ÇOCUK ACİL ve YOĞUN BAKIM DERGİSİ

Journal of Pediatric Emergency and Intensive Care Medicine

TÜRK ÇOCUK ACİL TIP VE YOĞUN BAKIM DERNEĞİ

Volume / Cilt: 11 **Issue / Sayı:** 1 **Year / Yıl:** 2024

E-ISSN: 2148-7332

1

galenos yayınevi

TÜRK ÇOCUK ACİL TIP VE YOĞUN BAKIM DERNEĞİ

ÇOCUK ACİL ve YOĞUN BAKIM DERGİSİ

Journal of Pediatric Emergency and Intensive Care Medicine

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Web: www.galenos.com.tr
Yayıncı Sertifika No/Publisher Certificate Number: 14521

Yayın Tarihi/Publication Date: Nisan 2024/ April 2024
ISSN: 2146-2399 **E-ISSN:** 2148-7332

Yılda üç kez yayımlanan süreli yayındır.
International periodical journal published three times in a year.

ÇOCUK ACİL ve YOĞUN BAKIM DERGİSİ

Journal of Pediatric Emergency and Intensive Care Medicine

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Owner: The Society of Pediatric Emergency and Intensive Care Medicine

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ÇOCUK ACİL ve YOĞUN BAKIM DERGİSİ

Journal of Pediatric Emergency and Intensive Care Medicine

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DOI: 10.4274/cayd.galenos.2023.37928
J Pediatr Emerg Intensive Care Med 2024;11:1-5

Household Intoxications: Does Non-pharmaceutical Mean Non-dangerous?

Ev İçi Zehirlenmeler: İlaç Değil Demek Tehlikeli Değil Demek mi?

Ayşe Gültekingil

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Abstract

Introduction: Intoxication with non-pharmaceutical substances within household environment is an important group of pediatric injuries seen in pediatric emergency departments. Our objective was to study clinical characteristics and outcomes of these exposures and compare them with pharmaceutical intoxications.

Methods: The study was designed as a retrospective cohort study. All patients between 0 and 18 years old presented to 3rd level teaching hospital pediatric emergency unit between May 1st 2016 and April 30th 2017 with a complaint of acute toxic exposure were included.

Results: Over one-year period, 0.52% of all patients presented to pediatric emergency department were toxic exposures. 44% of them were non-pharmaceutical exposures, most commonly cleaning products (49.5%), followed by carbon monoxide (19.2%) and hydrocarbon products (5.5%). Most common route of exposure was oral route (73.2%) and most of exposures were unintentional (97.9%). Respiratory symptoms were the most common manifestation (4.8%), followed by neurologic and cardiac manifestations (2.4%). 57% of patients were hospitalized, one patient admitted to pediatric intensive care unit (PICU). None of the patients died. When compared with pharmaceutical exposures, patients in non-pharmaceutical group were younger, accidental exposures and non-oral routes of exposure were more in this group. Less patients in household group were admitted to PICU. Cardiac manifestations were seen more in household group.

Conclusion: Household toxic exposures to non-pharmaceutical substances are common in childhood. Although mortality risk of pharmaceutical exposures is higher, household non-pharmaceutical exposures can also result in significant clinical manifestations therefore every effort should be taken to prevent accidental toxic exposures within household environment.

Keywords: Poisoning, intoxication, household, children

Öz

Giriş: Ev içinde ilaç dışı ajanlara maruziyet, çocuk acil polikliniklerinde sık gördüğümüz kaza biçimlerinden biridir. Bu çalışmada bizim amacımız bu tip zehirlenmelerin klinik özelliklerini ve sonuçlarını incelemek ve ilaçla zehirlenmelerle karşılaştırmaktır.

Yöntemler: Çalışma geriye dönük kohort bir çalışma olarak planlanmıştır. Üçüncü basamak bir eğitim araştırma hastanesine 1 Mayıs 2016 ve 30 Nisan 2017 arasında akut zehirlenme ile başvuran 0 ile 18 yaş arası tüm hastalar çalışmaya dahil edilmiştir.

Bulgular: Bir yıllık çalışma sürecinde başvuran tüm hastaların %0,52'si zehirlenme nedeni ile başvurmuştur, bunların %44'si ilaç dışı ajanlarla zehirlenmedir, ilaç dışı ajanlar içerisinde en sık karşılaşılan ajan temizlik ürünleridir (%49,5), bunu karbon monoksit (%19,2) ve hidrokarbonlar (%5,5) takip etmektedir. En sık oral yol ile zehirlenme gerçekleşmiştir (%73,2) ve maruziyetlerin çoğu kaza sonucu olmuştur (%97,9). En sık solunum yolu bulguları ile karşılaşılmıştır (%4,8), ikinci sırada kardiyolojik ve nörolojik bulgular görülmüştür (%2,4). Hastaların %57'si yatırılarak izlenmiş, bir hasta çocuk yoğun bakım ünitesine yatırılmıştır. Hastalarda mortalite görülmemiştir. İlaçla zehirlenmelerle karşılaştırıldığında ilaç dışı ajanlara maruziyetlerde çocuklar daha küçük yaştadır, kaza ile zehirlenme ve ağızdan alım harici yollarla zehirlenme daha sıktır. İlaç dışı zehirlenmelerde çocuk yoğun bakım ünitesine yatma sıklığı daha azdır. Ancak kardiyolojik bulgular ilaç dışı maruziyetlerde daha sık izlenmiştir.

Sonuç: İlaç dışı ajanlara maruziyet evlerde en sık görülen kaza biçimlerinde birisidir. Her ne kadar ilaçla zehirlenmelerde mortalite riski daha yüksek olsa da ilaç dışı ajanlara maruziyetler de morbidite ile sonuçlanabilmektedir. Bu nedenle bu maruziyetlere engel olmak için her türlü önlem alınmalıdır.

Anahtar Kelimeler: Zehirlenme, kaza, ev içi, çocuk

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Received/Geliş Tarihi: 04.05.2023 **Accepted/Kabul Tarihi:** 06.09.2023

Introduction

Intoxication with non-pharmaceutical substances within household environment is an important group of pediatric injuries seen in pediatric emergency departments (PED).[1,2] Most of these patients are observed either in pediatric observation unit in PED or in pediatric wards without complications and safely discharged, but in a small group, serious complications can be seen and admission to intensive care unit can be necessary, resulting in morbidity and rarely in mortality.[3]

There are two important groups of toxic exposures: Exposures to pharmaceutical substances and non-pharmaceutical household products.[2] Household products are easy to reach everyday products at home which account for almost half of toxic exposures.[1-6] Exposure to these substances usually cause clinically insignificant poisonings, however they can rarely result in morbidity and mortality. Therefore, it is important to be aware of clinical characteristics and outcomes of these group of intoxications to guide effective treatment and preventive measures. However, there are few studies in literature that analyze clinical features of household exposures generally and compare them with pharmaceutical exposures.[1]

The aim of this study is to define general characteristics and clinical outcomes of household non-pharmaceutical toxic exposures admitting to PED and compare them with pharmaceutical poisonings.

Materials and Methods

The study was designed as a retrospective cohort study. All patients between 0 and 18 years old presented to a tertiary care hospital pediatric emergency unit between May 1st 2016 and April 30th 2017 with a complaint of acute exposure to a toxic substance were included in the study.

Patients with chronic intoxications, food intoxications, intoxications from an unknown material and patients with illicit drug use were excluded from the study. Patients who left the hospital before completion of observation period and patients whose data were incomplete or missing were also excluded. If patients were exposed to different products at the same time, all products were recorded.

Information about patients were gathered from hospital data system. Age and gender of the patient, type of toxic compound, route of toxic exposure (oral, inhalational or cutaneous), reason of exposure (intentional or accidental), presence of cardiovascular, neurologic, respiratory and gastrointestinal findings, treatment at an emergency department (gastrointestinal lavage or active charcoal administration), admission to hospital [either pediatric ward or pediatric intensive care unit (PICU)], length of stay either in emergency unit or pediatric ward and final outcome were recorded for each patient. Palpitations, syncope, dizziness, chest pain, tachycardia, hypo/hypertension were considered as cardiac manifestations, headache, change in consciousness, convulsions were considered as neurological manifestations, abdominal pain, dysphagia, dyspepsia, vomiting were considered as gastrointestinal manifestations and cough and respiratory distress were considered as respiratory manifestations. Decision for admission to PICU was made with guidance of National Poisoning Center. Decision to discharge was made by consulting physician when half-life of toxic substance has expired and vital signs are stable.

Patients were classified into two groups: Pharmaceutical exposures and non-pharmaceutical household exposures. Two groups were compared according to admission state either to pediatric ward or intensive care unit, length of stay at pediatric emergency unit or pediatric ward, presence of cardiovascular, neurologic, respiratory of gastrointestinal findings and final outcome. Primary objective was to compare clinical outcomes of these groups, admission to pediatric ward or intensive care unit, length of observation period and frequency of clinical manifestations were compared for this purpose. Secondary objective was to compare clinical characteristics of these groups.

Statistical Analysis

SPSS 15.1 program was used for statistical analysis. Kolmogorov-Smirnov test was used for normality. Descriptive statistics were presented with frequencies and percentages for discrete variables and mean and standard deviation when variables were normally distributed or median and interquartile range (IQR) for continuous variables when variables were not normally distributed. Discrete variables of two groups were compared by Pearson chi-square test. Continuous variables were compared by student t-test. $P<0.05$ was considered statistically significant for all tests.

The study was reviewed and approved by Başkent University Medical Review Board at July 17th 2018 in accordance with Declaration of Helsinki with assigned project number KA 18/218.

Results

A total of 720 patients presented to PED with toxic exposure over one-year period, which accounted for 0.52% of all patients presented to PEM (720/138858). Twenty-four patients left PED before observation period is completed and medical records of twenty-nine patients were missing, so these patients were excluded from the study. Remaining 667 patients were enrolled to study.

Forty four percent (291/667) of all exposures were exposures to non-pharmaceutical substances and remaining 56% were

pharmaceutical exposures. Forty three percent of patients in non-pharmaceutical group were girls and median age of patients in this age group was 3 years old (IQR 2-15 years). Most common route of exposure in non-pharmaceutical group was oral route (73.2%) followed by inhalational route (26.8%). Household cleaning products were the most common agents (49.5%) followed by carbon monoxide (CO) (19.2%), thinner and other hydrocarbon products (5.5%), cosmetic products (5.2%) and ethanol and acetone (4.8%) in non-pharmaceutical group (Figure 1). Eight of 56 CO intoxication patients were saved from same house fire.

Most of exposures in non-pharmaceutical group were unintentional (97.9%). Only four patients were treated with gastric lavage and/or active charcoal (1.3%). Respiratory manifestations were most common (14 patients, 4.8%), especially in hydrocarbon group (4 patients, 26.6% in this group) followed by neurologic manifestations, cardiac and mucosal manifestations (7 patients each, 2.4%), gastrointestinal manifestations were seen only in three patients (1%). Endoscopic evaluation was performed on one patient revealing minor esophageal burns. One hundred sixty-six patients (57%) were hospitalized, one patient was admitted to PICU. None of the patients died. Median time of observation was 24 hours (IQR 24-48 hours).

When pharmaceutical and non-pharmaceutical groups were compared, several factors were found to be statistically significant. More patients in pharmaceutical group were admitted to PICU (10% in pharmaceutical group and 0% in household group, p=0.000). There was no statistically significant difference between neurological manifestations between groups, but cardiac manifestations were seen more frequently in household group (0% in pharmaceutical group and 2% in household group, p=0.036). Median age of household group was younger than pharmaceutical group and unintentional poisonings were also more frequent in household group (98% in household group and 64% in pharmaceutical group, p=0.000). Oral ingestions were more common in pharmaceutical group and gastrointestinal decontamination was more commonly performed in this group (100% oral ingestion in pharmaceutical group, p=0.000). Inhalational and cutaneous routes of exposure were seen significantly more in household group (Table 1).

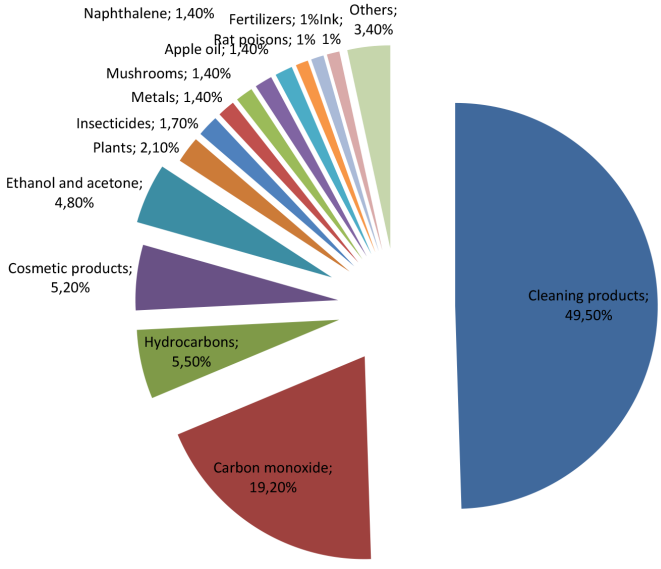

Figure 1. Distribution of non-pharmaceutical household substances that caused poisoning

Discussion

In our study, toxic exposures account for 0.5% of all pediatric emergency department visits and almost half of them (44%) were household non-pharmaceutical exposures similar with other studies in literature.[1-6] Most common household exposure was exposure to cleaning products that can be corrosive according to pH, ingested amount and concentration. In literature, many studies also showed that cleaning products are the most common substances that cause household intoxications, however some studies reached different results. In a study of Abdollahi et al.[7], hydrocarbon poisonings were the most common type of household intoxication. Environmental and cultural conditions can affect mechanism of poisoning, in urban environment, hydrocarbon and pesticide intoxications can be fewer and poisonings of cleaning products can be seen more.[8] Therefore environmental and cultural conditions should be considered when precautions to prevent household poisonings are put in practice.

Cleaning products usually do not cause systemic toxicity, however they can cause significant gastrointestinal mucosal damage according to pH, concentration and amount of substance ingested.[1,9-11] Ingestion usually occurs accidentally in children less than 10 years, but suicidal ingestions were also reported in literature.[8-12] In our study median age was 2 years (range 1-17 years), only four patients (2.7%) ingested these products intentionally, all of which are over 15 years old, which is similar with previous studies in literature.[9]

Immediate endoscopic evaluation in first 24-48 hours after ingestion of household product is rarely indicated, it is usually performed when ingested agent is strong alkali or acidic, ingested amount is large or patient is symptomatic or has serious oral burns.[9,11] In a study of Urganci et al.[10], author concluded that all bleach ingestions should undergo immediate endoscopy even if patient is asymptomatic as severity of symptoms is not correlated with degree of lesions in esophagus or stomach. Some reports suggest endoscopic evaluation of intentional ingestions even if patient is asymptomatic as suicidal ingestions can cause more severe

Table 1. Comparison of clinical characteristics and outcomes of pharmaceutical and non-pharmaceutical household poisonings

	Number of patients in pharmaceutical intoxication group (%)	Number of patients in household intoxication group (%)	p-value
Girls	208 (54%)	141 (48%)	0.114
Accident	244 (64%)	285 (98%)	0.000*
Suicide	130 (34%)	6 (2%)	0.000*
Oral route	381 (100%)	213 (73%)	0.000*
Inhalational route	0 (0%)	78 (27%)	0.000*
Transcutaneous route	0 (0%)	16 (5%)	0.000*
Gastric lavage treatment	162 (43%)	4 (1%)	0.000*
Active charcoal treatment	222 (58%)	3 (1%)	0.000*
Neurological complication	9 (2%)	7 (2%)	0.971
Cardiac complication	2 (0%)	7 (2%)	0.036*
Admission to pediatric ward	205 (54%)	166 (57%)	0.403
Admission to PICU	39 (10%)	1 (0%)	0.000*

PICU: Pediatric intensive care unit

injuries.[8,9,12] In our series, only one patient needed immediate endoscopic evaluation which revealed minor esophageal burns and discharged safely. Corticosteroids were not given as this treatment is controversial.[9,10] All patients were referred to gastroenterology department for follow-up.

CO poisonings is the second largest group in household intoxications in our study group. CO intoxications result in tissue hypoxia and it can result in headache, vomiting, dizziness, weakness, seizures, muscle cramps, visual alterations, alterations in consciousness and even coma.[13,14] CO usually occur due to improperly vented water heaters and stoves in winter months.[13,14] House fires can also result in CO exposure which can lead to morbidity and mortality.[14] In our study although eight of the patients were saved from an house fire, all cases which were discharged in good health. Main reason for that can be the central location of our hospital as time passing between poisoning and admission to hospital is short so effects of CO can be minimized. Also Salameh et al.[14] showed that patients in clusters have lower risk of intoxication, which could also have been positively affected our patients.

Third most common household exposure in our study was exposure to thinner and other hydrocarbon products. Main risk of hydrocarbon intoxications is inhalational injury to lungs.[15] In our study, four of the patients in this group (26.6%) had respiratory symptoms, they were admitted to pediatric ward and received antibiotic and supportive therapy and discharged uneventfully.

