Compare severity of Bronchopulmonary Dysplasia in Neonates with Respiratory Distress Syndrome Treated with Surfactant to without Surfactant

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Background: *The utilization of surfactant replacement therapy had been limited in treatment of respiratory distress syndrome (RDS) due to the high cost especially in developing countries. Nowadays, the National Health Insurance Policy has covered the cost of surfactant for the patients. Therefore, bronchopulmonary dysplasia (BPD) may be found increasing due to increased survival in patients with severe RDS.*

Objective: *To compare immediate treatment outcome of severity of BPD and outcome after hospital discharge in neonates with RDS who were treated with or without surfactant.*

Study design: *Retrospective cohort study.*

Material and Method: *The data of 54 infants who developed BPD after RDS at Queen Sirikit National Institute of Child Health between January 1st, 2003 and December 31th, 2005 were kept in database format. The database was analyzed for difference between groups and the outcome of immediate treatment, severity of BPD and outcome after hospital discharge were compared. The study group was BPD cases from RDS treated with surfactant compared to control (BPD cases from RDS treated without surfactant) groups.*

Results: *Forty-three (80%) from fifty-four cases had completed data and were included into the present study. There was no statistically significant difference in maternal conditions and neonatal conditions between groups. Antenatal steroid was prescribed more often in RDS without surfactant group than surfactant group. The mean birth weight and gestational age in surfactant and without surfactant groups were 1,179.1 $\pm$ 274.3 gm vs. 1,114.4 $\pm$ 338.3 gm and 29 $\pm$ 1.6 weeks vs. 29.2 $\pm$ 2.7 weeks respectively, but no significant differences were observed between groups. To compare the severity of RDS, only 17.6% of moderate to severe RDS in the control group was found, whereas 100% was found in the study group. Moderate to severe BPD cases were found more often in the control group (70.6%) than in the study group (61.6%), but no statistically significant difference was shown. The immediate complications, e.g. pneumothorax (5.9%) and pneumomediastinum (5.9%) were found in the control group, but pulmonary hemorrhage occurred more often in the study group than the control group (11.5% vs. 5.9%). For long-term follow-up, the development outcome was not different between groups.*

Conclusion: *The present study revealed no statistically significant difference in severity of BPD in neonates with RDS treated with and without surfactant groups. In addition, surfactant was useful in moderate to severe RDS because no early complication such as air leak syndrome was found in this group.*

Keywords*: RDS, BPD, Surfactant*

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An exogenous surfactant, either synthetic or extracted from animal lungs, is given through the endotracheal tube into the lungs for preterm with moderate to severe respiratory distress syndrome. These surfactants especially survanta can decrease the risk of death in hospitalized very-low-birth weight infants by 30%[1]. Overall however, surfactant has not reduced the incidence of BPD; maybe because surfactant increased the survival rate of extremely premature infants in general and some of these babies will develop BPD[2-6]. The utilization of surfactant replacement therapy has been limited in treatment of

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RDS due to the high cost especially in developing countries. Nowadays, the National Health Insurance Policy has covered the cost of surfactant for the patients. Bronchopulmonary dysplasia (BPD) has been increasing due to improvement in the treatment of severe RDS. Despite the widespread use of antenatal steroids and surfactant the incidence of BPD has not declined.

Objective

To compare immediate treatment outcome of severity of BPD and outcome after hospital discharge in neonates with RDS who were treated with or without surfactant.

Material and Method

The data of 54 infants who developed BPD after RDS at Queen Sirikit National Institute of Child Health between January 1st, 2003 and December 31th, 2005 were kept in database format and analyzed for the difference between neonates with RDS treated with surfactant and without surfactant. The severity of BPD, result of RDS treatment and outcome after discharge from the hospital in both groups, was compared. Preterm cases with congenital anomalies incompatible with life, cases with anti-HIV positive and cases with incomplete data were excluded from the present study. The definition of severity of BPD was classified according to United States National Institute of Health (USNIH)[7]. Infants with mild BPD were those who received supplemental oxygen for 28 days or more but not at 36 weeks postmenstrual age (PMA). Infants with an oxygen requirement less than 30% at 36 weeks PMA were moderate BPD and those who required > 30% oxygen or positive pressure ventilation at 36 weeks PMA were classified as the severe group. All survivors received head ultrasound, eye examination, hearing screening before discharge and were followed-up at the high risk clinic for developmental assessment (Denver II). The research protocol was fully approved by the institutional ethics committee.

Statistical analysis

Descriptive data were analyzed into percentage, mean and standard deviation. Comparison for continuous variables was 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 $p < 0.05$.

