Comparison Outcomes of Surfactant Therapy in Respiratory Distress Syndrome in Two Periods

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Background: *Exogenous surfactant replacement therapy has been a part of the routine care of preterm neonates with respiratory distress syndrome (RDS) since 1990s. In Thailand, the utilization of surfactant replacement therapy had been limited due to the high cost until the National Health Insurance Policy began in 2003 which covered the cost of surfactant. Nowadays surfactant replacement therapy is more frequently used at Queen Sirikit National Institute of Child Health, so the authors were interested in evaluating its use in RDS.*

Objectives: *To compare the outcome and complications of surfactant replacement therapy in newborns who were diagnosed with moderate to severe RDS during two times period.*

Study design: *Retrospective study.*

Material and Method: *The data of infants who were diagnosed as moderate to severe RDS and treated with surfactant at Queen Sirikit National Institute of Child Health between January 1st, 2003 and December 31th, 2005 were reviewed. The outcome of this study (Group II) was compared to the previous study conducted in 1999-2002 (Group I). The complications, mortality rate, association time of start surfactant and duration of ventilation were reviewed.*

Results: *The data of ninety-one moderate to severe RDS patients who received surfactant replacement therapy were reviewed. The mean birth weight and gestational age in this group were 1250 $\pm$ 435.57 gm and 29.38 $\pm$ 2.2 week less than in the first group 1,344 $\pm$ 452.37gm and 29.69 $\pm$ 2.61week. The second group showed statistical differences in antepartum hemorrhage (4.4%) and pregnancy induced hypertension (PIH) (17.6%) while the first group had 33.3% of antepartum hemorrhage and 3% of PIH. In neonatal conditions, there were statistical significant differences in anemia 28.6% in group II compared to 9% in group I and patent ductus arteriosus 67% in group II compared to 39.4% in group I. Surfactant was given earlier in life (4.75 $\pm$ 2.76 hours) in the second group compared to the first group (7.21 $\pm$ 4.92 hour) and the overall duration of patients on mechanical ventilation in Group II (6 days) was shorter than in Group I (16 days).This was especially more evident in patients who received surfactant within the first six hours of life. The immediate complication, pulmonary hemorrhage was found in more cases in Group I (33.3%) than in Group II (12.1%) but bronchopulmonary dysplasia (BPD) was found to be a late complication in more cases in Group II (46.1%) than in Group I (21.2%). The mean length of admission was longer in Group II (61.23 $\pm$ 41.08 days) compared to Group I (38.5 $\pm$ 23.48 days) and the mortality rate in Group II was 18.7% (17 cases) lower than Group I 33.3% (11 cases).*

Conclusion: *Surfactant therapy in moderate to severe RDS can shorten the duration of ventilation and decrease the mortality rate, but has no effect in decreasing the incidence of chronic lung disease. Nevertheless the earlier the surfactant therapy is started, the higher the survival rate.*

Keywords: *Respiratory distress syndrome, Surfactant, Comparison*

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Research efforts led to the first report of exogenous surfactant therapy (SRT) to treat respiratory distress syndrome (RDS) in 1980.In the 1990's, US Food and Drug Administration (FDA) approved of the first exogenous surfactant as part of the routine care of preterm neonates with respiratory distress syndrome (RDS)[1]. SRT remains an active research area with the publication of more than 85 articles since 2000, including 34 randomized controlled clinical trials (RCT) of SRT for the treatment of infants with RDS[2]. In Thailand, the utilization of surfactant replacement therapy had been limited due to the high cost until the National Health Insurance Policy began in 2003 and covered the cost of surfactant. Nowadays surfactant replacement therapy is more frequently used in our institute, so we were interested in evaluating its use in RDS.

Material and Method

The data of preterm infants (gestational age < 37 weeks, born at Rajavithi hospital) who were diagnosed with moderate to severe RDS and treated with surfactant at the Queen Sirikit National Institute of Child Health between January 1st 2003 and December 31th 2005 were reviewed and the outcome of this study (Group II) was compared to the results from a previous study conducted in our institution (1999-2002) as the first group (group I). Outborn preterm infants, infants with maternal anti HIV positive and congenital anomaly incompatible with life were excluded from study. All data were kept in database format. The differences-analyzed between the 2 groups included factors affecting RDS, complication, mortality rate, association between time of administering surfactant and duration of ventilation.

Statistical analysis

Descriptive data were analyzed as percentage, mean and standard deviation. The comparison for continuous variables were made by two tailed independent samples: Student *t*-test for normally distributed data and by Mann-Whitney rank sum test for non-normally distributed data. For comparison of categorical data, Chi-square test and Fisher's exact test were used wherever applicable. The computer program, SPSS, was used for statistical evaluation and the level of significance was set at $p < 0.05$ and all p-values reported in this trial are of the two-sided type.