Our study one of the few studies in literature that compares pharmaceutical and non-pharmaceutical toxic exposures and first study conducted in Turkey. Our results showed that more patients were admitted to PICU in pharmaceutical group. These results show that pharmaceutical exposures were expected to be more detrimental for patients, as in a study of Lacroix et al.[16], majority of intoxication patients admitted to PICU were pharmaceutical intoxication. However, when we considered manifestations, there were no statistical difference between groups for neurological manifestations, furthermore cardiac manifestations were seen more in non-pharmaceutical group. Respiratory and cutaneous manifestations were also seen in this group therefore non-pharmaceutical exposures can also result in significant clinical outcomes even if mortality risk is low. Gastric decontamination methods were performed less in household group not because they are harmless but gastric decontamination can not be performed for the most of the common household intoxications such as cleaning products, hydrocarbons and CO either because they are non-beneficial or they are even harmful.

Many studies showed that in childhood most of toxic exposures are unintentional, with small amounts of toxic substance and they usually happen at home.[1,2,5,6,8,10] Our results also showed that unintentional exposures are significantly more in non-pharmaceutical group when compared to pharmaceutical group. Unlabelled products used at home can increase the risk of non-pharmaceutical exposures as shown by Urganci et al.[10] Identifying the source of exposure and intervening to remove the source result in significant decreases in poisoning cases therefore household exposures should be studied in detail and right strategies should be developed and parents should be educated according to that to prevent household toxic exposures.[15]

Study Limitations

There are several limitations of this study. First, retrospective nature of the study may have resulted in some missed cases. Second, our study was conducted in a central hospital in

one of the main cities, therefore arrival time of patients to a tertiary care center is short, so prognosis of these patients can be better when compared to general population. Third, patients who left before completion of observation period were excluded from the study which may have caused selection bias. Fourth, mortality was not seen in our cohort therefore we could only compare morbidity between groups. Multicenter studies can give us more information about mortality and morbidity risks of household intoxications.

Conclusion

Household toxic exposures are common that usually happen unintentionally at home. Although need for admission to PICU is less for this group of toxic exposures, clinical manifestations can be seen as commonly as pharmaceutical exposures therefore every effort should be taken to prevent them and educate parents for safety.

Ethics

Ethics Committee Approval: The study was reviewed and approved by Başkent University Medical Review Board at July 17th 2018 in accordance with Declaration of Helsinki with assigned project number KA 18/218.

Informed Consent: Retrospective study.

Financial Disclosure: The author declared that this study received no financial support.

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Research Article / Özgün Araştırma

DOI: 10.4274/cayd.galenos.2023.93446
J Pediatr Emerg Intensive Care Med 2024;11:6-14

Clinical and Demographic Characteristics of Patients Brought to Pediatric Emergency Department by Ambulance

Çocuk Acil Servise Ambulans ile Getirilen Olguların Klinik ve Demografik Özellikleri

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Abstract

Introduction: In this study, clinical and demographic characteristics of cases brought to pediatric emergency department by ambulance were examined. We aimed to determine interventions and diagnoses of the patients, classify cases according to transfer place and type, evaluate appropriateness of referral, and contribute to the efficiency of the referral chain.

Methods: Five hundred forty two cases brought to pediatric emergency department by ambulance were followed up prospectively. Characteristics of cases were recorded from ambulance intervention form, automation system of our hospital, pediatric emergency service examination records and nurse observation records.

Results: 2.54% (n=542) of the cases came to our pediatric emergency department by ambulance. Green field applications were the highest in all months. 4.7% of the patients came from outside the city. 49.4% of the patients were taken from home, 48.8% from another hospital or health institution. 53.2% of the cases were primary cases, the cases brought although the referral was not accepted were 10.5%. The diagnoses of patients were compatible in 79.2%. Body temperature of most of the patients was not measured by the ambulance teams and the respiratory rate was not recorded. Four patients who underwent endotracheal intubation in the emergency department did not undergo endotracheal intubation in the ambulance. While 15.5% of the patients were discharged without need of any observation, the majority (55.7%) were followed up in the emergency observation unit. 89.9% of the patients were discharged with recovery, 1.5% referred, and 0.9% died.

Conclusion: Ambulances use is frequent in our city, emergency care in our hospital is provided to patients coming from within the city and from outside the city. Ambulance teams sometimes do not apply appropriate and necessary intervention to pediatric patients. Recording and interpretation of vital signs is important for timely and effective intervention. Real emergencies should also be recognized and inappropriate ambulance use should be prevented.

Keywords: Child, ambulance, transport, emergency department

Öz

Giriş: Bu çalışmada ambulans ile çocuk acil servise getirilen olguların klinik ve demografik özellikleri incelendi. Amacımız, ambulans ekiplerince ve acil serviste yapılan müdahaleleri ve konulan tanıları belirlemek, olguları transfer edilen yer ve transfer şekillerine göre sınıflamak, sevk uygunluğunu değerlendirmek ve bulgularımızla sevk zincirinin verimliliğini artırmaya katkıda bulunmaktır.

Yöntemler: Hastanemiz çocuk acil servisine ambulansla getirilen 542 olgu ileriye yönelik olarak izlendi. Olguların özellikleri ambulans müdahale formu, hastanemiz otomasyon sistemi, acil servis muayene defteri kayıtları ve hemşire gözlem kayıtlarından elde edildi.

Bulgular: Olguların %2,54'ü (n=542) çocuk acil servisimize ambulans ile gelmişti. Yeşil alan başvurusu tüm aylarda (%71,9-82,9) en fazlaydı. Hastaların %4,7'si şehir dışından gelmişti. Hastaların %49,4'ü evden, %48,8'i başka bir hastane ya da sağlık kurumundan alınmıştı. Transport şekline göre primer olgular %53,2, sevki kabul edilen olgular %36,1, sevki kabul edilmediği halde İl Acil Sağlık Hizmetleri Koordinasyon Komisyonu kararı ile getirilen olgular %10,5 idi. Ambulans ön tanıları ve acil serviste konulan tanılar incelendiğinde %79,2'sinde tanılar uyumluydu. Ambulans ekipleri tarafından hastaların çoğunun vücut sıcaklığının ölçülmediği ve solunum sayısının kaydedilmediği görüldü. Acil serviste endotrakeal entübasyon yapılan dört hastaya ambulansta endotrakeal entübasyon yapılmamıştı. Hastaların %15,5'i gözleme gerek kalmadan acil servisten taburcu edilirken, çoğunluğu (%55,7) acil gözlem ünitesinde takip edildi. Hastaların %89,9'unun şifa ile taburcu olduğu, %1,5'unun sevk olduğu, %0,9'unun eksitus olduğu görüldü.

Sonuç: İlimizde hastaneler arası nakilde ambulans kullanımının sık olduğu, hastanemizin şehir içi ve şehir dışından gelen hastalara acil bakım hizmeti verdiği, ambulans ekipleri tarafından çocuk hastalara bazen uygun ve gerekli müdahalede bulunulmadığı görüldü. Vital bulguların kaydedilmesi, yorumlanması, hastalara zamanında ve etkin müdahale açısından önemlidir. Çocuk hastalarda da gerçek acil durumlar tanınmalı ve uygunsuz ambulans kullanımının önüne geçilmelidir.

Anahtar Kelimeler: Çocuk, ambulans, transport, acil servis

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Received/Geliş Tarihi: 25.07.2023 **Accepted/Kabul Tarihi:** 16.11.2023

Introduction

An emergency is a medical condition that, in the absence of medical intervention, endangers a person's life, causes serious impairment in bodily functions, leads to serious loss of function in any body organ or part, and manifests itself with severe and acute symptoms.[1] Emergency health services (EHS) constitute many emergency care areas including triage, assessment, management and transportation of patients until their arrival to the emergency department, including patient management in the emergency department in cases of injury or illness.[2] Pediatric Emergency Health Services (PEHS) consists of prevention, access to EHS (recognition of the emergency, contacting the emergency system activated by telephone and sending an ambulance), triage and transport to the hospital, stabilization in the emergency department, inter-hospital transport, hospitalization, treatment and rehabilitation steps including trauma centers and pediatric intensive care.[3] Inappropriate use of EHS is one of the most important problems from past to present. It has been observed that ambulance use for non-emergencies may be related to demographic factors such as age, gender, and living in rural areas, as well as factors such as socio-economic level, presence of health insurance, presence of primary health care services, unmet needs in primary health care services, social status of patients and perceptions of urgency by caregivers.[4] Inappropriate use of EHS for children has also been reported and in a study, it was found that 61% of ambulances were used inappropriately.[5] Emergency departments are a vital component of EHS, providing service for 24 hours a day, 7 days a week all over the world for everyone in need.[6] It is the part that connects out-of-hospital health services with hospital health services.[7] Approximately 30% of emergency patients are children. Eighty percent of deaths in the childhood age group are due to emergency medical problems. Health care for these children should be provided by experienced physicians who have received special training for pediatric patients.[8] It is clear that any health problem developing in the pediatric age group will lead to both physiological and psychological damages in the future health of the individual.[9] In this study, our aim was to examine the characteristics of all pediatric patients brought to the pediatric emergency department of our hospital by EHS ambulance, to determine the interventions performed by the ambulance team, to determine the interventions performed in the emergency department, to compare the preliminary diagnoses of the ambulance team with the diagnoses made in the pediatric emergency department, to classify the cases according to the place and manner of transfer, to evaluate the appropriateness of referral, to determine how the patients and our clinic were affected as a result of this transfer, and to shed light on decision makers to increase the efficiency of the referral chain in the light of our findings.

Materials and Methods

In our study, the characteristics of pediatric patients who were brought to the Pediatric Emergency Department, Department of Pediatrics, Necmettin Erbakan University Meram Faculty of Medicine, between August 1, 2019 and December 31, 2019 were examined. The place and method of case selection, the interventions and preliminary diagnoses made by the EHS team, the interventions and preliminary diagnoses made in the emergency department, and the follow-up processes in the hospital were compared. Our study was a descriptive cross-sectional study and all cases were followed prospectively.

A form created by us for the cases participating in the study was filled in during the application. While filling out this form, the EHS Ambulance Intervention Form, our hospital automation system, emergency department's examination file records, and nurse observation records were utilized. Voluntary consent was obtained from the cases included in the study. Patients whose patient information could not be fully accessed or who came to the outpatient clinic by ambulance for another reason (patients who came to the outpatient clinic control by ambulance due to their health status, patients who came for consultation or examination, etc.) were not included in the study.

The form created for the cases included data on the patient's age, gender, date of admission, time of admission, where the patient came from (in the city and out of the city), the place where the EHS ambulance picked up the patient (home, another hospital or health institution, school, street and other places), the transfer method of the case (cases picked up from the scene, cases transferred from the scene to a hospital, or cases admitted to an outpatient hospital and interviewed and accepted for referral, cases referred to our hospital while being treated in a hospital and cases referred to us with the decision of the Provincial Emergency Health Services Coordination Commission (ASKOM) although they were not accepted by us), vital signs measured by the EHS ambulance team, interventions performed, preliminary diagnosis, whether the case had forensic characteristics, triage categories, whether the patient had a chronic disease; vital signs measured when the child was admitted to the emergency department, the interventions performed and the preliminary diagnosis made as a result of these interventions, the duration of the patient's stay in the emergency department, the total duration of the patient's stay in our hospital, the department where the patient was followed up, the outcome status in the department where the patient was followed up, and discharge diagnoses.

Statistical Analysis

SPSS 25 (Statistics for Windows, Version 25.0) package program was used for statistical analyses. Descriptive statistics were calculated in line with the characteristics of the variables

in the study. All categorical variables were summarized as number (n) and percentage (%). The Pearson chi-square test was used to compare the differences between categorical variables and the Mann-Whitney U test was used in cases where independent numerical variables were not normally distributed. The significance level was considered as p<0.05 in statistical analyses.

Results

During the study period, 21,806 patients were admitted to the pediatric emergency department of our hospital. Of these patients, 556 (2.54%) were brought by EHS ambulance. The study sample consisted of 542 cases, 286 (52.8%) boys and 256 (47.2%) girls. Fourteen patients with incomplete information were excluded from the study. When the distribution of the cases according to age groups was analyzed, it was seen that the highest rate was in the age range of 28 days-2 years (n=150, 27.7%) and the lowest rate was in the age range of 0-28 days (n=3, 0.6%).

When the time of admission was analyzed according to age groups, it was observed that the highest rate of admission was between 08:00 and 17:00 in all age groups (37.3-66.7%). When the emergency department diagnoses were analyzed according to age groups, it was observed that gastrointestinal system-related diseases in infants aged 0-28 days (n=2, 66.7%), neurological diseases in infants aged 28 days-2 years (n=66, 44%), neurological diseases in children aged 2-5 years (n=43, 30.9%), neurological diseases in children aged 5-11 years (n=58, 43.9%), respiratory system diseases in early adolescents (n=12, 26.8%) and neurological diseases in middle adolescents (n=24, 32.9%) were the most common diagnoses (p<0.001).

When the length of stay in the emergency department was analyzed, it was observed that the number of patients who stayed in the emergency department for 0-12 hours (n=246, 45.4%) was significantly higher than the other groups. However, the number of those who stayed in the emergency department for more than 7 days (n=6, 1.1%) was significantly lower than the other groups (p<0.001). In addition, when the total length of hospital stay of the cases was analyzed, it was seen that those who stayed in the hospital for 0-12 hours (n=152, 28%) and 1-7 days (n=194, 35.8%) were more than the other groups (p<0.001). In addition, the number of those who stayed in the hospital for more than 7 days (n=70, 12.9%) was significantly lower than the other groups (p<0.001).

Patients were evaluated according to triage categories. Four hundred-eleven patients (75.8%) were green, 122 patients (22.5%) were yellow, and 9 patients (1.7%) were red. The highest proportion of patients were significantly in the green triage category every month during the study period (p<0.001) (Table 1).

10.5% of the patients were forensic cases. It was observed that 25 (43.9%) of the forensic cases were male and 32 (56.1%) were female. When forensic cases were analyzed according to age groups, the highest rate (n=21, 36.8%) was in the 2-5 age group (p<0.001). When the application hours of forensic cases were analyzed, the highest rate of application was between 08:00 and 17:00 (n=24, 42.1%) (p<0.05). When the diagnoses of forensic cases in the emergency department were analyzed, it was found that statistically significantly more patients belonged to the group of cases diagnosed with intoxication (n=16, 28%) (p<0.001). Intoxication was followed by corrosive substance ingestion (n=12, 21%) and suicide (n=9, 15.7%).

Table 1. Triage categories of cases

Months		Green triage	Yellow triage	Red triage	Total	X^{2}*	p
August	**n**	80	25	-	105	95.77	**<0.001**
	%	76.2	23.8	-	100		
September	**n**	66	21	-	87	72.44	**<0.001**
	%	75.9	24.1	-	100		
October	**n**	101	20	1	122	138.71	**<0.001**
	%	82.8	16.4	0.8	100		
November	**n**	69	25	2	96	23.28	**<0.001**
	%	71.9	26	2.1	100		
December	**n**	95	31	6	132	94.34	**<0.001**
	%	72	23.5	4.5	100		
Total	**n**	411	122	9	542		
	%	75.8	22.5	1.7	100		

*: Obtained with the chi-square test

When the cases with chronic diseases were analyzed, it was seen that the highest rate (n=116, 44.4%) belonged to the group of cases diagnosed with neurological diseases (p<0.001). When the rates of admission according to the place of origin were analyzed, the rates of out-of-town admissions ranged between 2.3% and 8%. The rates according to the months of admission did not show a statistically significant difference (Table 2). A total of 253 patients (46.6%) were referred from 37 different hospitals. The highest rate of referrals was from Ereğli State Hospital (n=24, 9.5%), Konya Training and Research Hospital (n=18, 7.1%) and Karaman State Hospital (n=18, 7.1%) (p<0.001). When the locations of the cases were evaluated, it was seen that the majority of the cases were taken from the scene of the incident (47.9-57.5%) in all months (p<0.05).

