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High Flow Nasal Cannula in the Treatment of Respiratory Distress Syndrome in One Day-old Neonate

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Authors' contributions

This work was carried out in collaboration between all authors. Author RI designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors AS and SSA managed the literature searches, analyses of the study performed the spectroscopy analysis. Authors RI and SSA managed the experimental process and author RI identified the species of plant. All authors read and approved the final manuscript.

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ABSTRACT

Background: This study was carried out to compare high flow nasal cannula (HFNC) and nasal intermittent mandatory ventilation (NIMV) in respiratory support of one day-old neonates with respiratory distress syndrome (RDS).
Methods: This was a clinical trial conducted in neonatology wards of two university affiliated hospitals from Sep 2013 to Dec 2014. Inclusion criteria were gestational age of 30 to 35 weeks, appropriate weight for gestational age, clinical signs and symptoms of RDS, and RDS suggestive chest-X ray. All patients with RDS were treated with NIMV for one day. Those requiring NIMV respiratory support more than one day and showed the signs of respiratory distress were randomized into two groups of NIMV and HFNC. Each group consisted of 30 patients. Outcome measures included chronic lung disease, mechanical ventilation, failure to treatment, the time to

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establish full enteral feeding and the mortality rate. In addition, all complications were recorded. Characteristics of the two groups were compared at baseline and after the intervention.
Results: Mean gestational age of patients in NIMV and HFNC groups was 31.81 (1.83) and 31.83 (1.39) weeks, respectively. Distributions of sex, gestational age, height, head circumference, and Apgar scores at the first and fifth minute after the birth were not significantly different between the two groups. Mean (SD) duration of respiratory support after the 1st day was 16.48 (7.80) hours in NIMV group and 18.46 (6.95) in HFNC group (P=0.3). Mean (SD) duration of hospitalization in NICU was 3.24 (0.68) days in NIMV group and 3.2 (0.06) in HFNC group (P=0.8). Mean (SD) age when oral feeding was started, was 23.37 (5.78) hours in NIMV group and 20.13 (5.38) hours in HFNC group (P=0.03). Eleven patients (36.7%) in NIMV group vs. 2 patients in HFNC group required free oxygen therapy (P=0.005). No treatment failure, chronic lung disease, mechanical ventilation or endotracheal intubation was observed in any group. 100% vs. 10% in NIMV and HFNC groups, respectively, experienced grade 3 and 4 nasal mucosal damage (P<0.01).
Conclusion: HFNC was more tolerable than NIMV in the treatment of RDS in premature neonates' ≥30 week-old when applied after the first day of life.

Keywords: Respiratory distress syndrome; nasal intermittent mandatory ventilation; premature neonate; high flow nasal cannula; non-invasive respiratory support.

1. INTRODUCTION

Non-invasive respiratory supports require no insertion of endotracheal tube. They have been recognized as the proper substitute for mechanical ventilation in neonatal respiratory distress syndrome (RDS). Three well-recognized non-invasive methods are continuous positive airway pressure (CPAP), nasal intermittent positive airway pressure (NIPPV) and humidified oxygen delivered by high flow nasal cannula (HFNC) [1,2].

The effectiveness of NIPPV as the primary mode of support in neonatal RDS has been established [3,4]. HFNC was applied mostly for therapeutic measurement of viral upper and lower airway infections in older children and especially in recent years in the neonatal intensive care unit (NICU) [5-9]. More recently it has been also employed as the principal support for RDS in preterm neonates [10-13]. Both NIPPV and HFNC can also support the preterm neonates after extubating and can treat apnea in premature neonates [14,15]. The difficulty of NIPPV application, the small size of neonatal nostril and the risk of damage to the nasal mucosa by NIPPV led the researchers to find more feasible alternatives [6,16]. The Cochran review on HFNC concluded that there are not enough evidences to show the safety and effectiveness of HFNC in respiratory support of preterm neonates [17].

The current study was conducted to evaluate the safety and efficacy of HFNC compared with nasal intermittent mandatory ventilation (NIMV) in respiratory support of one day-old neonates with RDS.

