol recommended performing a second or third LISA. During the study period, indications for mechanical ventilation were severe respiratory failure (FiO_2 >0.5 and/or pH <7.2 and/or pCO_2 >60 mmHg), as well as frequent tactile stimulation or apneic episodes requiring IPPV at least twice within 12 hours.

Data collection

Descriptive data, short-term neonatal outcome

In the course of our studies, we collected general neonatal descriptive data, pre- and postnatal risk factors, and short-term outcome indicators by reviewing the hard-copy and electronic patient documentation.

Determination of LISA success rate and identification of predictors

The potential predictors were also aggregated using the patient documentation. During our investigations, we used the following definitions:

- successful LISA (LISA-S, avoidance of mechanical ventilation in the first 72 hours after the use of a single LISA)
- LISA failure (LISA-F, repetition of surfactant in any way and/or need for mechanical ventilation in the first 72 hours)
- CPAP failure (CPAP-F, need for mechanical ventilation for any reason in the first 72 hours)

Comparison of nasogastric tube and semi-rigid catheter use during LISA

During the study, the intervention was classified as technically successful if the pre-calculated total surfactant dose was administered during the first laryngoscopy. The duration of interventions, the number of laryngoscopic attempts, changes in FiO_2 and PEEP, reasons for failure and possible adverse events (desaturation (<90% SpO_2), bradycardia (<100/min heart rate for more than 10 seconds), tactile stimulation and /or apnea requiring IPPV, surfactant regurgitation, surfactant dispositio confirmed by careful suction of the orogastric tube) was recorded each time by an attending resident physician using a standardized form. The technical difficulty of the interventions was assessed using the modified Cormack-Lehane classification and the Viby-Mogensen point system. The vital parameters were

collected using a central monitor system (Philips Intellivue X2, Philips, Hamburg, Germany) at a frequency of 1 Hz and averaged every minute.

Statistical analysis

Continuous variables were analyzed using unpaired Student's T-test or one-way analysis of variance (ANOVA). For categorical variables, Pearson's $\chi 2$ or Fisher's exact test was performed. In order to identify the predictors of LISA-S, we first performed a one-factor regression analysis. During our multi-factor regression model, we used variables with a p value of less than 0.1 at the single-factor level. Collinearity was characterized by calculating Pearson's correlation coefficient, and in the case of a value above 0.6, one of the pair of variables showing a relationship was excluded from the regression model. The raw odds ratios calculated at the univariate level and the adjusted odds ratios calculated during the multivariate analysis were shown with their 95% CI values. The statistical analysis was performed using the SPSS V.25 program. Differences were considered significant at $p < 0.05$.

Ethics clearance

Both clinical trials, which form the basis of the thesis, were completed in compliance with the basic principles laid down in the Declaration of Helsinki created by the World Medical Association, and their implementation was approved by the Regional and Institutional Research Ethics Committee at the Division of Neonatology of the Department of Pediatrics of the University of Debrecen (DE RKEB IKEB 5348-2019 and DE RKEB/IKEB 5616-2020).

Results

Determination of LISA success rate and identification of predictors

Main characteristics of the studied population

During the study period, a total of 800 premature babies born before the 33rd gestational week were admitted to the Division of Neonatology of the Department of Pediatrics of the University of Debrecen . Out of 643 patients born at the Obstetrics and Gynecology Clinic, 158 patients underwent LISA. The average birth weight of the study population was 1025±347 grams, the average gestation period was 29.93±2.26 weeks. The proportion of boys born prematurely was 55.35%, and in 92.1% of cases, at least partial antenatal steroid prophylaxis took place. The average of one-minute Apgar values was 6.55±1.46, while those of two and three minutes were 8.04±0.8 and 8.5±0.67. The average recording temperature was 36.07±0.580C, while the median FiO_2 at the time of LISA was 0.35.

LISA outcome in the study population

In 86 cases (54%) LISA was successful (LISA-S), in 72 premature babies (46%) it was necessary to repeat surfactant administration and/or mechanical ventilation in the first 72 hours (LISA-F). Among the patients receiving LISA, CPAP failure occurred in 54 cases (34%) due to the following reasons: swe_2 >0.5 (n=36), acidosis (n=9), apnea (n=7, of which 2 cases were under LISA), PTX and hemodynamic instability (n=2), so mechanical ventilation was avoided in a total of 104 cases (65.8%). The success rate of the first LISA showed a gradual increase until the 28th gestational week, while between the 28th and 31st it was between 64.7-69.5%, and then it rose to over 80% among those born at the 32nd gestational week. At the same time, thanks to the success of the first and reLISAs, the proportion of CPAP-F cases - with the exception of the subpopulation of those born at the 26th week of gestation - gradually decreased with advancing gestational age.

