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ARAŞTIRMA / RESEARCH

Evaluation of acute respiratory distress syndrome cases in a pediatric intensive care unit

Çocuk yoğun bakım ünitesindeki akut solunum sıkıntısı sendromu vakalarının değerlendirilmesi

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Abstract

Purpose: The aim of this study was to evaluate the lung-protective mechanical ventilation strategy, early enteral nutrition, negative fluid balance, and adequacy of hospital resources in our pediatric intensive care unit.
Materials and Methods: This study included 32 patients who developed acute respiratory distress syndrome (ARDS) during their monitoring in the pediatric intensive care unit.
Results: According to their oxygenation status, 14 patients (43.8%) had mild ARDS, nine patients (28.1%) had moderate ARDS, and nine patients (28.1%) had severe ARDS. High-frequency oscillatory ventilation was applied to three patients (9.3%), and four patients (12.5%) received extracorporeal membrane oxygenation (ECMO) support. The most common complications were nosocomial infection (31.3%) and pneumothorax (12.5%). The mortality rate was 6.3%. The survival rate was 75.0% in patients with ECMO support. The patients with a higher Pediatric Index of Mortality (PIM-2) score confronted more severe ARDS, and non-pulmonary ARDS also progressed in advanced stages.
Conclusion: In patients with high PIM-2 and PELOD scores, attention must be given to the development of severe ARDS. The lung-protective mechanical ventilation support, early enteral nutrition, negative fluid balance practices, and the adequacy of hospital resources led to a successful survival rate in our study. However, multicenter randomized controlled trials are needed on this subject.
Keywords:. Acute respiratory distress syndrome, children, stage, survival

Öz

Amaç: Bu çalışmanın amacı akciğer koruyucu mekanik ventilasyon stratejisi, erken enteral beslenme, negatif sıvı dengesi ve hasta kaynaklarının yeterliliğinin akut solunum sıkıntısı sendromu olan çocuklarda sağ kalım üzerine etkisini değerlendirmektir.
Gereç ve Yöntem: Çalışmaya çocuk yoğun bakım ünitemizde akut solunum sıkıntısı sendromu gelişen 32 hasta dahil edildi.
Bulgular: Oksijenizasyon durumlarına göre 14'ü hafif (% 43.8), 9'u orta (% 28.1) ve 9'u ağır (% 28.1) evre akut solunum sıkıntısı sendromu gelişmiş idi. Üç hastaya (% 9,4) yüksek frekanslı osilasyon ventilasyon, dört (% 12,5) hastaya ekstrakorporeal membran oksjenizasyon desteği sağlandı. En sık görülen komplikasyonlar ventilatör ilişkili pnömoni (% 21.9) ve pnömotoraks (% 12.5) idi. Mortalite oranı % 6.3 idi. Ekstrakorporeal membran oksjenizasyon uygulanan hastalarda sağ kalım oranı %75 idi. Pediatric Index of Mortality-2 skoru yüksek olan ve non-pulmoner kaynaklı akut solunum sıkıntısı sendromu hastaların takibi sırasında gelişebilecek akut solunum sıkıntısı sendromunun şiddetinin daha ağır olduğu görüldü.
Sonuç: Akciğer koruyucu mekanik ventilasyon desteği, erken enteral beslenme, negatif sıvı dengesi ve yeterli hastane kaynakları sağkalımı arttırabilir. Ancak, çok merkezli randomize kontrollü çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Akut solunum sıkıntısı sendromu, çocuk, çocuk yoğun bakım

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INTRODUCTION

Acute Respiratory Distress Syndrome (ARDS) is a hypoxemic acute respiratory failure syndrome that develops as a result of an increase in alveolar-capillary membrane permeability due to various etiological reasons. ARDS characteristics include resistance to oxygen therapy, non-cardiogenic causes, and oedema in both lungs. The diagnostic criteria determined at the 2015 Paediatric Acute Lung Injury Consensus Conference (PALICC) are valid in the definition of ARDS[1].

