Innovation in Surfactant Therapy I: Surfactant Lavage and Surfactant Administration by Fluid Bolus Using Minimally Invasive Techniques

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Abstract

Innovation in the field of exogenous surfactant therapy continues more than two decades after the drug became commercially available. One such innovation, lung lavage using dilute surfactant, has been investigated in both laboratory and clinical settings as a treatment for meconium aspiration syndrome (MAS). Studies in animal models of MAS have affirmed that dilute surfactant lavage can remove meconium from the lung, with resultant improvement in lung function. In human infants both non-randomised studies and two randomised controlled trials have demonstrated a potential benefit of dilute surfactant lavage over standard care. The largest clinical trial, performed by our research group in infants with severe MAS, found that lung lavage using two 15ml/kg aliquots of dilute surfactant did not reduce the duration of respiratory support, but did appear to reduce the composite outcome of death or need for extracorporeal membrane oxygenation. A further trial of lavage therapy is planned to more precisely define the effect on survival. Innovative approaches to surfactant therapy have also extended to the preterm infant, for whom the more widespread use of continuous positive airway pressure (CPAP) has meant delaying or avoiding administration of surfactant. In an effort to circumvent this problem, less invasive techniques of bolus surfactant therapy have been trialled, including instillation directly into the pharynx, via laryngeal mask and via brief tracheal catheterisation. In a recent clinical trial, instillation of surfactant into the trachea using a flexible feeding tube was found to reduce the need for subsequent intubation. We have developed an alternative method of brief tracheal catheterisation in which surfactant is delivered via a semi-rigid vascular catheter inserted through the vocal cords under direct vision. In studies to date, this technique has been relatively easy to perform, and resulted in rapid improvement in lung function and reduced need for subsequent ventilation and duration of oxygen therapy. We are now commencing large-scale clinical trials of this method in preterm infants on CPAP.

Introduction

In considering surfactant therapy, innovation, the act of introducing something new, is anything but new. Since the earliest clinical studies of exogenous surfactant preparations nearly 50 years ago, a legion of surfactant re-
searchers have drawn on their ingenuity, and at times their courage, first to trial new surfactant preparations [1, 2], and then to refine them and refine their application. Such trials have been preceded and underpinned by bench and laboratory studies allowing a greater understanding of disease pathophysiology and the nuances of surfactant therapy to be gained.

Innovation in the field of surfactant therapy continues more than two decades after the drug first became commercially available. This review will focus on two relatively recent innovations in surfactant therapy in neonates: those of therapeutic lung lavage using surfactant preparations and bolus surfactant therapy using minimally invasive techniques.

Surfactant Lavage Therapy

Lung lavage can be defined as any procedure where fluid is instilled into the lung followed by an attempt to remove it by suctioning and/or postural drainage. Lung lavage as a therapeutic cleansing procedure has been applied to a number of lung diseases including pulmonary alveolar proteinosis, acute respiratory distress syndrome (ARDS), cystic fibrosis, lipid pneumonia and in the neonate meconium aspiration syndrome (MAS). Lavage therapy with repeated aliquots of saline is an established and effective treatment for alveolar proteinosis which in children and adults can be performed on one lung at a time using a bi-lumen endotracheal tube [3].

Lavage Therapy in MAS

Of all lung diseases in which lavage therapy has been applied, MAS in the newborn infant is arguably the condition in which it has the greatest potential to be effective. MAS results from a relatively acute influx of a noxious substance into a previously healthy and normally developed lung [4, 5]. The deleterious effects are seen to evolve over many hours as inhaled meconium migrates distally down the tracheobronchial tree. These observations lend credence to the notion that removal of meconium from the lung by lavage may interrupt the pathogenesis of the disease and thereby improve gas exchange and pulmonary mechanics.

