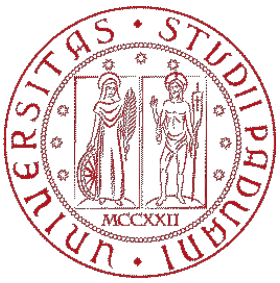

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TESI DI LAUREA

Rigid vs. Soft catheter for less invasive surfactant administration (LISA): a crossover randomized controlled manikin trial

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1. RIASSUNTO

1.1 **Background**

La tecnica LISA (somministrazione meno invasiva di surfattante) può essere svolta utilizzando cateteri rigidi o cateteri morbidi; tuttavia, il loro impatto sulla procedura in termini di facilità d'uso e successo non è stato ancora oggetto di valutazione. La scelta del catetere potrebbe influenzare la qualità della procedura stessa comportando ad esempio una prolungata durata ed una maggiore invasività della laringoscopia, con possibili conseguenze cliniche negative tipo bradicardia, ipossia e alterazioni emodinamiche.

1.2 **Obiettivi**

L'obiettivo dello studio è stato quello confrontare due differenti tipologie di cateteri per condurre la LISA, comparando nello specifico: i) tempo impiegato per posizionare il device in un manichino che simulava un neonato dal peso estremamente basso; ii) successo ottenuto nella procedura di posizionamento del device; iii) opinione dei partecipanti.

1.3 **Materiali e metodi**

Si è trattato di uno studio non in cieco, randomizzato, controllato e cross-over (AB/BA) condotto su manichino che simulava un neonato di peso estremamente basso. Ai partecipanti veniva chiesto di simulare la somministrazione di surfattante attraverso la tecnica LISA con un catetere rigido o con un catetere soffice. I partecipanti erano Specializzandi e Medici Strutturati di Terapia Intensiva Neonatale. La randomizzazione è stata eseguita utilizzando una lista di assegnazione computerizzata. L'outcome primario era il tempo totale di posizionamento del device. Gli outcome secondari erano il successo o meno della procedura al primo tentativo, il numero di tentativi necessari per raggiungere il corretto posizionamento del device in trachea, il raggiungimento di una adeguata profondità del device in trachea e l'opinione dei partecipanti sull'utilizzo del device.

1.4 Risultati

Il tempo mediano di posizionamento in trachea è risultato significativamente inferiore utilizzando il catetere rigido rispetto al catetere morbido (differenza mediana di -17 secondi, intervallo di confidenza del 95% da -26 a -12 secondi; p<0.0001). Il successo al primo tentativo del posizionamento in trachea del catetere rigido è stato ottenuto da 46 partecipanti su 50 (92%), mentre il successo al primo tentativo con il catetere morbido è stato ottenuto da 37 partecipanti su 50 (74%) (p=0.01). La mediana del numero di tentativi è stata di 1 (IQR 1-1) col catetere rigido e di 1 (IQR 1-2) col catetere morbido (p= 0.01). I partecipanti hanno espresso un parere più positivo a favore della procedura LISA con il catetere rigido rispetto a quello morbido in termini di difficoltà complessiva della procedura (p<0.0001), e inserimento del device in trachea (p<0.0001), maneggiamento del device (p<0.0001) e visualizzazione della glottide (p=0.01).

1.5 Conclusioni

L'utilizzo di un catetere rigido rispetto a un catetere morbido per eseguire la procedura LISA su un manichino estremamente pretermine risulta più veloce, più adeguato in termini di profondità di inserimento del catetere ed è più apprezzato dagli operatori. Ulteriori studi sono necessari per confermare i nostri risultati nella pratica clinica.

1.6 Registrazione

Lo studio è stato registrato in ClinicalTrials.gov NCT05388175.

2. ABSTRACT

2.1 Background

LISA can be provided using rigid or soft catheters, but possible differences in terms of easiness of use and success of the procedure are unknown. A difficult procedure may have some drawbacks such as the prolonged duration of the laryngoscopy needed to insert the device, which is likely to aggravate the invasiveness of the procedure and result in stressful consequences such as bradycardia, hypoxia and hemodynamic changes.

2.2 Objectives

The objectives of the study were to compare two different kinds of LISA catheters, specifically comparing: i) time of device positioning in a manikin simulating an extremely low birth weight infant, ii) success of the procedure of positioning the device, iii) participants' opinion.

2.3 Methods

This was an unblinded, randomized, controlled, crossover (AB/BA) trial of surfactant treatment with LISA with rigid catheter vs. LISA with soft catheter in a manikin simulating an extremely low birth weight infant. Participants were Neonatal Intensive Care Unite consultants and pediatric residents. Randomization was performed using a computer-generated random assignment list. The primary outcome measure was the total time of device positioning. The secondary outcomes were the success at the first attempt, the number of attempts to achieve the correct positioning of the device in the trachea, the achievement of the correct depth of the catheter in the trachea, and the participant's opinion on using the device.

2.4 Results

Median time of device positioning was shorter with rigid catheter vs. soft catheter (median difference –17 seconds, 95% confidence interval –26 to -12; $p<0.0001$). Success at first attempt was 46/50 with the rigid catheter (92%) and 37/50 with soft catheter (74%) ($p=0.01$). Median number of attempts was 1 (IQR 1-1) with rigid catheter and 1 (IQR 1-2) with soft catheter ($p=0.01$). Participants found

performing LISA with rigid catheter overall difficulty lower ($p<0.0001$), and they found easier to insert the rigid catheter in the trachea ($p<0.0001$). Participants also found easier handling the rigid catheter ($p<0.0001$) and to visualize the glottis ($p=0.01$).

2.5 Conclusions

Using a rigid versus a soft catheter to perform the LISA procedure on an extremely preterm manikin is faster, more adequate in terms of catheter insertion depth and is more appreciated by operators. Further studies are needed to confirm our findings in clinical practice.

2.6 Trial Registration

The study has been registered in ClinicalTrials.gov NCT05388175.

3. INTRODUCTION

3.1 RDS

Neonatal Respiratory Distress Syndrome (RDS) or Hyaline Membrane Disease is the consequence of a lack of surfactant in newborns' lungs.

Many preterm newborns are affected by RDS, as immature lungs are functionally deficient in surfactant.[1]

RDS is one of the most common reasons an infant gets admitted to the Neonatal Intensive Care Unit and it remains one of the main problems in preterm newborns.

The incidence of RDS is inversely proportional to gestational age. RDS is around 90% in babies born at 24 weeks of gestation, 80% at 28 weeks, 30% between 28-34 weeks, and <5% in >34 weeks of gestation according to data submitted to the Vermont Oxford Network during 2017.

Even though RDS remains the most important disease by incidence in premature infants, recent data show a reduction in mortality from nearly 100% to less than 10% in the last years.[1]

Besides prematurity, other risk factors can increase the likelihood of developing the respiratory disease such as:

- Genetic mutation of surfactant proteins genes, especially ABCA3;
- meconium stain amniotic fluid;
- male sex, weak androgenous hormones circulating can reduce the production of phospholipids;
- caesarean delivery;
- gestational diabetes, the insulin elevation reduces the production of surfactant proteins;
- chorioamnionitis and PPROM (prenatal pre-labour rupture of membranes).[2]

3.2 Diagnosis

Prenatal invasive techniques are nowadays rarely performed unless the presence of a pathological condition forces to schedule of premature delivery. What can be done in this field is an amniocentesis to establish the Lecitin/Sphingomyelin Ratio. L/S>2 implicates a reduced RDS risk, also the number of lamellar bodies can be measured. Lamellar bodies are the surfactant stocking system into type II pneumocytes, >50000 units/microL of amniotic fluid suggest maturity.

Anyway, with the advent of glucocorticoids antenatal prophylaxis, no invasive tests are required and the diagnosis of RDS is mainly on clinical post-natal bases.

Regarding the signs and symptoms: the tendency of air spaces to collapse till severe atelectasis due to lack of surfactant increases breathing work, principal signs are tachypnea, nasal flaring, chest retraction, and grunting.[2]

Tachypnea in the newborn is defined as respiratory rate > 60 breaths per minute.[3]

Obviously, breathing symptoms in a premature newborn are rather common nonspecific signs of breathing, cardiovascular, metabolic or systemic problems: this said we must look for the other signs of increased respiratory work to identify RDS cases.

Retraction, for example, is the sign that the newborn is using accessory muscles in the neck, sternum, and abdomen to breathe. Nasal flaring indicates the attempt to compensate for the higher resistance and higher breathing work by increasing the upper airway diameter. Noisy breathing may also indicate airway resistance. Grunting is an expiratory sound heard whenever glottis closes suddenly during expiration to maintain Functional Residual Capacity.[2]

Currently, post-natal imaging techniques can support the diagnosis of RDS.

Typical findings in chest radiography are diffuse atelectasis and ground glass appearance, also air bronchograms (bronchi overfilled with air despite the airless parenchyma around) can be observed.

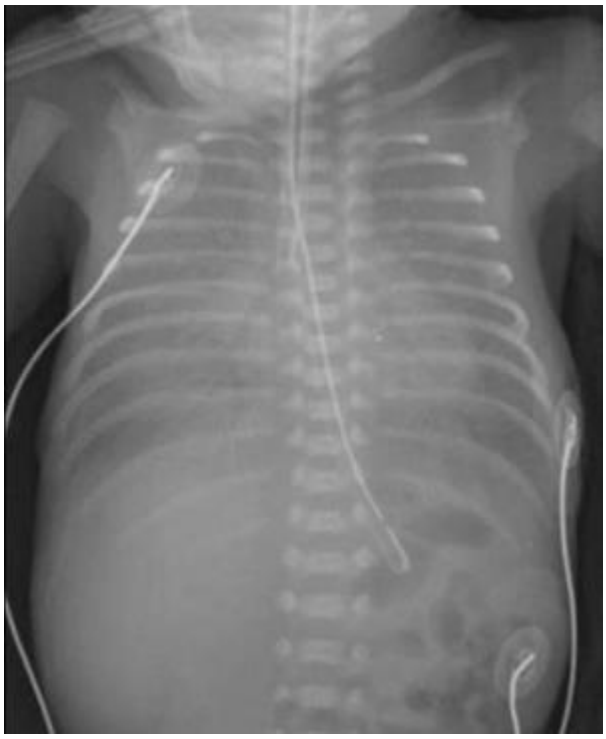


Figure 1: classic chest radiograph in a RDS infant

Echography also has a role in this field, abnormal lung consolidation, pleural lines abnormalities and disappearance of A lines are quite specific for RDS.

From a laboratorystic point of view, EGA can show hypercarbia and hypoxia.[1] It is very important to look for Streptococcus B infection as early sepsis can be rather indistinguishable from RDS.

RDS must be diagnosed and managed quickly, otherwise, respiratory failure and escalation to cardiac arrest can occur[2], it is necessaire to recognize symptoms and radiological findings as soon as possible.

3.3 Pathophysiology

As said surfactant deficiency is the fundamental cause of RDS pathophysiology.

