นิพนธ์ต้นฉบับ

ผลของการให้สารลดแรงตึงผิวต่ออัตราการเกิดโรคปอดอักเสบจากการใช้เครื่องช่วยหายใจในหอผู้ป่วยวิกฤตทารกแรกเกิด

ศริญญา ตั้งสิทธิโชค
กลุ่มงานกุมารเวชกรรม โรงพยาบาลพิจิตร

Received June 13, 2025 Revised September 16, 2025 Accepted September 26, 2025

บทคัดย่อ

ความเป็นมา: ปอดอักเสบที่เกี่ยวข้องกับการใช้เครื่องช่วยหายใจ (ventilator-associated pneumonia หรือ VAP) เป็นภาวะแทรกซ้อนที่สำคัญในทารกแรกเกิดที่ได้รับการช่วยหายใจด้วยเครื่องช่วยหายใจแบบใส่ท่อช่วยหายใจ ส่งผลให้มีอัตราการเจ็บป่วยและเสียชีวิตสูงขึ้น การให้สารลดแรงตึงผิวปอด (surfactant therapy) เป็นการรักษาที่ใช้กันอย่างแพร่หลายในภาวะหายใจลำบากตั้งแต่แรกเกิด (respiratory distress syndrome; RDS) ในทารกแรกเกิด แต่ผลกระทบของการใช้สารลดแรงตึงผิวต่ออุบัติการณ์ของ VAP ยังไม่ชัดเจน

วัตถุประสงค์: เพื่อประเมินว่าการให้สารลดแรงตึงผิวมีผลต่อการลดอุบัติการณ์ของ VAP ในทารกแรกเกิดที่ได้รับการช่วยหายใจด้วยเครื่องช่วยหายใจแบบใส่ท่อช่วยหายใจหรือไม่

วิธีการศึกษา: เป็นการศึกษาย้อนหลัง (retrospective study) โดยการทบทวนเวชระเบียนที่โรงพยาบาลพิจิตร ในทารกแรกเกิดที่เข้ารับการรักษาในหอผู้ป่วยวิกฤตทารกแรกเกิด (NICU) และใช้เครื่องช่วยหายใจแบบใส่ท่อช่วยหายใจ ระหว่างวันที่ 1 กันยายน พ.ศ.2555 ถึง 30 กันยายน พ.ศ.2564 แบ่งเป็น 2 กลุ่ม คือ กลุ่มที่ได้รับสารลดแรงตึงผิว และกลุ่มที่ไม่ได้รับสารลดแรงตึงผิว ข้อมูลประชากร ลักษณะทางคลินิก และผลลัพธ์ถูกรวบรวมและวิเคราะห์

ผลการศึกษา: มีทารกแรกเกิดเข้าร่วมทั้งหมด 132 ราย โดยแบ่งกลุ่มละ 66 ราย กลุ่มที่ได้รับสารลดแรงตึงผิวมีอุบัติการณ์ของ VAP ต่ำกว่ากลุ่มที่ไม่ได้รับอย่างมีนัยสำคัญ (ร้อยละ 27.3 เทียบกับ ร้อยละ 54.6, p value 0.002) นอกจากนี้ กลุ่มสารลดแรงตึงผิวยังมีระยะเวลาการช่วยหายใจด้วยเครื่องช่วยหายใจสั้นกว่าอย่างมีนัยสำคัญ (6 วัน เทียบกับ 8 วัน, p value 0.023) แต่ไม่พบความแตกต่างอย่างมีนัยสำคัญของระยะเวลาพักรักษาใน NICU หรืออัตราการตายระหว่างสองกลุ่ม

