MECHANICAL VENTILATION VS NASAL CPAP DURATION AND THE RISK OF LATE ONSET SEPSIS IN PREMATURE BABIES WITH RESPIRATORY DISTRESS SYNDROME

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ABSTRAK

Ventilasi mekanis sering diperlukan dalam pengelolaan sindrom gangguan pernapasan pada bayi prematur. Risiko sepsis onset terlambat dapat meningkat bersamaan dengan ventilasi mekanis yang lama. Tujuan penelitian ini untuk mengamati risiko sepsis onset terlambat pada lama penggunaan ventilator mekanik dan CPAP nasal. Penelitian ini menggunakan analisis retrospektif. Data dikumpulkan dari catatan medis dari neonatus prematur berisiko tinggi dengan ventilasi mekanis atau CPAP nasal di unit perawatan neonatal RS Husada Utama 1 April 2008 sampai 30 April 2011 dengan purposive sampling. Durasi ventilasi mekanis dan CPAP nasal diamati sebelum dan setelah 7 hari pada penempatan. Kultur darah dilakukan untuk menentukan risiko sepsis onset terlambat. Dilakukan analisis chi-square dan regresi logistik. Hasil: Dikumpulkan sebanyak 44 neonatus sangat berisiko prematur dengan ventilasi mekanik atau nasal CPAP (kelompok sepsis : n = 23 dan kelompok non sepsis non: n = 21). Demografi awal serupa antara kelompok. Ventilasi mekanik lama > 7 hari memiliki perbedaan yang signifikan pada risiko sepsis onset terlambat (p = 0,035). CPAP nasal > 7 hari tidak berbeda bermakna (p = 0,667). Burkholderia cepacia dan Klebsiella pneumonia sebagian besar ditemukan pada kultur darah. Kesimpulan: ventilasi mekanis berkepanjangan dapat meningkatkan risiko sepsis onset akhir prematur neonatus dengan sindrom gangguan pernapasan, sedangkan CPAP nasal dapat menurunkannya.

ABSTRACT

Mechanical ventilation is frequently required in the management of severely respiratory distress syndrome in premature babies. The risk of late onset sepsis may increase simultaneously with prolonged mechanical ventilation. Objective: To observe the risk of late onset sepsis on the mechanical ventilator and nasal CPAP duration use. Method: retrospective analysis. The data were collected from the medical record of highly risk premature neonates with mechanical ventilation or nasal CPAP in neonatal care unit of Husada Utama Hospital from April 1st 2008 to April 30th 2011 with purposive sampling. Mechanical ventilation and nasal CPAP duration were observed before and after 7 days on placement. Blood culture was performed to establish the risk of late onset sepsis. Chi-square and logistic regression analysis were performed. Result: A total of 44 highly risk premature neonates with Mechanical ventilation or nasal CPAP were enrolled (sepsis group: n= 23 and non sepsis group: n= 21). Baseline demographics were similar between the groups. Prolonged mechanical ventilation > 7 days have significant difference on the risk of late onset sepsis (p=0.035). Prolonged nasal CPAP > 7 days has no significant difference (p=0.667). Burkholderia cepacia and Klebsiella pneumonia mostly appeared in blood culture performance. Conclusions: Prolonged mechanical ventilation may increase the risk of late onset sepsis in premature neonates with respiratory distress syndrome, however nasal CPAP may decrease.

Keyword: *Premature neonates – prolonged mechanical ventilation – late onset sepsis*

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Abbreviations:
n-CPAP: nasal Continues positive airway pressure
PEEP: positive end expiratory pressure
UVCs: umbilical vein catheters

INTRODUCTION

Late-onset sepsis remains an important and potentially lethal complication among VLBW infants (Stoll et al. 2002, Bancalari & Moral 2006, Bijari et al. 2011). 21% of VLBW neonates who survived beyond 3 days of age had at least 1 episode of late-onset sepsis. The median age of onset for the first episode of late-onset sepsis was over 2 weeks of age. These infections are particularly poignant for parents and physicians because this complication affects VLBW infants who have survived early causes of mortality but remain at ongoing risk for infection. With increasing survival of ELBW preterm infants, late-onset sepsis will continue to be a challenging complication that affects other morbidities, length of hospitalization, cost of care, and mortality rates (Stoll et al. 2002, Lista et al. 2010). Infants who developed late-onset sepsis were on mechanical ventilation for significantly longer than those who were

uninfected and were significantly more likely to develop BPD. Decreasing the number of days on the ventilator and attention to ventilator-associated infection control issues (eg, reducing interruption of ventilator-endotracheal tube circuits) might reduce the rate of infection (Bancalari & Moral 2006, Bijari et al. 2011, Aly et al. 2008).