Although not admitted by us, 57 patients were admitted to the emergency department with the decision of ASKOM. Classification of the cases according to transportation methods is given in Table 3. When the preliminary diagnoses

Table 2. Places where 112 ambulance team picks up the patient

Age range	August		September		October		November		December	
	n	%	n	%	n	%	n	%	n	%
Another hospital or health institution	49	46.7	37	42.5	53	43.4	49	51	66	50
Home	52	49.5	47	54.0	62	50.8	43	44.8	64	48.5
School	-	-	1	1.1	1	0.8	2	2.1	1	0.8
Street	1	1	-	-	3	2.5	-	-	-	-
Other	3	2.9	2	2.3	3	2.5	2	2.1	1	0.8
Total	105	100	87	100	122	100	96	100	132	100

Table 3. How cases are brought by 112 ambulance teams by month

Months	Case type	n	%
December 2019	Cases taken from the scene	69	52.3
	Cases transferred from the scene to a hospital or admitted to an outpatient hospital and accepted for referral after consultation	36	27.3
	Cases referred to our hospital while being treated in another hospital	3	2.3
	Cases referred to us even though they were not accepted by ASKOM decision	24	18.2
	Total	132	100
November 2019	Cases taken from the scene	46	47.9
	Cases transferred from the scene to a hospital or admitted to an outpatient hospital and accepted for referral after consultation	39	40.6
	Cases referred to our hospital while being treated in another hospital	2	2.1
	Cases referred to us even though they were not accepted by ASKOM decision	9	9.4
	Total	96	100
October 2019	Cases taken from the scene	68	55.7
	Cases transferred from the scene to a hospital or admitted to an outpatient hospital and accepted for referral after consultation	36	29.5
	Cases referred to our hospital while being treated in another hospital	6	4.9
	Cases referred to us even though they were not accepted by ASKOM decision	12	9.8
	Total	122	100
September 2019	Cases taken from the scene	50	57.5
	Cases transferred from the scene to a hospital or admitted to an outpatient hospital and accepted for referral after consultation	33	37.9
	Cases referred to our hospital while being treated in another hospital	2	2.3
	Cases referred to us even though they were not accepted by ASKOM decision	2	2.3
	Total	87	100
August 2019	Cases taken from the scene	56	53.3
	Cases transferred from the scene to a hospital or admitted to an outpatient hospital and accepted for referral after consultation	37	35.2
	Cases referred to our hospital while being treated in another hospital	2	1.9
	Cases referred to us even though they were not accepted by ASKOM decision	10	9.5
	Total	105	100

ASKOM: Provincial Emergency Health Services Coordination Commission

reported by the ASKOM teams and the diagnoses made in the emergency department were analyzed, it was seen that the diagnoses of 43 (75.4%) patients were compatible, while the diagnoses of 14 (24.6%) patients were not compatible. When the emergency department and hospitalization durations of the patients who came with the decision of ASKOM were compared with other patients, no statistically significant difference was found between the emergency department and hospitalization durations. 10.5% of the patients who were admitted with the ASKOM decision were hospitalized in the intensive care unit, this rate was significantly higher than the other patients (p<0.05).

In the preliminary diagnoses reported by the EHS teams, neurologic diseases (28.7-38.5%) were the most common diagnoses in all months with statistical significance (p<0.05). Similarly, neurologic diseases (24.1-42.6%) were the most common diagnoses made in the emergency department (p<0.05). When the compatibility of the preliminary diagnoses of the patients before the emergency department and the diagnoses made in the emergency department was analyzed, it was observed that the diagnoses of 429 (79.2%) cases were compatible and 113 (29.8%) cases were incompatible.

The rates of evaluation of vital signs in the ambulance by the EHS teams are given in Table 4. When the interventions performed in the ambulance were compared with the interventions performed in the emergency department, it was observed that there was no significant difference between the rates of oxygen administration and cardiopulmonary resuscitation (p>0.05), whereas the rates of interventions such as intravenous access (p<0.001), monitoring (p<0.001), administration of fluids (p<0.001), administration of drugs (p<0.001) and intubation (p=0.045) were significantly higher in the emergency department (Table 5).

When the departments where the patients were followed up after diagnosis in the emergency department were analyzed, it was observed that the majority of the patients were followed up in the emergency inpatient observation unit (n=302, 55.7%). Only one patient with suicide attempt was referred to another hospital without being admitted to the emergency observation unit. When the discharge diagnoses of the patients were analyzed, neurologic diseases (n=195, 36%) and respiratory diseases (n=123, 12.7%) constituted the highest rates (p<0.001). When the final status of the patients after follow-up was analyzed, 89.9% were discharged, 7.7%

Table 4. Distribution of vital signs measured by 112 ambulance teams

Vital signs		n	%
Body temperature	Measured	167	30.9
	Not measured	374	69.1
Pulse	Measured	365	67.3
	Not measured	177	32.7
Respiration	Measured	120	22.2
	Not measured	421	77.8
Blood pressure	Measured	183	33.9
	Not measured	359	66.1
SpO_2	Measured	342	63.2
	Not measured	199	36.8
GCS	Measured	421	77.7
	Not measured	121	22.3

Table 5. Comparison of interventions in ambulance and emergency department

Interventions		Ambulance		Emergency service		X^2*	p
		n	%	n	%		
Oxygen administration	Yes	152	28.0	138	25.6	2.025	0.363
	No	390	72.0	404	74.5		
Vascular access	Yes	167	30.8	461	85.1	327.19	**<0.001**
	No	375	69.2	81	14.9		
Monitoring	Yes	144	26.6	473	87.3	407.21	**<0.001**
	No	398	73.4	69	12.7		
Giving fluid	Yes	19	3.5	460	84.9	731.17	**<0.001**
	No	523	96.5	82	15.1		
Administration of medication	Yes	25	4.6	320	59	370.01	**<0.001**
	No	517	95.4	222	41		
Intubation	Yes	0	0	4	0.7	4.02	**0.045**
	No	542	100	538	99.3		
Cardiopulmonary resuscitation	Yes	0	0	1	0.1	1.00	0.317
	No	542	100	541	99.9		

*: Obtained with the chi-square test

were discharged voluntarily, 1.5% were referred to another hospital and 0.9% were exitus (p<0.001).

Discussion

EHS ambulances are one of the most important parts of the health system, especially outside of a health institution, where patients with life-threatening conditions are first evaluated by a health personnel, necessary interventions and first treatments are made, saving lives and providing rapid transfer of patients. It is very important that the EHS ambulance is used appropriately for the most efficient continuation of EHS.

In studies conducted in our country, the rate of children transported to emergency departments by 112 ambulance has been reported as 2.15-3.2%.[10-12] In our study, 2.54% of the cases admitted to the pediatric emergency department of our hospital were transported by 112 ambulance. Different results have been reported about the use of EHS according to gender. In a study investigating the use of EHS according to age groups and genders, the rate of ambulance use by male gender varied between 46.5% and 58.6%.[13] In another study, the rate of male patients was reported as 49.8%.[14] In pediatric studies conducted in our country, ambulance use in male patients was reported as 57.7% and 51.1%.[10,12] In our study, 52.8% male and 47.2% female patients came by ambulance and no significant difference was found between genders. In studies on ambulance transport of pediatric patients, no clear age was used in the literature for the distinction between pediatric and adult patients. In one study, it was observed that ambulance was used in transportation to hospital with a rate of 4.2% in 0-2 years, 37.4% in 2-8 years and 58.4% in 8-14 years.[15] In a study conducted in our country, it was reported that patients aged 15-24 years had the highest rate of being brought to hospital by ambulance among pediatric patients.[16] In a study similar to our study, it was shown that 57% of pediatric patients aged 10-17 years were brought to the hospital by ambulance.[10] In our study, in contrast to these findings, the highest rate was 27.7% in children aged between 28 days and 2 years. We think that the fact that trauma cases are not admitted to the pediatric emergency department of our hospital and that trauma cases are mostly seen in the adolescent period may account for this difference.

In studies, ambulance use was examined according to the hours of the day and it was observed that it varied although there was no specific standard. In a study conducted in our country, it was observed that ambulance was most frequently used between 18:00 and 20:00.[16] In a pediatric study conducted in Adana, it was reported that 44.4% of the patients were admitted to the emergency department between 08:00 and 17:00, 43% between 17:00 and 24:00, and 12.6% between 24:00 and 08:00 by EHS ambulance.[11] Similarly, in our study, 77.6% of the patients were brought by ambulance between 08:00 and 24:00.

In a study of three thousand people including all age groups in our country, it was reported that the distribution according to triage evaluation was very urgent for 16.5%, urgent for 21.2% and non-urgent for 62.3%.[17] In a study conducted in Lithuania, it was reported that 78.2% of the patients were not urgent and 21.8% needed emergency care. In the same study, although 38.8% of the parents reported that they came to the emergency department because of the need for emergency care and deterioration of the child's health, emergency service specialists stated that this rate was only one fifth.[7] In a study conducted in our clinic in 1998, it was reported that 52% of the children brought to the pediatric emergency department were true emergency cases.[18] In our study, patients in the green field category were the most common with a rate of 71.9-82.9% in all months. This high rate indicates that the majority of the patients who came to the pediatric emergency department of our hospital by ASH ambulance were not real emergency patients. Some of the reasons for this high rate of ambulance use include the fact that families do not have private vehicles, they think that they can reach the hospital faster and be examined and treated faster with the EHS ambulance, they do not want to wait in the queue for examination in outpatient clinics during working hours, they want to benefit from EHS free of charge, they think that their children's condition is urgent even if it is not a real emergency and they are worried.

In our study, 10.5% of the patients brought by ambulance were forensic cases. In a previous one-year study conducted in our hospital, it was reported that 1.71% of the patients admitted to the pediatric emergency department were forensic cases.[19] In a study conducted in our country with 486 forensic cases, the most common reason for presentation in non-traumatic forensic cases (153 cases) was accidental drug ingestion with the rate of 13.8%. This was followed by suicide, food poisoning and carbon monoxide poisoning.[20] In another study, intoxications were most common in children aged 0-4 years (64%), traffic accidents were most common in the 5-9 age group (48%), battery was most common in the 10-14 age group (47%) and penetrating sharp instrument injuries were most common in children aged 15 years and above (93%).[21] In our study, the most common intoxications were observed between the ages of 28 days and 2 years (36.8%), the most common intoxications were observed between the ages of 2 and 5 years (33.3%), and corrosive substance ingestion (28.5%) ranked second. Between the ages of 12 and 14 years (80%) and over 14 years (62.5%), suicide was the most common. In a study conducted in our country, 53.8% of forensic cases were reported in the 0-59 months age group, and in another study, the most common age of

non-traumatic forensic cases was reported to be between 1 month and 4 years with a rate of 29.4%.[20,22] Similarly, in our study, the highest proportion of forensic cases was in the age group of 2-5 years with the rate of 36.8%, and the second most common age group was 28 days-2 years with the rate of 33.3%. The fact that children in these age groups are active, curious and interested in the environment may explain the high rate of forensic cases in this age group.

In a study conducted in Adıyaman in our country, chronic diseases were reported in 17.3% of patients brought to the emergency department by ambulance.[23] In our study, the rate of children with chronic diseases was 48.1% and 44% of these were neurologic diseases and 22.6% were diseases related to the respiratory system. The fact that our hospital is a tertiary university hospital, an important center for pediatric neurology and the only center for pediatric pulmonology in our province causes the number of patients followed up in these fields to be high and our hospital is the first choice of 112 teams when emergency healthcare services are required for our patients under follow-up.

During our study period, 4.7% of our patients were admitted from outside the city and came from neighboring cities. When the places where pediatric patients were picked up by 112 ambulance teams in our country were examined, it was observed that 42.9% of the patients were picked up from the street, 30% from home, and 4.3% from another hospital or healthcare institution in a study similar to our study.[10] In another study, 53% of the patients were taken from home and workplace and 24.6% from another health institution.[23] In our study, 49.4% of patients were taken from home, while 48.8% were taken from another hospital or health institution. It is seen that the use of EHS in inter-hospital transportation is quite high in our province.

When we examined the studies conducted in our country, we could not find a study on the mode of transportation of children using 112 EHS. In this respect, we think that our study is the first. When the cases brought by 112 were classified according to the mode of transport, the majority of the cases were primary cases taken from the scene with 289 cases (53.2%), but 196 cases (36.1%) accepted for transport also constituted a significant portion of our patients. In the five-month follow-up, 57 (10.5%) of the children brought by ambulance were brought with the decision of ASKOM even though they were not accepted by us. Since it takes time to arrange a place for these patients who come with the decision of ASKOM, there may be disruptions in the treatment of these patients. This rate increases to 18.2% especially in December when the number of patients is the highest. Like many hospitals, these are periods when our emergency and inpatient wards are completely full, emergency wards are extremely busy, and we cannot admit patients because we cannot provide them with the care they need. In order for patients to benefit from healthcare services in the best way possible in such situations, 112 healthcare teams should assess whether patients need emergency healthcare services at the scene, whether they need to be transported by ambulance, and whether they need to apply to the emergency department. Patients who can be treated at the scene should be provided with the care they need, patients who do not need tertiary care should be taken to other centers, and patients who are referred from other centers should be cared for in the hospital where they are present with consultations to the extent possible until a suitable place is arranged in our hospital. With this functioning, we believe that all pediatric patients will receive the quality EHS care they need.

In one of the pediatric studies, gastrointestinal emergencies were the most common and neurological emergencies were the third most common after trauma in pediatric patients brought by ambulance.[11] In another study, it was reported that the most common diagnoses were upper respiratory tract diseases, the second most common were febrile convulsions and epilepsy, and the third most common were lower respiratory tract infections.[12] In our study, when the emergency department diagnoses of the patients were evaluated, neurologic diseases were found to be the most common (36.7%), respiratory system diseases were the second most common (20.1%) and gastrointestinal system diseases were the third most common (19%). In a study conducted in our country, when 112 pre-diagnoses and emergency department diagnoses were compared, there was compatibility.[10] In our study, when 112 pre-diagnoses and emergency department diagnoses were examined, it was observed that the diagnoses of 79.2% of the cases were compatible, whereas the diagnoses of 29.8% of the cases were not compatible.

Assessment of vital signs is a critical part of the evaluation and care of pediatric patients in the prehospital setting.[24] In our study, it was observed that body temperature was not measured in 69.1%, respiratory rate was not checked in 77.8% and blood pressure was not measured in 66.1% of the patients by 112 teams during transportation. In the emergency department, body temperature was measured in 85% of the patients, respiratory rate was not checked in 90.6%, and blood pressure was not measured in 73.6%. It was found that body temperature was measured more frequently in the emergency department and other vital signs were measured more frequently by 112 teams. Respiratory rate and blood pressure measurements were low in both. This suggests that the importance of vital signs in the evaluation of children is still not fully understood and that the training of the relevant health personnel is inadequate in this regard. In

a study conducted in pediatric patients under 18 years of age, it was shown that pulse oximetry was performed in 19.8% of patients, cardiac monitoring was performed in 14.8%, blood glucose analysis was performed in 8.8%, and intravenous access was opened in 24% of patients.[25] In another study, 52.7% of the patients received intravenous access, while 14.1% received oxygen. In the same study, when the interventions in the emergency department were analyzed, 61.3% of the patients were given intravenous access and 53.7% were given oxygen.[23] In our study, it was observed that 30.8% of the patients had intravenous access, 26% were monitorized, 19% were given intravenous fluids, and 4.6% were administered medication by the 112 team. In the emergency department of our hospital, it was observed that 85.1% of the patients were intravenously accessed, 84.9% were given intravenous fluids and 59% were administered medication. In addition, there were four pediatric patients who were brought by 112 teams without endotracheal intubation and intubated in our emergency department. The reasons for this situation may be that 112 teams did not realize the seriousness of the clinical conditions of pediatric patients and there were no trained personnel to perform intubation in pediatric patients. In addition, an intra-osseous route was not opened in a patient presenting with shock. Considering that our patient with shock was exitus, intra-osseous access may be life-saving in cases where intravenous access is not possible.

One of the parameters indicating inappropriate use of ambulances and emergency departments is the length of stay of patients in the emergency department.[26] In our study, the rate of patients staying in the emergency department for 0-12 hours was 45.4%. Some of these patients were hospitalized in the wards. When we examined the length of hospital stay, 28% of the patients stayed in the hospital for 0-12 hours. In the light of this information, we can think that ambulances are used inappropriately in our province. It has been reported that one of the criteria for inappropriate use of ambulances is the discharge rate.[26] In a study conducted in our country, 16.8% of the patients were discharged after examination and treatment in the emergency department, while this rate was 62.6% in another study.[10,23] In our study, 15.5% of the patients were discharged without the need for observation after being evaluated in the emergency department, 28% of the patients left the hospital within the first 12 hours, and a high rate of 75.8% was evaluated as green triage area. All parameters should be evaluated together when assessing inappropriate use of ambulances. More studies on this issue are needed especially in pediatric patients. In our study, 89.9% of the patients were discharged with recovery, 7.7% were discharged voluntarily, 1.5% were referred and 0.9% were exitus.

Conclusion

As a result of this study, it was determined that in addition to the patients taken from the scene, the use of EHS ambulance in inter-hospital transportation in our province is very frequent, our hospital provides emergency care services to patients coming from the city and out of the city, and sometimes appropriate and necessary intervention is not provided to pediatric patients by ambulance teams. Recording and interpretation of vital signs in pediatric patients and appropriate training of healthcare personnel in this regard are important for timely and effective intervention in pediatric patients. Real emergencies should be recognized in pediatric patients and inappropriate ambulance use should be prevented.

***Information:** This article is excerpted from Gülüzar Gürhan's specialty thesis titled "Clinical and Demographic Characteristics of Cases Brought to Pediatric Emergency Department by 112 Ambulance".

Ethics

Ethics Committee Approval: Permission was received for our study from Necmettin Erbakan University Meram Faculty of Medicine Non-Drug and Medical Device Research Ethics Committee (decision no: 2019/2003).

Informed Consent: Informed consent was obtained from the patient's relatives and patients.

Authorship Contributions

Concept: G.G., F.A., Design: G.G., F.A., Data Collection or Processing: G.G., F.A., A.Y., E.T., A.O.K., A.A., Analysis or Interpretation: G.G., F.A., A.Y., E.T., A.O.K., A.A., Literature Search: G.G., F.A., Writing: G.G., F.A., A.A.

