Outcomes after Introduction of Minimally Invasive Surfactant Therapy in Two Australian Tertiary Neonatal Units

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Objective To assess the procedural and clinical outcomes associated with the introduction of minimally invasive surfactant therapy (MIST) into standard care at 2 tertiary Australian neonatal intensive care units.

Study design A prospective audit was designed before the introduction of MIST in 2018, with data collected over a period of 18 months. Procedural data were completed by the clinical team performing MIST, including clinical observations, medication use, and adverse events. The audit team collected demographic data and subsequent clinical outcomes from medical records.

Results There were 135 MIST procedures recorded in 122 infants. For the included infants, the median gestation was $30^{2/7}$ weeks (IQR, $27^{6/7}$ to $32^{2/7}$ weeks) and birth weight was 1439 g (IQR, 982-1958 g). During the MIST procedure, desaturation to a peripheral oxygen saturation of <80% was common, occurring in 75.2% of procedures. Other adverse events included need for positive pressure ventilation (10.6%) and bradycardia <100 beats per minute (13.3%). The use of atropine premedication was associated with a significantly lower incidence of bradycardia: 8.6% vs 52.9% ($P < .01$). Senior clinicians demonstrated higher rates of procedural success. The majority of infants (63.9%) treated with MIST did not require subsequent intubation and mechanical ventilation.

Conclusions MIST can be successfully introduced in neonatal units with limited experience of this technique. The use of atropine premedication decreases the incidence of bradycardia during the procedure. Success rates can be optimized by limiting MIST to clinicians with greater competence in endotracheal intubation. *(J Pediatr 2021;229:141-6)*.

Exogenous surfactant is an effective treatment for respiratory distress syndrome (RDS) in infants born premature. Surfactant has traditionally been administered via an endotracheal tube with a subsequent period of mechanical ventilation. In more recent years, an alternative approach involving surfactant administration via a narrow catheter, inserted into the trachea during spontaneous breathing, most commonly referred to as less invasive surfactant administration, or minimally invasive surfactant therapy (MIST) has come to prominence.[1,2]

Meta-analyses of randomized controlled trials assessing this approach have shown that, in comparison with surfactant administration by endotracheal tube, MIST is associated with reductions in mechanical ventilation, bronchopulmonary dysplasia, and death or bronchopulmonary dysplasia combined.[3] The 2019 update to the European Consensus Guidelines on the Management of RDS recommends MIST as the preferred method of surfactant treatment for spontaneously breathing infants receiving continuous positive airway pressure (CPAP) support.[4] This method is well-established in some settings, such as the German Neonatal Network.[5]

The use of MIST requires skill in laryngoscopy, typically learned from experience in neonatal endotracheal intubation. Intubation is a challenging procedure with potential complications. A registry study including >2600 neonatal intubations in 10 academic neonatal intensive care units (NICUs) reported the occurrence of ≥1 adverse event in 18% of intubations, with 4% of intubations complicated by severe adverse events.[6] First attempt intubation success was achieved in only 49% of procedures.

CPAP	Continuous positive airway pressure
FiO_2	Fraction of inspired oxygen
MCH	Monash Children's Hospital
MIST	Minimally invasive surfactant therapy
NICU	Neonatal intensive care unit
PPV	Positive pressure ventilation
RDS	Respiratory distress syndrome
RWS	Royal Women's Hospital
SpO_2	Peripheral oxygen saturation

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C.R. is supported by a National Health and Medical Research Council (NHMRC) Investigator Grant (1175634) and has received conference travel support from Fisher and Paykel. B.M. is supported by a Medical Research Future Fund (Australia) Next Generation Clinical Researchers Career Development Fellowship (MRF1159225). The other authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2020.10.025

Complications reported during studies of MIST include coughing, surfactant reflux, desaturation, bradycardia, and need for positive pressure ventilation (PPV).[1] The use of sedative premedication for MIST remains an area of debate. Recent studies report that premedication is associated with an improvement in infant comfort scores, but an increase in complications, including the need for PPV and desaturation.[7]

As MIST becomes more popular, it is important to assess whether the safety and effectiveness profile seen in practice is similar to that reported in randomized trials. Before the introduction of MIST into practice at 2 tertiary Australian NICUs, we planned a prospective audit with the aim of assessing the procedural and clinical outcomes associated with MIST.

