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Determining the effect of surfactant instillation time in the prognosis of RDS

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Abstract Background: RDS is the most common cause of respiratory problems of preterm infants in NICU and surfactant is its treatment, there is strong recommendation for early use of this drug for more effectiveness .The goal of this study is assessment the effects ofsurfactant instillation time in the prognosis of RDS
Material and method: 96 neonates with RDS according to the age of treatment with surfactant were divided in three groups: early (≤6h), late (6-48 h) and very late (≥48 h). The mortality, pneumothorax, pulmonary hemorrhage, IVH, duration of mechanical ventilation and duration of hospital stay were compared.
Result: 67.7% neonates were males. Means of gestational age and birth weight was 31.8±3 weeks and 1900±630gm respectively, 41.6% of neonates were in early group, 55.2%in late group and 3.1%| in very late group .The earliest time for instillation of surfactant was first hour and the latest time was 96th hour .The rate of pulmonary hemorrhage, pneumothorax & mortality in early group was more than late & very late groups., but there wasn't any differences in IVH and mean durationof mechanical ventilation and hospital stay.
Conclusion: Although there is evidence that earlier instillation of surfactant has better prognosis in neonates,but in this study prognosis of patients with late and very late treatment was good and this means that delayed utilization of this treatment is useful too.

Keyword:- *neonates,RDS, respiratory distress syndrome, surfactant, preterm*

I. INTRODUCTION

Respiratory distress syndrome (RDS) is the most common cause of respiratory problems in preterm infants in neonatal intensive care units (NICU) Lower gestational age is associated with higher incidence of RDS (1). Surfactant therapy is one of the most important treatments in this disease (2), although in recent years, it is determined that the early use of nasal continuous positive airway pressure (NCPAP) can decrease the need of endotracheal mechanical ventilation and surfactant instillation,. Recent recommendations emphasize that in more sever forms of disease that non responding to noninvasive mechanical ventilation, early instillation of surfactantendotracheal(in first two hours of life) improves the outcomes of patients (3), but in some situations, such as unavailability of drug, there isn't possibility of early use of that and in the other side there is controversy about delay use of surfactant. Surfactant can be associated with some complication such as transient hypoxemia and bradycardia, pulmonary hemorrhage ,patent duteousarteriosus (PDA) (4),but surfactant cause decrease incidence of pneumothorax and mortality in preterm infants.(5) . This research was done to response whether delay use of surfactant is as effective as early use or not and if the timing of surfactant therapy can be effect in complications of drug?

II. MATERIAL AND METHOD

This research is aretrospective cross-sectional study on neonates with RDS which were underwent surfactant replacement therapy in NICU of Shohada-e-Tajrish hospital in 2010. Ethical Committee of ShahidBeheshti medical university of science has approved this study. All neonates with history of surfactant therapy were included in this research. In all neonates with moderate to severe RDS based on clinical manifestations and radiologic findings that confirm the diagnosis of RDS,which needed to endotracheal mechanical ventilation, decision for surfactant therapy was made. The patients were admitted in our NICU were inborn and out born. In some situations that drug was not available soon after birth or the patient was referred from other hospitals, despite of our NICU's policy, the drug was used with delay. Two types of surfactant, survanta and curosurfe, were used and the selection of the type of drugwas not based on a special protocol and were just selected because of the availability of that. After surfactant therapy as early as possible patient tolerated ventilator therapy was stopped .According to the age of neonates in the time of surfactant replacement therapy, results oftreatment was compared in three age groups; early (neonates with ages of <6 hours), late (neonates'ages between 6 to 48 hours), and very late (neonates'age > 48 hours). The outcomes of the therapy such as mortality, pulmonary hemorrhage, intraventricular hemorrhage (IVH), pneumothorax, duration of

admission, and duration of mechanicalventilation were compared in these three groups. In order to show the qualitative variables we used frequency and for quantitative variables , mean and standard deviation were used. We compared the mean with T-test and the ratios with Chi-2 test. Also, relationship between quantitative variables were determined with correlation test. To investigate the relationship between surfactant therapy andneonatal outcomes, multivariate Logistic regression was used. Statistical software that we used was SPSS-11.Statistical significance was set at $P<0.05$.

III. RESULTS

In this study 96 neonates were enrolled. There were 31 female (32.2%) and 65 male (67.7%). Mean gestational age was 31.8±3.1week with the range of 25 to 39 weeks. Mean birth weight was 1900±630 gr..64 neonates (66.7%) were delivered by caesarian section (C/S) andthe rest bynormal vaginal delivery (NVD). Mean Apgar score at 5 minute of birth was 8. Mean hospital stay was 22.5±16.1 days with the range of 6hours to 77 days. Mean average age of surfactant replacement therapy was 12.7±15.2 hours with the range of 1(earliest time) to 96 hours (the latest time).40 patients (41.6%) were in early group, 53 neonates (55.2%) were in late group, and 3 (3.1%) were in very late group.As it shown in table-1The effect of timingof surfactant therapy and complications such as pulmonary hemorrhage, IVH, pneumothorax, duration of admission, duration of mechanical ventilation and mortality werecompared..According of this analysis mortality rate and pulmonary hemorrhage and pneumothorax were higher in neonates infirst group.Pulmonary hemorrhage was in 25%,7.5%, and 3.3 %.(P-value: 0.049). Inearly, late and very late respectively.Pneumothorax was in 25%, 3.8%, 0inearly, late and very late respectively andmortality in early group was in 37.5%, in late group 7.5% and in very late group was none.These results means that delayed surfactant replacement therapy is not accompanied with great incidence of complications such as pulmonary hemorrhage and pneumothorax or more mortality rate.