In a recent multi-center study, it was reported that 3% of pediatric intensive care unit (PICU) patients develop ARDS[2]; its mortality varies between 15–45%[2-8]. While the mortality rate is high, it varies according to the differences in the etiology of patients from different centers included in the study, quality of health care, and clinical practices[9]. The most common causes are sepsis and pneumonia, and it may develop due to primary lung disease or various extrapulmonary reasons. Treatment includes treating the primary disease and supportive treatments[1]. Studies also recommend lung-protective mechanical ventilation support, early enteral nutrition, negative fluid balance practices[1,10,11]. Although studies show that these recommendations can empower successful survival rates, current information on the outcomes of the children with ARDS that are managed with these recommendations is scarce. The adequacy of hospital resources (such as equipment, consumables, and personnel) causes different survival rates among centers as well as these recommendations. To our knowledge, this is the first study that evaluates the effect of these recommendations on the outcomes of the children with ARDS.

In this study, our primary objective was to evaluate the incidence of ARDS, its causes, underlying diseases, mechanical ventilator applications, treatment practices. The secondary objective was to observe the effect of these implementations on the survival rate in our PICU.

MATERIALS AND METHODS

This single center prospective observational study was conducted in an academic, tertiary PICU that accepted patients with various illnesses between January 1, 2016 and December 31, 2017. The study was approved by the Institutional Review Board of Cukurova University Faculty of Medicine (01.2017/60). Written informed consent was obtained from the patients' relatives for their anonymized information.

All patients who met the criteria for the diagnosis of ARDS as described in PALICC between one-month and 18-years-of-age and treated in the pediatric intensive care unit were included in the study[1]. Patients were defined as PARDS if they met PALICC criteria: hypoxemia ≤ 7 days after a known insult, new infiltration on radiograph, and $PaO_2/FIO_2 \leq 300$ for subjects on non-invasive support (full-face oronasal mask with continuous positive airway pressure ≥ 5 cmH_2O), or Oxygen index (OI) ≥ 4 for subjects on invasive support. Five patients with cyanotic heart disease, 22 patients within 7 days of cardiopulmonary bypass, and three patients preparing for or recovering from cardiac intervention were excluded from the study.

PALICC recommendations were taken as a reference for the diagnosis and staging the severity of ARDS[1]. A pressure-controlled mode was used in all patients, and preventive mechanical ventilation strategies were used in patients who received invasive mechanical ventilation support. In patients with invasive ventilation, the oxygen index or the oxygen saturation index was used to evaluate the oxygenation status, depending on the arterial blood gas possibility, and in patients with non-invasive ventilation, PAO_2/FiO_2 or SpO_2/FiO_2 rates were used[12,13]. The severity of lung disease is stratified into mild, moderate, and severe groups considering worst oxygenation status[1]. The incremental change was considered in recruitment maneuver. Positive end-expiratory pressure (PEEP) and peak inspiratory pressure (PIP) were increased by 5 cmH_2O every 30 seconds to a maximum of 20 mmH_2O and 40 mmH_2O, respectively. Patients were maintained at their current respiratory rate during recruitment maneuver. The pressures were decreased gradually to the final level before the recruitment maneuver. The Paediatric Index of Mortality (PIM-2) was used to evaluate disease severity on admission[14]. The PIM-2 was developed from and subsequently validated in a general mix of ICU patients that can be used to predict the risk of death for pediatric patients admitted to intensive care. Pediatric Logistic Organ Dysfunction (PELOD) scoring was used to evaluate organ failure[15]. PELOD is a frequently used scoring system to describe multiple organ dysfunction in pediatric patients. Providing enteral feeding within

the first 48 hours was defined as early enteral feeding[10].

Patients' ages, genders, primary diseases, PIM-2 and PELOD scores, ventilator-free days at 28 days (VFD), PICU and hospital stay lengths, mechanical ventilator parameters, worst values of oxygenation states, inotropic and other supportive treatments, complications, and causes of death developed during follow-up were recorded. The length of intubation was considered as the number of days between intubation and tracheostomy process in patients who required tracheostomy due to various reasons. Patients with tracheostomy at the time of PICU admission were not included in the calculation of VFD.

Statistical analysis

The IBM SPSS Statistics Version 20.0 package program was used for the statistical analysis of the data. Categorical measurements (characteristics of patients) were summarized as numbers and percentages, while numerical measurements were summarized as median and interquartile range (IQR) values. We used the chi-square test or Fisher exact test, whichever was appropriate, to compare categorical variables of ARDS stage and ARDS etiology. In comparison with numerical measurements between ARDS stage/etiology groups, Student's t-test or the Mann–Whitney U test was used, as appropriate. The level of statistical significance was accepted to be 0.05 in all tests.

