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Determination of the Incidence of Medical Device-related Pressure Injury in Pediatric Intensive Care Unit: A Single-center Study

Çocuk Yoğun Bakım Ünitesinde Tıbbi Alet Kaynaklı Basınç Yaralanma İnsidansının Belirlenmesi: Tek Merkezli Bir Çalışma

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Abstract

Introduction: To determine the incidence of pressure injuries caused by medical devices in the pediatric intensive care unit.

Methods: It is a prospective study of observational analytical type. Strengthening the Reporting of Observational Studies in Epidemiology guide was used in the study. It was conducted with 117 children in the pediatric intensive care unit of a gynecology and pediatrics hospital in the Southeastern Anatolia Region of Turkey between 01.01.2023 and 30.06.2023. In the study, data were collected using the information form together with the Braden and Braden Q scale. Data were analyzed with SPSS 25.0 statistical analysis program.

Results: It was determined that 53% of the children included in the study were male, 24.8% were hospitalized due to neurological diseases, 55.6% had chronic diseases and 74% were fed enterally. It was determined that the average age of the children was 37.46±40.98 (months), the average body weight was 15291.45±17364 (g), and the average height was 83.06±23.85 (cm). In the study, pressure injuries caused by medical devices occurred in 26.5% of the children, 35.7% of these pressure injuries caused by medical devices were 1st degree, 17.6% were ungraded wounds (Mucosa), 48.5% of the children were injured. It was observed that 2 injuries occurred in 100,000 children and 44.4% of the children had 5 or more medical devices. It was determined that the average number of days for injuries caused by medical devices was 38.63±41.91 days, the frequency of injuries per 1000 patient days was 14.98, and the rate of injuries caused by medical devices was 5.9%.

Conclusion: The study showed that a high rate of pressure injuries occurred due to medical devices. Appropriate care should be planned for children admitted to pediatric intensive care units by assessing the risk of injury caused by medical devices.

Keywords: Pediatric intensive care unit, pressure injuries, medical device-induced pressure injury, wound incidence

Öz

Giriş: Çocuk yoğun bakım ünitesinde oluşan tıbbi alet kaynaklı basınç yaralanması sıklığını belirlemektir.

Yöntemler: Gözlemsel analitik tipte ileriye yönelik bir çalışmadır. Çalışmada *Strengthening the Reporting of Observational Studies in Epidemiology* kılavuzu kullanıldı. Türkiye'nin Güneydoğu Anadolu Bölgesi'nde bir kadın doğum ve çocuk hastalıkları hastanesinin çocuk yoğun bakım ünitesinde 01.01.2023-30.06.2023 tarihleri arasında 117 çocuk ile yapıldı. Çalışmada veriler Braden ve Braden Q Ölçeği ile birlikte bilgi formu kullanılarak toplandı. Veriler SPSS 25.0 istatistiksel analiz programı ile çözümlendi.

Bulgular: Çalışmaya alınan çocukların %53'ünün erkek olduğu, %24,8'inin nörolojik hastalıklar nedeniyle yattığı, %55,6'sının süreğen hastalığı bulunduğu ve %74'ünün enteral yolla beslendiği belirlendi. Çocukların yaş ortalamasının 37,46±40,98 (ay), vücut ağırlık ortalamasının 15291,45±17364 (gr), boy uzunluğu ortalamasının 83,06±23,85 (cm) olduğu saptandı. Çalışmada çocukların %26,5'inde tıbbi alet kaynaklı basınç yaralanması oluştuğu, bu oluşan tıbbi alet kaynaklı basınç yaralanmaların %35,7'sinin 1. derece olduğu, %17,6'sının derecelendirilmeyen yara (mukozada), çocukların %48,5'inde 2 tane yaralanma oluştuğu ve çocukların %44,4'ünde 5 ve üstü tıbbi alet takılı olduğu görüldü. Tıbbi alet kaynaklı yaralanmanın oluşma gün ortalamasının 38,63±41,91 gün olduğu, 1000 hasta günü başına yara görülme sıklığının 14,98 ve tıbbi alet sayısının yaralanma oluşmasının oranı %5,9 olduğu belirlendi.

Sonuç: Çalışmada yüksek oranda tıbbi alet kaynaklı basınç yaralanmalarının oluştuğu görüldü. Çocuk yoğun bakım ünitelerine yatırılan çocuklara tıbbi alet kaynaklı yaralanma risk değerlendirmesi yapılarak uygun bakım planlanmalıdır.

Anahtar Kelimeler: Çocuk yoğun bakım ünitesi, basınç yaralanmaları, tıbbi alet kaynaklı basınç yaralanması, yara insidans

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Introduction

With scientific progress and technological innovations, the role of technology in the treatment and care of patients has increased. The use of technology in treatment and care services causes some problems as well as benefits. One of these problems is medical-device related pressure injuries (MDRPI) and accordingly, the disruption of skin integrity.[1] MDRPI is defined as localized injuries to the skin or subcutaneous tissues, including the mucosa, caused by intense/continuous pressure exerted on the skin/mucosa by medical instruments used for diagnosis and treatment purposes. The most important difference between a pressure injury (PI) and a MDRPI is that the force exerted by an instrument strapped or taped to the body, not by body weight, plays a significant role in the development of a MDRPI.[2-5] While medical instruments alone can cause skin-damaging pressure, they can also alter the microclimate of the skin by creating heat and moisture between the equipment and the skin, which can increase the risk of skin deterioration. In the first large-scale study emphasizing the importance of MDRPI, the incidence and prevalence of pressure injuries were examined by following 2.178 adult patients over an eight-month period.[6] As a result of the study, it was reported that the rate of hospital-acquired pressure injuries was 5.4% and 34.5% of these injuries developed in association with medical instruments. It was also stated that if a patient had a medical instrument, the likelihood of developing any type of PI would be 2.4 times higher. The first integrative study examining the factors associated with MDRPI in hospitalized children was conducted by Murray et al.[1] in 2013. The study included 32 articles with evidence levels ranging from IV to VII and a total of 2,745 sick children. A total of 18 medical devices causing pressure injuries were identified and 138 pressure injuries caused by medical devices were mentioned.[1] In 2016, the National Pressure Ulcer Advisory Panel defined MDRPIs as those resulting from the use of medical instruments for diagnostic or therapeutic purposes and as PIs in which the shape of the injured part was consistent with the medical instruments.[2] In 2017 position paper, the Wound, Ostomy and Continence Nurses' Society has stated that medical instruments can cause PIs in all age groups, primarily in acute intensive care settings, and in long-term care settings and home care. It has made a number of recommendations, including the identification of risk factors as the basis for the development of risk assessment tools, best practices, quality improvement interventions, and safe materials, and the conduct of research to prevent the occurrence of MDRPI in all health care settings.[7,8] In February 2019, an international group of medical, clinical and bioengineering experts agreed that medical instruments or non-medical objects that came into contact with or compressed the skin could cause cellular and tissue-level disruption, based on their evidence-based reviews of the etiology, assessment, prevention and management of MDRPI. In their statement, the instruments most commonly associated with MDRPI and the biomechanical causes of the risks they posed were identified and discussed. They also assessed which bioengineering designs and technologies could be used to prevent MDRPI, how to alleviate the frictional force on tissues and how to optimize the microclimate.[3]

MDRPIs are a significant problem in the pediatric population. In studies evaluating the incidence and risk factors of pressure injuries in hospitalized infants and children, it has been reported that all PIs are largely related to the use of medical instruments, and the incidence of MDRPI varied between 7% and 36.2%. [3,4,9-15] In studies conducted in Turkey, it has been reported that the prevalence of MDRPI in pediatric age groups ranged between 6.8% and 21%. [9,12]

The types and numbers of medical instruments frequently used in pediatric clinics vary according to the patient population, which creates variability in instrument-related risk. Data monitoring for MDRPI may contribute to more effective evaluation of strategies to prevent such adverse events and to the improvements in care. Today, research carried out to determine trends in the prevalence and incidence of MDRPI is becoming more important. The incidence study on pediatric MDRPI shows the likelihood of occurrence of MDRPI, helps to identify its causes and provides a more accurate understanding of the quality of care for hospitalized patients. The use of MDRPI rate per 1000 device-days for each device type is a reliable measure that reveals the true extent of the causes as it also addresses the time factor. The aim of this study was to examine the incidence of MDRPIs in a pediatric intensive care unit (PICU) and to determine the relationship between the medical instruments used and MDRPIs, the factors causing this health problem and the risk situations.

Materials and Methods

Research Type

It is an observational analytic type prospective study. The study was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology guideline used in observational studies.[16]

Study Population and Sample

The sample of the study consisted of children hospitalized in the PICU of a maternity and child hospital located in the Southeastern Anatolia Region of Turkey between 01.01.2023

and 30.06.2023 (for 6 months). During the specified period, 142 children were hospitalized in the PICU; however, 3 of these children were excluded from the study because they had PI when they arrived at the unit, 2 due to having skin diseases, and 20 due to being hospitalized daily. The study was conducted with 117 children who were hospitalized in the PICU and met the inclusion criteria.

Children between the ages of 1 month and 18 years, who did not have any skin problems, who had at least one medical device, and whose parents gave written and verbal consent were included in the study. Day cases and those with skin diseases were not included in the study.

Data Collection

The data of the study were collected by the researcher, who was working as a nurse in the PICU, by using the Braden Q scale, Braden risk assessment scale, information form including clinical and socio-demographic information of the children and MDRPI staging form.

Braden Q Scale

Curley et al.[10] developed the Braden Q scale by adapting the Braden scale for adults to children. They added tissue perfusion and oxygenation items to the Braden scale. The scale is an assessment tool used to evaluate the risk of pressure ulcer development in children aged 28 days to 5 years. Each item in the scale is scored from 1 to 4. For the interpretation of the scores obtained from the scale, 16-23 points are considered as moderate risk for PI development, 13-15 points as serious risk, 10-12 points as high risk, and 9 and lower points as very high risk.[10] The Turkish validity and reliability study of the scale was conducted by Güneş and Törüner[17] and the Cronbach alpha value of the scale was found to be 0.80.

Braden Risk Assessment Scale

It was developed by Braden et al. in 1987. The scale consists of 6 subscales: Sensory perception, skin moisture, activity, mobility, friction and shear, and nutritional status. It was adapted to the Turkish population by Oğuz and Olgun[18] and then for the second time by Pınar and Oğuz.[19] The total score of the scale ranges from 6 to 23; 12 points and below are considered very risky, 13-14 points are considered moderately risky and 15-16 points are considered low risky. In the present study, risk assessment of children over 5 years of age was performed with the Braden scale.[18,19]

Information Form

It was composed of 17 questions formed by reviewing the literature including information on gender, body weight, height and clinical characteristics etc. of the children.[10,13,18,19]

MDRPI Staging Form

The form was developed by the investigators according to the staging form accepted by the National PI Advisory Panel.[2] Skin pressure injuries were staged using the MDRPI staging system. For mucosal injuries, the staging system for skin pressure injuries was not applied, and they were considered as "mucosal membrane pressure injury".

Statistical Analysis

The data obtained in the study were uploaded to the SPSS 25.0 program and analyzed. Frequency, percentage, mean, minimum, maximum and standard deviation analyses were performed. In addition, MDRPI per 1000 patient days was calculated using the formula (number of wounds formed/ total number of hospitalization days * 1000).

Ethical Dimension of the Study

Before starting the study, ethics committee approval was obtained from the Ethics Committee of a Kilis 7 Aralık University with the decision numbered 2021/11-6 and research permission was obtained from the provincial health directorate to which the hospital was affiliated. Written and verbal consents were obtained from the families of the children for inclusion in the study. The study was conducted in accordance with the Declaration of Helsinki.

Results

Demographic and clinical characteristics of the pediatric patients evaluated in this study are summarized in Table 1. It was observed that 53% of the children participating in the study were male, neurological diseases (24.8%), cardiovascular problems (19.7%) and respiratory system disorders (17.1%) were found to be prominent among the reasons for hospitalization, and the presence of chronic diseases was determined in 55.6%. When the nutritional status was analyzed, it was observed that most of the children (74.5%) were fed with enteral nutrition. The mean age of the children was 37.46±40.98 months, the mean body weight was 15291.45±17364 g and the mean height was 83.06±23.85 cm. The mean values for the vital signs of the children were as follows: heart rate 119.66±20.63 min, respiratory rate 28.81±6.43 min, systolic blood pressure 102.72±12.63 mmHg and diastolic blood pressure 61.09±12.57 mmHg. The mean oxygen saturation, hemoglobin and serum albumin values of the children included in the study were 98.56±1.90%, 10.71±1.09 g/dL and 34.3±3.67 mg/dL, respectively. The mean Braden Q scale score was 10.36±1.90, the mean Braden scale score was 10.77±2.46 and the mean duration of hospitalization was 31.94±37.55 days (Table 1).

It was detected that a total of 941 medical devices were used in pediatric patients hospitalized in PICU. When the distribution of these devices was analyzed, it was seen that pulse oximetry probe (POP), blood pressure cuff and infusion pump were used in all of the children and the ratio was 12.4% for each of them in the total devices used. These devices were followed by electrocardiography (ECG) electrodes (12.2%), nasogastric catheter (NGS) (11.8%), and foley catheters (10.3%). Endotracheal tube (ETT) and intravenous catheters were used at similar rates (7.2%). These devices were followed by central venous catheters 5.4%, tracheostomy tubes 3.6%, nasal oxygen cannulas 1.8%, continuous positive airway pressure (CPAP) masks and heating devices 1% each, hemodialysis catheters 0.7% and gastrostomy tubes 0.6%, respectively (Table 2).

It was determined that 26.5% of pediatric patients treated in the PICU had MDRPI. When the number of MDRPIs was analyzed, it was found that 38.6% of the children had one MDRPI, 48.4% had two MDRPIs, 6.5% had three MDRPIs and 6.5% had four MDRPIs and the total number of MDRPIs was 56. Of these 56 MDRPIs, 35.7% were classified as grade 1, 39.2% as grade 2 and 7.1% as grade 3. The rate of ungraded PIs that developed in the mucosa was found to be 18.0%. When the number of medical instruments used in each child was analyzed, it was determined that 12.8% had two, 18.9% had three, 23.9% had four, and 44.4% had five or more medical instruments. The mean number of days of MDRPI development was 38.63±41.91 days and the incidence of injuries per 1000 patient days was 14.98. In addition, the ratio of the number of wounds according to the number of medical devices was determined as 5.9% (Table 3).

When Table 4 was analyzed, it was observed that the most common causes of grade 1 MDRPI were POP, ECG electrodes, similarly NGS and tension cuff, respectively. Grade 2 injuries

Table 1. Distribution of socio-demographic and clinical characteristics of pediatric patients (n=117)

Characteristics		**n**	**%**
Sex	Female	55	47.0
	Male	62	53.0
Diagnosis at hospitalization	Neurological diseases	29	24.8
	Cardiovascular	23	19.7
	Respiratory system	20	17.1
	Nervous system	19	16.2
	Metabolic diseases	16	13.7
	Emergency cases	10	8.5
Presence of chronic diseases	Yes	65	55.6
	No	52	44.4
Nutritional status	Oral	20	17.0
	Enteral	87	74.5
	Parenteral	10	8.5
		Mean ± SD	**Min-max**
Age (month)		37.46±40.98	2.0-185.0
Body weight (gram)		15291.45±17364	3000.0-90000.0
Height (cm)		83.06±23.85	54.0-164.0
Heart rate (min)		119.66±20.63	67.0-158.0
Respiratory rate (min)		28.81±6.43	20.0-60.0
Systolic blood pressure (mmHg)		102.72±12.63	78.0-139.0
Diastolic blood pressure (mmHg)		61.09±12.57	34.0-97.0
Saturation level (%)		98.56±1.90	92.0-100.0
Hemoglobin value (gr/dL)		10.71±1.09	6.90-13.8
Serum albumin value (mg/dL)		34.3±3.67	28.42-43.24
Braden Q scale score		10.36±1.90	7.0-15.0
Braden scale score		10.77±2.46	8.0-19.0
Hospitalization day		31.94±37.55	5.00-210.0

SD: Standard deviation

Table 2. Distribution of medical instruments used for children (n=117)

Medical devices used	n	%
Pulse oximeter probe	117	12.4
Tension cuff	117	12.4
Infusion pump	117	12.4
Electrocardiography electrode	115	12.2
Nasogastric catheter	111	11.8
Foley catheter	97	10.3
ETT tube	67	7.2
IV catheter	67	7.2
Central venous catheter	50	5.4
Tracheostomy tube	33	3.6
Nasal oxygen cannula	17	1.8
CPAP mask	10	1.0
Heating device	10	1.0
Hemodialysis catheter	7	0.7
Gastrostomy tube	6	0.6
Total*	941	100.0

*: There are children who used more than one tool, IV: Intravenous, ETT: Endotracheal tube, CPAP: Continuous positive airway pressure

were caused by ETT tube application, NGS and POP in equal rates, ECG electrodes and central venous catheter applications in similar rates, respectively. Grade 3 injuries were lower in number and were equally associated with NGS, POP and ECG electrodes. The causes of MDRPI that could not be evaluated due to the absence of mucosal injury were NGS, EET tube and nasal oxygen cannula, respectively.

In the study, 23.0% of NGS-induced injuries were determined as grade 1, 30.8% as grade 2, 7.7% as grade 3 and 38.5% as ungradable wound mucosa. Of the ETT tube-induced injuries, 30.0% were ungradable wound mucosa, 60% were grade 2 and 10% were grade 3. Of the POP-induced injuries, 50% were grade 1, 40% were grade 2 and 10% were grade 3. Of the injuries caused by ECG electrodes, 71.4% were grade 1 and 28.6% were grade 2. Of the injuries caused by tracheostomy cannula, 50% were grade 1 and 50% were grade 2. In both types of central venous catheter and CPAP mask injuries, 50% were grade 1 and 50% were grade 2. All of the injuries caused by nasal oxygen cannula were found to be ungradable wound mucosa and all of the injuries caused by gastrostomy tube were found to be grade 3. 100% of the Foley catheter injuries were grade 2 (Table 4).

Table 3. Medical-device related pressure injuries in children (n=117)

Medical-device related pressure injuries		n	%
Presence of medical-device related pressure injuries	Yes	31	26.5
	No	86	73.5
The number of wounds in children with medical-device related pressure injuries	1 wound	12	38.6
	2 wounds	15	48.4
	3 wounds	2	6.5
	4 wounds	2	6.5
	Total	**31**	**100.0**
The degree of medical-device related pressure injuries*	1. grade	20	35.7
	2. grade	22	39.2
	3. grade	4	7.1
	Non-graded Wound in mucosa	10	18.0
	Total	**56**	**100.0**
The number of medical devices used	2	15	12.8
	3	22	18.9
	4	28	23.9
	5 and above	52	44.4
	Total	117	100.0
	Mean ± SD	**Min-max**	
Day of the development of medical-device related pressure injuries	38.63±41.91	3.00-180.0	
Incidence of wound development per 1000 patient days	14.98 (56/3.736*1000)		
The ratio of wound number according to the number of medical devices	5.9 (56/941)		

*: More than one MDRPI were observed, MDRPI: Medical-device related pressure injuries, SD: Standard deviation

Table 4. The cause and degree of medical-device related pressure injuries in children (n=117)

Medical device used	1. grade		2. grade		3. grade		Non-graded Wound in mucosa		Total	
	n	%	n	%	n	%	n	%	n	%
Nasogastric catheter	3	23.0	4	30.80	1	7.70	5	38.5	13	100.0
ETT tube	0		6	60.00	1	10.0	3	30.0	10	100.0
Pulse oximeter probe	5	50.0	4	40.00	1	10.0			10	100.0
Electrocardiography electrode	5	71.4	2	28.6	0				7	100.0
Tracheostomy tube	2	50.0	2	50.0	0				4	100.0
Tension cuff	3	75.0	1	25.0	0				4	100.0
Central venous catheter	1	50.0	1	50.0	0				2	100.0
Nasal oxygen cannula			0		0		2	100	2	100.0
CPAP mask	1	50.0	1	50.0	0				2	100.0
Gastrostomy tube	0		0		1	100.0			1	100.0
Foley catheter	0		1	100.00	0				1	100.0
Total	20	35.7	22	39.2	4	7.1	10	18.0	56	100.0

CPAP: Continuous positive airway pressure, ETT: Endotracheal tube

Discussion

In the study conducted to determine the incidence of MDRPI in PICU, patients who met the inclusion criteria were observed by the researcher for 6 months between 01.01.2023 and 30.06.2023 and the data obtained were analyzed and discussed.

It was determined that most of the children followed up in the study were male, the mean age was 3 years, the leading reason for hospitalization was neurological diseases, more than half of them had chronic diseases and the majority of them were enterally fed. Their clinical values were within normal ranges and they were found to be at risk according to the evaluation of Braden scales. It is reported that most of the children hospitalized in PICUs are under 5 years of age, those with chronic diseases have more severe disease course and neurological patients should be hospitalized to protect the brain. It is known that patients hospitalized in PICUs are at risk for pressure injuries due to their poor clinical status, the device they are attached to or their inability to move due to unconsciousness. We can say that the fact that the clinical values of the children in the study were within normal limits was due to the treatment in the clinic. Semerci et al.[12] conducted a descriptive and retrospective study on 6.350 children, using data obtained in PICUs, Neonatal Intensive Care Units (NICUs) and Pediatric Clinics and they found that the prevalence of PI was 2.25% in all patients and 6.04% in PICU patients. They reported that the majority of the children were boys mostly in the age range from 0 month to 12 months and a total of 143 pressure injuries occurred in 59 children. At the same time, it was reported that medical instrument-induced pressure injuries occurred in 21% of patients hospitalized in PICU.[12] In a study performed by Başbakkal et al.[9] medical instrument-induced pressure injuries were reported to have occurred in 96 patients. It was determined that the majority of the children included in the study were male, 56 medical instrument-induced pressure injuries occurred in 31 children and NG, ETT and POP mostly caused pressure injuries. Children hospitalized in the PICU are compatible with previous studies in terms of the occurrence of pressure injuries caused by medical instruments.

In the study, the incidence of injuries per 1000 patient days was 14.98 and the number of medical instruments was 5.9%. In a study by Başbakkal et al.[9], it was reported that the incidence of injuries was 43.4 per 1000 patient days and 6.8% of medical instruments caused pressure injuries. In a study by Shimura et al.[20], it was reported that the occurrence of pressure injuries caused by medical instruments was 4.6 per 1000 patient days. In another study conducted in the United States of America in 8 hospitals and with 625 children, they found that the occurrence of medical instrument-induced pressure injuries was in 7 days per 1000 patient days.[13] The difference in medical instrument-induced injuries per 1000 patient days in the studies may be thought to be due to the conditions of the patients followed in countries, regions and clinics.

