Journal of Acute Disease

journal homepage: www.jadweb.org

Original article https://doi.org/10.12980/jad.6.2017JOAD_2016_46

Noninvasive ventilation in cancer children with acute respiratory failure

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ARTICLE INFO

Article history:
Received 18 Aug 2016
Received in revised form 7 Sep 2016
Accepted 25 Oct 2016
Available online 8 Dec 2016

Keywords:
Noninvasive ventilation
Respiratory
Children
Cancer

ABSTRACT

Objective: To establish the effectiveness of noninvasive ventilation in cancer children with acute respiratory failure.
Methods: The data of 33 cancer patients were obtained prospectively from six different pediatric intensive care units in Turkey between the years of 2012 and 2013.
Results: The diagnosis was leukemias in 25 (75.8%), lymphomas in 3 (9.1%) and other solid tumors in 5 (15.1%) patients. Pneumonia in 12 (36.3%) and sepsis in 15 (45.4%) patients were seen as the common reasons of respiratory failure. The mean PaO2/FiO2 ratios were (164.22 ± 37.24) and (126.80 ± 42.73) in noninvasive ventilation success and failure group, respectively. Noninvasive ventilation was successful in 18 (54.5%) patients. The failure group consisted of 15 patients required intubation. A total of 14 (42.4%) patients died. The clinical outcome in terms of success and failure was meaningful statistically ($P = 0.000\,1$).
Conclusions: Our results could encourage the use of noninvasive ventilation in children with cancer who develop acute respiratory failure. It should be considered as a useful therapeutic approach to avoid endotracheal intubation.

1. Introduction

Noninvasive ventilation (NIV) is a treatment for patients with respiratory dysfunction accomplished by an external interface and a positive pressure ventilator[1]. NIV has been applying increasingly in pediatric patients with acute respiratory failure of various etiologies. Several recent trials have shown major benefits of NIV as a preventive measure during episodes of acute hypoxemic respiratory failure in solid organ transplant patients or patients with severe immunosuppression, particularly related to hematological malignancies and neutropenia[2]. NIV may decrease the risk of life-threatening complications associated with invasive mechanical ventilation in patient with hematologic malignancies. Early initiation of NIV seems necessary to avoid endotracheal intubation and provide benefit to patients[3].

Few studies were presented about the using of NIV in children diagnosed with cancer. Some of studies had encouraging results in pediatric hematological malignancies. With our study in PICU (Pediatric Intensive Care Unit) setting, the experience of NIV was presented in cancer children with acute pulmonary disease. Our aim was to determine the acceptability of NIV in critically care children with cancer and to evaluate the activity of NIV clinically in these patients.

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The study protocol was performed according to the Helsinki declaration and approved by the ethics committee of Cukurova University (Document number: 12 and date: 01.03.2012). Written informed consent was obtained from the parents of patients who participated in this study.

The journal implements double-blind peer review practiced by specially invited international editorial board members.

2. Materials and methods

2.1. Study design and study population

This study is a prospective study conducted in six Turkish university hospitals (Akdeniz, Ege, Bezmialem, Cukurova, Ankara and Istanbul). In the study, 33 patients, aged between 1 and 18 years old, required NIV for acute respiratory failure were admitted to the PICU. The study was approved by the ethics committee of Cukurova University (Document number: 12 and date: 01.03.2012). Written informed consent was given by the parents of patients. We studied the success of NIV in a total population of 33 hematology and oncology patients who were referred to PICUs between April 2012 and June 2013.

For each patient, the following population features such as age, gender, cancer type (hematologic and organ cancers), disease status [active, remission, relapse/refractory or bone marrow transplantation (BMT)] and admission status to PICU (neutropenic or nonneutropenic), PICU length of stay and NIV hours were recorded. Malignancies included acute lymphoid leukemia, acute myeloid leukemia, chronic myeloid leukemia, non-Hodgkin (Burkitt and T-cell) lymphoma and Hodgkin disease, brain tumor, rabdomyosarcoma and neuroblastoma. The below parameters were received before beginning of respiratory assistance at the first PICU admission: measurements of Glasgow's coma score, Pediatric Logistic Organ Dysfunction (PELOD) and Pediatric Risk of Mortality (PRISM) III scores, blood cell count, baseline blood gases, in particular pH, PaO_2, $PaCO_2$ and PaO_2/FiO_2 ratio within the first 24 h of the patient's intensive care unit stay. Leukopenia was defined as a total white blood cell count of $< 1.0 \times 10^9$ cells/L. The blood gas results was obtained by using of peripheral arterial catheter. The symptoms of respiratory problems described by thorax X-ray, existence of hemodynamic instability (intense sepsis/septic shock) and various organ insufficiency were recorded. various organ insufficiency, intense sepsis/septic shock was identified based on the International Pediatric Sepsis Consensus Conference[4]. The observation of infiltrative area in the thorax X-ray was described as a symptom of pulmonary disease. The infiltration area of lung were classified as < 25%; 25% to 50%; 50% to 75%; and > 75%. The duration of hospitalization (in days) in PICU was also enrolled. The criteria for success or failure during NIV application designated outcome of diseases.