Lavage therapy of one form or another has been used in MAS for nearly 40 years, with the earliest reports documenting use of saline lavage in the delivery room to improve clearance of meconium from the airways of meconium-stained babies [6]. The unfavourable properties of saline as a lavage fluid, in particular its high surface tension, were quickly appreciated, with some infants manifesting transient tachypnoea after saline lavage, related to lavage fluid retention in the lung [7]. In this sense, the emergence of surfactant preparations available for clinical use allowed re-discovery of lung lavage therapy in neonates with MAS.

Laboratory Studies of Surfactant Lavage in MAS

Since the first report of a form of surfactant lavage therapy in experimental MAS [8] much important information has been gained from laboratory studies in a range of animal models of MAS [9]. In animals rendered hypoxic and acidic by meconium instillation, surfactant lavage first and foremost has been seen to be relatively well-tolerated with a consistent but relatively short-lived period of low oxygen saturation during and immediately after the lavage procedure [10]. Compared to non-lavaged controls, animals undergoing surfactant lavage have shown improvements in oxygenation and lung mechanics in the post-lavage period [8, 10–13], superior to those achievable with bolus surfactant therapy [11]. A clear advantage of surfactant-containing lavage fluid over saline has been noted [8, 11] and dilute surfactant has also been found to be a more effective lavage fluid than liquid or emulsified perfluorocarbon [10, 14]. Where measured, the recovery of meconium solids and pigment during surfactant lavage has been considerable [10–12, 15], but will inevitably be incomplete, particularly with the passage of time after meconium influx.

Beyond these fundamental observations, several more specific and highly relevant questions about the technique of lavage in MAS have been investigated in the laboratory.

How Much Lavage Fluid in Total?

Whilst total lavage volume – the amount of fluid instilled into the lung during the entire lavage procedure – has varied from 5 to 80 ml/kg in the experimental setting, studies specifically comparing different total lavage volumes appear to place the optimal volume at around 20–30 ml/kg [10, 16]. In the piglet model of MAS, our research group compared meconium recovery and aqueous fluid deposition with total lavage volumes of 15, 30, 45 and 60 ml/kg, and found 30 ml/kg to achieve an acceptable balance between recovery of meconium from the airspaces and retention of lavage fluid in the lung [10]. In the same experimental model, Jeng et al. [16] found total lavage volumes of 20 or 30 ml/kg to have more favourable effects on oxygenation and lung compliance in the post-lavage period than 10 ml/kg. Interpretation of

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this study is more difficult due to the different aliquot volumes used in each group.

How Much Lavage Fluid at One Time?
In experimental studies, lavage aliquot volume – the amount of fluid instilled into the lung at one time – has ranged from as little as 2 ml up to 15 ml/kg. In the few instances in which direct comparisons of aliquot volume have been made, there appears to be a clear advantage to instillation of a larger amount of fluid at once, rather than multiple smaller aliquots [10, 16, 17]. We have noted meconium recovery to be considerably enhanced using 15 ml/kg aliquots compared with either 8 ml/kg [17] or 3 ml [10], with the latter study showing favourable effects on oxygenation and lung mechanics in the post-lavage period. Jeng et al. [16] noted similar improvement in post-lavage lung function with aliquot volumes of 10 or 15 ml/kg compared to 5 ml, although total lavage volume also differed in these groups.

Experimental studies have also revealed that maximum aliquot volume is limited to around 15 ml/kg in ventilated animals because it is not possible to instil larger volumes of dilute surfactant into the gas-filled lungs of these subjects in an acceptably short time frame. This observation has been confirmed in experience with human infants [18].

How Best to Deliver and Recover the Fluid?
In order to minimise the transient deleterious effect of lavage on oxygenation, several investigative groups have proposed that both instillation and recovery of lavage fluid should be undertaken with positive pressure ventilation, or at the very least positive end-expiratory pressure, being applied throughout [11, 15, 19]. Recent studies would suggest that this approach significantly compromises the effectiveness of the lavage procedure with disconnection from ventilation during suctioning (i.e. no applied PEEP) being associated with greater recovery of both meconium and lavage fluid [17]. Gentle manual squeezing of the chest appears to confer an additional benefit both in terms of meconium and fluid recovery [17] and oxygenation in the post-lavage period [20].

