

## A Model for Analyzing the Results of Surfactant Administration In Neonatal Wards

MOHAMMAD JAVAD GHARIB<sup>1</sup>, BANAFSHEH DORMANESH<sup>2</sup>,  
ALIREZA AMINIAN<sup>3</sup>, KOROSH KOSARI<sup>3\*</sup> and SHARIN ASSADI<sup>4</sup>

<sup>1</sup>General Practitioner, AJA University of Medical Sciences , Tehran , Iran

<sup>2</sup>Department of Pediatric Nephrology, AJA University of Medical Sciences, Tehran, Iran.

3. Neonatologist , AJA University of Medical Sciences , Tehran , Iran.

<sup>4</sup>General Practitioner, Tehran University of Medical Sciences , Tehran , Iran.

\*Corresponding author E-mail : koroshkosari@yahoo.com

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### ABSTRACT

Surfactant has been increasingly popular for treatment of diverse neonatal pulmonary diseases including respiratory distress syndrome; many questions are still unsolved regarding its efficacy, short term and long term side effects though. This research was aimed to investigate all neonates treated by Surfactant in Khanevadeh hospital from 2011 to 2014 and follow them up to 6 months of age on a historical cohort model. 72 neonates got the fitting criteria with a mean gestational age, birth weight and admission duration of 2153, 33.5 and 15.4 respectively. 56.9% were treated by Survanta and Curosurf was prescribed for others. Death rate calculates to be 29.1% and 20.8% patients suffered from pneumothorax as a major side effect. Curosurf acted worse as it caused significantly longer admission and ventilation duration and higher pneumothorax probability. Incidence of lower respiratory tract infections under 6 months of age is measured 15.8% which is significantly more than total population. Regarding to this research, general outcome of this treatment module in Khanevadeh hospital is equal to national statistics and still not in the order of international ones. Survanta showed better outcomes comparing to Curosurf. Risk of lower respiratory tract infections under 6 months of age was higher after treating surfactants eventually.

**Keywords:** respiratory distress syndrome, Surfactant, lower respiratory tract infections.

### INTRODUCTION

The last century has witnessed a rise in the application of surfactant in treating the respiratory problems of infants. The major use of surfactant is observed among those infants afflicted with respiratory distress syndrome.

Among lung secretions, high density surfactant is observed in the 20<sup>th</sup> week of pregnancy, but this segregation will not reach the surface of the lung for a long time after this period. This material

is observed between the 28<sup>th</sup> to 32<sup>nd</sup> week of pregnancy in the amniotic fluid. The lung surfactant will reach a sufficient level after the 35<sup>th</sup> week. Secretion of surfactant is somehow dependant upon the existence of natural PH, temperature, perfusion and blood circulation. Lung Asphyxia, Hypoxia and Ischemia along with Hypovolemia and Hypotension will suppress the secretion of surfactant. Failure in secretion or release of surfactant along with small respiratory units and a high-capacity thorax will result in Atelectasis and, finally, revascularized Alveolis without condition.

This will all bring about hypoxia. A combination of hypercarbia, hypoxia and acidosis will result in the contraction of pulmonary veins and increase right to left shunt through the oval hole and ductus arteriosus and inside the lung. As a result, the lung blood flow decreases. Thus, the cells producing surfactant and vascular bed will be damaged and, as a result, protein substances will be effused into the alveoli space<sup>1</sup>.

Thus, this syndrome is usually caused by the early delivery of kids before the lung surfactant reaches the sufficient level, which is generally on the 35<sup>th</sup> week of pregnancy<sup>2</sup>. In the lower pregnancy ages, respiratory distress syndrome is significantly more frequent. Nearly, 80% of the kids with a pregnancy age of less than 28 weeks have been reported to be suffering from this problem<sup>3</sup>. Thus, it is advisable to inject surfactant through the trachea up to 24 hours after the birth of the endangered kids<sup>2</sup>. This has resulted in an improvement of the prognosis of all respiratory diseases during this period. However, there are still many unknown aspects about this treatment method. There are a lot of ambiguities about the type of pharmaceutical composition, consumption method, precise indications of consumption, simultaneous respiratory support, and the long-term or short-term side effects of this method.