Methods

MIST was introduced into standard care at 2 Melbourne NICUs: Monash Children's Hospital (MCH) in March 2018, and at The Royal Women's Hospital (RWH) in August 2018. Although a small group of clinicians at each center had limited experience in MIST from participating in a clinical trial, the majority were inexperienced in this technique before its introduction into routine practice.[8] Infants eligible for MIST were from 23 to 40 weeks' gestational age at MCH, and from 29 to 36 weeks' gestational age at RWH, receiving CPAP support with a clinical and/or radiologic diagnosis of RDS. Other eligibility criteria common to both sites included adequate spontaneous respiratory drive, and a required fraction of inspired oxygen (FiO_2) of 0.30-0.35 or higher to maintain a target peripheral oxygen saturation (SpO_2) of 91%-95%, although infants receiving a lower FiO_2 could be treated at attending neonatologist discretion. Infants were ineligible for MIST if they had circulatory compromise, a diagnosis other than RDS, major congenital anomalies, recurrent apnea, were enrolled in a conflicting research study, or were judged to need immediate endotracheal intubation and mechanical ventilation.

The MIST protocol in both centers stipulated that infants should receive sucrose for analgesia, and that intravenous atropine should be administered before the procedure to decrease the risk of bradycardia. No sedative or muscle relaxant medications were used for MIST. A loading dose of caffeine was recommended for infants of <32 weeks' gestational age or <1250 g at birth, and any other infant with apnea, before the procedure to encourage maintenance of spontaneous breathing. It was expected that the clinician performing MIST was already proficient in direct laryngoscopy for endotracheal intubation. The device used for MIST in both centers was a vascular catheter, as described by Dargaville et al.[1] If removal of the CPAP interface was required to facilitate laryngoscopy, our guidelines recommended replacement of the interface during surfactant administration. Poractant alfa (Curosurf, Chiesi Farmaceutici, Parma, Italy) was the surfactant preparation used in both centers. It was recommended that surfactant be administered in small boluses over a period of 30-180 seconds, pausing if surfactant reflux or irregular breathing was observed. Videolaryngoscopy was not routinely available at either center during the time period of the audit. One center provided education sessions, including the opportunity for staff to learn the MIST technique on a neonatal manikin, before introduction. At both centers, clinicians with experience with MIST provided bedside supervision for staff members making their first attempt at the procedure.

An audit form was used by the clinical team to record procedural data, including clinical observations, medication use, and adverse events at the time of the procedure and during the 4 hours immediately afterward. A MIST attempt was judged to have occurred when the laryngoscope was inserted into the infant's mouth, regardless of whether the catheter was inserted. The attempt was regarded as ending when both the laryngoscope and catheter had been removed from the mouth. Adverse events such as desaturation and bradycardia were recorded if occurring at any time during the procedure, including both laryngoscopy and surfactant administration. Blood gas results (arterial, capillary, or venous were permitted) were recorded before the procedure and within 4 hours after the procedure, if performed. For infants receiving MIST more than once, procedural data were reported for the first MIST procedure only. The audit team collected demographic data and later clinical outcomes from electronic or written medical records. The local Human Research Ethics Boards approved data collection as part of a quality assurance process at each center. No sample size was specified for the study. The audit team estimated that an audit period up to August 2019, providing 18 months of data from MCH and 12 months from RWH, would be sufficient to draw meaningful conclusions about practice.