What Concentration of Surfactant Should Be Used in the Lavage Fluid?
Using commercially available surfactant preparations at full concentration for lavage appears neither economically sound nor therapeutically optimal. The cost of undiluted surfactant used for large volume lavage in a term infant would seem prohibitive, being 15–20 times more than that of single-dose surfactant therapy in a preterm infant. Additionally, the viscosity of undiluted surfactant is a barrier to rapid instillation and effective recovery by suction.

Experimental data would suggest that a surfactant phospholipid concentration of about 5 mg/ml is optimal for lavage. In vitro testing demonstrates that at concentrations ≥5 mg/ml most surfactant preparations are relatively resistant to inhibition both by meconium [21, 22] and by plasma proteins [23]. An in vivo comparison of different surfactant concentrations (2.5, 5 and 10 mg/ml) for lavage in the rabbit model of MAS found that a surfactant concentration of 10 mg/ml gave somewhat better post-lavage gas exchange compared with 5 mg/ml, with both these groups considerably better than those with lavage fluid containing 2.5 mg/ml phospholipid [12].

Surfactant Lavage in Ventilated Human Infants with MAS
Experience of surfactant lavage in human infants consists of case reports (reviewed previously [9]), non-randomised studies with concurrent or historical control groups [13, 18, 24–30], two randomised controlled trials (RCTs) comparing surfactant lavage with standard care [31, 32] as well as a small RCT comparing surfactant lavage followed by bolus surfactant therapy with bolus surfactant alone [33]. A systematic review and meta-analysis of the non-randomised studies and RCTs is now available [34].

As with the laboratory investigations, lavage therapy in human infants has been conducted using a wide range of total lavage volumes (6–48 ml/kg), aliquot volumes (2–15 ml/kg) and surfactant phospholipid concentrations (2.5–12 mg/ml, most commonly about 5 mg/ml). The lavage procedure has been undertaken at an average time after birth of 3–23 h using a variety of different instillation and suctioning techniques. Particularly in the non-randomised studies, criteria for selection of infants to receive lavage are widely variable and arbitrary, and the reported outcomes are somewhat inconsistent.

Non-Randomised Studies of Dilute Surfactant Lavage in MAS
A total of 80 ventilated infants with MAS have received dilute surfactant lavage in the non-randomised studies reported to date, and their outcomes compared with 105 non-lavaged controls (historical or concurrent) [34]. Details of these studies have recently been summarised along with a meta-analysis [34]. Notwithstanding their diverse study designs, these investigations have
noted reductions in death or need for extracorporeal membrane oxygenation [ECMO; relative risk (RR) 0.35; 95% CI: 0.13–0.94], air leak (RR 0.52; 95% CI: 0.28–0.96) and duration of oxygen therapy (weighted mean difference –1.19 days, 95% CI: –1.67 to –0.72) [34]. The conclusion drawn in each of the individual reports was that RCTs of lavage therapy were needed to definitively assess its value.

RCTs of Dilute Surfactant Lavage in MAS

Two RCTs comparing dilute surfactant lavage with standard care have been completed [31, 32] and a meta-analysis is available [34]. An earlier study enrolling 15 infants including 6 receiving dilute surfactant lavage has been published in conference proceedings only (without control data) [35] and is not discussed further.

