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Research Article

Surfactant Replacement Therapy in Preterm Infants with Respiratory Distress Syndrome

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Abstract

Objective: To study the neonatal morbidity and case fatality in preterm infants with respiratory distress syndrome treated with different methods of administration of surfactant replacement therapy.

Study design: This cross-sectional analytic study included 104 preterm infants, who had respiratory distress syndrome during one year period. The sample was divided into prophylactic, early and late rescue groups, according to earliest time of surfactant administration.

Results: The mean gestational age was 29.7 ± 4.5 (range: 24–37) weeks, 32 infants (30.77%) of 24–28 weeks, 40 (38.46%) were of 28+1/7 - 32 weeks and 32 (30.77%) at 32+ 1/7 - 37 weeks. Prophylactic surfactant was administered in 44 (42.3%), early rescue in 37 (35.6%) and late rescue in 23 (22.1%). 98 (94.2%) received one dose of surfactant. Mechanical ventilation was applied in 78 (75%). 93 (89.4%) had at least one complication, sepsis was the most common in 67 (64.4%), sepsis was significantly higher among infant who received prophylactic surfactant (88.6%) (P2=0.001). The highest case fatality was in infants who received prophylactic surfactant (77.3%), (P=0.001.).

Conclusion: Prophylactic surfactant was administered in majority of preterm neonates with respiratory distress syndrome. Sepsis was the most common complication and was significantly higher among infant who received prophylactic surfactant, which in turn was associated with higher case fatality rate.

Keywords: Preterm infants; Neonate; Surfactant replacement therapy; Respiratory distress syndrome; Continuous positive airway pressure; Mechanical ventilation

Abbreviations

RDS: Respiratory Distress Syndrome; CPAP: Continuous Positive Airway Pressure; MV: Mechanical Ventilation; GA: Gestational Age; BWT: Birth Weight; CS: Cesarean Section; NVD: Normal Vaginal Delivery; NICU: Neonatal Intensive Care Unit; ETT: Endotracheal Tube

Introduction

Prematurity is one of the most perplexing problems in perinatal care. Since the discovery of a surfactant deficiency as the primary etiology of hyaline membrane disease, attempts have been made to supplement Surfactant in the premature infant [1].

Respiratory distress syndrome (RDS) is the most common serious disease affecting the newborn. As a result of the successful marriage between clinical investigation, applied and basic sciences, the mortality of RDS has dropped from about 50% to close to 5% [2]. Endogenous surfactant is a biochemical compound composed of phospholipids, neutral lipids, and proteins that forms a layer between the terminal airways/alveolar surfaces and the alveolar gas [3-5]. In 1959, Avery and Mead published a landmark paper that correctly hypothesized that the clinical entity known as HMD was deficiency of the surface tension lowering material or surfactant [4,6]. Surfactant replacement was established as an effective and safe therapy for immaturity-related surfactant deficiency by the early 1990s. Systematic reviews of randomized, controlled trials confirmed that surfactant administration in preterm infants with established RDS reduces mortality, decreases the incidence of pulmonary air leak, and lowers the risk of chronic lung disease or death at 28 days of age [7,8]. Exogenous surfactant, used as a drug for the treatment of RDS of the newborn infant has been extensively studied over the past 15 years by means of many randomized controlled trials (RCTs) [9].

A prophylactic, or preventive surfactant strategy is defined as intubation and surfactant administration to infants at high risk of developing RDS for the primary purpose of preventing worsening RDS rather than treatment of established RDS; this has been operationalized in clinical studies as surfactant administration in the delivery room before initial resuscitation efforts or the onset of respiratory distress or most commonly, after initial resuscitation but within 10 to 30 minutes after birth [10]. This contrasts with a rescue or treatment surfactant strategy, in which surfactant is given only to preterm infants with established RDS. Rescue surfactant is most often administered within the first 12 hrs after birth; early rescue is defined as surfactant treatment within 1 to 2 hrs of birth, and late rescue is defined as surfactant treatment 2 or more hrs after birth [9].