Table 1:Comparing neonatal outcome based on the age of patients

	Early(n=40) <6 hour	Late(n=53) 6-48 hour	Very Late(n=3) >48hour	P-Value
Pulmonary Hemorrhage	N=10(25%)	N=4(7.5%)	N=1 (3.3%)	0.049
Pneumothorax	N=10(25%)	N=2(3.8%)	-	0.007
Ventricular hemorrhage	N=2(5%)	N=5(9.4%)	-	0.636
Duration of ventilator	4.1±1.7	4.1±1.6	2.3±1.5	0.911
Duration of admission	21.8±17.7	23.5±15.3	16.7±7.6	0.207
Death	N=15(37.5%)	N=4(7.5%)	-	0.01

Table 2 showed comparisons of neonatal outcomes(mortality,pneumothorax,pulmonary hemorrhage, and ventricular hemorrhage) based on the meanage of surfactant therapy .This comparisons showed that mortality rate and pneumothorax were higher in mean lower neonatal age in the time of surfactant replacement therapy.

Table 2: Comparing neonatal outcomes based on the mean age of surfactant therapy

Neonatal Outcome		Mean age of surfactant therapy(Hour)	P-Value
Death	Yes(N=19)	3.6±2.5	0.003
	No(N=77)	14.9±16.3	
Pneumothorax	Yes(N=12)	4±2.6	0.034
	No(N=84)	13.9±15.9	
Pulmonary hemorrhage	Yes(N=15)	7.2±11.8	0.129
	No(N=81)	13.7±15.7	
Ventricular hemorrhage	Yes(N=7)	14.8±16.6	0.703
	No(N=89)	12.5±15.3	

In order to examine the relationship between age of receiving surfactant with variables such as the length of the ventilation, duration of admission and Apgar score at 5 minutes of birth, the correlation coefficient of variables have been examined(-0.113)and there was no meaningful relationship.(P-value:0.332), But there was meaningful relation between Apgar at birth with age of surfactant therapy.(correlation coefficient:+0.363)(P-value<0.001). Also ,meanApgar in dead neonates was 5.06±1.4 and in alive neonates was 7.8±1.3 that is shown us a meaningful correlation between Apgar and mortality.(P-value<0.001)
The correlation coefficient between age of receiving surfactant with gestational age was +0.363(P-value<0.001) and between neonatal weight and age of surfactant therapy was +0.245(P-value=0.006) that was meaningful relation.In another analysis neonates were divided in two groups by Apgar score lower and upper than 6 in table3.

Table 3.comparing neonatal outcome based on mean age of treatment and Apgar score

Apgar	Neonatal outcome		Mean age of surfactant therapy(Hour)	P-Value
6≥	Death	Yes(N=11) No(N=6)	3.4±1.8 7.7±5.6	0.033
	Pneumothorax	Yes(N=6) No(N=11)	4.5±3.5 5.2±4.4	0.749
	Pulmonary hemorrhage	Yes(N=6) No(N=11)	3±1.7 6±4.6	0.145
>6	Ventricular hemorrhage	Yes(N=0) No(N=17)	-- 4.94±4	--
	Death	Yes(N=8) No(N=71)	3.9±3.3 15.6±16.7	0.045
	Pneumothorax	Yes(N=6) No(N=73)	3.5±1.4 15.3±16.6	0.008
	Pulmonary hemorrhage	Yes(N=9) No(N=70)	10±14.9 14.9±16.5	0.394
	Ventricular hemorrhage	Yes(N=77) No(N=2)	9.6±8.9 13.5±10.8	0.612

According to the results of this study it seems that confounding factors affect the relationship between time of starting treatment and neonatal outcome. Therefore, multivariate Logistic regression model is used for detecting the relationship between variables with outcome. It is shown that there was no independental relationship between death with time of surfactant therapy, birth weight with gestational age. But there was an independental relationship between death and Apgar score. Also, there was no statistical independent relationship between pneumothorax and pulmonary hemorrhage with time of surfactant therapy.