Surfactant is a lipoprotein made of cholesterol, phospholipids and proteins, it is synthesized by type II pneumocytes into alveolar spaces as tubular myelin, its function is to decrease the surface tension of air-water interface keeping alveolus open.[4] Type II pneumocytes store surfactant in lamellar bodies, once secreted in extracellular space surfactant forms a lipid monolayer[1].

While the main function of phospholipids, especially dipalmitoyl phosphatidylcholine, is to keep surface tension low, surfactant-related proteins of low molecular weight play a crucial role in immune defense and particles clearance[5]. There are five characteristic proteins in surfactant, SP-A and SP-D are defense proteins and play an immune role, SP-B and SP-C promote adsorption and spread of surfactant.[5]

Normally FRC Functional Residual Capacity prevents alveoli to collapse at the end of exhalation. The newborn chest wall is mainly composed of cartilage, it is more pliable and predisposed to atelectasis.[6]

Surfactant plays a role in maintaining FRC, as it keeps normal the pulmonary Compliance, or rather the change in Volume for every given change in Pressure. When surfactant is missing the strength of respiratory muscles will be no longer capable to create the needed amount of Pressure to keep alveoli open, this increases the incidence of atelectasis.

Lung injury occurs when surfactant is missing leading to atelectasis, moreover, this causes edema which can inactivate surfactant further.[1]

When alveoli collapse, air can no longer reach the alveolar-capillary membrane, this impedes the blood from oxygenating and causes a V/Q mismatch, hypoxia, and, eventually, respiratory failure.[1]

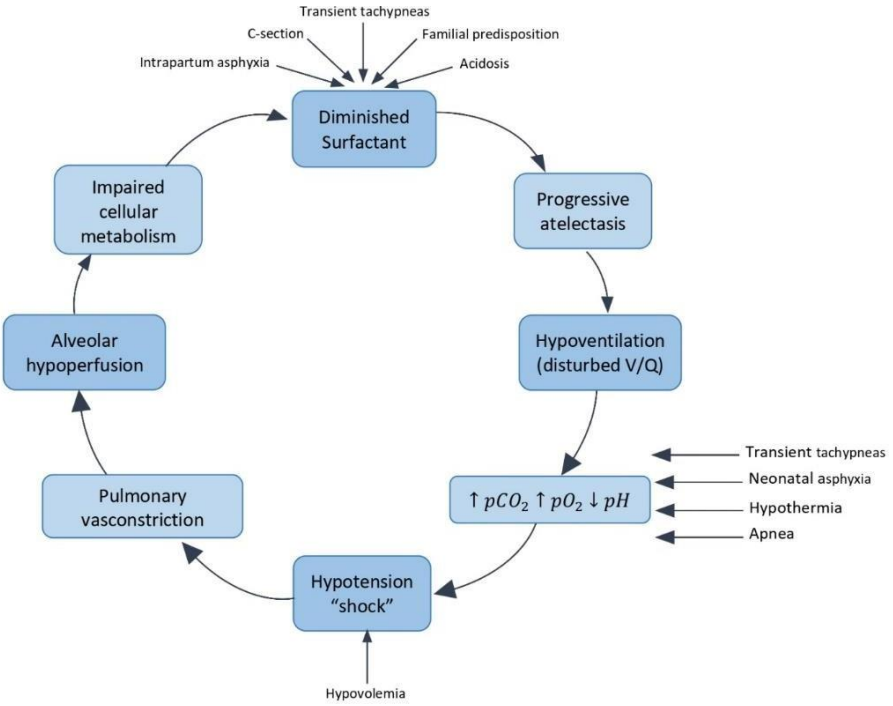


Figure 2: Pathogenesis of RDS

Unfortunately, surfactant deficiency is very common whenever maturity and adequate lung development is not reached.

Lung development begins in the embryonic period and continues in early childhood.

Prenatal lung development recognizes four main phases, plus the alveolar phase, ongoing during growth after birth:

- Embryonic period, weeks 0 to 6 of gestation
- Pseudoglandular period, weeks 6 to 16
- Canalicular period, weeks 16 to 24-28
- Saccular period, till 36 weeks
- Alveolar, 36+

Although the periods of development are different from one another there is some overlap in terms of weeks.[7]

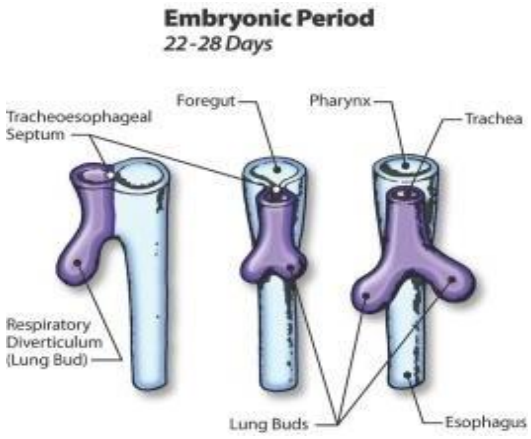


Figure 3, Embrionic development

The first embryonic stage begins during the fourth week after conception, a small bug bulges out of the foregut at the pharynx. This lung bud elongates and forms the trachea, larynx, and the initial bronchi, in the following weeks the initial bronchus forms three buds on the right, and two on the left, lobes will develop. In this phase laryngeal lumen closes.

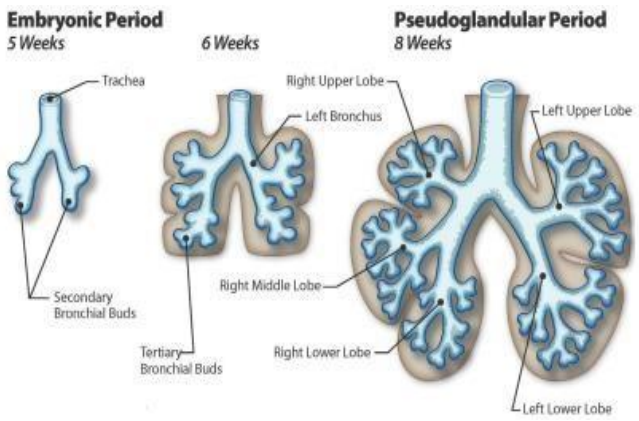


Figure 4, Embryonic to Pseudoglandular period

Further branching of the bronchi occurs during the second period of lung development, the pseudoglandular stage. The thorax cavity splits from the abdomen cavity, laryngeal lumen gets reopened. There is a significant development of the bronchioles until the bronchial divisions are completed at about 16 weeks' gestation.

During canalicular stage, respiratory bronchioles form with alveular ducts that will later form primitive alveoli. In this phase the vessel system develops too, by the end of canalicular period (16- 28 weeks), gas exchange begins. Type II cells are just starting to appear.

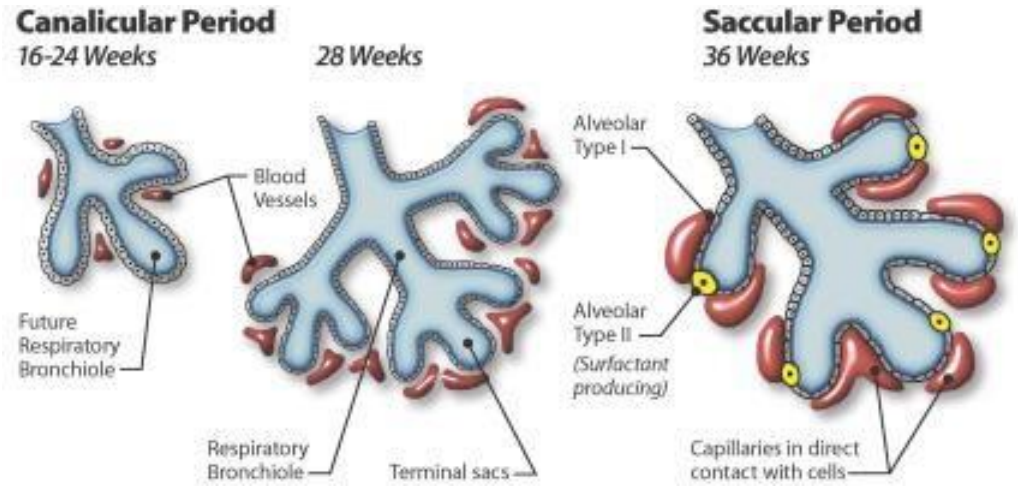


Figure 5, Canalicular to Saccular period

The fourth period is called the saccular or terminal sac period. During this stage, the alveolar ducts are producing primitive alveoli called terminal saccules. Type II cuboidal pneumocytes are producing surfactant throughout this period, but the levels would be less than at term. Most infants with RDS happen to be born in this gestational phase.

The fifth period is called the alveolar stage, where true alveoli are formed, this stage continues after birth. Type II Pneumocytes are completely mature at this point. In fact, a great amount of alveolar septation and microvascular maturation occurs after birth.[6] Bronchopulmonary dysplasia can occur during this stage.[8]

3.4 Management Guidelines

Being RDS so common, not only it is important to reach a correct diagnosis as soon as possible but also the proper therapeutical management is crucial.

The current way to manage properly RDS is described by European Consensus Guidelines[9] in the Management of Respiratory Distress Syndrome, now updated to 2019: the aim is to maximize survival while minimizing adverse effects of interventions, such as BPD.

RDS management begins with prenatal care.

First, it is crucial to identify the risk of spontaneous preterm delivery in pregnant women. This risk can partially be identified by knowing women with previous preterm delivery and by measuring cervical length associated with fibronectin's

test. In these cases, it is necessary to consider interventions to prolong gestation while preparing the fetus for birth.

Mothers at risk of premature delivery should be transferred to tertiary centers where appropriate skills are available and there is expertise in VLBW babies.

Tocolytics (oxytocin and Ca-cannel blockers) can be used to permit safe transfer in uterus and allow corticosteroids to take effect.

Corticosteroids are very important, a single course of prenatal drugs given to mothers with anticipated preterm delivery reduces RDS, clinicians should offer this treatment to all women at risk of preterm delivery till 34 weeks' gestation. A single repeat course may be given until 32 weeks' gestation if birth does not occur within 7 days.

$MgSO_4$ should be administered to women in imminent labour before 32 weeks' gestation.

Delivery room stabilization is the following fundamental step.

Preterm babies with RDS are usually expected to try to breathe during transition at birth although they will normally struggle to keep alveolar aeration, therefore "*Supporting transition*" instead of "*Resuscitation*" is preferred in babies with RDS.

Guidelines recommend delayed clamp of umbilical cord for at least 60 s, in case of emergency milking technique could be an alternative.

Stimulation of the infant helps establish spontaneous breathing, keeping the adequate temperature of the room (around 26 degrees) and the baby by Infant Warmer use and wrapping bag is recommended.

Focusing on respiratory support, spontaneously breathing babies should be stabilized on CPAP while Intubation should be reserved for babies nonresponding to CPAP according to guidelines. In fact, CPAP can only be applied in spontaneous breathing infants otherwise the ventilation per minute would not allow adequate CO^2 exchange. The CPAP pressure level is conventionally set at 6-9 cm H_2O.