2. METHODS

2.1 Study Design and Patients

The current study was a clinical trial carried out in neonatology wards of two different hospitals (Beheshti and Alzahra) affiliated with Isfahan University of Medical Sciences from Sep 2013 to Dec 2014 (Fig. 1). The ethical committee of the Isfahan University of Medical Sciences approved the study protocol (Iranian clinical trial ethical code, 393515). An informed written consent was obtained from all parents whose newborns were enrolled in the study.

Newborns with the following inclusion criteria were included in the study: Gestational age of 30 to 35 weeks, appropriate weight for gestational age, clinical signs and symptoms of RDS such as grunting, cyanosis, intercostal and subcostal retraction, and RDS suggestive chest-X ray.

2.2 Intervention

All patients with RDS were treated with NIMV during first 30 minutes after birth. The goal was to maintain the oxygen saturation (SPO2) between 92 to 95 percent. The right hand SPO2 was measured in all patients. NIMV was started with PIP of 14 to 20 cmH2O, flow of 6 to 10 lit/min, PEEP of 4-6 cm H2O, respiratory rate of 15-30 per minute and inspiratory time (Ti) of 0.45. To maintain appropriate SPO2, the pressure (PEEP and PIP) was gradually increased to the maximum level and consequently, the FIO2 was increased. If FIO2>35% was necessary, the patient would be

placed under the administration of surfactant with INSURE method. Before surfactant administration, arterial blood gas (ABG) was measured.

In all patients, caffeine was administered intravenously. The loading dose was 20 mg/kg, and the maintenance dose was 5 mg/kg/d. The criteria of NIMV failure and the indications for mechanical ventilation were as follow: presence of apnea, blood PH<7.2, PCo2>60 mmHg and respiratory failure.

NIMV discontinuation was done according to the clinical picture when SPO2 was between 92 and 95%, respiratory distress was absent, PIP was <14 cmH2O, PEEP was <4 cm H2O and FIO2 <30%. If oxygen therapy was necessary, it would be continued by oxy-hood or through incubator to keep the oxygen saturation between 85 and 92%.

Patients who required NIMV respiratory support >24 hours and showed signs of respiratory distress plus FIO2 ≥30% were randomized into two groups. Simple randomization was employed to allocate the neonates within each group. NIMV group involved those who received continual NIMV support until the criteria of NIMV failure were met. HFNC group included those who received no more NIMV support. Their oxygen therapy was provided by HFNC system. Each group consisted of 30 patients. Patients with pleural effusion, congenital pneumonia, chromosomal abnormalities, anatomical anomalies or cyanotic heart disease were not included in the study (Fig. 1).

In HFNC group, oxygen was heated to 37ºC by oxygen humidifier. The circuit was RT329 (Fisher and Paykel Healthcare, Salter Lab, Arvin, California). The external diameter of the nasal cannula was 2 mm. The nasal cannula was attached to the specific circuit and was connected to the chamber exit while the entrance of chamber was adjusted by the blender through a pressure manifold. The humidifying system attached to the circuit through a heater wire and temperature probe.