Results

The completed data of forty-three cases (80%) of BPD from fifty-four cases were reviewed. There were no statistically significant differences in neonatal conditions and maternal conditions between groups except antenatal steroid which was prescribed more often in the control group than study group. The mean birth weight and gestational age in the present study and control groups were 1,179.1 $\pm$ 274.3 gm vs. 1,114.4 $\pm$ 338.3 gm and 29 $\pm$ 1.6 weeks vs. 29.2 $\pm$ 2.7 weeks respectively, which was not of statistically significant difference between groups as shown in Table 1 and 2. There were no statistically significant differences in mode of delivery, Apgar scores, neonatal conditions and blood gases as shown in Table 2. 17.6% cases had moderate to severe RDS in the control group, but occurred 100% in the study group. Moderate to severe BPD cases were found more often in the control group (70.6%) than the study group (61.6%), but no significantly statistical difference was observed, as shown in Table 3.

The immediate complications, *e.g.* pneumothorax (5.9%) and pneumomediastinum (5.9%) were found only in the control group but the authors found more cases of patent ductus arteriosus and pulmonary hemorrhage in the surfactant group than in the control group (73.08, 11.5% vs. 58.8%, 5.9%). No statistical difference in either intraventicular hemorrhage or retinopathy of prematurity was found, as shown in Table 2 and 4.

For long-term follow-up, the authors found the development outcome was not statistically different between the groups but there were more cases of bronchopulmonary dysplasia in the study group than the control group as shown in Table 5.

Discussion

Although the widespread use of antenatal steroids and surfactant has caused an associated reduction in the incidence and severity of respiratory distress syndrome[1] (RDS), the incidence of BPD has not declined. According to a previous report by the authors on BPD from two periods, the incidence has increased from 21.2% to 46.1% which is the same as the other reports[8-10]. The authors found moderate to severe RDS in the control group less than in the study group but there was a greater number of moderate to severe BPD cases in the control group compared to the

Table 1. Demographic datas of mothers in study and control groups

Data of mother	Study group n = 26 (%)	Control group n = 17(%)	p-value
ANC ≥ 4 time, n (%)	12 (46.1)	13 (76.5)	0.063
Mother age, year*	26.1 (6.7)	28.5 (4.9)	0.214
Antenatal corticosteroid, n (%)			
No	19 (73)	8 (47)	0.0003
Complete	3 (11.5)	4 (23.5)	
Incomplete	4 (15.5)	5 (29.5)	
Maternal condition, n (%)			
Prolonged PROM	3 (11.5)	3 (17.6)	0.667
APH	2 (7.6)	1 (5.8)	1.000
PIH	3 (11.5)	2 (11.7)	1.000
Infection, n (%)	2 (7.6)	1 (5.9)	1.000
Urinary tract infection	1 (50)	1 (100)	
Chorioamnionitis	1 (50)	0 (0)	
Twin pregnancy, n (%)	7 (26.9)	7 (41.2)	0.329
GDM n, (%)	2 (7.6)	0 (0)	0.511

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

Table 2. Comparative data of newborn at birth between groups

Data of newborn	Study group n = 26 (%)	Control group n = 17 (%)	p-value
Male, n (%)	10 (38.5)	10 (58.8)	0.191
Gestational age, wk*	29 (1.6)	29.2 (2.7)	0.891
Birth weight, g*	1,179.1 (274.3)	1,114.4 (338.3)	0.494
Size for gestational age, n (%)			
AGA	24 (92.3)	15 (88.2)	1.000
SGA	2 (7.7)	2 (11.8)	
Mode of delivery, n (%)			
Vaginal	17 (65.4)	12 (70.6)	0.722
Cesarean section	9 (34.6)	5 (29.4)	
Apgar scores*			
1 min	5.2 (2.1)	4.8 (2.5)	0.574
5 min	7.1 (1.7)	6.5 (2.2)	0.336
Neonatal condition, n (%)			
Asphyxia	15 (57.6)	11 (64.7)	0.646
Acidosis	10 (38.4)	4 (23.5)	0.343
Hypothermia	1 (3.8)	3 (17.6)	0.284
Hypotension	15 (57.6)	5 (29.4)	0.069
Anemia	13 (50)	9 (52.9)	0.85
Hypoglycemia	3 (11.5)	0 (0)	0.266
Symptomatic PDA	19 (73.1)	10 (58.8)	0.329
Blood gas*			
pH	7.29 (0.1)	7.35 (0.11)	0.093
PCO_2	41.8 (8.2)	40.8 (14.6)	0.795
HCO_3	20.3 (4.1)	22.7 (6)	0.138
BE	-5.1 (4.3)	-3 (3.9)	0.12

PDA: patent ductus arteriosus, * = mean (SD), BE: base excess

Table 3. Comparative severity of RDS and bronchopulmonary dysplasia(BPD) in two groups