CPAP should simulate normal transition trough gradually rising saturations, as it occurs in healthy newborns in the very first 10 minutes after birth, going from about 60% to 90%.

Babies who require intubation should be given surfactant.

3.4.1 Surfactant therapy according to 2019 European Guidelines

Guidelines put out two main issues upon the question *"When to treat with Surfactant?"*

On one hand, we must consider how the main purpose of surfactant is to avoid long term intubation, so it should be given immediately when intubation is required as part of stabilization; on the other hand, some infants with milder disease get to improve autonomously without surfactant, avoiding the discomfort of laryngoscopy.

Anyway, the actual severity of RDS and how it will progress is difficult to determine. 2013 Guidelines suggested that surfactant should be given whenever FiO2 required during CPAP use is > 0.30 in very immature babies (<30 weeks' gestation). Moreover, Guidelines suggest administrating more than one dose of surfactant to reduce air leaks, but this is not that simple in infants who are maintained in non-invasive ventilation, need for redosing can be however reduced by giving a larger dose at the beginning.

Nowadays it is clear that prophylactic use of surfactant in infants at very high risk of RDS is better than rescue therapy, anyway the risk size remains clinically determined. Prophylactic surfactant should be administered in concurrence of coexisting risk factors such as maternal diabetes, male sex, asphyxia, and sepsis, while antenatal steroids and prolonged rupture of membranes are positive prognostic factors and reduce the risk of RDS.[5] It is not always possible to determinate which infants will manifest respiratory symptoms.

Disadvantage of prophylactic treatment is overtreatment leading in many cases to intubation, moreover, prophylaxis therapy compared with stabilization by receiving CPAP associated with selective surfactant administration showed an increased risk of BPD or mortality.[8]

Selective surfactant therapy avoids overtreatment, especially in those born after 28 weeks of gestation. Selective treatment can be distinguished in Early Treatment vs Later Rescue Therapy[5] .

Early replacement is provided in symptomatic infants before the occurrence of inflammation, within a couple of hours after birth, this guarantees a decreased risk of mortality, BPD, and air leaks.[10] Later surfactant replacement is given by the time of respiratory failure when intubation and mechanical ventilation are required.

After surfactant is administered lung function improves, first there is a rapid improvement in oxygenation and inflation of atelectatic segments, ventilation-perfusion matching improves, after that, Compliance and Functional Residual Capacity get better.[5]

Regardless of the time of administration, Surfactant therapy is crucial in the management of RDS, unfortunately, intratracheal administration is an important cause of lung damage. Many trials and studies are currently focusing on finding new and better ways of administration, avoiding the harmful effects of intubation and mechanical ventilation such as BPD.

Surfactant administration methods are:

- Bolus administration through tracheal intubation;
- INSURE technique, allows surfactant to be given without Mechanical Ventilation ongoing;
- New methods using catheters with the infant under nCPAP (LISA, …), it is reasonable to recommend these methods in spontaneously breathing babies stable on CPAP.

  One of the advantages of using a small catheter is to reduce the temptation to continue MV after administration of surfactant, but this complicates the issue of sedation in a fragile child on CPAP.
- Nebulization methods are now in ongoing trials;
- Laryngeal mask administration.

Exogenous surfactants can be classified into three main groups[11]. Most used drugs are the animal-derived ones, so-called "*Natural Surfactant*", their phospholipids concentration is around 80% and they contain low molecular weight proteins SPs. Surfactant can also be pharmacologically synthesized, the "*Artificial Surfactant*" of first-generation is mainly made of dipalmitoylphosphatidylcholine and is protein-free, a second generation of "*Artificial Surfactant*" is emerging, also containing recombinant proteins.

To be more accurate, a fourth category of drug can be identified, it is "*Human Surfactant*" derived from amniotic fluid during caesarean section, it is extremely difficult to collect and has never been used in clinical practice on a widespread scale.[11]

Surfactant types currently available in Europe are animals' natural ones, trials show that maximum advantage is given by 200 mg/kg of Poractant Alfa, a derived porcine surfactant, compared to lower doses of bovines' surfactants.

Cochrane meta-analysis comparing natural surfactant (provided with SP-A, SP-B, SP-C and SP-D proteins) to synthetic non-protein surfactant confirmed that natural surfactant reduces the risk of BPD and pneumothorax.[1]

Surfactant therapy may also be useful whenever although lungs maturity, secondary surfactant inactivation occurs due to severe pneumonia, pulmonary haemorrhage or meconium aspiration syndrome.

What happens after acute stabilization of newborns with RDS is also very important to optimize the outcomes of RDS management.

According to Guidelines oxygen supplementation is given targeting saturations between 90% and 94%, these targets reduce the risk of severe retinopathy of prematurity ROP.

Regarding Non-Invasive respiratory support, it is essential to manage preterm infants without MV where possible. Recommendations are to start CPAP from birth in all babies < 30 weeks' gestation at risk of RDS with early rescue surfactant when needed.

Despite efforts to keep preterms on CPAP, some small infants will require MV to inflate the atelectatic lung, with all the well-known consequences. Fortunately, some babies with RDS managed with early surfactant therapy will often require short-term ventilation and are rapidly weaned to lower settings.

Targeting CO^2 levels allowing permissive Hypercarbia, using Caffeine as an early respiratory stimulant and administrating postnatal steroids are strategies to cut short MV duration and reduce inflammation and risk of BPD.

Also, the topic of pain and sedation in the management of the many procedures that a baby with RDS undergoes is problematic. The balance between the attempt to minimize MV and proper analgesia when needed must be pursued.

In this field, LISA has shown advantages giving a better chance of success without sedation.

3.5 Modes of Surfactant Administration

Modes of administering Surfactant have been rapidly progressing. Being RDS the most common disease in preterm and newborn infants[1], the necessity to find a way of administration that can maximize the benefits of surfactant therapy while minimizing the consequences of the administration itself is crucial.

Adverse effects of RDS treatments can be significant, anyway, the risk/benefit ratio remains low.

For some time, the only way to administrate surfactant was to directly give it intubating with endotracheal tube as interface. The dose (1.5 to 4 mL/kg body weight, depending on the preparation) was instilled into the lung in divided aliquots, each of which was administered in a different body position[5], the infant would then stay in artificial mechanical ventilation for a certain period.

Exposure to mechanical ventilation, no matter how brief, is known to cause many adverse effects in newborns, developing BPD due to volotrauma, barotrauma and biotrauma is the main one. The infant will then need oxygen therapy for at least 28 days if born before 32 weeks gestation or beyond 36 weeks postmenstrual age.

It is exactly in the context of RDS treatment with prolonged artificial ventilation that BPD was first described by Northway et al. in 1967 in New English Medical Journal.

Inflammatory response provoked by eMV is crucial in BPD, the great number of cytokines and inflammatory cells provoke protease activation leading to fibrosis and abnormal lung development.[11] In 1999 Jobe et al. described a "new BPD", caused by processes interfering with lung development, such as mechanical ventilation.[1]

BPD must be prevented as much as possible due to the poor-term neurological outcomes associated.[8]

Studies focused on reducing the chronic inflammatory damage caused by mechanical ventilation of medium-long duration, INSURE method has therefore developed.

Verder et al.[12] showed that the INSURE (INtubation, SURfactant delivery using an endotracheal tube and Extubation after a brief period of mechanical ventilation) approach was effective in reducing the need for subsequent mechanical ventilation in preterm infants with moderate-to-severe RDS receiving nasal continuous positive airway pressure (nCPAP) ventilation.

INSURE technique comprises intubation-administration-extubation, after extubation nCPAP is continued. The reduction of BPD is approximately 50%[13]. This method also reduces the need for MV after extubation, the duration of oxygen therapy and NEC disease[14].

Still, the risks of BPD and lung injury are not abolished although few mechanical breaths INSURE implicate.

A meta-analysis "Avoiding Endotracheal Ventilation to Prevent Bronchopulmonary Dysplasia[11]" evaluated seven RCTs comprising 3289 patients. It pointed out, again, how avoiding eMV and stabilizing premature infants on early nasal Continuous Positive Airway Pressure nCPAP in the delivery room may reduce BPD incidence. Early trials in the meta-analysis compared the effects of MV versus INSURE, the

following ones compared INSURE to surfactant application during nCPAP via a thin catheter as an interface, without any intubation at all. The outcome studied was death or BPD in preterms <30 weeks' Gestational Age. Avoiding eMV led to a reduction in the incidence of death or BPD with odds ranging from 0.63 to 0.97.

The trend is now to avoid eMV despite a higher risk of hypercapnic respiratory failure, in some cases later leading to rescue intubation. Beyond the higher risk of Bronchopulmonary Dysplasia, endotracheal intubation itself is also a stressful and painful procedure, in addition, it may be associated with hemodynamic instability: hypoxia, desaturation, hypercapnia, bradycardia, and transient increase of intracranial pressure[15].

An Umbrella Review[8] of systematic meta-analysis delved into all the strategies to prevent bronchopulmonary dysplasia in preterm neonates, Continuous Positive Air Pressure, early selective surfactant with less invasive administration, corticosteroids prophylaxis appeared to be the most successful prevention strategies.

Once shown the disadvantages of endotracheal intubation and mechanical ventilation, as brief as it can be, alternatives have been implemented to reduce the invasiveness of surfactant administration thus avoiding endotracheal intubation altogether.

Options, as before said, are early administration of surfactant via a thin catheter during spontaneous breathing, without intubating, the aim is to improve the success of nCPAP. Other methods include aerosolized administration, pharyngeal administration, laryngeal mask airway-guided administration.

Gopel et al[16]. compared surfactant therapy via standard administration (INSURE) versus surfactant treatment during spontaneous breathing via a thin catheter inserted into the trachea by laryngoscopy. The intervention group had a lower need for mechanical ventilation and a lower oxygen need at 28 days of life. Preterm infants with a gestational age from 26 to 28 weeks of less than 1,5 kg were enrolled. The researchers do not recommend the use of small catheters to give surfactant in infants above 32 weeks as there is no evidence of reducing BPD in

this group, moreover, more mature infants often struggle and need sedation drugs that may interfere with spontaneous breathing which is crucial to make LISA work.

Techniques that use a thin catheter as an interface to administer surfactant are known as Less Invasive Surfactant Administration (LISA) or Minimally Invasive Surfactant Treatment (MIST) or Minimally Invasive Surfactant Administration (MISA).[17] Recent literature suggests that LISA reduces the need for mechanical ventilation and BPD's mortality. Many studies also proved decreased intraventricular hemorrhage, probably due to a lower incidence of hypocarbia and following fluctuation of cerebral blood flow in preterm babies that are known to have poor autoregulation.[10]

Meta-analyses point in the direction that LISA is more effective than standard treatment both in short and long-term outcomes.