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Further research is needed to define potential limitations on the type of patients for which early surfactant with rapid extubation is appropriate (such as very premature infants <750 grams) and to determine the optimal threshold of severity of respiratory distress syndrome for which to intervene with transient intubation for the purpose of surfactant administration [11].

Previous report from the same center mention the use of surfactant in limited number of patients as INSURE [12], but no previous Iraqi study on the use of Surfactant replacement therapy in preterm babies with RDS, so this study aimed to study neonatal morbidity and case fatality in preterm infants with respiratory distress syndrome treated with different methods of administration of surfactant.

Patients and Methods

In this cross-sectional analytic study, data of 104 preterm infants were collected from NICUs of nursing home hospital with GA of 24-37 weeks who had RDS and who were born from the 1st of January 2014 till the 31th of December 2014. The Ethical committee of Children Welfare Teaching Hospital and Nursing home Hospital approved the study. Sixty-Eight neonates were delivered in private nursing home hospital, 19 were referred from Baghdad teaching hospital and 17 were referred from private hospitals in Baghdad.

The NICU was established in January 2011 as first NICU in Baghdad as 6 beds with 3 SLE 2000 ventilators donated by Turkish government, and Bubble CPAP bought by our hospital, and then 3 Drager baby log 8000 with conventional and high frequency ventilation modes were bought. The surfactant (Survanta, Abbott) was used on limited basis as it was initially bought from private sector, but administered freely to patients who needed it. In 2012, surfactant started to be distributed freely by Ministry of Health to governmental hospitals. Other difficulties we face were irregular availability of blood gas analysis and TPN [12].

Assessment of GA was according to Ballard score and last menstrual period. In Ballard scoring system, estimation of gestational age by examination for physical and neurological criteria of maturity, this is accurate to ± 2 wk [13].

The 104 preterm infants were divided into three groups (prophylaxis, early rescue, and late rescue treatment groups) depending on the time of surfactant therapy for treatment of RDS.

A prophylactic or preventive surfactant strategy was defined as intubation and surfactant administration to infants at high risk of developing RDS (infants less than 30 weeks or low birth weight <1,000 g) for the primary purpose of preventing worsening RDS rather than treatment of established RDS within 10 min to 30 min after birth**.** In a rescue or treatment surfactant strategy, the surfactant was given only to preterm infants with established RDS. Surgical cases, meconium aspiration, congenital lung diseases, or syndromes had been excluded.

The included neonates were admitted and followed in NICU, for short term outcome including morbidity and case fatality during the first 28 days of life; and observing the development of complications following replacement therapy in these study groups as sepsis, pulmonary hemorrhage, air leak, Bronchopulmonary dysplasia etc. Anonymous data were collected included: GA, BWT, gender, mode of delivery, intubation need, surfactant therapy (type, dosage, frequency, and clinical indications). For all patients, an animal-derived Beractant (Survanta, the only type available in Iraq) minced bovine lung extract was used. The indications for surfactant therapy were according to American academy guidelines; committee on fetus and newborn, including preterm infant with clinical RDS especially in those with low (GA and BWT), radiological evidence of RDS as fine reticulo granular appearance and air bronchogram on chest X-ray; those with high ventilator requirements as FIO2 need >40% of inspired oxygen to maintain appropriate arterial pressure [7].

The surfactant was administered after Inserting appropriate nasogastric tube that has been cut to a suitable length so as not to protrude beyond the tip of the ETT on insertion through the ETT. No positional changes were required for surfactant given in delivery room. Surfactant was delivered as a bolus as fast as it can be easily pushed through the catheter and then Continue PPV with adjustments to settings if there is bradycardia or desaturation [14].

The first dose of surfactant was given as early as possible to the preterm infants requiring MV for RDS. The repeat dose was given 4 hr to 6 hrs later if FiO2 is still >0.30 with optimal tidal volume settings for those below 32 weeks and if FiO2 >0.40 and CXR still shows moderate to severe RDS ("white" CXR) for those infants >32 weeks gestational age [14].