สรุป: การให้สารลดแรงตึงผิวสัมพันธ์กับการลดอุบัติการณ์ของ VAP ในทารกแรกเกิดที่ได้รับการช่วยหายใจด้วยเครื่องช่วยหายใจแบบใส่ท่อช่วยหายใจ ผลการศึกษานี้ชี้ให้เห็นว่า การใช้สารลดแรงตึงผิวอาจมีประโยชน์นอกเหนือจากการรักษา RDS โดยช่วยลดความเสี่ยงของการเกิด VAP ในประชากรทารกที่เปราะบางกลุ่มนี้
คำสำคัญ: สารลดแรงตึงผิว, ทารกแรกเกิดวิกฤต, ภาวะหายใจลำบากตั้งแต่แรกเกิด, โรคปอดอักเสบจากการใช้เครื่องช่วยหายใจ

Effects of surfactant therapy on the incidence of ventilator-associated pneumonia in neonatal intensive care unit

Sarinya Thangsittichok

Department of Pediatrics, Phichit Hospital

Abstract

Background: Ventilator-associated pneumonia (VAP) is a significant complication in neonates requiring invasive mechanical ventilation, leading to increased morbidity and mortality. Surfactant therapy is commonly used to manage respiratory distress syndrome (RDS) in neonates, but its impact on VAP incidence remains unclear.

Objective: To evaluate whether surfactant administration results in a reduced incidence of VAP in neonates requiring invasive mechanical ventilation.

Methods: A retrospective study was conducted at Phichit Hospital, including neonates who had been on invasive mechanical ventilator in the neonatal intensive care unit (NICU) between September 1, 2012 and September 30, 2021. Infants were divided into two groups: Those who received surfactant therapy and those who did not. Data on demographics, clinical characteristics, and outcomes were collected and analyzed.

Results: A total of 132 neonates were enrolled in this study, with 66 allocated to each group. The surfactant group had a significantly lower incidence of VAP (27.3%) compared to the non-surfactant group (54.6%) (p value 0.002). Additionally, the surfactant group had a shorter duration of mechanical ventilation (6 days vs. 8 days, p value 0.023). There was no significant difference in the duration of NICU stay or mortality rates between the two groups.

Conclusion: Surfactant therapy was associated with a reduced incidence of VAP in neonates requiring invasive mechanical ventilation. These findings suggested that surfactant therapy might have additional benefits beyond treating RDS, potentially reducing the risk of VAP in this vulnerable population.

Keywords: Surfactant replacement therapy, Respiratory distress syndrome, NICU, Ventilator- associated pneumonia (VAP)

Introduction

Ventilator-associated pneumonia (VAP) is a common and severe complication in neonates undergoing invasive mechanical ventilation in neonatal intensive care units (NICUs). VAP is defined as pneumonia that develops more than 48 hours after the initiation of mechanical ventilation, which is not present at the time of intubation.[1] It is a major cause of morbidity, contributing to prolonged hospitalization, extended use of antibiotics, and increased mortality in neonates.[2,3]

The pathogenesis of VAP in neonates is multifactorial. Contributing factors include the immaturity of the immune system, prolonged use of endotracheal tubes, and bacterial colonization of the respiratory tract.[4] The VAP incidence ranges from 1.4 to 7 episodes per 1,000 ventilator days in developed countries and from 16.1 to 89 episodes per 1,000 ventilator days in developing nations.[5] In Thailand, Nuntiyagul reported a 29.5% VAP incidence among 105 mechanically ventilated preterm infants, with VAP rates varying by birth weight: 8.6, 9, and 3 per 1,000 ventilator days in infants weighing <1,000 g, 1,001–1,500 g, and 1,501–2,000 g respectively.[6]

Surfactant replacement therapy (SRT) is a cornerstone in the treatment of respiratory distress syndrome (RDS) in preterm infants. Surfactant improves pulmonary compliance and reduces the severity of lung injury, potentially decreasing the duration of mechanical ventilation.[7-9] Early or prophylactic administration has been shown to reduce mortality and improve clinical outcomes, particularly when used in conjunction with non-invasive ventilation strategies.[10-12]