Terminologies like LISA, MIST, and Take Care although the differences in the devices and procedures are sometimes used indifferently. Therefore, Pandita et al.[10] proposed a classification of surfactant administration techniques to make the terminology uniform and universally understandable. The term "*SurE*" (Surfactant administration without endotracheal tube) was coined to include all thin catheter methods.[10]

Like INSURE, thin catheter methods can only be used in spontaneously breathing infants with stable hemodynamics. Because the larynx is not obstructed by an endotracheal tube, vocal cords are allowed to adduct with each other, moreover spontaneous breathing uniforms the spread and the absorption of the drug across airway spaces.[10]

During catheter administration, nCPAP can be continued to maintain good FRC of the lung.[10]

According to a recent meta-analysis by Bellos et al. the short-term advantages provided by LISA compared with INSURE are lower rates of mortality (OR 0.64), BPD (OR 0.57), and periventricular malacia (OR 0.66), necrotizing enterocolitis (OR

0.67). The need for mechanical ventilation within 72 hours has been the primary short-term outcome in the majority of the studies about SurE techniques.

SurE techniques were also reported to have long-term outcomes, such as better neurodevelopment outcomes in babies born at 25-26 weeks of gestation, explanation could be the reduced brain hypoxia normally associated with mechanical ventilation.[18]

Generally speaking, surfactant administration using any thin catheter is not the simplest procedure, therefore, for a good success rate, this technique requires to be performed by expert neonatologists trained in the technique. The paucity of training and lack of expertise for the procedure in neonates<26 weeks result in reduced use of LISA in many centers, but it is exactly in babies born at<28 weeks of gestation that the advantages of LISA are maximized.[19]

Still, the placement of a catheter interface into the trachea requires laryngoscopy. This is limiting the advantages although it does not implicate endotracheal intubation, indeed a prolonged laryngoscopy to position the catheter can result in consequences such as bradycardia, hypoxia, hemodynamic changes. Also, surfactant reflux can sometimes occur after catheter administration. Obviously, we also have to consider that the thin and resistant catheter used during LISA technique is not useable for mechanical ventilation if needed.

Recent literature advocated for reliable studies comparing LISA with INSURE, to shed even more light on the advantages of LISA.[20]

Because of the limits of LISA, other methods and interfaces such as surfactant administration via supraglottic airways device (SAD) are currently being studied.[17] Administration via laryngeal mask airway LMA is a way to administer the drug by a supraglottic airway device interface shaped like a tube that is placed in the hypopharynx and covers the supraglottic structure, isolating the trachea.

The two main advantages are to reduce invasiveness by precluding laryngoscopy and to perform an easier administration requiring fewer operators' training.[21]

It was investigated in piglets models the relative deposition of surfactant in the lung via LMA, compared to bolus installation via endotracheal tube[22]. Surfactant deposition was measured by scintigraphy. According to the results standard LMA administration was obtained to deposit 40% of the originally given dose, INSURE administration was obtained to deposit 88% of it. Moreover, a new interface has been tested: LMA using a camera to place surfactant below vocal cords with the use of a catheter introduced under the control of the video camera.[22]

However, much is still to be studied in the use of LMA during the management of RDS, there is a lack of studies about using LMA in extremely low birth weight neonates who are at maximum risk of surfactant deficiency due to the technical difficulty of using LMA small-sized in such infants.

The newest and still studied methods to administer surfactant recently identified are intraamniotic instillation, pharyngeal instillation and nebulization in spontaneously breathing infants.

Aerosolized surfactant, for example, would not require infants to be intubated and would enhance the distribution of surfactant into the lungs, this procedure still requires laryngoscopy. To aerosolize the drug would anyway avoid the necessity of intubation.

Much about these new alternative modes of administration must be cleared.

The current state of the art still suggests that Less Invasive Surfactant Administration LISA is superior in reducing the need for mechanical ventilation and the risk of death or BPD.[23] Moreover, it appears to reduce major complications related to lifelong disabilities with lower rates of intraventricular hemorrhage.[24]

LISA remains an extremely promising way to administrate surfactant, it is not only a single technical procedure but rather a component of a complex care bundle supporting the transition of a premature baby to extrauterine life guaranteeing a “soft landing”[19].

3.6 Methods to perform Less Invasive Surfactant Administration

The procedural aim is to deposit surfactant beyond vocal cords via a thin catheter to allow surfactant to spread widely.

To reach this procedural aim a variety of different devices and technical approaches have been developed around Europe.

Name	Device type	Procedure/instruments	Referance
INSURE	Endotracheal tube	Layngoscope	Verder et al.
Cologne method	Flexible suction catheter	Layngoscope+Magill forceps	Kribs et al.
Hobart method	Semi-rigid vascular catheter Device name: fo example, Lisacath	Layngoscope, no forceps	Dargaville et al.
Take Care method	Flexible nasogastric tube	Layngoscope, no forceps	Kanmaz et al.
Laryngeal Mask method	Special device placed in hypopharynx	No Layngoscope, no forceps	Roberts et al.
Aerosal Method	No catheter Nebuliser with, for example, mask/prongues	No Layngoscope, no forceps	Pillow et al.
Pharyngeal Surfactant	Flexible short tube and syringe Injection into the pharynx	No Layngoscope, no forceps	Kattwinkel et al.

Figure 6: Methods to perform Less Invasive Surfactant Administration

In Germany, around 2007 Angela Kribs wondered if the great benefits given by nCPAP can be taken advantage of although the necessity to administer surfactant therapy.

The method Kribs et al.[25] developed consisted of administering surfactant by a feeding tube with one orifice marked 1,5 cm above the tip, connected to a syringe filled with surfactant. The catheter was clamped with Magill forceps and inserted into the trachea under direct laryngoscopy after a dose of atropine. The catheter was placed so that the mark was visible at the vocal cords. Surfactant was injected after fixation of the catheter with fingers and removal of the laryngoscope. After finishing the procedure, the gastric feeding tube was aspirated to ensure the drug was not into the stomach accidentally.

This method is also called the *Cologne method*.

As said, in this method the catheter is placed with Magill forceps into the trachea under direct laryngoscopy, the catheter is thin and soft such as the ones used as gastric feeding tubes.

Around 2013 Kanmaz et al.[26] managed to modify Cologne method in the so-called *Take Care* technique.

Kanmaz modified Kribs' technique aiming to take better care of infants from 26 to 28 weeks of gestational age. The time limit to the procedure was shorted from 60 to 30 seconds, a single type of surfactant (porctant alfa) was administered, and a shorter catheter length was used without any forceps utilization during application. A 5F flexible nasogastric tube was used. Desired depths insertions beyond the vocal cord were 1.0, 1,5, 2.0 cm respectively in infants with 25 to 26, 27 to 28, and 29 to 32 weeks GA. After catheter placement laryngoscope was removed. Kanmaz et al. have developed a technique to deliver surfactant quickly and safely without the use of forceps.

This technique resulted in a lower rate of mechanical ventilation and less BPD when compared with infants treated with endotracheal intubation administration of surfactant.

The main alternative to the classic German device (soft catheter) was proposed by Dargaville et al. [27] in the *Hobart method.*

This method consisted in the use of a stiff vascular 16G narrow-bone vascular catheter of 130mm in length inserted through vocal cords under direct vision using a standard laryngoscope and Miller 00 blade. If the catheterization attempt failed after 30s nCPAP was reinstated for one minute. The rigid catheter used in the study can be passed straight along the laryngoscope blade. Not using forceps to insert the device beyond vocal cords allows a better view, this could make the procedure easier, moreover, the catheter is way thinner than an endotracheal tube and the tip is malleable.

Premedications were not given in the study and Porcine surfactant (100 mg/kg) was then instilled followed by reinstitution of CPAP. Dargaville et al.[27] reported that babies of GA>28 weeks poorly tolerate LISA, this opens the possibility to consider the role of sedation and premedications for LISA administration.

Pandita et al.[10] in a 2021 Review recommend the use of atropine and fentanyl to prevent vagal stimulation and pain. Non-pharmacological measures like containment can also be useful. The use of propofol, instead, increases the risk of desaturation during the procedure.

Dargaville et al. also reported the importance of continuing nCPAP during the procedure to prevent derecruitment.

The primary outcome was the reduction in intubation in the first 72h compared with historical controls. Other outcomes recorded by Dargaville et al. using a vascular catheter were further surfactant need, pneumothorax, PDA requiring indomethacin, and BPD incidence. The comparison was made with a historical control group of 15-28 weeks infants managed in the period 2006-2008 with the INSURE technique.

Basically, the *Hobart method* is a modification of the regular German method (*Cologne method*). Physicians may find this method easier. Of note, a difficult procedure may have some drawbacks such as the prolonged duration of the laryngoscopy needed to insert the device, which is likely to aggravate the invasiveness of the procedure and result in stressful consequences such as bradycardia, hypoxia and hemodynamic changes.

Still, the trauma of laryngoscopy remains a great limitation, especially without sedation.

We hypothesized that less invasive surfactant administration through a rigid vascular catheter might be an easier procedure with a higher rate of success compared to a soft catheter inserted by using Magill forcep.

An easier procedure may have advantages such as the reduction of the duration of the laryngoscopy needed to insert the device, which is likely to reduce the invasiveness of the procedure and stressful hypoxic and hemodynamic consequences.

4. OBJECTIVES

The “PICOT” question of this study was:

P: in extremely low birth weight infants with RDS

I: does LISA with rigid catheter

C: compared to LISA with soft catheter,

O: change the time of device positioning (primary outcome), success of the procedure and participant’s satisfaction (secondary outcomes)?

The primary objective of this trial was to compare the time of device positioning with LISA with rigid catheter vs. LISA with soft catheter in a manikin simulating an extremely preterm infant. Further objectives were to compare the success of the procedure of positioning the device with LISA with rigid catheter vs. LISA with soft catheter, and participant’s satisfaction.

5. METHODS

5.1 Setting

The present study was conducted in the Neonatal Intensive Care Unit of the Woman and Child Health Department of Padua University Hospital as coordinating center and Fondazione Poliambulanza of Brescia as participating center. The scenario consisted of an extremely low birth weight infant needing surfactant administration (neonatal simulator manikin: Premature Anne, Laerdal Medical Corporation, Stavanger, Norway).

5.2 Study design

This was an unblinded, randomized, controlled, crossover (AB/BA) trial of surfactant administration with LISA rigid catheter vs. LISA soft catheter in a manikin simulating an extremely low birth weight infant (clinicaltrial.gov NCT05388175).

5.3 Inclusion and exclusion criteria

Level III NICU consultants and residents were eligible to participate.

There were no exclusion criteria for this study, besides refusal to participate.

5.4 Randomization

All participants were randomly assigned to AB or BA arms in a 1:1 ratio.

Randomization was performed using a computer-generated random assignment list.

Arm assignments were included in sealed opaque envelopes sequentially numbered.

5.6 Procedure

Participants in AB arm were assigned to carry out the procedure with a rigid catheter (LISAcath®, Chiesi Farmaceutici, Parma Italy), followed by the procedure with a soft catheter (VYGON, Ecouen, France), (Figure 7). Participants in BA arm were assigned to the reverse sequence.

A 6-hour washout period was included to reduce any carryover effect.