Dichotomous data are reported as number (percentage) and compared using the Fisher exact test. Continuous data are reported as median and IQR and when applicable range, and compared using Wilcoxon rank-sum test.

Results

During the audit period, 122 infants were treated with MIST, of whom 75 were at MCH and 47 at RWH. The demographics of included infants are shown in Table I. Almost

Table I. Demographics of included infants

Variables	Median (IQR) or No. (%)
Birth gestation, wk	$30^{2/7}$ ($27^{6/7}$ to $32^{2/7}$)
Birth weight, g	1439 (982-1958)
Antenatal steroids, any received*	99 (81.8)
Cesarean delivery	80 (65.6)
Multiple birth	44 (36.1)
Female sex	50 (41.0)
Outborn	29 (23.8)
1-Minute Apgar score*	7 (5-8)
5-Minute Apgar score*	9 (8-9)
Caffeine received before MIST	65 (53.3)

*Data missing for 1 infant.

all infants were preterm (120/122 [98.4%]), with the majority (86/122 [70.5%]) being born at <32 weeks of gestation, and 31 of 122 (25.4%) at <28 weeks of gestation. The most preterm infant was born at $23^{6/7}$ weeks of gestation. There were 29 infants born at nontertiary centers and transferred to MCH or RWH before receiving MIST. During the same time period, within the gestational age eligibility criteria, 282 infants in the 2 audit centers received surfactant treatment by any route; therefore, 43.3% of surfactant-treated infants received MIST.

The median age at which the first MIST procedure was performed was 7 hours (IQR, 3-22 hours), and treatment was during the first 24 hours of life for 98 of 122 infants (80.3%). Infants who were <28 weeks gestational age were treated at a median of 2 hours (IQR, 2-5 hours). Procedure outcomes are shown in **Table II**. Desaturation to an SpO_2 of <80% occurred commonly, in 73.3% of infants, and the median time for recovery of SpO_2 of >80% was 31 seconds (IQR, 15-60 seconds) from onset of desaturation in these infants. The rate of desaturation was similar in those infants for whom the nasal CPAP interface remained in place throughout the procedure (71/98 [72.5%]) and those for whom it was removed (14/17 [82.4%]). Bradycardia occurred in 13.9% of procedures and atropine was administered in 85.9% of procedures. Atropine use was associated with a reduction in incidence of bradycardia (9/105 [8.6%] vs 9/17 [52.9%] in procedures without atropine; $P < .01$).

Other documented adverse events were oral mucosa trauma, occurring in 2 procedures, and aspiration of milky fluid (that could indicate esophageal surfactant delivery or surfactant reflux) from the gastric tube after the procedure, recorded in 6 of the 135 procedures (4.4%).

First attempt success was achieved in 66 of 122 procedures (54.1%), with success within 2 attempts in 103 of 122 procedures (84.4%). The maximum number of attempts required to complete the MIST procedure was 5. A single infant became apneic during laryngoscopy, before surfactant administration, resulting in cessation of MIST and endotracheal intubation, with eventual endotracheal tube surfactant administration. Surfactant was administered in all other recorded MIST procedures. Procedural success rates differed by clinician experience level, with success achieved by attending neonatologists in 39 of 47 attempts (83.0%), by neonatal fellows in 79 of 121 attempts (65.3%), and by pediatric residents in 2 of 13 attempts (15.4%; $P < .01$).

Table II. MIST procedure data (reported for first procedure only)

Variables	Median (IQR) or No. (%)
Age at first MIST procedure, h	7 (3-22)
Premedication	
Atropine	105 (86.1)
Sucrose	74 (60.7)
Total number of attempts	1 (1-2)
Surfactant dose administered, mg/kg*	195 (139-204)
Bradycardia <100 bpm	17 (13.9)
Desaturation to SpO_2 <80%†	85 (73.3)
PPV†	11 (9.2)
Visible surfactant reflux†	41 (34.8)
Coughing/gagging during procedure†	22 (18.3)
Nasal interface removed during MIST	17 (14.1)

*One infant is excluded because the MIST procedure was abandoned before administration of surfactant.
†Some data were missing for oxygen saturation (6 procedures), PPV (3 procedures), surfactant reflux (4 procedures), coughing/gagging during procedure (2 procedures), nasal interface removed (1 procedure).