IV. DISCUSSION:

Our study showed that delay instillation of surfactant didn't have correlation with poor outcome, even mortality, pneumothorax and pulmonary hemorrhage were lower in late and very late group andpatients which had delayed surfactant replacement therapy, had suitable and acceptable results and neonatal outcome. In our study, 67.7% of neonates were male, this results matches with higher incidence of RDS in males(6). On the other side the mean gestational age in our study was 31.8±3.1 weeks and it is in accordance with the high incidence of this disease in preterm neonates. Recent studies in very preterm infants showed that early usage of noninvasive mechanical ventilation(NCPAP) within thefirst minutes after birth in delivery room can significantly decrease need for surfactant replacement therapy and endotracheal mechanical ventilation.(7) and be accompanied with more better outcome of them. In our study we didn't use early CPAP in delivery room but in NICU in cases with milder form of RDS, as initial modality NCPAP was used.Many research showed that surfactant therapy can decrease mortality rate in neonatal periods (8). In our research mortality ratein early groupwassignificantly higher than other two groups (37.5%, versus 7.5% and zero respectively)(P-value: 0.001)…Neonatal mortality was related to many factors and timing of surfactant therapy as a rescue therapy of respiratory distress syndrome has partly effect on it along with other important factors such as ventilator therapy and other complex neonatal care. In fact more critically ill neonates, the ones that need earlier assisted ventilation and surfactant therapy and also have more mortality and morbidity (such as pneumothorax and pulmonary hemorrhage) ..This does not mean that earlier surfactant therapy cause more mortality and morbidity .However the number of the neonates in 3 groups weren't similar and this is one of limitation of our study because of retrospectively pattern of our research.

In research was done by Bevilaqua,(9) such as our study timing of surfactant therapy was compared between two group :very early -VE- treated:within the first 15 minutes of life and the other at age 16- 180 minutes (early -E- treated). One single dose of surfactant was administered in 77.8% of VE babies and 45.3% in the E group, while 18.5% VE and 36.8% E received two doses, 3.7% VE and 16.3% E were given three doses.The main outcomes did not differ in the two groups: mortality at 28 days of life, age at death, pneumothorax, intraventricularhemorrhage grade 3-4, retinopathy of prematurity grade 3-4, patent ductus arteriosus and oxygen dependency at 36 wks post-conceptional age.In another study was done by Stevens in 2007(10) they conclude that early surfactant replacement therapy with extubation to NCPAP compared with later selective surfactant replacement and continued mechanical ventilation with extubation from low ventilator support is associated with less need mechanical ventilation, lower incidence of BPD and fewer air leak syndromes

One complications of RDS and mechanical ventilation (invasive and noninvasive types) is pneumothorax. and one benefit of surfactant therapy is decrease rate of this complication such as a study was done by AbdolrezaMalek 1n 2011(11), they showed that in 400 newborns under mechanical ventilation Surfactant replacement therapy was recorded in 32.4% of cases with pneumothorax compared to 60.4% of neonates under ventilation without pneumothorax, which was significantly different (P= 0.017.However in research of Malek the timing of surfactant therapy didn't compar..Prolonged mechanical ventilation can be accompanied by higher incidence of air leak syndrome and pneumothorax.In our research the rate of pneumothorax in early group was more than late and very late group despite much lower days of positive pressure ventilation of mechanical ventilation, may be because of more severe form of RDS in those patients. In another study was done by Colin in 2008In infants born at 25-to-28-weeks' gestation, early nasal CPAP was compared with intubation ,results of their research showed that the CPAP group had more incidences of pneumothorax because the CPAP group didn't received surfactant in comparison with intubation group (12)
Pulmonary hemorrhage is another side effect of surfactant.(13)In 4-6% of patients with history of surfactant therapy during 48-72 hour after usage pulmonary hemorrhage was happened. However there are many other risk factors for this complication in neonates such as sepsis, mechanical ventilation, hypothermia and etc. In our study this complication occur in early group more than late and very late group. It seems that more critically conditions of patients in early group can justify more complications.

Our study such as another studies (14) showed that there was a meaningful correlation between low Apgar score and mortality.(P-value<0.001).One of criteria of hypoxic ischemic encephalopathy (HIE) is 5 minutes low Apgar score in addition to fetal acidemia ,lethargy and loss of Consciousness and seizure and multiorgan damage in neonates (12).Determination the effect of only one factor(low Apgar score) without considering others ,does not seem logical.The mean average of admission time and hospital stay in early,late and very late group was 21.8,23.5, 16.7 days respectively and there was not a significantly differenc between them.(P-value=0.207).It is expected that more critically ill neonates needs more prolonged hospital stay but because of mean gestational age of our patients was 31.6 weeks ,mean average of admission time was similar.
Although these results are not compatible with Yost and Stevens's studies but they are match with Revilaqua's study. In study of Yost and Stevens it was declared that early surfactant replacement therapy has much better results but in our study we found that neonates who reach equipped surfactant therapy centers later should have treatment like others and they can have favorable results like early group. Duration of mechanical ventilation in 3 groups did not have a meaningful difference.

V. CONCLUSION:

According to the studies it is obvious that administration of surfactant as soon as possible(less than 2 hours of birth) improves the prognosis of neonates and it is recommended in most studies to have early surfactant therapy in neonates with RDS for better prognosis. Based on results of our study neonatal mortality and some complications of RDS (pneumothorax pulmonary hemorrhage) in neonates was less in delayed surfactant replacement therapy. Therefore, we found that delayed surfactant therapy can be very effective and if we use this drug even in older age in neonates, it has a very good effectiveness.

VI. RELEVANT DECLARATION OF INTEREST:

Authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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