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

Financial Disclosure: The authors declared that this study received no financial support.

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Research Article / Özgün Araştırma

DOI: 10.4274/cayd.galenos.2023.38268
J Pediatr Emerg Intensive Care Med 2024;11:15-20

Evaluation of Children Who Swallowed Safety Pins

Çengelli İğne Yutan Çocukların Değerlendirmesi

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Abstract

Introduction: Cases of swallowed safety pins are often observed in Turkey because of the tradition of pinning a blue eye bead on children to ward against evil. This study aimed to evaluate the diagnosis, endoscopic management, and long-term follow-up of children who were admitted to our hospital with a complaint of swallowing safety pins.

Methods: A retrospective evaluation was made of the clinical characteristics of 47 pediatric patients who were treated because of a swallowed safety pin between 2010 and 2022 in a tertiary level healthcare center.

Results: The cases comprised 24 (51.1%) females and 23 (48.9%) males with a median age of 10 months (range, 5 months-15 years). The median age of the females was observed to be approximately 5 months older than that of males (p<0.003). Of the total sample, 40 (85%) infants were breastfed. In all cases, the foreign body had been swallowed by accident. The majority of the cases (n=25, 53.2%) were resident in the province where the hospital is located, and the other cases presented from surrounding provinces. The localization of the swallowed safety pin in the gastrointestinal system was observed in the stomach (n=26, 65.3%), first esophageal stricture (n=10, 21.3%), second esophageal stricture (n=6, 12.8%), third esophageal stricture (n=2, 4.2%), duodenum (n=3, 6.4%), and cecum (n=3, 6.4%). The safety pin was removed endoscopically in 31 (66%) cases. In 2 cases, the safety pin was observed to be lodged in the duodenum. Of the pins removed, the end was open in 25. In 15 cases, as the safety pin was seen to be closed, it was left for spontaneous elimination. Surgery was required in 1 case because the safety pin was embedded in the cecum. No complications were observed in any patient during or after the procedures.

Conclusion: The swallowing of safety pins is frequently observed, especially in the breastfeeding period of infants. In most cases, safety pins can be safely removed using an endoscopic method without complications.

Keywords: Foreign body ingestion, safety pin, child, endoscopy

Öz

Giriş: Ülkemizde çocuklara nazar boncuğu takma geleneği nedeniyle çengelli iğne yutma olgularına sık rastlanmaktadır. Bu çalışmada hastanemize çengelli iğne yutma şikayetiyle başvuran çocukların tanı, endoskopik yöntemle tedavisi ve uzun dönem izlemlerinin değerlendirilmesi amaçlandı.

Yöntemler: Bir üçüncü basamak sağlık merkezinde 2010-2022 yılları arasında çengelli iğne yutma nedeni ile değerlendirilmiş olan 47 çocuk olgunun klinik özellikleri geriye dönük olarak değerlendirildi.

Bulgular: Olguların 24'ü (%51,1) kız ve ortanca yaşları 10 ay (5 ay-15 yıl) idi. Kız çocukların ortanca yaşının erkek çocuklardan yaklaşık 5 ay daha büyük olduğu gözlendi (p<0,003). Bu çocuklardan 40'ı (%85) süt çocuğu idi. Olguların tümü yabancı cismi kazayla yutmuştu. Olguların çoğunluğu (n=25, %53,2) hastanemizin bulunduğu ilden, diğerleri ise çevre illerden başvurmuştu. Çengelli iğnelerin gastrointestinal sistemde bulundukları yerlerin sırası ile mide (n=26, %65,3), özofagus 1. darlık (n=10, %21,3), özofagus 2. darlık (n=6, %12,8), özofagus 3. darlık (n=2, %4,2), duodenum (n=3, %6,4) ve çekum (n=3, %6,4) olduğu görüldü. Çengelli iğne endoskopik olarak olguların 31'inde (%66) çıkarılabildi. Bu olgulardan 2'sinde çengelli iğnenin duodenuma saplanmış olduğu gözlendi. Çıkarılan çengelli iğnelerin 25'inin ucu açık idi. Olguların 15'inde ucu kapalı çengelli iğnenin izlem sonucunda kendiliğinden çıktığı gözlendi. Bir olguda çengelli iğne çekuma gömüldüğü için cerrahi yolla çıkarıldı. İşlemler sırasında ve sonrasında hiçbir olguda herhangi bir komplikasyon gözlenmedi.

Sonuç: Çengelli iğne yutma özellikle süt çocukluğu döneminde sık görülmektedir. Olguların çoğunda çengelli iğneler endoskopik yöntemle güvenli ve komplikasyonsuz bir şekilde çıkarılabilmektedir.

Anahtar Kelimeler: Yabancı cisim yutma, çengelli iğne, çocuk, endoskopi

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Received/Geliş Tarihi: 12.10.2023 **Accepted/Kabul Tarihi:** 25.12.2023

***This study was presented as an oral presentation at the 3rd Eastern Pediatrics Congress held in Diyarbakır between 28 September 1 October 2023.**

Introduction

Foreign body ingestion continues to be a significant health problem that is frequently seen throughout the world,[1] and is seen more often especially in children below the age of 5 years.[2] It is reported to lead to the death of approximately 1500 children per year in the United States.[3] Although 80% of foreign bodies in the gastrointestinal system are eliminated spontaneously, they can sometimes lead to severe morbidity and even death.[4] It has been reported that safety pins swallowed by children constitute 1% of foreign body aspirations, but this rate is higher in some regions of the world.[5] Studies in Turkey have reported that safety pin swallowing constitutes 8-14% of foreign body aspiration in children.[6,7] There is a cultural tradition in Turkey of attaching blue beads and gold to infants with a safety pin. Infants often pull the safety pin out and open it; thus, an open-ended safety pin is accidentally swallowed.[8] Cervical, thoracic, and abdominal radiographs are used to determine the location of the foreign body.[2] Safety pins can be removed easily and without complications using the endoscopic method.[1] Safety pins that cannot be removed or seen with the endoscopic method must be followed with radiography until they spontaneously pass. Those that do not spontaneously pass out may need to be surgically removed.[6] This study aimed to evaluate the diagnosis, endoscopic management, and long-term follow-up of children who were admitted to our hospital with a complaint of swallowing safety pins.

Materials and Methods

Approval for this study was granted by the Non-Interventional Research Ethics Committee of Fırat University (decision no: 16/25, dated: 29.12.2022). This retrospective study included 47 pediatric patients who presented at the Pediatric Gastroenterology, Hepatology, and Nutrition Clinic of Fırat University Medical Faculty Hospital between 2010 and 2022 with the complaint of a swallowed safety pin. The patient records were examined in detail, and the clinical, endoscopic, and radiological data were recorded on a form created for the study.

Statistical Analysis

Data obtained in the study were statistically analyzed using IBM SPSS version 22 software. The Mann-Whitney U test was used in the statistical evaluations. Results are expressed as mean ± standard deviation (SD). A value of $p<0.05$ was accepted as statistically significant.

We used an algorithmic proposal for the technique of endoscopic removal of ingested safety pins (Figure 1). Informed consent was obtained from the parents of all the children before the endoscopy procedure.

Endoscopic Procedure

To determine the localization of the foreign body, neck, chest, and abdominal radiographs were obtained from all patients. In cases where a safety pin was detected in the esophagus, upper gastrointestinal endoscopy was urgently performed, regardless of fasting status, because of the risk of perforation. In cases where the safety pin was determined in the esophagus, an emergency upper endoscopy procedure was performed because of the risk of perforation. The safety pin in the esophagus was pushed into the stomach. In cases with an empty stomach during the endoscopy, the safety pin was removed immediately. In cases where the stomach was determined to be full of food, endoscopy was repeated after 6-8 h and the safety pin was removed. In cases of safety pins detected in the stomach and duodenum, a 6-h fasting period was waited. Midazolam was administered at a dose of 0.1 mg/kg for sedation in all cases. Following this procedure, sedation was terminated with the administration of flumazenil. The patients were monitored after the procedure, and oral feeding was started 2-4 h later. Then, children without nausea or vomiting during follow-up were discharged.

Flexible gastroscopes, 5 mm and 9 mm in diameter (Olympus 170, 190, and 260, Tokyo, Japan) were used during the esophagogastroduodenoscopy procedures. To remove foreign bodies, rat-tooth and crocodile-mouth forceps were used. Immediately after removal of the foreign body, endoscopy was repeated to evaluate the gastrointestinal mucosa. Cases in which the foreign body could not be visualized or removed during endoscopy were followed up with radiographs until spontaneous elimination of the foreign body.

In addition to the clinical and laboratory findings of the children who swallowed safety pins, endoscopic and radiological data were examined. Treatment and complications were investigated, and the data were compared with the relevant literature.

Results

The 47 cases comprised 24 (51.1%) females and 23 (48.9%) males with a mean age of 10 months (range, 5 months-15 years). The mean age of the children was 12 months for females and 7 months for males, and the difference between the genders was determined to be statistically significant ($p<0.003$). The distribution of cases by age and gender is shown in Table 1. In all cases, the foreign body had been swallowed by accident. It was determined that the most common complaint was the family noticing that the child had

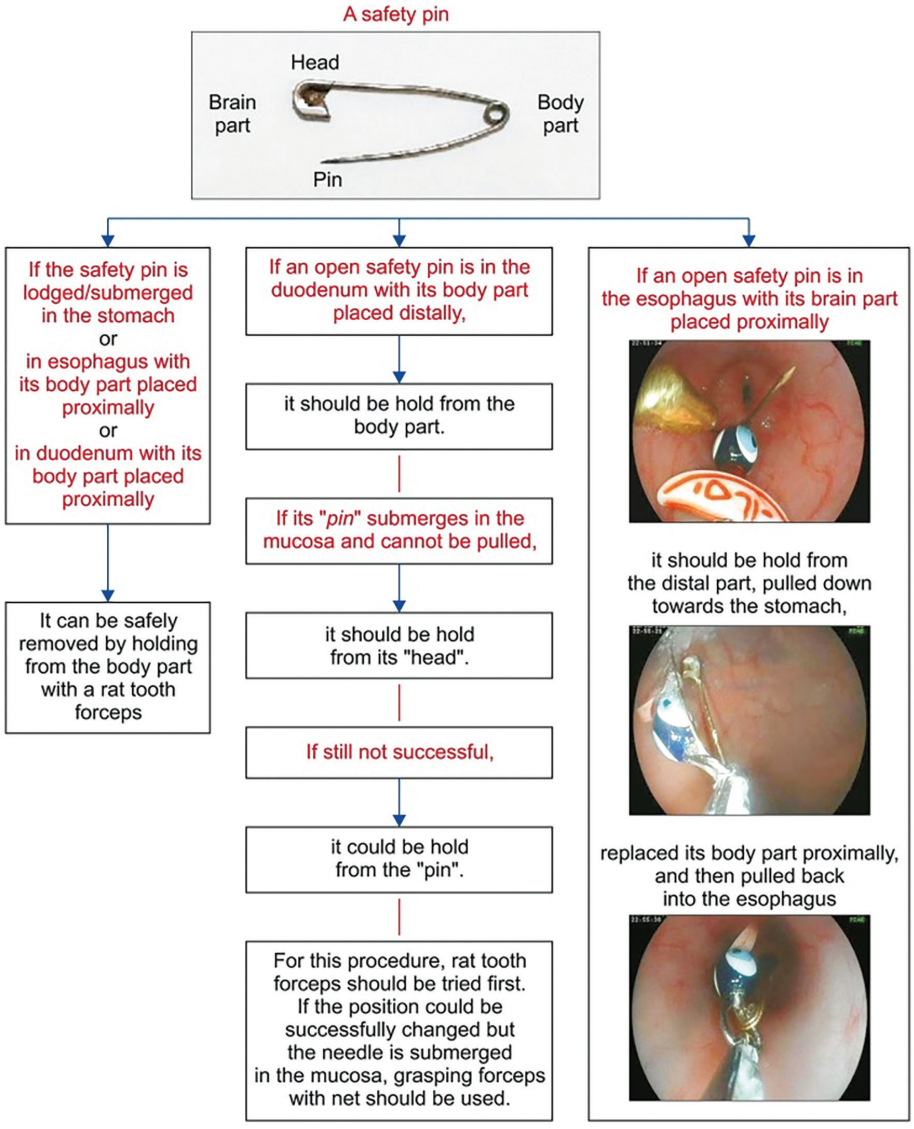

Figure 1. Algorithmic proposal for the technique of endoscopic removal of ingested safety pins[8]

swallowed a foreign object, inability to suckle in infants, and difficulty swallowing in older children.

Most presentations were seen to have been made in March and the fewest in January. The province of residence of the cases was primarily Elazığ, followed by Bingöl, Muş, and Van. The place of residence of the patients and their distance in kilometers and hours by road to the endoscopy center are given in Table 2.

The time from swallowing the safety pin to presentation at the hospital was examined, and this time was 3-6 h for patients who lived in the province where the hospital is located. Cases coming from outlying towns in the same province presented within 6-12 h, and cases accepted from other provinces were seen to have presented at the pediatric emergency department within 12-48 h.

Radiological and endoscopic examinations revealed that the safety pin was localized most often in the stomach, followed by the first esophageal stricture and the second esophageal stricture (Table 3, Figure 2). An open-ended safety pin in the stomach is shown in Figure 3. The safety pin was observed to have lodged in the duodenum in two cases, and these were removed endoscopically (Figure 4).

The safety pins were removed by the endoscopic route in 31 (66%) cases and with surgery in 1 case because the safety pin was embedded in the cecum. Of the safety pins removed endoscopically, 25 were observed to be open. The 15 cases in which the foreign body could not be removed or seen by the endoscopic method was followed up with daily radiological imaging in the hospital and waited to pass spontaneously.

Table 1. Distribution of subjects by age and gender					
Gender	**Number**	**Percentage**	**Minimum age**	**Maximum age**	**Mean age**
Male	23	48.9	6 months	3 years	7 months
Female	24	51.1	5 months	15 years	12 months
Total	47	100	5 months	15 years	10 months
Comparisons of the ages of male and female children p<0.003					

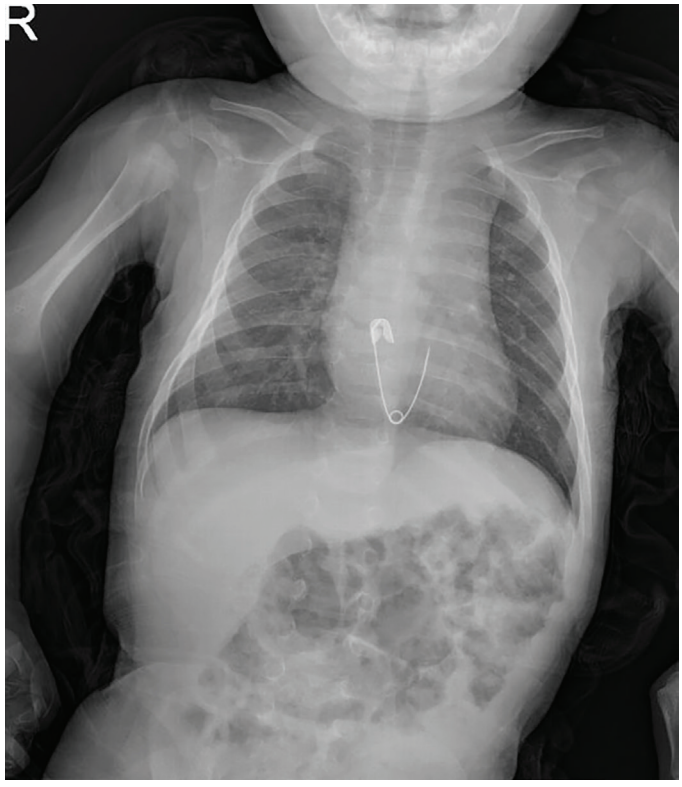

Figure 2. Radiological appearance of an open-ended safety pin in the medial esophagus

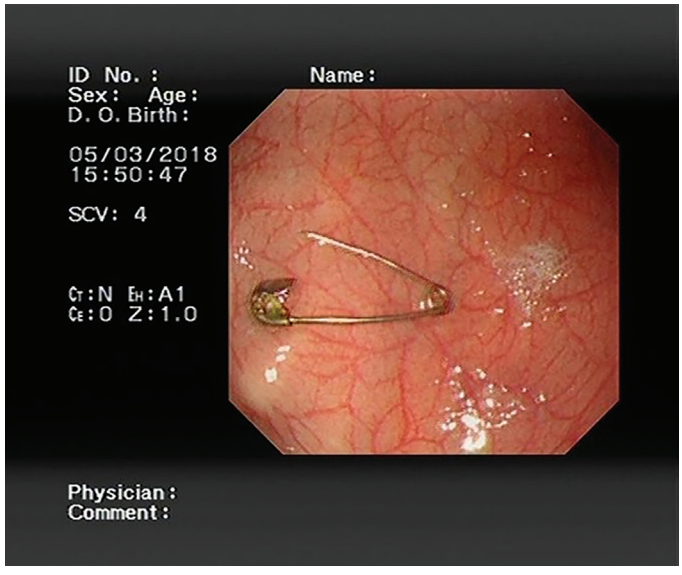

Figure 3. Endoscopic appearance of an open-ended safety pin in the stomach fundus

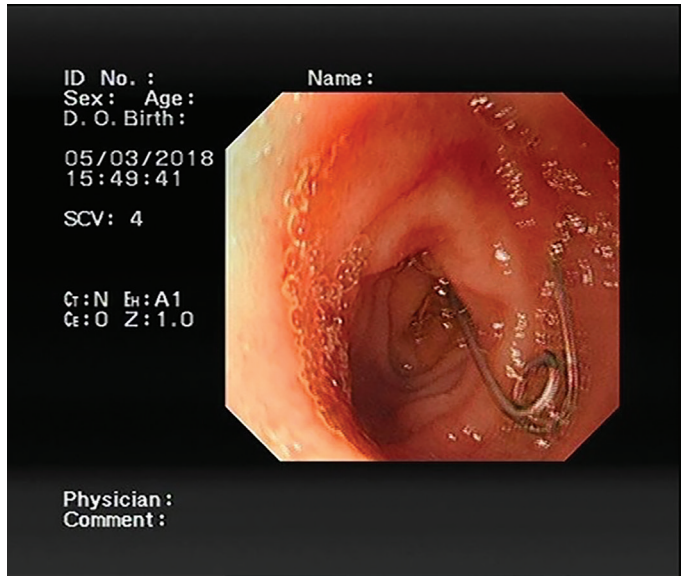

Figure 4. Endoscopic appearance of an open-ended safety pin lodged in the duodenum

Table 2. Places of residence of the cases and their distance to the center where endoscopy was performed			
Place of residence	**Number and percentage of cases (n, %)**	**Distance by road in kilometers**	**Distance by road in hours**
Elazığ	25 (53.2)	-	-
Adıyaman	1 (2.1)	240	4
Bingöl	6 (12.8)	140	2
Bitlis	1 (2.1)	390	6
Diyarbakır	1 (2.1)	150	2
Kars	1 (2.1)	520	7
Malatya	1 (2.1)	100	1.5
Muş	5 (10.6)	260	3.5
Siirt	1 (2.1)	340	5
Tunceli	1 (2.1)	80	1.5
Van	3 (6.4)	520	7

Other than erosion due to the procedures used to remove the foreign body, no complications such as perforation or death were observed in any case.