The soft catheter was placed in the trachea by using Magill forcep with direct visualization of the vocal cords with a laryngoscope[16].

The study outcomes were recorded by an external observer during the simulations.

After each attempt, the external observer evaluated the correct positioning using a laryngoscope, and the participant was instructed to repeat the procedure in case of incorrect positioning.

The maximum time granted for each attempt was 60 seconds[16]. If the procedure was not done within 60 seconds, the participant paused for 60 seconds, then he/she performed another attempt. The procedure was repeated until achievement of correct positioning of the device. The total time of device positioning was calculated as the sum of the times of all attempts needed to achieve a correct device positioning.

At the end of each simulation, participants were asked to grade the difficulty in using the device (not difficult; mildly difficult; moderately difficult; very difficult; extremely difficult) overall and regarding four specific aspects (handling the device, visualizing the glottis, inserting the device in the trachea). All procedures were video-recorded, (Fig. 8).

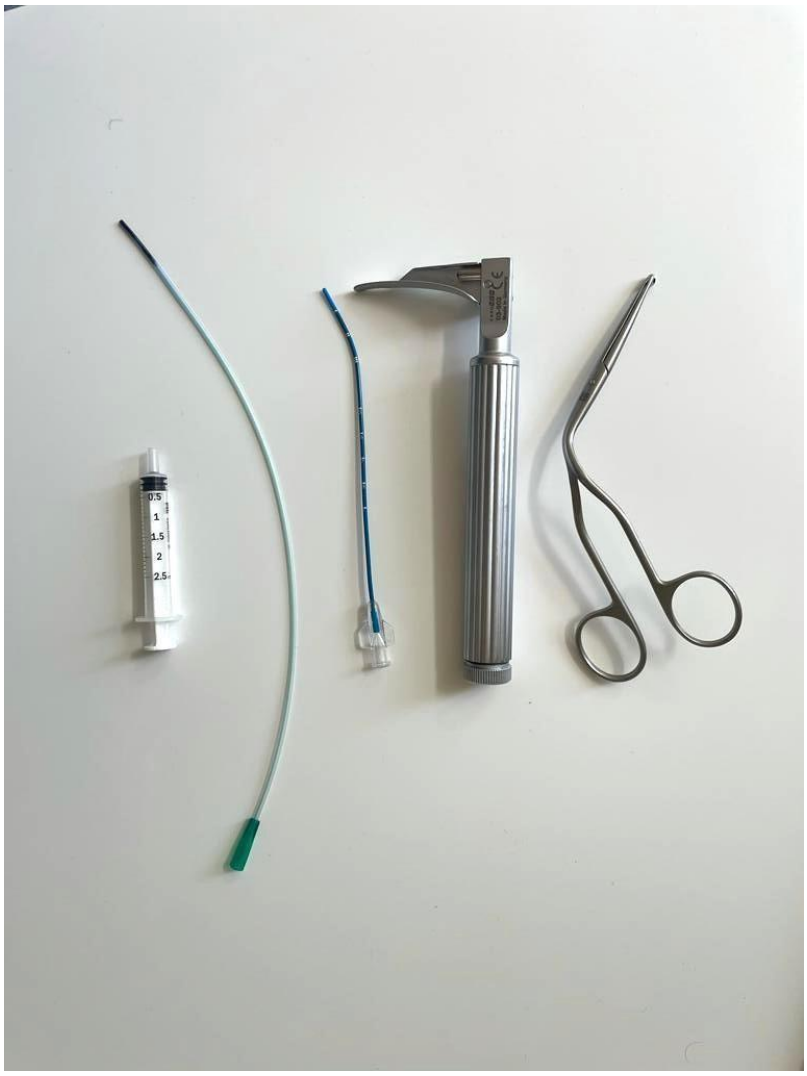


Figure 7, Devices for surfactant administration used in the trial: soft catheter (VYGON, Ecouen, France) and rigid catheter (LISAcath®, Chiesi Farmaceutici, Parma Italy)

Figure 8, scan to see the videos of the two LISA procedures.

5.7 Outcome measures

The primary outcome measure was the total time of device positioning. The time of device positioning was defined as the time elapsed from the positioning of the laryngoscope in the manikin mouth to the connection of the syringe to the catheter.

After the first attempt, the correct positioning (defined as the achievement of the positioning of the device in the trachea) was evaluated by the external observer using a laryngoscope, and the procedure was repeated in case of incorrect positioning.

Hence, the total time of device positioning was calculated as the sum of the time of device positioning in all attempts.

The secondary outcome measures were:

- the success of the first attempt,
- the number of attempts to achieve the correct positioning (as defined above) of the device in the trachea,
- participant's opinion on using the device (evaluated using a Likert scale).

5.8 Sample size

The literature does not offer any knowledge on the time of device positioning or the magnitude of prolonged duration of the laryngoscopy with potential clinical consequences.

Hence, we aim to enroll all eligible 24-50 participants. These sample sizes had the chance of detecting a standardized effect size ranging from 0.40 to 0.59 with 80% power and ranging from 0.46 to 0.69 with 90% power in a crossover design (the full range is displayed in Figure 9). Sample size calculation was performed using R 4.1 (R Foundation for Statistical Computing, Vienna, Austria).

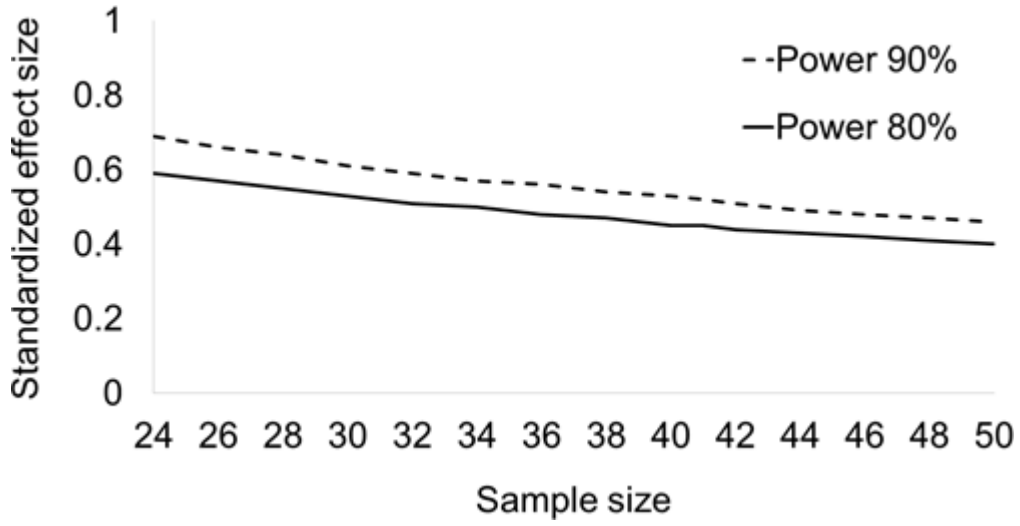


Figure 9: Detectable standardized effect sizes according to sample size and power in a crossover AB/BA design

5.9 Recruitment

Written and oral information was offered to the participants by a competent professional trained in neonatal resuscitation. Consent to use the data was obtained by all participants.

5.10 Blinding

Due to the characteristics of the intervention, neither caregivers nor outcome assessors were masked to treatment allocation.

However, the statistician performing data analysis was masked to treatment allocation.

5.11 Guidelines for Management

Before starting the study, the participants joined a meeting where all the details of the study protocol were presented.

During each simulation, an external observer recorded the study outcomes.

5.12 Data collection

Information on participants (age, sex, experience), randomization sequence and outcome measures were collected by an observer who was not involved in the simulation. Data were recorded in a data sheet designed for this study and maintained in order to protect confidentiality before, during, and after the trial by the principal investigator in a personal computer protected by password.

All data were collected by an observer not involved in the simulation.

The following information were registered in a Case Report Form: randomization sequence, participant age, and experience, study outcomes (as described before).

5.13 Abbreviations

LISA: less invasive surfactant administration; RDS: respiratory distress syndrome.

5.14 Trial Registration

The study has been registered in ClinicalTrials.gov NCT05388175.

6. STATISTICAL ANALYSIS

This crossover trial applied an AB/BA scheme, which is uniform within sequences and periods, hence removing any period and sequence effects. In addition, the washout period was chosen to reasonably prevent any carryover effects.

Data were summarized as median and interquartile range (IQR) (numerical variables) or absolute frequency and percentage (categorical variables).

Numerical outcome measures were not Normally distributed (according to the q-q plots), thus were compared between the two arms using the Wilcoxon signed-rank test and effect sizes were reported as median difference with bootstrap 95% confidence interval.

Binary outcome measures were compared between the two arms using the McNemar test and effect sizes were reported as difference in proportion for paired data with 95% confidence interval.

Participants' opinions about difficulty in using the device were evaluated using a Likert scale and compared between the two arms using the Wilcoxon signed-rank test.

All tests were 2-sided and a p-value less than 0.05 was considered statistically significant. Statistical analysis was performed using R 4.1 (R Foundation for Statistical Computing, Vienna, Austria).

7. RESULTS

The trial included 50 participants (21 males and 29 females, median age 32 years, IQR 30-38) who were randomly assigned to the trial arms (Figure 10).

Median experience in neonatal intensive care was 1 year (IQR 1-6). Experience in surfactant treatment with rigid catheter was >20 cases in four participants, 10-20 cases in five participants, 5-10 cases in two participants and <5 cases in 39 participants. Experience in surfactant treatment with soft catheter was 5-10 cases in one participant and <5 cases in 49 participants.

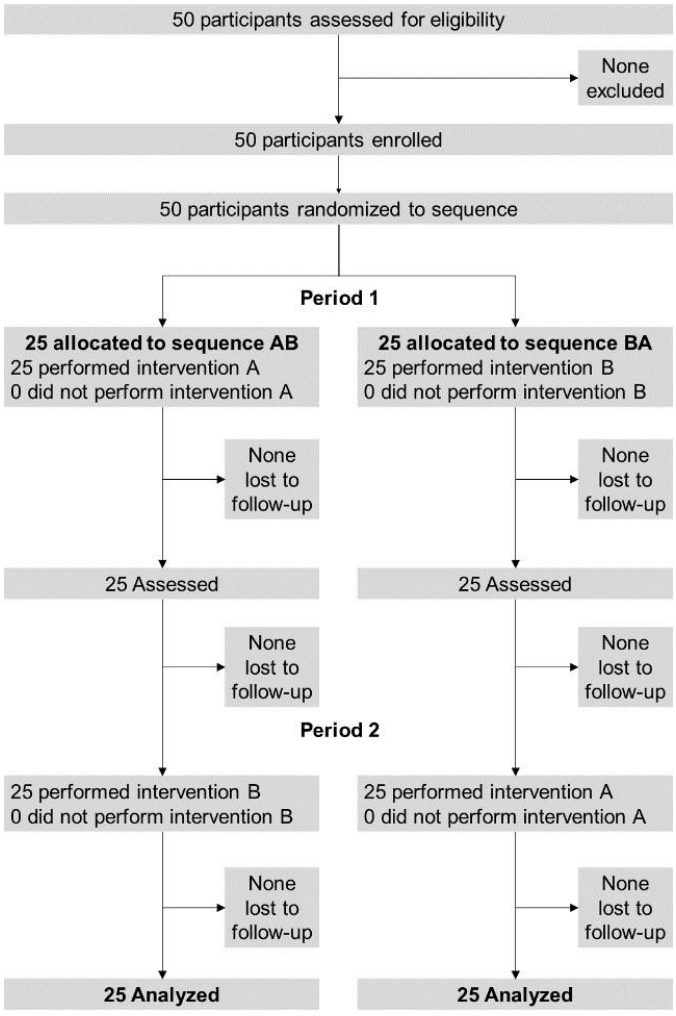


Figure 10, CONSORT flow diagram.