Infants were monitored closely after surfactant administration with a pulse oximeter and regular blood gas measurements if available. Ventilator settings were promptly decreased to reduce the risk of pneumothorax and ventilator induced lung injury. Extubation to CPAP was considered if the oxygen requirement is less than 30% and there are minimal pressure requirements [14].

Statistical analysis

Data of the 104 RDS infants were entered and analyzed by using the statistical package for social sciences version 22, IBM, US, 2013. Descriptive statistics were presented as mean, standard deviation (SD), frequencies (No.) and proportions (%). Chi square and Fishers exact test were used alternatively to compare frequencies. Level of significance (p. value) was set at ≤ 0.05 to be considered as significant and, <0.001 to be highly significant. The results and findings were introduced in tables and paragraphs by using the Microsoft Office software, Words, version 2013, for windows.

Results

A total of 104 preterm infants with mean GA was 29.7 ± 4.5 (range: 24 - 37) weeks, 32 infants (30.77%) of 24 - 28 weeks, 40 (38.46%) were at 28+1/7 - 32 weeks and 32 (30.77%) at 32+ 1/7 - 37 weeks. Males were 58 (55.77%) and females were 46 (44.23%) with a male to female ratio of 1.26:1 (Table 1).

CS delivery was reported in 68 (65.38%) and the NVD in 36 (34.62%). Single birth was reported in 72 (69.23%), twins in 21 (20.19%) (Table 1).

Prophylactic surfactant was administered in 44 infants (42.3%), early rescue in 37 (35.6%) and late rescue in 23 (22.1%). Majority of the infants 98/104 (94.2%) received one dose of surfactant and 6 (5.8%) received 2 doses while none of the infants received three doses. MV was applied in 78 (75%) and CPAP was applied in 26 infants (25%). Nasal cannula was not applied in this study (Table 2).

Out of the 104 RDS infants, 93 (89.4%) had at least one complication and 11 infants (10.6%) had no complications. Sepsis was the most incident complication in 67 (64.4%) followed by Nasal trauma in 18 (17.3%), Air-leaks in 13 (12.5%), Pulmonary

hemorrhage in 6 infants (5.8%). PDA and BPD were less frequent in 3 (2.9%) and 2 (1.9%) infants, respectively. Some infants had more than one complication simultaneously (Table 3).

Out of the 104 RDS infants, 47 (45.2%) were alive and 57(54.8%) died, giving an overall case fatality rate of 54.8%.

Three comparisons were performed, for each complication; the first one was prophylactic *vs.* early rescue surfactant, the second was prophylactic *vs.* late rescue and the third between early and late rescue surfactant. The rate of sepsis was significantly higher among those infant who received prophylactic surfactant (88.6%) as compared to early rescue (45.9%), (P1=0.001), and the Late rescue (P2=0.001) while no statistically significant difference between early and late rescue regarding the incidence of sepsis, (P3=0.59). Conversely, no statistically significant difference had been found between the methods of surfactant, in other complications, in all comparison, P>0.05 (Table 4).

The highest case fatality was reported among infants who received prophylactic surfactant (77.3%) than early (43.2%), (P=0.003), or late rescue (30.4%), (P=0.001). The fatality was higher in early than late rescue group, however, the difference between these two methods of rescue surfactant was statistically insignificant (P=0.42). These findings indicated that early rescue surfactant reduced fatality by 34.1% and late rescue by 46.9% than prophylactic surfactant (Table 5).

The fatality rate had significant (P<0.05) inverse correlation with the GA, where 26 infants died out of the 32 infants whose GA 24-28 weeks with the higher fatality rate of (45.6%). The fatality rate was 35.1% among the 40 infants with GA of 28+1/7 -32 weeks and the lower fatality rate (19.3%) was reported in those with GA of 32+1/7 - 37 weeks (Table 6).

Table 1: The studied group (N=104).