In the study, it was determined that NG, ETT and POP were the first three instruments causing medical instrument-related injuries. It can be thought that NG, ETT and POP are the most commonly used medical devices in PICUs, and at the same time, the areas where these devices are attached are sensitive. It is estimated that MDRPI develops due to the sensitivity of the regions where the NG and ETT tubes are attached and it

is very difficult to prevent the pressure of these instruments attached there. Başbakkal et al.[9] found that NG, ETT and ECG electrode were the most common causes of pressure injuries caused by medical devices. Kim et al.[21] reported that the rate of pressure injuries related to medical instruments was 11.9% in a study on 184 pediatric patients in the PICU of a university hospital in Korea and 54.2% of these injuries were caused by intubation tubes, 37.5% by high-flow oxygen cannulas and 8.3% by saturation probes. In a 5-year study conducted nationwide in pediatric and NICUs, Ventilacion et al.[22] found that 50% of pressure injuries were caused by nasal intubation tubes. In our study and other studies conducted in the literature, it was observed that the instruments causing MDRPIs were similar.

These rates vary between 1% and 27% in PICUs and NICUs.[23,24] Kohr and Curley[23] found that the rate of pressure-related injuries in pediatric patients was 27.7% in a study conducted in Switzerland. In a study conducted by Pellegrino et al.[24] on 523 children in different hospitals in Brazil, they reported a hospital-acquired PI rate of 7.1%; 25% of pressure injuries were associated with medical devices and 94% were observed in children with medical devices. In a study conducted in Turkey, it was reported that the rate of medical device-related pressure injuries was 37.5%.[9] In the present study, the rate of medical device-related injuries was 26.5%. The high incidence of medical instrument-induced pressure injuries in children is thought to be due to the lower resistance of children's skin to pressure.

In a study by Başbakkal et al.[9] it was reported that 22.9% of children had 1st degree pressure injuries, 89.5% of children with injuries had 5 or more medical devices attached, and 33.3% of medical device-induced pressure injuries were caused by NGS. In another study, it was reported that 24% of medical device-induced pressure injuries in children were 1st degree and most injuries were caused by NGS.[25] In the study, it was observed that 50% of the medical instrument-induced pressure injuries in children were grade 1 and NG was the most common medical instrument causing pressure injuries. In our study and in the literature, it is seen that NG is the medical instrument that most frequently causes MDRPIs. Since there is no adipose tissue under the skin of the nose, it can be stated that even the smallest pressure can prevent circulation and cause injury.

Study Limitations

The study has some limitations. These limitations include the fact that the study was conducted in a certain hospital in a certain region, that health professionals working in the clinic were not investigated because only patients were examined in the study, and that other reasons other than medical devices were not addressed.

Conclusion

As a result of the study, it was observed that MDRPIs developed at a high rate in children. NGS, ETT tubes, POP and ECG electrodes, which are frequently used in PICUs, were found to be the most common causes of MDRPIs. The strength of the study is that it will be used as a source for future research on MDRPIs and will also be used to guide studies on the prevention of MDRPIs. In addition, another strength of the study is that it may lead to the establishment of guidelines and protocols for the prevention of injuries caused by medical devices used in PICUs and it reveals the importance of nursing care.

In order to prevent the development of MDRPI, it is firstly necessary to select the appropriate size of the instrument for the child, to fix the instrument correctly and to evaluate the fixation tension regularly, to prefer products that minimize tissue damage, and to follow the manufacturer's recommendations on the use and care of the instrument. However, it is critical to assess the skin and mucosa under and around the medical instrument to detect early signs of pressure. Regular repositioning of the medical instrument will help to reduce the shear force of the pressure at the interface of the skin and the instrument and redistribute the pressure. Emphasis should be given on using a prophylactic dressing under the instrument and discontinuing the use of the instrument as soon as possible to reduce the risk of MDRPI.

Priority should be given to the education of healthcare team members and patient relatives about the developmental potential of PI. Assessment of the child, interventions applied and ongoing care needs should be recorded. All healthcare team members should work together (as a team) for creating and implementing a care plan.

This article suggests that standardized, multicomponent interventions for MDRPI prevention (e.g., the use of risk assessment scales to assess the relocation and repositioning of the device, how often to assess the skin and mucosa under and around the medical device, what type of dressings to use between the medical device and the skin, etc.) should be tested in larger-sampled, randomized, controlled trials for children admitted to intensive care units.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Ethics Committee of a Kilis 7 Aralık University with the decision numbered 2021/11-6 and research permission was obtained from the provincial health directorate to which the hospital was affiliated. The study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Written and verbal consents were obtained from the families of the children for inclusion in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ş.Ç., Concept: E.E., A.B.C., Ş.Ç., Design: E.E., A.B.C., Data Collection or Processing: E.E., Ş.Ç., Analysis or Interpretation: E.E., Z.Ç., A.B.C., Ş.Ç., Literature Search: E.E., Z.Ç., Writing: E.E., Z.Ç., A.B.C.

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Effects of Yarrow (Achillea millefolium) Extract on Acute Lung Injury: An Experimental Study

Civanperçemi (Achillea millefolium) Ekstresinin Akut Akciğer Hasarı Üzerindeki Etkileri: Deneysel Bir Çalışma

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Abstract

Introduction: Pro-inflammatory/anti-inflammatory cytokine and oxidant/antioxidant imbalances develop in acute respiratory distress syndrome cases, a significant cause of morbidity and mortality in childhood. This study aims to investigate whether Achillea millefolium, with its antioxidant and anti-inflammatory effects, can be used in the treatment of acute lung injury.

Methods: A total of 36 male Wistar rats were divided into four groups. Acute lung injury was induced by cecal ligation and puncture (CLP). Serum samples were analyzed for TNF-α, IL-10, native thiol, total thiol, and disulfide levels. Lung samples were examined using hematoxylin-eosin staining.

Results: A significant difference was observed in TNF-α values among groups (p=0.003). CLP group showed higher TNF-α values compared to the control group (50.88±5.21 vs. 34.13±9.89 pg/mL, p=0.002), and histologically demonstrated increased scores of lymphocytes, fibroblasts, histiocytes, neutrophils, hemorrhage, and congestion (p=0.006, p<0.001, p=0.007, p=0.001, and p=0.001, respectively). TNF-α values in the CLP+AM group showed a statistically significant decrease compared to the CLP group (50.88±5.21 vs. 38.59±11.65 pg/mL, p=0.035), and histologically, scores of lymphocytes, fibroblasts, histiocytes, neutrophils, hemorrhage, and congestion were reduced (p=0.017, p=0.005, p=0.007, p=0.001, and p=0.02, respectively). CLP+D group also showed a non-significant decrease in TNF-α values compared to the CLP group (50.88±5.21 vs. 39.31±5.09 pg/mL, p=0.055), but histologically, congestion, fibroblast, and histiocyte scores were significantly reduced (p=0.015 and p=0.002,

Öz

Giriş: Çocukluk çağı için önemli bir morbidite ve mortalite nedeni olan akut solunum sıkıntısı sendrom tablolarında pro-enflamatuvar/anti-enflamatuvar sitokin ve oksidan/anti-oksidan dengesizlikleri gelişmektedir. Bu çalışmada antioksidan ve anti-enflamatuvar etkileri olan Achillea millefolium'un akut akciğer hasarı tedavisinde kullanılıp kullanılamayacağını test etmektir.

Yöntemler: Toplam 36 adet erkek Wistar cinsi rat 4 gruba bölündü. Akut akciğer hasarı çekal ligasyon ve punksiyon (CLP) ile oluşturuldu. Serumdan alınan örneklerde TNF-α, IL-10, native tiyol, toplam tiyol ve disülfit seviyeleri çalışıldı. Akciğerden alınan örnekler hematoksilen-eozin boyası ile boyanarak incelendi.

Bulgular: Gruplar arasında TNF-α değerleri açısından anlamlı bir fark saptandı (p=0,003). CLP grubunda kontrol grubuna göre yüksek TNF-α değerleri saptandı (50,88±5,21 vs. 34,13±9,89 pg/mL, p=0,002), histolojik olarak da bu tablolarda lenfosit, fibroblast ve histiosit, nötrofil, hemoraji ve konjesyon skorlarının arttığı gösterilmiştir (sırasıyla p=0,006, p<0,001, p=0,007, p=0,001 ve p=0,001). TNF-α değerleri CLP grubuna göre CLP+AM grubunda istatistiksel açıdan anlamlı bir azalma göstermekteydi (50,88±5,21 vs. 38,59±11,65 pg/mL, p=0,035), histolojik olarak da bu tablolarda lenfosit, fibroblast ve histiosit, nötrofil, hemoraji ve konjesyon skorlarının düşürülebildiği gösterilmiştir (sırasıyla p=0,017, p=0,005, p=0,007, p=0,001 ve p=0,02). Yine CLP grubuna göre CLP+D grubunda da TNF-α değerlerinde istatistiksel açıdan anlamlı olmayan bir azalma vardı (50,88±5,21 vs. 39,31±5,09 pg/mL, p=0,055), ancak histolojik olarak bu tablolarda konjesyon, fibroblast ve histiosit

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Abstract

respectively). There was no statistically significant difference among other groups (p>0.05).

Conclusion: This study suggests that Achillea millefolium, with its anti-inflammatory effect, may be used in the treatment of acute lung injury. However, clinical studies are needed to support these findings.

Keywords: Achillea millefolium, acute lung injury, TNF-α

Öz

skorları istatistiksel olarak anlamlı oranda düşürebildi (sırasıyla p=0,015 ve p=0,002). Diğer gruplar arasında ise istatistiksel olarak anlamlı bir farklılık yoktu (p>0,05).

Sonuç: Bu çalışma Achillea millefolium'un enflamasyonu baskılayıcı etkisi ile akut akciğer hasarının tedavi edilmesinde kullanılabileceğini düşündürmektedir. Bu sonucun klinik çalışmalarla desteklenmesi gerektiğini düşünmekteyiz.

Anahtar Kelimeler: Achillea millefolium, akut akciğer hasarı, TNF-α

Introduction

Acute respiratory distress syndrome (ARDS) is a clinical picture characterized by hypoxia, impaired gas exchange, decreased lung compliance and increased physiological dead spaces as a result of direct or indirect damage to the alveolar structure due to many different causes.[1] ARDS can be seen in all age groups and studies have shown that the incidence in childhood is 2-12.8/100,000.[2,3] ARDS, which is an important cause of morbidity in childhood, also has a serious mortality rate, which has been shown to be 24% in some studies.[4]

There is no specific treatment for ARDS yet; current treatments can be summarized as ventilation or supportive therapies to protect the patient from hypoxia. The high morbidity/mortality rates of ARDS and the lack of a definitive treatment are the main reasons for numerous studies on the issue.

Yarrow [Achillea millefolium (AM)] is a plant from the asteraceae family. Its sesquiterpene and flavonoid compounds give AM antioxidant, anti-inflammatory, antibacterial, antiviral and analgesic properties,[5] for which it is used in traditional medicine for the treatment of hypertension, diabetes mellitus, hepatobiliary disorders, gastrointestinal disorders and wound healing.[6] The aim of this study was to test whether AM, which has antioxidant and anti-inflammatory effects, could be used in the treatment of acute lung injury (ALI).

Materials and Methods

Ethical approval was obtained from Bolu Abant İzzet Baysal University Experimental Animals Ethics Committee (no: 2021/35).

Preparation of AM Extract

Yarrow flowers collected in season were purchased from herbalists. The extraction of AM flowers was carried out by maceration method. Each 100 g of dry powder of AM flower was mixed with 600 mL ethanol (95%) and kept at 25 °C in the dark for two days. After two days, the extract mixture was filtered and the liquid part (ethanol) was transferred into a glass vial.[7] The solvent was then removed using a rotary evaporator set at 40 °C, resulting in AM extract in the vial. This extract was stored in the refrigerator at +4 °C until use.

Establishment of the Experiment Model

Male Wistar rats weighing 200-250 grams were purchased from the Experimental Animal Research and Application Center of our university. The rats were maintained under standard laboratory conditions (relative humidity 50-70%, room temperature 19±2 °C, 12-h light, 12-h dark cycle) and fed a standard diet and water ad libitum. The care of the rats and all surgical procedures were planned in accordance with the Universal Declaration of Animal Rights.

A total of 36 rats were randomly divided equally into 4 groups;

Rats in the sham group underwent laparotomy under xylazine/ketamine anesthesia and the abdominal incision was closed.

Cecal ligation and puncture (CLP) group rats were anesthetized with xylazine/ketamine anesthesia, and after laparotomy, the cecum was exposed and ligated under the ileocecal valve. The distal three-quarters of the cecum was punctured twice with a 20-gauge needle and a small amount of feces was extruded to ensure patency of the punctures. The exposed cecum was returned to the abdomen, after which the abdominal wall was closed in layers using sterile 6-0 surgical sutures. 1 mL of sterile 0.9% NaCl was administered subcutaneously.[8]

Rats in the CLP+AM group received 400 mg/kg AM extract intraperitoneally 14 hours after CLP was performed by the same method.[7]

Rats in the CLP + dexamethasone+AM (CLP+D) group received 400 mg/kg AM extract and 1.5 mg/kg dexamethasone intraperitoneally 14 hours after CLP was performed with the same method.[9]

Blood Collection and Sacrification

All rats were left in wire cages at room temperature and in a brightly lit environment 18 hours after the procedure, 90/10 mg/kg xylazine/ketamine IM anesthesia was administered[10], 5 mL of blood was collected intracardiacly, then the right lung was removed by opening the thorax and fixed in 10%

buffered formaldehyde for histological evaluation. The blood samples were centrifuged at 4000 rpm for 10 min and stored in ependorf tubes at -80 °C until the study.

Biochemical Tests

Blood samples were analyzed for inflammatory and anti-inflammatory cytokines TNF-α and IL-10 as well as thiol-disulfide levels. TNF-α and IL-10 (SinoGeneClon Biotech Co. Ltd., China) levels were determined by micro ELISA method according to the kit instructions. Serum thiol-disulfide homeostasis was analyzed by the new automated measurement method developed by Erel et al.[11], which measured native thiol (NT), total thiol (TT) and disulfide levels.

Histological Assessment

For histomorphologic examination, lung tissues obtained from rats were fixed in 10% formalin. The lung tissues were cut and traced in such a way that the widest surfaces were seen and then embedded in paraffin. Sections with 3 µm thickness were taken from the prepared paraffin blocks and stained with hematoxylin-eosin stain. The sections were evaluated by a pathologist under a LEICA DM 2000 LED light microscope. On histopathological examination of the lung tissue, the presence of lymphocytes around the bronchi and vessels, polymorphonuclear leukocyte infiltration, abscess formation, clustering of lipid-laden macrophages in the alveoli, alveolar hemorrhage, vascular congestion and alveolar wall thickening (fibroblasts and histiocytes in the alveolar wall) were evaluated and scored semiquantitatively from 0 to 4 (0: minimal damage, 1: mild damage, 2: moderate damage, 3: severe damage and 4: maximum damage).[12-14] Hematoxylin eosin stained sections were photographed at different magnifications with the Infinity 3 Analyze Release 6.5 imaging system.

Statistical Analysis

SPSS program was used for statistical analysis. Data were expressed as mean ± standard deviation. The Kolmogorov-Smirnov test was used to analyze the conformity of the groups to normal distribution, and One-Way Analysis of Variance followed by Bonferroni tests were used for biochemical data that showed normal distribution. The Kruskal-Wallis analysis was employed to evaluate the differences in histopathologic scores that did not show normal distribution, and the Mann-Whitney U test was used to compare significant changes between the groups. The value of $p<0.05$ was considered significant.

Results

Biochemical Evaluations

There was no significant difference in TT values between the groups (p=0.089). Lower TT values were found in the CLP group compared to the control group, but this change was not statistically significant (p=0.99). TT values showed a statistically insignificant increase in the CLP+AM group compared to the CLP group (p=1) (Table 1).

There was no significant difference between the groups in terms of NT values (p=0.17). Lower NT values were found in the CLP group compared to the control group, but this difference was not statistically significant (p=0.75). NT values showed a non-statistically significant increase in the CLP + AM group compared to the CLP group (p=1) (Table 1).

There was no significant difference between the groups in terms of disulfide values (p=0.075). Higher disulfide values were found in the CLP group compared to the control group, but this difference was not statistically significant (p=0.1). Disulfide values showed a statistically insignificant decrease in the CLP + AM group compared to the CLP group (p=1) (Table 1).

There was a significant difference between the groups in terms of TNF-α values (p=0.003). Higher TNF-α values were found in the CLP group compared to the control group (50.88±5.21 vs. 34.13±9.89 pg/mL, p=0.002). TNF-α values showed a statistically significant decrease in the CLP + AM group compared to the CLP group (50.88±5.21 vs. 38.59±11.65 pg/mL, p=0.035), and there was also a decrease in TNF-α values in the CLP+D group compared to the CLP group, but this decrease was not statistically significant (50.88±5.21 vs. 39.31±5.09 pg/mL, p=0.055) (Table 1, Figure 1).

There was no significant difference in IL-10 values between the groups (p=0.25). Lower IL-10 values were found in the CLP group compared to the control group, but this change was not statistically significant (p=0.51). IL-10 values showed

Table 1. Variation of biochemical parameters between groups

	Control	CLP	CLP + AM	CLP + D	p
TT (µmol/L)	341.08±61.36	317.65±57.15	324.09±37	275.09±59.78	0.089
NT (µmol/L)	281.99±62.78	243.16±50.75	249.9±24.83	228.52±56.76	0.17
Disulfide (µmol/L)	29.91±13.76	37.24±13.16	37.09±13.06	22.91±10.72	0.075
TNF-α (pg/mL)	34.13±9.89	50.88±5.21	38.59±11.65	39.31±5.09	**0.003**
IL-10 (pg/mL)	11.49±7.5	7.16±2.48	8.27±3.24	10.82±5	0.25

CLP: Cecal ligation and puncture, AM: Achillea millefolium, D: Dexametazon + AM, TT: Total thiol, NT: Native thiol, TNF: Tumor necrosis factor

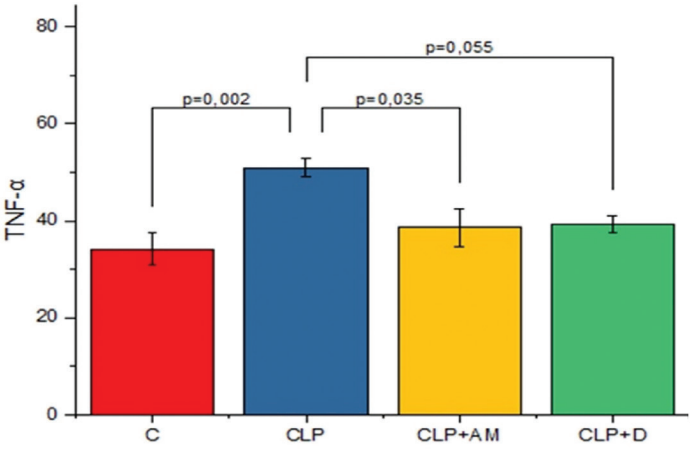

Figure 1. Variation of TNF-α values between groups
C: Control, CLP: Cecal ligation and puncture, AM: Achillea millefolium, D: Dexamethasone + AM, TNF: Tumor necrosis factor

a non-statistically significant increase in the CLP + AM group compared to the CLP group (p=1) (Table 1).

Histological Evaluations

There was a significant difference in lymphocyte scores between the groups (p<0.001). There was a significant difference in lymphocyte scores between CLP and control groups (1.87±0.99 vs. 0.55±0.52, p=0.006) (Figure 2 a-c). Lymphocyte scores were significantly lower in the CLP + AM group compared to the CLP group (1.87±0.99 vs. 0.55±0.52, p=0.017) (Figure 2e), but no such difference was found in the CLP + dexamethasone + AM group (1.87±0.99 vs. 1.77±0.44, p=0.95) (Table 2, Figure 2g, Figure 3a).

There was a significant difference in neutrophil scores between the groups (p=0.004). A significant difference was found in lymphocyte scores between CLP and control groups (1±0.92

Table 2. Comparison of lung histologic scores according to groups

Characteristics	Control	CLP	CLP + AM	CLP + D	p
Lymphocyte*	0.55±0.52	1.87±0.99	0.88±0.33	1.77±0.44	<0.001
Neutrophil*	0.0±0.51	1±0.92	0.0±0.0	0.33±0.7	0.004
Macrophage*	0.0±0.0	0.12±0.35	0.0±0.0	0.33±0.5	0.093
Fibroblast and histiocyte*	0.22±0.44	2.12±0.64	0.77±0.83	0.66±0.7	0.001
Hemorrhage*	0.22±0.44	1.62±0.51	0.33±0.5	1±0.7	<0.001
Congestion*	0.66±0.5	2.62±0.91	1.66±0.5	1.55±0.52	<0.001
Abscess*	0.0±0.0	0.12±0.35	0.0±0.0	0.0±0.0	0.33

CLP: Cecal ligation and puncture, AM: Achillea millefolium, D: Dexametazon + AM, *: Mann-Whitney U

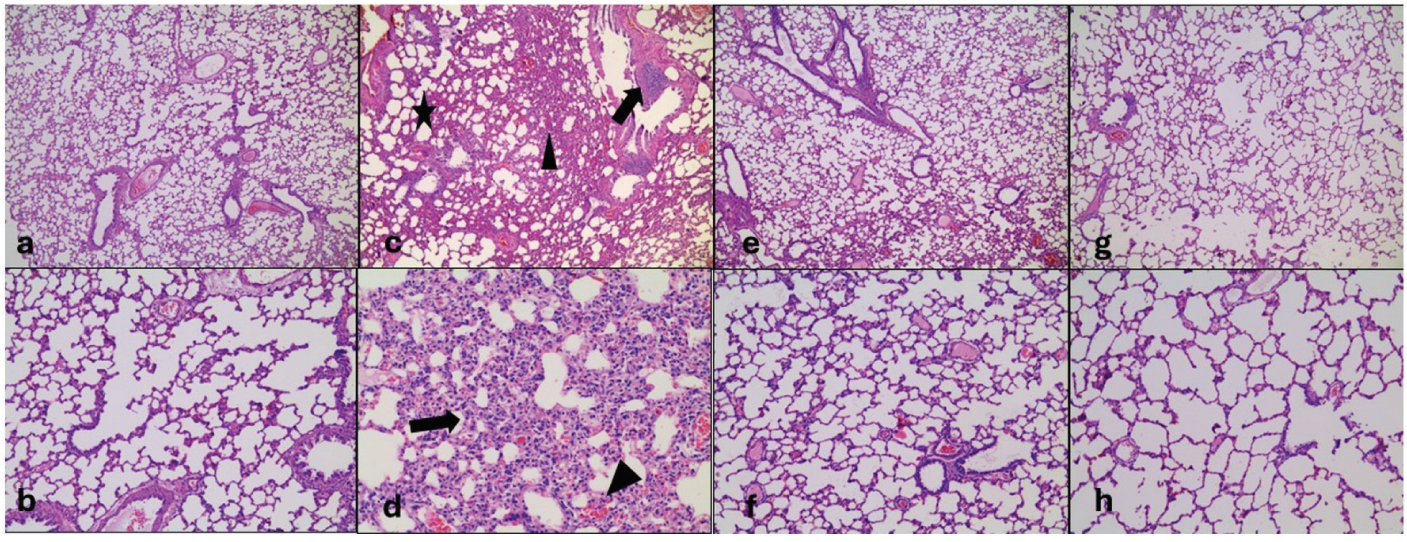

Figure 2. H&E stained sections showing histologic changes in lung tissue (a) Control group: No obvious inflammation and alveolar wall thickening, HEX40; b) Control group: No alveolar hemorrhage and vascular congestion, HEX100; c) CLP group: Peribronchial lymphocytic inflammation is evident (black arrow), alveolar wall thickening (black arrowhead) and areas of alveolar hemorrhage (black asterisk) are present, HEX40; d) CLP group: Alveolar wall thickening and neutrophilic inflammation (black arrow), vascular congestion (black arrowhead), HEX100; e) CLP + Achillea millefolium group: No alveolar wall thickening and inflammation, HEX40; f) CLP+Achillea millefolium group: No alveolar wall thickening and inflammation, mild congestion present, HEX100; g) CLP + dexamethasone + Achillea millefolium group: No significant alveolar damage and inflammation, HEX40; h) CLP + dexamethasone +Achillea millefolium group: No significant alveolar damage and inflammation, HEX100)
H&E: Hematoxylin and eosin, CLP: Cecal ligation and puncture

vs. 0.0±0.51, p=0.007) (Figure 2 a,b,d). Lymphocyte scores were significantly lower in the CLP + AM group compared to the CLP group (1±0.92 vs. 0.0±0.0, p=0.007) (Figure 2f), but not in the CLP + dexamethasone + AM group (1±0.92 vs. 0.33±0.7, p=0.1) (Table 2, Figure 2h, Figure 3c).