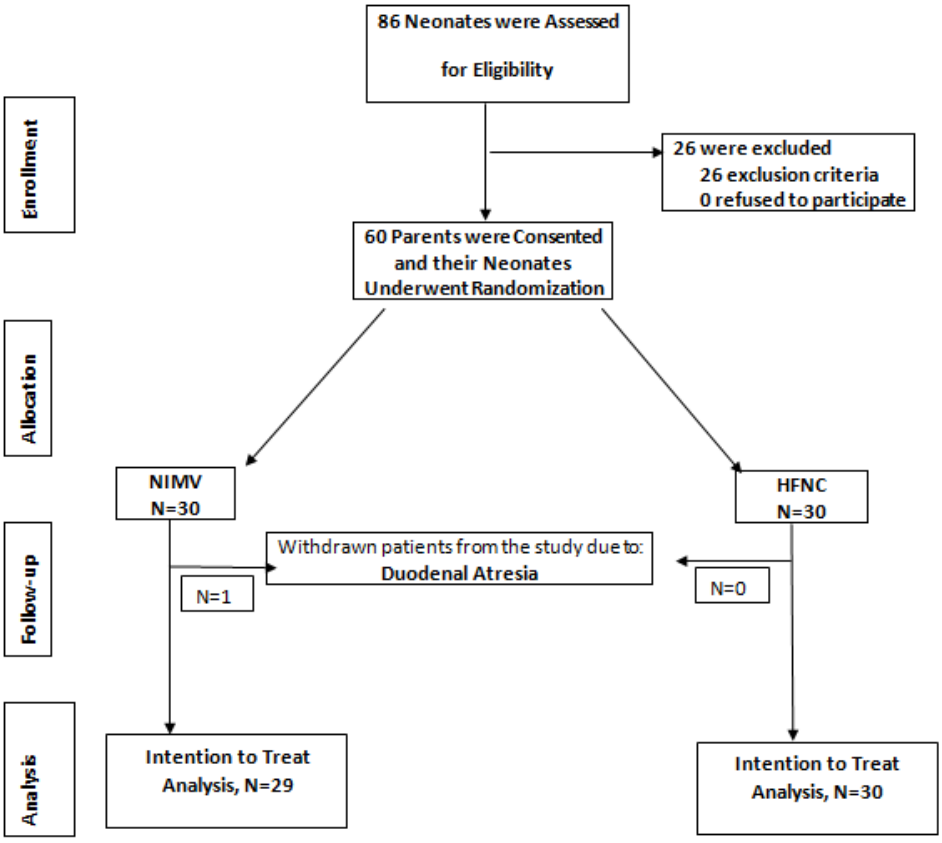

Fig. 1. Consort flowchart of the study

The minimum respiratory flow rate of oxygen was 2 L/min and the optimum was calculated based on the patient's weight [0.68W (kg) + 0.92] [14]. Therefore, based on weight of neonates, the minimum and maximum of flow rate in HFNC group were 2 and 2.41 L/min, respectively. When oxygen saturation was 21% and the patient had no more respiratory distress, HFNC was discontinued.

2.3 Outcomes

The following outcomes were measured in all patients: chronic lung disease, mechanical ventilation, failure to treatment, the time to reach full enteral feeding and the mortality rate. Furthermore, the complications of each treatment were recorded and compared including pneumothorax, pneumopericardium, nasal trauma, nosocomial sepsis, necrotizing enterocolitis, pulmonary hemorrhage, cerebral hemorrhage and patent ductus arteriosus (PDA). The patient was considered to have chronic lung disease when supplemental oxygen was continued after 36 week postconceptional age (PCA) of the baby who was born before 32 week of gestational age.

Nasal mucosa was examined and the level of nasal trauma was determined based on the following grading system: level 1, completely healthy, level 2, erythematous, level 3, erythematous and edematous, level 4, erythematous, edematous and thickening, and level 5, erythematous, edematous, thickening, and obstruction with or without bleeding. Nosocomial sepsis was diagnosed when the culture of blood or cerebrospinal fluid (CSF) taken five days after birth was positive. Necrotizing enterocolitis was established when the patient was diagnosed with pneumatosis intestinalis or required the related surgical intervention. Intraventricular hemorrhage was detected by brain ultrasound carried out by a trained neonatologist within the first 72 hours, and at 7^{th} and 14^{th} days after birth. PDA was suspected by the clinical picture and was confirmed by echocardiography.

The nurses were also surveyed to compare the difficulty of the two methods.

2.4 Statistical Analysis

Characteristics of the two groups were compared at baseline and after intervention. For nonparametric variables, Mann-Whitney U test was used and for parametric variables, student t test was applied. P values less than 0.05 were considered significant. SPSS version 17 (Chicago, IL) was used for data analysis.

3. RESULTS

30 patients were enrolled in each study group which included 31 female and 29 males. The mean (SD) gestational age of all neonates was 31.82 (1.60). Distributions of sex, gestational age, height, head circumference, and Apgar scores at the first and fifth minute after the birth were not significantly different between the two groups (Table 1). Furthermore, the arterial blood gas parameters and the therapeutic measurements before intervention were not significantly different between NIMV and HFNC groups (Table 1).