Discussion

Safety pin aspirations are frequently seen in young children and can cause serious morbidity and mortality. The aim of

Table 3. Radiological and endoscopic localization of the safety pin

Localization	Number (n)	Percentage (%)
First esophageal stricture	10	21.3
Second esophageal stricture	6	12.8
Third esophageal stricture	2	4.3
Stomach	26	55.3
Duodenum	2	4.3
Cecum	1	2.1
Total	47	100

this study was to draw attention to the fact that safety pins can be safely and rapidly removed using the endoscopic method. In a previous study, 14 (70%) of 20 children who had swallowed safety pins were determined to be female, and the mean age of the cases was reported to be 9.5 months (range, 3.5-140 months).[8] In another study that examined 15 cases of ingested safety pins, the mean age was reported to be 5.4 years (range, 7 months-16 years).[9] The age of 7 infants who had swallowed safety pins in another study was in the range of 3.5-12 months, and 4 (57%) cases were female.[10] In a study of 49 children who swallowed safety pins, the mean age was reported to be 8 months (range, 4-24 months), and 30 cases (61%) were male.[11] A study published in 2016 reported a mean age of 11 months (range, 4 months-4 years) of children with ingested safety pins.[7] Although differences can be seen in the ages of children who have swallowed safety pins, this is generally seen in children younger than 5 years.[12] The present study findings are consistent with the data in the literature.

In the current study, 25 (53.2%) of the cases were residents of Elazığ, and 22 (46.8%) came from surrounding provinces. The cases who lived in the center of the province reached the hospital in a short time (3-6 hours), and as the distance increased, the time to presentation increased (3-48 hours).

Although the rate of safety pins within foreign bodies swallowed by children is low, they can lead to life-threatening complications. A study from another country reported this rate to be 3.3%.[13] In Turkey, it has been reported that safety pins are swallowed by 36-47% of children who have ingested a foreign body.[14,15] More recent studies published in 2015 and 2016 in Turkey reported that safety pins were swallowed by 8-14% of cases of foreign body ingestion.[6,7] The decrease in this rate in Turkey over the years can be considered to be due to an increase in the socio-economic and cultural levels.

Localization of the swallowed safety pins was observed most often in the stomach, followed by the first and second esophageal strictures. Previous studies have determined that safety pins are most often localized in the esophagus, stomach, and duodenum.[6-8] Our study findings are consistent with data in the literature.

Safety pins can sometimes lodge in the duodenum. In a previous study, 11.5% of ingested safety pins were reported to have stuck in the duodenum, and duodenotomy was performed in these cases.[7] During endoscopy in the current series, the safety pins were lodged in the duodenum in two cases, and these were removed endoscopically. The low number in the current study was thought to be due to early intervention in the cases.

In one of the current study cases, the safety pin could not be removed endoscopically, and during clinical follow-up, it was observed that the safety pin was embedded in the cecum. Because the safety pin did not emerge spontaneously within 15 days, laparotomy was performed and the pin was removed. It is rare that safety pins become stuck in the colon. In a study by Gün et al.[11], as a safety pin remained in the colon for a long-time in one case, laparotomy was performed. Erginel et al.[7] also reported that laparotomy was performed in only one case because a safety pin remained in the colon for a long period. The present study findings are consistent with the data in the literature.

In this study, no complications were observed because of the rapid and appropriate management approach applied to pediatric patients who swallowed safety pins. The treatment approach we applied was in accordance with the literature.[1,2,10]

In this study, the number of cases requiring surgical treatment was low compared with the literature. It is thought that this may be because of the rapid and appropriate approach to the cases.

It has been observed that the anxiety and stress on patients and families has decreased because of the rapid and uncomplicated treatment of children who swallowed safety pins using the endoscopic method.

Study Limitations

The limitations of our study are that it is retrospective and the number of cases is low. Because our study population was small, our results cannot be generalized; therefore, multicenter studies covering a larger number of cases are required.

Conclusion

The swallowing of safety pins in pediatric cases is seen most often during the breastfeeding period. Safety pins can be safely removed using an endoscopic method without complications. In recent years, there has been an increase in the number of centers in Turkey where endoscopic procedures can be performed. Children who have swallowed a safety pin must be sent quickly to a center where interventional procedures can be performed, thereby preventing potential morbidity and mortality.

Information: The statistical analysis of the study was conducted by Assoc. Prof. Mehmet Onur Kaya, a faculty

member at Fırat University Faculty of Medicine, Department of Medical Statistics.

Ethics

Ethics Committee Approval: Approval for this study was granted by the Non-Interventional Research Ethics Committee of Fırat University (decision no: 16/25, dated: 29.12.2022).

Informed Consent: Informed consent was obtained from the parents of all the children before the endoscopy procedure.

Authorship Contributions

Surgical and Medical Practices: U.D., Y.D., Concept: U.D., Y.D., Design: U.D., Y.D., A.M.K., Ş.A., F.K., Data Collection or Processing: U.D., Y.D., A.M.K., Ş.A., F.K., M.A.Ç., Analysis or Interpretation: U.D., Y.D., A.M.K., Ş.A., F.K., Literature Search: U.D., Y.D., M.A.Ç., Writing: U.D., Y.D.

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

Financial Disclosure: The authors declared that this study received no financial support.

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Research Article / Özgün Araştırma

DOI: 10.4274/cayd.galenos.2024.17894
J Pediatr Emerg Intensive Care Med 2024;11:21-8

The Effect of Finger Puppet Show on the Level of Children's Pain and Fear During the Incision Suturation in Paediatric Emergency Service: A Randomized Controlled Trial

Çocuk Acil Servisinde Kesi Sütürasyonu Sırasında Uygulanan Parmak Kukla Gösterisinin Çocukların Ağrı ve Korku Düzeyine Etkisi: Randomize Kontrollü Çalışma

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Abstract

Introduction: This study evaluated the effect of finger puppet applied during incision saturation, to mitigate the level of pain and fear of children in the emergency department. Children with incisional sutures were recruited by convenience sampling from the pediatric emergency department of a university hospital in a city in Turkey.

Methods: This study used a random controlled experimental design and had a calculated sample size of 65. There were consisted of 33 children in the study group and 32 children in the control group. A puppet show was performed on the children in the experimental group during the incision suturation while no procedure was applied to the children in the control group. The pain and anxiety levels of the children in the control and experimental groups were measured during the incision suturation. The "personal information form", "Wong-Baker faces pain rating scale" and "children's fear scale'' were used to collect data. The chi-square test, Mann-Whitney U test, Wilcoxon test, and Fridman test were used to analyse the data.

Results: A statistically significant difference was found between the children in the control and experimental groups in terms of the levels of pain and fear ($p<0.05$). The pain and fear levels of children in the experimental group were lower than the control group.

Conclusion: It was concluded in the study that the puppet show performed during the incision suturation influenced the reduction of the pain and fear associated with the procedure.

Keywords: Incision suturation, pain, fear, child, puppet, nurse

Öz

Giriş: Kesi sütürasyonu nedeniyle acil servise gelen çocuklarda sütür esnasında uygulanan parmak kuklanın işleme bağlı gelişen ağrı ve korku düzeyine etkisini değerlendirmek amacıyla yapılmıştır. Kesi sütürasyonu ile gelen çocuklar, Türkiye'de bir şehirdeki üniversite hastanesinin çocuk acil servisinden kolayda örnekleme yoluyla alınmıştır.

Yöntemler: Bu çalışmada randomize kontrollü deneysel desen kullanılmış ve örneklem büyüklüğü 65 olarak hesaplanmıştır. Araştırmada deney grubunda 33 ve kontrol grubunda 32 çocuk araştırma grubunu oluşturmuştur. Araştırmanın uygulanmasında deney grubunda yer alan çocuklara kesi sütürasyonu sırasında kukla gösterisi yapıldı, kontrol grubundaki çocuklara ise kesi sütürasyonu sırasında herhangi girişim yapılmamıştır. Deney ve kontrol grubunu oluşturan çocukların kesi sütürasyonu sırasında ağrı ve anksiyete düzeyleri değerlendirildi. Verilerin toplanmasında "kişisel bilgi formu", "Wong-Baker yüzler ağrı değerlendirme ölçeği" ve "çocuk korku ölçeği" kullanılmıştır. Verilerin analizinde; ki-kare testi, Mann-Whitney U testi, Wilcoxon testi ve Fridman testi kullanılmıştır.

Bulgular: Deney ve kontrol grubundaki çocuklar ağrı ve korku düzeyleri açısından karşılaştırıldığında istatistiksel olarak aralarında anlamlı bir farklılık saptanmıştır ($p<0,05$). Deney grubundaki çocukların ağrı ve korku düzeyleri kontrol grubundakilere göre daha düşük olduğu belirlenmiştir.

Sonuç: Çalışmada kesi sütürasyonu sırasında yapılan kukla gösterisinin işleme bağlı gelişen ağrı ve korkuyu azaltmada etkili olduğu sonucuna varılmıştır.

Anahtar Kelimeler: Kesi sütürasyonu, ağrı, korku, çocuk, kukla, hemşire

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Received/Geliş Tarihi: 13.12.2023 **Accepted/Kabul Tarihi:** 25.01.2024

Introduction

When a patient has an unexpected trauma or disease, emergency care entails quick interventions by skilled medical teams to prevent more harm or patient death.[1] Emergency departments are fast-paced environments of chaotic trauma, where decisions need to be made quickly.[2] There are many reasons why children of various ages come to the emergency department, and because of their unique needs -distinct from those of adults- they require special treatment.[3]

In their daily routines, children may unexpectedly experience illness, potentially leading them to a hospital where unexpected and discomforting medical treatments may be administered.[4] Specifically, natural disasters, serious illnesses or accidents, diseases that threaten their lives or their caregivers, and migration include a traumatic experience for children. It is known that a significant number of children exposed to traumatic events develop maladaptive emotional and behavioral responses, and their development and adaptation mechanisms are impaired.[5] In addition, children experience a traumatic process if cuts occur in any part of their body after accidents. It has been reported that nursing interventions applied during incision suturation relieve the child's worries and fears.[6]

Treating children for trauma involves multiple stages that can elicit various emotional reactions, such as distress, unease, fear, and anxiety. Both the American Academy of Pediatrics and the American Pain Society (APS) highlight the significance of reducing stress and pain, even during routine medical procedures. It is critical to ensure prompt and effective pain management during procedures that may cause discomfort. By doing so, children's ability to endure pain in subsequent procedures can be improved.[7] Nurses play a vital and central role in evaluating and addressing pain.[8] They differentiate themselves from the rest of the healthcare community in pain management by understanding the patient's situation and communicating directly with the patient to understand past experiences and coping mechanisms related to pain.[9]

The APS highlighted that just evaluating and easing pain is not enough for young patients (APS). At the diagnostic stage, factors such as the location, type, intensity, expression, presence of factors associated with the pain, and pain scale scores[10] are essential to evaluate.

Managing pain, fear, and anxiety in pediatric care often hinges on the power of distraction.[11] This diversion should captivate the child's attention across multiple senses, engaging sight, sound, and touch to be more effective. Proven techniques range from the familiar -vibrant cartoons, playful balloon creations, or calming music- to the innovative- immersive virtual reality experiences, mesmerizing kaleidoscopes, or interactive distraction cards. These versatile methods can be implemented in brief bursts for acute pain or sustained durations for chronic cases.[12-14]

This study examined the impact on pain and anxiety levels in 4 to 10 years children presenting to a university pediatric emergency department of a finger puppet show performed during incisional suturing. In this study, one hypothesis was suggested: Puppet show has an effect on pain and fear during incision suturing.

The current study put forward two hypotheses:

Hypothesis 0: The finger puppet show has no effect on pain and fear during incision suturing.

Hypothesis 1: The finger puppet show has an effect on pain and fear during incision suturing.

Materials and Methods

Design

The purpose of this randomized controlled trial was to assess the effectiveness of multiple methods for incisional suturing in pediatric patients at a university hospital's pediatric emergency department. From March to October 2021, we enrolled children requiring suture procedures following minor injuries. This non-blinded design allowed for close monitoring and intervention throughout the study period.

Sample

The study recruited children with incisional sutures through convenience sampling from a university hospital pediatric emergency department in a town in Turkey.

Sample selection criteria include:

1. The child is being between the ages of 4-10,

2. Children with Turkish-speaking parents.

3. The child is having a cut in any part of his/her body that requires suturation.

4. The parent and child agree to participate in the study and provide written consent.

The sample size was calculated using G-Power 3.1, which required a minimum sample size of 65 participants. Power analyses were performed with a power of 95%, a type 1% error probability of 5%, and an effect size of 0.8. Seventy-three children presented to the emergency department for incisional suturing during the study period. The study selected a sample of 65 children for participation, adhering to strict inclusion criteria. Random assignment to the experimental or control group was made for those who underwent incision suturing. Numbers 1 to 65 were allocated to the two groups without duplication during randomization using a computer program. The CONSORT flowchart is illustrated in Figure 1.[15]

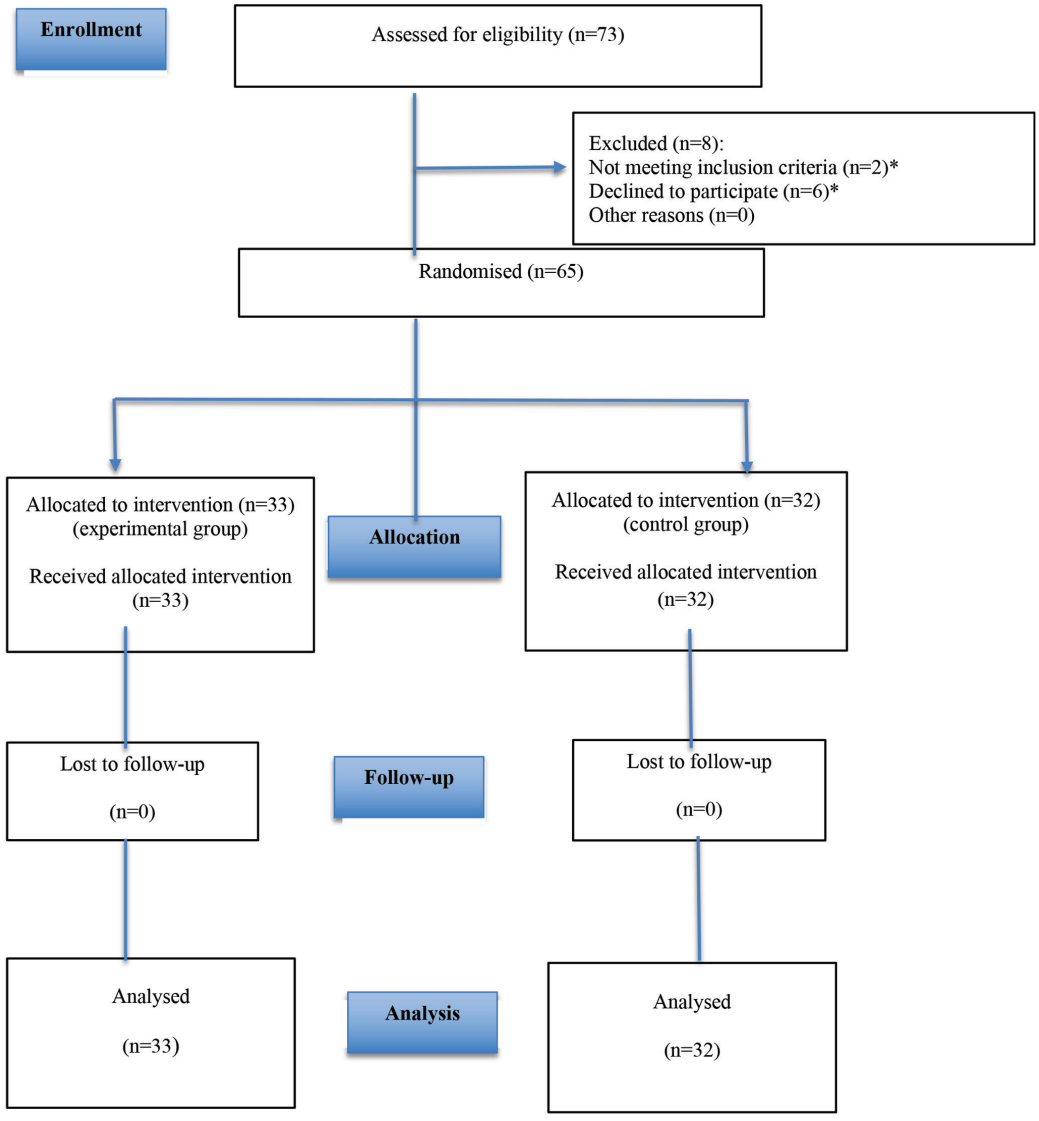

Figure 1. CONSORT diagram

Instruments

Personal information: The personal information form used in the evaluation of socio-demographic features of the parents and children was prepared by the researcher in line with the literature.[3,7,12,16-19]

Wong-Baker faces pain rating scale (WBS): For effectively measuring pain in children aged 3-18, the WBF, developed by Wong and Baker[20], employs a combination of facial expressions and a 0-to-10 numeric scale. This widely used tool enables accurate and straightforward pain assessment in pediatric settings. The degrees of facial expression correspond to increasing levels of pain, as described in our study, with a Cronbach's Alpha of 0.809.

