Journal of Paediatrics and Child Health

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ORIGINAL ARTICLE

Risk Factors in Addition to Short and Long-Term Outcomes With Thin Catheter Surfactant Administration Failure in Preterm Infants: A Retrospective Analysis

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Received: 17 October 2023 | **Revised:** 25 November 2024 | **Accepted:** 30 December 2024

Funding: The authors received no specific funding for this work.

ABSTRACT

Objective: To evaluate the incidence of thin catheter surfactant administration (TCA) failure and compare short and long-term neonatal outcomes who failed TCA or did not.

Design: Single-center retrospective cohort study. Infants between 25 and 30 weeks of gestational age with respiratory distress syndrome and receiving 200 mg/kg poractant alfa via thin catheter administration were included. TCA failure was defined as the need for early mechanical ventilation (< 72 h). Infants were divided into two groups those who failed TCA or those who did not.

Results: The TCA failure rate was 24.6%. Initial oxygen requirement (0.39% vs. 0.36%) and the number of small for gestational age infants were significantly higher in the TCA failure group (15% vs. 7.9%). Infants who failed TCA had a higher pneumothorax (6.7% vs. 1.1%, $p = 0.03$), BPD (15% vs.5.5%, $p = 0.02$), late-onset sepsis (36.7% vs. 18%, $p = 0.04$), retinopathy of prematurity rates (11.7% vs. 3.3%, $p = 0.02$) and an increased duration of respiratory support. However, Bayley Scales of Infant Development II scores were comparable between groups at 18 and 26 months of corrected age.

Conclusion: Infants who fail TCA are at increased risk for short-term complications despite favourable long-term neurodevelopmental outcomes. Identifying infants at risk of TCA failure may help early prevention of morbidities and individualise their management.

1 | Introduction

Respiratory distress syndrome (RDS) is the most common cause of respiratory failure in premature infants caused by pulmonary immaturity and surfactant deficiency. Exogenous surfactant administration effectively improves survival in RDS [1–3]. Furthermore, previous trials demonstrated that exogenous surfactant administration prevents pneumothorax and death [1, 2]. Conventional surfactant treatment is the administration of surfactant into the trachea via an endotracheal tube placed with direct laryngoscopy. This practice requires intubation and positive pressure ventilation during the procedure. It is known that mechanical ventilator contributes to the development of bronchopulmonary dysplasia (BPD) in this population at risk [4]. To avoid prolonged invasive mechanical ventilation, intubation, administration of surfactant and extubation technique (INSURE) have been used since the early 1990s [5]. However, even the most immature infants are stabilised with nasal continuous positive airway pressure (CPAP), so combining surfactant administration with continuing CPAP treatment led investigators to develop less invasive surfactant administration techniques via thin catheters.

The administration of surfactant with a thin catheter was first reported by Verder et al. in 1992 [6]. Later on, Kribs et al. improved that technique and applied surfactant to 41 premature babies with a thin catheter in 2007 [7]. Since then, several randomised controlled studies and meta-analyses have been published that confirm thin catheter surfactant administration (TCA) has favourable effects on decreased need for mechanical ventilation, the incidence of death and bronchopulmonary dysplasia (BPD), major complications and in-hospital mortality [8–10]. Recently, the European Consensus Guidelines on the management of RDS suggested TCA as the method of choice in preterm infants with good respiratory drive stabilised under CPAP yet required surfactant treatment with high-quality evidence [11]. However, the population that will most benefit from TCA is yet to be defined; knowledge is scarce about the risk factors of TCA failure and the outcomes of infants who fail TCA.

We aimed to compare the mortality, morbidity and neurodevelopmental outcomes of infants treated successfully and failed treatment with TCA.

2 | Material and Method

2.1 | Study Design

This observational retrospective cohort study was conducted in Zekai Tahir Burak Maternity Teaching Hospital (Ankara, Turkey), a level 3 neonatal intensive care unit, between January 2013 and December 2017. Babies born between $25^{0/7}$ and $29^{6/7}$ weeks of gestation, were diagnosed with RDS, and received surfactant (200 mg/kg poractant alfa) by TCA technique and who had neurodevelopmental evaluation included in the study. The local ethics committee approved the study (No: 2018/011).