Acute respiratory failure was defined as an acute and rapid deterioration of respiratory function leading to hypoxemia in blood gas tensions as PaO_2 < 60 mmHg while breathing air, or a $PaCO_2$ > 50 mmHg[5]. Both clinical condition of the patient and the work of breathing were important factors when deciding of NIV. Patients were selected regardless of the underlying cancer type contributed to respiratory failure. Exclusion criteria were: cardiorespiratory arrest, hemodynamic instability despite vasoactive treatment, Glasgow coma score <8, contraindications to NIV (facial or digestive tract surgery). Patients with NIV after extubation were not included, although it was used as a method of weaning from mechanical ventilation in this study. Also babies below one year old and children who had coagulopathy and major congenital malformations were excluded.

2.2. Applying of NIV

The study group included NIV was identified in children who applied NIV as a primary mechanical ventilation method. NIV was continuously applied for at least 24 h and provided by bilevel pressure ventilation (BIPAP vision; Respironics; Murrysville, PA) or assisted spontaneous breathing (Evita 4; Drager Medical, Telford, PA, USA). Ventilatory mode was oriented an inspiratory pressure support with positive end-expiratory pressure. Bilevel devices were constituted in the spontaneous mode reply to an alteration of phase in inspiratory flow rate with the providing a preset level of positive pressure. The ventilator was not induced in response to flow changes in the timed mode, but at a set rate distributing of intermittent pulses of positive airway pressure. NIV was applied through pressure-support ventilation using a nasal mask (Fisher & Pykel flexiFit Auckland, New Zealand and Respironics comfortful Andover, MA. USA) hold on to a ventilator. Ventilatory masks were provided for the best fit and comfort to the children with cancer. For the patients good collaboration, positive end-expiratory pressure and inspiratory positive airway pressure with a minimal flow were provided. The ventilator settings such as positive end-expiratory pressure between 3 and 8 cm H_2O to which inspiratory pressures up to 10 cm H_2O were added. After that, positive end-expiratory pressure was step by step raised to regulate oxygenation for achieving oxygen saturation as 90% and a decrease in oxygen demand. An augmentation in ventilation was considered by reducing in pCO_2. A well-trained critical care team managed cautiously the patients during NIV.

The application was continuous for the first 6 h and no limit was set on the duration unless failure appeared. NIV was considered to be successful if the patient remained in spontaneous respiration for at least 48 h after the withdrawal of NIV and therefore did not need endotracheal intubation. The major criterion for intubation was defined as a high oxygen necessity as FiO_2 > 80% one hour after the beginning of NIV[3].

2.3. Statistical analysis

Data were tested with descriptive statistical methods (mean values ± SD). In addition, categorical variables were evaluated by the χ^2 test. The student's *t* test (for parametric data) or the Mann–Whitney *U* test (while not normally distributing of the continuous variables) were used for contrasting of continuous variables, as appropriate. Data were analyzed using number Cruncher statistical system 2007 statistical software (Utah, USA) and *P*-values $P < 0.05$ were considered to be statistically significant.

3. Results

Between April 2012 and June 2013, 33 patients, 16 (48.5%) boys and 17 (51.5%) girls with mean age (9.54 ± 5.67) years old, were assigned to NIV. Information of potentially eligible patients who were admitted was only obtained from six centers during the study period. The diagnosis was leukemia in 25 (75.8%), lymphoma in 3 (9.1%) and solid tumor in 5 (15.1%) patients. A total of 15 (45.5%) patients had active disease (first diagnosed disease or continuing therapy), 1 (3%) in complete remission and 14 (42.4%) was in relapse. Pneumonia in 12 (36.3%) and sepsis in 15 (45.5%) patients were seen as the

common reasons for acute respiratory failure. The applying of NIV was successful in 18 (54.5%) patients. The breakdown on the number of NIV successful/failure cases (15) were recorded in different centers (Akdeniz 7/5, Ege 4/4, Bezmialem 3/1, Cukurova 2/3, Ankara 1/1 and Istanbul 1/1), respectively. The characteristics of patients at enrollment were listed in Table 1.