Results

The data of ninety-one moderate to severe RDS patients who received surfactant replacement therapy were reviewed. The mean birth weight and gestational age in the second group were 1,250 $\pm$ 435.57 gm and 29.38 $\pm$ 2.2 week respectively which was less than in the group I (1,344 $\pm$ 452.37 gm and 29.69 $\pm$ 2.61week) as shown in Table 1.

There were statistically significant differences in antepartum hemorrhage (APH) and pregnancy induced hypertension (PIH) between Group II (4.4% and 17.6% respectively) and Group I (33.3% and 3% respectively) as shown in Table 2. In neonatal conditions, there were statistical significant difference in anemia (28.6% in Group II compared to 9% in Group I) and patent ductus arteriosus (67% in Group II compared to 39.4% in Group I) as shown in Table 4.

The surfactant was administered earlier in Group II (4.75 $\pm$ 2.76 hours) compared to Group I (7.21 $\pm$ 4.92 hour) and the overall median durations of patients on mechanical ventilation in Group II (6 days) were shorter than in Group I (16 days) especially in patients who received surfactant within the first six hours of life as Table 3.

Immediate complication of pulmonary hemorrhage was found more in Group I (33.3%) than in Group II (12.1%) but PDA and BPD (bronchopulmonary

Table 1. Demographic data of RDS treated with surfactant in two periods

Characteristics	Group II n = 91 case (%)	Group I n = 33 case (%)	p-value
Male gender	50 (55)	23 (69)	0.14
Birth weight* (gm)	1250 (435.57)	1344 (452.37)	0.29
Gestational age* (week)	29.38 (2.25)	29.69 (2.61)	0.51
AGA	84 (92.3)	30 (90)	0.80
SGA	6 (6.6)	2 (6)	0.91
LGA	1 (1.1)	1 (3)	0.45

AGA: appropriate for gestational age, SGA: small for gestational age, LGA: large for gestational age
* = mean ($\pm$ SD)

Table 2. Data of mother between groups

Characteristics	Group II n = 91 case (%)	Group I n = 33 case (%)	p-value
ANC* (time)	3.59 (2.66)	3.24 (2.87)	0.52
Number of ANC	74 (81.3)	26 (78.8)	0.75
PROM ≥ 18 hours	6 (6.6)	6 (18.1)	0.054
APH	4 (4.4)	11 (33.3)	0.007
Multiple delivery	24 (26.4)	7 (21.2)	0.55
PIH	16 (17.6)	1 (3)	0.04
DM	4 (4.4)	0	0.57
Antenatal steroid			
Complete	11 (12.1)	3 (9.1)	0.64
Incomplete	17 (18.7)	4 (12.1)	0.39
None	63 (69.2)	26 (78.8)	0.29

ANC: antenatal care, PROM: prolonged rupture of membrane, APH: antepartum hemorrhage,
PIH: pregnancy induced hypertension, DM: diabetes mellitus
* = mean (± SD)

Table 3. Comparative outcome of data of treatment in newborn between groups

Treatment	Group II n = 91 case (%)	Group I n = 33 case (%)	p-value
Ventilation mode			
IMV	68 (74.7)	25 (75.7)	0.90
IMV and HFOV	23 (25.3)	8 (24.3)	
Duration of ventilation in surfactant administered cases** (≤ 6hr) (day)	12.85 (6)	16.19 (16)	0.06
Surfactant (n)			
1 dose	82 (90.1)	30 (90.9)	0.89
2 doses	9 (9.9)	3 (9.1)	
Age at surfactant (hours)	4.75 (2.76)	7.21 (4.92)	0.001
Surfactant administered within 6 hour	73 (80.2)	17 (51.5)	0.03
Inotrope infusion	42 (46.1)	19 (57.5)	0.26
Blood component transfusion	41 (45)	22 (66.6)	0.03

IMV: intermittent mandatory ventilation, HFOV: high frequency oscillatory ventilation
* = mean (± SD)
** = mean (median)

dysplasia) were found more frequently in Group II (67% and 46.1%) than in Group I (39.4% and 21.2%) as shown in Table 4.

The length of admission was longer in this study group (61.23 ± 41.08 days) compared to the previous study (38.5 ± 23.48 days). The mortality rate in this study was 18.7% (17 cases) which was less than the previous study 33.3% (11 cases)as shown in Table 5.