Exclusion criteria were major congenital anomalies, intubation in the delivery room, different types/doses of surfactant, death before discharge and missing medical records.

2.2 | Surfactant Therapy

Infants with signs of respiratory distress (tachypnea, retractions, grunting and cyanosis) and typical x-ray and blood gas findings were diagnosed as RDS. The Turkish Neonatal Society guideline was strictly followed in managing RDS and surfactant treatment [12].

Thin catheter surfactant administration: Babies stabilised with a T-piece resuscitator in the delivery room were placed on non-invasive ventilation support with a short bi-nasal cannula (INCA nasal cannulae set; Ackrad Labs/Cooper Surgical, Trumbull, CT). Surfactant treatment was considered when infants required ≥ 0.4 FiO_2 to maintain a 90%–95% saturation. The so-called Take Care technique comprehensively described elsewhere [13], was used to administer surfactant. In the Take Care method, a 5F nasogastric tube was inserted into the trachea under direct laryngoscopy while CPAP treatment continued and was not interrupted. Porcine surfactant (Curosurf; Chiesi Farmaceutici, Parma, Italy) was administered at 200 mg/kg bolus in 30–60 s. Skilled and experienced staff neonatologists or senior neonatology fellows administered surfactant. At least three experienced healthcare workers were available during the procedure. Non-pharmacologic treatments, such as facilitated tucking, swaddling and so on, were performed during the procedure. No sedatives or analgesics were used. All infants received a loading dose of 20 mg/kg caffeine citrate in the first 24 h of life, followed by 5–10 mg/kg/day maintenance. An additional dose of surfactant was considered if there were ongoing findings of respiratory distress and ≥ 40% FiO2 requirement. If the patient did not meet the intubation criteria, the second dose of surfactant was also given via the Take Care method.

The criteria for noninvasive ventilation failure were: Hypoxemia despite FiO_2 requirement ≥ 0.6, respiratory acidosis (pH < 7.2) under CPAP level ≥ 7 cm H_2O and recurrent apnea.

Invasive mechanical ventilation requirement in the first 72 h of life was defined as TCA failure.

2.3 | Neonatal Outcomes

Demographics; maternal age, gestational age in weeks, birth weight, mode of delivery, gender, small for gestational age (SGA), administration of antenatal steroids, preterm premature rupture of membranes (PPROM), chorioamnionitis, preeclampsia, gestational diabetes, APGAR scores were obtained from medical records. Respiratory outcomes; two or more surfactant requirements, pneumothorax, invasive and non-invasive respiratory support duration and oxygen therapy duration were evaluated. The duration of hospitalisation and postmenstrual age (PMA) at discharge, body weight and head circumference of the infants were recorded.

The National Institute of Health (NIH) definition was used in diagnosing and staging BPD [14]. Bell classification was used for necrotizing enterocolitis (NEC) staging [15]. Papile classification was used for intraventricular haemorrhage (IVH) [16]. Retinopathy of prematurity was diagnosed and staged in light of International classification [17]. Late-onset neonatal sepsis (LOS) was defined as sepsis with the onset of symptoms beyond 72 h of postnatal life. Clinical chorioamnionitis was suspected if the mother and infant had one of the following signs: Maternal fever, uterine tenderness, fetal heart rate changes, maternal tachycardia and foul-smelling amniotic fluid.

An independent developmental paediatrician performed Bayley scales of infant development version II (BSID II) at corrected 18–36 months of age. Neurodevelopmental impairment was defined as having at least one of the following morbidities deafness, blindness, BSID II scores < 70 in either mental or psychomotor evaluation and cerebral palsy.

2.4 | Statistical Analysis

IBM SPSS Statistics 22 program was used for statistical analysis. The Shapiro–Wilk test was used to determine whether the variables were normally distributed. We described the variables with non-normal distribution as median (range) and those with normal distribution as mean ± SD (Standard Deviation). The chi-square

test was used to analyse categorical variables, the Mann–Whitney U test was used to analyse numerical data with abnormal distribution and the *t*-test was for normally distributed data. A *p* value less than 0.05 was considered statistically significant.