Children's fear scale (CFS): McMurtry et al.'s[21] CFS, a validated tool for assessing fear in children, was employed in this study to evaluate pre- and post-intervention anxiety levels. Adapted from the faces anxiety scale used for adults in intensive care units, the CFS employs five pictures with lines and faces to rate fear from "0" to "4". The score directly correlates with fear levels, starting from "No fear felt" (score of "0") to "Most severe fear" (score of "4"). The scale's Turkish validity and reliability were established by Gerçeker et al.[16], with a Cronbach's Alpha of 0.798 in our study.

Data Collection

The researcher received "play therapy practitioner training" from the continuing education application and research center of a university before starting the study.

Prior to the procedure, both the experimental and control groups of children underwent the administration of the "personal information form", the "WBS", and the "CFS". The researcher, after gathering essential information about the child from their parents via the "introductory characteristics form for parents and children", assessed the child's facial expressions using the "WBS" and the "CFS".

A minute after the suturation process began, the children in the experimental group performed a finger puppet show by the researcher that lasted an average of 10 minutes. During the show, children were queried about various aspects, including their family members' names, the school they attended, their daily activities, preferred toys, the future profession they envisioned, and the hero of their dreams. Then, they were told tales appropriate for their age group. While the control group received the standard suturing procedure without any additional intervention, children in the experimental group participated in a pre-suturing puppet show. Subsequently, both groups participated in pain and fear assessments. For the control group, these assessments were conducted 11 minutes after the start of the suturing process, while the experimental group completed them immediately following the puppet show.

Adhering to the study protocol, all participants -regardless of group allocation- engaged in the assessment process precisely 15 minutes after the conclusion of their incision suturing procedure. This standardized assessment, encompassing the WBS and the CFS, aimed to ensure consistent data collection across experimental and control groups.

Ethical Considerations

Prior to commencing data collection, the study meticulously adhered to ethical guidelines by securing both informed consent from parents and verbal assent from their children. Further safeguarding participants' well-being, the study protocol received prior approval (2020/18) from a Zonguldak Bülent Ecevit University's Non-Interventional Clinical Research Ethics Committee. Moreover, the research-conducting institution granted all necessary approvals (16734702/903.99).

Statistical Analysis

In the study, frequency and percentage were used to analyze categorical variables. Minimum and maximum scores, arithmetic mean scores, and standard deviation scores were calculated in descriptive statistics. When the distribution of the scores of the groups was examined, it was accepted that the scores were not normally distributed since the Kolmogorov-Smirnov test scores were below 0.05 and the skewness and kurtosis coefficients were out of the specified ranges; therefore, non-parametric statistics were used. The Mann-Whitney U test compared the scores of the two independent groups to analyze group scores. Scores across stages (pre-procedure, during the procedure, post-procedure) were compared using the Friedman test, with the Wilcoxon test identifying groups with significant differences in repeated measurements. The study employed the Pearson chi-squared test for categorical variables and the independent samples t-test for continuous variables to analyze the distribution of participants across various characteristics within the sample. All data analyses were conducted using the SPSS 22.0 statistical software package. The significance level for testing hypotheses was set at 0.05, and a 95% confidence interval was used for interpreting the results.

Results

The results of the descriptive features of the children in the experimental (n=33) and control (n=32) groups are given in Table 1.

There was no notable distinction in the distribution of children between the experimental group (n=33) and the control group (n=32) concerning descriptive features like age, location, and cause of incision suturing ($p>0.05$); however, a difference was detected in the distribution of prior hospital experience for the incision suturation ($p<0.05$) (Table 1).

When comparing the pain scores of children in both the experimental and control groups across the pre-procedure, during-procedure, and post-procedure stages, no statistically significant difference was observed in the pre-procedure pain scores between the two groups ($U=497.500$; $p>0.05$). These results suggest that the groups were comparable regarding pre-procedure pain scores.

However, a distinction in pain scores between the experimental and control groups emerged during the procedure and post-procedure stages ($U_{\text{during the procedure}}=91.500$; $p<0.05$ and $U_{\text{post-procedure}}=154.500$; $p<0.05$). Examination of median values revealed that the pain median scores for the control group during the procedure and post-procedure were statistically higher than those for the experimental group (Table 2).

When the results of the differentiation between the pain scores of the groups within the stages (pre-procedure, during the procedure, and post-procedure) were examined, a statistically significant difference was found between the pre-procedure, during the procedure, and post-procedure scores in the experimental group ($\chi^2=61.107$; $p<0.05$). In the analysis, the pain scores of the experimental group during the procedure were found to be significantly lower than the pre-procedure ($Z=-4.613$; $p=0.000$), the post-procedure pain scores to be significantly lower than the pre-procedure ($Z=-5.182$; $p=0.000$), and the post-procedure pain scores to be

significantly lower than the pain scores during the procedure (Z=-5.097; p=0.000) (Table 2).

In the control group, a statistically significant difference was found between the pre-procedure and the post-procedure pain scores (χ^2=41.570; p<0.05). There was a significant increase in the pain scores of the control group during the procedure compared to the pre-procedure (Z=-2.285; p=0.022). The post-procedure pain scores were found to be significantly lower than the pre-procedure (Z=-4.139; p=0.000) and the post-procedure pain scores to be significantly lower than the pain scores during the procedure (Z=-4.996; p=0.000) (Table 2).

In the conducted study, no statistically significant distinction surfaced in the pre-procedure fear scores between the experimental and control groups (U=417.500; p>0.05). These results imply that, concerning pre-procedure fear scores, the groups were essentially equivalent. However, a notable variance emerged between the fear scores of the experimental and control groups during the procedure and the post-procedure ($U_{\text{during the procedure}}$=217.500; p<0.05 and $U_{\text{post-procedure}}$=195.500; p<0.05). Upon scrutinizing the mean values, it became evident that the fear scores of the control group during the procedure and post-procedure were statistically higher than those of the experimental group (Table 3).

When the results of the differentiation between the fear scores of the groups within the stages (pre-procedure, during-procedure, and post-procedure) were examined, a statistically significant difference was found between the pre-procedure, during-procedure, and post-procedure scores of the experimental group (χ^2=55.412; p<0.05). In the analysis, the fear scores during the procedure were found

Table 1. Descriptive features of the children

		Experimental group (n=33)		Control group (n=32)		Test ve p-value
		Mean ± SD	Min-max. (median)	Mean ± SD	Min-max. (median)	
Age		±6.97	4-10 (7)	6.38±1.82	4-10 (6)	t=1.264; p=0.211[a]
		n	%	n	%	
The site of incision suturation	Head	26	48.1	28	51.9	χ^2=0.877 p=0.0349[b]
	Hand-arm-leg	7	63.6	4	36.4	
The cause of incision suturation	Fall-	20	52.6	18	47.4	χ^2=0.127 p=0.722[b]
	Crash-cuts with a sharp object	13	48.1	14	51.9	
Prior hospital experience for incision suturation	Yes	9	81.8	2	5.4	χ^2=5.107 p=0.024
	No	24	44.4	30	55.6	

SD: Standard deviation, [a]: Independent samples t-test, [b]: Pearson chi-square test

Table 2. Comparison of the pre-procedure, during the procedure and post-procedure pain scores of the experimental and control groups

	The pre-procedure (1)		During the procedure (2)		The post- procedure (3)			
	Median	Min-max.	Median	Min-max.	Median	Min-max.	Friedman test**	Difference***
Experimental group (n=33)	2.00	1-3	1.00	1-2	0	0-1	χ^2=61.107; p=0.000	2,3<1 2<3
Control group (n=32)	2.00	0-5	3	1-5	1	0-3	χ^2=41.570; p=0.000	2>1; 3<1 3<2
Mann-Whitney*	U=497.500; p=0.663		U=91.500; p=0.000		U=154.500; p=0.000			

*: Mann-Whitney U test, **: Friedman test, ***: Wilcoxon test

Table 3. Comparison of the pre-procedure, during the procedure and post-procedure fear scores of the experimental and control groups

	The pre-procedure (1)		During the procedure (2)		The post-procedure (3)			
	Median	Min-max.	Median	Min-max.	Median	Min-max.	Friedman test**	Difference
Experimental group (n=33)	2.00	1-3	1.00	1-3	0	0-2	χ^2=55.412; p=0.000	2,3<1; 2<3
Control group (n=32)	2.00	0-4	2.00	1-4	1	0-3	χ^2=37.196; p=0.000	2>1; 3<1; 3<2
Mann-Whitney*	U=417.500; p=0.121		U=217.500; p=0.000		U=195.500; p=0.000			

*: Mann-Whitney U test, **: Friedman test

to be significantly lower than the pre-procedure (Z=-4.315; p=0.000), the post-procedure fear scores to be significantly lower than pre-procedure (Z=-5.182; p=0.000), and the post-procedure fear scores to be significantly lower than the fear scores during the procedure (Z=-5.048; p=0.000) (Table 3).

Within the control group, a statistically notable difference emerged in the fear scores across the pre-procedure, during-procedure, and post-procedure stages (χ^2=37.196; p<0.05). Specifically, there was a noteworthy surge in the fear scores during the procedure compared to the pre-procedure (Z=-2.289; p=0.022). Additionally, the post-procedure fear scores demonstrated a significant decrease both compared to the pre-procedure (Z=-3.844; p=0.000) and during the procedure (Table 3).

Discussion

Recognizing the diverse influences of biological and psychological factors on pain perception in children, our randomized controlled trial employed rigorous baseline assessments to match the control and experimental groups on key descriptive features. This thorough approach, yielding no notable differences (p>0.059), strengthens our results' internal validity and generalizability, minimizing potential bias and increasing confidence in the observed outcomes.

Homogeneous distribution of features such as age, site and cause of incision suturation, and prior hospital experience, which were thought to affect the pain and fear levels of children, was ensured in the experimental and control groups, and the possibility of being affected by these features was eliminated while assessing the efficiency of the implementation.

Although children cannot express themselves truly and fully, they show their pain with their looks, postures, and gestures.[22] Numerous approaches, both pharmacological and non-pharmacological, exist to alleviate pain and anxiety in children during medical procedures. The utilization of non-pharmacological methods by nurses has seen an uptick in recent years.[23] Playing games is an enjoyable activity for the child and is essential in supporting the child's physical, cognitive, motor, language, social and intellectual development. In the literature, it has been reported that playing games is effective in reducing the anxiety and negative emotions of children in the hospital.[24] In the study conducted by Campbell and Brown[25], nursing students gave preschool children information about hand washing, tooth brushing, and hospital dread using a teddy bear for six weeks. They asked for feedback from their parents via e-mail. Parents stated that their children's level of knowledge increased, and their fear of the hospital decreased.[25] In our study, the effectiveness of the finger puppet shows in reducing the pain during the incision suturation was investigated, and the mean scores of the "WBS" during the procedure and the post-procedure were found to be significantly different between the groups. It was determined that the mean pain scores of the children in the experimental group who performed the puppet show during the procedure and the post-procedure were significantly lower than those of the children in the control group.

When the literature was reviewed, it was reported in the study conducted by Cohen et al.[26] that watching cartoons during the procedure was effective in reducing pain and stress in vaccinated children between the ages of 4 and 6. In the study conducted by Lemos et al.[27] with children aged 3-12, it was reported that therapeutic play had a distracting effect on the pain during the intravenous procedures. In the study by Chen et al.[28], 136 children between the ages of 7 and 12 were made to wear virtual reality glasses during the intravenous injection, and it was stated that the pain and fear of the children reduced. In the study conducted by Ballard et al.[29], the use of distracting kits (finger puppet, stress ball, musical toy) during needle procedures in children between the ages of 3 months-2 years and 3-5 years was reported to be effective in reducing their perception of pain. The study by Hartling et al.[30] reported that playing music during intravenous catheter intervention in children aged 3-11 significantly reduced pain and anxiety. In the study by Risaw et al.[31], distraction cards were used in 120 children aged 4-6 during the phlebotomy, and they were reported to be effective in reducing pain. In the study by Mutlu and Balcı[17], it was reported that making children between the ages of 9-12 inflate balloons and cough while taking blood relieved the pain. In the study conducted by Karakaya Suzan et al.[18], it was reported that the puppet show applied to circumcised children during the procedure reduced the pain and anxiety. Similar to the studies conducted on painful procedures, our study also found that the finger puppet show, a non-pharmacological distraction method, was found to be effective in reducing the pain of children caused by the procedure.

The pain increases the level of anxiety in children and makes the examination difficult since it causes psychological and physiological changes in the body.[32] He et al.[33] reported that the anxiety of children and their parents who played therapeutic games for an hour decreased. In our study, while there was no significant difference between the pre-procedure fear scores of the experimental and control groups, it was found that the fear scores indicated a difference during the procedure and the post-procedure. The mean fear scores of the control group during the procedure and the post-procedure were statistically higher than the experimental group.

When the literature was reviewed, in the study conducted by Bergomi et al.[34] with 150 children during the intravenous intervention, the pain and anxiety levels of the animated cartoon group were found to be lowest in the children they divided into the control group, the buzzy device group, both the buzzy device and animated cartoon group and the animated cartoon group. According to a systematic review led by Barreiros et al.[35], the use of "audiovisual distraction methods" on children aged 4-10 was found to decrease fear and concerns related to dental treatment. A puppet show was used to reduce the anxiety of elementary school children during medical procedures in another study by Topan and Ozturk Sahin.[19] The puppet show was administered to the experimental group once a week for four weeks, resulting in a reported effectiveness in reducing children's fear of medical procedures. In the study conducted by Ghabeli et al.[36] with 60 children between the ages of 3 and 8, the children in the experimental group who were sent to the operation with the toy they preferred had less anxiety and higher satisfaction than those in the control group. In the systematic review by Eijlers et al.[37], it was reported that the virtual reality glasses that were used during tooth extraction, treatment of burns, blood collection and treatment of oncological patients reduced children's pain and anxiety. In the study conducted by Nguyen et al.[38] with 40 children with leukemia between the ages of 7 and 12, music was played during lumbar puncture, and children were reported to have lower anxiety levels afterward. Upon comparing the research findings with existing literature, this study determined the effectiveness of distraction methods, such as the finger puppet show, in alleviating children's fears during medical procedures. Similar results were noted in other studies, indicating a consistent outcome, which can be considered as a positive finding.

Study Limitations

This study acknowledges limitations inherent to its population and setting, as it was conducted within a specific province's pediatric emergency department of a state hospital. These limitations are due to defined inclusion and exclusion criteria that might limit generalizability to different settings or broader pediatric populations. In addition, the fact that the finger puppet show was not compared with another intervention and that the children in the control group did not have any interventions may explain some of the between-group variations in pain and anxiety. Therefore, in future research, we would recommend comparing the finger puppet show with another intervention (for the control group).