Wiswell et al. [31] investigated lavage with a total lavage volume of 48 ml/kg in 6 equal aliquots (8 ml/kg), using KL4 surfactant (Surfaxin®; Discovery Laboratories, Doylestown,Pa., USA) at a concentration of 2.5 mg/ml (first 4 aliquots) and 10 mg/ml (final 2 aliquots). For this phase I/II trial, ventilated infants with MAS of moderate severity were recruited (oxygenation index: limits 8–25, mean 12). Fifteen infants were randomised to lavage therapy (at a mean age of 14 h), and 7 to standard care. The lavage procedure was performed under cover of sedation with or without muscle relaxation and was relatively protracted (duration 50–60 min). PEEP was maintained during instillation and positive pressure ventilation continued during suction. No clear differences were noted between the randomisation groups in use of rescue therapies or duration of ventilation or air leak, although there was a non-significant trend towards more rapid reduction in oxygenation index after lavage therapy [31]. On the basis of these results a phase III study was planned and commenced, but recruitment was halted after the enrolment of about 60 infants with little apparent prospect of re-starting [Thomas Wiswell, pers. commun., November 2007].

More recently, our research group has conducted a multicentre international collaborative trial of dilute surfactant lavage in MAS (the lessMAS trial – lavage with exogenous surfactant suspension in meconium aspiration syndrome) [32]. Enrolment required a mean airway pressure ≥12 cm H2O and alveolar-arterial oxygen difference ≥450 mm Hg, and thus targeted infants with relatively severe MAS. At the time of randomisation, oxygenation index was 25 and 22 in the lavage and control groups, respectively. Thirty-one infants were randomised to lavage therapy; 1 infant with cardiorespiratory insta-

bility did not receive lavage and was excluded from further analysis. The lavage protocol consisted of two 15 ml/kg aliquots of bovine surfactant (Survanta®; Abbott Australasia, Kurnell, N.S.W., Australia) diluted in warmed saline to a concentration of 5 mg/ml. Each aliquot was instilled and recovered in a 60-second sequence with a pause between aliquots until oxygenation saturation (SpO2) recovered to above 80%. The ventilator circuit was disconnected both for instillation of lavage fluid and for suctioning, and fluid recovery during suction was enhanced by manual vibratory chest squeezing. Lavage was undertaken at a mean age of 14 h and was performed under cover of sedation with the use of muscle relaxants strongly encouraged. Average time for completion of both lavage aliquots was 14 min. Thirty-five infants were randomly assigned to a control group in which dilute surfactant lavage was not performed. Both groups could receive, at the discretion of the treating clinicians, all forms of ventilatory support including ECMO where available, inhaled nitric oxide and bolus surfactant therapy.

The main findings of the lessMAS trial were that lavage therapy did not appear to alter the duration of mechanical respiratory support (the primary outcome), but fewer infants receiving lavage died or required ECMO: 10% (3/30) compared with 31% (11/35) in the control group (OR 0.24; 95% CI: 0.06–0.97) [32]. A trend towards increase in survival was noted in 7 centres in which ECMO was not available with a mortality rate of 5.3% (1/19) in infants receiving lavage and 29% (6/21) in control subjects (OR 0.14; 95% CI: 0.02–1.3). The 2 × 15 ml/kg lavage protocol was associated with a transient reduction in SpO2 without substantial heart rate or blood pressure alterations. Mean airway pressure was more rapidly weaned in lavaged infants compared to controls in the first 48 h after randomisation. The conclusion drawn was that dilute surfactant lavage may improve survival, especially in units not offering ECMO, but that a larger trial would be required to more precisely define the effect on mortality [32]. Along these lines, a further and larger trial is planned to be conducted in neonatal intensive care units in which MAS remains prominent and ECMO is unavailable.

Pooled results of the two RCTs of dilute surfactant lavage suggest a lower risk of death or need for ECMO in infants randomised to lavage (fig. 1) [34] as well as a trend towards a reduction in pneumothorax (RR 0.39; 95% CI: 0.08–1.95). Duration of ventilation, oxygen therapy and hospital stay were not substantially different between lavaged infants and controls [34].

As an alternative approach a regimen consisting of dilute surfactant lavage followed by bolus surfactant thera-
py (100 mg/kg) has been compared with bolus surfactant only in a small clinical trial [33]. Those infants receiving lavage (n = 7) showed more rapid improvement in oxygenation and reduction in mean airway pressure than the 6 infants treated with bolus surfactant only. No differences in duration of ventilation or oxygen therapy were discernible. Given the small size of the trial, this therapeutic approach requires further scrutiny before any conclusion can be drawn.