There was a significant difference in fibroblast and histiocyte scores between the groups (p=0.001) and a significant difference in fibroblast and histiocyte scores between CLP and control groups (2.12±0.64 vs. 0.22±0.44, p<0.001). Fibroblast and histiocyte scores were significantly lower in the CLP + dexamethasone +AM group compared to the CLP group (2.12±0.64 vs. 0.66±0.7, p=0.002). Fibroblast and histiocyte scores were also significantly lower in the CLP+AM group compared to the CLP group (2.12±0.64 vs. 0.77±0.83, p=0.005) (Table 2, Figure 3b).

There was a significant difference in hemorrhage scores between the groups (p<0.001). There was a significant difference in hemorrhage scores between CLP and control groups (1.62±0.51 vs. 0.22±0.44, p=0.001). Hemorrhage scores were also significantly lower in the CLP + AM group compared to the CLP group (1.62±0.51 vs. 0.33±0.5, p=0.001), but no such difference was found in the CLP + dexamethasone+AM group (1.62±0.51 vs. 1±0.7, p=0.064) (Table 2, Figure 3d).

There was a significant difference in congestion scores between the groups (p=0.001) and a significant difference in congestion scores between the CLP and control groups (2.62±0.91 vs. 0.66±0.5, p=0.001). Congestion scores were significantly lower in the CLP + dexamethasone + AM group compared to the CLP group (2.62±0.91 vs. 1.55±0.52, p=0.015). Congestion scores were also significantly lower in the CLP+AM group compared to the CLP group (2.62±0.91 vs. 1.66±0.5, p=0.02) (Table 2, Figure 2f, Figure 3e).

There was no significant difference in macrophage and abscess scores between the groups (p=0.093 and p=0.33, respectively) (Table 2, Figure 2e).

Discussion

AM has a significant suppressive effect on inflammation, suggesting that it can be used in conditions such as ALI/ARDS.

Sepsis is a high mortality organ dysfunction that develops after immune dysfunction in the organism. In many cases, ALI/ARDS develops due to the cytokine storm during sepsis, which occurs directly or indirectly due to alveolar damage and lung epithelial damage.[1] Mortality in ARDS caused by sepsis has been found to be 30-40% higher than other causes.[15] For this reason, we used sepsis induced by the CLP method in rats in our study.

Cytokines released by different cells are messenger molecules that play an active role in the regulation of biological processes and are essential for the regulation of both local

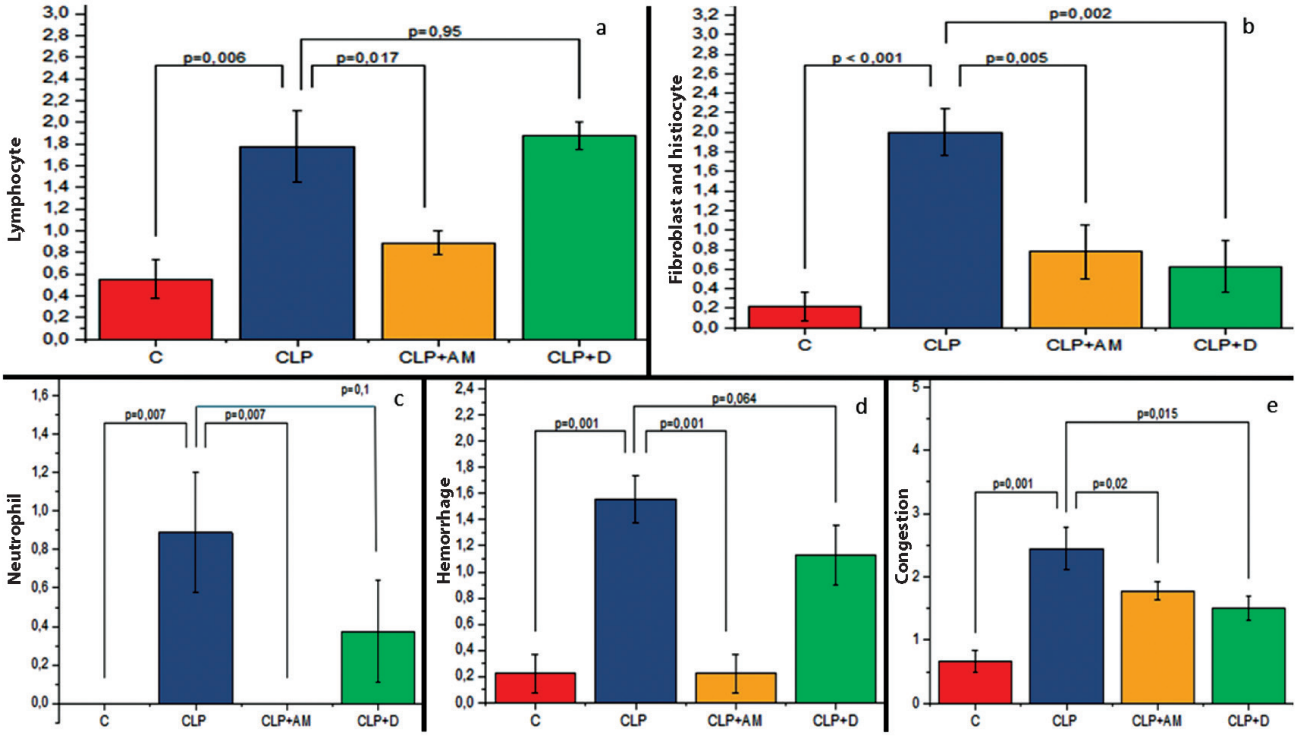

Figure 3. Change in histologic scores between groups
C: Control, CLP: Cecal ligation and puncture, AM: Achillea millefolium, D: Dexamethasone + AM

and systemic inflammatory responses. The main production goal of cytokines is to eliminate the harmful agent, but sometimes the response results in damage to the organism due to exaggerated levels of cytokines produced and the effect of other cells stimulated, the most important example of this is ARDS, which is characterized by a cytokine storm.[1] One of the most important cells involved in these conditions is macrophages. Macrophages, which have an important role in the protection of the human body from harmful organisms and pathogens, release various pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, IL-8, etc. when activated to stimulate other defense mechanisms.[16] TNF-α, one of the most important pro-inflammatory mediators, is a cytokine that normally plays an active role in mechanisms such as cell proliferation, cellular differentiation and apoptosis. In inflammatory conditions, TNF-α stimulates neutrophil migration to the site of inflammation and the release of other pro-inflammatory cytokines.[17] M1 macrophages stimulated by the NF-κB pathway have been shown to take an active role in TNF-α production in addition to free oxygen radicals and IL-6.[18] TNF-α levels, which increase in the initial stages of ARDS in which macrophages play an active role, decrease in the recovery periods. Therefore, methods to decrease TNF-α levels, which is the most important cytokine that causes alveolar destruction in the initial stage of ARDS, have been investigated, and as a result of these investigations, it has been shown that inhibition of M1 macrophages decreases TNF-α levels, and this effect contributes to the decrease in the severity and mortality of the clinical picture of ARDS.[19] In our study, it was also shown that TNF-α levels increased in AM caused by sepsis, and histologically, this change was supported by the increase in lymphocyte, fibroblast and histiocyte, neutrophil, hemorrhage and congestion scores. Sesquiterpenes in the structure of AM are known to suppress this inflammation by inhibiting arachidonic acid metabolism.[20] In an experimental study, AM was shown to reduce inflammation by 35%.[21] In our study, it was shown that TNF-α values decreased in rats with CLP, which were given AM, and histologically this change was supported by the decrease in lymphocyte, fibroblast and histiocyte, neutrophil, hemorrhage and congestion scores.

An important molecule known to suppress inflammatory processes is dexamethasone. One of the most important cytokines affected by dexamethasone in inflammatory processes is TNF-α.[22] In our study, TNF-α values were found to decrease in the dexamethasone-treated group compared to the other groups, although not statistically significant. However, histologically, the decrease in congestion, fibroblast and histiocyte scores in this group was statistically significant.

The immune system is responsible for protecting the host from pathogenic microorganisms by triggering inflammatory processes. Cells that play an active role in inflammation secrete pro-inflammatory cytokines that mediate the activation of other cells and the release of other cytokines, and can also produce anti-inflammatory cytokines to suppress these inflammatory processes when necessary. In cases where the inflammatory response is excessive, the host is also harmed. Therefore, the presence of anti-inflammatory processes is very important. The most important cytokine involved in balancing anti-inflammatory processes is IL-10.[23,24] This cytokine is produced by M2 macrophages, monocytes, neutrophils and T helper cells.[25] Studies on ARDS have shown that IL-10 levels, which decrease in the initial stages of the condition, increase during recovery periods.[26] Increased IL-10 levels inhibit inflammatory processes and restore the disturbed inflammatory-anti-inflammatory balance. In cases where the expected increase in IL-10 levels is not achieved, inflammatory processes get out of control, leading to an increase in the severity of lung injury and thus increasing the morbidity and mortality.[27] Studies have found that AM shows anti-inflammatory activity by increasing IL-10 levels.[21] In our study, the increase in IL-10 levels provided by AM administration was not statistically significant.

One aspect of the damage that occurs in ALI/ARDS following sepsis is the disruption of oxidant-antioxidant metabolism in favor of oxidative stress. SORs in ALI/ARDS pave the way for damage to the alveolar endothelium.[27] Cysteine plays an important role in preventing oxidative damage with its functional thiol group. Thiol compounds are oxidized by the sulfhydryl groups in them to form reversible disulfide bonds, thus playing an active role in maintaining the thiol-disulfide balance.[28] Studies on ALI/ARDS have found a relative decrease in antioxidant molecules, but an increase in the oxidized forms of these molecules and disulfide values.[29]

Studies have shown that AM is a potent antioxidant.[30] In our study, NT and TT values decreased in the CLP group compared to controls, but this decrease was not statistically significant. Again, although these values increased in the CLP group given AM, these increases were not statistically significant.

Conclusion

This study suggests that AM may be used in the treatment of ALI/ARDS due to its biochemical and histologic suppressive effect on inflammation.

Ethics

Ethics Committee Approval: Ethical approval was obtained from Bolu Abant İzzet Baysal University Experimental Animals Ethics Committee (no: 2021/35).

Informed Consent: N/A.

Footnotes

Authorship Contributions

Concept: B.Y., M.B., Design: B.Y., A.Ç., A.B.Y., Data Collection or Processing: S.E.D., M.A., Analysis or Interpretation: S.E.D., M.A., Literature Search: B.Y., M.B., M.F.B., Writing: B.Y., M.B., M.F.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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Evaluation of Patients Who Were Followed Up After Pediatric Cardiac Surgery in the Pediatric Intensive Care Unit: 6 Years of Experience

Çocuk Yoğun Bakım Ünitesinde Pediyatrik Kalp Cerrahisi Sonrası Takip Edilen Hastaların Değerlendirilmesi: 6 Yıllık Deneyim

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Abstract

Introduction: This study aimed to evaluate the outcomes and clinical conditions observed during the postsurgical follow-up of children with congenital heart disease at a single center that initiated pediatric cardiac surgery in 2015.

Methods: A retrospective analysis of pediatric patients who underwent cardiac surgery between October 1, 2015, and December 31, 2021 was conducted. Demographic, preoperative, perioperative, and postoperative data were collected from echocardiographic, perfusion, and clinical records. Statistical analyses were performed using appropriate methods.

Results: A total of 692 pediatric patients underwent surgical treatment for congenital heart disease. The most common defects were ventricular, atrial, and tetralogy of Fallot. The most common preoperative risk factors were malnutrition and failure to thrive. Complications, such as respiratory issues, arrhythmias, and acute kidney injury, were observed. The overall mortality rate was 3.6%. Mortality rates varied according to specific congenital heart disease defects and risk categories.

Conclusion: This study provides valuable insights into the postsurgical follow-up of pediatric patients with congenital heart disease, highlighting the importance of risk stratification, preoperative evaluation, and postoperative care. The findings of this study contribute to the global understanding of congenital heart disease management and outcomes. Further research should focus

Öz

Giriş: Bu çalışma, 2015 yılında çocuk kalp cerrahisinin başladığı tek bir merkezde doğuştan kalp hastalığı olan çocukların cerrahi sonrasında izlem sırasında gözlenen sonuçları ve klinik durumları değerlendirmeyi amaçlamaktadır.

Yöntemler: 1 Ekim 2015 ile 31 Aralık 2021 tarihleri arasında kalp cerrahisi geçiren pediatrik hastaların geriye dönük bir analizi yapılmıştır. Demografik, preoperatif, perioperatif ve postoperatif veriler; ekokardiyografi raporları, perfüzyon raporları ve klinik kayıtlardan toplanmıştır. İstatistiksel analizler uygun yöntemler kullanılarak gerçekleştirilmiştir.

Bulgular: Toplam 692 çocuk hasta doğuştan kalp hastalığı nedeniyle cerrahi işlem geçirdi. En yaygın görülen kusurlar ventriküler septal defekt, atriyal septal defekt ve fallot tetralojisiydi. Preoperatif risk faktörleri arasında en sık malnütrisyon ve büyüme geriliği bulunmaktaydı. En sık solunum sorunları, aritmiler ve akut böbrek hasarı gibi komplikasyonlar gözlemlendi. Genel mortalite oranı %3,6 idi. Mortalite oranları belirli doğuştan kalp hastalığı kusurları ve risk kategorilerine bağlı olarak değişiyordu.

Sonuç: Bu çalışma, çocuk doğuştan kalp hastalığı hastalarının cerrahi sonrası takibi konusunda değerli veriler sunarak, risk gruplarının, preoperatif değerlendirmenin ve postoperatif bakımın önemini vurgulamaktadır. Bulgular, doğuştan kalp hastalığı yönetimi ve sonuçları konusunda katkıda bulunmaktadır. Bu hastalarda uzun dönem sonuçların değerlendirilmesi, risklerin azaltılması, mortalite

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Abstract

on risk adjustment, long-term outcomes, and strategies to reduce complications and mortality in this vulnerable population.

Keywords: Pediatric cardiac surgery, pediatric intensive care unit, complications, outcomes

Öz

ve komplikasyonları azaltmaya yönelik stratejilerin geliştirilmesi hedeflenerek çalışmaların yapılması gerekmektedir.

Anahtar Kelimeler: Pediyatrik kalp cerrahisi, çocuk yoğun bakım ünitesi, komplikasyonlar, sonuçlar

Introduction

The most common congenital malformations are congenital heart diseases (CHD). The incidence of CHD worldwide is 8-23 per 1000 births and is gradually increasing.[1-5] The frequency of CHD varies according to the population evaluated, diagnostic criteria used, and research methods.[4,5] There is a need for surgical treatment at varying rates depending on the type and severity of CHD. The success of surgical procedures depends on many factors.[6] For this reason, healthcare centers have used various risk classification systems to determine the risks and difficulty levels of pediatric heart surgeries. The STS-European Society of Cardio-Thoracic Surgery (STAT) Mortality Categories and Risk Adjustment for Congenital Cardiac Surgery (RACHS-1) Mortality Categories are methods used in risk stratification of performed procedures.[7,8] Various complications, including cardiovascular and non-cardiovascular systems, can be observed after pediatric cardiac surgery.[9] Cardiac arrest, arrhythmias, and low cardiac output syndrome (LCOS) are among the cardiovascular complications that may occur. Apart from the cardiovascular system, pulmonary/thoracic, infections, gastrointestinal, hepatic, neurological, hematological, and kidney complications can be observed.[10] Several registries have been conducted around the world to determine outcomes and advance the quality of treatment in patients with CHD.[11] The present study aimed to evaluate the results and clinical conditions observed during the postsurgical follow-up of children with CHD, which began in our center in 2015. In this way, we aim to identify crucial factors to reduce mortality and morbidity rates in patients in the future.

Materials and Methods

We retrospectively analyzed a series of pediatric patients who underwent cardiac surgery between October 1, 2015, and December 31, 2021. Cardiac surgery was performed on six hundred ninety-two pediatric patients, and these patients were subsequently evaluated. We scrutinized the preoperative, perioperative, and postoperative data extracted from echocardiography, perfusion, and clinical, inpatient, and operative notes of all patients.

The preoperative characteristics of the patients, including sex, cardiac and non-cardiac comorbidities, age at surgery, body weight at surgery, primary diagnosis of CHD, preoperative risk factors, and underlying genetic condition, were thoroughly examined. Preoperative risk factors are defined in the Appendices of the World Database for Pediatrics and Congenital Heart Surgery website.[12]

The outcome variables in this study included in-hospital death, mechanical ventilation (MV) duration in hours, the existence of the need for extracorporeal membrane oxygenation (ECMO) and kidney replacement therapy (RRT), pediatric intensive care unit (PICU) duration in days, hospital duration in days, STAT mortality categories, and RACHS-1 mortality categories.

The postoperative complications included acute kidney injury, pleural effusion requiring chest tube placement, atelectasis, junctional ectopic tachycardia, complete atrioventricular block, and major adverse events. Significant major adverse events included unplanned reoperation, complete heart block requiring the implantation of a permanent pacemaker, sudden cardiac arrest, and death. Acute kidney injury (AKI) is defined in accordance with the pediatric risk, injury, failure, loss, end-stage kidney disease criteria.[13] LCOS is defined as the use of ≥3 inotrope and is associated with the following: Tachycardia, oliguria, decreased skin perfusion, metabolic acidosis, or vasopressin requirement for hypotension and/or shock in the postoperative period. Pulmonary hypertension is defined as a clinically significant elevation of pulmonary arterial pressure requiring intervention.[14] Acute liver dysfunction was defined as liver dysfunction that met the PODIUM criteria, including aspartate aminotransferase >100 IU/L, alanine aminotransferase >100 IU/L, glutamyl transpeptidase >100 IU/L, total bilirubin >5 mg/dL or direct or conjugated bilirubin >2 mg/dL.[15] Systemic inflammatory response syndrome (SIRS) was determined according to the international pediatric sepsis consensus criteria, that is, the presence of at least two of the following four criteria with either abnormal temperature or leukocyte count as an obligate criterion: Core temperature >38.5 °C or <36 °C, tachycardia (irrespective of inotropic support) defined as mean heart rate >2 standard deviations (SD) beyond normal for age, mean respiratory rate >2 SD above normal for age, elevated or reduced age-specific leukocyte count or >10% immature neutrophils. Bypass-related SIRS is defined as SIRS occurring within the first 48 hours after bypass, at which no other etiological causes are detected.[16,17]

This retrospective study was approved by University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Institutional Ethics Committee (2022/04-34) and was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences version 23.0 software (Armonk, NY: IBM Corp). The normal distribution of variables was evaluated using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk test). A descriptive analysis was performed using frequency tables for categorical variables, while means and SD were used to describe normally distributed variables. Medians and ranges were used to describe variables with non-normal distribution.

Results

In total, 692 patients underwent surgical treatment for CHD during the study period. Their demographic characteristics are presented in Table 1. The median patient age at operation was 14 months (range, 5-51.75 months). Among the patients, 348 (50.3%) were male. The median body weight of the patients was 8.5 kg (range, 5.53-15 kg) at the time of surgery. The most common defect was ventricular septal defect (VSD) (n=191, 27.6%), followed by atrial septal defect (ASD) (n=94, 13.6%), and tetralogy of Fallot (ToF) (n=57, 8.2%) (Table 2). Pre-existing diseases were present in 157 patients (22.7%); the most common genetic anomaly was Down syndrome (n=76, 11%). There were no non-cardiac anomalies in 542 (78.3%) patients. The most common non-cardiac anomaly was a craniofacial anomaly (n=113, 16.3%) (Figure 1). Among all patients, 409 (59.1%) had no preoperative risk factors, 157 (22.7%) had 1 risk factor, 73 (10.5%) had 2 risk factors and 53 (7.7%) had 3 or more risk factors. The number of preoperative risk factors was significantly higher in patients who died (0.66±1.01 vs. 2.08±1.92; p<000.1). The most frequent risk factors were malnutrition (n=175, 25.3%) and failure to thrive (n=105, 15.2%) (Table 3). Figures 2 and 3 represent the risk categories for cases submitted, stratified by STAT and RACHS-1 mortality categories, respectively. A total of 563 (81.4%) patients underwent an initial major cardiac procedure, whereas 129 (18.6%) had reoperation. The majority of surgical cases were transported to the operating room either electively (n=675, 97.5%) or urgently (n=17, 2.5%).