Median time of device positioning was 19 seconds (IQR 15-25) with rigid catheter and 40 seconds (IQR 28-66) with soft catheter (median difference -17 seconds, 95% confidence interval -26 to -12 seconds; $p<0.0001$) (Table 1).

Positioning the device in the trachea at the first attempt was achieved by 46 participants with rigid catheter (92%) and 37 participants with soft catheter (74%) ($p=0.01$; Table 1).

The median number of attempts to insert the device in the trachea was 1 (IQR 1-1) with rigid catheter and 1 (IQR 1-2) with soft catheter ($p=0.009$; Table 1).

Table 1. Outcome measures

	Outcome measure	Procedure with rigid catheter	Procedure with soft catheter	Comparison of rigid vs. soft catheter	
Primary outcome		median (IQR)	median (IQR)	p-value (Wilcoxon signed-rank test)	Median difference (bootstrap 95% confidence interval)
	Total time of device positioning, seconds	19 (15-25)	40 (28-66)	<0.0001	-17 (-26 to -12)
Secondary outcomes		median (IQR)	median (IQR)	p-value (Wilcoxon signed-rank test)	Median difference (bootstrap 95% confidence interval)
	Number of attempts to insert the device in the trachea	1 (1-1)	1 (1-2)	0.009	0 (0 to 0)
		n (%)	n (%)	p-value (McNemar test)	Difference in proportion for paired data (95% confidence interval)
	Positioning the device in the trachea at the first attempt	46 (92%)	37 (74%)	0.01	18% (3% to 32%)

Participants' opinions on difficulty in using the device are displayed in Figure 11 (full data in Supplementary Table 1).

Overall, the participants found the rigid catheter easier to use (Figure 11D, p<0.0001), especially concerning handling (p<0.0001, Figure 11A), visualizing the glottis (p=0.01, Figure 11B) and insertion in the trachea (p<0.0001, Figure 11C).

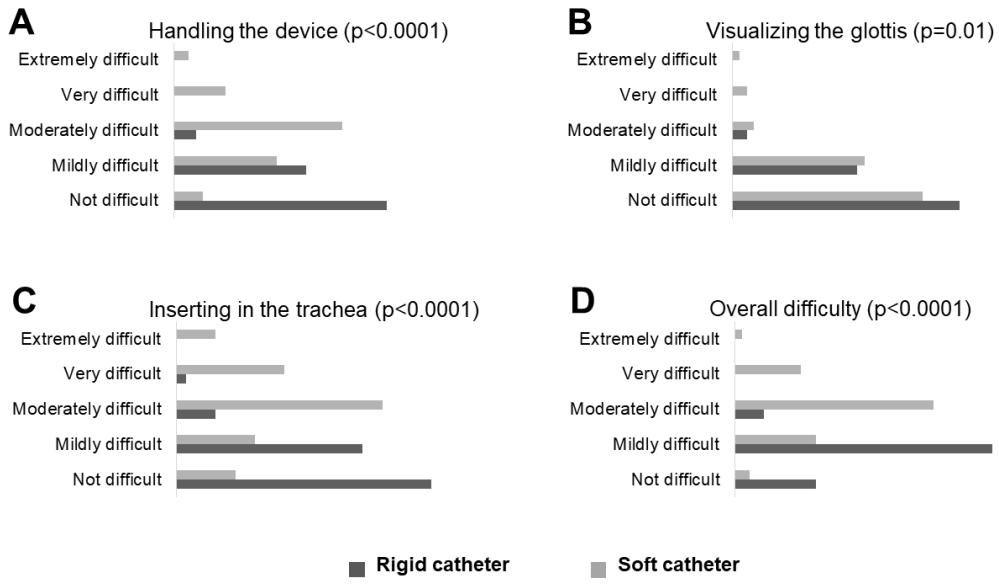
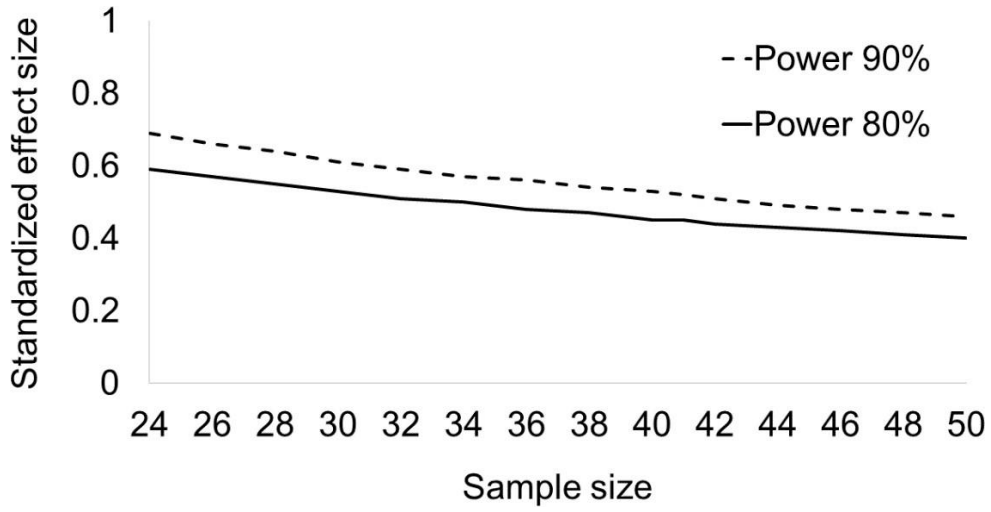


Figure 11, Participants' opinions about difficulty in using the device (evaluated using a Likert scale).

7.1 Supplementary material

Supplementary Figure 9. detectable standardized effect sizes according to sample size ranging from 24 to 50 participants and power of 80% or 90% in a crossover AB/BA design



Supplementary Table 1. Participant ratings (Likert scale) of the difficulty in using the device.

Aspect	Procedure with rigid catheter: n (%)	Procedure with soft catheter: n (%)
Difficulty in handling the device:		
1 not difficult	29 (58)	4 (8)
2 mildly difficult	18 (36)	14 (28)
3 moderately difficult	3 (6)	23 (46)
4 very difficult	0 (0)	7 (14)
5 extremely difficult	0 (0)	2 (4)
Difficulty in visualizing the glottis:		
1 not difficult	31 (62)	26 (52)
2 mildly difficult	17 (34)	18 (36)
3 moderately difficult	2 (4)	3 (6)
4 very difficult	0 (0)	2 (4)
5 extremely difficult	0 (0)	1 (2)
Difficulty in inserting the device in the trachea:		
1 not difficult	26 (52)	6 (12)
2 mildly difficult	19 (38)	8 (16)
3 moderately difficult	4 (8)	21 (42)
4 very difficult	1 (2)	11 (22)
5 extremely difficult	0 (0)	4 (8)
Overall difficulty:		
1 not difficult	11 (22)	2 (4)
2 mildly difficult	35 (70)	11 (22)
3 moderately difficult	4 (8)	27 (54)
4 very difficult	0 (0)	9 (18)
5 extremely difficult	0 (0)	1 (2)

8. DISCUSSION

The results of the present trial showed that a rigid catheter should be preferred to a soft catheter to conduct LISA procedure.

These results are in agreement with the initial hypothesis of the study.

Regarding the primary outcome, data showed that using a stiff device to administer surfactant could save about 17 seconds (p value<0.0001) to accomplish the procedure, from the placing of laryngoscopy to the administration of the drug. The median time of device positioning was 19 seconds for LISA with rigid catheter, while the operators took a median time of 40 seconds for the positioning of the soft catheter with the use of a Magill forcep.

A shorter procedure to administer surfactant through the catheter means a shorter duration of laryngoscopy, this can reduce adverse events associated with the invasiveness of the procedure such as bradycardia, hypoxia, and other hemodynamic changes. Data from previous study conducted in adults undergoing anesthesia[28] , show that laryngoscopy causes discomfort due to the traction applied to the blade: this causes several autonomic reflexes such as catecholamine release that leads to pulmonary hypertension, intracranial hypertension and arrhythmias.

Most of participants were able to insert the device in the trachea at the first attempt in both procedures, suggesting that this specific aspect (numbers of attempts to insert LISA catheter in the airways) is unlikely to drive the choice for LISA interface (rigid vs. soft catheter). However 25% of participants needed two or more attemps (IQR 1-2) to insert the soft catheter. The success at the first attempt was significantly lower with the rigid catheter (p value= 0.01) suggesting that also this advantage should be taken into account.

Extremely low birth weight infants are more frequently in need for surfactant treatment. In such small patients, it is very important positioning the device at the

correct depth, because a wrong depth could partially nullify the benefits of surfactant or cause relevant clinical demages (i.e. pneumothorax, air-leaks). Most (92%) participants achieved the correct positioning (depth) of the device at the first attempt with the rigid catheter, while only 74% of participants accomplished the same results with the soft catheter. The rigid catheter had a higher success rate in this secondary outcome of 18% (p 0.01). These findings suggest the LISA procedure with a rigid catheter may increase the effectiveness of the treatment and reduce potential adverse outcomes.

When the participants' opinions about the difficulty in using the devices were asked, it was clear that the difficulty of correctly inserting the device in the trachea, and the overall difficulty, in general, were significantly reduce with the rigid catheter.

In addition, the handling of the device itself and the capacity of visualizing the glottis were in favor of the rigid catheter. The need of the Magill forcep to manage the soft catheter compared to the direct handling of the rigid catheter may explain such a preference.

Literature shows advantages in Less Invasive Surfactant Administration compared with classic endotracheal intubation plus mechanical ventilation and probabily even compared with the INSURE approach. Benefits of LISA were shown and reviewed in the meta-analysis "Avoiding Endotracheal Ventilation to Prevent Bronchopulmonary Dysplasia[11]".

Seven RCTs including 3289 patients were considered. The study outcome was death or BPD in preterms <30 weeks' Gestational Age.

Beyond the higher risk of Bronchopulmonary Dysplasia, endotracheal intubation itself is also a stressful and painful procedure, associated with hemodynamic instability[15]. Regarding long-term implications related to lifelong disabilities due to the RDS treatment, LISA reduced severe ventricular hemorrhages and increased

the combined survival with adverse events[24]. Cystic periventricular leukomalacia and retinopathy requiring laser therapy seemed to occur less frequently[24].

