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Catheter And Laryngeal Mask Endotracheal Surfactant Therapy: the CALMEST approach as a novel MIST technique

Ilaria Vannozzi MD, Massimiliano Ciantelli MD, Francesca Moscuzza MD, Rosa T. Scaramuzzo MD, PhD, Davide Panizza MD, Emilio Sigali MD, Antonio Boldrini MD & Armando Cuttano MD

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RUNNING HEAD: CALMEST

AUTHORS: Ilaria Vannozzi, MD[1], Massimiliano Ciantelli, MD[1], Francesca Moscuzza, MD[1], Rosa T. Scaramuzzo, MD, PhD[1], Davide Panizza, MD[3], Emilio Sigali, MD[1], Antonio Boldrini, MD, Professor[1-2], Armando Cuttano, MD[1]

AFFILIATIONS:

[1]Centro di Formazione e Simulazione Neonatale "NINA", U.O. Neonatologia, Azienda Ospedaliero-Universitaria Pisana. Via Roma, 67 – 56126 Pisa (Italy)

[2] Università di Pisa (Italy)

[3] Istituto di Scienze della Vita, Scuola Superiore Sant'Anna. Piazza Martiri della Libertà, 33 – 56125 Pisa (Italy)

CORRESPONDING AUTHOR:

Rosa T. Scaramuzzo, MD, PhD

U.O. Neonatologia, Azienda Ospedaliero-Universitaria Pisana

Via Roma, 67 - 56126 Pisa (Italy)

Phone: +39 050 992654

Fax: +39 050 992611

E-mail: rosa.scaramuzzo@gmail.com

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Abstract

Purpose: Neonatal Respiratory Distress Syndrome (RDS) is a major cause of mortality and morbidity among preterm infants. Although the INSURE technique for surfactant replacement therapy is so far the gold standard method, over the last years new approaches have been studied, i.e. LISA or MIST. Here we propose an originally modified MIST, called CALMEST (Catheter And Laryngeal Mask Endotracheal Surfactant Therapy), using a particular laryngeal mask as a guide for a thin catheter to deliver surfactant directly in the trachea.

Materials and Methods: We performed a preliminary study on a mannequin and a subsequent *in vivo* pilot trial.

Results and Conclusions: This novel procedure is quick, effective and well tolerated and might represent an improvement in reducing neonatal stress. Ultimately, CALMEST offers an alternative approach that could be extremely useful for medical staff with low expertise in laryngoscopy and intubation.

Background

Neonatal Respiratory Distress Syndrome (RDS) contributes to a high rate of mortality and morbidity among preterm infants. Lung immaturity and surfactant deficiency are the main causes of this disease. Notably, surfactant dysfunction also leads to respiratory failure in a broader group of disorders targeting term infants, such as meconium aspiration syndrome[1], congenital pneumonia [2], and rare cases of mutations of the genes encoding surfactant proteins B and C [3, 4] .

The traditional therapeutic approach for RDS was based on early endotracheal intubation, surfactant administration and mechanical ventilation. In 1994, to reduce the duration of mechanical ventilation, a new approach for surfactant administration called INSURE (INtubation, SURfactant administration, Estubation) was set up. Nowadays, this procedure represents the gold standard technique [2, 5]. However, INSURE still suffers from several limitations, including tracheal intubation and mechanical ventilation, even though the latter occurs only for a short time. In light of

these considerations, over the last years, alternative approaches to surfactant administration have been studied and introduced.

Kribs et al. described the LISA technique (Less Invasive Surfactant Administration) to deliver surfactant to spontaneously breathing neonates on CPAP: surfactant was instilled in the trachea through a thin catheter introduced by Magill forceps during direct laryngoscopy [6]. LISA procedure does not include mechanical ventilation; however, this technique still requires laryngoscopy, thus leading to potential damage to soft tissues and ultimately to the use of analgesic drugs.

Trevisanuto et al. tested the laryngeal mask (LM) to deliver surfactant (MIST - Minimally Invasive Surfactant Therapy). This approach seems to be effective and minimally invasive since there is no need for intubation or premedication [7]. However, surfactant is delivered by a supraglottic device and endotracheal administration of full drug dose is not guaranteed; moreover, a short period of intermittent positive pressure ventilation (IPPV) is needed.

In light of these considerations, we hypothesized that these two techniques (LISA and MIST) might be combined together, preserving the benefits of each of them. Therefore, we developed a novel approach that requires to use a particular laryngeal mask as a guide for a thin catheter to deliver surfactant directly into the trachea. We termed this procedure CALMEST (Catheter And Laryngeal Mask Endotracheal Surfactant Therapy).

Methods

In order to describe and validate our method, we performed a preliminary study in simulation on a mannequin and a subsequent *in vivo* pilot trial (reviewed and approved by Azienda Ospedaliero-Universitaria Pisana, AOUP Institutional Review Board).

First phase (simulation): fifteen neonatologists, expert in airway manipulation, operating in the Neonatal Intensive Care Unit of AOUP, were enrolled for a training program. Each operator performed five attempts on a mannequin to optimize technical skills and evaluate procedure feasibility.

We used a neonatal simulator (SimNewB™ - Laerdal Company) and the Air-Q self-pressurizing™LM (size 0.5 (BW<2 kg) or 1 (BW>2 kg) – Cookgas LLC, Mercury Medical), commercially distributed both for ventilation and difficult airways management thanks to a special patented design (i.e. a conduit for intubation, by fiber optic or stylet technique). We took advantage of this conduit to directly insert a thin catheter into the trachea for surfactant administration.