Although surfactant therapy is well established for treating RDS in neonates, its effect on preventing ventilator-associated pneumonia (VAP) remains unclear. Most previous studies have focused on respiratory outcomes, leaving a knowledge gap regarding infectious complications. In addition, few studies have compared outcomes between infants who received surfactant and those who did not, limiting our understanding of its potential protective effect against VAP. Since 2015, Phichit Hospital has implemented surfactant replacement therapy (SRT) as part of its standard neonatal care protocol, while neonates born prior to this period did not receive SRT. This study aims to address this gap by evaluating the association between surfactant administration and VAP incidence in neonates requiring invasive mechanical ventilation, using a historical control group of infants who did not receive surfactant.

Methods

This retrospective study was conducted at the NICU of Phichit Hospital, Thailand analyzing medical records of neonates admitted between September 1, 2012, and September 30, 2021. Eligible participants were neonates aged 0–28 days, with a gestational age of 24–41 weeks, who required invasive mechanical ventilation for more than 24 hours. Infants with congenital anomalies incompatible with life and those intubated for less than 24 hours were excluded. Beginning in 2015, surfactant replacement therapy (SRT) was incorporated into the hospital's standard protocol and administered to neonates with moderate to severe RDS. All included neonates required invasive ventilation, corresponding to moderate to severe RDS. Participants were divided into two groups: those who received at least one dose of surfactant (surfactant group) and those who did not (control group). A sample size of approximately 57 per group was calculated using Stata version 17, targeting 80% power and a 0.05 significance level.[13,14] Data collected included demographics, clinical characteristics, surfactant therapy details, ventilation duration, VAP diagnosis, and outcomes such as NICU stay and mortality. VAP was diagnosed based on clinical symptoms, radiological findings, and microbiological evidence.

Statistical Analysis

Continuous variables were summarized as mean ± SD or median (IQR) and compared using student's t-test or Mann–Whitney U test (depending on type of data distribution); categorical variables were expressed as frequencies and percentages and compared using Chi-square or Fisher's exact test (depending on type of data distribution). Logistic regression identified independent predictors of VAP and mortality. Potential confounders, including gender, gestational age, birth weight, APGAR score, prenatal maternal medication pre-intubation CPAP, number of intubation attempts and outcome, were selected based on clinical relevance and adjusted in multivariable models. Adjusted odds ratios (aOR) with 95% confidence intervals (CI) were reported. Statistical significance was set at p value < 0.05. All analyses were performed using Stata version 17.

Results

A total of 132 neonates were enrolled, with 66 infants in each group (surfactant and no surfactant). In this study, exogenous surfactant therapy was administered using either beractant (Survanta, AbbVie Inc.) or poractant alfa (Curosurf, Chiesi Farmaceutici) depending on availability, with a median time to administration of approximately 13 hours and 45 minutes after birth. Baseline characteristics are summarized in Table 1. The surfactant group had a significantly lower mean gestational age (30.0 ± 4.2 vs. 32.9 ± 4.8 weeks, p value < 0.001) and a higher proportion of infants weighing under 1,000 g (42.4% vs. 24.2%, p value 0.008) compared to the no-surfactant group. There were no significant differences in gender distribution (p value 0.096) or APGAR scores at 1 minute (p value 0.336). Antenatal dexamethasone and maternal antibiotic use were more common in the surfactant group (68.2% vs. 27.3% and 62.1% vs. 22.7%, respectively; both p values < 0.001). Use of nasal CPAP prior to intubation and frequency of intubation did not differ significantly between groups (p value 0.667 and p value 0.117, respectively). Clinical outcomes, including discharge and mortality rates, were comparable between groups (p value 0.204), though mortality was higher in the surfactant group (27.3% vs. 16.7%).