There are, however, some concerns regarding the LISA approach[28] including lack of pathophysiological bases the presence of significant flaws in larger available trials. Moreover, detractors of LISA consider the small catheters inadequate for surfactant spreading into airways and lung parenchyma.

The main LISA methods were described by Kribs et al.[25] and by Dargaville et al.[27] , respectively known as the *Cologne* and the *Hobart* methods.

Kribs et al.'s procedure[25] uses a soft catheter completely similar to the one used in the present study, it is handed by using a Magill forcep, and currently represents the German approach to conduct LISA. The advantages of this kind of surfactant administration were to reduce short-term severe complications compared with conventional intubation in historical controls. The trial also showed a higher rate of successful tracheal positioning with the small soft catheter and a lower rate of desaturations and bradycardias. The new procedure also proved to be able to reduce by one-third the overall intubation and mechanical ventilation.

On the other hand, Dargaville et al.'s[27] also compared the use of a small catheter (a narrow-bore vascular rigid catheter) to administer surfactant, with historical controls treated with endotracheal intubation, the new approach could avoid intubation and prevent pneumothorax.

Cologne and *Hobart* methods currently represent the basis of the new less invasive surfactant administration techniques. However, both studies only compared the catheters' use with endotracheal intubation in historical controls, and no direct comparisons between the two catheters can be found in literature.

To our knowledge, this trial is the first attempt to compare the two main LISA methods.

8.1 Strengths of the study

The strengths of the present study include: i) to our knowledge, this trial is the first attempt to compare the two main LISA methods; ii) the study design: this was an unblinded, randomized, controlled, crossover (AB/BA) trial. Although blindness in the caregivers and/or outcome assessors could not be realized due to the characteristics of the interventions themselves, we were able to mask the statistician performing data analysis; iii) the setting we simulated for this trial was very close to clinical practice, especially because of the materials utilized. The catheters and the laryngoscopy are exactly the ones normally in use in the Neonatal Intensive Care Units around the world which conduct LISA as a part of treatment for RDS. Moreover, the manikin was 700g, close to the average weight that preterms infants have at surfactant treatment; iv) this trial also managed to exceed the minimum numerosity requested (24 participants) for the statistical analysis to detect a standardized effect size. Moreover, physicians with great heterogeneity in years and kinds of experience were enrolled in this trial. Participants were pediatric residents at different years of their Residency training, and consultants recently over their Residency or instead, with many years of experience in the Neonatal Intensive Care field. This variety makes the results easily appliable and extendable to different contests and hospitals with different skills in neonatal reanimation of the staff.

9. LIMITATIONS

The characteristics of the interventions did not allow to conduct this trial in real newborn infants therefore a manikin was used (Fig.12). It did not move or cry, so the still-to-be-solved problem of the potential need for sedation[10] was not in the field.

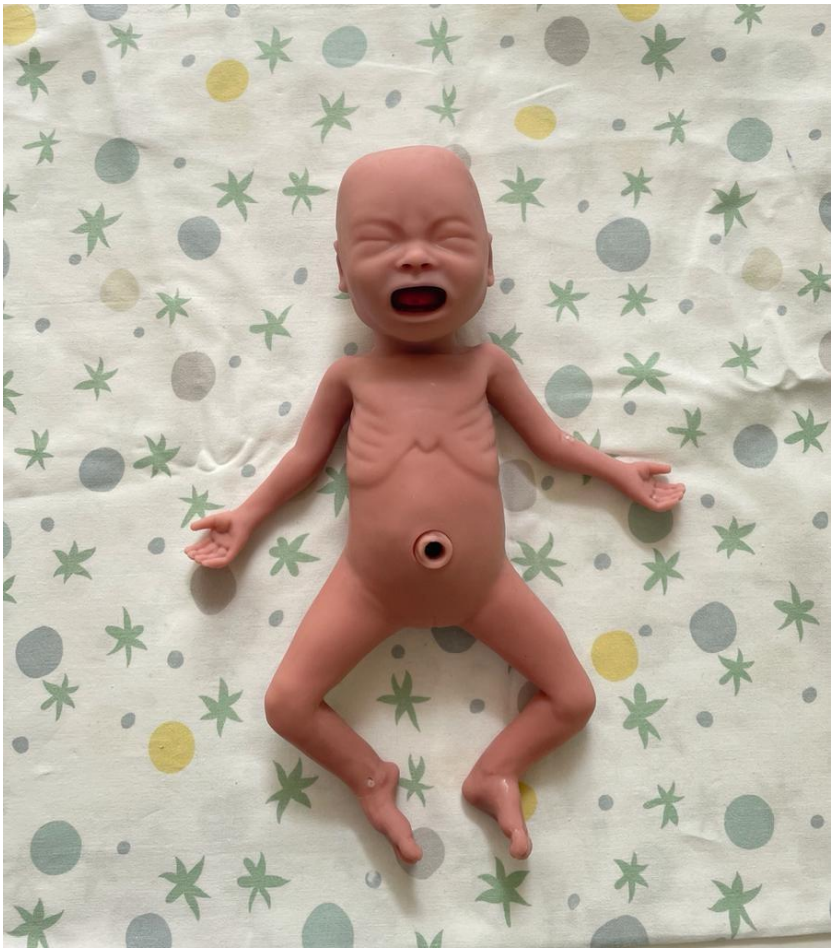


Figure 12, Extremely Low Bith Weight Infant manikin model.

Moreover, the interventions took place in a quiet room, very different from the contest of a delivery room or a Neonatal Intensive Care Unit ward's room. We can say that the setting implicated a low-stress environment, participants' emotional involvement can be a strong variable to consider in clinical practice during the

complex care bundle of supporting the transition of a premature baby to extrauterine life.

The very different contest does not permit to automatically generalize the results in alive infants and actual clinical practice.

Another limit of the present trial is the low amount of experience of most participants in performing LISA according to the Cologne method: through a soft catheter. Only one of our 50 participants used the soft catheter in clinical practice more than five times, and he was a consultant with more than thirty years of experience in NICU. Experience in surfactant treatment with the rigid catheter, instead, was >20 cases in four participants, 10-20 cases in five participants, 5-10 cases in two participants, and <5 cases in 39 participants. To overcome the difference in practice and experience the outcome assessors allowed the participants to try the procedure with the soft catheter once, before the actual data recording.

Different data about experience cases may be found among NICU's residents and consultants in Germany or in other neonatal units.

Having LISA great advantages in the management of RDS, it will probably be a procedure utilized on a progressively larger scale, therefore it is important to understand which technical aspects can be implemented and which catheter should be preferred. Our findings may give useful information to health care providers about practical aspects of the most used approaches for surfactant administration.

An easier procedure in such a common treatment may have several advantages. Such as a shorter duration of laryngoscopy with all its consequences in terms of invasiveness and stressful outcomes on an already fragile premature infant, the standard patient in which LISA is needed.

10. CONCLUSION

Our results show a significant difference between the two more frequently used catheters to perform the LISA procedure.

Using a rigid versus a soft catheter to perform the LISA procedure on an extremely preterm manikin is faster, more adequate in terms of catheter insertion depth and is more appreciated by operators. Further studies are needed to confirm our manikin findings in clinical practice.

11. BIBLIOGRAFIA

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12. APPENDIX 1- STUDY PROTOCOL

TITLE: Does LISA with rigid catheter change the time of device positioning compared to LISA with soft catheter in extremely low birth weight infants with RDS? A crossover randomized controlled manikin trial.

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ABSTRACT

Background: LISA can be provided using rigid or soft catheters, but possible differences in terms of easiness of use and success of the procedure are unknown. A difficult procedure may have some drawbacks such as the prolonged duration of the laryngoscopy needed to insert the device, which is likely to aggravate the invasiveness of the procedure and result in stressful consequences such as bradycardia, hypoxia and hemodynamic changes.

Objectives: i) time of device positioning, ii) success of the procedure of positioning the device, iii) participant's satisfaction.
Methods: This is an unblinded, randomized, controlled, crossover (AB/BA) trial of surfactant treatment with LISA with rigid catheter vs. LISA with soft catheter in a manikin simulating an extremely low birth weight infant. Participants will be level III NICU consultants and residents. Randomization will be performed using a computer-generated random assignment list. The primary outcome measure will be the total time of device positioning. The secondary outcomes will be the success of the first and participant's satisfaction.

Trial registration: the study will be registered in ClinicalTrials.gov after Ethics Committe approval.

Keywords: less invasive surfactant administration (LISA); simulation scenario

Funds: this is a no-profit study. No funds have been planned for this study.

Background

Respiratory distress syndrome (RDS) remains a significant problem for preterm babies, although management has evolved gradually over the years resulting in improved survival for the smallest infants but with unacceptable rates of bronchopulmonary dysplasia (BPD). Of the 8,156 babies from Europe for whom data were submitted to the Vermont Oxford Network during 2017, RDS was coded for about 80% of babies born at 28 weeks' gestation increasing to 90% at 24 weeks' gestation. (1) The management of RDS, as recommended in the fourth update of "European Guidelines for the Management of RDS", includes prediction of risk of preterm delivery, timely use of antenatal steroids, correct delivery room management and surfactant administration. (2) Surfactant replacement therapy is a crucial part of management of RDS, and newer protocols for its use recommend early administration and avoidance of mechanical ventilation. (2)

During the last decade, new techniques to administer surfactant have been promoted, based on their presumed lesser invasiveness. They consist of the administration of surfactant through a narrow non- ventilatable tube (usually a feeding or vascular catheter or a dedicated one of similar diameter) instead of a regular endotracheal tube (ETT). These techniques have been variably called less invasive surfactant administration (LISA), minimally invasive surfactant therapy (MIST) or minimally invasive surfactant administration (MISA). (3) Since the 2016 Guideline, there have been further randomised trials and meta-analyses comparing these methods. These suggest that LISA is superior in terms of reducing need for MV and the combined outcome of death or BPD. (3-6)

LISA can be provided using rigid or soft catheters (7,8), but possible differences in terms of easiness of use and success of the procedure are unknown. Of note, a difficult procedure may have some drawbacks such as the prolonged duration of the laryngoscopy needed to insert the device, which is likely to aggravate the invasiveness of the procedure and result in stressful consequences such as bradycardia, hypoxia and hemodynamic changes.

The "PICOT" question of this study is:
P: in extremely low birth weight infants with RDS
I: does LISA with rigid catheter
C: compared to LISA with soft catheter,
O: change the time of device positioning?

The main objective of this trial will be to compare the time of device positioning with LISA with rigid catheter vs. LISA with soft catheter in a manikin simulating an extremely low birth weight infant. Further objectives will be to compare the success of the procedure of positioning the device with LISA with rigid catheter vs. LISA with soft catheter, and participant's satisfaction.

Methods

Study design

This is an unblinded, randomized, controlled, crossover (AB/BA) trial of surfactant treatment with LISA rigid catheter vs. LISA soft catheter in a manikin simulating an extremely low birth weight infant.