Table 1. Demographic characteristics, operative variables and postoperative complications of patients

Variable		Patients (n=692)
Age (months), median (interquartile range)		14 (5-51.75)
Weight (kg), median (interquartile range)		8.5 (5.52-15)
Males, n (%)		348 (50.3%)
Pre-existing disease, n (%)	Other syndromes	77 (11.1%)
	Down syndrome	76 (11%)
	Mental retardation	3 (0.4%)
	Asthma	2 (0.3%)
	Epilepsy	1 (0.1%)
Bypass time (min), mean ± SD		69.3±33.4
Aortic cross-clamp time (min), mean ± SD		52.2±26.9
Reoperation rate, n (%)		129 (18.6%)
Outcomes		
MV time (hours), median (interquartile range)		3 (2-4)
PICU hospitalization duration (days), median (interquartile range)		3 (2-5)
Total hospitalization duration (days), median (interquartile range)		6 (5-9)
Total complications, n (%)		149 (21.5%)
Mortality, n (%)		25 (3.6%)
Complications		
Respiratory events (%)	Pleural effusion	36 (5.2%)
	Pulmonary atelectasis	34 (4.9%)
	Chylothorax	9 (1.3%)
	Pneumothorax	5 (0.7%)
	Diaphragm paralysis	1 (0.1%)
Acute kidney injury, n (%)		50 (7.2%)

Table 1. Continued

Variable		Patients (n=692)
Arrhythmia, n (%)	Junctional ectopic tachycardia	28 (4%)
	Transient complete AV block	9 (1.3%)
	Permanent complete AV block	1 (0.1%)
	First-degree AV block	1 (0.1%)
	Second-degree AV block	1 (0.1%)
	Nodal rhythm	1 (0.1%)
	Frequent ventricular extrasystoles	1 (0.1%)
	Ventricular tachycardia	1 (0.1%)
Low cardiac output syndrome, n (%)		28 (4%)
Acute liver dysfunction, n (%)		12 (1.7%)
Pulmonary hypertension, n (%)		7 (1%)
Bypass-related systemic inflammatory response syndrome, n (%)		6 (0.9%)
Pericardial effusion/tamponade, n (%)		6 (0.9%)
Shunt dysfunction, n (%)		3 (0.4%)
Mediastinitis, n (%)		2 (0.3%)
Major adverse event rate, n (%)		1 (0.9%)

PICU: Pediatric intensive care unit, SD: Standard deviation, MV: Mechanical ventilation, AV: Atrioventricular

Table 2. The types of congenital cardiac defects, procedures and outcomes of patients

Diagnosis, n (%)	Procedure	n (%)	Mortality, n (%)
Ventricular septal defect, 192 (27.7)	Repair	151 (78.6)	0 (0)
	Debanding and repair	25 (13)	0 (0)
	Pulmonary artery banding	16 (8.3)	2 (12.5)
Atrial septal defect, 94 (13.6)	Repair	94 (13.6)	0 (0)
Tetralogy of Fallot, 48 (6.9)	Complete repair	44	0 (0)
	MBT shunt	4	1 (25)
Tetralogy of Fallot with pulmonary atresia, 15 (2.2)	Rastelli	10 (66.7)	2 (20)
	MBT shunt	3 (20)	0 (0)
	Central shunt	2 (13.3)	1 (50)
Double-outlet right ventricle, 53 (7.7)	Complete repair	39 (73.6)	0 (0)
	MBT shunt	4 (7.5)	1 (25)
	Pulmonary artery banding	1 (1.9)	0 (0)
	Rastelli	9 (16.9)	0 (0)
Vascular ring, 44 (6.4)	Division	18 (40.9)	0 (0)
	Division and re-anastomosis	7 (15.9)	0 (0)
	Aortopexy	19 (43.2)	0 (0)
Atrioventricular septal defect, complete, 22 (3.2)	Complete repair	20 (90.9)	5 (25)
	Pulmonary artery banding	2 (9.1)	0 (0)
Atrioventricular septal defect, partial, 19 (2.8)	Complete repair	19 (100)	1 (5.3)
Aort coarctation. 34 (4.9)	End-to-end anastomosis	24 (70.6)	0 (0)
	Patch aortoplasty	10 (29.4)	0 (0)
Hypoplastic right ventricle.20 (2.9)	Glenn shunt	9 (55)	2 (22.2)
	Pulmonary artery banding	5 (25)	1 (20)
	MBT shunt	3 (15)	3 (100)
	Central shunt	1 (5)	0 (0)

Table 2. Continued

Diagnosis, n (%)	Procedure	n (%)	Mortality, n (%)
Hypoplastic left ventricle, 9 (1.3)	Pulmonary artery banding	4 (44.4)	2 (50)
	Norwood stage 2	1 (11.1)	0 (0)
	Norwood comprehensive stage 2	2 (22.2)	1 (50)
	Atrial septectomy	1 (11.1)	1 (100)
	Fontan	1 (11.1)	0 (0)
Patent ductus arteriosus, 22 (3.3)	Surgical closure	22 (100)	0 (0)
PAPVC 16 (2.3)	Repair	16 (100)	0 (0)
TAPVC =4 (0.6)	Repair	4 (100)	0 (0)
Discrete subaortic membrane, 11 (1.6)	Resection of the membrane	11 (100)	0 (0)
Truncus arteriosus, 3 (0.4)	Rastelli	3	0 (0)
c-TGA, 2 (0.3)	Pulmonary artery banding	1 (50)	0 (0)
	VSD closure	1 (50)	1 (100)
An anomalous origin of the coronary artery, 6 (0.9)	Unroofing	6 (100)	0 (0)
Interrupted aortic arch, 3 (0.4)	Aortic arch reconstruction	3 (100)	0 (0)
Cardiac tumor, 1 (0.1)	Resection	1 (100)	0 (0)
Cor triatriatum, 2 (0.3)	Membrane resection	2 (100)	0 (0)
Complete AV block, n=3 (0.4)	Pacemaker implantation	3 (100)	0 (0)
Ebstein anomaly, 2 (0.3)	Cone repair + Glenn shunt	1 (50)	0 (0)
	Glenn shunt	1 (50)	0 (0)
Supramitral ring, 2 (0.3)	Resection	2 (100)	0 (0)
Pulmonary artery stenosis 13 (1.9)	Pulmonary artery reconstruction	13 (100)	0 (0)
Pulmonary valve disease, 24 (3.5)	PVR	13 (50)	0 (0)
	Conduit replacement	4 (15.4)	0 (0)
	Valvuloplasty	7 (26.9)	0 (0)
Mitral valve disease, 7 (1)	MVR	4 (57.1)	0 (0)
	Valvuloplasty	3 (42.9)	0 (0)
Aortic valve disease, 12 (1.7)	AVR	8 (66.7)	0 (0)
	Valvuloplasty	4 (33.3)	0 (0)
Scimitar syndrome, 4 (0.6)	Complete repair	4 (100)	0 (0)
Other, 5 (0.7)	Repair	5 (100)	1 (20)

AV: Atrioventricular, VSD: Ventricular septal defect

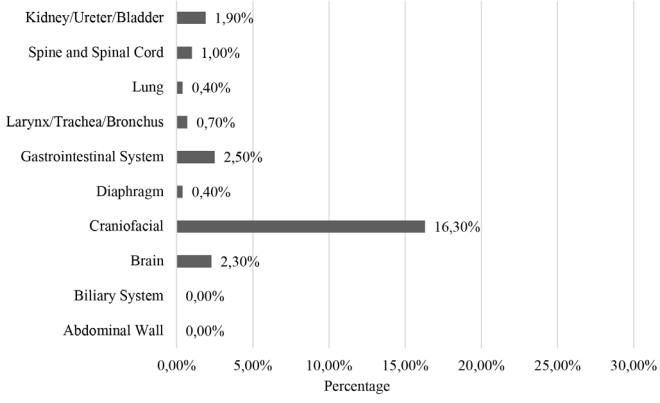

Figure 1. Non-cardiac congenital anatomic abnormality

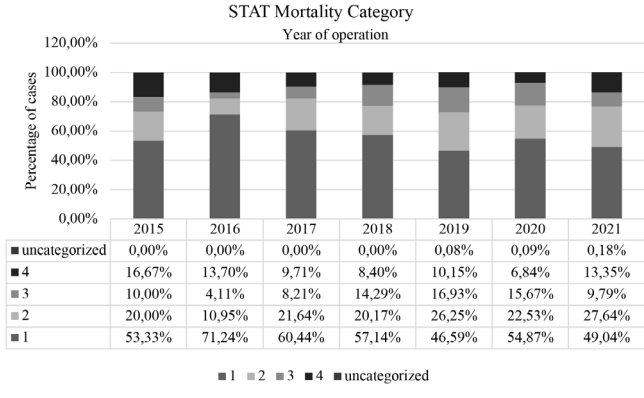

Figure 2. STAT mortality category by years
STAT: European Society of Cardio-Thoracic Surgery

Of all patients, 62.4% (n=432) underwent bypass during surgery. The mean cardiopulmonary bypass (CPB) time was 69.3±33.4 minutes (range, 10-217 minutes). The mean aortic cross-clamp (ACC) time was 52.2±27 minutes (range, 13-180 minutes).

ECMO support was provided to a small percentage of patients (n=2, 0.3%). A total of 149 (21.5%) patients experienced at least 1 postoperative complication (Table 1). The most common complications were postoperative respiratory complications (n=85, 12.3%); arrhythmia (n=43, 6.2%); and AKI (n=50, 7.2%). One patient (0.1%) with kidney failure required kidney replacement therapy. The median [interquartile range (IQR)] MV duration, PICU stay, and hospital stay of the patients were 3 hours (2-4 hours), 3 days (2-5 days), and 6 days (5-9 days), respectively.

Overall mortality rate was 3.6 (n=25). Table 4 presents hospital mortality by year for the STAT and RACHS-1. The mortality rate following VSD repair was 1%, the following ASD repair was 0%, and following ToF correction was 1.8%. Mortality for most STAT category 1 and 2 procedures ranged from 0.3% to 2%, with higher STAT categories showing substantially higher rates. Mortality for most RACHS-1 category 1 and 2 procedures ranged from 0% to 1.2%.

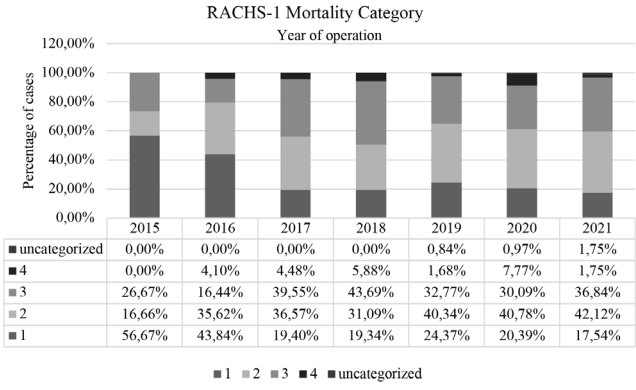

Figure 3. RACHS-1 mortality category by years
RACHS-1: Mortality Categories and Risk Adjustment for Congenital Cardiac Surgery

Discussion

This study is the first to evaluate the data of all patients who were followed up for 6 years from the initial day of congenital heart surgery follow-up at our center. This research has the potential to enhance the quality of our center, not only through the utilization of international classification and risk scoring systems, but also by incorporating real-time reports. The findings of our study on the postsurgical follow-up of children with CHD at our center in 2015 align with previous

Table 3. Preoperative risk factors

Preoperative risk factors	n	%
None	409	59.1
Malnutrition	175	25.3
Failure to thrive	105	15.2
Greater than 2 hospital admissions for non-cardiac infections in last 3 months	52	7.5
Neurological deficit	44	6.4
Endocrine abnormalities	43	6.2
Seizure	20	2.9
Shock, resolved at the time of surgery	10	1.4
Mechanical ventilation for cardiorespiratory failure	8	1.2
Respiratory failure not requiring ventilation	7	1
Bronchopulmonary dysplasia	6	0.9
Kidney dysfunction	5	0.7
Tracheostomy present	5	0.7
Cardiopulmonary resuscitation	4	0.6
Sepsis	3	0.4
Other	3	0.4
Coagulation disorder	2	0.3
Asthma	2	0.3
Pacemaker present	1	0.1
Kidney failure requiring dialysis	1	0.1

Table 4. Mortality by years

Year of operation	Total number	Mortality number (%)	STAT category mortality (n)					RACHS-1 category-related mortality, n				
			1	2	3	4	UC	1	2	3	4	UC
2015	30	1 (3.33%)	0	1	0	0	0	0	1	0	0	0
2016	73	5 (6.85%)	0	2	1	2	0	0	2	3	0	0
2017	134	2 (1.49%)	0	0	0	2	0	0	0	2	0	0
2018	119	7 (5.88%)	0	0	3	4	0	0	0	6	1	0
2019	119	6 (5.04%)	0	0	2	3	1	0	0	4	1	1
2020	103	0 (0%)	0	0	0	0	0	0	0	0	0	0
2021	114	4 (3.5%)	0	0	1	3	0	0	0	3	1	0
Total	692	25 (3.6%)	0	3	7	14	1	0	3	18	3	1

UC: Uncategorized, RACHS-1: Mortality Categories and Risk Adjustment for Congenital Cardiac Surgery, STAT: European Society of Cardio-Thoracic Surgery

research conducted in different regions. The incidence of CHD varies globally, as reported in various studies. For instance, the Guangdong Registry of Congenital Heart Disease in China reported an incidence consistent with our findings.[1] Similarly, studies conducted globally have highlighted the changing landscape and burden of CHD.[2-5] In a multicenter study conducted in our country, the most common cardiac defects requiring surgery were VSD, ASD, and ToF.[18] Correspondingly, in our study, the most common cardiac defects were VSD, ASD, and ToF.

Furthermore, the presence of genetic anomalies, particularly Down syndrome, was consistent with previous reports.[2] In one study, 9.9% had a documented genetic syndrome, with the majority of patients having Down syndrome (72%). In the same study, the most common non-cardiac anomalies were the gastrointestinal system, larynx/trachea/bronchus, craniofacial, kidney/ureter/bladder, and brain anomalies, respectively.[19] Notably, our study identified a higher prevalence of craniofacial anomalies than other non-cardiac anomalies, warranting further investigation. After craniofacial anomalies, the order of frequency was gastrointestinal system, brain, and kidney/ureter/bladder. Genetic anomalies were present in 153 patients (22.1%); the most common genetic anomaly was Down syndrome (49.7%).

In one study, a preoperative risk factor was present in 25% of the patients. The most frequent risk factors were failure to thrive/malnutrition and respiratory issues.[19] In another study, the most common preoperative risk factors were mechanical MV and pulmonary hypertension. However, malnutrition and failure to thrive were not assessed as preoperative risk factors in this study. Additionally, in the same study, the mortality rate increased with the number of risks factors.[18] Similarly, our study revealed a relationship between risk factors and mortality. The distribution of preoperative risk factors observed in our study, such as malnutrition (25.3%) and failure to thrive (15.2%), is consistent with the existing literature.[6-8] These risk factors contribute to the complexity and management of CHD cases, necessitating appropriate preoperative evaluation and perioperative care.

In this study, the majority of surgical cases were scheduled as elective procedures (86%) or urgent procedures (12%). CPB was used in most cases (93%). The median duration of CPB was 84 min (IQR: 63-120 minutes), and the median ACC time was 52 min. Approximately 80% of patients in this study were categorized under STAT and RACHS-1 categories 1 and 2.[19] Another study involving 325 surgeries reported that 83% of them were performed with CPB support, whereas 17% were conducted without CPB support. The median CPB time was 120 min (IQR: 88-158 minutes), and the median ACC time was 41 min (IQR: 24-58 minutes).[9] In our study, 62.4% of patients underwent bypass during the surgical procedures. The mean durations of CPB and ACC were consistent with the existing literature. Furthermore, the distribution of patients according to STAT and RACHS-1 categories corresponded with that of previous studies, with the majority falling into categories 1 and 2. The surgical cases were primarily elective (97.5%), with a small proportion classified as urgent (2.5%).

In numerous studies, the most prevalent complications during the postoperative period are respiratory conditions.[20-23] In a study exclusively involving infants, respiratory complications were the most frequent, exceeding 20%. In this study, bleeding was identified in 19.2% of patients, arrhythmia in 16.9%, and AKI in 6.9%.[20] Notably, the rate of excessive bleeding, which was significantly higher than that observed in our study, may be attributed to the fact that the study focused solely on infants, with newborns being the majority. In a study by Murni et al.,[22] pleural effusion (14.8%) and atelectasis (6.2%) were the most common respiratory complications. The most common cardiac complications observed in this study were arrhythmia (18.6%) and LCOS (19.8%). Although the specific types of arrhythmias were not specified, the complete atrioventricular (AV) block rate was 5.8%. In a multicenter study conducted in Turkey, respiratory complications were the most common, with 32.1% of patients experiencing at least one complication. In this study, the requirement of postoperative ECMO was observed in 3.9% of patients, and LCOS was detected in 6.1%.[18] The occurrence of postoperative complications in our study, such as respiratory complications (12.3%), arrhythmia (6.2%), and AKI (7.2%), aligns with findings from other investigations. We found that 21.5% of patients experienced at least one postoperative complication. ECMO support was utilized in a small percentage of patients (0.3%). St. Louis et al.[19] reported a need for ECMO of 0.2%. Studies report variable (3-42%) incidences of AKI after cardiac surgery in children.[23-26] In previous studies, it has been observed that 4-8% of patients with AKI require RRT.[19,27,28] In our study, AKI was detected in 7.2% of patients, with 2% of these patients requiring RRT. Discrepancies in the incidence and need for RRT in AKI-related studies are attributed to variations in the selected patient populations and differences in AKI definitions. In our study, the low incidence of RRT requirement may be attributed to the inclusion of patients, such as those with vascular rings, who do not require bypass and are often excluded in many studies. In a study evaluating arrhythmias after postoperative cardiac surgery, junctional ectopic tachycardia (JET) (45.2%) and complete AV block (27.3%) were the most common.[29] Similarly, in our study, JET (65.1%) and transient complete AV block (20.9%) were the predominant arrhythmias. These complications underscore the necessity of vigilant postoperative monitoring and appropriate management strategies to minimize adverse outcomes.

We found that the median MV duration, PICU stay, and hospital stay were 3 hours, 3 days, and 6 days, respectively. Although the durations of ICU and hospitalization in our study were comparable to those reported in the literature, the MV duration was notably shorter. In other studies, the median MV duration was reported to be 12-18 hours, PICU stay 1-3 days, and hospital stay 6 days.[22,30,31]

In terms of mortality, our study reported an overall mortality rate of 3.8%. Various studies reported mortality rates ranging from 2.6% to 13.6%.[18,19,22,32] Mortality rates varied according to specific CHDs and the STAT and RACHS-1 categories. Comparisons with the existing literature revealed similar trends, with higher mortality rates associated with complex procedures.[18,19] In our study, mortality for most STAT categories 1 and 2 ranged from 0.3% to 2%, with the higher STAT categories showing substantially higher rates. Mortality for most RACHS-1 category 1 and 2 procedures ranged from 0% to 1.2%.

Study Limitations

It is essential to acknowledge the limitations of our study, including its retrospective nature and single-center design. These limitations may have affected the generalizability of our findings. Other study limitations include the absence of long-term follow-up and the exclusion of patients in the mortality categories STAT category 5, RACHS-1 category 5, and 6. This exclusion was attributed to the fact that the newborn patient group was not included in the follow-up. However, our study provides valuable insights into the existing body of knowledge on the post-surgical follow-up of children with CHD. Additionally, it provides important data regarding the 6-year experience of a center where congenital heart surgery has been performed in a developing country and its role in this process.

Conclusion

In conclusion, our study provides valuable data on the results and clinical conditions observed during the postsurgical follow-up of children with CHD at our center since 2015. The findings align with previous research, thereby contributing to a global understanding of CHD management and outcomes. Further research, collaborations, and the use of clinical databases and registries will continue to enhance our understanding of pediatric cardiac surgery and improve patient care. Future studies should focus on risk adjustment methods, long-term outcomes, and interventions to reduce complications and mortality rates in this vulnerable population.

Ethics

Ethics Committee Approval: This retrospective study was approved by University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Institutional Ethics Committee (2022/04-34) and was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.B.A., G.Ö., F.D., E.P.K., O.I., Ü.A., A.R.B., Concept: A.B.A., G.Ö., A.R.B., Design: A.B.A., G.Ö., Data Collection or Processing: G.Ö., F.D., E.P.K., Analysis or Interpretation: A.B.A., G.Ö., O.I., Ü.A., A.R.B., Literature Search: A.B.A., G.Ö., F.D., E.P.K., O.I., Ü.A., A.R.B., Writing: A.B.A., G.Ö., F.D.

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Research Article / Özgün Araştırma

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Renal Angina Index As A Predictor of Acute Kidney Injury Development in Critically Ill Children Admitted to Pediatric Critical Care Units: A Prospective Observational Study

Pediatrik Yoğun Bakım Ünitelerine Kabul Edilen Kritik Durumdaki Çocuklarda Akut Böbrek Hasarı Gelişiminin Öngörücüsü Olarak Renal Anjina İndeksi: Prospektif Gözlemsel Bir Çalışma

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Abstract

Introduction: Acute kidney injury (AKI) is a major cause of morbidity and mortality in critically ill children. The incidence of AKI is approximately 10%, with mortality of 11-40%. Traditional methods delay the diagnosis of AKI, and it is essential to combine clinical and laboratory parameters. Renal angina index (RAI) scoring aids in the early recognition of the risk of developing AKI. There are few studies on RAI in children; hence, the present study was undertaken. To determine the proportion of children with positive RAI who develop AKI on day 3. The secondary objective was to measure the association between positive RAI scores and short-term outcomes.

Methods: This hospital-based prospective observational study. All children who met the inclusion criteria and were admitted to the pediatric intensive care unit were included. RAI was calculated on day 0 and AKI development was monitored on day 3. An RAI score of 8 was considered positive.

Results: Of the 93 children, 26 were RAI-positive, among whom 21 (80.77%) developed AKI. The sensitivity of RAI in predicting the development of AKI on D3 was 65.38% [95% confidence interval (CI) 44.33-82.79%], specificity was 88.06% (95% CI 77.82-94.7%) and accuracy was 81.72%. A positive RAI score is independently associated with an increased need for mechanical ventilation and increased mortality.

Conclusion: The RAI score obtained upon admission is a simple yet reliable tool for predicting the development of severe AKI. Positive RAI is also an independent predictor of morbidity and mortality in critically ill children.

Keywords: Acute kidney injury, creatinine, critically ill children, mortality and morbidity

Öz

Giriş: Akut böbrek hasarı (ABH), kritik durumdaki çocuklarda önemli bir morbidite ve mortalite nedenidir. ABH sıklığı yaklaşık %10, mortalite oranı ise %11-40'tır. Geleneksel yöntemler ABH tanısını geciktirir ve klinik ve laboratuvar parametreleri birleştirmek esastır. Renal anjina indeksi (RAI) skorlaması, ABH gelişme riskinin erken tanınmasına yardımcı olur. Çocuklarda RAI ile ilgili az sayıda çalışma olduğu için bu çalışma yapılmıştır. RAI pozitif olan ve 3. günde ABH gelişen çocukların oranını belirlemek ve ikincil olarak da pozitif RAI skorları ile kısa vadeli sonuçlar arasındaki ilişkiyi ölçmek amaçlanmıştır.