No death was recorded during the study period. Other outcome measures and the complications of interventions are summarized and compared in Table 2. The mean duration of respiratory support was not significantly different between the two groups (Table 2). Likewise, the mean (SD) duration of hospitalization in NICU, the mean (SD) duration of post-NICU hospitalization, and the mean (SD) age of full oral feeding were similar between NIMV and HFNC groups (Table 2). But, the mean (SD) age of patients when oral feeding was started was significantly lower in HFNC group. No treatment failure was recorded in both groups. No patient had chronic lung disease and no one required mechanical ventilation or endotracheal intubation. Interestingly, 11 patients (36.7%) in NIMV group required free oxygen therapy. Two patients were treated with oxy-hood and 9 ones with incubator. On the other hand, only 2 patients (6.7%) in HFNC group required oxygen therapy which was conducted by incubator (P=0.005). The mean (SD) time of oxygen therapy after discontinuation of intervention was 11.22 (7.00) hours in NIMV group and 13.5 (14.84) hours in HFNC group (P=0.72). No neonate required NIMV or HFNC again after discontinuation of intervention.

The ease of intervention was significantly different between the two groups (Table 2). The prevalence of intraventricular hemorrhage, 72 hours and one week after the birth, neonatal infection, PDA, and apnea were not significantly different between the two groups (Table 2). But, damage to the nasal mucosa was significantly more severe in NIMV group than in HFNC group (Table 2). No neonate developed pneumothorax, NEC or pulmonary hemorrhage.

Table 1. Demographic and baseline characteristics compared between the two groups

Newborn demographic factors and characteristics		NIMV group N=29	HFNC group N=30	P-value
Sex	Female, n (%)	18 (58.1%)	13 (41.9%)	0.19
	Male, n (%)	11 (39.3%)	17 (60.7%)	
Gestational age, mean (SD), weeks		31.81 (1.83)	31.83 (1.39)	0.95
Weight, mean (SD), g		1624 (319.32)	1626 (280.91)	0.98
Height, mean (SD), cm		42.10 (4.38)	42.03 (3.78)	0.94
Head circumference, mean (SD), cm		30.34 (2.11)	29.96 (1.66)	0.44
1st minute Apgar score, mean (SD)		6.03 (1.59)	6.13 (1.61)	0.81
5th minute Apgar Score, mean (SD)		8.31 (0.84)	8.33 (1.09)	0.92
PO2 before starting the treatment, mmHg, mean (SD)		58.19 (17.85)	59.56 (13.80)	0.74
PCO2 before starting the treatment, mmHg, mean (SD)		42.92 (7.93)	44.79 (8.40)	0.38
BE before starting the treatment		5.96 (1.80)	4.94 (2.26)	0.06
PH before starting the treatment		7.28 (0.04)	7.30 (0.05)	0.12
Prenatal steroids, n (%)		15 (44.4)	19 (55.9)	0.36
Surfactant, n (%)		22 (53.7)	19 (46.3)	0.22
Age when received surfactant, mean hour (SD)		1.57 (0.58)	1.56 (0.61)	0.95
Number of surfactant doses, mean (SD)		1.13 (0.35)	1.31(0.67)	0.28
Surfactant type	Survanta	8 (66.7)	4 (33.3)	0.11
	Curosurf	8 (88.1)	13 (61.9)	
	Bovine lipid extract (bLES)	6 (75)	2 (25)	

Table 2. Outcome measures and complications compared between the two groups

Outcome measures & complications		NIMV group	HFNC group	P- value
Total respiratory support, mean hours (SD)		40.06 (7.70)	42.46 (6.95)	0.21
Respiratory support after the 1st day, mean hours (SD)		16.48 (7.80)	18.46 (6.95)	0.30
NICU hospitalization period, mean days (SD)		3.24 (0.68)	3.20 (0.06)	0.81
Post-NICU hospitalization period, mean days (SD)		6.79 (2.69)	6.4 (2.22)	0.54
Age when oral feeding began, mean hours (SD)		23.37 (5.78)	20.13 (5.38)	0.032
Age when full oral feeding established, mean hours (SD)		133.66 (30.03)	135.33 (22.85)	0.80
Nurses survey on the ease of Intervention, n (%)	Easy	0 (0)	30 (100)	P<0.01
	Moderate	22 (75.9)	0 (0)	
	Difficult	7 (24.1)	0 (0)	
Intraventricular Hemorrhage, 72 hours after the Birth, n (%)	Normal	29 (93)	26 (86.7)	0.35
	Grade 1	0	3 (10)	
	Grade 2	2 (6.9)	1 (3.3)	
	Grade 3	0	0	
Intraventricular Hemorrhage, One week after the Birth, n (%)	Normal	26 (89.7)	29 (96.7)	0.29
	Grade 1	1 (3.4)	0	
	Grade 2	2 (6.9)	1 (3.3)	
	Grade 3	0	0	
Damage to the Right nasal Mucosa, n (%)	Grade 1	0	3 (10)	<0.01
	Grade 2	0	24 (80)	
	Grade 3	22 (75.9)	3 (10)	
	Grade 4	7 (24.1)	0	
Damage to the Left nasal Mucosa, n (%)	Grade 1	0 (0)	4 (13.3)	<0.01
	Grade 2	0 (0)	23 (76.7)	
	Grade 3	19 (65.5)	3 (10)	
	Grade 4	10 (34.5)	0	
Neonatal infection, n (%)		2 (6.9)	0 (0)	0.23
PDA, n (%)		1 (3.4)	0 (0)	0.49
Apnea, n (%)		1 (3.4)	2 (6.7)	0.50