Table 1 Baseline characteristics of infants with and without surfactant therapy

Characteristics	**No surfactant (n=66)**	**Surfactant (n=66)**	**p value**
Gender †			0.096
Female	27 (40.9%)	17 (25.8%)	
Male	39 (59.1%)	49 (74.3%)	
Gestational Age ‡ (weeks)	32.9 (4.8)	30.0 (4.2)	<0.001
Birth Weight † (grams)			0.008
<1,000	16 (24.2%)	28 (42.4%)	
1,000–1,500	23 (34.9%)	30 (45.5%)	
1,500–2,500	13 (19.7%)	3 (4.6%)	
>2,500	14 (21.2%)	5 (7.6%)	
APGAR score at 1 minute†			0.336
>7	30 (45.5%)	24 (36.4%)	
5–7	18 (27.3%)	26 (39.4%)	

Characteristics	No surfactant (n=66)	Surfactant (n=66)	p value
<5	18 (27.3%)	16 (24.2%)	
Maternal Dexamethasone†			<0.001
Yes	18 (27.3%)	45 (68.2%)	
No	48 (72.7%)	21 (31.8%)	
Maternal Antibiotics†			<0.001
Yes	15 (22.7%)	41 (62.1%)	
No	51 (77.3%)	25 (37.9%)	
NPCPAP Prior to ETT†			0.667
Yes	15 (22.7%)	12 (18.2%)	
No	51 (77.3%)	54 (81.8%)	
ETT Frequency (times) †			0.117
1	54 (81.8%)	61 (92.4%)	
>1	12 (18.2%)	5 (7.6%)	
Outcome†			0.204
Discharge	48 (72.7%)	45 (68.2%)	
Referral	7 (10.6%)	3 (4.5%)	
Dead	11 (16.7%)	18 (27.3%)	

Data are n (%) for categorical variables and mean ± SD or median (IQR) for continuous variables.

†Chi-square or Fisher's exact test for categorical variables.

‡Student's t-test or Mann–Whitney U test for continuous variables.

The incidence of ventilator-associated pneumonia (VAP) was significantly lower in the surfactant group compared to the no-surfactant group (27.3% vs. 54.6%, p value 0.002), as presented in Table 2. There was no significant difference in the median length of NICU stay between the groups (21.5 vs. 17.5 days, p value 0.960). Notably, the surfactant group experienced a significantly shorter duration of mechanical ventilation (median 6 vs. 8 days, p value 0.023). However, when adjusted for ventilation exposure, the VAP rate per 1,000 ventilator days did not differ significantly between the groups (17.6 vs. 19.1, p value 0.993),

suggesting that while surfactant therapy might reduce the overall incidence of VAP, the risk per ventilator day remained comparable.

Table 2 VAP incidence and clinical parameters in surfactant versus no-surfactant groups

Variable	No surfactant (n=66)	Surfactant (n=66)	p value
VAP Incidence†	36 (54.6%)	18 (27.3%)	0.002
Day Admit‡	17.5 (10–39)	21.5 (6–39)	0.960
Day Ventilation (VD)‡	8 (4–20)	6 (3–11)	0.023
VAP Rate (per 1,000 VD) ‡	19.1 (11.5–32.1)	17.6 (10.7–45.9)	0.993

Data are n (%) for categorical variables and median (P25–P75) for continuous variables.

†Chi-square test for categorical variables.

‡Mann–Whitney U test for continuous variables.

In multivariable logistic regression adjusting for potential confounders (gender, gestational age, birth weight, APGAR score, antenatal dexamethasone, maternal antibiotics, pre-intubation CPAP, number of intubation attempts, and outcome), surfactant therapy remained independently associated with a significantly reduced risk of VAP (adjusted odds ratio 0.26, 95% CI 0.10–0.66, p value 0.005). None of the other variables showed a statistically significant association with VAP as demonstrated in Table 3 and Figure 1.