Table 1
Patient characteristics at PICU admission [*n* (%)].

Characteristics		Values
Gender	Boy	16 (48.5)
	Girl	17 (51.5)
Type of underlying malignancy	Leukemia	25 (75.8)
	Lymphoma	3 (9.1)
	Solid tumor	5 (15.1)
Status of disease	Active disease	15 (45.5)
	Remission	1 (3.0)
	Relapse/refractory	14 (42.4)
	BMT	3 (9.1)
Admission status to PICU	Neutropenic	17 (51.5)
	Non-neutropenic	16 (48.5)
Radiotherapy to the lung	Received	5 (15.2)
	Non-received	28 (84.8)
Organ failure	Yes	24 (72.7)
	No	9 (27.3)
Reason of acute respiratory failure	Pneumonia	12 (36.3)
	Pulmonary edema	3 (9.1)
	Sepsis	15 (45.5)
	Septic shock	1 (3.1)
	Metastasis	2 (6.1)
Chest X-Ray	< 25%	3 (9.1)
Infiltration area	25%–50%	10 (30.3)
	50%–75%	13 (39.4)
	> 75%	7 (21.2)
NIV status	Success	18 (54.5)
	Failure	15 (45.5)

Table 2 presents blood gas analysis and vital data (Respiratory rate, heart rate, PRISM, PELOD and Glasgow coma score) at PICU admission in NIV success and failure group. PaO_2/FiO_2 ratio was calculated at the first admission. The mean PaO_2/FiO_2 ratios were (164.22 ± 37.24) and (126.80 ± 42.73) in NIV success and failure group, respectively. The difference was significant statistically (P = 0.011). While the median length of PICU stay was (6.65 ± 4.36) in NIV succsess group, (15.32 ± 46.21) days were seen in NIV failure group. There was no significant difference statistically between two group (P = 0.777). The mean duration of NIV was (52.46 ± 44.31) and (55.82 ± 56.72) h in patients who were success and failure group, respectively. No statistically significant differences were found for NIV hours in patients who were successful and failure (P = 0.624).

Gender and type of underlying malignancy had no significance in between success and failure group. Disease status referred active, remission, relapse/refractory and BMT showed prominent difference between in NIV success and failure group (P = 0.016). At the PICU, 8 (44.44%) patients were neutropenic. Although NIV was unsuccessful in these patients than that of nonneutropenic, no prominent significance was seen (P = 0.373). Septic shock had an effect on NIV, distinctly (P = 0.027) and the failure group showed increased rate. Steroid use were stated for the success and failure group (seven success and twelve failures in children who applied NIV). Statistically significant difference was found in both group (P = 0.017), but not inotropic and granulocyte colony stimulating factor use. Table 3 shows intensive care unit and outcome in whole cancer children and NIV group (success and failure group of NIV).

Table 3
Characteristics between patients with NIV success and failure.

Characteristics		NIV success (n = 18)		NIV failure (n = 15)		P value
Age (years)		8.39 ± 5.10		11.28 ± 6.53		0.163
Gender	Boy	8	44.40%	8	53.30%	0.611
	Girl	10	55.60%	7	46.70%	
Type of underlying malignancy	ALL	9	50.00%	6	40.00%	0.405
	AML	3	16.67%	6	40.00%	
	KML	0	0.00%	1	6.67%	
	Burkitt lymphoma	1	5.56%	0	0.00%	
	T-cell lymphoma	0	0.00%	1	6.67%	
	Hodgkin lymphoma	1	5.56%	0	0.00%	
	Neuroblastoma	0	0.00%	1	6.67%	
	Medulloblastoma	1	5.56%	0	0.00%	
	Pons glioma	1	5.56%	0	0.00%	
	Rabdomyosarcoma	1	5.56%	0	0.00%	
	Yolk salk tumor	1	5.56%	0	0.00%	
Status of disease	Active disease	12	66.67%	3	20.00%	0.016
	Remission	1	5.56%	0	0.00%	
	Relapse/refractory	5	27.78%	9	60.00%	
	BMT	0	0.00%	3	20.00%	
Admission status to PICU	Neutropenic	8	44.44%	9	60.00%	0.373
	Nonneutropenic	10	55.56%	6	40.00%	
Sepsis	Yes	16	88.89%	13	86.67%	0.846
	No	2	11.11%	2	13.33%	
Septic shock	Yes	4	22.22%	9	60.00%	0.027
	No	14	77.78%	6	40.00%	
Inotropic use	Yes	18	100.00%	4	26.70%	0.144
	No	0	0.00%	11	73.30%	
Steroid use	Yes	7	38.89%	12	80.00%	0.017
	No	11	61.11%	3	20.00%	
GCSF use	Yes	7	38.89%	6	40.00%	0.948
	No	11	61.11%	9	60.00%	
Last status	Alive	18	100.00%	1	6.67%	0.000 1
	Exitus	0	0.00%	14	93.33%	