3 | Results

Data from 243 infants who fulfilled the inclusion criteria were analysed. Sixty infants (24.6%) who failed TCA were included in the TCA failure group, and the others who were successfully treated with TCA were included in the TCA success group. Maternal and neonatal characteristics of the groups are summarised in Table 1. Initial oxygen requirement ($p=0.01$) and the number of SGA infants were significantly higher ($p=0.047$), whereas the frequency of PPROM was significantly lower ($p=0.026$) in the TCA failure group. The other demographic characteristics were similar between groups (Table 1). Multinominal logistic regression analysis revealed that SGA is an independent TCA failure risk factor after adjustments to the initial FiO_2 requirement and PPROM (OR 4.1 CI 1.3–13.1, $p=0.015$).

Respiratory morbidities, along with the other common neonatal morbidities, are represented in Table 2. The frequency of pneumothorax ($p=0.034$), moderate–severe BPD ($p=0.025$) and duration of mechanical ventilation ($p=0.007$) were significantly higher in the TCA failure group (Table 2). Stages 3 and 4 ROP rates were higher ($p=0.024$), and the time to full enteral feeding ($p=0.024$) was increased in the TCA failure group. Moreover, proven LOS rates were significantly higher in the TCA failure group ($p=0.04$) (Table 2).

The scores of BSID II and cerebral palsy rates were similar between groups and are represented in Table 3. One infant in each group presented a refractory disorder and required eyeglasses (0.5% vs. 1.7%, $p=0.43$). There was no blindness in both groups. Four (2.2%) babies in Group 2 had hearing loss and required a hearing aid, whereas none had hearing loss in Group 1 ($p=0.575$). Only one infant in Group 1 was diagnosed with an autism spectrum disorder.

4 | Discussion

Although the TCA of surfactant has become increasingly used, current knowledge about infants who failed TCA and long-term outcomes is scarce. Our results demonstrated that infants who failed TCA have comparable neurodevelopmental outcomes with controls despite the higher rates of pneumothorax, moderate–severe BPD and longer duration of mechanical ventilation.

In a relatively large sample-sized multicenter study in which TCA was administered to ≤27 weeks infants, TCA failure was found to be 65% at 22 weeks and 37.8% at 26 weeks [18]. Moreover, it was shown that TCA failure changed inversely with gestational week. Additional risk factors contributing to TCA failure were SGA and high oxygen demand in the first 12 h [18]. In our study, TCA failure rates were significantly lower (25%) than Hartel et al. reported, which can be explained by our population's higher mean gestational age. In this retrospective cohort, the mean gestational age was 28 weeks in both groups, yet Hartel et al. studied infants < 27 weeks [18]. Surprisingly, gestational age was comparable in both groups who failed TCA or did not in our study; however, similar to the above-mentioned study, the number of SGA infants and initial oxygen requirement was significantly higher in the TCA failed group. We thought that chronic intrauterine hypoxia, pulmonary hypoplasia and

TABLE 1 | Maternal and neonatal characteristics of the groups.

	TCA failure ($n=60$)	TCA success ($n=183$)	*p*
Maternal age, years, mean ± SD	27.3 ± 6,6	29.2 ± 6,3	0.43
Gestational age, weeks, mean ± SD	28 ± 1.5	27.9 ± 1.3	0.13
Birth weight, g, mean ± SD	1049 ± 247	1080 ± 217	0.21
Caesarean delivery, *n* (%)	52 (86.7)	149 (81.4)	0.43
Male gender, *n* (%)	29 (48.3)	90 (49.2)	0.94
SGA, *n* (%)	9 (15)	10 (7.9)	**0.04**
Antenatal steroids, *n* (%)	43 (71.7)	141 (77)	0.39
PPROM, *n* (%)	6 (10)	44 (24)	**0.02**
Clinical chorioamnionitis, *n* (%)	3 (5)	17 (9.3)	0.41
Preeclampsia, *n* (%)	12 (20)	22 (12)	0.13
Apgar score at 1 min, median (range)	5 (2–7)	6 (2–8)	0.16
Apgar score at 5 min, median (range)	7 (4–9)	8 (5–10)	0.18
Initial FiO_2 requirement, %, mean ± SD	38.9 ± 7.93	36.0 ± 7.43	0.01
Initial CPAP level, mean ± SD	5.9 ± 1.1	5.9 ± 1.2	0.74

Note: A *p* value < 0.05 was considered to be significant are highlighted in bold.
Abbreviations: PEEP, positive end-expiratory pressure; PPROM, preterm premature rupture of membranes; SGA, small for gestational age.