Nasal continuous positive airway pressure (CPAP) is increasingly used for the treatment of respiratory distress in premature neonates. Compared with intubation or mechanical ventilation, CPAP is associated with decreased incidence of bronchopulmonary dysplasia and sepsis, and with a trend toward decreased incidence of retinopathy of prematurity and intraventricular hemorrhage (Aly et al. 2008, Shim et al. 2011, Campbell et al. 2006). In this study, we prospectively observed prolonged mechanical ventilation and nasal CPAP on the risk of late onset sepsis in premature neonates with respiratory distress syndrome.

MATERIALS AND METHODS

The study was retrospectively done at NICU of Husada Utama hospital, conducted for 3 years (April 1st 2008 until April 30th 2011). The premature infants with birth weights less than 2000 g and gestational age < 34 weeks who had a mechanical ventilation or nasal CPAP on NICU admission were eligible for the study. Infants with gastrointestinal abnormalities including gastroschizis and omphalocele, or infants with congenital heart disease with intra cardiac shunting were excluded. The parents or legal guardians of the patients gave informed consent before enrollment.

Mechanical ventilation

Following ETI, Pressure AC with positive end expiratory pressure (PEEP) (50–70 mmH2O) was controlled with a tidal volume of 5-8 ml/kg, hypercapnia was not allowed. Peak inspiratory pressure was limited to 200–300 mmH2O. End expiratory pressure was increased in increments of 20–30 mmH2O up to 100 mmH2O, until the required FiO2 was <0.6. Mechanical ventilation was administered with an Avea Viasys ventilator.

Following improvement in the clinical condition, blood gas and the ventilator parameters (RR, SpO2, gas exchange values), when spontaneous breathing reappeared, ventilator settings were changed to synchronized intermittent mandatory ventilation (rate 4–7 breaths/min) for weaning from mechanical ventilation. Pressure support (100 to 120 mmH2O), was adjusted to achieve a spontaneous tidal volume of 8 to 10 ml/kg/min and a respiratory rate of <25 breaths/min, with accessory muscle activity absent. All patients were weaned from the ventilator by reducing the level of pressure support by 40 mmH2O twice and then decreasing the ventilator rate by two breaths/min at 2 hour intervals, as tolerated. Patients who tolerated an intermittent mandatory ventilation rate of 0.5 breaths/min, a pressure support level of 80 mmH2O, and an FiO2 of < 0.5, followed by extubation if respiratory rate remained <25 breaths/min and PaO2 >75 mm Hg.

As the clinical condition and blood gas and the ventilator parameters (RR, SpO2, gas exchange values) improved, ventilation support was tapered off by progressively reducing the number of daily trials, or was stopped if the improvement remained stable (SpO2 >90%, RR < 25 breaths/min).

Airway Care

Suctioning by endotracheal tube was performed using a sterile, open-circuit technique, with a disposable suction catheter. Infants were pre-oxygenated and were ventilated manually with a self-inflating bag between suction catheter passes. Drops of sterile normal saline solution were instilled to liquefy tracheal secretions. Tracheal suctioning was performed during routine care according to unit policy for nurses (usually every 8 hours or as needed), without involvement or interference by any of the investigators. Ventilator circuits were not changed routinely in the NICU.

Nasal Continuous Positive Pressure Ventilation

Patients in the CPAP group were instructed in the use of the nasal prong, through which CPAP was delivered by Arabella. CPAP was increased in increments of 20– 30 mmH2O repeatedly up to 80–150 mmH2O until the F?O2 requirement was < 0.6. The CPAP level was adjusted on the basis of continuous oximetry and measurements of arterial blood gases. CPAP was stopped if the respiratory rate was < 25 breaths/ min, PaO2 > 75 mm Hg with a FiO2 of > 0.5 without ventilator support.

Blood Cultures

Blood culture test was performed in premature babies with suspected sepsis based on clinical symptoms, complete blood test and CRP using VITEX method. Whole blood (0.3–1.0 mL) was placed in sterile Isolator tubes and sent to the microbiology laboratory. Blood was streaked onto blood and chocolate agar plates and then incubated for 5 days under aerobic conditions.