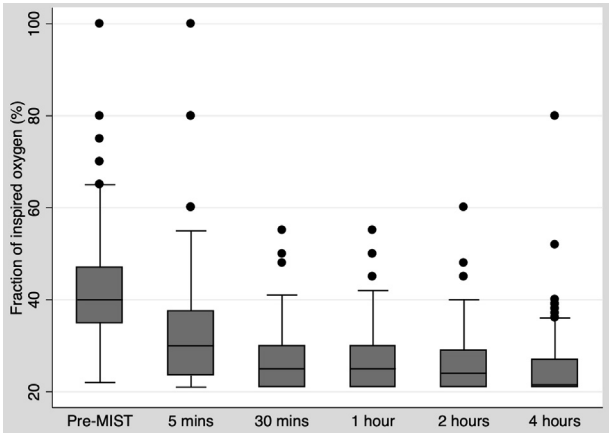

Figure. FiO2 before and after MIST. Boxes denote median and IWR. Whiskers denote adjacent values (those within 1.5 times the IQR from the 25th and 75th percentiles, respectively). Dots represent outliers.

Within the total study population, 62 infants had paired blood gas samples performed before and within 4 hours after MIST. Improvements were seen in pH from median of 7.27 (IQR, 7.20-7.33) to 7.32 (IQR, 7.27-7.35; $P < .01$) and in the partial pressure of carbon dioxide from 55.5 mm Hg (IQR, 45.2-63.0 mm Hg) to 47.7 mm Hg (IQR, 43.6-56.5 mm Hg; $P < .01$). All infants were receiving supplementary oxygen before MIST, and for 115 of 122 procedures (94.3%), the FiO_2 was ≥0.30. The median FiO_2 decreased during the 4 hours after the administration of MIST (**Figure**). The FiO_2 at all post-MIST time points was significantly lower than the pre-MIST FiO_2 ($P < .01$) and at 4 hours had decreased from a median of 0.40 (IQR, 0.35-0.47) to 0.22 (IQR, 0.21-0.27). Compared with the FiO_2 at 4 hours, the median FiO_2 at 24 and 48 hours were similar, being 0.22 (IQR, 0.21-0.28; $P = .87$) and 0.21 (IQR, 0.21-0.25; $P = .10$), respectively, and at 72 hours had decreased further to 0.21 (IQR, 0.21-0.24; $P < .01$).

Clinical outcomes for infants treated with MIST are shown in **Table III**. The majority of infants avoided mechanical ventilation both during the first 72 hours of life (71.3%) and during admission (63.9%). Two infants received their first dose of MIST as a "rescue" treatment after extubation, after a first dose of surfactant via endotracheal tube, and were not subsequently reintubated. Thirteen infants received MIST twice. Among the infants receiving a second MIST procedure, mechanical ventilation during admission occurred in 3 of 13 infants (23.1%).

Table III. Clinical outcomes

Outcomes	Median (IQR) or No. (%)
MV during first 72 hours of life	35 (28.7)
MV during admission	44 (36.1)
Pneumothorax receiving treatment	10 (8.2)
Bronchopulmonary dysplasia*	31 (36.5)
Grade 3-4 intraventricular hemorrhage†	5 (4.1)
Death before discharge	5 (4.1)
Duration of respiratory support, d‡	17 (6-56)
Duration of oxygen treatment, d	4 (2-35)
Home oxygen treatment	5 (4.1)
Duration of admission, d	30 (12-68)

MV, mechanical ventilation.
*Bronchopulmonary dysplasia was defined as receipt of respiratory support and/or supplementary oxygen at 36 weeks of corrected gestation, and recorded for infants <32 weeks of gestation at birth only.
†Cranial ultrasound scans were performed for all infants <32 weeks of gestation at birth and any other infant judged to be at risk of neurological abnormality. Infants who did not meet criteria for ultrasound examination have been classed as no grade 3-4 intraventricular hemorrhage.
‡Some data are missing for duration of respiratory support (1 infant), duration of oxygen treatment (11 infants), and duration of admission (1 infant).