Yöntemler: Bu çalışma hastane tabanlı ileriye yönelik gözlemsel bir çalışmadır. Dahil edilme ölçütlerini karşılayan ve çocuk yoğun bakım ünitesine kabul edilen tüm çocuklar çalışmaya dahil edildi. RAI 0. günde hesaplandı ve ABH gelişimi 3. günde izlendi. RAI skorunun 8 olması pozitif olarak kabul edildi.

Bulgular: Doksan üç çocuktan 26'sında RAI pozitifti ve bunların 21'inde (%80,77) ABH gelişti. D3'te ABH gelişimini öngörmede RAI'nın duyarlılığı %65,38 [%95 güven aralığı (CI) %44,33-82,79], özgüllüğü %88,06 (%95 CI %77,82-94,7) ve doğruluğu %81,72 idi. Pozitif bir RAI skoru bağımsız olarak mekanik ventilasyon ihtiyacının ve mortalitenin artmasıyla ilişkilidir.

Sonuç: Başvuru sırasında elde edilen RAI skoru, şiddetli ABH gelişimini öngörmek için basit ancak güvenilir bir araçtır. Pozitif RAI aynı zamanda kritik durumdaki çocuklarda morbidite ve mortalitenin bağımsız bir belirleyicisidir.

Anahtar Kelimeler: Akut böbrek hasarı, kreatinin, kritik hasta çocuklar, mortalite ve morbidite

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Introduction

The prevalence of acute kidney injury (AKI) among critically ill children is increasing. The reported incidence of AKI in pediatric intensive care units is 10%.[1,2] There is an incremental increase in the morbidity and mortality rates with an increase in the severity of AKI. Mortality from AKI is reported to range from 11-40%.[3-6] There is improvement in patient outcomes with early prediction of AKI.

AKI is defined as an abrupt loss of kidney function, leading to a rapid decline in the glomerular filtration rate (GFR). Over the last decade, various classification systems have been developed to define and assess AKI severity. The kidney disease improving global outcome (KDIGO) and pediatric risk injury failure loss of function criteria were the most widely accepted.

Traditionally, AKI was diagnosed based on elevated serum creatinine (SCr) levels. However, the levels of SCr remains normal, till most of the renal injury has occurred.[1,7,8] Also the values of SCr levels are affected by various factors, such as age, height, gender, body mass index, and hydration status.[9] To avoid delays in the recognition of AKI, combined clinical and laboratory parameters can help in the early prediction of the development and severity of AKI.

The renal angina model proposed by Goldstein and Chawala[10] provided risk stratification for the development of AKI in critically ill children. RAI was validated in children by Basu et al.[2] The renal angina index (RAI) combines risk factors (admission to intensive care unit, solid organ or stem cell transplantation, mechanical ventilation and use of inotropes) and early signs of loss of function (increase in SCr and extent of fluid accumulation).

The RAI is a simple and easy index of the onset of AKI in critically ill children and aids in the early detection of AKI, thereby allowing for timely intervention. This scoring system is particularly valuable in developing countries because of its minimal requirement for additional laboratory investigations. The RAI demonstrates greater discriminative accuracy than the traditional creatinine-based indicators of renal injury.

Materials and Methods

We conducted a prospective single-center observational study from August 2022 to August 2023. The study was approved by the Ethics Committee of the research. The study was conducted at the SDM College of Medical Sciences and Hospital, Dharwad, India (SDMIEC/2022/359) after obtaining informed consent from the parents or legal guardians of all participants.

Children aged between 1 month and 14 years who met the criteria for PICU admission (paediatrics index of mortality-3 criteria)[11] were included in the study. Children who had AKI stage 2 at the time of admission to the PICU, children who are known to have chronic kidney disease, and children with a duration of PICU stay of less than 72 hours were excluded from the study.

Children who met the inclusion criteria were enrolled in the study. All relevant data, including anthropometry, demographic parameters, admission diagnosis, comorbidities, vital signs, and other clinical and laboratory parameters, were recorded in a predesigned proforma.

Baseline SCr levels were calculated using Jefery's method on day 0 of admission (within 8 hours admission to PICU). Repeat SCr was performed on day 3, between 72 and 96 hours of admission to the PICU, to assess the severity of AKI. The RAI was determined for all enrolled subjects between 8 and 12 hours from the time of PICU admission on day 0.

The RAI was defined as the product of the risk group score and renal injury score.[2] RAI score given in Table 1. RAI score ranges from 1 to 40. The RAI was calculated by multiplying the risk and injury scores assigned (risk score × FO% score or risk score × GFR score), whichever was worse. The index RAI ≥8 was considered positive for renal angina positive (RA +) and a score of less than 8 considered as RA negative (RA-). Both groups were compared for primary outcome parameters, such as the development and severity of AKI, and risk factors for AKI development. The secondary outcome parameters were the duration of PICU stay, need for mechanical ventilation, development of acute respiratory distress syndrome (ARDS), and mortality. Fluid overload (FO) was calculated using the following formula:

FO = total intake (Lt) total output 100

Weight at admission to the PICU

Table 1. Renal angina index in children

Risk strata		
Risk criteria		**Score**
Admission to the ICU		1
Solid organ or stem cell transplantation		3
Mechanical ventilation or inotrope		5
Injury strata		
S creatinine level relative to baseline	**Fluid accumulation (%)**	
Decreased or unchanged	<5	1
>1-1.49*	5-10	2
1.5-1.99*	11-15	4
>2*	>15	8

ICU: Intensive care unit

All children were closely monitored for AKI development. The severity of AKI is defined using KDIGO staging.[12] According to KDIGO guidelines, AKI is defined as any of the following: An increase in SCr by 0.3 milligrams per deciliter (mg/dL) or more within 48 hours, an increase in SCr to 1.5 times the baseline within the last 7 days, or urine output less than 0.5 milliliters/kilogram/hour (mL/kg/h) for 6 hours. The AKI classification is shown in Table 2. Both the RA+ and RA groups were compared for the following outcome parameters: development of AKI and its severity. The RAI score was also co-correlated with risk factors for the development of AKI and short-term outcomes in these children in terms of duration of PICU stay, need for mechanical ventilation, development of ARDS, and mortality. Based on the KDIGO guidelines, stage 3 AKI is defined as an increase in SCr up to 3 times from baseline, a SCr level of >4.0 mg/dL (354 micromol/L), or the initiation of renal replacement therapy.

Statistical Analysis

All data were entered in Microsoft Excel version 2023 and analyzed using SPSS software version 23.0 for Windows (IBM Corp., Armonk, NY, USA). The categorial variables are presented as percentages, and the continuous variables are presented as the mean ± standard deviation (SD) or median. RAI score predictive ability was assessed by calculating sensitivity, specificity, positive predictive value, and negative predictive value. To predict the severity of AKI on day 3, receiver operating characteristic curves for day 0 RAI score and SCr were constructed. Other risk factors associated with AKI development were assessed using univariate and multivariate logistic regression. The categorical variables are presented as percentages. The numerical variables were compared using Student's t-test and the chi-square test. A p-value of 0.05 was considered statistically significant.

Results

As shown in Figure 1, out of the 125 children admitted to the PICU during the study period, 93 children who met the inclusion criteria were included in the study. Seven out of 125 children had elevated serum creatinine at admission, 12 children had PICU stay for less than 72 hours, 4 did not give consent for the study, day 3 serum creatinine was not measured in 4 children, and 5 who took discharge against medical advice were excluded from the study.

In present study 63.44% (n=59) were male. The majority of children aged less than 1 year (27.54%), as depicted in Figure 2. The mean age of the participants was 3.8 years (SD=4.05). The median height of the participants was 80 cm (QR=52) and median weight was 9 kg (QR=10.3).

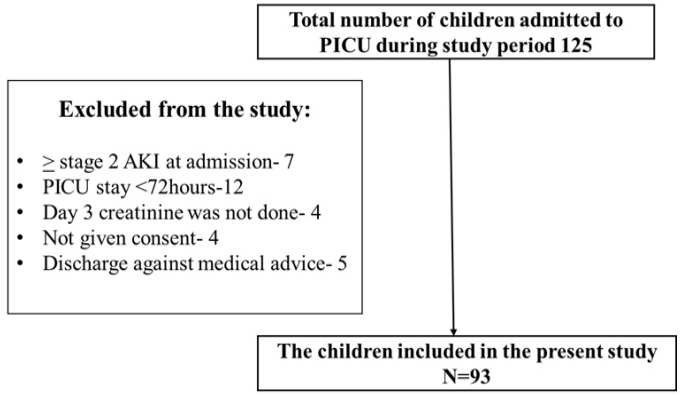

Figure 1. Flow chart of study participants
AKI: Acute kidney injury, PICU: Pediatric critical care unit

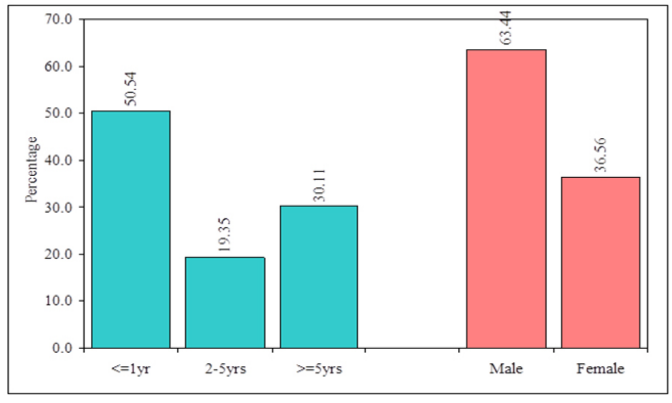

Figure 2. Demographic profile of the participants

Table 2. KDIGO staging of AKI in children

Stages	Serum creatinine	Urine output
Stage 1	1.5-1.9 times baseline Or >0.3 mg/dL increase	<0.5 mL/kg/hr for 6-12 hours
Stage 11	Increase >2-2.9 times baseline	<0.5 mL/kg/hr for >12 h
Stage 111	3.0 times the baseline Or >4 mg/dL initiation of renal replacement therapy in patients <18 hours, decrease in eGFR to <35 mL/min/1.73 m	<0.3 mL/kg/h for 24 hours or anuria for 12 hours

eGRF: Estimated glomerular filtration rate, AKI: Acute kidney injury, KDIGO: Kidney disease improving global outcome

In the present study, the prevalence of AKI was 22.58% (n=21). A positive RAI score was observed in 27.96% (n=26). Among children with positive RAI, 80.77% (n=21), 80.77% developed AKI. Of 72.04% (n=67), children were RAI negative, and none developed AKI. The association between positive RAI and AKI development is statically significant.

As shown in Table 3, the mean SCr level on day 0 was 0.40 and that on day 3 was 0.57; this difference in mean SCr was not statistically significant (p-value =0.1421).

Table 4 shows that RAI performed at the time of admission to predict the subsequent development of AKI on day 3 of admission had a specificity of 88.06%, sensitivity of 65.38%, and accuracy of 81.72%.

Figure 3 depicts the receiver operating characteristic curve constructed for assessing the individual values of day 0 RAI for predicting AKI on day 3, with an area under curve of 0.7672.

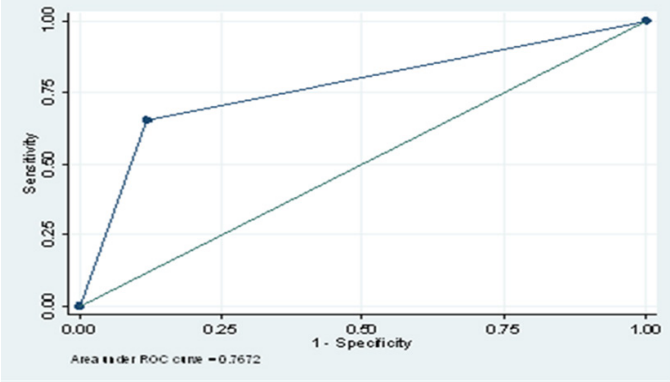

Figure 3. ROC curve for RAI and day 3 serum creatinine
RAI: Renal angina index, ROC: Receiver operating characteristic, area under curve =0.7672

Univariate regression analysis performed to evaluate the effect of individual parameters showed that the use of mechanical ventilation, inotrope, nephrotoxic drugs, presence of ARDS, and day 0 positive RAI score were significantly associated with the occurrence of severe AKI on day 3. Multivariate analysis showed that a positive day 0 RAI score was independently associated with the occurrence of Severe AKI on day 3, nephrotoxic drug usage, and need for mechanical ventilation, is show in Table 5.

Table 6 shows significant correlation between RAI score and elevated SCr level on day 3 and the development of AKI on day 3.

In the present study, the mortality rate was 23.6% (n=22). Among the 26 children who were RAI-positive, the mortality rate was 69.2% (n=18). The RAI was associated with increased mortality, and this association was statistically significant.

Discussion

The present study is a hospital-based prospective observational study. Results showed that a positive RAI obtained at admission was useful in predicting the development of AKI by day 3. RAI outperformed conventional baseline SCr level predicting AKI. The study, which included children with a similar range of disease severity (as accessed using PIM-3 score at admission), had a notably higher proportion of younger children in the RAI-positive group than in the RAI-negative group.

In the present study, 22.58% of children admitted to the PICU developed AKI on day 3 admission. Compared with previous studies done by Gawadia et al.[1], Basu et al.[2], Mehta et al.[13] and Naik et al.[4], the incidences of AKI were 70%, 13.6%,

Table 3. Compression of serum creatinine levels on days 0 and 3

Sr. Cr.	Mean	SD	Median	Quartile range
Sr. Cr. day 0	0.40	0.18	0.37	0.25*
Sr. Cr. 3	0.57	0.56	0.36	0.34*
Z-value	1.4680			
P-value	0.1421			

Data expressed as median (min-max), and mean, SD: Standard deviation, *Wilcoxon's matched-pair test

Table 4. Sensitivity, specificity, accuracy, and positive and negative predictive values of RAI

Statistic	Value	95% CI for OR
Sensitivity	65.38%	44.33% to 82.79%
Specificity	88.06%	77.82%-94.70%
Positive likelihood ratio	5.48	2.70 to 11.11
Negative likelihood ratio	0.39	0.23-0.67
Positive predictive value	68.00%	51.15%-81.18%
Negative predictive value	86.76%	79.33%-91.80%
Accuracy	81.72%	72.35% to 88.98%

CI: Confidence interval, OR: Odds ratio, RAI: Renal angina index

36.1%, and 90%, respectively. This variation in the incidence of AKI may be attributed to several factors, such as diagnosis at admission, presence of FO, use of nephrotoxic drugs, presence of sepsis, and MODS. The incidence of AKI increases with increasing severity of illness.

Severe AKI was observed in 80.77% of RAI-positive children. These study results are in line with the studies conducted by Gawadia et al.[1] and Menon et al.[14], where severe AKI was observed in 72% and 80% respectively. In present study, approximately 80% of children with positive RAI developed AKI on day 3 of admission. These results are in good agreement with the studies of Gawadia et al.[1] and Basu et al.[2] However, predictive value was lower in studies by Sethi et al.[16] and Kaur et al.[17] The predictive ability of RAI in the development of severe AKI on day 3 was AUC 0.76 with 95% confidence interval (CI) of 0.72-0.88, which was similar to the studies by Basu et al.[15] (AUC=0.86, with 95% CI of 0.75-0.86) and Sethi et al.[16] (AUC =0.73, 95% CI of 0.61-0.82).

In the present study, 26 children were RAI positive, among whom 10 (38.46%) developed ARDS, 24 (92.3%) required mechanical ventilation, and 18 (69.23%) required one or more inotropic supports. The study by Gawadia et al.[1] showed that among children with positive RAI, 71% required mechanical ventilation and 78% needed inotropic support. In another

Table 5. Association between individual parameters and positive RAI using univariate analysis

Factors	RAI <8	%	RAI ≥8	%	Total	%	Chi-square	p-value
Duration of stay								
<7 days	45	67.16	18	69.23	63	67.74	0.0370**	0.8480
≥7 days	22	32.84	8	30.77	30	32.26		
Sepsis								
Absent	46	68.66	14	53.85	60	64.52	1.7950**	0.1800
Present	21	31.34	12	46.15	33	35.48		
ARDS								
Absent	59	88.06	16	61.54	75	80.65	8.4410**	0.0040*
Present	8	11.94	10	38.46	18	19.35		
Nephrotoxic drugs								
No	25	37.31	4	15.38	29	31.18	4.1970**	0.0400*
Yes	42	62.69	22	84.62	64	68.82		
Inotropes								
No	57	85.07	8	30.77	65	69.89	26.2510**	0.0001*
Yes	10	14.93	18	69.23	28	30.11		
Mechanical ventilation								
No	49	73.13	2	7.69	51	54.84	32.3910**	0.0001*
Yes	18	26.87	24	92.31	42	45.16		
Stages of AKI								
Stage 0	67	100.0	5	19.23	72	77.42	69.8990**	0.0001*
Stage 1	0	0.00	21	80.77	21	22.58		
Mortality								
Recovered	63	94.03	8	30.77	71	76.34	41.5070**	0.0001*
Death	4	5.97	18	69.23	22	23.66		
Total	67	100.0	26	100.0	93	100.00		

**: Chi-square test, *: Independent t-test and p-value is <0.05, univariate regression analysis performed to evaluate the effect of individual parameters on positive AKI, AKI: Acute kidney injury, RAI: Renal angina index, ARDS: Acute respiratory distress syndrome

Table 6. Correlation between serum creatinine levels on days 0 and 3 and AKI stage with RAI

Variables	Correlation between RAI scores and			
	n	Spearman R	t-value	p-value
Serum creatinine level at day 0	93	0.0451***	0.4306	0.6678
Serum creatinine level on day 3	93	0.5751**	6.7059	0.0001*
Stage of AKI on day 3	93	0.7405**	10.5113**	0.0001*

***: Spearman's rank correlation,**: Student's t-test, *: Independent t-test, p-value <0.05 is taken as statistically significant, AKI: Acute kidney injury, RAI: Renal angina index

study by Menon et al.[14] showed 1.68% required mechanical ventilation, and 8.6% had a prolonged hospital stay among RAI-positive children.

The present study observed that there was increased mortality among RAI-positive children, accounting for 68.23% (p=0.0001). These results co-relate with the study by Gawadia et al.[1] and Menon et al.[14] where the mortality rates were 24% and 18.3% respectively.

In the present study, positive AKI was associated with increased severity of AKI on day 3. These children tended to have an increased incidence of ARDS, shock requiring inotropic support, need for mechanical ventilation, and increased mortality. Furthermore, logistic regression suggested that there was an independent association between positive RAI performed at admission, severity of AKI, increased need for mechanical ventilation, and mortality. These results are in parallel with those of Gawadia et al.[1] and Kaur et al.[17]

Study Limitations

The study should have included a large sample. Only short-term outcomes were analyzed; long-term follow-up of these children had not been done.

Conclusion

The RAI is a simple yet reliable predictor of the development of AKI in critically ill children. A positive RAI score emerges as a superior tool to help in the early reorganization of development AKI. This score is more useful in developing countries because it requires fewer investigations and can be easily applied in resource settings. The discriminative accuracy of RAI surpasses that of traditional creatinine-based renal injury parameters. Additionally, RAI has an independent predictive value for AKI severity, morbidity, and mortality in critically ill children.

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Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of the research. The study was conducted at the SDM College of Medical Sciences and Hospital, Dharwad, India (SDMIEC/2022/359).

Informed Consent: Informed consent from the parents or legal guardians of all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.S., K.D.S., D.P., Concept: A.S., K.D.S., D.P., Design: A.S., K.D.S., D.P., Data Collection or Processing: A.S., K.D.S., D.P., Analysis or Interpretation: A.S., K.D.S., D.P., Literature Search: A.S., K.D.S., D.P., Writing: A.S., K.D.S., D.P.

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Research Article / Özgün Araştırma

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Serum Level of High-mobility Group Box Protein-1 in Children with Sepsis, Severe Sepsis and Septic Shock

Sepsis, Ağır Sepsis ve Septik Şoklu Çocuklarda Yüksek Hareketli Grup Kutu Protein-1'in Serum Düzeyleri

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Abstract

Introduction: Sepsis is an important risk factor for morbidity and mortality in children. Early recognition of sepsis as the most important step in reducing morbidity and mortality. Due to the limitations of current diagnostic tests (i.e., poor sensitivity and delayed results), new research is needed to identify sepsis biomarkers. High mobility group box protein-1 (HMGB1) is one of the late mediators of sepsis. Comparing serum HMGB1 levels between healthy children and those with sepsis is the main goal of our research.

Methods: This prospective multicenter clinical trial. We prospectively collected 43 cases of sepsis treated (3 months to 17 years old) in two different pediatric intensive care units between January 1 and June 30, 2017. The sepsis group was subdivided into sepsis, severe sepsis, and septic shock. The patient and healthy control groups were compared (n=28). The following clinical situations were noted: Pediatric risk of mortality III (PRISM III) and pediatric logistic organ dysfunction (PELOD) scores; need for mechanical ventilation; presence of septic shock; need for plasmapheresis and renal replacement therapy; and death.

Results: Patients with sepsis had significantly increased HMGB1 levels compared with the healthy controls. Serum HMGB1 level was not associated with PELOD and PRISM scores (p>0.05). Serum HMGB1 levels were higher in patients with mortality than in those who survived, but the difference was not statistically significant.

Conclusion: Our study results showed that serum HGMB1 levels were higher in children with sepsis than in healthy children, and HMGB1 levels were also higher in patients with septic shock than in those without shock. More research is required to determine the response to therapy in children with sepsis in the pediatric critical care unit by serially measuring serum HGMB1 levels during the follow-up period.

Keywords: Sepsis, septic shock, high mobility group box protein-1, children, pediatric intensive care unit, mortality risk score

Öz

Giriş: Sepsis, çocuklarda morbidite ve mortalitenin önde gelen nedenlerinden biridir. Sepsisin erken tanınması, morbidite ve mortaliteyi azaltmak için en önemli adımdır. Mevcut tanı testlerinin sınırlamaları nedeniyle (yani zayıf hassasiyet ve gecikmeli sonuçlar), sepsis biyobelirteçlerini tanımlamak için yeni araştırmalara ihtiyaç vardır. Yüksek hareketli grup kutu protein-1 (HMGB1) sepsisin geç mediyatörlerinden biridir.