Table 3. Adjusted effect of surfactant therapy on ventilator-associated pneumonia in neonates

variable	Adjusted Odds Ratio	95% Confidence Interval	p value
surfactant therapy	0.26	0.10–0.66	0.005

Adjusted odds ratios were obtained from multivariable logistic regression. The model was adjusted for gender, gestational age, birth weight, APGAR score at 1 minute, antenatal dexamethasone, maternal antibiotics, pre-intubation CPAP, number of intubation attempts, and outcome (discharged vs. others).

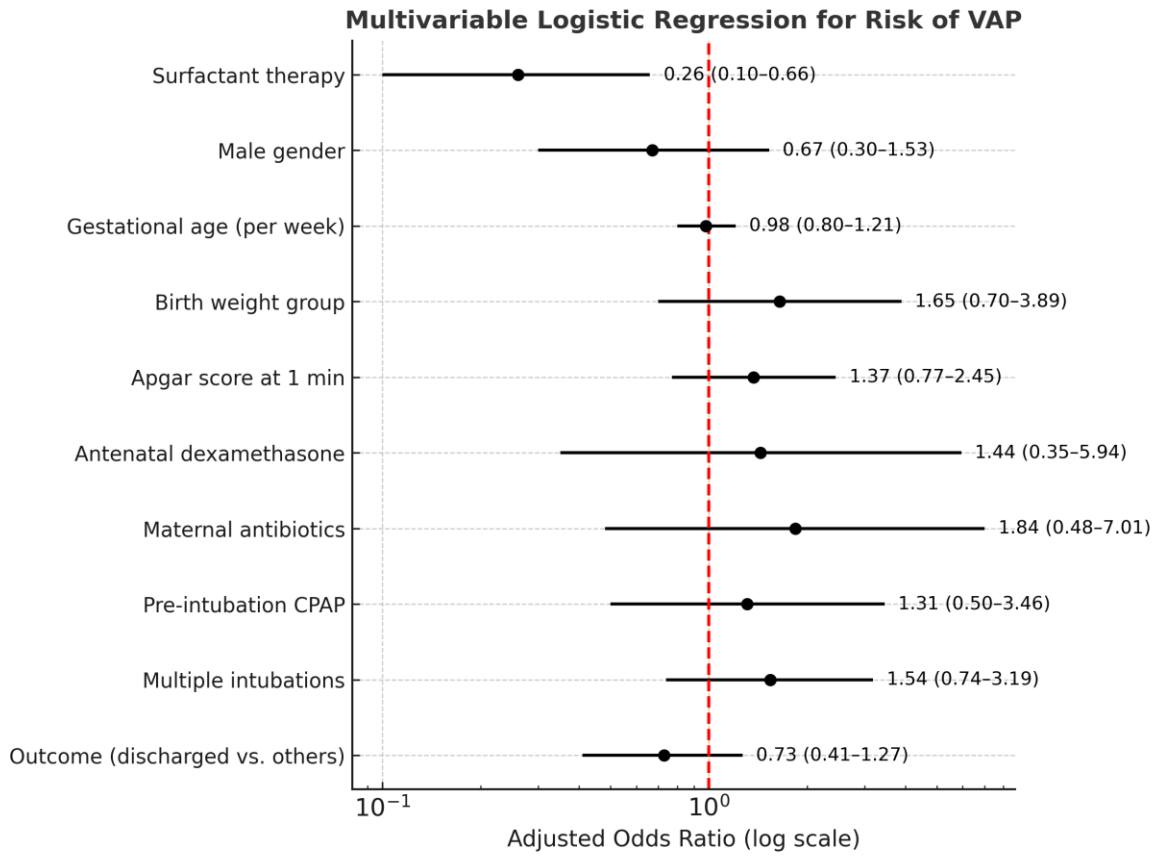

Figure 1. Forest plot of multivariable logistic regression for risk factors of ventilator-associated pneumonia (VAP) in neonates.