Comparison of LISA-S and LISA-F preterm infants

Compared to premature babies successfully treated with LISA, those treated unsuccessfully were born with a significantly shorter gestational time (28.62 weeks vs 27.11 weeks, $p<0.001$), a lower birth weight (1134.07 grams vs 895.56 grams, $p<0.001$) and a worse general condition (1-minute Apgar 6.78 vs 6.28, $p=0.031$), their body temperature measured at the time of NIC admission was significantly lower (36.24 0C vs 35.88 0C, $p<0.001$), and the incidence of moderate hypothermia was higher among them (22.1% vs 50%, $p<0.01$). No significant differences were found between the LISA-S and LISA-F study groups regarding the other examined pre- and postnatal risk factors.

Examination of potential predictors

Among the 39 variables we examined, several potential predictive factors were identified during the one-factor regression analysis, however, after the collinearity tests, only 9 variables remained for further statistical analysis. With the help of our model based on multifactorial logistic regression, we finally managed to identify 6 independent variables that predict the outcome of LISA: admission temperature showed a strong correlation with LISA success (OR=3.56, 95% CI 1.715-7.394), the elevated (>10mg/L) CRP value reduced the chance of LISA-S (OR=0.280, 95% CI 0.101-0.775), also birth weight (OR=1.003, 95% CI 1.002-1.004) and maternal age (OR=0.923, 95% CI 0.860-0.991) in addition to the highest RSS (respiratory severity score, RSS=CPAP pressure in cm of water x FiO_2)(OR=0.463, 95% CI 0.232-0.925; every 0.1 increment reduced the chance of LISA-S by 5.4%), and poractant alfa dose <200mg/kg body weight (OR=0.254, 95% CI 0.108-0.597) also proved to be a significant predictor. Antenatal steroid prophylaxis (both incomplete and complete) did not show a significant correlation with the outcome of the LISA in the premature infants we examined, even during the univariate regression analysis. The area under the curve of the ROC curve created using the predictive variables of the regression model is 0.85.

Predictors of the outcome of repeated LISA

62 premature babies received a second surfactant treatment, 31-31 in the form of S-ETT and LISA. In 18 cases (58%) of the latter, it was possible to avoid mechanical ventilation and another repetition of surfactant administration (reLISA-S). Despite the relatively low number of items, we performed similar calculations as detailed above in order to examine potential predictors of the reLISA outcome. None of the examined variables showed significance during the univariate regression analysis, nor did we manage to identify a predictor that showed a significant correlation with the reLISA outcome during the multivariate analysis.

The short-term outcome of the studied population depends on the success of the LISA

Compared to those successfully treated with a single LISA, the LISA-F premature babies required significantly longer hospital care, and among them, the incidence of all examined adverse events, except for ROP, was higher. Due to the small number of cases, we could not draw statistically reliable conclusions regarding PVL, NEC requiring laparotomy, or mortality.

Comparison of nasogastric tube and semi-rigid catheter use during LISA

The main characteristics of the premature babies selected for the study

LISA was performed at least once in 59 premature babies during the study period. Due to insufficient documentation, three patients were excluded, so we finally included the first intervention of 56 premature babies in the analysis. Regarding the entire population, the median gestational age (interquartile range) was 29.8 (27.3; 31.0) weeks, the birth weight was 1305 (935; 1838) grams, while the mean RSS value registered before LISA was 2.1 (1.8; 2.8). No significant differences were found in any of the characteristics between the groups of preterm infants treated with nasogastric tube (SRC) and semi-rigid catheter (NGT).