ALL: Acute lymphoblastic leukemia; GCSF: Granulocyte colony stimulating factor.

Table 2
Blood gas analysis and vital data.

	Mean ± SD	NIV success (n = 18)	NIV failure (n = 15)	P value
Arterial pH	7.40 ± 0.06	7.42 ± 0.06	7.39 ± 0.07	0.279
Arterial pCO_2 (mmHg)	40.60 ± 12.90	42.11 ± 14.69	38.88 ± 10.79	0.485
PS	9.20 ± 3.60	9.50 ± 3.27	8.90 ± 4.23	0.727
RR (breath rate/min)	45.21 ± 13.69	45.06 ± 15.82	45.40 ± 11.17	0.944
HR (hearth rate/min)	145.36 ± 17.84	147.78 ± 18.81	142.47 ± 16.78	0.403
PRISM III 1 day	11.45 ± 7.08	12.67 ± 6.02	10.06 ± 8.32	0.536
PELOD 1 day	13.45 ± 8.91	11.98 ± 6.52	14.75 ± 11.51	0.148
GCS 1 day	14.09 ± 1.37	13.94 ± 1.66	14.27 ± 0.96	0.512
PaO_2/FiO_2 ratio	147.21 ± 43.50	164.22 ± 37.24	126.80 ± 42.73	0.011
The lenght of PICU stay (day)	11.33 ± 31.08	6.65 ± 4.36	15.32 ± 46.21	0.777
The duration of NIV (h)	58.00 ± 51.45	52.46 ± 44.31	55.82 ± 56.72	0.624

Data are expressed as mean ± SD at the first admission to PICU; P-values are referred to the differences between NIV success and failure group.

The NIV failure patients who indicated intubation were fifteen. Refractory hypoxemia as the primary diagnosis closely anticipated the need for endotracheal intubation. A total of 33 patients of 14 (42.4%) were applied invasive ventilation and they died. The clinical outcome in terms of NIV success and failure was different statistically ($P = 0.000\,1$) (Table 3).

4. Discussion

Although the role of NIV is not well defined in pediatric-age patients with acute respiratory distress, it is increasingly being applied safely in children. The success rate of NIV was found as 74.2% in previous studies[6]. Dohna-Schwake *et al.* presented that NIV had a valuable impact in children with acute pulmonary insufficiency and 38% of patients practised NIV were found as failure in their study[7]. We found the success rate of NIV as 54.5% in children affected by acute respiratory distress. We believed that most patients diagnosed neutropenic, sepsis and severe septic shock were successful in our study. In one study performed by Lum *et al.* pediatric patients had 76% success result[8]. Along with these studies, the results emerged from our study motivated the applying of NIV in cancer children who diagnosed acute pulmonary problem to be necessary ventilation.

In the present study, the underlying malignancy type did not associated with NIV success or failure. One study presented that organ cancers were determinant evident for NIV failure in critically care children[3]. Since chemotherapeutic agents used for malignancies can lead to the tissue damage, pulmonary problems likely may occur[2]. Because of small sample size, our investigation could lead to not statistically significant result. Depuydt *et al.* showed that patients with relapse/refractory status had bone marrow insufficiency due to extensive chemotherapy. In addition, it was reported that patients with hematologic cancers also had the same risk[9]. The status of the disease had an effect on NIV success in the present study. While 9 of 14 patients with relapse/refractory were failure, that of 12 with active disease had success during the applying of NIV. An immunosupression caused by an intensive chemotherapy could cause to NIV failure in relapse/refractory patients.