4. DISCUSSION

The current study demonstrated that HFNC and NIMV were similarly effective in the treatment of premature one day-old neonates with RDS. Outcome measures including the duration of respiratory support, the duration of hospitalization in NICU, the duration of post-NICU hospitalization, the age of full oral feeding, the number of treatment failures, occurrence of chronic lung disease, and the requirement for mechanical ventilation or endotracheal intubation showed no significant difference between the patients in NIMV group vs. those in HFNC group. Patients in HFNC group were significantly younger when started the oral feeding. Moreover, more than a third of patients in NIMV group vs. <7% of those in HFNC required oxygen therapy.

Woodhead et al. [18] compared neonates supported with standard HFNC group with those who were supported by Vapotherm in a cross-over study. They showed that the latter group had significantly lower respiratory efforts and nasal injuries. Iranpour et al. and Abdel Hady et al. *each* conducted a randomized clinical trials to compare HFNC vs. NCPAP [19,20]. They found no specific difference in outcomes between the two groups. Similarly, Sasi's retrospective study showed the same results [12]. In Abdel Hady et al. study, NCPAP group had shorter duration of oxygen therapy and respiratory support [20]. In Campell et al. [21] clinical trial, more neonates on HFNC required reintubation than the neonates of NCPAP group. Furthermore, after extuabtion, HFNC group experienced apnea and bradycardia more frequently than the other group.

Two important characteristics of HFNC in our study which were significantly different than NIMV were the ease of application of respiratory support system and the severity of damage to nasal mucosa. None of the nurses who applied both methods rated NIMV as an easy method of treatment whereas all of them considered HFNC as an easy therapeutic measurement. All of the neonates who had respiratory support through NIMV, experienced grades 3 or 4 of nasal mucosal damage whereas only 10% of those in HFNC group had either grade 3 or 4 of nasal mucosal damage. Similarly, two clinical trials and a review article of HFNC method pointed out the growing evidence of the preference of nurses for HNFC and its higher feasibility compared to other methods of neonatal non-invasive ventilation [11,22,23].

The current study had some limitations. It was conducted in two university-affiliated hospitals. Then, the study population was homogenous which limited the external validity of the results. The sample size was small and the patients were not followed up after hospital discharge. We suggest to include large number of patients and to follow up them after hospital discharge in multiple centers in the future investigations.

5. CONCLUSION

HFNC was more tolerable than NIMV in the treatment of RDS in premature neonates' ≥30 weeks after the first day of life.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Kann IC, Solevag AL. Economic and health consequences of non-invasive respiratory support in newborn infants: a difference-in-difference analysis using data from the Norwegian patient registry. BMC Health Serv Res. 2014;14:494.
2. Shaffer TH, Alapati D, Greenspan JS, Wolfson MR. Neonatal non-invasive respiratory support: Physiological implications. Pediatr Pulmonol. 2012; 47(9):837-47.
3. Roberts CT, Davis PG, Owen LS. Neonatal non-invasive respiratory support: synchronised NIPPV, non-synchronised NIPPV or bi-level CPAP: What is the evidence in 2013? Neonatology. 2013; 104(3):203-9.
4. Davis PG, Morley CJ, Owen LS. Non-invasive respiratory support of preterm neonates with respiratory distress: continuous positive airway pressure and nasal intermittent positive pressure ventilation. Semin Fetal Neonatal Med. 2009;14(1):14-20.
5. Beggs S, Wong ZH, Kaul S, Ogden KJ, Walters JA. High-flow nasal cannula therapy for infants with bronchiolitis. Cochrane Database Syst Rev. 2014;1: CD009609.
6. Lee JH, Rehder KJ, Williford L, Cheifetz IM, Turner DA. Use of high flow nasal cannula in critically ill infants, children, and adults: A critical review of the literature. Intensive Care Med. 2013;39(2):247-57.