The technical implementation of LISA and the difficulty of interventions

The technical success rate of LISA (technical success: the pre-calculated surfactant dose was completely administered during the first laryngoscopy) in the entire study cohort was 39/56 (69.6%). In the case of 14 (25.0%) premature babies, two laryngoscopies were necessary, and in another 3 (5.4%) three laryngoscopies. There was no significant difference between the two devices regarding the number of failed interventions (7/21, 33.33% in the NGT group and 10/35, 28.57% in the SRC group, p=0.068). Regarding the technical conditions and feasibility of the interventions (best laryngoscopic image according to the modified Cormack-Lehane classification and distribution according to the Viby-Mogensen intubation score) there was no significant difference between the two study groups (p=0.802 and 0.478, respectively).

Adverse events

During the study period, a total of 81 LISA-related adverse events were registered in 47 premature infants (82.4%), the distribution of which showed no significant differences between the NGT and SRC groups. There were no device failures during the interventions.

Vital parameters

No significant difference was observed between the two groups in terms of the oxygen saturation and heart rate averages recorded in identical minutes. When using the nasogastric tube, compared to the SRC group, in the 3rd, 4th and 5th minutes of the interventions, a significantly higher FiO_2 was needed to ensure the SpO_2target range (in chronological order, 0.62 vs 0.48, p=0.024; 0.61 vs 0.37, p<0.001 ; 0.48 vs 0.37 p=0.001).

Short-term outcome indicators

No significant differences were observed between the short-term outcome indicators (CPAP-F, pneumothorax, O_2 requirement on day 28, cerebral hemorrhage, retinopathy of prematurity, enterocolitis necrotisans requiring laparotomy, death) of premature infants treated with NGT and SRC.

Discussion

Determination of LISA success rate and identification of predictors

One of the main goals of our studies was to determine the success rate of LISA and the predictors of the outcome. In the course of our work, contrary to the reports examining the topic, LISA failure was not only identified with the need for mechanical ventilation occurring in the first 72 hours after the intervention, but we supplemented its definition with the need to repeat surfactant administration. The reason for this was that, at the time our study was carried out, the care of premature babies suffering from clinically significant RDS after the first LISA - in the absence of adequate data – was quite heterogeneous: while in some NICs the intervention was repeated several times, other working groups in cases refractory to therapy, surfactant administration was repeated via endotracheal intubation. Taking into account the above, we focused on predicting the success of single LISA (successful avoidance of mechanical ventilation in the first 72 hours following the use of LISA), in order to facilitate the identification of the population of premature babies who benefit most from the use of LISA.

In the course of our work, we examined significantly more potential prognostic factors than the previous publications, a total of 39. Using our model based on multifactorial logistic regression, we identified 6 independent predictors (birth weight, maternal age, admission body temperature, highest RSS, CRP level detected in the first hour or at the time of LISA, poractant alfa dose and CRP value), which can be used to estimate the success of LISA probability (AUC ROC 0.85).

FiO_2 is the most frequently used parameter for the diagnosis of RDS, assessment of severity, and determination of necessary interventions. Regarding the relationship between the development of FiO_2 and the outcome of LISA, the data so far are contradictory. In their retrospective study, Janssen et al found no correlation between the development of FiO_2 and the failure of LISA. In contrast, Kruczek and his work group identified the highest FiO_2 before surfactant administration as an independent risk factor for CPAP failure after LISA. During our study, we were also unable to confirm the relationship between the FiO_2 registered before LISA and the outcome of the intervention, however, we found it to be a reliable predictor when applied together with the CPAP end pressure in the form of RSS.

n the course of our study, we also observed a previously observed relationship between the outcome of LISA and hypothermia. Among the identified predictors, the recording temperature is one of the first modifiable factors. Premature babies have an increased tendency to hypothermia, and below normal core temperature at the time of admission is a strong predictor of morbidity and mortality in all gestational age groups. The connection between RDS and hypothermia is known, but the cause-and-effect relationship between them is questionable, because a low core temperature at the time of admission can be a consequence of a worse general condition, a complicated transition, and also prolonged stabilization in the delivery room. The investigation also highlighted a weakness in the department's delivery room care, as the core temperature at the time of admission of premature babies treated in our department was lower than the identical median of the Vermont-Oxford Network in each year of the examined period (2014: 36.1^{0}C vs 36.6 ^{0}C, 2015: 35.9^{0}C vs 36.6^{0}C, 2016: 36.0^{0}C vs. 36.6^{0}C, 2017: 36.1^{0}C vs 36.7^{0}C, 2018: 36.0^{0}C vs 36.7^{0}C, 2019: 36.0^{0}C vs 36.7^{0}C), based on which the management of our center started assessing the necessary actions.