RESULTS

Our study included 32 patients who were hospitalized in the PICU and diagnosed with ARDS. The median age of patients was 44 (IQR, 18-132) months, and 16 of the patients were male (50.0%). The predicted mortality rate of the patients was 47.1%, according to PIM-2 scores, and the PELOD score was 20.5. The characteristics of the patients are given in Table 1.

A recruitment maneuver was performed on 29 patients (90.6%). Prone position was applied to 11 patients (34.3%), surfactant treatment to 14 (43.8%), iNO to 1 (3.0%), blood product transfusion to 13 (40.6%), and inotropic therapy to 16 (50.0%). High-frequency oscillatory ventilation was applied to three patients (9.3%), and four patients (12.5%) received extracorporeal membrane oxygenation (ECMO) support. Early enteral feeding was provided to 28 patients (87.5%), and the median duration of providing enteral feeding was 10 (IQR, 4-18) hours. During their treatment, 31 patients (97%) remained in a negative fluid balance, and one patient (3%) remained in a positive fluid balance.

Table 1. Characteristics of patients

Variable	n(%)
Sex (Male)	16 (50.0)
Age (months)	44 (18-132)
Primary disease	
Neurological	10 (31.3)
Nephrologic	4 (12.5)
Hemato-Oncologic	4 (12.5)
Immunological	4 (12.5)
Metabolic	3 (9.1)
Cardiac	1 (3.0)
None	6 (18.8)
ARDS stage	
Stage 1 (Mild)	14 (43.8)
Stage 2 (Moderate)	9 (28.1)
Stage 3 (Severe)	9 (28.1)
Complication	
Ventilator associated pneumonia	7 (21.9)
Pneumothorax	4 (12.5)
Urinary system infection	2 (6.3)
Blood stream infection	1 (3.1)
Death	2 (6.3)

ARDS: Acute respiratory distress syndrome

When patients were evaluated according to their worst values of oxygenation status, 14 had developed mild ARDS (43.8%), nine patients (28.1%) had moderate, and nine patients (28.1%) had severe ARDS. The relationship of some characteristics of the patients with the ARDS stages were evaluated (Table 2). When the distribution of etiologic causes by disease stage was considered, five of the pulmonary ARDS cases (20.0%) were Stage 3, and four of the non-pulmonary ARDS cases (57.1%) were Stage 3. It was seen that non-pulmonary ARDS progressed mostly in severe stages ($p = 0.039$). Higher PIM-2 scores were associated with severe ARDS development ($p = 0.010$). ARDS stages were also found to be associated with higher PIP, PEEP, and mean airway pressure ($p = 0.001$). Although there was a relationship between the stage of ARDS and ventilator-free days, it was not statistically significant ($p = 0.054$). There was no statistically significant relationship between the ARDS stage and the length of PICU and hospital stay ($p > 0.05$).

Table 2. Relationship of some clinical conditions with ARDS stages

	Cohort (n=32)	ARDS Stage			p
		Stage 1 (n=14)	Stage 2 (n=9)	Stage 3 (n=9)	
ARDS n(%)					
Pulmonary	25 (78.1)	13 (52.0)	7 (28.0)	5 (20.0)	**0.039**
Non-pulmonary	7 (21.9)	1 (14.3)	2 (28.6)	4 (57.1)	
PIM-2 (%)	47.1 (23.8-65.7)	28.9 (23.7-57.5)	24.0 (16.0-59.6)	65.7 (55.6-93.3)	**0.010**
PELOD	20.5 (13.8-30.8)	19.7 (11-50)	21.4 (11-31)	33.1 (11-51)	**0.043**
Maximum PIP	28 (24-32)	24 (21-28)	28 (26-30)	35 (32-36)	**0.001**
Maximum PEEP	8 (6-10)	7 (6-8)	7 (7-10)	10 (9-12)	**0.001**
Maximum MAP	16 (12-19)	12 (11-16)	14 (13-17)	20 (19-21)	**0.001**
28-day VFD (days)*	17 (5-22)	18 (15-23)	18 (15-22)	0 (0-19)	0.054
Length of PICU stay (days)	20 (13-36)	18 (14-37)	19 (13-25)	35 (13-50)	0.542
Length of hospital stay (days)	33 (23-51)	38 (23-43)	28 (19-58)	35 (18-66)	0.904

ARDS: Acute respiratory distress syndrome, MAP: Mean airway pressure, OI: Oxygen index, OSI: Oxygen saturation index, PEEP: Positive end-expiratory pressure, PELOD: Pediatric Logistic Organ Dysfunction, PICU: Pediatric intensive care unit, PIM-2: Pediatric Index of Mortality, PIP: Peak inspiratory pressure, VFD: Ventilator free-days; *2 patients of Stage 1 and 1 patient of Stage 2 were excluded due to tracheostomy at the admission to the PICU.