No clinical trial has yet directly compared dilute surfactant lavage with bolus surfactant therapy in ventilated infants with MAS. Bolus treatment has become established as an adjunct in the management of MAS in many centres, ostensibly to reduce the likelihood of requiring ECMO [36]. Enthusiasm for a head-to-head comparison may be dampened by the findings of two recent RCTs in settings in which ECMO was unavailable that did not demonstrate any benefit of bolus surfactant therapy in reducing mortality or major pulmonary outcomes in MAS [37, 38].

Lavage in Human Infants – Observations and Conclusions
Can Lavage Remove Meconium, and How Much Lavage Fluid Remains?
A considerable but as yet unquantified amount of meconium appears to be removed from the lung by lavage in ventilated infants with MAS. Both meconium solids and soluble pigment are present in the effluent, but in haemorrhagic fluid may not be apparent before centrifugation (fig. 2). A single study has reported lavage return fluid to contain 12% meconium solids (w/v) [13], but no estimate of the actual amount of pure meconium recovered from the lung has yet been made. The lavage return fluid also shows variable degrees of macroscopic blood staining (33 and 86% in the trial of Wiswell et al. [31] and the lessMAS trial [32], respectively) which we have interpreted as being reflective of the haemorrhagic alveolitis known to occur in MAS [39]. There has been no suggestion of new pulmonary haemorrhage as a result of lavage therapy. Average fluid return during lavage in the controlled trials has been 50 [31] and 46% [32], amounting to deposition of 24 and 16 ml/kg of aqueous fluid in the lung, respectively. This fluid appears to clear from the lung relatively rapidly, possibly aided by high activity of fluid-clearing sodium channels [40], the presence of surfactant [41] and a transient increase in ventilator pressures in the post-lavage period [32].

<table>
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<tr>
<th>Death or need for ECMO</th>
<th>RR (95% CI)</th>
<th>Events intervention</th>
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<td>Randomised controlled trials</td>
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<td>Wiswell et al. [31], 2002</td>
<td>0.47 (0.03, 6.43)</td>
<td>1/15</td>
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<td>Dargaville et al. [32], 2011</td>
<td>0.32 (0.10, 1.04)</td>
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<td>Overall (I² = 0.0%, p = 0.794)</td>
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Fig. 1. Meta-analysis of controlled trials of dilute surfactant lavage. Forest plot showing RR and 95% CI for outcome of death or need for ECMO in two RCTs of dilute surfactant lavage in MAS [31, 32]. Re-drawn from Choi et al. [34], with permission.

Fig. 2. Lavage return fluid. Pooled return fluid from 2 × 15 ml/kg dilute surfactant lavage in an infant with MAS. Prior to centrifugation (a) the fluid is haemorrhagic in appearance; after centrifugation and decanting the supernatant shows considerable meconium staining (b).
Can Lavage Be Performed Safely in Critically Ill Infants with MAS?

Dilute surfactant lavage in the ventilated infant with MAS must balance the competing interests of removing sufficient meconium to potentially interrupt disease progression and ensuring that physiological stability can be restored after the procedure. Whilst unquestionably more effective in cleansing the lung, larger aliquot volumes and disconnection of the ventilator circuit for suctioning also inevitably cause more significant and prolonged hypoxaemia during the procedure [10]. In human infants our experience suggests that with prior training, careful patient selection, adequate preparation and precise execution, 2 × 15 ml/kg lavage can be performed with relative safety by local neonatal staff in critically unwell infants with MAS and co-existent pulmonary hypertension. Transient hypoxaemia with desaturation to fetal levels is likely with each lavage aliquot (fig. 3a), but in most infants recovery to baseline occurs within 5 min of completion of the lavage sequence (fig. 3b). Accompanying bradycardia is more likely if sedation is inadequate [31]. As stipulated in the lessMAS trial we would recommend delaying or avoiding lavage where there is pre-existing severe hypoxaemia (pre-ductal SpO₂ <85% in FiO₂ 1.0), hypotension (mean blood pressure <35 mm Hg) and/or acidosis (arterial pH <7.20). Non-compliance with these guidelines may lead to serious exacerbation of pulmonary hypertension; one such infant in the lessMAS trial, with marked hypoxaemia pre-lavage, did not improve post-lavage and died of refractory pulmonary hypertension 3 h after the procedure [32].