Setting

The study will be conducted at the University Hospital of Padova as coordinating center (daniele.trevisanuto@unipd.it) and Fondazione Poliambulanza of Brescia as participating center (paolo.villani@poliambulanza.it).

Inclusion criteria

Level III NICU consultants and residents will be eligible to participate in the study.

Exclusion criteria

There are no exclusion criteria for this study.

Randomization

All participants will be randomly assigned to AB or BA arms in a 1:1 ratio. Randomization will be performed using a computer-generated random assignment list. Arm assignments will be included in sealed opaque envelopes sequentially numbered.

Procedure

Participants in AB arm will be assigned to perform the procedure with LISA rigid catheter, followed by the procedure with LISA soft catheter. Participants in BA arm will be assigned to the reverse sequence. A washout period of 6 hours (one procedure in the morning and one in the afternoon) will be included to reduce any carryover effect.
During each simulation, an external observer will record the study outcomes.
After the first attempt, the correct positioning will be evaluated by the external observer using a laryngoscope, and the procedure will be repeated in case of incorrect positioning.

The maximum time allowed for each attempt will be 60 seconds [7]. If the procedure is not completed in 60 seconds, the participant will stop for 60 seconds, then he/she will perform another attempt. The procedure will be repeated until correct positioning of the device will be achieved.
The total time of device positioning will be calculated as the sum of the times of all attempts needed to achieve a correct device positioning.

Outcome measures

The primary outcome measure will be the total time of device positioning. The time of device positioning was defined as the time elapsed from the positioning of the laryngoscope in the manikin mouth to the connection of the syringe to the catheter. As the procedure would be repeated in case of device not in the trachea, the total time of device positioning will be calculated as the sum of the time of device positioning in all attempts.
The secondary outcome measures will be the success of the first attempt (defined as the achievement of the correct positioning of the device in the trachea as assessed by the external observer using a laryngoscope), the number of attempts to achieve the correct positioning of the device in the trachea, and participant's opinion on using the device (evaluated using a Likert scale).

Sample size

The literature does not offer any information on the time of device positioning or the magnitude of prolonged duration of the laryngoscopy with potential clinical consequences. Hence, we aim to enroll all eligible 24-40 participants. In a crossover design, such sample sizes will have the chance of detecting a range of standardized effect sizes as reported in Figure 1. Sample size calculation was performed using R 4.1 (R Foundation for Statistical Computing, Vienna, Austria).

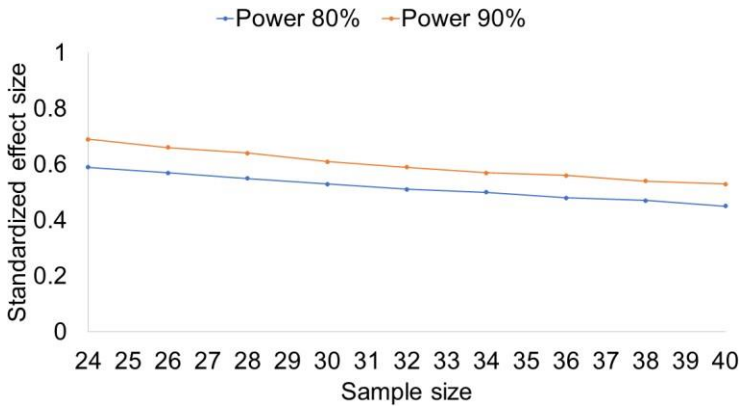

Figure 1. Detectable standardized effect sizes according to sample size and power in a crossover AB/BA design

Recruitment

Written and oral information will be offered to the participants by a competent professional who is trained in neonatal resuscitation. Consent to use the data will be obtained by all participants.

Blinding

Due to the characteristics of the intervention, neither caregivers nor outcome assessors will be masked to treatment allocation. However, the statistician performing data analysis will be masked to treatment allocation.

Guidelines for Management

Before starting the study, the participants will join a meeting where all the details of the study protocol will be presented. During each simulation, an external observer will record the study outcomes.

Data collection

Data will be recorded in a data sheet designed for this study and maintained in order to protect confidentiality before, during, and after the trial by the principal investigator in a personal computer protected by password. All data will be collected by an observer not involved in the simulation. The following information will be registered: randomization sequence, participant age and experience, study outcomes (as described before).

Statistical analysis

Continuous data will be expressed as mean and standard deviation or median and interquartile range, and categorical data as number and percentage.

The study will include a washout period that was chosen to reasonably prevent carryover effects. Since tests for carryover effect are generally underpowered, the inclusion of an adequate washout period is strongly recommended to prevent carryover effects. (9)

The primary outcome measure will be compared between the two procedures using a paired Student t test, or using the two-sample t test approach on paired data (i.e. two-sample t test applied to the differences between period in the two arms) (10) if imbalances in the AB/BA crossover design will occur (i.e. dropouts). Period effects will be also tested for with a similar approach (i.e. two-sample t test applied to the differences between methods in the two arms). (10)

The success of the first attempt will be compared between the two procedures using McNemar test.

Participant's satisfaction (evaluated using a Likert scale) will be compared between the two procedures using Mann-Whitney test.

All tests will be 2-sided and a p-value less than 0.05 will be considered statistically significant. Statistical analysis will be performed using R 4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Duration of study

After obtaining approval from the Ethics Committee, we expect to perform the study in two weeks.

Ethical considerations

The trial is being submitted to the Ethics Committees of the participating centers. All participants will provide written informed consent and all data will be anonymized.

Compliance to protocol

Compliance will be defined as full adherence to protocol. Compliance with the protocol will be ensured by the principal investigator and the local collaborators; they will be responsible for local data collection.

Dissemination policy

The results of the trial are expected to be published in a scientific journal and to be presented in medical seminars and conferences. The final reporting will follow the CONSORT Report guidelines (http://www.consort-statement.org).

Abbreviations

LISA: less invasive surfactant administration; RDS: respiratory distress syndrome.

Competing interests

The authors declare that they have no competing interests.

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13. APPENDIX 2- STUDY CRF

Codice partecipante: Sede: _____

CASE REPORT FORM

TITLE: Does LISA with rigid catheter change the time of device positioning compared to LISA with soft catheter in extremely low birth weight infants with RDS? A crossover randomized controlled manikin trial.

Informazioni sul partecipante
Nome_____Cognome _____ Medico: a) specialista b) specializzando Età _____ Anni di esperienza in TIN _____ Numero di somministrazioni di surfattante con tubo endotracheale: a) <5 b) 5-10 c) 10-20 d) >20 Numero di somministrazioni di surfattante con LISA (catetere rigido): a) <5 b) 5-10 c) 10-20 d) >20 Numero di somministrazioni di surfattante con LISA (catetere morbido): a) <5 b) 5-10 c) 10-20 d) >20

Compilato da_____Data _____

Codice partecipante: Sede: _____

Procedura 1

indicare il device usato: □ LISA rigido □ LISA morbido

Outcome

Outcome	Definizione	Risultato
Tempo totale di posizionamento (in secondi)	Tempo dall'inizio della laringoscopia al corretto posizionamento in trachea. Il tempo limite per ciascun tentativo è di 60 secondi. Se sono necessari più tentativi, va sommato il tempo di ciascun tentativo.	
Successo al primo tentativo (si/no)	È stato ottenuto il corretto posizionamento in trachea al primo tentativo?	
Numero di tentativi	Quanti tentativi sono stati necessari per ottenere il corretto posizionamento in trachea?	
Raggiungimento della corretta profondità in trachea	È stata raggiunta la corretta profondità in trachea della punta?	

Compilato da_____Data _____

Codice partecipante: Sede: _____

Procedura 1

indicare il device usato: □ LISA rigido □ LISA morbido

Soddisfazione del partecipante

Aspetto	Definizione	Risposta
Maneggiare il device	Hai sperimentato difficoltà nel maneggiare il device?	□ 1 per nulla □ 2 un po' □ 3 abbastanza □ 4 molto □ 5 moltissimo
Visualizzare la glottide	Hai sperimentato difficoltà nel visualizzare la glottide?	□ 1 per nulla □ 2 un po' □ 3 abbastanza □ 4 molto □ 5 moltissimo
Inserimento del device in trachea	Hai sperimentato difficoltà nell'inserire il device in trachea?	□ 1 per nulla □ 2 un po' □ 3 abbastanza □ 4 molto □ 5 moltissimo
Profondità corretta	Hai sperimentato difficoltà nel posizionare il device alla corretta profondità?	□ 1 per nulla □ 2 un po' □ 3 abbastanza □ 4 molto □ 5 moltissimo
Difficoltà complessiva	Qual è stata la difficoltà complessiva che hai sperimentato nell'usare il device?	□ 1 nessuna difficoltà □ 2 lieve difficoltà □ 3 moderata difficoltà □ 4 molta difficoltà □ 5 elevata difficoltà

Compilato da_____Data _____

Codice partecipante: Sede: _____

Procedura 2

indicare il device usato: □ LISA rigido □ LISA morbido

Outcome

Outcome	Definizione	Risultato
Tempo totale di posizionamento (in secondi)	Tempo dall'inizio della laringoscopia al corretto posizionamento in trachea. Il tempo limite per ciascun tentativo è di 30 secondi. Se sono necessari più tentativi, va sommato il tempo di ciascun tentativo.	
Successo al primo tentativo (si/no)	È stato ottenuto il corretto posizionamento in trachea al primo tentativo?	
Numero di tentativi	Quanti tentativi sono stati necessari per ottenere il corretto posizionamento in trachea?	
Raggiungimento della corretta profondità in trachea	È stata raggiunta la corretta profondità in trachea della punta?	

Compilato da_____Data _____

Codice partecipante: Sede: _____

Procedura 2

indicare il device usato: □ LISA rigido □ LISA morbido

Soddisfazione del partecipante

Aspetto	Definizione	Risposta
Maneggiare il device	Hai sperimentato difficoltà nel maneggiare il device?	□ 1 per nulla □ 2 un po' □ 3 abbastanza □ 4 molto □ 5 moltissimo
Visualizzare la glottide	Hai sperimentato difficoltà nel visualizzare la glottide?	□ 1 per nulla □ 2 un po' □ 3 abbastanza □ 4 molto □ 5 moltissimo
Inserimento del device in trachea	Hai sperimentato difficoltà nell'inserire il device in trachea?	□ 1 per nulla □ 2 un po' □ 3 abbastanza □ 4 molto □ 5 moltissimo
Profondità corretta	Hai sperimentato difficoltà nel posizionare il device alla corretta profondità?	□ 1 per nulla □ 2 un po' □ 3 abbastanza □ 4 molto □ 5 moltissimo
Difficoltà complessiva	Qual è stata la difficoltà complessiva che hai sperimentato nell'usare il device?	□ 1 nessuna difficoltà □ 2 lieve difficoltà □ 3 moderata difficoltà □ 4 molta difficoltà □ 5 elevata difficoltà

Compilato da_____Data _____