According to the results of several studies, the suboptimal dose of poractant alfa adversely affects the results of surfactant treatment, despite this, dose rounding is still a common phenomenon worldwide. In our study, poractant alfa doses below 200 mg/kg reduced the chance of LISA-S. During the application of thin-catheter surfactant delivery techniques, the amount of surfactant administered can play a major role. In silico, De Luca reported a significantly higher phospholipid loss of up to 11% when using the nasogastric tube compared to the endotracheal tube. According to the available data, the amount of surfactant remaining in this form in various catheters can be significantly reduced by emptying the device with a bolus of air at the end of the procedure. Regarding LISA, the importance of avoiding underdosing is emphasized by the 4.6-38.6% incidence of surfactant reflux during the procedure. In the light of our results, we revised the Department's LISA protocol and made recommendations for accurate dosing and avoiding dose rounding.

Similar to the study investigating the risk factors of mechanical ventilation after LISA, our working group also observed a strong correlation between the success of a single LISA and the increase in CRP,

which is understandable given that infection and inflammation significantly influence the therapeutic response to surfactant treatment.

In contrast to the results of Janssen et al., in our study, we did not detect a correlation between antenatal steroid prophylaxis and the outcome of LISA, which is presumably due to the high rate of high ANS treatment in both the LISA-S and LISA-F groups.

In our cohort, the success rate of LISA - with the exception of those at 26 weeks - increased parallel to the progress of gestation until the 28th week. In about 60% of premature babies born at the 24-25th weeks, it was possible to avoid mechanical ventilation in the first 72 hours, which rate corresponds with the data published by other working groups. In addition, it is important to emphasize that in case of the infants born at the 24-25th weeks, compared to those born at the 26th week of gestation, the prevalence of LISA-F was higher. This phenomenon can be explained by the selection bias of the selected population, because in the study period, in case of those born at the 24-25th weeks, endotracheal intubation had already performed in the delivery room. In their case, we only started the stabilization with early CPAP who were born in the best condition compared to those born at 26 weeks, among whom this ratio was significantly higher. This more liberal use of early CPAP may explain the exceptionally high LISA-F rate in this age group.

Our research is a novelty compared to the existing literature as we were the first to examine clinical variables potentially predicting the outcome of reLISA. Surfactant administration was repeated in 39.1% of the study population (61 premature babies). reLISA was performed in 31 premature babies, of which 18 cases (58%) could avoid mechanical ventilation in the first 72 hours. Presumably due to the low number of items, it was not possible to identify a predictor that would show a significant correlation with the success of reLISA. Since our investigation, one publication has so far been published regarding the outcome of the repeated LISA. According to the data of Kleijkers et al., CPAP failure occurred in 42% of cases after repeating the LISA – which is in line with our results –, and CPAP failure showed a significantly higher risk in case of extreme immaturity (OR=2.6, 95% CI 1.2-5.8) or FiO_2 >0.5 (OR=5.4, 95% CI 2.0-14.7).

Compared to LISA-F premature babies, we observed significantly lower mortality and – with the exception of ROP – lower morbidity rates among premature babies successfully treated with single LISA. In this regard, it is important to note that our retrospective study is not suitable for establishing a cause-and-effect relationship, which requires a prospective study. In addition to all this, it can be said that the fact of a successful LISA indicates a favorable prognosis in premature babies suffering from RDS.

When evaluating our results, it is important to take into account some limiting factors, one of which is the retrospective nature of the study. It is also important that although there was a strict set of criteria for endotracheal intubation and surfactant treatment in the delivery room, based on the subjective judgment of the provider, they could override them in some cases, within their own competence, which could have an impact on the composition of the studied population – primarily the subpopulation of extremely immature premature babies.

Comparison of nasogastric tube and semi-rigid catheter use during LISA

Since the introduction of LISA, several of the methods implemented with flexible and semi-rigid devices have been published. There is a limited amount of data available regarding the effect of the selection of the device on the technical success and the number of adverse events during the intervention, which causes significant difficulties in the development of local LISA guidelines and the adaptation of the intervention to particular situations. During the post hoc analysis of our prospective data collection, we compared the use of the flexible nasogastric tube and the semi-rigid catheter, examined the effect of the catheter type on the success of the first LISA experiment and the occurrence of adverse events.