Yöntemler: Bu ileriye dönük çok merkezli bir klinik çalışmadır. İki farklı çocuk yoğun bakım ünitesinde 1 Ocak-30 Haziran 2017 tarihleri arasında tedavi edilen 43 sepsis olgusu (3 ay-17 yaş arası) ileriye dönük olarak toplanmıştır. Sepsis grubu sepsis hastaları, ağır sepsis olguları ve septik şok olarak alt gruplara ayrılmıştır. Hasta grubu sağlıklı kontrol grubu (n=28) ile karşılaştırılmıştır. Aşağıdaki klinik durumlar not edilmiştir: Pediyatrik mortalite riski III (PRISM III) ve pediyatrik lojistik organ disfonksiyonu (PELOD) skorları; mekanik ventilasyon ihtiyacı; septik şok varlığı; plazmaferez ve renal replasman tedavisi ihtiyacı; ve ölüm.

Bulgular: Sepsisli hastalarda sağlıklı gruba kıyasla HMGB1 anlamlı derecede artmıştır. Serum HMGB1 düzeyleri PELOD ve PRISM skorları ile ilişkili bulunmamıştır (p>0,05). Serum HMGB1 düzeyleri mortalitesi olan hastalarda hayatta kalanlara kıyasla daha yüksekti, ancak istatistiksel olarak anlamlı değildi.

Sonuç: Çalışma sonuçlarımız serum HGMB1 düzeylerinin sepsisli çocuklarda sağlıklı çocuklara kıyasla daha yüksek olduğunu ve HMGB1 düzeylerinin de septik şoklu hastalarda şoksuz sepsis bulgularına kıyasla daha yüksek olduğunu göstermiştir. Sepsisli çocukların çocuk yoğun bakım ünitesindeki takipleri sırasında serum HGMB1 düzeylerinin seri olarak değerlendirildiği ve tedaviye yanıtın bir belirteci olarak kullanıldığı ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Sepsis, septik şok, high mobility group box protein-1, çocuk, çocuk yoğun bakım, mortalite risk skoru

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Introduction

Severe sepsis and septic shock are clinical manifestations of sepsis, which is an infection-related systemic inflammatory response syndrome.[1] The rising prevalence of severe sepsis and septic shock, which affect millions of people annually and kill one in every four (often higher) cases, is an important issue in health care.[2] Sepsis is a potentially fatal organ failure caused by a host's dysfunctional reaction to infection.[3] It is one of the leading causes of admissions to pediatric intensive care unit (PICU). Severe sepsis is defined as an infection with at least one acute organ dysfunction.[4] Sepsis-associated organ dysfunction in children is characterized by severe infection resulting in either non-cardiovascular or cardiovascular organ dysfunction. Septic shock is defined as a severe infection resulting in hypotension, the need for vasoactive medication, or impaired perfusion.[5,6]The management of corticosteroids is complex and requires fluid resuscitation, appropriate administration of antibiotics, vasoactive drugs, and, under specific conditions, corticosteroids. In addition, the use of mechanical ventilators, plasmapheresis, and renal replacement therapy (RRT) can be necessary.[5]

The inflammatory response is the most prominent feature of sepsis. Therefore, studies have been conducted on the host immune response to develop new therapeutic strategies. Pro-inflammatory cytokines [e.g., tumor necrosis factor (TNF)-a and interleukin (IL)-1b] can cause tissue damage, metabolic acidosis, hypotension, multiple organ failure, and even death.[7] Approximately 30 years ago, high-mobility group (HMG) chromosomal proteins were identified in mammalian cells and given the name "HMG" due to their electrophoretic mobility in polyacrylamide gels.[8] The role of HMG1 as a non-histone chromosomal protein in DNA binding and its ability to alter the DNA helical structure was initially recognized in 1978.[9]

High mobility group box protein-1 (HMGB1) is a nuclear protein produced as part of the circulation of oxidative stress by activated macrophages and monocytes. It has pro-inflammatory characteristics. It continues to be evaluated as a potential treatment option because of its prolonged increase of 12-18 hours following TNF-α peaks.[10,11] HMGB1 seems to be a late modulator of life-threatening systemic inflammation in animal models, as well as a participant in delayed endotoxin mortality and systemic inflammation.[12-14] HMGB1 levels were previously studied in critically ill patients with sepsis, severe infection, or acute respiratory distress syndrome.[15,16] However, these studies were limited to a small number of patients in heterogeneous patient groups, especially adults. The purpose of the current study was to assess serum HMGB1 levels in children with sepsis at the time of diagnosis and to further explore its association with scoring systems, laboratory results, and outcomes.

Materials and Methods

Patients admitted to the two different PICUs were evaluated for sepsis prospectively between January 1 and June 30, 2017. Both PICUs are located in two large cities and serve as tertiary care centers for the region. Children aged 3 months to 17 years have been enrolled. Children who were treated due to sepsis at another center were excluded.

Baseline demographic characteristics, including age, sex, and underlying disease (chronic renal dysfunction, heart disease, neurological diseases such as epileptic/genetic syndromes, etc.) have been noted. Laboratory examinations, including hemoglobin, white blood cell count, platelet count, serum C-reactive protein, procalcitonin, fibrinogen, lactate, serum blood urea nitrogen, creatinine, aspartate transaminase, alanine transaminase, and albumin levels, were noted. The pediatric risk of mortality III (PRISM III) and pediatric logistic organ dysfunction (PELOD) scores of all patients were calculated and noted upon admission. Septic shock was defined as persistent hypotension despite adequate fluid resuscitation for at least 1 h. The primary aim of this study was to compare serum HMGB1 levels between children with sepsis and healthy children. The sepsis group was subdivided into sepsis, severe sepsis, and septic shock. Age- and sex-matched healthy children (without chronic and underlying conditions) served as controls. The following clinical situations were noted: Need for mechanical ventilation; Vasoactive amine requirement; Blood product administration; Need for plasmapheresis and RRT; and death. Their relationship with the HMGB1 level was also analyzed.

After the diagnosis of sepsis, which was confirmed by the pediatric intensivist, informed consent was obtained from the parents of the children. Blood cultures and serum samples were collected at the time of sepsis diagnosis. Serum samples were stored at 20 °C until serum HMGB1 analysis. HMGB1 was measured using a commercially available ELISA.

Statistical Analysis

Means and standard deviations were used to summarize quantitative data. Qualitative results were summarized using percentages and quantities. Because of the skewed nature of the data and the small sample size, simple univariate comparisons were performed using non-parametric techniques: Mann-Whitney U rank-sum test was used for quantitative data, and the chi-square test for homogeneity was used for qualitative data. Statistical significance was determined using a two-tailed p-value 0.05.

Results

The present research included 43 children diagnosed with sepsis in two tertiary PICUs using the "Surviving Sepsis

Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock" (1), as well as 28 healthy children as a control group. The demographic and clinical findings and laboratory parameters of children with sepsis are summarized in Tables 1 and 2. The patients were subdivided into three groups: children with sepsis, severe sepsis, and septic shock. A total of 7 patients had an underlying disease (2 patients with congenital heart disease, 5 patients with epilepsy). CRP and procalcitonin levels were significantly higher among patients with sepsis ($p<0.001$) and were significantly higher in the septic shock group compared with the sepsis group ($p<0.001$).

The serum HMGB1 level in the control group was 3.28±0.84 ng/mL. The median HMGB1 concentration of the patient group was 16.3 ng/mL [interquartile range (IQR) 5.3-23.8] and was significantly higher in children with sepsis than in the controls ($p<0.0001$) (Figure 1). When we compared serum HMGB1 levels among children with sepsis, severe sepsis, and septic shock, significantly increased HMGB1 levels were observed in children with septic shock ($p<0.05$ for both) (Figure 2). Serum HMGB1 level was not associated with PELOD and PRISM scores ($p>0.05$). The serum HMGB1 level was 25.7 ng/mL (IQR 4.86-65.5) and higher in the mortality group than in the surviving group (Figure 3).

Twenty-seven (62.7%) of 43 patients with sepsis (cases) required mechanical ventilation (MV). The mean MV time was 6.25±7.8 d. In the case group, the HMGB1 level was

Table 1. Demographic and clinical characteristics of the sepsis and control group

	Control group (n=28)	Sepsis group (n=43)
Age (months)	35.2±47.6 (6-160)	45.9±50.2 (3-200)
Gender (girls/boys)	15/13	22/21
Fever (°C)	36.1±0.6	37.9±1.22
Heart rate (per min.)	92±43	152±23
Respiratory rate (per min.)	26±12	36±19
Capillary refilling time (seconds)	1.5± 0.2	2.8±1.4
PRISM score	0	19.3±11.1
PELOD score	0	16.5±13.5

PRISM: Pediatric risk of mortality, PELOD: Pediatric logistic organ dysfunction

Table 2. Laboratory parameters of sepsis and control group

	Control group (n=28)	Sepsis group (n=43)
Hemoglobin (g/dL)	11.9±3.0	8.9±2.0
WBC (mm^3)	5700 (4800-7600)	11660 (1300-58900)
Platelet count ($10^3/mm^3$)	200 (162-460)	143 (500-789)
Fibrinogen (mg/dL)	260±95	313±167
C-reactive protein (mg/L)	3.1 (2.0-5.0)	59 (17.0-101.2)
Procalcitonin (ng/mL)	0.03 (0-0.04)	12.16 (3-86)
Blood urea nitrogen (mg/dL)	11.9 (5-16)	12.9 (2-73)
Creatinine (mg/dL)	0.32 (0.2-0.6)	0.67 (0.04-2.25)
AST (IU/L)	20 (12-40)	58 (13-4100)
ALT (IU/L)	12 (9-22)	46.5 (6-3450)
Albumin (g/dL)	3.8 (3.6-4.9)	2.78±0.6
Lactate (mmol/L)	0.9 (0.8-1.6)	2.7 (0.7-22)
HMGB1 (ng/mL)	3.28±0.84	16.3 (5.3-23.8)
PaO_2/FiO_2	-	252±92

WBC: White blood cell count, HMGB: High-mobility group box protein-1, PAO_2/FiO_2: Ratio of arterial oxygen partial pressure to fractional inspired oxygen, AST: Aspartate transaminase, ALT: Alanine transaminase

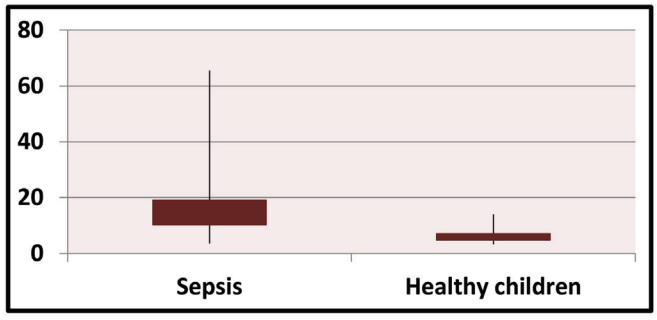

Figure 1. Serum high mobility group box protein-1 levels in sepsis and control groups

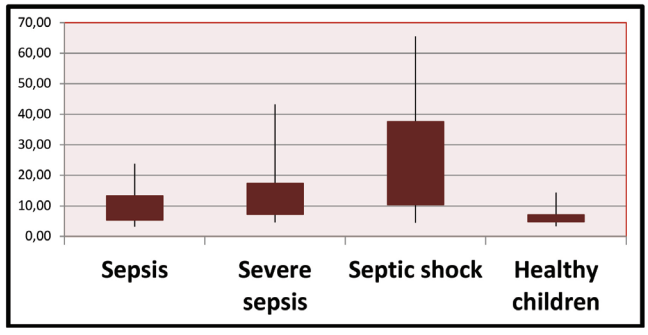

Figure 2. Serum high mobility group box protein-1 levels in children with sepsis, severe sepsis, and septic shock compared with healthy children

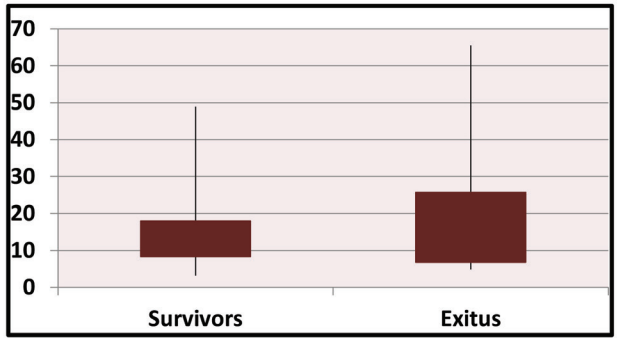

Figure 3. Serum high mobility group box protein-1 levels regarding to prognosis

not associated with the need for MV or the time (d) for MV. Concerning hemodynamic changes. In the patient group, 31 children (72%) required the usage of vasoactive amines. Twenty-eight patients (65.1%) needed a transfusion of bloo1d components. Nine patients (20.9%) received Intravenous immunoglobulin and five patients (11.6%) required corticosteroid treatment. Concerning renal function, the median serum creatinine level was 0.67 (QR 0.04-2.25) mg/dL among the case group. Eighteen patients in the case group (41.8%) had acute kidney injury secondary to sepsis, and eight (18.6%) required renal replacement therapy. Plasmapheresis was performed in six patients (13.9%) with thrombocytopenia associated with multi-organ failure.

The average length of stay of patients in the PICU was 14 days (2-58). Twenty-one (67.4%) were discharged from the PICU before 28 days, six (13.9%) stayed for more than 28 days, and sixteen (37.2%) died.

Discussion

The function of HMGB1 in pediatric disorders needs to be clarified because disease characteristics differ between children and adults. In the present study, we evaluated the relationship between HMGB1 levels and the severity of several pediatric sepsis syndromes and outcomes, such as sepsis, severe sepsis, and septic shock. In all pediatric sepsis situations have higher levels of HMGB1 than healthy participants. There was a significant association between the severity of pediatric sepsis and HMGB1 level. Sepsis is mediated by late-stage HMGB1, as opposed to earlier inflammatory agents like TNF-α and IL-1β. According to the findings of our research, the serum HGMB1 level of children can be a useful marker for both the presence of sepsis and the diagnosis of septic shock.

Clinical observational studies have demonstrated that HMGB1 levels significantly increase in the serum of patients with suspected infection, pneumonia, and sepsis. HMGB1 is typically found at a plasma level of 5 ng/mL in healthy animals and healthy individuals. However, in patients with septicemia, HMGB1 levels are elevated to an average of 25.2 ng/mL in survivors and 83.7 ng/mL in non-survivors.[13] In our present study, HMGBl levels of healthy children were compared, and the result showed that HMGB1 levels of the control group (3.28±0.84 ng/mL) were lower than those of the sepsis group [16.3 ng/mL (IQR 5.3-23.8) ($p<0.001$). The findings suggested that HMGB1 levels were related to both the development and onset of sepsis. In addition, the serum HMGB1 level of patients in the septic shock group [37.6 ng/mL (IQR 10.4-65.5)] was higher than that of the sepsis group ($p<0.05$).

The role of HMGB1 in the severity and outcome of pediatric sepsis syndromes has not been extensively studied. Serum HMGB1 levels were higher in septic patients who died from infection than in those who survived, indicating that this protein should be further studied as an option for therapy.[14] Sundén-Cullberg et al.[15] observed a rise in serum HMGB1 levels during sepsis. The results revealed that IL-6, IL-8, IL-10, and TNF-α levels were considerably elevated in the shock group. However, contrary to our findings, the authors observed no major difference in HMGB1 levels between the severe sepsis and septic shock patient groups.[15] A different investigation found that the degree of organ failure during septic shock was connected with the plasma concentration of HMGB1 and that the concentration increased over time in patients who were more severely affected.[16] Currently, our understanding of the relationship between local HMGB1 release, serum HMGB1 levels, infection site damage, and organ damage in patients with sepsis remains incomplete.

Similarly, Pavare et al.[17] demonstrated that LPS-binding protein, IL-6, and CRP are correlated with the severity of infections in children, although HMGB1 does not appear to play a significant role. One explanation could be that the investigators looked at early inflammation, whereas HMGB1 is frequently raised in the later phases of sepsis. Our study evaluated HMGB1 levels at the time of sepsis diagnosis without repetitive measurements, but we found a significant difference between the sepsis and septic shock patient groups. Consequently, the impact of HMGB1-induced inflammatory activation in several systems has gained interest. HMGB1 has been highlighted as an alarming sign associated with various disorders connected with inflammation.[18]Although there is currently no efficient treatment for sepsis that results in a high rate of mortality and morbidity, the identification of HMGB1 as a strong late cytokine mediator of endotoxemia and sepsis has opened up new research avenues for the development of therapies for sepsis. Delayed treatment targeting HMGB1 within 24 hours after experimental sepsis is an effective and unique treatment strategy for life-threatening sepsis. Nevertheless, further investigation is needed in other crucial domains, such as the mechanisms governing the release of HMGB1 from cells, surface receptors that engage with HMGB1, and intracellular signal transduction pathways through which HMGB1 acts as a pro-inflammatory cytokine.[18] Examining these issues will enhance our understanding of the role of HMGB1 and potentially provide a way for the development of targeted and time-sensitive treatment medicines that can decrease the severe mortality and morbidity associated with sepsis.

Conclusion

Our study results showed that serum HGMB1 levels were higher in children with sepsis than in healthy children, and HMGB1 levels were also higher in patients with septic shock

than in those without shock. A recent study showed that serum HGMB1 levels are higher in children with multi-organ failure. Our study results also showed a higher proportion of patients who died due to sepsis; however, we did not show statistical significance.

Study Limitations

A limitation of our study is the difference in the definitions of sepsis and septic shock in the years when our study was conducted. We also did not evaluate the kinetics of inflammation markers, such as CRP, PCT, and HMGB1 repeatedly during hospitalization. Further studies with serial evaluation of serum HGMB1 levels during the follow-up period of children with sepsis in pediatric intensive care units using as a marker of response to therapy are needed.

Ethics

Ethics Committee Approval: This study was approved by the Eskişehir Osmangazi University Local Ethical Committee (11.01.2016/05).

Informed Consent: After the diagnosis of sepsis, which was confirmed by the pediatric intensivist, informed consent was obtained from the parents of the children

Footnotes

Authorship Contributions

Concept: E.K., D.Y., E.Ç.D., Design: E.K., D.Y., E.Ç.D., Data Collection or Processing: E.K., Ö.Ö.H., F.E., G.B., Analysis or Interpretation: E.K., D.Y., E.Ç.D., Literature Search: E.K., Writing: E.K., E.Ç.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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Research Article / Özgün Araştırma

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Awakening ECMO During Pediatric Extracorporeal Membrane Oxygenation: A Single-center Experience

Pediyatrik Ekstrakorporeal Membran Oksijenasyonu Sırasında Uyanık ECMO: Tek Merkez Deneyimi

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Abstract

Introduction: Recently, some centers have used extubation during extracorporeal membrane oxygenation (ECMO) to eliminate barotrauma and volutrauma as a lung rest strategy. This study aims to demonstrate the use of extubation during ECMO in children.

Methods: This retrospective study was conducted from January 1, 2015, to April 1, 2023, in our pediatric intensive care unit.

Results: In this study, we presented six cases that were extubated during ECMO support. In addition, we followed 130 pediatric patients on ECMO in the same period. Two patients were primarily diagnosed with cardiomyopathy, one with myocarditis, two with congenital heart defect, and one with necrotizing pneumonia. The median age of patients was 99 (interquartile range 25-75) (16.5-192) months, and all were male. Venoarterial ECMO was connected to 4 patients, and venovenous ECMO was connected to 2 patients. Six patients were extubated during ECMO on the 5th, 12th, 3rd, 4th, 3rd and 14th days of their treatment, respectively. While the patients were extubated, three of them were supported by biphasic positive airway pressure, one was supported by nasal continuous positive airway pressure, and two were provided with supplementary oxygen. Three patients were extubated under ECMO and discharged.

Conclusion: The risk of mechanical ventilation related complications such as volutrauma and barotrauma could minimized in patients extubated under ECMO. In addition, sedatives, analgesics, and

Öz

Giriş: Son zamanlarda, bazı merkezler ekstrakorporeal membran oksijenasyonu (ECMO) sırasında hastaları ekstübe ederek akciğer dinlenme stratejisi olarak barotravma ve volütravmayı ortadan kaldırmayı planlamışlardır. Bu çalışmada, ECMO desteği sırasında ekstübe edilen çocuk hastaların klinik sonuçlarını göstermeyi planladık.

Yöntemler: Bu geriye dönük çalışma, 1 Ocak 2015 ile 1 Nisan 2023 tarihleri arasında çocuk yoğun bakım ünitemizde gerçekleştirilmiştir.

Bulgular: Bu çalışmada, ECMO desteği sırasında ekstübe izlenen altı çocuk hasta sunulmuştur. Aynı zaman aralığında merkezimizde 130 çocuk hasta ECMO'da izlendi. ECMO'da uyanık takip edilen hastalardan ikisi kardiyomiyopati, ikisi doğuştan kalp hastalığı, biri miyokardit ve biri nekrotizan pnömoni tanısına sahipti. Hastaların median yaşı 99 (çeyrekler arası aralık 25-75) (16,5-192) aydı ve hastaların hepsi erkekti. Dört hasta venoarteriyel ECMO, 2 hastaya venovenöz ECMO'ya bağlandı. Altı hasta ECMO'ya bağlandıktan sonra sırasıyla 5., 12., 3., 4., 3. ve 14. günlerinde ekstübe edildi. Hastalar ekstübe edildikten sonra üç hastaya Bifazik pozitif hava yolu basıncı, bir hastaya nazal sürekli pozitif hava yolu basıncı non-invaziv solunum desteği verildi. ECMO altında ekstübe edilen üç hasta taburcu edildi.

Sonuç: ECMO desteği sırasında ekstübe edilen hastalarda volutravma ve barotravma gibi mekanik ventilasyonla ilişkili komplikasyon riski en aza indirilebilir. Ayrıca, sedatifler, analjezikler ve kas gevşeticilerle

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Abstract

muscle relaxant related complications such as delirium, muscle weakness, or prolonged ventilation could reduced via awake ECMO.

Keywords: Extracorporeal membrane oxygenation, extubation, mechanical ventilation, child

Öz

ilişkili komplikasyonlar olan deliryum, kas zayıflığı veya uzun süreli ventilasyon, uyanık ECMO ile azaltılabilir.