Discussion

According to the National Health Policy, surfactant was categorized as an essential drug for RDS in 2003. We had more cases of surfactant administration in the treatment for RDS in the second group (n = 91 case) than in the first group (n = 33cases). A similar study reported from Japan on the use of surfactant in two times period between 1982-1986 and 1987-1991 too. The result of that study showed a better outcome in the second group than in the first group in the survival rate and disconnection rate from oxygen therapy[5]. The premature baby with a gestational age of less than 30 weeks would receive more benefits from prophylactic surfactant therapy in RDS because the incidence of RDS decreases with increasing gestational

Table 4. Comparative outcome between groups in early and late complication

Complication	Group II n = 91 case (%)	Group I n = 33 case (%)	p-value
Pulmonary hemorrhage	11 (12.1)	11 (33.3)	0.006
Anemia	26 (28.6)	3 (9)	0.02
Pneumothorax	6 (6.6)	1 (3)	0.44
PIE	11 (12.1)	6 (18.1)	0.38
Pneumomediastinum	1 (1.1)	0	0.54
PDA	61 (67)	13 (39.4)	0.006
BPD	42 (46.1)	7 (21.2)	0.01
ROP	22 (24.2)	6 (18.1)	0.48
NEC	38 (41.8)	9 (27.2)	0.14
IVH	28 (30.8)	8 (24.2)	0.48
Sepsis	23 (25.3)	15 (45.4)	0.03

PIE: pulmonary interstitial emphysema, PDA: patent ductus arteriosus, BPD: bronchopulmonary dysplasia, ROP: retinopathy of prematurity, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis

Table 5. Comparative outcome of treatment

Outcome of treatment	Group II n = 91 case (%)	Group I n = 33 case (%)	p-value
Admission* (days)	61.23 (41.08)	38.5 (23.48)	0.003
Survived	74 (81.3)	22 (66.7)	0.08
Death	17 (18.7)	11 (33.3)	0.08

* = mean ($\pm$ SD)

age[6]. The factors concerning the mother in this study showed statistical differences in antepartum hemorrhage (4.4%) and pregnancy induce hypertension (PIH) (17.6%) while the previous study showed 33.3% antepartum hemorrhage and 3% PIH. In neonatal conditions, there were statistically significant differences in anemia (28.6% compared to 9%) and patent ductus arteriosus (67% compared to 39.4%) between groups. These factors can affect the severity of RDS and outcome of treatment. There were very few patients in both groups who received antenatal steroid. The origins of this practice came in 1972 from the pioneering work of Liggins and Howie, they showed a significant reduction in the incidence of respiratory distress syndrome in preterm babies whose mothers had received antenatal corticosteroids. These agents are thought to improve surfactant production, and there is also an associated reduction in the risk of neonatal intraventricular haemorrhage, necrotising enterocolitis, hyperbilirubinaemia, and neonatal death[7]. The surfactant was administered a much younger age group (4.75 $\pm$ 2.76 hours) in the second group than in the first group (7.21 $\pm$ 4.92 hour) and the overall duration of patients on mechanical ventilation in the second group (6 days) was shorter than the first one (16 days) especially in patients who received surfactant within six hours of life. The result of this showed benefits for preterm babies with RDS because transbronchial surfactant replacement dramatically improves gas exchange and arterial oxygenation as in literature[4]. Most of the infants received surfactant as an early rescue (within 6 hours after birth, 80.2% in the second group and 51.5% in the first group). The incidence of coexisting morbidities in preterm infants, such as bronchopulmonary dysplasia, intraventricular hemorrhage, retinopathy of prematurity and necrotizing enterocolitis has not changed with surfactant as previously reported in literature[8-12], but authors found more cases of PDA and BPD in this study than in the previous study. The risk of developing BPD after the use of prophylactic surfactant compared with rescue surfactant has been reported in previous studies with variable results not different[8,13], decreased[14,15] and increased[16]. The length of admission was longer in the second group

(61.23 ± 41.08 days) compared to the first one (38.5 ± 23.48 days) due to more survivors. The mortality rate was 18.7% (17 cases) less than the previous study 33.3% (11 cases).

Conclusion

The authors found the benefit of surfactant therapy in moderate to severe RDS cases, which can shorten the duration of ventilation and decrease the mortality rate, but has no effect in decreasing the incidence of chronic lung disease. Nevertheless, the earlier the surfactant therapy is introduced, the higher the survival rate.