TABLE 2 | Comparison of neonatal morbidities between groups.

	TCA failure ($n=60$)	TCA success ($n=183$)	p
Two or more doses of surfactant, *n* (%)	13 (21.7)	30 (16.4)	0.43
Pneumothorax, *n* (%)	4 (6.7)	2 (1.1)	**0.03**
BPD, moderate–severe, *n* (%)	9 (15)	10 (5.5)	**0.02**
Duration of IMV, day, median (range)	4 (1–52)	0 (0–51)	<0.01
Duration of NIV, day, median (range)	7 (3–63)	4 (1–38)	<0.01
Supplemental oxygen, day, median (range)	11 (1–47)	5 (1–75)	<0.01
Proven LOS, *n* (%)	22 (36.7)	33 (18)	**0.04**
IVH ≥ grade II, *n* (%)	4 (6.7)	7 (3.8)	0.47
PVL, *n* (%)	2 (4.5)	7 (5.6)	1
NEC ≥ stage II, *n* (%)	4 (6.7)	7 (3.8)	0.47
ROP stage 3–4, *n* (%)	7 (11.7)	6 (3.3)	**0.02**
HsPDA, *n* (%)	25 (41.7)	59 (32.4)	0.21
Duration of hospitalisation, days, mean ± SD	63.8 ± 23.9	60.3 ± 21.6	0.22
PMA at discharge, weeks, mean ± SD	37.9 ± 2.1	37.1 ± 2.2	0.59
Weight at discharge, gram, mean ± SD	2164 ± 431	2099 ± 372	0.37
Head circumference at discharge, cm, mean ± SD	31.8 ± 1.4	31.9 ± 1.7	0.89

Note: A p value < 0.05 was considered to be significant are highlighted in bold.
Abbreviations: BPD, bronchopulmonary dysplasia; HsPDA, hemodynamically significant patent ductus arteriosus; IVH, intraventricular haemorrhage; MV, mechanical ventilation; NEC, necrotizing enterocolitis; NIV, non-invasive ventilation; PMA, postmenstrual age; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

TABLE 3 | Neurodevelopmental outcomes of the groups.

	TCA failure ($n=60$)	TCA success ($n=183$)	p
MDI, mean ± SD	85.4 ± 15.7	87.3 ± 13.9	0.47
PDI, mean ± SD	79 ± 16.5	82 ± 15.2	0.33
MDI < 70, *n* (%)	13 (21.7)	26 (14.2)	0.22
PDI < 70, *n* (%)	14 (23.3)	29 (15.8)	0.24
Neurodevelopmental impairment, *n* (%)	16 (26.7)	38 (20.8)	0.37
Cerebral palsy, *n* (%)	3 (5)	3 (1.6)	0.16

Abbreviations: MDI, mental developmental index; PDI, psychomotor developmental index.

inflammation, the pathophysiological underlying causes in SGA infants, may interfere with alterations in surfactant function, RDS severity and treatment failure. However, this relationship needs to be supported by further studies. Yet, the PPROM rates were significantly lower in the TCA failure group, which we thought was an incidental finding due to the retrospective design.

The neonatal outcomes of infants who fail TCA depend on various factors, including the underlying reason for the failure and the severity of the RDS [18–20]. Recently Janssen et al. studied the TCA failure risk factors and neonatal outcomes; they reported that lower gestational age, elevated C reactive protein, lack of antenatal steroids and low surfactant dose are associated with TCA failure [19]. Furthermore, TCA failure is related to decreased survival rates without serious adverse events, prolonged mechanical ventilation and increased grade > 2 IVH[19]. Similarly, our results showed that in infants who failed TCA, duration of mechanical ventilation, rates of BPD, pneumothorax, LOS and ROP were significantly higher. We thought that significant increases in ROP and BPD rates are related to increased LOS rates, which can be further explained with a longer duration of mechanical ventilation. The increased duration of respiratory support and intubation requirement can also explain increased LOS rates in TCA-failed infants.