Conclusion – What Is the Current Role of Lavage Therapy?

In the developed world the relative rarity of MAS [42] coupled with the complex array of available intensive care supports including ECMO mean that dilute surfactant lavage may have little to offer as an adjunctive therapy for MAS. In developing and newly industrialised countries MAS remains problematic, in one study accounting for 10% of all cases of neonatal respiratory failure with a mortality of 39% [43]. The available clinical trial data suggest that in this context lung lavage may provide benefit, specifically a decrease in mortality and possibly a reduction in pneumothorax [34]. We strongly recommend that prior to adoption of dilute surfactant lavage in any centre, staff should be instructed on the technique and practise it on a resuscitation mannequin and/or animal model of MAS.
**Surfactant Administration via Fluid Bolus Using Minimally Invasive Techniques**

*The Changing Landscape for Surfactant Therapy in Preterm Infants*

For the preterm infant with RDS related to surfactant deficiency, exogenous surfactant administration has been a cornerstone of therapy for more than two decades. With the evolution and refinement of intensive care for preterm infants, the place of surfactant therapy is now changing [44]. The more widespread use of nasal continuous positive airway pressure (CPAP) as the initial mode of respiratory support means many preterm infants with RDS now avoid intubation in the delivery room or in early post-natal life [45, 46]. This approach also means delaying or avoiding administration of surfactant, which until recently has only been given via an endotracheal tube. In large clinical trials in preterm infants ≤29 weeks’ gestation, treatment with CPAP from birth without administration of surfactant resulted in fewer ventilator days [47, 48] and trends towards an overall lower risk of bronchopulmonary dysplasia (BPD) compared to intubated controls [47–49].

Notwithstanding the overall results of RCTs of CPAP as primary therapy, the fact remains that many preterm infants starting on CPAP ultimately require intubation, most usually because of unremitting RDS [47]. Those failing CPAP in the first 72 h are known to be at risk of adverse outcomes, in particular pneumothorax and BPD [50–52]. Moreover, infants at higher risk of CPAP failure are identifiable based on oxygen requirement in the first hours of life [51] suggesting that further improvement in outcome for infants managed initially with CPAP may be possible with early identification and selective surfactant treatment for the subgroup with more severe RDS.

Recognizing the merits of early surfactant [53], the technique of ‘intubation, surfactant administration and extubation’ (INSURE) has been investigated in preterm infants on CPAP. Whilst some clinical trials have found a reduced need for mechanical ventilation with INSURE [54, 55], others have not, mostly attributable to difficulty with extubation after the procedure [49, 56]. This limitation and the difficulty of the intubation itself [57] has deterred many clinicians from using INSURE in clinical practice.

**Bolus Surfactant Therapy Using Minimally Invasive Techniques**

In view of the difficulties associated with INSURE, less invasive means of delivering bolus surfactant to pre-term infants on CPAP have been pursued [58–61]. These techniques, along with aerosolisation [see Pillow and Minocchieri, this vol., pp 337–344], have been given the label minimally invasive surfactant therapy [61]. Their intent is to avoid intubation in an infant who with the help of a dose of surfactant may well be able to continue on CPAP and not require positive pressure ventilation in the first critical days when the lung appears most vulnerable to ventilator-induced injury. These methods also largely rely on spontaneous ventilatory effort rather than repetitive positive pressure inflations to distribute the bolus of surfactant down the tracheobronchial tree and may result in more rapid and complete tissue incorporation of surfactant phospholipid [62].