Using surfactant for the treatment of respiratory diseases among the infants began roughly two decades ago in our country. Currently, many types of natural and artificial surfactants have achieved international confirmations. Although in our country and, also, in the neonatal ward of Khanevadeh hospital, two brands of natural surfactants including SURVANTA and Curosurf are more popular with pediatricians<sup>4</sup>. Due to the various results, the treatment results, consumption side effects and the response level of this medicine has never been a subject on international research<sup>5</sup>. Thus, several attempts have been made in order to report the cases of consumption, determine the frequency of side effects and prescribe standard instructions.

The neonatal ward of the Khanevade Hospital of IRIGF was opened two years ago. The presence of an active delivery ward and several

resorts to that center from other hospitals have contributed to registration of several cases of respiratory diseases and, as a result, repetitive consumption of surfactant in medical records of patients. According to the guidelines of many credible centers in the world, researches to gather information about these treatment methods and their points of weakness and challenge are required in order to control the quality of the service<sup>6</sup>. The principle goal of this research is to identify the results of using this treatment method and compare it against the previous domestic and foreign results achieved.

Respiratory distress syndrome of kids is the major case where surfactant is utilized. As defined, these conditions include detection of respiratory distress after birth in premature infants, increasing need for oxygen and respiratory supports and positive findings in the radiography of the rib cage such as reduction of air, reticular granularity, and air Bronchogram<sup>5</sup>. Except for this major pathology, other issues such as transient tachypnea of the newborn, meconium aspiration and resisting pneumosepsis are the other cases where surfactant is used. The favorable treatment results of using surfactant in treating respiratory diseases such as the respiratory distress syndrome of the infants are manifested in signs and symptoms such as improved respiratory activities, lower number of breathes, improvement of lung sounds, improved radiographic representation of the chest and more natural results of vascular blood analysis<sup>5-6</sup>. The most important challenge about applying this treatment is the side effects defined for it. Domestic researches have reported the following frequencies: 23% to 48% for Pneumothorax, 6.05% for secondary sepsis, 3.67% for open vascular duct, 3.42% for lung bleeding, and 13% for broncho-pulmonary dysplasia<sup>5,8</sup>. However, the following frequencies were reported in the major studies conducted abroad: 3% for ventricular bleeding, 9.2% for PDA, 6.1% for lung bleeding, and 3.4% for BPD<sup>9</sup>.

One of the major arguments about consumption of this treatment method is the pre-diagnosis of these patients in the early years of their life. It is noteworthy that many patients who are treated by this method are also threatened by

many infectious and non-infectious diseases such as low birth weight and less gestational age. Thus, measuring the long-term side effects of this treatment method is a great challenge. This can probably explain the contradictory results of these researches. For instance, 2 researches conducted by 2 separate research teams have reported a 60% possibility of respiratory infections in the early years of the patients treated with 60% surfactant, while the other research has reported no significant difference with other patients<sup>9,10</sup>. No major researches have been conducted in our country in order to study the final sequel of such patients. On the other hand, there is no trustworthy statistics about the prevalence of respiratory infections among infants and little kids. It is only through the regional statistics of WHO that we can have a credible assessment of our country<sup>11</sup>. Over a 6-month follow up period, the research team studied the occurrence of lower respiratory infections as the most important infectious factors causing death among infants in our country. Considering the type of research, the prevalence levels were compared against the reliable statistics issued by WHO about Iran.