Anahtar Kelimeler: Ekstrakorporeal membran oksijenasyonu, ekstübasyon, mekanik ventilasyon, çocuk

Introduction

Extracorporeal membrane oxygenation (ECMO) is a widely used life-saving intervention for children with circulatory and respiratory failure that is refractory to standard therapies.[1] Due to advances in extracorporeal life support (i.e., technical devices, cannulation technique, specialized ECMO teams), ECMO has become a safe tool in pediatric intensive care.[2] These developments in ECMO may be used for pediatric and adult patients for weeks for recovery and bridge therapy to left ventricular assist device implantation or transplantation.[2] ECMO performs this by regulating cellular respiration, improving tissue oxygenation, and allowing CO_2 removal.[3] It is, however, an invasive treatment method and can cause potential serious complications. ECMO has been considered the last treatment option to be used only when traditional treatments do not respond and only for a sufficient duration until the patient may be returned to more "standard" support modalities (mechanical ventilation, inotropic support, and cardiopulmonary resuscitation).[3]

During ECMO, patients are often prescribed a lot of sedatives-analgesics and invasive mechanical ventilation (MV) to avoid fatal decannulation and facilitate ECMO performance. Sedation also reduces oxygen consumption, thereby improving arterial oxygen transport and organ perfusion. Nevertheless, both sedation and MV may cause complications.[4] Long-term sedation and neuromuscular blockade therapy may cause muscle weakness, disability, tolerance, delirium, or prolonged recovery time. Possible invasive MV-related complications include tracheal irritation due to the intubation tube, discomfort, and the need for more sedation. In addition, it might cause ventilator-related complications, such as ventilator-associated pneumonia, pneumothorax, or respiratory muscle weakness.[3] There is a growing interest in reducing exposure to narcotics, sedatives, and neuromuscular blocking agents and keeping ECMO patients awake and mobile to maintain muscle strength and shorten recovery times. Recently, a method of extubation from MV under ECMO, especially for patients with respiratory failure and as a bridge therapy to lung transplantation, has emerged.[5-8] However, extubation practices and management options during ECMO in pediatric intensive care units have not been adequately reported. This study presents the clinical findings of six children who were electively extubated during ECMO, along with an expanded discussion of two representative cases.

Materials and Methods

Patients

This retrospective study was conducted from 2015 to 2023 in our pediatric intensive care unit. We present six cases of extubation during ECMO support. In addition, we followed up 130 pediatric patients on ECMO during the same period. Patient demographic data and clinical and laboratory data were obtained from medical records.

In our clinic, 130 pediatric patients have been connected to ECMO so far, and 6 of them have been extubated during ECMO. Based on the extubation protocol in our clinic;

1. The patient's FiO_2<40% and SpO_2>92% in IMV,

2. No respiratory effort at low pressures and minimal settings in the IMV,3. The patient becomes conscious after discontinuing sedation,4. After monitoring the IMV in continuous positive airway pressure (CPAP)/pressure support ventilation (PSV) mode (PSV 6, positive end-expiratory pressure 6 FiO_2 40%) for 1-2 hours, there is no respiratory effort, and the patient is extubated if there is no acidosis or hypercarbia in the blood gas.

Ethical Considerations

Voluntary consent was obtained from the families of the patients included in the study. The study was approved by the Institutional Review Board of the Ankara University Faculty of Medicine (approval number: İ06-384-23, 2023/06).

Statistical Analysis

Statistical analyses were performed using SPSSv26.0 (Statistical Package for Social Sciences for MacOS, Inc., USA). Descriptive variables are presented as frequencies and proportions (%). Continuous variables are presented as median (lower-upper limit) values.

Results

Six children were extubated during ECMO support. The median age of patients was 99 [interquartile range (IQR) 25-75] (16.5-

192) months, and all were male. Two patients were primarily diagnosed with cardiomyopathy, one with myocarditis, two with congenital heart defects, and one with necrotizing pneumonia. Venoarterial (VA) ECMO was connected to 4 patients, and venovenous-venoarteriovenous (VV) ECMO were connected to 2 patients. The peripheral ECMO was connected in five patients, whereas the central ECMO was connected in one patient. One patient who was connected to VV ECMO subsequently underwent venoarteriovenous (VAV) ECMO due to cardiogenic shock. Five patients were connected to ECMO for cardiac failure, and one patient was connected to respiratory failure.

Six patients were extubated during ECMO on the 5th, 12th, 3rd, 4th, 3rd and 14th days of treatment, respectively. The median number of days extubated during ECMO was 4.5 (IQR3-12.5) days. The durations of remaining extubation while on ECMO were 8, 9, 3, 6, 13, and 3 days for six patients, respectively. The median day of extubation duration under ECMO was 7(IQR 3-10) days. While the patients were extubated, three received biphasic positive airway pressure (BIPAP), one received nasal-CPAP (N-CPAP), and two were provided with supplementary oxygen. Five patients were reintubate during ECMO. Four patients were intubated due to increased respiratory distress, and one patient was intubated after decannulation. ECMO complications were observed in 4 patients, including bleeding in 4 cases, limb ischemia in 1 case, and circuit clotting in 3 cases. Three patients who were extubated under ECMO survived. Two patients were discharged with no neurological sequel.

Case 1

A 3-year-old male patient was transferred to our pediatric intensive care unit (PICU) following video-assisted thoracoscopic surgery (VATS) for necrotizing pneumonia and empyema. When the patient was admitted to intensive care, chest tubes were placed in both hemithorax. The chest X-ray taken in another center revealed pleural effusion, and the fluid was exudated via thoracentesis (Figure 1A). It was reported that the patient had cavitary lesions and consolidation areas that were evaluated in favor of bilateral necrotizing pneumonia and bilateral pleural effusion on CT thorax. The patient had respiratory distress and desaturation, requiring intubation. VATS was performed on the 2nd day of hospitalization. The patient was diagnosed with necrotizing pneumonia and metapneumovirus and was intubated following video-assisted thoracoscopic surgery (VATS). Oseltamivir was administered after the pleural fluid sample tested positive for influenza A (H1N1) and bocavirus via polymerase chain reaction (PCR). In addition, meropenem, vancomycin, and levofloxacin were initiated. On the 7th day of PICU admission, the patient was admitted to venovenous (VV) ECMO because of severe hypoxemia and respiratory acidosis in a high ventilator setting. The ECMO settings were an RPM of 4500/min and LPM of 1200 mL/min. Cardiac arrest occurred twice, and cardiopulmonary (CPR) resuscitation was performed within 5 and 12 min, respectively. The patient was extubated on the 12th day of ECMO, and BIPAP was subsequently applied at the full-face interface (Figure 1B, C). He was decannulate on

Figure 1. (A) Chest X-ray of patient 1 on the first day of PICU admission, showing poor pleural effusion and lung parenchyma. (B) Awake ECMO and supported by non-invasive mechanical ventilation via full face interface. (C) Lung parenchyma was better on chest X-ray when the child was discharged to the infectious ward
PICU: Pediatric intensive care unit, ECMO: Extracorporeal membrane oxygenation

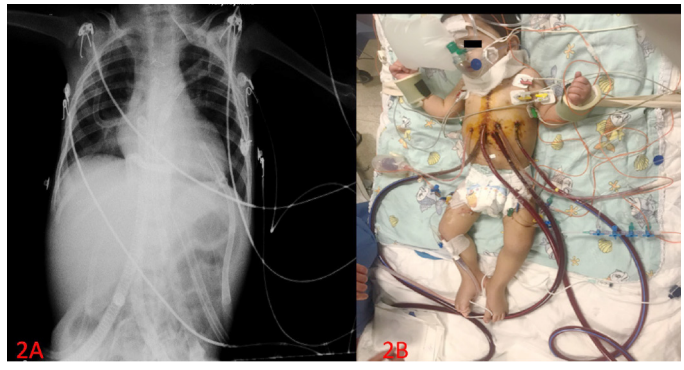

Figure 2. (2A) Patient 2' chest X-ray and (2B) appearance during mechanical biventricular support; he is extubated and only given oxygen support

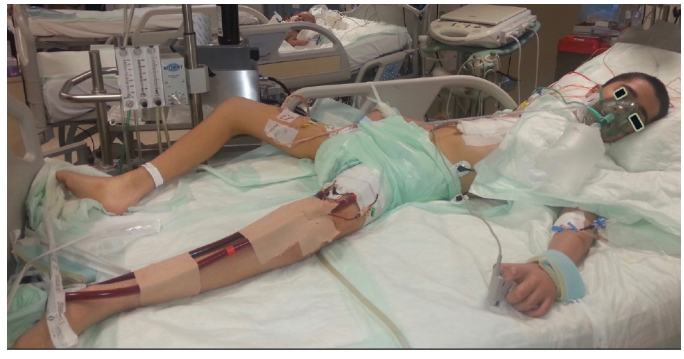

Figure 3. Patient 3 was extubated despite femoral ECMO, and a non-rebreathing mask was applied
ECMO: Extracorporeal membrane oxygenation

the 22nd day of ECMO, but BIPAP was continued until two days after ECMO removal. The patient was subsequently transferred to the pediatric infection disease unit on the 38th day of PICU admission with normal vital signs. He was discharged on the 44th day of hospitalization.

Case 2

A 17-month-old male patient was admitted to our PICU after the establishment of central VA ECMO due to fulminant myocarditis. The patient's cardiac function was poor, with an ejection fraction of the left ventricular of 15%, and there was severe metabolic acidosis and recurrent ventricular tachycardia. ECMO was connected for these reasons. When the patient was admitted to the PICU, the ECMO settings were RPM 5200/min and LPM 1100/min. On the 2nd day of PICU admission, we changed to a central ECMO cannulation site as VA-ECMO was set biventricular separately (for left ventricular, from apex of the left ventricle to ascending aorta; for right ventricle, from right atrium to pulmonary artery). Via a levitronix support device. The patient was started on lidocaine and amiodarone because of ventricular tachycardia attacks. Influenza A was identified as the cause of myocarditis based on respiratory viral PCR panel analysis. On the 3rd day of PICU admission, the ECMO circuit was changed because of a thrombus.

We decided to extubate him due to the clinical state of the lung, and neurologic findings were good despite biventricular dysfunction in the heart. The patient was extubated on the 10th day of ECMO, and subsequently, a non-rebreathing mask was applied (Figure 2A). On the 15th day, the right ventricular support device was removed, and the patient was reintubate before surgery. On the 22nd day after left support device placement, the patient was extubated again (Figure 2B). The left support device was removed on day 26, but the patient was not intubated. On the 34th day of admission, the patient was transferred to the cardiology department with intermittent ventricular tachycardia and a good neurological state.

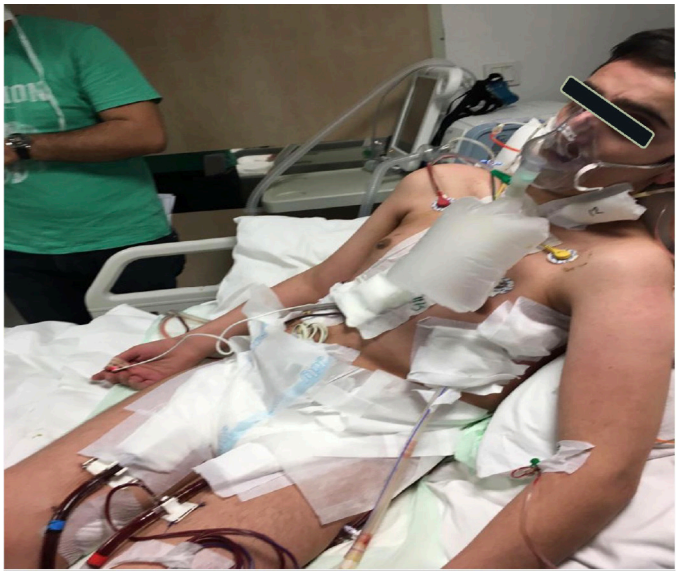

Figure 4. Image of Patient 4 during ECMO extubation. He could communicate and be fed at the same time
ECMO: Extracorporeal membrane oxygenation

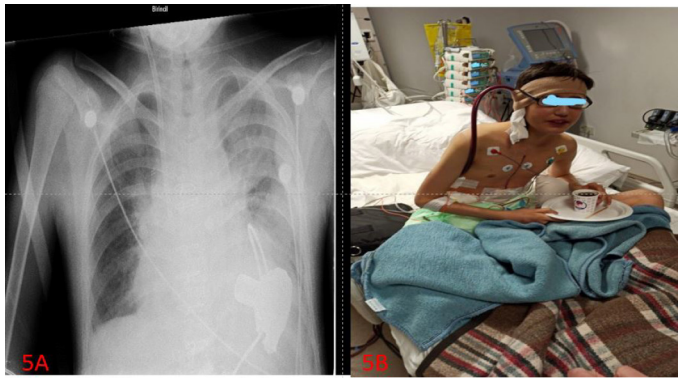

Figure 5. (A) Patient 5' chest X-ray during extubation while under VV ECMO and LVAD implantation. (B) Patient 5 could speak easily and eat breakfast during awake
ECMOLVAD: Left ventricular assist device, ECMO: Extracorporeal membrane oxygenation, VV: Venoarteriovenous

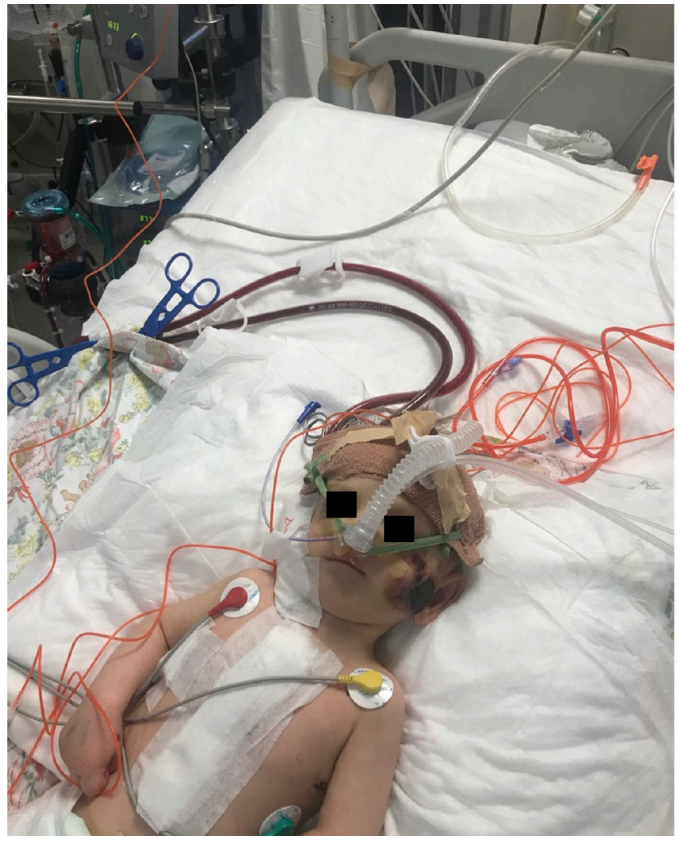

Figure 6. Patient 6 was supported by N-CPAP during awake ECMO
ECMO: Extracorporeal membrane oxygenation, N-CPAP: Nasal-continuous positive airway pressure

Table 1. Patients' demographic, diagnoses and clinical features

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (y)	3,5	1,5	16	16	13	1
Gender	Male	Male	Male	Male	Male	Male
Weight (kg)	18	11	40	54	50	7.5
Height (cm)	95	80	145	170	170	67
BSA (m2)	0.73	0.50	1.28	1.54	1.47	0.38
Primary disease	Necrotizing pneumonia	Myocarditis	Epstein anomaly	Dilated cardiomyopathy-implanted LVAD Heart transplanted	Discordant criss-cross heart	Ventricular septal defect, patent ductus arteriosus
ECMO indication	Respiratory	Cardiac	Cardiac	Cardiac	Cardiac	Cardiac
ECMO type	VV	VA	VA	VA	VV, VA-V	VA
Venous cannula insertion site	RIJV	Right atrium-left atrium (BVAD)	LFV	RFV	RFV, RIJV	RIJV
Artery cannula insertion site	N	Pulmonary artery-Ascending aorta (BVAD)	LFA	RFA	RFA	Ascendin aorta
Duration of ECMO (days)	23	28	6 (47)	46	28	16
Complications during ECMO	Bleeding	Clotting in circuit	Limb ischemia	Bleeding, clotting in circuit	Bleeding, Clotting in circuit	Bleeding
Sedation type during ECMO	Midazolam, fentanyl	Midazolam, fentanyl	Midazolam	Midazolam	Midazolam, fentanyl	Midazolam, fentanyl
Sedation used during post extubation on ECMO	Fentanyl	Fentanyl	N	N	N	N
Duration of extubation (days)	8	5 (under BVAD), 4 (under LVAD)	3	6	13	3
Extubation day under ECMO	5.	12.	3.	4.	3.	3.
Respiratory support while extubated under ECMO	BIPAP	Oxygen mask	BIPAP	BIPAP	Oxygen mask	N-CPAP, BIPAP
Reintubation during ECMO	Y	Y	Y	Y	Y	N
Reintubation indication	Respiratory distress	when removing the cannula RVAD	Respiratory distress and hypotension	Respiratory distress and hypotension	Respiratory distress and hypotension	
On the day after decannulation, it was extubated	Yes	Yes	N	N	N	Y
Length of duration between decannulation and discharge (days)	8	8	N	N	N	95
Neurological sequeal	None	None				
Outcome	Survived	Survived	Non-survived	Non-survived	Non-survived	Survived

BSA: Body surface area, VA: Venoarterial, VV: Venovenous, VA-V: Venoarterio-venous, Y: Yes, N: No, RIJV: Right internal jugular vein, RFA: Right femoral arteria, LFA: Left femoral arteria, LFV: Left femoral vein, BVAD: Biventriculary asist device model, BiPAP: Bilevel positive airway pressure, N-CPAP: Nasal-continuous positive airway pressure

The demographic characteristics, diagnoses, and clinical features of the patients are presented in Table 1. Image of the other patients during awake ECMO are shown in Figures 3-6 respectively.

Discussion

Patients are often subjected to severe sedation and invasive MV to avoid fatal decannulation during ECMO running.[4,8] Some centers use extubation during ECMO to completely eliminate barotrauma and volutrauma as a lung rest strategy in adults.[9] Sedation reduces oxygen consumption, thereby improving arterial oxygen transport and organ perfusion, and decreases the irritative effect of the endotracheal tube.[4,8] However, complications such as sedation habits, dose increase, delirium, or neuromuscular decompression may occur due to sedation. In addition, clinical conditions such as stroke may be masked in patients under sedation.[3,4,10] Benefits include reduced sedation need, increased mobility, and enhanced

interaction with the environment. However, the adoption of this application requires careful planning. Patients who are extubated can be reintubate again.[11] In our study on sedation therapy under ECMO, two patients were treated with midazolam and four were treated with midazolam and fentanyl. After extubation while still connected to the ECMO, the dose of sedation treatment was reduced and then stopped.

In addition, awake ECMO is important to assess the clinical and neurological status before transplantation in patients who are candidates for lung transplantation followed by on ECMO.[12] The practice of awake ECMO may strengthen the transplant candidacy by improving the neuromuscular condition of these patients through physiotherapy and advanced nutrition.[12]

A study on awake ECMO in adults was beneficial for pulmonary transplant candidates.[13] In this study, patients intubated during ECMO required longer invasive respiratory support after transplantation and longer intensive care unit stays compared with the awake ECMO group.[13] The 6-month survival rate was higher in the awake ECMO group in this study.[13]

Pediatric awake ECMO was first reported by Anton-Martin et al.[3]. This study was conducted between 1996 and 2013 with 16 pediatric patients who were extubated while receiving ECMO support. There were 511 patients connected to ECMO. Fourteen of them were connected to ECMO due to respiratory failure and 2 patients for cardiac reasons. Eleven patients had VV ECMO, and 5 patients had VA ECMO. Three patients were reintubate due to arrhythmia and intracranial bleeding. During ECMO, the extubation time was reported as an average of 6 days. Eleven patients who were extubated during ECMO survived.[3] In our study, we reported 6 cases with awake ECMO and followed up 130 pediatric patients who were connected to an ECMO for the same period of time in our PICU.

Similarly, in a study conducted by Schmidt et al.[2] 6 pediatric patients were extubated under ECMO. Six patients were connected to VA ECMO support for cardiac reasons. The number of days extubated under ECMO was 9.5 days, and the mean time to extubation was 78% of the total ECMO time in these patients. The mean duration of ECMO was 17.4 days. One patient was lost during follow-up.[2]

In this study, we presented 6 cases that were extubated while under ECMO. Four of the patients were connected to VA ECMO, and two of them were connected to VV ECMO. Patient 2 was connected to central ECMO, while the others were connected to peripheral ECMO. The durations of our patients' stays at ECMO were 23, 28, 47, 46, 28, and 16 days, respectively. The patients were extubated while still connected to ECMO on the 5th, 12th, 3rd, 4th, 3rd, and 14th days, respectively. Extubation under ECMO was performed on the 8th, 9th (5 days when the right support device was removed, 4 days when the left support device was removed), 3rd, 6th, 13th, and 3rd days, respectively.

During ECMO, an average extubation time was reported as an average of 7-8 days. Two patients who underwent VV ECMO had the longest extubation time. During awake ECMO, three patients were supported by BIPAP, one patient was supported by N-CPAP, and two patients were given only oxygen supplement. Except for patients 1 and 6, four patients were reintubate for various reasons during ECMO support. Patients 3, 4, and 5 were intubated during decannulation. These patients were reconnected to ECMO because of their worsening status on the same day after decannulation, and three patients were lost despite all interventions during follow-up. Patient 2 was intubated during decannulation, and then patient 2 was extubated. Patient 6 was intubated 29 days after ECMO decannulation. Three patients were extubated during ECMO support and survived.

In our study, ECMO-related complications were observed. ECMO complications are common, including bleeding, stroke, limb ischemia, thrombosis, and infection.[14] Although the most common complications are bleeding (30-40%) and infection (31%), it has been reported that there is at least one major complication in more than half of ECMO patients.[14] In our study, bleeding was observed in four of the patients as an ECMO complication. The ECMO set was changed in 3 patients due to thrombus (changed twice in one patient). None of the patients underwent incidental ECMO decannulation. All patients were treated with heparin during ECMO. The heparin dose was evaluated using activated clotting time and activated partial thromboplastin time tests. CRRT treatment was administered to patients 3, 4, and 5 due to the fluid load under ECMO.

The implementation of awake ECMO requires meticulous team planning and a thorough evaluation of the potential benefits and risks to the patient. To avoid the risks of decannulation, under the supervision of the patient's parents, nurses, and physicians, the patient's cannula was also fixed with a coban bandage, and a mesh cap was placed in the exit of the cannula.

Before performing extubation during ECMO, the benefits of extubation should be determined on a patient-based basis. Before this procedure, the expected time to ECMO, possibility of accidental decannulation of the ECMO circuit during extubation, and possibility of emergency reintubation should be considered. This important decision should be made by a multidisciplinary team, and the patient's family should be informed about this issue.

Conclusion

As a result, the risk of mechanical ventilation-related complications, such as volutrauma and barotrauma, is minimized in patients extubated under ECMO. In addition, sedatives, analgesics, and muscle relax-related complications, such as delirium, muscle weakness, and prolonged ventilation, are reduced via awake ECMO. In patients whose sedation needs are reduced, communication with the environment increases, and clinical conditions such as stroke may be noticed more easily.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Review Board of the Ankara University Faculty of Medicine (approval number: İ06-384-23, 2023/06).

Informed Consent: Voluntary consent was obtained from the families of the patients included in the study.