Severity of RDS/BPD	Study group n = 26 (%)	Control group n = 17 (%)	p-value
Severity of RDS, n (%)			< 0.01
Mild	0 (0)	14 (82.4)	
Moderate to severe	26 (100)	3 (17.6)	
Severity of BPD, n (%)			0.822
Mild	10 (38.4)	5 (29.4)	
Moderate	13 (50)	10 (58.8)	
Severe	3 (11.6)	2 (11.8)	

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

Complication	Study group n = 26 (%)	Control group n = 17 (%)	p-value
Pulmonary hemorrhage, n (%)	3 (11.5)	1 (5.9)	1.000
Pneumothorax, n (%)	0 (0)	1 (5.9)	0.395
Pneumomediastinum, n (%)	0 (0)	1 (5.9)	0.395
Pulmonary interstitial, n (%) emphysema	1 (3.8)	0 (0)	1.000
Retinopathy of prematurity, n (%)	8 (30.7)	6 (35.3)	0.757
Stage I	5 (62.5)	4 (66.6)	
Stage II	0 (0)	1 (16.7)	
Stage III	3 (37.5)	1 (16.7)	
Intraventricular hemorrhage, n (%)	13 (50)	6 (35.3)	0.342
Grade I	7 (53.8)	2 (33.3)	
Grade II	4 (30.7)	1 (16.7)	
Grade III	2 (15.5)	2 (33.3)	
Grade IV	0 (0)	1 (16.7)	

Table 5. Comparative outcome in one year follow-up at Queen Sirikit National Institute of Child Health

Outcome	Study group n = 26 (%)	Control n = 16 (%)	p-value
Follow-up, n (%)	19 (73)	14 (87.5)	
Development, n (%)			
Normal development	17 (89.5)	9 (64.2)	0.10
Delayed development	2 (10.5)	5 (35.7)	
Spastic CP, n (%)	2 (10.5)	0 (0)	0.49
BPD, n (%)	6 (31.5)	0 (0)	0.03
Seizure, n (%)	1 (5.2)	0 (0)	1.00
Hearing impairment	0 (0)	0 (0)	-
Death	0 (0)	0 (0)	-

surfactant group but it had insignificant statistical difference. This explains why the patients in the control group can develop moderate to severe BPD despite more than eighty percent of cases being mild RDS. In the present study, antenatal steroid was prescribed in the control group more often than in the surfactant group (53% vs. 27%) and has statistical significance. The antenatal steroid had shown protective effect to decrease the severity of RDS in the control group which is in agreement with the large meta-analysis by Crowley[11]. The mean birth weight and gestational age in the present study and control groups were not statistically different which is different from the other report that found more cases of BPD in neonates less

than 27 weeks[12]. Similar to previous studies, the authors found more cases of patent ductus arteriosus and pulmonary hemorrhage in the surfactant group than in the control group[12,13]. Air leak syndrome such as pneumothorax and pneumomediastinum were found more in control cases than in surfactant groups similar to the previous reports[3,15]. There were no significant differences in duration, type of ventilator modes and mean airway pressure in the surfactant and control groups. This shows that surfactant can help moderate to severe RDS patients to wean from the respirator as quickly as neonates with mild RDS without surfactant treatment. The authors found more cases of BPD in the study group than in the control group with statistical difference and the authors found more cases of normal development in study group in one year follow-up too.

Conclusion

The authors found no statistically significant difference in severity of BPD in RDS babies treated with and without surfactant groups. However, surfactant was useful in moderate to severe RDS because no early complication such as air leak syndrome was found in this group.

Potential conflicts of interest

None.

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การศึกษาความรุนแรงของโรคปอดเรื้อรังในโรค respiratory distress syndrome ในทารกที่ได้รับสาร surfactant เปรียบเทียบกับที่ไม่ได้รับสาร surfactant

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ภูมิหลัง: *เนื่องจากสาร surfactant มีราคาสูง จึงเป็นข้อจำกัดในการรักษาผู้ป่วย respiratory distress (RDS) ในประเทศที่กำลังพัฒนา แต่ในปัจจุบัน หลังจากได้เริ่มระบบหลักประกันสุขภาพถ้วนหน้าเป็นต้นมา ทำให้มีการใช้สาร surfactant เพิ่มมากขึ้นในผู้ป่วยที่มีภาวะ RDS ทำให้ผู้ป่วยอายุครรภ์น้อย มีอัตราการรอดชีวิตเพิ่มขึ้น และทารกที่รอดชีวิตเป็นโรคปอดเรื้อรัง (Bronchopulmonary dysplasia, BPD) เพิ่มขึ้น*