## MATERIALS AND METHODS

Retrospective Cohort method was adopted to conduct this research on all those patients who were hospitalized in the neonatal ward of Khanevade Hospital of IRIGF since its establishment in mid 2011 up to 2014. The proposal of this research was first confirmed by the general research board of the Medical Sciences University of the Army. After inquiring the necessary introduction letters, the researcher commenced his works in neonatal ward. Resorting to the office of neonatal ward, the researcher extracted the particulars and file number of all those patients who were hospitalized in the ward during the above said period due to various types of differential diagnosis except for Jaundice. Totally, the particulars of 513 patients were extracted.

The entrance criteria included all the kids diagnosed with various respiratory problems such as respiratory distress syndrome of infants, meconium aspiration, pneumosepsis and transient tachypnea of newborn who were hospitalized in

this ward and were treated by one of the specialist using surfactant. Those patients who were treated with surfactant before resorting to Khanevade Hospital and no complete information about their treatment process was available in the hospital were removed from the study. Considering the patients below the age of 6 months, those kids whose family we could not find or those who died before the age of six months due to lower respiratory diseases were also excluded.

Finally, 72 patients entered the study. The files of all these patients were extracted and their complementary information was put into Excel worksheets. The input method of data into this software was designed according to the idea of researchers and by studying the texts previously designed and attached to the proposal.

As the phone numbers of these patients were stored in the data base of the hospital, we began a follow up of these patients. According to the proposal, the supplementary information of those patients who up to the age of 6 months were hospitalized there (as testified by their parents) was registered. If the patients did not respond on the first call, the researcher would try to contact their parents for three times. The researcher could finally contact the family of 39 patients. Considering the death of two of these patients and keeping in mind that one of these deaths was due to lower respiratory infection, 38 patients were selected for the final analysis.

Finally, all the information was fed to SPSS v20. The information was then processed using chi square, independent T test, ANOVA, Linear Regression and Pearson Correlation. The significance level in all these tests was set to 0.05.

## RESULTS

72 patients met the criteria to enter this research. Among them, 45 (62.5%) were male. Their weights ranged from 700 to 2800 grams and the average and the standard deviation of their weights were 2153 and 895 grams respectively. Among all these infants, 51 (70.8%) could survive. The average time these kids were hospitalized was 15.4 days, while this period among the dead patients was 7.5

days. The average Apgar score of these kids was 6.25 (the scores ranged from 3 to 9).

Their mothers ranged from 23 to 34 years old with the average age of 28.3 years old. 41 kids were the result of the first pregnancy, 16 were the result of the second pregnancy, 16 were the result of the third pregnancy and 3 were the result of the fourth pregnancy. 55 mothers had no previous abortions, while 15 had one and 2 had two experiences of abortion. The average pregnancy length of the mothers was 33.5 weeks (ranging from 26 to 39 months). 15 mothers had experienced PROM well before the commencement of the active phase of pregnancy. 65 mothers had their delivery through Cesarean among whom 9 were repetition of previous Cesarean, 3 were to stop the decline of natural childbirth, 20 were due to pregnancy with twins or more, 16 were elective Cesarean, 14 were due to PROM, and 4 were the emergency termination of pregnancy due to Preeclampsia.

Of the 72 infants, 41 were treated using Survanta and 31 were treated using Curosurf. The average time for applying surfactant was 19.51 hours after delivery with the minimum time being 6 hours after birth. 56 patients received surfactant only once and 16 received surfactant twice. The average

oxygen pressure of vascular blood before the injection of surfactant was 62.18 which increased up to 73.6 after the injection. The average carbon dioxide pressure of vascular blood before the injection of surfactant was 44.47 which reduced up to 38.73 after the injection. The average acidity of the vascular blood based on PH increased from 7.29 to 7.36 after the injection of surfactant.

After receiving surfactant, the patient would spend an average of 5.0069 days under ventilation. However, those patients who survived spent an average of 4.098 days under mechanical ventilation. Of 72 infants who received surfactant in this hospital, only 15 experienced Pneumothorax. 7 patients experienced Pneumothorax on the first day after injection, 3 experienced it in the second day and the rest had an experience of Pneumothorax on the 3<sup>rd</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 9<sup>th</sup>, and 10<sup>th</sup> day after injection.