Footnotes

Authorship Contributions

Concept: E.G., T.K., Design: E.G., E.B., F.K., M.C.S., A.G., T.K., Data Collection or Processing: E.G., E.B., F.K., M.C.S., A.G., T.K., Analysis or Interpretation: E.G., E.B., M.C.S., A.G., T.U., Ö.S.C., E.Ç., M.Ç., Z.E., A.R.A., T.K., Literature Search: E.G., T.U., Ö.S.C., E.Ç., M.Ç., Z.E., A.R.A., T.K., Writing: E.G., T.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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Beyond the Expected: Importance of Recognizing Intussusception in Diabetic Ketoacidosis

Beklenenin Ötesinde: Diyabetik Ketoasidozda Unutulmaması Gereken Bir Tanı: İnvajinasyon

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Abstract

Diabetic ketoacidosis (DKA) generally presents as an initial manifestation of Type 1 diabetes mellitus, particularly in children. While symptoms like abdominal pain, vomiting, and nausea are commonly associated with DKA, clinicians should also consider rare situations such as intussusception. Intussusception, a rare clinical diagnosis in adolescents, can result from lead points and metabolic changes. This case report highlights the occurrence of intussusception in an adolescent with DKA and explores the potential mechanisms linking these two conditions.

Keywords: Diabetic ketoacasosis, adolescent, intussusception

Öz

Diyabetik ketoasidoz (DKA) genellikle özellikle çocuklarda Tip 1 diabetes mellitusun ilk belirtisi olarak ortaya çıkar. Karın ağrısı, kusma ve bulantı gibi semptomlar genellikle DKA ile ilişkilendirilirken, klinisyenler invajinasyon gibi nadir durumları da göz önünde bulundurmalıdır. Ergenlik dönemi için nadir bir klinik tanı olan invajinasyon, öncü noktalar ve metabolik değişikliklerin bir sonucu olabilir. Bu olgu sunumu, DKA'lı bir ergende invajinasyon oluşumunu vurgulamakta ve bu iki durumu birbirine bağlayan potansiyel mekanizmaları incelemektedir.

Anahtar Kelimeler: Diyabetik ketoasioz, ergen, invajinasyon

Introduction

Type 1 diabetes mellitus is a prevalent chronic condition in childhood, and its incidence varies according to age, sex, geography, and ethnicity.[1] While polyuria and polydipsia are persistent symptoms lasting for several days, abdominal pain, nausea, and vomiting frequently emerge as notable presenting complaints. The severity of abdominal pain can mimic characteristics of an acute abdomen.[2] In the clinical evaluation of patients with diabetes, clinicians are urged to exercise caution and diligence in discerning the etiology of abdominal pain, particularly in cases where the discomfort persists because it may herald an underlying disease process.

Intussusception refers to a condition wherein a proximal segment of the intestine invaginates into the distal segment, resulting in intestinal obstruction, a potentially life-threatening event.[1] Although this condition is commonly observed in childhood, particularly in individuals aged below 2 years, it is not typically anticipated in older age groups.[3] The prevailing notion suggests that organic lesions acting as lead points are often responsible for causing intussusception in adults.[4] However, metabolic disorders, including acidosis, thyroid hormone imbalance, and hyperglycemia, can induce dysrhythmia and gastrointestinal dysmotility, potentially leading to intussusception even in the absence of structural abnormalities.[1,5,6]

In this report, we present an intussusception in an adolescent patient with diabetic ketoacidosis (DKA), review the literature, and investigate the possible mechanism of this condition.

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Case Report

A 14-year-old girl previously diagnosed with type 1 diabetes mellitus was admitted to our emergency service department because of nausea, severe abdominal pain, and general deterioration. Her parents were recently divorced, which led to non-compliance with treatment and several hospital admissions with DKA. Physical examination on admission showed that she was lethargic, and tenderness was detected in all quadrants of the abdomen, whereas no signs of defensive tenderness or rebound tenderness were observed. The detailed examination results were as follows: Blood pressure: 95/55 mmHg; respiratory rate 22 bpm, heart rate: 110 bpm, body temperature, 36.8 °C.

Laboratory examination revealed a blood sugar level of 494 mg/dL and urine ketone level was significantly elevated, more than four times the normal range, at >15 mmol/L. Blood gas analysis revealed severe metabolic acidosis (pH: 7.08, pCO_2: 19 mmHg, HCO_3: 8.2 mmol/L, Base excess: -22.8 mmol/L). complete blood count (CBC) indicated an increase in the white blood cell count (28.3x10³/µL) and the percentage of neutrophils (96%). Other parameters of CBC, plasma electrolytes, renal, and liver function were normal (Table 1). Her glycosylated hemoglobin A1c level was 12.7%, indicating poorly controlled diabetes.

In this case, the patient primarily presented with severe abdominal pain without other accompanying symptoms, except for one or two cases of vomiting before hospital admission. Throughout the hospital stay, the patient was managed non-orally. Although there was a slight decrease in abdominal pain, it persisted. Physical examination specifically revealed tenderness in the bilateral lower quadrants of the abdomen. Initially, an abdominal X-ray (Figure 1) did not reveal any significant findings beyond normal gastric gas patterns. However, due to persistent abdominal pain, ultrasonography of the abdomen was performed. Ultrasound revealed a 2-centimeter peripheral hypoechoic ring, commonly known as the target sign, suggesting the presence of intussusception. This finding led to further evaluation and management by the surgical team, who performed hydrostatic reduction. These details underscore the critical nature of continuous assessment in cases of severe DKA in which abdominal pain persists, highlighting the necessity of thorough imaging studies to exclude other serious abdominal pathologies, such as intussusception.

Discussion

DKA is the second most frequent presentation of T1DM and is characterized by symptoms, including nausea, vomiting, abdominal pain, and hyperventilation, which can escalate to lethargy and coma.[1,2,7,8]

Gastrointestinal manifestations are prevalent among individuals with diabetes, with a substantial cohort reporting various symptoms during diabetic clinic visits. These symptoms encompass gastro-esophageal reflux, dysphagia, early satiety, nausea, vomiting, anorexia, abdominal distension or bloating, dyspepsia, abdominal pain, diarrhea, and constipation.[3] Hyperglycemia is recognized as a prominent contributor to gastroparesis,[9,10] whereas hyperkalemia and metabolic acidosis have also been associated with gastrointestinal dysmotility.[11-13] Both acute hyperglycemia

Table 1. Laboratory values at diagnosis and follow-up for the case

	At presentation	6th hour	12th hour	24th hour	48th hour
pH	7.08	7.2	7.31	7.36	7.42
pCO_2 (mmHg)	19.0	28.8	30.6	37.3	36.5
HCO_3 (mmol/L)	8.2	12.2	16.8	21.3	24.1
Base excess (mmol/L)	-22.8	-15.6	-9.8	-3.5	-0.4
Blood glucose level (mg/dL)	494	170	180	140	134
Creatinine (mg/dL)	1.09	0.78	0.61		0.6
Plasma sodium (mmol/L)	148	140	141	139	140
Plasma potassium (mmol/L)	4.8	4.0	3.9	3.8	4.1
Lactate (mmol/L)	2.7	2.9	1.2	1.5	0.9
CRP (mg/dL)	8.9				
Urine ketone (mmol/L)	>15	12	8	6	0
WBC (10³/µL)	28.3				8.1
NEU (%)	91.6				38.3
Hemoglobin (g/dL)	15.1				12.8
Platelet (10³/µL)	542				385

CRP: C-reactive protein, WBC: White blood cell

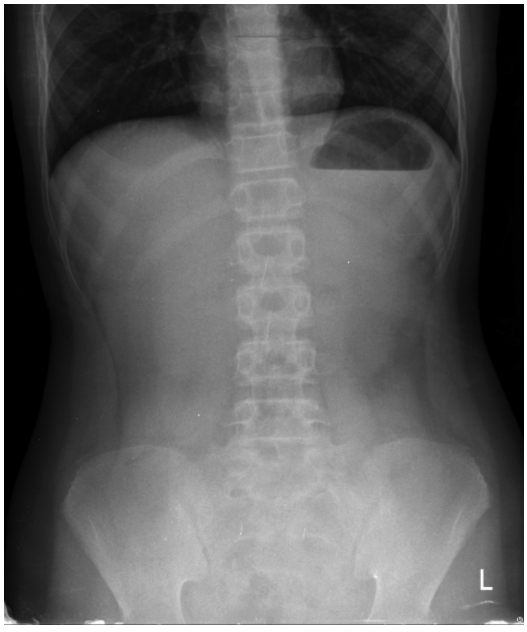

Figure 1. Abdominal radiography of the patient at presentation

and inadequate glycemic control are correlated with small-bowel dysmotility.[11,14] Byrne et al.[15] employed intestinal manometry to demonstrate that acute hyperglycemia induces delayed jejunal transit time and diminished contraction.[12] Numerous studies have reported impaired gastrointestinal motility resulting from acute hyperglycemia.[5,16,17] Abdominal pain may be linked to increased bile duct and gallbladder pressure during acute hyperglycemia.[17] Conversely, chronic poor glycemic control can lead to diabetic parasympathetic autonomic neuropathy, culminating in gastrointestinal dysmotility.[18] Furthermore, dehydration associated with DKA can result in gastrointestinal hypoperfusion, potentially manifesting as constipation, abdominal pain, vomiting, and, in rare instances, intussusception.[3,13]

Intussusception is a surgical emergency; if left untreated, it can cause severe complications (perforation, peritonitis, sepsis etc.).[19] The classic triad of abdominal pain, vomiting, and currant jelly stools occurs in only one-third of the patients.[20] The pathogenesis of intussusception is generally considered to be related to a lead point, such as the Meckel diverticulum, polypoidal and submucosal lesions, and masses.[21] However, in some cases, Chron's disease, Celiac disease, acidosis, thyroid hormone imbalance, hyperglycemia, and electrolyte imbalance can lead to intussusception.[6,13,22]

In the available literature, cases of DKA coupled with intestinal invagination in adults have been documented, but a notable scarcity of reported pediatric cases is limited. A comprehensive review revealed a limited number of cases in children, thereby accentuating the rarity of such cases among this age demographics. When comparing the age and clinical characteristics of our patient with those in the literature, it becomes evident that pediatric cases are distinctly scarce, warranting heightened clinical awareness.[23,24] In our case of DKA, persistent abdominal pain despite standard corrective treatment prompted further investigation, leading to the diagnosis of intussusception via abdominal ultrasonography. This scenario highlights the complexity of diagnosing DKA complications because hyperglycemia is known to affect gastrointestinal motility, potentially contributing to conditions like intussusception. Studies have suggested that hyperglycemia can cause significant disruptions in motility, including delayed jejunal transit times and reduced contraction amplitudes, which might not only impair glucose absorption but also predispose patients to gastrointestinal pathologies. While speculation remains on the possibility of additional intussusceptions, the observed clinical improvement suggests a potential spontaneous resolution in some cases, emphasizing the need for cautious monitoring in pediatric patients with T1DM who present with similar complexities. Timely intervention remains paramount, serving as a reminder to clinicians that the prospect of spontaneous resolution may not be guaranteed in certain scenarios, necessitating proactive and vigilant approaches to avoid potential complications.

In spite of correcting dehydration, acidosis, and electrolyte imbalances; if abdominal pain persists, clinicians must remember acute abdominal causes. Intussusception, a rare cause of acute abdomen in adolescents and adults compared with the child population, must be recognized and treated immediately.

Ethics

Informed Consent: Informed consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.A., E.U., O.U., M.D., D.Y., Concept: E.U., M.D., D.Y., Design: E.U., O.U., Data Collection or Processing: C.A., E.U., Analysis or Interpretation: C.A., Literature Search: C.A., E.U., M.D., D.Y., Writing: C.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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Massive Pulmonary Hemorrhage As A Complication of Intrapleural Streptokinase Therapy

İntraplevral Streptokinaz Tedavisinin Bir Komplikasyonu Olarak Masif Pulmoner Hemoraji

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Abstract

Intrapleural streptokinase therapy (IST) is commonly used to manage pediatric parapneumonic effusion. Although considered safe, rare complications, such as pulmonary hemorrhage, have been reported, particularly in high-dose IST administration in patients with coexisting coagulopathy or trauma. We report a case of massive pulmonary hemorrhage following IST in a 14-month-old child with left parapneumonic effusion. He initially presented to the hospital with community-acquired pneumonia, and intravenous antibiotic therapy was initiated. Subsequently, he developed left complex parapneumonic effusion, with worsening respiratory distress requiring non-invasive ventilation. Chest tubes were inserted using the blind method and were complicated by traumatic insertion. Four hours after IST, the patient developed severe respiratory distress with profuse bleeding from the oronasal cavity. He required intubation and was ventilated for four days. There was no coagulopathy. Respiratory support was gradually weaned off, and the patient was discharged well after a six-week course of antibiotics. Healthcare providers should be vigilant regarding the risk of pulmonary hemorrhage, particularly in high-risk patients. Ultrasound-guided chest tube insertion, patient assessment before IST, and close monitoring during and after therapy may help minimize this adverse event. Further research is warranted to better understand the safety profile of IST in children.

Keywords: Intrapleural fibrinolytic, pediatric intensive care, pediatric respiratory

Öz

İntraplevral streptokinaz tedavisi (IST), çocuk parapnömonik efüzyonu yönetmek için yaygın olarak kullanılmaktadır. Güvenli olduğu düşünülse de özellikle koagülopati veya travmanın eşlik ettiği hastalarda yüksek doz IST uygulamasında akciğer hemoraji gibi nadir komplikasyonlar bildirilmiştir. Bu yazıda, sol parapnömonik efüzyonu olan 14 aylık bir çocukta IST'yi takiben gelişen masif akciğer hemoraji olgusu sunulmuştur. Hasta başlangıçta toplum kökenli pnömoni ile hastaneye başvurdu ve damar içi antibiyotik tedavisi başlandı. Daha sonra hastada sol kompleks parapnömonik efüzyon gelişti ve solunum sıkıntısı kötüleşerek non-invaziv ventilasyon gerektirdi. Göğüs tüpleri kör yöntem kullanılarak yerleştirildi ve travmatik yerleştirme nedeniyle komplike oldu. IST'den dört saat sonra, hastada oronazal boşluktan bol miktarda kanama ile birlikte ciddi solunum sıkıntısı gelişti. Entübasyon gerekti ve dört gün boyunca ventile edildi. Koagülopati yoktu. Solunum desteği kademeli olarak kesildi ve hasta altı haftalık bir antibiyotik tedavisinin ardından taburcu edildi. Sağlık hizmeti sağlayıcıları, özellikle yüksek riskli hastalarda akciğer hemoraji riski konusunda dikkatli olmalıdır. Ultrason kılavuzluğunda göğüs tüpü yerleştirilmesi, IST öncesi hastanın değerlendirilmesi ve tedavi sırasında ve sonrasında yakın izlem ile bu advers olay sıklığı en az seviyeye indirilebilir. Çocuklarda IST'nin güvenlik profilini daha iyi anlamak için daha fazla araştırma yapılması gerekmektedir.

Anahtar Kelimeler: İntraplevral fibrinolitik, pediyatrik yoğun bakım, pediyatrik solunum

Introduction

Parapneumonic pleural effusion is a common complication of bacterial pneumonia in children in developing countries.[1] Approximately 25% of these patients develop empyema thoracis.[2] Empyema thoracis is defined as the collection of pus in the pleural cavity.[2] The progression of parapneumonic pleural effusion into empyema thoracis is divided into three stages: Exudative, fibropurulent, and organized.

Despite its significant prevalence, the management of empyema thoracis among children remains challenging for clinicians.[3] Intrapleural fibrinolytic therapy, such as

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streptokinase, urokinase, and alteplase, have been reported to be beneficial for dissolving fibrinous clots, preventing fluid sequestration, and improving drainage of the pleural fluid.[3,4] However, no universal guidelines have been established to provide definitive criteria and optimal timing for intrapleural streptokinase therapy (IST).[5] The safety and efficacy profiles of this therapy have been established in the adult population, but data in the pediatric population is limited.[1] We report a case of massive pulmonary hemorrhage that complicated intrapleural fibrinolytic therapy. The educational objectives of this case report are to highlight a crucial gap in our understanding of the safety and efficacy of such interventions, particularly in the pediatric population. This finding emphasizes the need for further studies on the safety profile of intrapleural streptokinase.

Our case report serves as a valuable reference for clinicians navigating the complexities of pediatric care in resource-constrained settings and promoting a more nuanced understanding of the risks associated with intrapleural fibrinolytic therapy. Our institution does not require ethical approval for reporting individual cases. Written consent from the parent or guardian was obtained prior to submission.

Case Report

H was born at 31 weeks of gestation with a birth weight of 1.42 kg via emergency lower segment caesarian section for severe pre-eclampsia. He was admitted to the neonatal intensive care unit (ICU) due to prematurity with moderate respiratory distress syndrome. He was initially ventilated for 3 h and required oxygen support for a total of 5 days throughout his hospital stay. He was discharged on day 31 of life at a corrected age of 35 weeks 3 days.

Subsequently, he had two episodes of pneumonia at the age of 5 and 11 months, for which he required a short hospital stay, with the highest oxygen requirement being high-flow nasal cannula during the second admission. He tested positive for respiratory syncytial virus during the first episode of pneumonia at 5 months of age.

At 14 months of age, he presented to the hospital with a 2-day history of cough, runny nose, and rapid breathing. He was diagnosed with community-acquired pneumonia, and intravenous antibiotic therapy was initiated. He required low oxygen supplementation and was discharged after 3 days with oral antibiotics. However, he presented again after 1 day of discharge with acute respiratory distress. At the time of presentation, he required nasal prong oxygen and was started on intravenous cefuroxime for partially treated pneumonia. The chest radiograph on admission showed consolidation over the right lower zone.

On day 5 of admission, he developed worsening respiratory distress requiring non-invasive ventilation. Repeat chest radiography revealed a pleural effusion on the left side. This was confirmed on ultrasound thorax on the next day, which showed minimal complex left pleural effusion with thickened pleura. Thus, a chest tube was inserted using intrapleural streptokinase.

Chest tubes were inserted using the blind method and were complicated by multiple traumatic attempts. After several hours, the chest tube was dislodged, and a second chest tube with intrapleural streptokinase was inserted on the subsequent day. Four hours later, he developed profuse bleeding from the nasal and oral cavities and severe respiratory distress. He was intubated and transferred to the ICU for close monitoring.

In the ICU, he developed further episodes of pulmonary hemorrhage associated with anemia necessitating packed-cell transfusion. His coagulation profile was normal. Platelet levels were mildly high at $622x10^9$/L. No other evidence of bleeding disorders or secondary infection was observed. Repeat ultrasound thorax showed a left pleural effusion with echogenic moving debris/sediment within, with a depth of 1.7 cm and thickened pleura. The chest tube was removed after 4 days, and the patient was ventilated for the same duration. Respiratory support was gradually weaned over 11 days. Blood cultures were negative. Investigations for pulmonary tuberculosis were negative. He completed intravenous crystallized penicillin and ceftriaxone for a total of 14 days and subsequently completed oral cefuroxime for another month. He was discharged home after 16 days of admission with metered dose inhaler fluticasone and salbutamol.

Discussion

The use of IST for the management of parapneumonic effusion has a longstanding history that dates back to its introduction by Tillett and Sherry.[6] Numerous studies have since explored the efficacy and potential risks associated with various fibrinolytic therapies. The primary rationale for employing fibrinolytic in parapneumonic effusion is their ability to disrupt pleural septations and loculations that impede drainage, consequently facilitating improved drainage, hastening recovery, and mitigating the need for surgical interventions, such as thoracotomies or video-assisted thoracoscopic surgeries.[7]

The use of intrapleural fibrinolytic in pediatric cases was first documented in 1993 by Handman and Reuman[8] who utilized urokinase. Subsequent studies have reported a high success rate among pediatric patients,[3] demonstrating increased pleural fluid drainage and shorter hospital stays.[9] However, the use of fibrinolytic therapy is not without its inherent

risks, including therapy failure and pulmonary hemorrhage. In adults, identified risk factors for pulmonary hemorrhage include traumatic chest tube insertion, coagulopathy, concurrent administration of systemic anticoagulants[10,11] and the presence of other medical comorbidities.[11]

Limited case reports exist regarding pulmonary hemorrhage in children subjected to fibrinolytic therapy. Anevlavis et al.[12] reported a 6-year-old boy with no significant risk factors who developed pulmonary hemorrhage after alteplase therapy. In a study involving 73 pediatric and adolescent cases,[13] two patients developed pulmonary hemorrhage, which was thought to be related to the necrotic pulmonary process itself rather than the administration of alteplase.

Despite advancements, universal guidelines specifying definitive criteria and optimal timing for intrapleural streptokinase in pediatric populations have not been established,[5] and the existing basic guidelines for managing parapneumonic effusions have shown low adherence.[14] To enhance current intrapleural fibrinolytic practices and minimize adverse effects, specific prerequisites must be met, including ultrasound-guided chest tube insertion and proper training for safe chest tube insertion.[14,15] The British Thoracic Society guidelines[15] recommend that chest drains be inserted by adequately trained personnel to reduce the risk of complications, emphasizing the operator's skill in correctly identifying the safe triangle location.

Rahman et al.[14] demonstrated significant benefits of t-PA and the addition of DNase, including improved fluid drainage in patients with pleural infection and reduced frequency of surgical referral and duration of hospital stay. Thus, attention should be given to determining the suitable dose and duration of fibrinolytic therapy, the choice of fibrinolytic agents, and their combination with DNAse.[14] Further studies are required to determine the optimal therapy.

Close monitoring during and after treatment is crucial, particularly for patients with identified risk factors. Assessing suitable and low-risk candidates is imperative, necessitating a thorough pre-procedure evaluation to ensure the absence of pre-existing thrombocytopenia and coagulopathy. The British Thoracic Society guidelines recommend correcting any coagulopathy or platelet defect before drain insertion and advocating routine pre-procedure checks of platelet count and prothrombin time in patients with risk factors, such as those on hemodialysis, following cardiac surgery, or after chemotherapy.[15]

Conclusion

IST remains a valuable therapy for managing pediatric parapneumonic effusion. Healthcare providers should be vigilant regarding the risk of pulmonary hemorrhage, particularly in high-risk patients. Ultrasound-guided chest tube insertion, patient assessment before IST, and close monitoring during and after therapy may help minimize this adverse event. Further research is warranted to elucidate the risk factors associated with pulmonary hemorrhage in children with IST.

Ethics

Informed Consent: Written consent from the parent or guardian was obtained prior to submission.

Footnotes

Authorship Contributions

Concept: A.M.K., Design: A.W.A.R., C.Y.L., A.M.K., Data Collection or Processing: A.W.A.R., C.Y.L., A.M.K., Analysis or Interpretation: A.W.A.R., C.Y.L., A.M.K., Literature Search: A.W.A.R., C.Y.L., A.M.K., Writing: A.W.A.R., C.Y.L., A.M.K.

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