Discussion

This audit demonstrates successful adoption of MIST into standard practice at 2 tertiary NICUs in Australia. This treatment was applied in a population ranging in gestational age from $23^{6/7}$ weeks to term, but primarily composed of very preterm infants born at <32 weeks of gestation, the group at highest risk of RDS. Surfactant administration was successfully completed in all but 1 procedure, in which the infant required intubation for apnea.

Exogenous surfactant administration, whether by endotracheal tube or minimally invasive catheter, is associated with the risk of short-term adverse effects, including desaturation, bradycardia, and transient airway obstruction.[9]

Bradycardia of <100 bpm was infrequent in our population, occurring in 13.9% of procedures. Atropine was omitted in 14.1% of procedures, and the use of atropine was associated with a significantly lower incidence of bradycardia. We observed rates of bradycardia in infants treated with or without atropine (9% vs 53%) that were similar to previous reports, and our findings support routine use of atropine to prevent bradycardia during the MIST procedure.[1,7,10-12] Desaturation to an SpO_2 of <80% was common in our audit population, occurring in the majority of procedures (73.3%) with a median recovery time 31 seconds, similar to rates in nonsedated infants in a prior randomized trial.[7] Given the known benefits of surfactant treatment, brief desaturation during or after administration is likely to be acceptable to most clinicians. We noted that these desaturations occurred despite the nasal CPAP interface being kept in place throughout the majority of MIST procedures (85.9%). It is unclear whether maintaining the nasal CPAP interface during MIST is of any substantial benefit, particularly because it may impede the view of the practitioner carrying out the laryngoscopy. However, we cannot exclude the possibility that desaturations may have been more severe or prolonged if the nasal interface had been removed routinely.

The use of PPV was relatively infrequent in our population, occurring in 9.2% of procedures. This rate is similar to the one reported in one of the larger published randomized trials, and compares favorably with previously reported rates in other smaller studies, which were 33%-44% in nonsedated infants and 93%-100% in infants receiving sedation before MIST.[1,7,11-13] Although our protocol specifically recommends a loading dose of caffeine before the MIST procedure for very preterm infants to encourage spontaneous breathing, other studies have also incorporated this approach, so this does not adequately explain the lower rate of PPV we observed.[7]

We did not use any sedative medication during MIST and did not formally score infant comfort or pain during the procedure. Although sedation may improve infant comfort, it is associated with increased adverse events such as desaturation, need for PPV, and in some studies need for endotracheal intubation, which occurred during just one of 135 MIST procedures in our audit.[7,12,14] Identification of strategies to optimize infant comfort during MIST, without adverse side effects, remains an important priority for future study.

First attempt success was achieved in 54% of procedures, a rate similar to that for endotracheal intubation during a large registry study.[6] We noted higher rates of success for more experienced clinicians. MIST guidelines at both institutions state that the MIST procedure should be performed only by staff with established competence in endotracheal intubation. The low success rate achieved by pediatric residents supports an approach of restricting performance of the MIST procedure to more senior clinicians with established competency in laryngoscopy.