Variable	category	No. of patients. No	%
Gestational age (wk)	24 - 28	32	30.77
	28+1/7 - 32	40	38.46
	32+ 1/7 - 37	32	30.77
	Mean ± SD	29.7 ± 4.5	-
	Range	24 - 37	
Gender	Male	58	55.77
	Female	46	44.23
Mode of delivery	C/S	68	65.38
	NVD	36	34.62
Number of birth	Single	72	69.23
	Twin	21	20.19
	Triplet	10	9.62
	Quadriplet	1	0.96

Table 2: Distribution of clinical data of the studied group (N=104).

Complication	Prophylactic (n=44)		Early Rescue (n=37)		Late Rescue (n=23)				
	No.	%	No.	%	No.	%	P 1	P2	P3
Sepsis	39	88.6	17	45.9	11	47.8	0.00*	0.00*	0.59
Nasal trauma	6	13.6	7	18.9	5	21.7	0.56	0.49	0.52
Air leaks	4	9.1	5	13.5	4	17.4	0.73	0.43	0.72
Pulmonary H.	3	6.8	2	5.4	1	4.3	0.79	0.57	0.67

P1: Prophylactic *vs.* Early rescue; P2: Prophylactic *vs.* Late Rescue; P3: Early *vs.* Late Rescue, *significant at P<0.05

Table 3: Distribution of complications among the 104 infants.

	Complication*	No.	%
Complication	Sepsis	67	64.4
	Nasal trauma	18	17.3
	Air-leaks	13	12.5
	Pulmonary hemorrhage	6	5.8
	PDA	3	2.9
	BPD	2	1.9

*Some patients had more than one complication

Lower incidence of sepsis (46.2%), air leaks (0.0%), and pulmonary hemorrhage (3.8%) was found in infants on the CPAP compared to 70.5%, 16.7% and 6.4%, respectively in infants on MV. The differences were statistically significant for sepsis and air leaks (P<0.05), but not significant in pulmonary hemorrhage (P>0.05).

Nasal trauma was more incident among those on CPAP (34.6%) compared to 11.5% in those on MV (P=0.035). PDA and BPD were also more incident among infants on CPAP rather than those on MV, however the differences were statistically insignificant in these two complications (P>0.05) (Table 7).

Moreover, 5/26 infants in CPAP group (19.2%) had no complication, compared to only 6/78 in MV group (7.7%), indicated that the complications were more incident in MV group than in CPAP group (P=0.02) (Table 7).

Eighteen (69.2%) infants on CPAP were alive *vs.* 29(27.2%) on MV. Lower fatality rate was reported in infants on CPAP than those on MV; 8(30.8%) *vs.* 49(62.8%), respectively, (P=0.008).

Discussion

Previous trials of surfactant therapy in premature infants have demonstrated a survival advantage associated with prophylactic therapy as an immediate bolus, compared with the rescue treatment of established RDS. The optimal strategy for prophylactic therapy, however, remains controversial [15].

This study included 104 preterm newborn who were admitted to NICU in one year. Forty-Four babies (42.3%) whose GA 30 weeks or weight < one kg received prophylaxis surfactant while seventy babies (57.7%) received a rescue treatment. A number of studies have evaluated whether surfactant should be given to all babies at significant risk for developing RDS or only after the development of significant disease [16]. A study reviewed seven RCTs of prophylactic versus rescue therapy. These were all trials that used natural surfactants. Six of the RCTs enrolled babies less than 30 weeks of gestation and one enrolled babies of 29 to 32 weeks of gestation. Mortality, both before 28 days and before hospital discharge, was reduced by prophylactic surfactant treatment. This difference may be related to the referral of many infants from Baghdad hospital or other private hospital in Baghdad, so the time of administration was delayed in many cases. Surgical cases, meconium aspiration, congenital lung diseases, or syndromes have been excluded whatever the gestational ages.

In this study, 65% of babies were delivered by C/S and 34% by NVD, this is similar to many other studies [17,18], which showed increase incidence of RDS in C/S than NVD. The results indicate that

Table 4: Relationship between complications and method of surfactant administration.