Organisms were isolated by either culture system identified with standard microbiologic techniques.

Statistical analysis

Data were presented in distribution tabulation and data analysis was performed with a computer assisted statistical package (SPSS ver. 12.0). Descriptive analysis of mechanical ventilation duration and risk of sepsis, blood culture of the patient were calculated. Chi-square analysis and logistic regression were performed in the laboratory data.

RESULTS

Data from April 1st 2008 until April 30th 2011 revealed the premature neonates with mechanical ventilator and nasal CPAP were 44 samples. All of them were eligible for analysis, 23 in sepsis group and 21 in no sepsis group. The characteristics of the sample are listed in table 1.

Table 1. Characteristic of High Risk Premature Neonates Who had a mechanical ventilator in NICU

Parameters	Sepsis n=23 (%)	No Sepsis n=21 (%)	*P*
Gender			.121
Female	7 (38.9)	11 (61.1)	
Male	16 (61.5)	10 (38.5)	
Birth weight (g)	1428.3 (SD 324.33)	1450.0 (SD 321.71)	.52
Gestational age			.467
< 30 week's	9 (50.3)	7 (43.8)	
> 30 week's	14 (50)	14 (50)	
Apgar score			.322
≤ 6	8 (61.5)	5 (38.5)	
> 6	15(48.4)	16 (51.6)	
Mechanical ventilator			.068
Yes	18 (62.1)	11 (37.9)	
No (n-CPAP)	5 (33.3)	10 (66.7)	
Days of UVC			.456
<14	7(25)	21(75)	
>14	11(68.8)	5(31.2)	

Table 1 shows that the results has no significant difference based on the gender, birth weight, gestational age, apgar score in premature babies with sepsis risk treated in NICU Husada Utama hospital. However baby with mechanical ventilator shows to have higher risk compared with n-CPAP. In this case: 18 premature neonates with mechanical ventilator and 5 with n-CPAP affected by sepsis. Neonates with apgar score less than 6 during the labor have higher risk affected by sepsis, on the other hand apgar score more than 6 shows lower risk. Days of UVC have no significant difference in blood culture result in premature neonates treated in NICU Husada Utama hospital. Days of UVC less than 14 days show 7 neonates suspected sepsis is positive, in fact blood culture performance shows negative in 21 neonates. Days of UVC more than 14 days show blood culture performance in 11 neonates with blood culture positive evidence.

Table 2. Mechanical ventilator Duration and The Risk of Sepsis in Premature Neonates

Days of Mechanical ventilator	Sepsis	
	Positive n(%)	Negative n(%)
<7 days	6 (46.2)	7(53.8)
>7 days	12 (75)	4(25)

Chi Square X2test p=0.035*

Table 2 shows that days of mechanical ventilation have significant difference in the risk of sepsis in premature neonates treated in NICU Husada Utama hospital (p=0.035). Days of mechanical ventilation more than 7 days show blood culture performance in 12 neonates with blood culture positive evidence.

Table 3. Nasal CPAP Duration and The Risk of Sepsis in Premature Neonates

Days of Nasal CPAP	Sepsis	
	Positive n(%)	Negative n(%)
<7 days	5 (35.7)	9(64.3)
>7 days	0(0)	1(100)

Chi Square X2test p=0.667

Table 3 shows that day of nasal CPAP has no significant difference in the risk of sepsis in premature neonates treated in NICU Husada Utama hospital (p=0.667). Days of nasal CPAP less than 7 days show blood culture performance in 5 babies with blood culture positive evidence.

Table 4 shows the types of microorganism appeared in blood culture in 44 premature neonates treated in NICU Husada Utama hospital. *Burkholderia cepacia* and *Klebsiella pneumonia* mostly appeared in blood culture

performance. Of 23 neonates suspected sepsis 12 show no organism growth on blood culture performance.