A Cochrane meta-analysis published in 2021 reported that the administration of surfactant via thin catheter compared with the administration via an ETT is associated with reduced risk of death or BPD, less intubation in the first 72 h and reduced incidence of major complications and in-hospital mortality [8]. Several recent studies further supported that TCA of surfactant is feasible and should be the method of choice due to hdecreased composite outcome of death and BPD, even in extremely preterm infants [9]. However, only a few studies currently report TCA's effect on long-term outcomes. In the very first study published by Portah et al. authors reported the neurodevelopmental outcomes of ≤ 27 weeks infants who underwent surfactant administration without intubation and no statistically significant difference regarding the neurodevelopmental school-age outcome in children treated after implementing the surfactant without intubation procedure, even though surviving infants had been more immature and survival rates had increased [21]. However, Teig et al. reported better neurocognitive and pulmonary outcomes in infants treated with TCA compared with standard care at corrected 3 years of age [22]. Both studies are retrospective observational studies that compare the thin catheter surfactant treatment era with historical controls; results were not generated from a randomised controlled study. The first long-term follow-up study that reports the 2-year neurodevelopmental outcomes of the 'avoid mechanical ventilation (AMV)' trial demonstrated that BSID II scores were similar in infants randomised to receive TCA or standard care [23]. All the above-mentioned studies compared TCA with intubation and mechanical ventilation, yet no substantial evidence suggests better long-term outcomes in TCA-treated infants. Previously several studies

demonstrated that thin catheter administration is also a comparable method with INSURE (Intubate-Surfactant-Extubate); even in some randomised controlled trials, it has been shown that TCA is associated with reduced non-invasive respiratory support failure and duration of mechanical ventilation [12, 24–27]. Regarding long-term outcomes of INSURE versus TCA, only a single report with a small sample size demonstrated no differences in the follow-up neurodevelopmental and respiratory outcomes at 24 months postmenstrual age [27]. To our knowledge, no published report currently studies the long-term neurodevelopmental outcomes of infants who failed TCA; furthermore, our results suggested that TCA failure is not associated with worse long-term outcomes. The very first study that compared TCA with the sham procedure and aimed to be powered for long-term neonatal outcomes, the so-called OPTIMIST-A study recently published and demonstrated that TCA compared with sham treatment did not reduce the incidence of death or NDD by 2 years of age [28–30].

Despite all the previous evidence indicating favourable neonatal outcomes, the patient group that will benefit most from TCA has not yet been defined. Using a clinical scoring system that will be developed with the data obtained from the results of studies may help to choose appropriate infants for TCA. Unfortunately, no clinical score was performed before the TCA decision in our study.

The study's main limitations are its retrospective design and relatively low sample size. The results rely on clinical documentation, so they should be interpreted carefully. Since the risk factors for TCA failure and non-invasive ventilation failure are similar, the adverse outcomes could not only be attributed to the surfactant administration technique itself. The fact that accompanying preterm morbidities (air leaks, hemodynamically significant PDA, etc.) that may cause non-invasive ventilation failure in early postnatal life were not identified may have caused these patients also to be evaluated as TCA failure. Moreover, long-term pulmonary outcomes were not recorded and subjected to the study. Increased risk of sepsis, BPD and ROP in the TCA failure group, demonstrated in our study, should be confirmed with further, large and adequately powered studies.

In conclusion, TCA is an effective alternative to intubation and mechanical ventilation for administering surfactant to preterm infants with RDS. However, TCA failure remains common, especially the tinier infants frequently need intubation and mechanical ventilation, which can increase complications such as sepsis and BPD. Healthcare providers should closely monitor infants who undergo TCA and intervene promptly if necessary to minimise the risk of TCA failure and associated complications.

Author Contributions

Hayriye Gozde Kanmaz Kutman: conceptualization, methodology, data curation, writing – original draft preparation, writing – reviewing and Editing. **Betül Siyah Bilgin:** writing – original draft preparation. **Mehmet Buyuktiryaki:** data curation and investigation. **Gulsum Kadioglu Simsek:** data curation and investigation. **Fuat Emre Canpolat:** statistical analysis, supervision, reviewing and editing. All authors reviewed the results and approved the final version of the manuscript.

Acknowledgements

The authors have nothing to report.

Ethics Statement

The institute's committee approved the study protocol and obtained ethical approval.

Conflicts of Interest

The authors declare no conflicts of interest.

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