Of 39 infants whose families we managed to contact, 6 experienced such infections over the first 6 months. Of these 6, 1 died in the age of 2 months in the hospital due to the side effects of this infection. 1 patient also died because of the previous congenital disease shortly after being discharged from the hospital aging only 2 months.

**Table 1: The information associated with the comparison of treatment results using surfactant and curosurf**

variable	patients treated using SURVANTA	patients treated using curosurf	p-value
number	41	31	
childbirth weight <1500gr	6	10	0.081
1500gr	36	20	
pregnancy age	34.6	32.05	<0.05
hospitalization period	12.9	18.9	<0.05
length of ventilation	2.9	7.9	<0.05
death toll	8	13	0.075
Apgar	6.3	6.1	<0.05
injection hour	22.4	14.6	<0.05
changes in vascular oxygen pressure	14.4	7.3	0.371
changes in vascular carbon dioxide	-4.2	-7.8	0.901
changes in vascular blood PH	0.077	0.078	0.685
occurrence of Pneumothorax	4	11	0.05
occurrence of lower respiratory infections	3	3	0.407

According to this research, the average birth weight and the pregnancy age of those patients who died was significantly more than those who survived. The frequency of PROM among those who survived was much less than those who died. Among those who experienced Pneumothorax, those who died experienced it far later than the others. No significant relationship was observed between hospital death and infant's gender, mother's age, early childbirth Apgar, length of mechanical ventilation and the type of surfactant consumed.

No significant relationship was observed between early childbirth Apgar and those factors influencing the prognosis of the patients such as hospitalization period, length of mechanical ventilation, occurrence of hospital death, changes in vascular blood analysis and occurrence of lower respiratory infections below the age of 6 months.

The type of surfactant consumed has influenced the treatment results of some patients. The information associated with it is listed here:

Analysis of the vascular blood is always one of the signs indicating the effectiveness of surfactant in improving the lung performance of the patients. Using Paired sample t test, changes in vascular blood analysis results before and after the injection of surfactant was proved. Then, the relationship between various variables and indexes and changes in vascular blood indexes were also taken into consideration. It was proved that the faster injection of surfactant was associated with higher levels of oxygen and vascular blood PH, however, no significant changes in the vascular blood carbon dioxide was observed.

Of all the indexes and changes in vascular blood indexes, the time for the occurrence of Pneumothorax was only associated with changes in the vascular blood carbon dioxide. In other words, the less the vascular blood carbon dioxide reduces in response to surfactant, Pneumothorax will take place later. The childbirth weight of those patients who experienced Pneumothorax was significantly less than their corresponding group. Patients with less weight experienced Pneumothorax later.

In the treatment protocol of the neonatal ward of Khanevade Hospital, injection of surfactant will be indicated only for the initial resistant cases. Repetition of surfactant injection is only associated with the reduction of vascular blood carbon dioxide as the criteria for the final performance of the patients' respiration. Those patients who found themselves needing surfactant again are more probable to experience lower respiratory infections.

The occurrence of lower respiratory infections during the first 6 months of life in this research is 15.78%. The occurrence of these infections in our country is reported to be 5% according to reliable sources. Using general z-test, we may conclude that the possibility for the occurrence of lower respiratory infections below 6 months among those kids who have received surfactant is more than other infants. Even after dividing infants into 2 groups including those below and above 1500 grams in order to remove the influence of childbirth weight, the possibility of the occurrence of lower respiratory infections below 6 months was more among those infants who had received surfactant compared to other infants. The only significant relationship was found between occurrence of lower respiratory infections and initial oxygen pressure and carbon dioxide pressure after prescription of surfactant. In the patient group, childbirth weight was less and the length of hospitalization and mechanical ventilation was more than what was observed in the other group. No relationship was observed between occurrence of respiratory infections and gender, birth order, number of abortions and time for prescribing surfactant.