Table 4. Pathogens that Caused Sepsis in Premature Neonates

Microorganisms	Blood Culture	
	n	%
Acinetobacter baumanii	1	2.3
Burkholderia cepacia	4	9.1
Candida albicans	1	2.3
Enterobacter asburie	1	2.3
Klebsiella pneumoniae	4	9.1
Escherichia coli	0	0
Pseudomonas aeroginosa	0	0
Enterobacter cloacae	0	0
Stenotrophomonas maltophila	1	2.3
No organism growth	12	27.3

DISCUSSION

The overall mortality rate among premature infants with very low birth weight and late-onset sepsis is reportedly as high as 17%–19%, mainly because of gram-negative bacterial and fungal infections (Makhoul et al. 2002, 2005). Mechanical ventilation can damage the immature lung by over distension produced by excessive tidal volume because of excessive peak inspiratory pressure or prolonged inspiratory time, excessive positive end-expiratory pressure (PEEP) or trapped gas, insufficient functional residual capacity (FRC) because of low PEEP, oxygen toxicity and inadequate conditioning of the inspired gas temperature and humidity (Shim et al. 2011, Morley et al. 2008, Subramaniam et al. 2000). In addition, when the airway is invaded with an endotracheal tube, there is an increased risk of airway colonization and infection with pathogens. Therefore, the use of CPAP can protect against the development of BPD by avoiding the need of mechanical ventilation and by reducing the risk of bacterial colonization via the endotracheal tube.

In this study, previous BSI was a significant independent risk factor associated with the development of Ventilator Associated Pneumonia (VAP), and the duration of endotracheal intubation was marginally significant in extremely preterm neonates. The presence of a tube in the trachea plays a primary role in the pathogenesis of VAP. It interferes with the clearance of respiratory secretions and organisms that is conducted by cilia of mucosal cells in a non intubated trachea (Aly et al. 2008, Panigada et al. 2003, Subramaniam et al. 2000). It seems logical that keeping the breathing circuit and endotracheal tube in a vertical position at a level higher than the trachea would allow respiratory secretions, mixed with bacteria, to travel passively by gravity to the terminal airway and to alveoli. The effect of gravity on bacterial colonization, VAP, and mobilization of secretions was first reported in an animal study by Panigada et al. (2003). Indeed, when the endotracheal tube was placed horizontal or just below horizontal, animals showed no altered bacterial colonization in their airways and distal alveoli after 72 hours of continuous ventilation. Positioning of the trachea facilitated sliding of respiratory secretions along the endotracheal tube wall, so that the secretions drained by the force of gravity to the outside, eliminating the need for tracheal suctioning (Aly et al. 2008, Reininger et al. 2005, Stoll et al. 1996).

Important pathogenic determinants of endotracheal tubes infection are 1) the material of which the device is made and 2) the intrinsic virulence factors of the infecting organism (Morley et al. 2008, Apisarnthanarak et al. 2003, Panigada et al. 2003). Some materials also have surface irregularities that enhance the microbial adherence of certain species (eg, coagulase-negative staphylococci, *Acinetobacter calcoaceticus*, and *Pseudomonas aeruginosa*); These materials are especially vulnerable to microbial colonization and subsequent infection (Lista et al. 2010, Davis et al. 2009). The literature shows that there are microorganisms more prevalent in late onset sepsis. The gram-positive cocci are responsible for 65% of infections, while the most prevalent are the Staphylococcus epidermidis (31%) and the Staphylococcus aureus (14%). The gram-negative bacilli account for 30% of infections and the most prevalent are the Pseudomonas sp (7%) and the *Escherichia coli* (6%). Infection by *Candida SP* is responsible for the remaining 5% of catheter-related infections (Bizzarro et al. 2005, Stefanescu et al. 2003, Gunduzet al. 2005). Coagulase negative staphylococcus was the dominant infection (55.6%) within the first 2 weeks, whereas Gram negative bacteria were dominant pathogens (58.3%) after the first 2 weeks (Gunduzet al. 2005). However, the most frequent microorganism isolated in cultures in this study was *Burkholderia cepacia* and *Klebsiella pneumonia*.

Several limitations should be considered when interpreting our data. We conducted the study on a large cohort of patients over a 3-year period, because our unit has low incidence of late onset sepsis. Several confounding factors still persist in this study. Underlying disease, total parenteral nutrition, UVCs/PICCs insertion, Histamine 2 antagonis drug administration, antenatal corticosteroid, nosocomial infection were the risk of late onset sepsis in premature neonates with prolonged mechanical ventilation.

CONCLUSION

Late-onset sepsis remains an important and potentially lethal complication in premature neonates. Prolonged mechanical ventilation may increase the risk of late onset sepsis in premature neonates with respiratory distress syndrome, however nasal CPAP may decrease. *Burkholderia cepacia* and *Klebsiella pneumonia* mostly appeared in blood culture performance.