Complication	Prophylactic (n=44)		Early Rescue (n=37)		Late Rescue (n=23)				
	No.		%	No.	%	No.	%	P 1	P2	P3
Sepsis	39		88.6	17	45.9	11	47.8	0.001*	0.001*	0.59
Nasal trauma	6		13.6	7	18.9	5	21.7	0.56	0.49	0.52
Air leaks	4		9.1	5	13.5	4	17.4	0.73	0.43	0.72
Pulmonary H.	3		6.8	2	5.4	1	4.3	0.79	0.57	0.67
PDA	0		0	1	2.7	2	8.7	0.46	0.11	0.55

P1: Prophylactic *vs.* Early rescue; P2: Prophylactic *vs.* Late Rescue; P3: Early *vs.* Late Rescue
*significant at P<0.05

Table 5: Relationship between outcome and method of surfactant administration.

Outcome	Prophylactic (n=44)		Early Rescue (n=37)		Late Rescue (n=23)		P 1	P2	P3
	No.	%	No.	%	No.	%	0.003*	0.001*	0.42
Alive	10	22.7	21	56.8	16	69.6			
Dead	34	77.3	16	43.2	7	30.4			

P1: Prophylactic *vs.* Early rescue; P2: Prophylactic *vs.* Late Rescue; P3: Early *vs.* Late Rescue
*significant at P <0.05

Table 6: Relationship between outcome and gestational age.

Gestational age (week)	Outcome				p
	Alive		Dead		
	No.	%	No.	%	
24-28	6	12.8	26	45.6	0.001*
28+1/7 -32	20	42.6	20	35.1	
32+1/7 - 37	21	44.7	11	19.3	
Total	47	100	57	100	

*significant at P<0.05

Table 7: Relationship between Ventilation mode and complications.

Complications	Ventilation mode				P
	CPAP (n=26)		M.V. (n=78)		
	No.	%	No.	%	
Sepsis	12	46.2	55	70.5	0.033*
Nasal trauma	9	34.6	9	11.5	0.014*
Air leaks	0	0	13	16.7	0.035*
Pulmonary hemorrhage	1	3.8	5	6.4	0.69
PDA	1	3.8	2	2.6	1
BPD	2	7.7	0	0	0.06
No complications	5	19.2	6	7.7	0.02*

*Significant at P<0.05

infants born by CS without labor have a higher risk for neonatal RDS than infants born vaginally or by CS after a trial of labor [18].

When comparing between prophylaxis and rescue treatment, higher rate of sepsis and fatality rate was found in prophylaxis group than rescue, this may be due to extreme prematurity of such group, improper transport measures, bad obstetrical management, and improper strategies of infection control.

Seventy- five percent of babies who received surfactant need MV and only 25% need CPAP, while other studies advise rapid surfactant administration and extubation to CPAP or high flow nasal cannula. It is notable that infants as immature as 24 weeks' gestational age were enrolled in many of the trials. In a subgroup analysis in the SUPPORT trial, the most immature infants (born at 24 and 25 weeks' gestation) got benefit mostly from the CPAP strategy. Many extremely preterm infants can be managed with CPAP only; early application of nasal CPAP (without surfactant administration) was successful in 50% of infants weighing ≤ 750 g at birth in one retrospective review [19]. Surfactant administration can be expensive, particularly in low-resource settings. Additionally, intubation and MV may not be possible or desirable in institutions with limited resources.

CPAP provides an alternative for early respiratory support in resource-limited settings. Emerging evidence indicates that early CPAP is an effective strategy for respiratory support in extremely preterm infants. CPAP appears to be at least as safe and effective as early surfactant therapy with MV [20]. This diversity may be due to bad clinical situation of arriving babies or bad technique in our center and bad decision making by the medical staff.