Implications for Emergency Nurses

Non-pharmacological methods play a crucial role in alleviating pain and fear in children. Despite their significance, the application of techniques is limited for pediatric emergency nurses. Given the urgent and meticulous nature of emergency services, the chosen method should be straightforward and swift. Hence, employing cost-effective and uncomplicated non-pharmacological techniques, such as the use of a finger puppet during invasive procedures like incision suturing, not only diminishes children's pain and fear but also facilitates a swifter and more careful execution of invasive interventions.

Conclusion

The study determined that the finger puppet show, implemented during incision suturing, effectively mitigated pain and fear in children. Given the challenging nature of incision suturing in pediatric emergency services because of pain, fear, and trauma, the use of non-pharmacological distraction methods, such as the finger puppet show, is recommended for pediatric emergency nurses in clinical settings.

Ethics

Ethics Committee Approval: Further safeguarding participants' well-being, the study protocol received prior approval (2020/18) from a Zonguldak Bülent Ecevit University's Non-Interventional Clinical Research Ethics Committee. Moreover, the research-conducting institution granted all necessary approvals (16734702/903.99).

Informed Consent: Prior to commencing data collection, the study meticulously adhered to ethical guidelines by securing both informed consent from parents and verbal assent from their children.

Authorship Contributions

Concept: G.F.E., A.T., Design: G.F.E., A.T., Data Collection or Processing: G.F.E., A.T., Analysis or Interpretation: G.F.E., A.T., Literature Search: G.F.E., A.T., Writing: G.F.E., A.T.

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

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/cayd.galenos.2023.71677
J Pediatr Emerg Intensive Care Med 2024;11:29-56

Continuous Renal Replacement Therapy (CRRT) Protocol in Critically Ill Children

Kritik Hasta Çocuklarda Sürekli Renal Destek Tedavi (CRRT) Protokolü

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Keywords: Critically ill child, extracorporeal therapy, renal replacement, renal failure
Anahtar Kelimeler: Kritik hasta çocuk, ekstrakorporeal tedavi, renal replasman, böbrek yetmezliği

Introduction

Continuous renal replacement therapy (CRRT) has seen a rising utilization in critically ill children in recent years, owing to technological advancements and the emergence of user-friendly devices.[1,2] However, survival in children receiving CRRT does not increase in parallel with advances in technology. We believe that implementing protocol-based practices will make an important contribution to increasing survival in children receiving CRRT. For this reason, our CRRT Working Group has prepared the protocol below to guide your practices by updating it in line with new data.

1. Definition of Continuous Renal Replacement Therapies and Methods Used

Continuous renal replacement therapies are extracorporeal support systems in which solute and/or water clearance is achieved in the time desired by the clinician using dialysis (diffusion-based solute removal) and/or filtration (convection-based water and solute removal) methods.[3]

Terminology

1. Route; vascular access is necessary for blood flow to reach the extracorporeal system

Venovenous route - This is a vascular access method that does not require arterial access. Two separate catheters are placed in two veins or a double-lumen catheter in a single vein. Blood is directed to the extracorporeal system using a pump.

Advantage - No arterial intervention is required. Fast and predictable blood flow is provided.

Disadvantage - A pump is required to access the extracorporeal system. Air embolism, thrombosis, or stenosis of the venous system may develop.

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Received/Geliş Tarihi: 26.07.2023 **Accepted/Kabul Tarihi:** 27.07.2023

2. Working principle; clearance is achieved by diffusion in hemodialysis and convection in hemofiltration.

Clearance is the rate at which solute is removed from the body. Clearance is indicated by the letter "K". Solute clearance is the volume of the desired substance removed from the blood in one unit of time.

K = Removal rate (excreted solute concentration-solute blood concentration)/solute blood concentration

$K = V \times CU_F/C_\beta$

CU_F/C_β = for many solutes the sieving coefficient is assumed to be 1

V = Effluent rate [dialysis rate + ultrafiltration (UF) rate]

Diffusion - Solutes move across a semipermeable membrane due to a concentration difference. Solutes are removed by moving from the high-concentration area to the low-concentration area. Small molecular weight (<1000 Dalton) solutes are removed from the membrane by this method.

Dialysate fluid - This is the fluid that provides the diffusion gradient. Dialysate fluid and blood currents are reversed to increase the concentration difference between compartments.

Convection - A system in which solutes are removed by solvent flow through a semipermeable membrane by creating a hydrostatic pressure difference. In this approach, solutes of varying sizes, ranging from small to medium molecular weights, are extracted from the membrane using water as the carrier within the plasma.

Replacement fluid - It is the solution used to replace the excess plasma removed to prevent hypovolemia in the patient while convection-based water filtration is provided.

Adsorption - The mechanism by which solutes, especially medium to large solutes, are excreted from the body by adhering to the surface of a semipermeable membrane.

Hemodialysis (HD) - A renal replacement method that provides diffusion-based clearance. Small molecular weight solutes are cleared.

Hemofiltration (HF) - A renal replacement method that provides convection-based clearance. Convective transport of small and medium molecular weight solutes in the same direction as water is provided. Solute removal capacity is lower than diffusion-based renal replacement methods.

Hemodiafiltration (HDF) - It is a renal replacement method in which diffusion and convection clearance are used together.

Ultrafiltration (UF) - Removal of water from a semipermeable membrane by creating a pressure gradient (hydrostatic, osmotic, or oncotic).

Filtration fraction (FF) - It is the ratio of the UF rate to the blood flow rate.

3. Treatment methods; today, blood flow is delivered to the filter using roller pumps, single venous access (continuous venovenous = CVV) using a double-lumen dialysis catheter is sufficient.

Slow continuous ultrafiltration (SCUF) - A treatment in which water is removed slowly and over a long period from the patient's blood through a filter. It is used for fluid overload indications when UF is the goal.

Continuous venovenous hemofiltration (CVVH) - This treatment method involves the removal of significant amounts of water through a filter, along with residual substances, achieved by creating transmembrane pressure. As large quantities of water are extracted through the membrane, small to medium molecular weight solutes are concurrently carried along (convection). Hypovolemia in the patient during hemofiltration is prevented with replacement fluid. Replacement fluid can be added to the system before (predilution) and/or after (post-dilution) filtering. In predilution, the diluted blood interacts with the membrane, diminishing the likelihood of filter clotting. With post-dilution, as the quantity of blood in contact with the filter increases, clearance is enhanced. Nevertheless, insufficient blood flow rates can lead to a high filter fraction, increasing the risk of filter blockage.

Continuous venovenous hemodialysis (CVVHD) - A treatment method in which the clearance of small molecular weight solutes is achieved through concentration gradient (diffusion). The factor that provides the concentration gradient is the dialysis solution that moves around the membrane in the opposite direction to the blood flow.

Continuous venovenous hemodiafiltration (CVVHDF) - It is a treatment method in which clearance by diffusion and convection are used together. Dialysate is used for diffusion and replacement fluids are used for convection.

2. Selection of Continuous Renal Replacement Method

Currently, insufficient data is showing that any method is superior.[3-5] Things to consider when choosing a treatment method:

1. Accessibility to the method
2. Experience of the clinician
3. Clinical diagnosis and hemodynamic status of the patient
4. Vascular access
5. Targeting fluid and/or solute removal

The selection of a continuous renal replacement method should not be generalized; rather, it should be based on individual patient characteristics and needs. If addressing fluid overload is the primary concern, hemofiltration should be favored in CRRT applications. Conversely, if the focus is on

solute clearance (such as ammonia, lactate, urea, etc.), HD would be the preferable choice. High-flow HF or HDF may be preferred in patients with multiple organ failure and patients requiring more clearance. Table 1 shows the treatment methods recommended for use in various diseases.

3. Indications for Continuous Renal Replacement Therapy

Indications for renal replacement therapy (RRT) in acute kidney injury (AKI) and general indications:[6-10]

1. For cases where fluid overload remains unresponsive to medical therapy, including conditions like hypertension, congestive heart failure, pulmonary edema, and fluid-induced respiratory failure that do not respond to diuretics, particularly when the cumulative fluid load exceeds 10%, hemofiltration should be considered as a preferred option within the CRRT approach.

2. Hyperkalemia refractory to medical treatment

3. Severe azotemia and symptomatic uremia (presence of encephalopathy)

4. Severe metabolic acidosis

5. Uncontrollable and progressive hypo- or hypernatremia

6. Hyperphosphatemia

7. Tumor lysis syndrome, Crush syndrome

8. Providing the necessary UF to maintain enteral and parenteral nutrition, treatments, blood product replacements

9. Sepsis, septic shock, and multiple organ failure

10. Cardiogenic shock after cardiac surgery

11. Liver failure

12. Urea cycle defects, hyperammonemia, and organic acidemias

13. Removal of toxins and poisons that may be dialyzed, drug overdose

14. Hyperthermia

Advantages of CRRT over other RRTs:

1. CRRT is an effective method for reducing or preventing fluid overload in critically ill children due to its slow and continuous fluid removal capability. While intermittent hemodialysis (IHD) can achieve the UF target rapidly, CRRT aids in maintaining cardiovascular balance by distributing UF over an extended period. CRRT preparations should be initiated when the fluid overload unresponsive to diuretic treatments surpasses 5% of body weight, while the commencement of CRRT itself is recommended when the fluid overload exceeds 10%.[11]

2. It is useful in maintaining metabolic balance by continuous removal of harmful particles. Although IHD is more effective in solute removal, CRRT is useful in preventing fluctuating courses due to its continuity.[4,5]

3. In patients with impaired renal function and decreased urine output, CRRT removes the daily required amount of fluid and enables the use of drugs, nutrition, and blood products without fluid overload. A balanced fluid balance can be achieved with CRRT compared to IHD.

Table 2 presents a summary of the advantages and disadvantages of selecting CRRT over peritoneal dialysis (PD) and IHD among renal replacement systems.

4. Vascular Access

The hemodialysis catheter should be inserted with ultrasonography guidance by teams experienced in vascular access. An insufficient diameter and improper placement of the central catheter are among the most crucial factors contributing to the shortened lifespan of the filter (Table 3). The right internal jugular vein should be preferred as the site of the central venous double-lumen dialysis catheter.

If vascular access cannot be obtained from the right internal jugular vein, the next preferable option is the left internal jugular vein, followed by the femoral vein. The subclavian vein should only be considered if vascular access cannot be

Table 1. CRRT methods that can be preferred according to diseases

Underlying disease	Method
Acute or chronic kidney failure	CVVHD
Sepsis	CVVH
Fluid overload	CVVH
Multiple organ failure	CVVH
Multiple organ failure after bone marrow transplantation	CVVH
Liver failure	CVVH/CVVHDF
Inborn error of metabolism	CVVHD/CVVHDF
Tumor lysis syndrome	CVVHD
Poisonings	CVVHD-albumin should be added to the dialysis solution

CVVH: Continuous venovenous hemofiltration, CVVHD: Continuous venovenous hemodialysis, CVVHDF: Continuous venovenous hemodiafiltration

obtained in both the jugular and femoral regions. The site should be chosen according to the patient's condition.[12] Three-way dialysis catheters are also accessible in our country. While the femoral vein can be utilized for vascular access in patients with bleeding risk, it is preferable to avoid placing the dialysis catheter in the femoral region for patients with increased intra-abdominal pressure. Additionally, the size of the dialysis catheter should be determined based on the child's weight (Table 3). Nevertheless, it is advisable to prioritize the placement of the catheter with the largest diameter that is suitable for the patient's weight.

5. Filter Selection

Size and membrane structure should be considered when choosing a filter for CRRT.[13,14]

1. Filters with large surface areas have a high FF and a low probability of hemoconcentration. The selection of an excessively large filter causes a decrease in the blood flow rate in the filter. If the total volume of the filter and set exceeds 10% of the child's blood volume, "blood priming" should be conducted, as outlined in Appendix 1 of the blood-washing (priming) protocol.

2. The filter material comprises microtubules or plate-like membranes made of polyacrylonitrile nitrate (AN-69, AN69 ST), polysulfone (PS), or polyarylethersulfone (PAES). Filter selection should be based on the patient's weight and the indication for the procedure. Table 4 provides an overview of commonly used devices and filters available in our country.

6. Filling the Filter (Priming)

Before commencing the treatment, it's essential to purge the air from the filter and fill it with a balanced solution. Often, 0.9% NaCl is utilized for filter filling. Before the procedure, it is common practice to add 2-5 units of heparin per mL of 0.9% NaCl. For patients prone to bleeding, the initial flush can be conducted using 0.9% NaCl with added heparin, while subsequent flushes can be performed with 0.9% NaCl without added heparin.

In patients with hemodynamic instability, the filter can be filled with 5% albumin or blood. There are different opinions about when to prime the filter with blood. It is recommended to prime the filter with blood if the patient weighs <5-6 kg, if the patient weighs 10-11 kg and is hemodynamically unstable, or if the filter volume is >10% of the patient's weight. Another perspective suggests that the filter should always be primed with blood if the patient weighs less than 10 kg. For patients weighing more than 10 kg, the decision should be made based on the clinical circumstances. The blood priming protocol is shown in Appendix 1.[15,16]

Table 2. Comparison of renal replacement therapy methods

	CRRT	Peritoneal dialysis	Intermittent hemodialysis
Continuous treatment can be done	Yes	Yes	No
Risk of hemodynamic instability	Low	Low	High
Ease of application	Difficult	Easy	Difficult
Ability to achieve fluid balance	Yes	Variable	Yes
Metabolic control	Yes	Variable	Yes
Optimal nutrition	Yes	No	No
Anticoagulation	Yes	No	Yes
Stable intracranial pressure	Yes	Variable	Variable
Need for vascular access	Yes	No	Yes
Continuous detoxification	Yes	Variable	No
Cost	The most expensive	Cheaper	Expensive
Abdominal surgery and V-P shunt	Yes	No	Yes

CRRT: Continuous renal replacement therapy

Table 3. Temporary hemodialysis catheter sizes that can be used according to the patient's weight

Patient's weight	Catheter diameter (double lumen)	Preferred site (vein)
Newborn	6.5-7 French	Internal vein/femoral/subclavian
3-6 kg	7 French	Internal jugular/femoral/subclavian
6-15 kg	8 French	Internal jugular/femoral/subclavian
15-30 kg	9 French	Internal jugular/femoral/subclavian
>30 kg	10-12.5 French	Internal jugular/femoral/subclavian

Table 4. Frequently used devices and filters in our country

Firm	Weight (kg)	Hemofilter name	Membrane type/structure	Membrane surface area (m^2)	Filter and set total volume (mL)
Fresenius	3-10	AV Paed	PS/MT	0.2	72
	10-30	AV 400S	PS/MT	0.75	135
	>30	AV 600S	PS/MT	1.4	246
	>30	AV 1000S	PS/MT	1.8	276
Baxter	8-15	Prismaflex HF20	PAES/MT	0.2	58
	>30	Prismaflex HF1000	PAES/MT	1.15	165
	>30	Prismaflex HF1400	PAES/MT	1.4	186
	15-30	Prismaflex M60	AN69/MT*	0.6	93
	>30	Prismaflex M100	AN69/MT*	0.9	153
	>30	Prismaflex M150	AN69/MT*	1.5	189
Carpediem	>2.5	HCD 0075	PS	0.075	27
	>2.5	HCD 015	PS	0.15	33
	>2.5	HCD 025	PS	0.25	41

AN69: Acrylonitrile, MT: Microtubule, PAES: Polyaryletersulfone, PS: Polysulfone. *Pay attention to "Bradykinin release syndrome" in patients who need to fill the filter with blood (priming), have acidosis or are taking ACE inhibitors (see bradykinin release syndrome prevention protocol (Appendix 2)

7. Adjustment of Treatment Doses

Blood Flow Rate

In patients undergoing CRRT, it is crucial to adjust the blood flow rate (BFR) appropriately to ensure sufficient clearance.[17,18] The BRF is determined based on body weight and typically remains constant regardless of the method applied. It is depicted in Table 5.

Table 5. Blood flow rates according to body weight in CRRT

Patient (kg)	Blood flow rate (mL/kg/min)
3-6	8-12
6-15	5-8
15-30	4-6
>30	2-4

Dialysate Rate

In CRRT methods operating on the diffusion principle (such as CVVHD and CVVHDF), dialysate is utilized to establish a concentration gradient on both sides of the membrane, enhancing solute transfer through rapid dialysate flow. The dialysate rate is determined accordingly. The dialysate rate is often sufficient when set at 2000 mL/1.73 m^2/h or 20-30 mL/kg/h. As an expert opinion, we recommend that the dialysis rate should be based on the patient's weight in kilograms to avoid administering higher dialysis rates than necessary, particularly in infants weighing less than 10 kilograms.

Example: If the patient is 0.6 m^2, dialysis rate=2000 X 0.6/1.73=693 ≈ 690 mL/hour

In certain special cases such as poisoning and metabolic comas with hyperammonemia, the dialysis rate can be escalated to as high as 8000 mL/1.73 m^2/h (equivalent to 40-60 mL/kg/h) to guarantee adequate clearance.[19-22] In patients undergoing continuous dialysis for intoxication (such as CVVHD or CVVHDF), adding albumin (at a concentration of 2-4 g/dL) to the dialysis solution can enhance efficiency. It's important to recognize that patients undergoing high-flow HD are prone to electrolyte imbalances. Therefore, close monitoring is essential, and if there is no immediate necessity, medium-flow HF should be considered instead.[23,24] Especially in patients weighing less than 10 kg, severe electrolyte imbalances may occur during high-flow hemofiltration. Therefore, special attention and caution should be exercised in these cases.[25,26]

Ultrafiltration Rate

Two critical features of CRRTs contribute to highly efficient fluid removal:

a) The utilization of highly permeable membranes

b) The continuous nature of the technique.