We put the LM in place on the mannequin using a water based lubricant. Next, we linked the LM airway connector to a T-piece infant resuscitator (RD1300-10 T-piece Circuit™ and NeoPuff™, Fisher and Paykel Healthcare). Finally, we passed a PVC umbilical vein catheter (8 Fr size, Vygon) through the duckbill port of the T-piece circuit. The depth of insertion was previously estimated adding the distance between the upper lip and the terminal part of the T-piece circuit (7 cm overall) to normal depth of tube insertion [6 cm + weight (kg)].

To verify that the catheter was placed correctly into the trachea, we removed the LM and checked by video-laryngoscopy.

We captured the perception of participants in the simulation phase by a questionnaire.

Second phase (in vivo):

Inclusion criteria: birth weight >1500 g, 5' Apgar score ≥7, arterial cord gas analysis with pH ≥7,10 and BE ≤-10, signs of surfactant need for RDS (need of FiO_2 ≥0.35 to maintain SpO_2 levels between 85% and 95% and consistent radiographic findings), written informed consent given by parents of each infant. All patients enrolled had to be supported in nCPAP for at least 30 minutes before the procedure to guarantee adequate lung recruitment.

In contrast to the previous simulation, during our *in vivo* test, we intended to avoid laryngoscopy to check the correct catheter position into the trachea: therefore, we linked the catheter through a 15 mm tube connector (tube size 3.5 mm) to an end-tidal CO_2 monitor (IntelliVue MP50™, Philips). We registered the end-tidal CO_2 wave in less than 15 seconds, thus confirming the correct position of the catheter.

Surfactant administration (dose of 150-200 mg/kg of poractant alfa Curosurf™, Chiesi) was divided into 3 to 5 slow boluses of 1 ml each through the catheter; in the meantime, the newborn remained

in spontaneous breathing with CPAP given by T-piece resuscitator (with LM). We removed the LM at the end of the procedure, and then we continued respiratory support with nCPAP (Infant Flow Sipap ™, CareFusion).

Results

In the first phase, the number of successful attempts was 70 out of 75 (93,3%). The proposed questionnaire generally assessed a good satisfaction, mainly due to procedure feasibility and to the short time required. The first phase was also important to optimize methodological details (e.g. check techniques for correct position) and to confirm the overall equipment (type of catheter, depth of insertion, etc).

In the second phase, we enrolled and treated four patients. For all of them, CALMEST procedure was correctly performed at the first attempt and they all reported clinical improvement demonstrating adequate surfactant administration [table 1]. The whole procedure lasted about 5 minutes overall and was well tolerated by patients. No major adverse effects such as bradycardia, desaturations and coughing were observed, thus avoiding the use of analgesia/sedation.

Conclusions

This new approach, despite the small number of patients enrolled, results safe and easy to perform. The technique is minimally invasive since it avoids laryngoscopy and associated premedication, which are often used in LISA. On the other hand, the greatest benefit of LISA is conserved because spontaneous breathing in CPAP is possible during the whole procedure.

Compared to previous reports of surfactant administration with a LM, we avoided use of IPPV, preserving lungs from baro-volutrauma, and surfactant was instilled directly into the trachea and not in the supraglottic space.

We aimed to explore a new method, so the clinical phase was necessarily limited to a small sample. In fact, our intention was not to perform a drug trial, but we aimed to propose a novel procedure based on the combination of routinely used medical devices. Further studies on large clinical

cohorts are needed to confirm the efficacy of CALMEST approach. However, in our opinion, this method might represent an important improvement to reduce neonatal stress, and ultimately it might be extremely useful for medical staff having low expertise in laryngoscopy and intubation. This particular type of LM, combined to a thin catheter, ensures surfactant administration under the glottis, optimizing the use of LM previously described for surfactant delivery. Moreover, the short time needed to perform the procedure makes the operator sure that laryngeal mask can be well tolerated.

Laryngeal mask suffers from one main limitation: this technique cannot be used for infants weighing less than 1500 g. We hope that in the future manufacturers may develop smaller devices so as to extend the application of our technique and its benefits to all newborns. Nevertheless, at the present time we are confident that CALMEST can be useful for patients with RDS born in Spoke hospitals; generally, they are late preterms and can be assisted even by operators having low expertise in laryngoscopy.

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Our study was reviewed and approved by the AOUP Institutional Review Board.

Disclosure of interests

The authors report no conflicts of interest.

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Features	Patient 1	Patient 2	Patient 3	Patient 4	Mean±SD
GE (weeks$^{+\text{ days}}$)	40^{+0}	34^{+3}	36^{+5}	36^{+6}	36.5(wks)±2.1
BW (g)	3624	1900	3464	3165	3038.3±677.5
Sex	M	F	M	M	
Delivery	spontaneous	urgent CS	CS	urgent CS	
Prenatal Steroids	NO	NO	NO	NO	
Clinical Frame	ARDS	IRDS	IRDS	IRDS	
Air-Q SP® LM size	1	0.5	1	1	
CALMEST Timing (hours since birth)	12	26	3	9	12.5±8.4
FiO_2 pre/post(3h)-CALMEST	0.35/0.21	0.45/0.24	0.40/0.25	0.45/0.21	0.41±0.04/ 0.23±0.01
$SatO_2$ pre/post(3h)-CALMEST (%)	84/98	87/98	89/96	85/99	86.3±1.9/ 97.8±1.0
RR pre/post(3h)-CALMEST (bpm)	115/78	94/64	110/76	65/60	96.0±19.5/ 69.5±7.7
Silverman Score pre/post(3h)-CALMEST	5/1	5/3	5/3	7/3	5.5±0.9/ 2.5±0.9
CXR Grading pre-CALMEST	IV (sx); I (dx)	II	I	I	

Table 1- PATIENTS' DETAILED DESCRIPTION