Table 3. Relationship of some clinical conditions with ARDS etiology

	Pulmonary (n=25)	Non-pulmonary (n=7)	p
PIM-2 (%)	28.9 (23.7-60.1)	65.7 (55.4-95.6)	**0.006**
PELOD	20.0 (12.0-25.5)	31.0 (20.0-42.0)	**0.030**
Maximum PIP	26 (22-30)	29 (32-35)	**0.008**
Maximum PEEP	7 (6-9)	11 (10-12)	**0.001**
Maximum MAP	14 (11-16)	20 (19-22)	**0.001**
OI	8.6 (6.6-15.5)	18.6 (14.3-31.0)	**0.020**
OSI	7.6 (6.3-12.4)	15.5 (13.1-20.7)	**0.001**
28-day VFD (days)*	19 (15-23)	0 (0-16)	**0.015**
Length of PICU stay (days)	16 (12-32)	27 (15-50)	0.242
Length of hospital stay (days)	28 (14-43)	59 (35-66)	**0.007**

ARDS: Acute respiratory distress syndrome, MAP: Mean airway pressure, OI: Oxygen index, OSI: Oxygen saturation index, PEEP: Positive end-expiratory pressure, PELOD: Pediatric Logistic Organ Dysfunction, PICU: Pediatric intensive care unit, PIM-2: Pediatric Index of Mortality, PIP: Peak inspiratory pressure, VFD: Ventilator free-days; *3 patients of pulmonary group were excluded due to tracheostomy at the admission to the PICU.

When the causes were evaluated it was found that ARDS originated from pulmonary causes in 25 patients (78.1%) and non-pulmonary causes in seven patients (21.9%). While sepsis was the cause of all non-pulmonary ARDS, 24 of the pulmonary ARDS developed due to pneumonia, and one developed due to aspiration pneumonia. The resource of sepsis among non-pulmonary ARDS patients was blood stream in five patients, and urinary system in two patients. The disease severity scores of non-pulmonary ARDS patients were higher; more support was needed during hospitalization, and these differences were significant ($p < 0.05$). The comparisons of pulmonary and non-pulmonary ARDS data are given in Table 3.

The most common complications were nosocomial infection (31.3%) and pneumothorax (12.5%). While

one patient died due to multiple organ failure, and one patient from refractory hypoxemia, the mortality rate was 6.3%. Three (75.0%) of the four patients with ECMO support survived. Ventilator-free day duration was 17 (IQR, 5-22) days; the length of PICU stay was 20 (IQR, 13-36) days, and the length of hospital stay was 33 (IQR, 23-51) days.

DISCUSSION

Despite the developments in the lung-protective low-tidal-volume ventilation strategy in the last 20 years, pediatric ARDS-related mortality is still high[1]. The observational PARDIE study, which included 145 international centers and evaluated the effectiveness of the PALICC definition, was published in 2019[2]. According to this study, ARDS affects 3% of PICU patients, and the new ARDS classification successfully predicts mortality risk. However, as is known, the lung-protective mechanical ventilation strategy, early enteral nutrition, negative fluid balance, and adequacy of hospital resources (such as equipment, consumables, and personnel) cause different survival rates among centers[9]. We used the PALICC definition in our study and achieved better results than previously published studies.

ARDS can develop due to many different physiological mechanisms with similar clinical features as a result of various pulmonary and non-pulmonary etiologies. ARDS with pulmonary causes may progress more severely than ARDS due to extrapulmonary causes. In our study, 78.1% of the patients had pulmonary, and 21.9% had non-pulmonary ARDS. While all non-pulmonary ARDS cases developed due to sepsis, 24 of the pulmonary ARDS cases developed due to pneumonia. Non-pulmonary sepsis was shown to be associated with higher mortality rates[16,17]. In our study, the disease severity (PIM-2 and PELOD scores) of patients who developed non-pulmonary ARDS was more severe. Therefore, non-pulmonary ARDS patients needed more mechanical ventilation support. The mortality rate in pulmonary ARDS was 4.0%, while the mortality rate of non-pulmonary ARDS was 14.3%. Due to the insufficient number of patients, statistical analysis could not be performed.