Nasal trauma as complications was found in 17.3%, which occur mainly in babies who were exposed to nasal prongs of CPAP for long period while in other study nasal trauma range from 40% to 88% [21]. Nasal traumas are a frequent complication of nCPAP, especially in preterm neonates, but long-term cosmetic sequelae are very rare. The above study provides a description of nasal trauma and proposes a simple staging system [21]. In an Iraq study, some degree of nasal trauma was found in babies receive nasal CPAP or weaned from ventilator to CPAP ranging from 24% to 44% of total babies which is slightly higher than this study results [22].

High rate of sepsis was found mainly in prophylaxis group 88.6% and less in early rescue 45.9% and late rescue 47.8%, which is statistically significant, while other secondary complications such as air leaks, pulmonary hemorrhage, and PDA are not statistically significant between the three strategies. This is not compatible with other studies which all show decrease incidence of complication with prophylaxis surfactant [7].

Few studies have compared prophylactic surfactant with early rescue treatment, and early rescue treatment with late rescue treatment [11,15,23,24]. Although limited, the results of such studies indicate that surfactant administered prophylactically or as soon as possible in the course of respiratory distress is more effective than late rescue surfactant at improving outcomes.

High fatality rate was found in prophylaxis group 77.3%, 43.2% in early and 30.4% in late rescue groups. When comparing with other studies, much less mortality rate was found as shown in Turkish study (19%) [25] and in another study with MR not exceed 12% [26] , this may be due to smaller GA of such group, lower BWT, severity of asphyxia and respiratory distress at birth, in addition to other undiagnosed complication such as early IVH.

In this study, the complications were more incident in MV group than in CPAP group. Low incidence of sepsis (46.2%), air leaks (0.0%), and pulmonary hemorrhage (3.8%) in infants on the CPAP, compared to 70.5%, 16.7% and 6.4% respectively in infants on MV. Some studies show CPAP exposure of premature infants with RDS is protective against chronic lung disease, intraventricular hemorrhage and sepsis compared to MV. No differences were observed regarding air leak syndrome or death [27]. Others show CPAP is not fully safe and can still result in serious complications if not managed properly [28].

Conclusion

Prophylactic surfactant was administered in majority of preterm infants with RDS. Most of studied neonates received one dose of surfactant, MV as respiratory support rather than the CPAP, and had at least one complication. Sepsis was the most common complication and was significantly higher among infant who received prophylactic surfactant. Lower rate of sepsis was found in infants on the CPAP than on MV. The case fatality rate was 54.8%. The highest was reported among infants who received prophylactic surfactant and low fatality rate in infants on CPAP than those on MV.

This study recommends that Infants who are at a significant risk of RDS may need to be stabilized first and then given the surfactant and rapid weaning to CPAP and also improve infection control in NICU.