References

1. Fujiwara T, Maeta H, Chida S, Morita T, Watabe Y, Abe T. Artificial surfactant therapy in hyaline-membrane disease. Lancet 1980; 1: 55-9.
2. Halliday HL. Recent clinical trials of surfactant treatment for neonates. Biol Neonate 2006; 89: 323-9.
3. Jobe AH. Pulmonary surfactant therapy. N Engl J Med 1993; 328: 861-8.
4. American Academy of Pediatrics. Committee on Fetus and Newborn. Surfactant replacement therapy for respiratory distress syndrome. Pediatrics 1999; 103: 684-5.
5. Konishi M, Chida S, Shimada S, Kasai T, Murakami Y, Cho K, et al. Surfactant replacement therapy in premature babies with respiratory distress syndrome: factors affecting the response to surfactant and comparison of outcome from 1982-86 and 1987-91. Acta Paediatr Jpn 1992; 34: 617-30.
6. Robertson PA, Sniderman SH, Laros RK Jr, Cowan R, Heilbron D, Goldenberg RL, et al. Neonatal morbidity according to gestational age and birth weight from five tertiary care centers in the United States, 1983 through 1986. Am J Obstet Gynecol 1992; 166(6 Pt 1): 1629-41.
7. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics 1972; 50: 515-25.
8. Soll RF, Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev 2001; 2: CD000510.
9. Hoekstra RE, Jackson JC, Myers TF, Frantz ID III, Stern ME, Powers WF, et al. Improved neonatal survival following multiple doses of bovine surfactant in very premature neonates at risk for respiratory distress syndrome. Pediatrics 1991; 88: 10-8.
10. Kattwinkel J, Bloom BT, Delmore P, Davis CL, Farrell E, Friss H, et al. Prophylactic administration of calf lung surfactant extract is more effective than early treatment of respiratory distress syndrome in neonates of 29 through 32 weeks' gestation. Pediatrics 1993; 92: 90-8.
11. Merritt TA, Hallman M, Berry C, Pohjavuori M, Edwards DK III, Jaaskelainen J, et al. Randomized, placebo-controlled trial of human surfactant given at birth versus rescue administration in very low birth weight infants with lung immaturity. J Pediatr 1991; 118: 581-94.
12. Morley CJ. Systematic review of prophylactic vs rescue surfactant. Arch Dis Child Fetal Neonatal Ed 1997; 77: F70-4.
13. Kendig JW, Notter RH, Cox C, Reubens LJ, Davis JM, Maniscalco WM, et al. A comparison of surfactant as immediate prophylaxis and as rescue therapy in newborns of less than 30 weeks' gestation. N Engl J Med 1991; 324: 865-71.
14. Dunn MS, Shennan AT, Zayack D, Possmayer F. Bovine surfactant replacement therapy in neonates of less than 30 weeks' gestation: a randomized controlled trial of prophylaxis versus treatment. Pediatrics 1991; 87: 377-86.
15. Kresch MJ, Clive JM. Meta-analyses of surfactant replacement therapy of infants with birth weights less than 2000 grams. J Perinatol 1998; 18: 276-83.
16. Pelkonen AS, Hakulinen AL, Turpeinen M, Hallman M. Effect of neonatal surfactant therapy on lung function at school age in children born very preterm. Pediatr Pulmonol 1998; 25: 182-90.

การศึกษาผลของการใช้สารลดแรงตึงผิวในผู้ป่วย respiratory distress syndromeในทารกในช่วงปี พ.ศ. 2546-2548 เปรียบเทียบกับการศึกษาปี พ.ศ. 2542-2545

อุไรวรรณ โชติเกียรติ, นภสรณ์ พรมวงศ์, วิบูลย์ กาญจนพัฒนกุล, มิรา โคราษา, วราภรณ์ แสงทวีสิน, สุนทร ฮ้อเผ่าพันธ์

ภูมิหลัง: *การให้สารลดแรงตึงผิวถือเป็นการรักษาที่สำคัญซึ่งช่วยลดอัตราการตายในผู้ป่วย RDS ได้ตั้งแต่ ปี พ.ศ. 2533 แต่ในระยะเวลาที่ผ่านมามีข้อจำกัดในการใช้สารลดแรงตึงผิวค่อนข้างมากเพราะมีปัญหาค่าใช้จ่ายค่อนข้างสูง ตั้งแต่ปี พ.ศ. 2546 เป็นต้นมาเมื่อมีโครงการประกันสุขภาพขึ้นมา ได้มีการใช้สารลดแรงตึงผิวในผู้ป่วย RDS เพิ่มมากขึ้นในสถาบันแห่งนี้ จึงควรมีการศึกษาผลของการรักษา*