**Bolus Surfactant Therapy by Pharyngeal Instillation**

Although established several decades ago as a method of initial surfactant delivery [63], the method of pharyngeal surfactant instillation shortly after birth has been largely forgotten. Kattwinkel et al. [58] rediscovered the technique and have used it in preterm infants of gestational age 27–30 weeks. Most infants studied showed an oxygenation response indicative of surfactant delivery to the lung; 10 of the 23 infants (43%) required intubation before 72 h, most of whom were born by Caesarean section. The need to instil surfactant into the pharynx of the preterm infant during delivery and before the first breath would appear to be the major barrier to the wider uptake of this method.

**Bolus Surfactant Therapy by Laryngeal Mask**

In a group of 8 infants of gestational age 28–35 weeks, Trevisanuto et al. [59] reported the placement of a laryngeal mask airway without sedation through which surfactant was administered by rapid bolus followed by positive pressure inflations. Improvement in oxygenation was noted in all cases; 2 infants were subsequently intubated including one with a pneumothorax. The applicability of this technique seems limited given the lack of familiarity of most neonatal clinicians with the laryngeal mask and the difficulty with placement of the device in infants <28 weeks’ gestation.

**Bolus Surfactant Therapy by Tracheal Catheterisation**

Several methods of surfactant delivery via brief tracheal catheterisation in spontaneously ventilating infants on CPAP have now been described [60, 61] and there is growing interest in this approach [64].
Initially described by Verder et al. [65], a technique of surfactant instillation in which a narrow bore flexible feeding tube is positioned in the trachea with Magill’s forceps has been championed by Kribs et al. [60]. The catheter is placed without sedation and with optional use of atropine. After feasibility studies [60, 66] and multicentre evaluation [67], a RCT of surfactant administration with this technique has been reported [the AMV trial – avoiding mechanical ventilation] [68]. Infants with a gestational age of 26–28 weeks were enrolled if they were being managed on CPAP and required FiO₂ > 0.30 in the first 12 h of life. Randomisation was to receive surfactant via a thin catheter (the intervention group, n = 108), or to continue on CPAP (n = 112). All infants were thereafter managed with CPAP unless intubation criteria were reached, including a FiO₂ threshold that varied from 0.30 to 0.60 between participating centres. The main trial result was that infants in the intervention group had a lower rate of subsequent positive pressure ventilation (28 vs. 45%); no clear difference in the rate of pneumothorax or other adverse events was seen. Interpretation of the results is complicated by the fact that only 60% of infants randomised to the intervention group received surfactant via thin catheter and also by the variable approach to management of the control group as determined by the different centre-specific intubation thresholds [64]. Nevertheless, the finding of a reduction in the need for mechanical ventilation after surfactant administration via thin catheter is an important one, and led the authors to speculate that this approach to surfactant delivery may be included in a regimen of individualised gentler care for preterm infants in the future [68].

The surfactant delivery method reported by Kribs et al. [60] has several technical difficulties that may limit its widespread adoption. Clinicians who solely practise oral intubation will be unfamiliar with Magill’s forceps and may find them cumbersome and hard to use. Additionally, the flexible feeding tube may be difficult to insert through the vocal cords and also difficult to maintain in position once inserted. For these reasons, and with the recognition of the potential benefits of minimally invasive surfactant therapy, our research group has developed an alternative and novel technique (the ‘Hobart method’) using a narrow bore semi-rigid vascular catheter (fig. 4) inserted through the vocal cords under direct vision using a laryngoscope without the need of Magill’s forceps [61]. An initial evaluation of this method was conducted in 25 preterm infants of 25–34 weeks’ gestation [61]. Surfactant was successfully administered in all cases and all infants continued on CPAP after the procedure. Oxygenation improved significantly after surfactant administration, suggesting adequate surfactant delivery, and treated infants showed a trend towards a reduction in need for intubation < 72 h compared to historical controls [69].