The usefulness of NIV has been widely demonstrated in immunocompromised adults[2,10-12]. While requiring of mechanical ventilation for the pulmonary disease, particularly immunosuppressed patients generally came face to face miserable outcome. It was presented by Fuchs *et al.* that 27% of immunosuppressed children responded to NIV[13]. The survival rate in neutropenic children was 42.1% in our investigation. Several recent trials have shown major benefits of NIV as a preventive measure during episodes of acute hypoxaemic respiratory failure in solid organ transplant patients or patients with severe immunosuppression, particularly related to hematological malignancies and neutropenia[14]. Even though neutropenic patients [17/33 (51.5%)] with acute respiratory failure showed no meaningful outcome in our NIV practice, that of few [8/17 (47%)] with NIV conducted in a successful manner in PICU. In collaboration with these data, cancer children may have benefit from NIV during the immunosuppression period.

NIV was mainly used for the treatment of patients with acute severe hypoxic failure[10]. The lower initial oxygen requirement expressed by the PaO_2/FiO_2 ratio was reported in patients with NIV[9]. In one study, patients who practiced successful NIV had prominent oxygenation recovery in the course of NIV application at first hour. Even though there wasn't a statistically significant level, the distinction of increased PaO_2/FiO_2 ratio was seen in all treatment period[3].

Our findings also indicate that considerably improved PaO_2/FiO_2 was recorded during the first hour in NIV success group. Munoz-Bonet *et al.* pointed that the using of NIV was possible; therefore NIV can lead to avoid an endo-tracheal intubation in children[15]. Invasive mechanical ventilation in patient with cancer may increase the risk of life-threatening complications. The length of hospital stay and mechanical ventilation are important risk factors for development of ventilator-associated pneumonia in adult cancer patients[16]. Accordingly, it could be concluded that early initiation of NIV seemed necessary to avoid the possible risks of endo-tracheal intubation and provided benefit to patients. However, we need to verify these findings in a prospective controlled study in children with cancer.

Previous studies were associated with sustained improvement of reduction in PICU length of stay in patients applied NIV[2,10,17-19]. Although the meaningful relationship was not established in our study, the mean duration of hospitalization was much longer in NIV failure group than that of success group in PICU. Other studies also support these data. Other investigation performed by Piastra. *et al* pointed that children with NIV had shorter period of hospitalization and PICU[3]. Also the success of NIV reduced NIV hours as well as the length of PICU stay in children with cancer in the present study. It could be thought that NIV provided short PICU stay and NIV duration in cancer children.

Pancera *et al.* reported that the majority of patients with worse hemodynamic status were NIV failure[6]. A recent prospective study stated that mortality rates can be reduced in pediatric patients with NIV[18]. In comparison to the others, the mortality rate (93.33%) was high among patients with hemodynamic instability in our NIV failure group. As can be observed from our patient characteristics, septic shock was associated with NIV failure. Almost all patients used inotropic agent. Once again, it seems therefore likely that an important finding in our analysis was to diagnose acute respiratory failure early and NIV application should be done without delay. Depuydt *et al.* reported that a majority of patients required immediate endotracheal intubation as well as vasopressor therapy because of circulatory shock[9]. In one study, when patients with circulatory shock

arrived in an advanced stage of respiratory failure, a reduced potential benefit of NIV was reported[19]. Although we believed that NIV failure could be seen in cancer patients who had severe hemodynamic status, the similar vital data and severity scores of all patients could be incapable for presenting of NIV success in our small population. Much comprehensive investigation should be performed in terms of clarifying the beneficence of NIV for cancer children.

The present study had some limitations. Our investigation lacked a control arm. Other an important limitation was the decision of ventilation type planned by the patients' physician according to severe respiratory failure. The respiratory predictive factors of clinical features could not be used in our study as well. Therefore, large multicenter controlled study should be warranted to predict outcomes more reliably.

In conclusion, NIV should be considered a favorable treatment approach to abstain from endotracheal intubation while ameliorating of cancer children who suffering from acute pulmonary problem indicating the ventilation type. The requirement of intubation could be decreased in children with NIV. In spite of few sample, it is conceivable the regarding of NIV in children diagnosed with malignancy. Our experience also suggests that NIV should not be postponed. Large pediatric studies are required to reveal the usefulness of NIV and who will benefit from NIV in the future.

Conflict of interest statement

The authors report no conflict of interest.

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