วัตถุประสงค์: *เพื่อศึกษาผลการรักษาผู้ป่วยหายใจลำบากที่อาการรุนแรงปานกลางถึงรุนแรงมากในผู้ป่วย RDS ที่ได้รับสารลดแรงตึงผิว ปัจจัยที่มีผลต่อการรักษาด้วยสารลดแรงตึงผิว, รวมทั้งภาวะแทรกซ้อนที่เกิดขึ้นจากการใช้สารลดแรงตึงผิว*

รูปแบบการศึกษา: *เป็นการศึกษาแบบย้อนหลัง*

วัสดุและวิธีการ: *เก็บข้อมูลจากแฟ้มประวัติของผู้ป่วยที่คลอดในโรงพยาบาลราชวิถีและเข้ารับการรักษาต่อในสถาบันสุขภาพเด็กแห่งชาติมหาราชินีโดยได้รับการวินิจฉัยว่าคลอดก่อนกำหนด และมีภาวะหายใจลำบากที่อาการรุนแรงปานกลาง ถึงรุนแรงมากในผู้ป่วย RDS ซึ่งได้รับการรักษาด้วยสารลดแรงตึงผิว ตั้งแต่ 1 มกราคม พ.ศ. 2546 ถึง 31 ธันวาคม พ.ศ. 2548 จำนวน 91 ราย เป็นกลุ่มศึกษา โดยศึกษาข้อมูลพื้นฐาน ภาวะแทรกซ้อน อัตราการตายทารก และวิเคราะห์ความสัมพันธ์ระหว่างอายุที่เริ่มให้สารลดแรงตึงผิว กับจำนวนวันที่ใช้เครื่องช่วยหายใจเปรียบเทียบกับผู้ป่วย ในปี พ.ศ. 2542-2545*

ผลการศึกษา: *ผู้ป่วยในกลุ่มศึกษาครั้งนี้ 91 ราย เปรียบเทียบกับ 33 รายในกลุ่มเปรียบเทียบ อายุครรภ์เฉลี่ย 29.38 $\pm$ 2.25 สัปดาห์ น้ำหนักแรกเกิด เฉลี่ย 1,250 $\pm$ 435.57 กรัม ซึ่งมีแนวโน้มต่ำกว่า จากกลุ่มแรกคือ 29.69 $\pm$ 2.61 สัปดาห์ และ 1,344 $\pm$ 452.37 กรัม ปัจจัยที่มีผลต่อการรักษาพบว่า อุบัติการณ์ของ APH ในกลุ่มศึกษาน้อยกว่าในกลุ่มแรก (4.4% เทียบกับ 33.3%) แต่พบ PIH มากกว่า (17.6% เทียบกับ 3%) เปรียบเทียบสภาวะแรกคลอดพบภาวะซีดและการเกิด PDA ในกลุ่มศึกษามากกว่ากลุ่มก่อนหน้านี้ คือ 28.6% เทียบกับ 9%, และ 67% เทียบกับ 39.4% อายุเฉลี่ยที่เริ่มให้สารลดแรงตึงผิวพบว่าในกลุ่มศึกษาให้เร็วขึ้น คือ 4.75$\pm$2.76 ชั่วโมง เทียบกับ 7.21$\pm$4.92 ชั่วโมง และระยะเวลาเฉลี่ยการใช้เครื่องช่วยหายใจสั้นลงจาก 16 วัน เป็น 6 วันในกลุ่มที่เริ่มให้สารลดแรงตึงผิวเร็วใน 6 ชั่วโมงแรก ภาวะแทรกซ้อนที่เกิดขึ้น พบว่า การเกิด pulmonary hemorrhage น้อยลงคือ 12.1% กับ 33.3% แต่พบการเกิด BPD ในกลุ่มศึกษามากกว่า คือ 46.1% เทียบกับ 21.2% ระยะเวลาการนอนโรงพยาบาลนานขึ้น แต่จำนวนผู้ป่วยที่เสียชีวิตน้อยลง คือ 61.23 $\pm$ 41.08 วัน เทียบกับ 38.5 $\pm$ 23.48 วัน, และ 17 ราย (18.7%) เทียบกับ 11 ราย (33.3%) ตามลำดับ*

สรุป: *การรักษาผู้ป่วย moderate to severe RDS ด้วยสารลดแรงตึงผิว พบว่าระยะเวลาการใช้เครื่องช่วยหายใจสั้นลง และอัตราการตายน้อยลง แต่อุบัติการณ์การเกิด BPD ไม่เปลี่ยนแปลง โดยผลรวมแล้วการให้สารลดแรงตึงผิวในระยะเวลาที่เร็วขึ้นช่วยเพิ่มอัตราการรอดชีวิตของผู้ป่วยได้มากขึ้น*