Adjusted odds ratios (aOR) with 95% confidence intervals (CI) were shown for surfactant therapy and potential confounding variables. The vertical dashed line indicated no effect (OR = 1). Surfactant therapy was associated with significantly lower odds of VAP (aOR 0.26, 95% CI 0.10–0.66, p value 0.005).

The distribution of bacterial pathogens causing ventilator-associated pneumonia (VAP) did not differ significantly between infants receiving surfactant therapy and those who did not as demonstrated in Table 4. The most common pathogens in the no-surfactant group were *Klebsiella pneumoniae* (15.2%) and *Pseudomonas aeruginosa* (12.1%), while in the surfactant group *Acinetobacter baumannii* was more frequent (13.6%). Notably, a significantly higher proportion of infants in the surfactant group had no identified pathogen (71.2% vs. 45.5%, p value 0.005).

Table 4 Distribution of bacterial pathogens causing VAP in infants with and without surfactant therapy

Pathogen†	No Surfactant (n=66)	Surfactant (n=66)	p value
P. aeruginosa	8 (12.1%)	3 (4.6%)	0.206
K. pneumoniae	10 (15.2%)	4 (6.1%)	0.156
A. baumannii	6 (9.1%)	9 (13.6%)	0.585
Mixed	5 (7.6%)	1 (1.5%)	0.208
Other	7 (10.6%)	2 (3.0%)	0.164
NA (no pathogen identified)	30 (45.5%)	47 (71.2%)	0.005

Data are n (%).†Comparisons between groups were performed using **Chi-square test or Fisher's exact test**, as appropriate.

Discussion

This retrospective study found that surfactant administration significantly reduced the incidence of VAP among neonates requiring mechanical ventilation. The surfactant group had a VAP incidence of 27.3% compared to 54.6% in the control group (p value 0.002). Furthermore, the surfactant group experienced shorter median durations of mechanical ventilation (6 vs. 8 days, p value 0.023), suggesting that surfactant therapy may enhance lung function, enabling earlier extubation and potentially reducing VAP risk.

Our findings supported previous literature indicating that surfactant reduced the need for prolonged ventilation in neonates with RDS.[7,10,15] In addition to improving gas exchange and lung compliance, surfactant therapy might help reduce lung inflammation, a key factor in both the pathogenesis of bronchopulmonary dysplasia (BPD) and susceptibility to infection.[16]

Although surfactant's effect on infection prevention is likely indirect, its role in shortening the duration of mechanical ventilation may disrupt the chain of events leading to VAP, which includes biofilm formation on endotracheal tubes and impaired mucociliary clearance.[4,17] This aligns with data from similar studies that have emphasized the importance of reducing ventilation time as a means of decreasing VAP rates.[5-6]

Despite the lower incidence of VAP in the surfactant group, the presence of multi-drug-resistant organisms such as *Acinetobacter baumannii* and *Klebsiella pneumoniae* in both groups highlighted the persistent challenge of infection control in the NICU setting, particularly in low- and middle-income

countries.[5,18] Enhanced infection prevention protocols, including hand hygiene, ventilator circuit care, and antibiotic stewardship, remained crucial components of VAP reduction strategies.[19]

Importantly, the protective association between surfactant therapy and reduced VAP incidence persisted even after adjusting for major neonatal and maternal confounders. However, the study had several limitations, including its retrospective design, potential for selection bias, and the absence of standardized protocols for surfactant administration. Additionally, the single-center setting might limit the generalizability of the findings. Future prospective, multicenter studies are warranted to better establish causality and to identify optimal surfactant administration strategies for reducing the incidence of ventilator-associated pneumonia (VAP) in neonates.

Conclusion

In conclusion, surfactant therapy was associated with a reduced incidence of VAP in neonates requiring invasive mechanical ventilation. These findings suggested that surfactant therapy might have additional benefits beyond treating respiratory distress syndrome, potentially reducing the risk of VAP in this vulnerable population. Further research is warranted to confirm these results and explore the underlying mechanisms.

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