The lung-protective mechanical ventilation strategy is known to reduce mortality and morbidity in the management of ARDS. According to PALICC, medium-level raised PEEP (10–15 cm H_2O) values have been suggested, and in children with severe ARDS who need PEEP over 15 cm H_2O, plateau pressure limitations should be considered, and oxygen delivery with respiratory system compliance and hemodynamic markers should be closely monitored[1]. In their prospective studies, Wong et al. applied the lung-protective mechanical ventilation strategy protocol they created in line with PALICC recommendations to 63 of 132 pediatric patients with ARDS[18]. When disease severity, organ dysfunction, and oxygenation indices were stabilized, the lung-protective mechanical ventilation protocol was associated with a lower mortality rate. In our study, protective mechanical ventilation strategies, low tidal volume, limited peak pressure, sufficient PEEP, permissive hypoxemia, and permissive hypercapnia were applied in all patients. It was observed that maximum PEEP support applied to patients increased in direct proportion to ARDS stages.

American Society for Parenteral and Enteral Nutrition (ASPEN) recommends providing enteral feeding in the early period (24–48 hours) if there are no contraindications in patients with ARDS[10]. They also recommend preparing a nutritional plan to facilitate the healing of pediatric patients with ARDS; enteral feeding must be assured as soon as possible to maintain their growth and provide their metabolic needs. Studies have shown that a positive fluid load adversely affects clinical outcomes and increases mortality rates in patients with ARDS[6,19]. Fluid therapy management that provides adequate intravascular fluid volume and optimal oxygenation without positive fluid balance in pediatric patients with ARDS has been recommended[11]. In our study, early enteral nutrition and negative fluid balance were adopted as a treatment strategy. Early enteral feeding was achieved in 87.5% of patients, and a negative fluid balance was achieved in 96.9%.

Today, there are several scores used to assess the severity of diseases and mortality probabilities of pediatric patients who need intensive care. PIM-2 is a reliable marker used to assess the disease severity within the first hour of PICU admission. In our study, when mortality scores of the patients were evaluated according to ARDS stages, we found that the patients with a high PIM-2 score developed ARDS at a later stage. While there was no significant difference between PIM-2 scores of patients in Stage 1 and Stage 2 (28.9 and 24.0), the PIM-2 score of patients who developed Stage 3 ARDS was 65.7, and it was statistically significant ($p = 0.010$). In addition, there was a positive relationship between the ARDS stage

and PELOD scores (p = 0.043). Multi-center studies have shown that any additional organ failure increases mortality in pediatric patients with ARDS[5,16].

ARDS is a serious problem with high morbidity and mortality. Mortality is high in pediatric ARDS, and this rate varies according to the differences in the etiology of patients from different centers included in the study, clinical practices, and health care competency[9]. A multi-center study conducted by Khemani et al. showed a significant difference in pediatric ARDS mortality between high and low-income countries (15% and 31%, respectively)[2]. In a USA study that included two large, academic PICUs, conducted with 798 children, the reported mortality rate was 19%[5]. In a single-center study conducted in India, the mortality rate was found to be 45%[6]. In our study, while the mortality rate was 6.3% in the whole cohort, four patients were supported with ECMO, and the survival rate was 75%. The lung-protective mechanical ventilation support, early enteral nutrition, negative fluid balance practices, and the adequacy of our hospital resources led to a successful survival rate in our study.

Our study includes some limitations. First, because of the nature of the observational study without control group, it is unfeasible to exactly evaluate the influence of the PALICC recommendations on outcomes. Small sample size also complicated to carry out multifactorial analysis for outcomes.

As a result, ARDS remains an important cause of mortality in PICUs. In patients with high PIM-2 and PELOD scores, attention must be given to the development of severe ARDS. The lung-protective mechanical ventilation support, early enteral nutrition, negative fluid balance practices, and the adequacy of hospital resources led to a successful survival rate in our study. However, multicenter randomized controlled trials are needed on this subject.

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