7. Milesi C, Boubal M, Jacquot A, et al. High-flow nasal cannula: Recommendations for daily practice in pediatrics. Ann Intensive Care. 2014;4:29.
8. Milesi C, Baleine J, Matecki S, et al. Is treatment with a high flow nasal cannula effective in acute viral bronchiolitis? A physiologic study. Intensive Care Med 2013;39(6):1088-94.
9. Wraight TI, Ganu SS. High-flow nasal cannula use in a paediatric intensive care unit over 3 years. Crit Care Resusc. 2015; 17(3):197-201.
10. Spentzas T, Minarik M, Patters AB, Vinson B, Stidham G. Children with respiratory distress treated with high-flow nasal cannula. J Intensive Care Med. 2009; 24(5):323-8.
11. Saslow JG, Aghai ZH, Nakhla TA, et al. Work of breathing using high-flow nasal cannula in preterm infants. J Perinatol. 2006;26(8):476-80.
12. Sasi A, Malhotra A. High flow nasal cannula for continuous positive airway pressure weaning in preterm neonates: A single-centre experience. J Paediatr Child Health. 2015;51(2):199-203.
13. Roberts CT, Dawson JA, Alquoka E, et al. Are high flow nasal cannulae noisier than bubble CPAP for preterm infants? Arch Dis Child Fetal Neonatal Ed. 2014;99(4):F291-F295.
14. Sreenan C, Lemke RP, Hudson-Mason A, Osiovich H. High-flow nasal cannulae in the management of apnea of prematurity: A comparison with conventional nasal continuous positive airway pressure. Pediatrics. 2001;107(5):1081-3.
15. Gizzi C, Montecchia F, Panetta V, et al. Is synchronised NIPPV more effective than NIPPV and NCPAP in treating apnoea of prematurity (AOP)? A randomised cross-over trial. Arch Dis Child Fetal Neonatal Ed. 2015;100(1):F17-F23.
16. Lee HY, Rhee CK, Lee JW. Feasibility of high-flow nasal cannula oxygen therapy for acute respiratory failure in patients with hematologic malignancies: A retrospective single-center study. J Crit Care. 2015; 30(4):773-7.
17. Wilkinson D, Andersen C, O'Donnell CP, De Paoli AG. High flow nasal cannula for respiratory support in preterm infants. Cochrane Database Syst Rev. 2011;(5): CD006405.
18. Woodhead DD, Lambert DK, Clark JM, Christensen RD. Comparing two methods of delivering high-flow gas therapy by nasal cannula following endotracheal extubation: A prospective, randomized, masked, crossover trial. J Perinatol. 2006; 26(8):481-5.
19. Iranpour R, Sadeghnia A, Hesaraki M. High-flow nasal cannula versus nasal continuous positive airway pressure in the management of respiratory distress syndrome. 2011;29:761-771. J Isfahan Med School. 2011;29:761-71.
20. Bdel-Hady H, Shouman B, Aly H. Early weaning from CPAP to high flow nasal cannula in preterm infants is associated with prolonged oxygen requirement: A randomized controlled trial. Early Hum Dev. 2011;87(3):205-8.
21. Campbell DM, Shah PS, Shah V, Kelly EN. Nasal continuous positive airway pressure from high flow cannula versus infant flow for preterm infants. J Perinatol. 2006; 26(9):546-9.
22. Roberts CT, Manley BJ, Dawson JA, Davis PG. Nursing perceptions of high-flow nasal cannulae treatment for very preterm infants. J Paediatr Child Health. 2014; 50(10):806-10.
23. Manley BJ, Dold SK, Davis PG, Roehr CC. High-flow nasal cannulae for respiratory support of preterm infants: A review of the evidence. Neonatology. 2012;102(4): 300-8.

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