## DISCUSSION AND CONCLUSION

The death rate in our study was reported around 29.17% which was more than the level reported in domestic and foreign studies. The previous studies have reported the following levels: 24% in Ahmadpour *et al.*<sup>5</sup>, 23.5% in Khalili *et al* (18), and, finally, 14.7% in Zhonghua *et al*<sup>8</sup>.

Of the patients who entered this plan, 20.8% got afflicted with Pneumothorax. 8.3% of the patients were also reported to suffer from lung

bleeding. Ahmadpour *et al*<sup>3</sup> reported a frequency of 48% for Pneumothorax and a frequency of 3.42% for lung bleeding. Afje *et al*<sup>1</sup> reported a frequency of 23% for Pneumothorax, while Zhonghua *et al* reported a frequency of 6.4% for lung bleeding. We may conclude that the occurrence of Pneumothorax in this study was far less compared to domestic researches, although the levels of lung bleeding in these patients was more than what was recorded in our previous studies.

SURVANTA and Curosurf were the 2 main brands used in this hospital over the last two and a half years. The previous domestic and foreign researches have found contradictory results about the effectiveness and the side effects of these 2 medicines. For instance, in the studies conducted by Fallahi *et al*<sup>4</sup> and Saieedi *et al*<sup>4</sup> no significant difference was observed between these two medicines in terms of the occurrence of results such as Pneumothorax, lung bleeding, pneumonia associated with ventilator, open vascular duct and intra-ventricular hemorrhage and the length of using ventilator. In the studies conducted by Hashemian Nejad *et al*<sup>5</sup> and Ramanathan *et al*<sup>5</sup>, SURVANATA had shown a better performance in terms of reducing the length of mechanical ventilation and the quicker commencement of food nutrition. In our study, the length of hospitalization and mechanical ventilation in the patients treated with Curosurf was significantly more. On the other hand, the occurrence of Pneumothorax as one of the major side effects among these patients was reported to be more among those treated with Curosurf. However, no difference was observed between these 2 medicines in terms of the final hospital death rate.

Many of the previous researches had studied the higher effectiveness of surfactant in the second and third dozes in the cases of resistance against the first doze. For instance in the study conducted by Dunn *et al*<sup>6</sup>, multi-doze treatment with surfactant ended in better results such as better provision of oxygen and lower length of mechanical ventilation compared with single-doze treatments. In treating the streptococcal pneumonia of infants,

Marshall *et al*<sup>7</sup> have suggested using repetitive dozes of surfactant as an appropriate treatment method. In the above-said hospital, prescription of repetitive dozes of surfactant is only used as treatment strategy against the cases that resist the initial doze. The level of oxygen increase and vascular blood carbon dioxide decrease as indicators of significance in the repetitive dozes of surfactant is reported to be more.

Finally, the occurrence of lower respiratory infections during the first 6 months of life in the patients was 15.78%. according to Roudan *et al*, the occurrence of lower respiratory infections in the region was 0.10 infant a year which would be equal to 5% for 6 months. This indicates the higher levels of occurrence of respiratory infections in this plan, while none of the patients in this plan were diagnosed with broncho-pulmonary dysplasia (a proven danger factor in lower respiratory infections). This is in line with the results of Szabo *et al*<sup>8</sup> and Halliday *et al*<sup>9</sup>.

Meanwhile, a significant relationship was observed between occurrence of lower respiratory infections and early oxygen pressure and carbon dioxide pressure after the injection of surfactant. We can say that the initial oxygen pressure is largely influenced by the conditions and the initial pathology, and the carbon dioxide pressure after the injection of surfactant represents the chronic respiratory conditions and the demand for post-surfactant ventilation. Thus, the occurrence of respiratory infections is mostly influenced by the initial pathology of the lung and it is less influenced by hospital treatments. As it was emphasized in the discussion of the length of ventilation, as the need for ventilation increases due to higher level of vascular blood carbon dioxide, the possibility for the occurrence of respiratory infections also increases.

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