A formal two-site feasibility study of the Hobart method has recently been completed in 61 infants of 25–32 weeks’ gestation, with the results thus far published in abstract form only [69]. Infants on CPAP were eligible for inclusion if needing CPAP pressure ≥ 7 cm H₂O and FiO₂ ≥ 0.30 (25–28 weeks) or ≥ 0.35 (29–32 weeks). Surfactant (100–200 mg/kg Curosurf®, Chiesi Farmaceutici, Parma, Italy) was administered via the Hobart method to which several modifications have been made from the original description, including continuation of CPAP via prongs throughout the procedure and a slower rate of surfactant administration than previously, in 3–4 boluses over 15–30 s [70]. Compared to historical controls achieving the same CPAP and FiO₂ thresholds, surfactant-treated infants showed a reduction in need for intubation < 72 h and a shorter duration of oxygen therapy.

All available evidence suggests that both techniques of surfactant instillation by brief tracheal catheterisation are safe and relatively well tolerated. In the case of the Hobart method the procedure has been able to continue to completion in every infant with none requiring intubation within an hour of surfactant administration. Reflex bradycardia during laryngoscopy is seen in approximate-
ly one third of the cases [69] and usually resolves simply by easing the pressure of the laryngoscope blade on the hypopharyngeal wall. Nursing staff assisting with the procedure have not expressed concern that infants experienced undue discomfort during laryngoscopy or surfactant administration. Nevertheless, the safety and tolerability of these techniques require continued evaluation.

On the basis of our results and the encouraging findings of the AMV trial [68], we have proposed large-scale studies of minimally invasive surfactant therapy in preterm infants on CPAP, separated into two gestation ranges: 25–28 weeks [OPTIMIST-A trial (collaborative paired trials investigating minimally-invasive surfactant therapy), ACTRN12611000917932] and 29–32 weeks (OPTIMIST-B trial, ACTRN12611000916943) [71]. These paired multicentre collaborative RCTs will compare surfactant administration via the Hobart method with standard care (continuation of CPAP). Eligibility for enrolment will be based on the need for CPAP with a pressure of 5–8 cm H2O and FiO2 ≥ 0.30 at an age < 6 h (OPTIMIST-A, 25–28 weeks) or ≥ 12 h (OPTIMIST-B, 29–32 weeks). Eligible infants will be randomised to receive surfactant (Curosurf®) via the Hobart method of tracheal catheterisation or to continue on CPAP. The surfactant dose will be 200 mg/kg (OPTIMIST-A) or 100 mg/kg (OPTIMIST-B). The intervention will be masked from the duty clinicians. The primary outcomes are death or BPD (OPTIMIST-A) and duration of mechanical respiratory support (OPTIMIST-B) with multiple secondary end-points, including major neonatal morbidities, need for intubation and surfactant therapy, durations of mechanical respiratory support and oxygen therapy, applicability and safety of the minimally invasive surfactant therapy procedure, and outcome at 2 years (OPTIMIST-A). The OPTIMIST-A trial aims to enrol 606 infants, giving 90% power to detect a 33% reduction in death or BPD from the anticipated rate of 38% in the control arm, α = 0.05. The OPTIMIST-B trial will enrol 454 infants, giving 90% power to detect a 25% reduction in duration of respiratory support from the anticipated 4.0 days (geometric mean) in the control arm, α = 0.05. These trials will thus have sufficient power to give definitive information about the place of surfactant delivery by brief tracheal catheterisation in preterm infants on CPAP.

**Conclusion**

The perennial quest for improvement and refinement of care for newborn infants with respiratory disease along with the ready availability of exogenous surfactant preparations provide the impetus for continued innovation in surfactant therapy. As a result, neonatal clinicians have been afforded new and potentially useful alternatives to standard therapy for neonatal lung disease.

**Disclosure Statement**

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