วัตถุประสงค์: *เพื่อศึกษาความรุนแรงของ BPD และผลการรักษา ในผู้ป่วยทารกที่มีภาวะ RDS ที่ได้รับสาร surfactant เปรียบเทียบกับทารกที่ไม่ได้รับสาร surfactant รวมทั้งพัฒนาการและภาวะแทรกซ้อน หลังผู้ป่วยจำหน่ายจากโรงพยาบาล*

รูปแบบการวิจัย: *เป็นการศึกษาแบบย้อนหลัง (retrospective cohort study)*

วัสดุและวิธีการ: *เก็บข้อมูลจากแฟ้มประวัติของผู้ป่วยที่เข้ารับการรักษาในสถาบันสุขภาพเด็กแห่งชาติมหาราชินี โดยเป็นทารกคลอดก่อนกำหนดที่มีภาวะ RDS ได้รับการรักษาด้วยสาร surfactant หรือไม่ได้รับสาร surfactant ตั้งแต่ 1 มกราคม พ.ศ. 2546 ถึง 31 ธันวาคม พ.ศ. 2548 และได้รับการวินิจฉัยว่ามีภาวะ BPD ร่วมด้วย จำนวน 54 ราย โดยบันทึกข้อมูลใน database เพื่อประเมิน ความรุนแรงของภาวะ BPD ปัจจัยที่มีความสัมพันธ์ที่ทำให้ความรุนแรงของ BPD แตกต่างกัน รวมทั้งผลการติดตามผู้ป่วยหลังจำหน่ายจากโรงพยาบาล*

ผลการศึกษา: *จำนวนทารกที่มีข้อมูลครบ 43 ราย (80%) จากทั้งหมด 54 ราย พบว่าไม่มีความแตกต่างกันของข้อมูลสภาวะก่อนคลอดของมารดาและข้อมูลพื้นฐานของทารก และสภาวะก่อนคลอดของมารดา ยกเว้นในกลุ่มที่ไม่ได้รับสาร surfactant มารดาได้รับสาร steroid ก่อนคลอด (antenatal steroid) มากกว่ากลุ่มที่ได้รับสาร surfactant น้ำหนักแรกเกิดเฉลี่ย อายุครรภ์เฉลี่ย คือ 1,179.1 $\pm$ 274.3 กรัม และ 1,114.4 $\pm$ 338.3 กรัม และอายุครรภ์เฉลี่ย 29 $\pm$ 1.6 สัปดาห์กับ 29.2 $\pm$ 2.7 สัปดาห์ตามลำดับซึ่งไม่มีความแตกต่างกัน เมื่อเปรียบเทียบความรุนแรงของ RDS ในทารกทั้งสองกลุ่มพบว่ากลุ่มที่ไม่ได้รับสาร surfactant มีความรุนแรงระดับ moderate ถึง severe 17.6% ในขณะที่กลุ่มที่ได้รับสาร surfactant มีความรุนแรงระดับ moderate ถึง severe 100% ความรุนแรงของ BPD ในทารกทั้งสองกลุ่มนี้ไม่มีความแตกต่างกันทางสถิติ แต่พบว่าในกลุ่มที่ไม่ได้รับสาร surfactant มีความรุนแรงของ BPD ในระดับ moderate ถึง severe มากกว่ากลุ่มที่ได้รับสาร surfactant คือ 70.6% เปรียบเทียบกับ 61.6% ตามลำดับในกลุ่มที่ไม่ได้รับสาร surfactant พบภาวะแทรกซ้อนระยะสั้น คือ pneumothorax 1 ราย (5.9%) pneumomediastinum 1 ราย (5.9%) แต่พบ pulmonary hemorrhage ในกลุ่มที่ได้รับสาร surfactant มากกว่าคือ 11.5% เปรียบเทียบกับ 5.9% ตามลำดับผลการติดตามผู้ป่วยหลังจำหน่ายจากโรงพยาบาลพบว่าพัฒนาการในผู้ป่วยทั้งสองกลุ่มไม่แตกต่างกัน*

สรุป: *จากการศึกษาพบว่าไม่มีความแตกต่างกันของความรุนแรง BPD ในกลุ่มที่ได้รับสาร surfactant เมื่อเปรียบเทียบกับกลุ่มที่ไม่ได้รับสาร surfactant อย่างไรก็ตามการให้สาร surfactant ในผู้ป่วยที่มีความรุนแรงของ RDS ระดับ moderate ถึง severe ยังคงมีประโยชน์ เนื่องจากไม่พบผู้ป่วยที่มีภาวะแทรกซ้อนระยะสั้นคือ air leak syndrome ในกลุ่มที่ได้รับสาร surfactant เมื่อเปรียบเทียบกับกลุ่มที่ไม่ได้รับสาร surfactant*