Changes in neonatal clinical practice have resulted in decreased intubation opportunities for trainees; strategies to improve training of junior staff in laryngoscopy, for both endotracheal intubation and MIST, are an important priority in neonatal clinical training. Clinical trials show that videolaryngoscopy increases rates of intubation success by trainees, and would allow for a second operator to confirm the correct positioning of the MIST catheter.[15,16] Videolaryngoscope devices were not routinely available for MIST at either of our participating centers during the audit period. Data published from the NEAR4NEOS Registry identified videolaryngoscopy use during neonatal intubation to be associated with lower odds of adverse events, and the use of this approach during MIST may present an opportunity to improve practice and enhance training.[6]

In response to MIST, we saw a rapid and sustained improvement in FiO_2 requirement during the 4 hours after the procedure, as has been documented in previous studies.[1,11,13] Further improvement was seen between 4 and 72 hours, along with improvements in pH and pCO_2. These improvements may not be solely attributable to MIST, because some infants might have improved in response to

respiratory support without surfactant; however, they are consistent with previous findings in smaller populations.[1,11]

It is not possible to draw firm conclusions from the later clinical outcomes observed in this selected group of infants, which excludes infants who did not meet criteria for surfactant treatment and those who received endotracheal tube surfactant. Appropriately identifying infants suitable for MIST, rather than endotracheal tube surfactant, is important. Our findings indicate that such an approach was used, with infants receiving MIST representing 43.3% of all infants receiving surfactant in our specified population.

The proportions of infants in our cohort avoiding mechanical ventilation during the first 72 hours of life (71%) and during hospital admission (64%) are within the range that might be expected for infants receiving MIST. Meta-analyses of randomized trials reported that 77% of infants avoided mechanical ventilation within 72 hours, and 50% during admission.[3] Similarly, a report of >1000 infants treated with MIST in the German Neonatal Network found that 59% of infants avoided mechanical ventilation during admission.[17] Our rate of pneumothorax (8%) was also similar to prior reports from randomized, controlled trials and large cohorts. Centers with substantial MIST experience advocate for its use as part of a bundle of care with a focus on transition to early neonatal life.[5] Observed outcomes may improve as centers accumulate experience in managing these infants.

The strengths of this audit include the size of the population and the use of a prospectively designed audit form, allowing contemporaneous recording of outcomes of interest by the treating clinical team. Limitations include the absence of a control group and some apparent deviations from the treatment protocol, although this reflects real-world practice.

Future priorities include the identification of strategies to minimize the need for mechanical ventilation after MIST. Risk factors associated with MIST failure include a lower gestational age at birth, lack of exposure to antenatal steroid treatment, elevated C-reactive protein, and lower surfactant dose.[18] Infants in our cohort received MIST at median 7 hours of age (2 hours in infants <28 weeks of gestation at birth), consistent with an early rescue approach to surfactant treatment recommended in European guidelines.[4] Some units may prefer a prophylactic approach in which MIST is performed in the delivery room shortly after birth, allowing for earlier surfactant treatment in the most preterm infants. Our approach allows additional time to gain intravenous access for the administration of caffeine and atropine, which may decrease the risk of adverse events during the MIST procedure. It is unclear whether allowing for a period of lung recruitment on nasal CPAP before MIST has a beneficial effect on surfactant distribution within the lung.

Additional factors may influence the response to surfactant beyond its action within the airways. In response to MIST, preterm infants demonstrate improvements in pulmonary blood flow and measures of right heart function on echocardiography.[19] This finding may be particularly important for infants with fetal growth restriction, who are more likely to have cardiovascular maladaptation and may benefit from individualized therapy targeting pulmonary vascular mechanics and right heart function.[20]

In conclusion, this prospectively designed audit demonstrates that MIST can be successfully introduced in NICUs with limited experience of this technique. Success rates can be optimized by restricting the performance of MIST to clinicians with established competence in endotracheal intubation, and routine use of atropine decreases the risk of bradycardia during the procedure. The optimal approach to sedation remains uncertain, and further research into methods to increase rates of procedural success, and enhance clinical outcomes in the highest risk infants, is required. ■

Submitted for publication Jul 10, 2020; last revision received Oct 9, 2020; accepted Oct 12, 2020.

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