Similar to Bhattacharya and his colleagues' unpublished retrospective data collection, in contrast to the in vitro studies, we did not detect any significant difference between the two devices regarding the technical outcome of LISA when used by experienced neonatologists. Our observations have since been confirmed by a small number of RCTs. According to our results, compared to the traditional nasogastric tube, the use of the semi-rigid device was associated with significantly better oxygenation during the

procedure and in the following minutes. We did not notice any significant difference between the two tested devices in terms of the number of adverse events or the short-term mortality and morbidity indicators.

The generalizability of our results has three main limiting factors. First, our study reflects the local practice of one clinical center. Secondly, in contrast to most Western European and North American centers, where LISA is mainly performed by trainees, all interventions during the study period were performed by a neonatologist specialist highly skilled in endotracheal intubation and performing LISA with a nasogastric tube, which could be a significant bias. This may be a significant distortion factor when comparing the two devices, as it is also suggested by the results, according to which less qualified neonatologists prefer the use of semi-rigid catheters to the traditional flexible gastric tube. Finally, we consider it important to note that after the end of the study, immediately before the publication of the data, LISAcath was withdrawn from circulation by the manufacturer for safety reasons. In this regard, we would like to point out that the production lots used during the study were not recalled, there were no device failures or adverse events resulting from this during the study period, and in our opinion, our results can be generalized to the use of other semi-rigid catheters on the market (e.g. Surfcath, Vygon, Swindon, UK; AngioCath).

Conclusion

Exogenous surfactant replacement is the most effective therapeutic tool for the treatment of RDS. In the past decade, several methods have been developed that can be implemented with early CPAP and thereby avoid mechanical ventilation. According to the results of recent systematic reviews and meta-analyses, in comparison with other methods of surfactant administration, the use of LISA proved to be the most favorable in premature infants with RDS. Despite this, the number of cases associated with adverse outcomes and requiring mechanical ventilation after LISA is still significant. Prevention of CPAP failure after LISA plays a central role in improving the outcome of the affected population. The focus of our work was the examination of clinical and technical factors influencing the success of LISA.

According to our results, after LISA performed in preterm infants born before the 33rd week of gestation, it is relatively often necessary to repeat surfactant administration or mechanical ventilation in the first 72 hours. In this population, the success of a single LISA is associated with favorable mortality and morbidity indicators. Independent predictors of the outcome of the first LISA are birth weight, maternal age, body temperature on admission, the highest RSS registered in the first hour or detected at the time of LISA, the dose of poractant alfa and the value of CRP. Our predictive model can help in identifying the premature population that benefits the most from the use of a one-time LISA, as well as in personalizing treatment indications.

Based on our tests, it can be concluded that LISA can be performed equally well by experienced neonatologists with the two compared catheter types. The choice of device did not influence the technical success or safety of the intervention. Based on the better oxygenation observed during its use, the semi-rigid catheter proved to be more advantageous than the nasogastric tube. Our results may contribute to the development of local recommendations for other NICs.

The new scientific results of the evaluation, the candidate's own findings

1. Independent predictors of the outcome of the first LISA are birth weight, maternal age, body temperature on admission, highest RSS registered in the first hour or observed at the time of LISA, poractant alfa dose and CRP value.
2. Prevention of hypothermia during initial stabilization and adequate surfactant dosing can increase the success rate of LISA and improve the outcome of the treated population.
3. LISA can be performed by experienced neonatologists with equal efficiency using a flexible nasogastric tube or a semi-rigid catheter, the choice of device did not affect the technical success or safety of the intervention.
4. Based on the more favorable oxygenation observed during its use, the use of a semi-rigid catheter is preferable to a nasogastric tube.

Keywords

prematurity, respiratory distress syndrome, surfactant, continuous positive airway pressure, non-invasive ventilation

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List of publications related to the dissertation

1. **Balázs, G.**, Pécsi, I., Fehér, C., Katona, N., Kotormán, T., Kovács, P. B., Márki, M., Pataki, I., Riszter, M., Rózsa, T., Bélteki, G., Kovács, T., Balla, G., Balajthy, A.: Comparison of flexible nasogastric tube and semi-rigid catheter during less invasive surfactant administration.
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