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References

1. Miller EP, Armstrong CL. Surfactant Replacement Therapy Innovative Care for the Premature Infant. J Obstet Gynecol Neonatal Nurs. 1990;19(1):14-7.
2. Hallman M, Saarela T. Respiratory Distress Syndrome: Predisposing Factors, Pathophysiology and Diagnosis. In: Buonocore G, Bracci R, Weindling M, Editors. Neonatology, A practical approach to neonatal management, Chap 62. Italy: Springer. 2012;441-54.
3. Jobe A. Surfactant treatment for respiratory distress syndrome. Respir Care. 1986;31(6):467-76.
4. Avery ME, Mead J. Surface properties in relation to atelectasis and hyaline membrane disease. AMA Am J Dis Child. 1959;97(5):517-23.
5. Berry DD. Neonatology in the 1990's: surfactant replacement therapy becomes a reality. Clinical Pediatrics. 1991;30(3):167-72.
6. Hallman M, Gluck L. Phosphatidylglycerol in lung surfactant. III. Possible modifier of surfactant function. J Lipid Res. 1976;17(3):257-62.
7. Engle WA. American Academy of Pediatrics Committee on Fetus and Newborn. Surfactant replacement therapy for respiratory distress in the preterm and term neonate. Pediatrics. 2008;121(2):419-32.
8. Soll RF. Synthetic surfactant for respiratory distress syndrome in preterm infants. Cochrane Database Syst Rev. 2000;(2):CD001149.
9. Bahadue FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Cochrane Database Syst Rev. 2012;11:CD001456.
10. Polin RA, Carlo WA; committee on fetus and newborn. Surfactant Replacement Therapy for Preterm and Term Neonates with Respiratory Distress. Pediatrics 2014;133;156.
11. Escobedo MB, Gunkel JH, Kennedy KA, Shattuck KE, Sanchez PJ, Seidner S, et al. Early surfactant for neonates with mild to moderate respiratory distress syndrome: a multicenter, randomized trial. J Pediatr 2004;144:804-8
12. Hameed NN, Ra'id Khalil Abdul Jaleel R, Saugstad OD. The use of continuous positive airway pressure in preterm babies with respiratory distress syndrome: a report from Baghdad, Iraq. J Matern Fetal Neonatal Med. 2013;27(6):629-32.
13. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. J Pediatr. 1991;119(3):417-23.
14. Imam H, Phak NH, Thomas T. Pediatric protocols For Malaysian Hospitals, 3rd edition. 2012;15:91-2.
15. Kendig JW, Ryan RM, Sinkin RA, Maniscalco WM, Notter RH, Guillet R, et al. Comparison of two strategies for Surfactant prophylaxis in very premature infants: a multicenter randomized trial. Pediatrics 1998;101(6):1006-12.
16. Soll RF, Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database syst Rev. 2001.
17. Jaina NJ, Krusea LK, Demissieb K, Khandelwalc M. Impact of mode of delivery on neonatal complications: Trends between 1997 and 2005. The Journal of Maternal-Fetal & Neonatal Medicine. 2009;22(6):491-500.
18. Curet LB, Zachman RD, Rao AV, Poole WK, Morrison J, Burkett G. Effect of mode of delivery on incidence of respiratory distress syndrome. Int J Gynaecol Obstet. 1988;27(2):165-70.
19. Ammari A, Suri M, Milisavljevic V, Sahni R, Bateman D, Sanocka U, et al. Variables associated with the early failure of nasal CPAP in very low birth weight infants. J Pediatr. 2005;147(3):341-7.
20. Pfister RH, Soll RF. Initial respiratory support of preterm infants: the role of CPAP, the INSURE method, and noninvasive ventilation. Clin Perinatol. 2012;39(3):459-81.
21. Fischer C, Bertelle V, Hohlfeld J, Forcada-Guex M, Stadelmann-Diaw C, Tolsa JF. Nasal trauma due to continuous positive airway pressure in neonates. Arch Dis Child Fetal Neonatal Ed. 2010;95(6):F447-51.
22. Hameed NN, Raiees YR. Continuous Positive Airway Pressure and Nasal Trauma in Neonates: a descriptive prospective study. IOSR-JDMS. 2015;14(11):110-6.
23. Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Cochrane Database Syst Rev. 2000;(2):CD001456.
24. Gortner L, Wauer RR, Hammer H, Stock GJ, Heitmann F, Reiter HL. Early versus late surfactant treatment in preterm infants of 27 to 32 weeks' gestational age: a multicenter Controlled clinical trial. Pediatrics. 1998;102(5):1153-60.
25. Sürmeli-Onay O, Korkmaz A, Yigit S, Yurdakök M. Surfactant therapy in late Preterm infants: respiratory distress syndrome and beyond. Turkish J Pediatrics. 2012;54:239-46.
26. Ramanathan R. Surfactant therapy in preterm infants with respiratory distress Syndrome and in near-term or term newborns with acute RDS. J Perinatology. 2006;26(1):551-6.
27. Pérez LA, González DM, Álvarez KM, Díaz-Martínez LA. Nasal CPAP versus Mechanical ventilation in 28 to 32-week preterm infants with early Surfactant administration. Biomedica. 2014;34(4):612-23.
28. Garg S, Sinha S. Non-invasive Ventilation in Premature Infants: Based on Evidence Or Habit. J Clin Neonatol. 2013;2(4):155-9.