REFERENCES

1. Aly H, Badawy M, El-Kholy A, Nabil R, Mohamed A (2008). Randomized, Controlled Trial on Tracheal Colonization of Ventilated Infants: Can Gravity Prevent Ventilator-Associated Pneumonia? Pediatrics;122:770-4
2. Apisarnthanarak A, Holzmann G, Hamvas A, Olsen MA, Fraser VJ (2003). Ventilator-associated pneumonia in extremely preterm neonates in a neonatal intensive care unit: characteristics, risk factors, and outcomes. Pediatrics 112:1283–9
3. Bancalari E, Moral T (2006). Continuous positive airway pressure: early, late, or stay with synchronized intermittent mandatory ventilation? J Perinatol 26:S33–7
4. Bijari BB, Malekiyan A, Niknafs P, Baneshi MR (2011). Bubble–CPAP vs. Ventilatory–CPAP in Preterm Infants with Respiratory Distress. Iran J Pediatr 21(2):151-8
5. Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG (2005). Seventy-Five Years of Neonatal Sepsis at Yale: 1928–2003. Pediatrics 116:595–602
6. Campbell DM, Shah PS, Shah V, Kelly EN (2006). Nasal continuous positive airway pressure from high flow cannula versus Infant Flow for preterm infants. J Perinatol 26:546–9
7. Davis PG, Morley CJ, Owen LS (2009). Non-invasive respiratory support of preterm neonates with respiratory distress: Continuous positive airway pressure and nasal intermittent positive pressure ventilation. Sem Fetal Neonatal Med 14(1):14-20
8. Gunduz M, Unlugenc H, Ozalevli M, Inanoglu K, Akman H (2005). A comparative study of continuous positive airway pressure (CPAP) and intermittent positive pressure ventilation (IPPV) in patients with flail chest. Emerg Med J 22:325–9
9. Lista G, Castoldi F, Fontana P, Daniele I, Cavigioli F, et.al. (2010). Nasal continuous positive airway pressure (CPAP) versus bi-level nasal CPAP in preterm babies with respiratory distress syndrome: a randomised control trial. Arch Dis Child Fetal Neonatal 95:F85–9
10. Makhoul IR, Sujov P, Smolkin T, Lusky A, Reichman B (2002). Epidemiological, clinical and microbiological characteristics of late-onset sepsis among very low birth weight infants in Israel: a national survey. Pediatrics 109:34–9
11. Makhoul IR, Sujov P, Smolkin T, Lusky A, Reichman B (2005). Pathogen-Specific Early Mortality in Very Low Birth Weight Infants with Late-Onset Sepsis: A National Survey. Clinical Infectious Diseases 40:218–24
12. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB (2008). Nasal CPAP or Intubation at Birth for Very Preterm Infants. N Engl J Med 358:700-8.
13. Panigada M, Berra L, Greco G, Stylianou M, Kolobow T (2003). Bacterial colonization of the respiratory tract following tracheal intubation: effect of gravity: an experimental study. Crit Care Med.31(3):729 –37
14. Reininger A, Khalak R, Kending J, Ryan R, Stevens T, Reubens L et al. (2005). Surfactant admin-istration by transient intubation in infants 29 – 35 weeks' gestation with respiratory distress syndrome decreases the likeli-hood of later mechanical ventilation: a randomized controlled trial. J Perinatol 25(11):703–8.
15. Shim GH, Kim SD, Kim HS, Kim SD, Lee HJ, Lee JA et.al. (2011). Trends in Epidemiology of Neonatal Sepsis in a Tertiary Center in Korea: A 26-Year Longitudinal Analysis, 1980-2005. J Korean Med Sci 26: 284-9
16. Stefanescu BM, Murphy WP, Hansell BJ, Fuloria M, Morgan T, Aschner JL (2003). A Randomized, Controlled Trial Comparing Two Different Continuous Positive Airway Pressure Systems for the Successful Extubation of Extremely Low Birth Weight Infants. Pediatrics;112:1031–8
17. Stoll BJ, Gordon T, Korones SB, et al. (1996). Late-onset sepsis in very low birth weight neonates: a report from the National Institute of Child Health and Human Development Neonatal Research Network. J Pediatr.; 129:63–71
18. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et.al. (2002**).** Late-Onset Sepsis in Very Low Birth Weight Neonates: The Experience of the NICHD Neonatal Research Network. Pediatrics 110:285–91
19. Subramaniam P, Henderson-Smart DJ, Davis PG (2000). Prophylactic nasal continuous positive airways pressure for preventing morbidity and mortality in very preterm infants (Review) Cochrane Collaboration Syst Rev 2.