With CRRT, there is indeed potential for the removal of a considerable amount of fluid. However, the amount of fluid that can be removed is not unlimited. It is contingent upon factors such as pump speed, the duration of treatment, patient tolerance, and the gradual decline in filter efficiency over time. In pediatric intensive care units (PICUs), the target UF rate should be 1-2 mL/kg/hour. Blood and blood products should be removed at twice the rate of administration. The UF rate can be augmented in hemodynamically stable patients

where fluid overload is the primary concern. In such instances, it is calculated using the formula: hourly fluid outflow rate + hourly net fluid balance = urine output rate (plus any other losses) + UF rate.

Example: If the net UF rate is targeted at 2 mL/kg/hour in a 30 kg child, and the patient receives 80 mL of fluid per hour, with a urine output of 1 mL/kg/hour, then the UF rate can be calculated as follows:

UF rate = Fluid intake - Urine output

= (80 mL/hour) + (30 kg x 2 mL/kg/hour) - (30 kg x 1 mL/kg/hour)

= 80 mL/hour + 60 mL/hour - 30 mL/hour

= 110 mL/hour

Therefore, the UF rate will be 110 mL/hour.

In PICUs, it's possible to remove more fluid than the targeted amount based on determined hemodynamic parameters. However, it's essential to monitor and regulate this process to prevent the FF from exceeding 0.35-0.4.

FF= UF rate/plasma flow rate

Plasma flow rate= [BFR x (1-hematocrit)]

Example: Let's consider a patient weighing 10 kg, with a BFR set at 60 mL/min and a hematocrit level of 30%. In this case, the maximum UF rate can be determined as follows:

1. Calculate the plasma flow rate:

Plasma flow rate = BFR × (1 - hematocrit)

= 60 mL/min × (1-0.3)

= 60 mL/min × 0.7

= 42 mL/min

= 42 mL/min × 60 min/hour

= 2520 mL/hour

2. Determine the maximum UF rate using the FF constraint:

FF = UF rate/Plasma flow rate

0.35 = UF rate/2520 mL/hour

Solve for UF rate:

UF rate = 0.35×2520 mL/hour

≈882 mL/hour

So, the UF rate can be up to approximately 882 mL/hour, which is approximately 80 mL/kg/hour for a 10 kg patient.

Fluid Balance Management During Continuous Renal Replacement Therapy

Accurate calculation of a patient's CRRT-related and daily fluid management data is essential for maintaining a clear fluid balance. This is typically achieved using a monitoring form, where device settings and planned hourly fluid balance are recorded. In the intensive care unit (ICU), the fluid requirements of patients are often not static and should be evaluated at frequent intervals.

Daily oral and/or intravenous fluid intake of patients may exceed normal levels, and additional fluid infusions may be necessary based on clinical indications. For instance, if 600 mL of fresh frozen plasma needs to be administered two hours before an invasive procedure, adjustments to the fluid balance plan should be made. This change should be documented, including the rationale behind it and the duration for which it will be continued.

Furthermore, it's recommended to divide all fluid balance goals for the patient into 12-hour time intervals and diligently record them. This approach allows for better monitoring and adjustment of fluid management strategies according to the patient's evolving clinical condition.

Practical Advice

Training of nurses and doctors is important to achieve the goals. CRRT instructions should be legible and include the name, signature, and contact number of the relevant physician. The fluid balance should be recorded hourly, and the final balance should be created by calculating additional fluid in and out. This documentation can be computerized or added to the bedside form by the nurse (Figure 1).

Expected Outcome, Potential Problems, Points to Consider and Benefits

Systematic fluid administration instructions, administration, and monitoring of fluids during CRRT ensure that the patient receives the planned treatment efficiently and safely. This approach minimizes errors (persistent fluid overload or dangerous intravenous volume depletion). The most frequently observed problem is usually associated with downtime[27] (filter blockage, or system self-rotation during being out of the unit for surgery or radiologic imaging - Appendix 2.[16] In the presence of these conditions, fluid withdrawal cannot be accomplished as previously planned. If the patient loses five hours, this will significantly hinder achieving the planned fluid removal target. In such a situation, nurses and physicians should be vigilant about the consequences, and appropriate arrangements should be made accordingly. Safe compensation for fluid removal spread over 12 or 24 hours should be ensured, and the hourly net UF rate should be increased. It is necessary to be very careful in patients whose fluid removal may be problematic and to evaluate the patient's fluid balance at frequent intervals.

Another problem encountered is frequent interruption of therapy due to device alarms. In some agitated patients, patients with a femoral catheter who flexes their leg frequently, and patients with a subclavian catheter who sit upright in bed or move, machine alarms are triggered frequently. In addition,

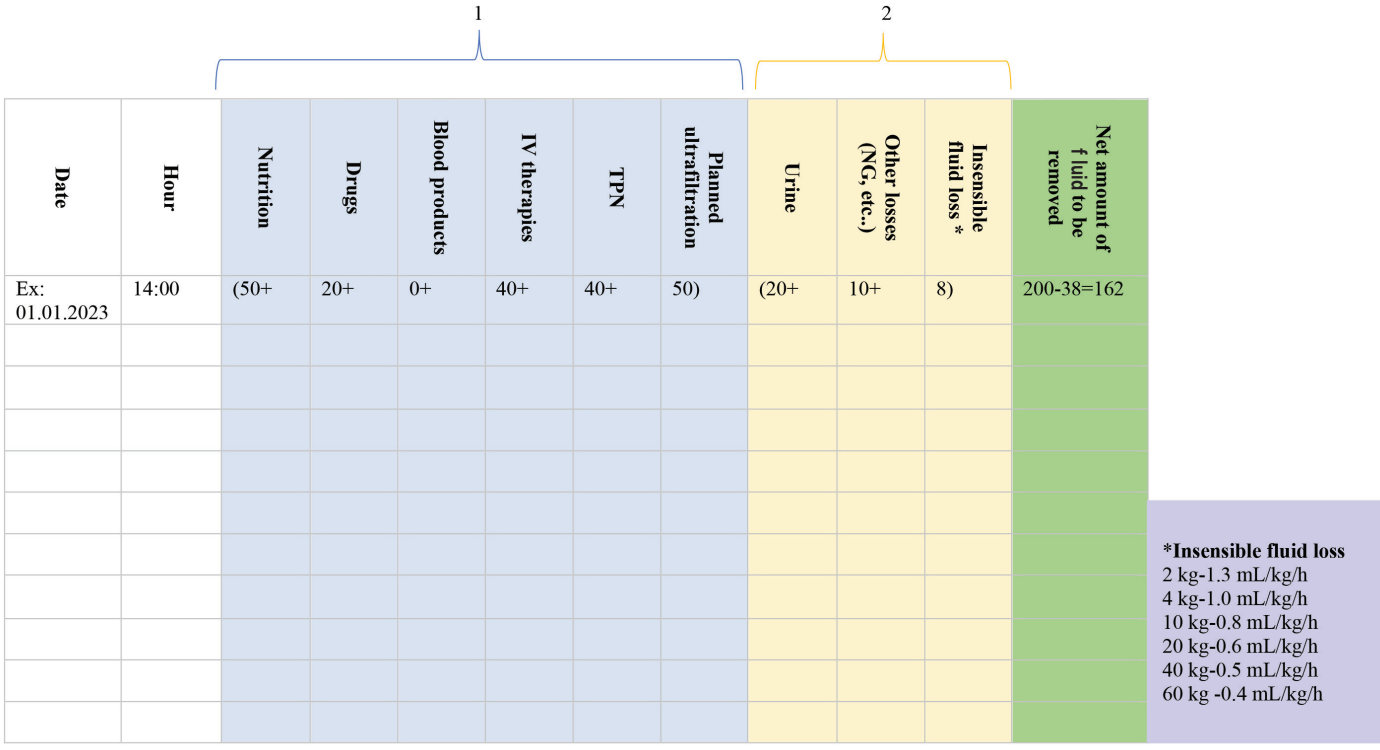

Figure 1. Ultrafiltration chart in CRRT: The total amount of fluids to be extracted equals the sum of fluids in column number 1 minus the sum of fluids in column number 2

other alarms activated during processes such as changing fluid bags or retrieving the waste bag also cause pauses. These can lead to a loss of 5-10 minutes per hour and, when calculated for the day, can add up to a significant loss of time and hinder the achievement of the goal. It is usually possible to overcome the problem by carefully planning a higher fluid removal target than the initial target. Most modern devices allow the user to check how much fluid has been removed in a given period. Frequent checks should be performed to obtain accurate fluid loss data to be used in the patient's fluid balance calculations. Finally, device-induced fluid removal errors may lead to the development of circulatory imbalance.[28]

Replacement Fluid Rate

In CRRT methods working on the principle of convection, small and medium molecular weight solutes are pushed to the opposite side of the membrane by creating transmembrane pressure. A high filtration rate increases the amount of convection but creates a risk of hypotension. Therefore, the UF volume should be partially replaced by using a replacement solution.

Different formulas have been proposed for the calculation of replacement fluid rates in different sources. The replacement fluid rate can be determined as 2000 mL/1.73 m^2/hour. Another recommendation is to set the replacement fluid rate as 30 mL/kg/hour for mid-flow filtration and 40-90 mL/kg/hour for high-flow filtration. Medium-flow filtration is frequently applied. In the application where dialysis and filtration are performed together (CVVHDF), the effluent flow rate consists of the sum of dialysate and replacement fluids.

Example: If the dialysate and replacement rates are 2000 mL/1.73 m^2/hour, the effluent flow rate is 4000 mL/1.73 m^2/hour.

Experimental studies have shown positive effects of high-flow CRRT on shock, immunoparalysis, and apoptosis.[29,30] High-flow CRRT has been recommended for use in pediatric patients with cancer-related ARDS and sepsis. However, in a later prospective study conducted in pediatric patients, no effect of increasing the CRRT dose on the outcome was found.[31-35] Therefore, the determination of filtration dose in CRRT should be patient-specific.[36] In patients on CRRT due to metabolic disease, the replacement fluid rate should be adjusted to keep ammonia or lactate levels within normal limits.

Replacement solution can be administered prefilter (pre-dilutional) and postfilter (post-dilutional). The benefits of using pre-dilutional replacement fluid are (a) increased urea clearance and (b) prolonged filter life. However, when pre-dilutional replacement is used, the concentrations of many solutes reaching the filter will decrease, and the clearance coefficients will decrease. In new technology devices, predilution and post-dilution can be performed simultaneously.

There is insufficient evidence, but it is recommended to set 1/3 of the total replacement fluid rate as pre-dilutional and 2/3 as pos-dilutional. The use of the replacement solution before and/or after filtering should be decided according to the individual characteristics of the patient.

Anticoagulation Selection and Dosage

CRRT in children is performed using relatively lower BFRs and small-diameter catheters compared to adults, the possibility of clotting in the circuit is high and anticoagulation should be applied.[37] However, non-anticoagulation factors must be optimized for adequate filter life. Ten basic recommendations in order of importance to prolong filter life are listed below:[38]

1. Correct circuit preparation

- Adequate flushing

- Not using bicarbonate-based solution during priming

- Adding heparin to the priming fluid

2. Ideal location of the catheter

- Right internal jugular

- Femoral

3. Checking vascular access and confirming adequate blood flow through both lumens

4. BFR appropriate for the patient's weight

5. Use of biocompatible membrane

6. Use of bicarbonate-based solutions

7. Adding predilution replacement fluid

8. Use of diffusive clearance

9. Adjusting the air-retaining column

10. Adding post-dilution replacement solution

11. Training at regular intervals

12. Fast response to alarms

Anticoagulation can be done using different methods. Citrate and heparin are the most used anticoagulants in modern practice. In addition, the proportion of centers performing prostacyclin anticoagulation has been increasing in recent years.

Heparin is infused into the circuit before the blood enters the filter, intending to achieve prolonged activated partial thromboplastin time (aPTT) and activated clotting time (ACT) within the filter. Heparin anticoagulation is easy to administer but there is a risk of bleeding. The heparin protocol is shown in Appendix 3.

Regional anticoagulation is provided with citrate. Citrate is infused into the circuit before the blood enters the filter and calcium is infused before the blood leaves the filter and returns to the patient. The amount of citrate is adjusted to chelate calcium in the blood. The amount of calcium to be infused after the filter should be adjusted according to the citrate dose and citrate should not enter the systemic circulation. Patients using citrate anticoagulation require a separate, preferably central route for calcium infusion and a calcium-free dialysis solution. The basic rationale for citrate anticoagulation is to maintain a citrate concentration of 2.5-3 mmol per liter in the solution-independent extracorporeal circuit. The formulation to be used for this is:

Citrate dose = $Q_{citrate}$ x $C_{citrate}$/BFR

$Q_{citrate}$; citrate blood flow rate

$C_{citrate}$; citrate concentration of the solution

BFR; blood flow rate

Using the formulation, the citrate rate can be adjusted according to the targeted citrate concentration in the extracorporeal circuit based on the citrate solution content and BFR in our unit. The net citrate load that the patient must metabolize depends on the citrate dose, BFR, and total effluent rate. For instance, in citrate treatment at a concentration of 3.0 mmol/L - for regional 18/0 - the citrate replacement solution rate varies. It's 1200 mL/hour when the blood flow rate is 120 mL/min, 1500 mL/hour when the blood flow rate is 150 mL/min, and 1800 mL/hour when the blood flow rate is 180 mL/min. Consequently, the net citrate load to be metabolized increases as the blood flow rate rises. The effects of blood flow rate and total effluent rates on citrate load are shown in Table 6.

The citrate protocol is shown in Appendix 4.

Table 6. Effects of blood flow rate and total effluent rate on metabolic citrate load

Blood flow rate	Citrate solution rate required to keep citrate dose constant	Effluent rate (dialysis + filtration)	Metabolic citrate load
↑	↑	-	↑
-	-	↓	↑
↑	↑	↓	↑
↓	↓	-	↓
-	-	↑	↓
↓	↓	↑	↓

Citrate is metabolized in the mitochondria of the liver, kidney, and skeletal muscles. Citrate anticoagulation works well for most patients, but it is contraindicated in certain patient groups where citrate cannot be efficiently metabolized to bicarbonate. Patients who may have problems with citrate metabolism are those with mitochondriopathy or mitochondrial dysfunction (usually mild hyperlactatemia up to 4 mmol/L is not a problem). Citrate should be used with caution in patients with severe circulatory failure, liver failure, and in infants (<2 years).[39] If lactate levels are ≥4 mmol/L in patients with circulatory failure, there is an increased risk of citrate accumulation (known as the citrate lock phenomenon), and citrate use should be approached with caution. Similarly, it has been shown that the risk of citrate accumulation is high if the lactate level is ≥4 mmol/L or prothrombin activity is below 25% in patients with hepatic dysfunction or failure.[40]

Citrate may lead to citrate lock phenomenon (excessive citrate binds free calcium, total calcium/ionized calcium ratio becomes >2.5, ionized calcium level decreases, metabolic acidosis and hypercalcemia may be observed), hypomagnesemia, metabolic alkalosis, or acidosis.

In patients who develop citrate lock phenomenon, citrate anticoagulation should be discontinued if the problem persists despite protocol adjustments (reducing blood flow and citrate rates, increasing dialysis and/or replacement rates, and/or using calcium-free replacement solution).

In a pediatric CRRT study comparing prospective heparin and citrate anticoagulation, it was demonstrated that the duration of CRRT circuit usage was prolonged, and there was a low probability of bleeding in patients treated with citrate.[41,42]

Epoprostenol (Prostacyclin): Epoprostenol has been increasingly utilized for anticoagulation in patients undergoing CRRT in recent years.[43] Epoprostenol may be administered to patients for whom citrate anticoagulation is not advisable or in the presence of any of the following circumstances:

1. The patient has a heparin allergy or heparin-induced thrombocytopenia syndrome

2. There is antithrombin III deficiency

3. The filter clogging occurs twice within 24 hours with heparin treatment

Epoprostenol is applied at 5 nanograms/kg/min (2-8 nanograms/kg/min) before the filter. Once diluted, epoprostenol can remain stable at room temperature for 24 hours. It should be administered using a filter from a separate central venous catheter.

In scenarios 1 and 2 as described above, epoprostenol can be initially employed as the sole agent for anticoagulation. However, in scenario number three, it is advised to combine a heparin infusion at a rate of 5 U/kg/hour with epoprostenol.

In patients at risk of bleeding, characterized by a platelet count less than 50,000/mm^3, a prothrombin time (PT) >25 seconds, or aPTT >60 seconds, anticoagulation may pose a risk. In such instances, several measures can be undertaken:

1. Insertion of a large-diameter catheter to mitigate the risk of clotting.

2. Maintaining a high BFR.

3. Infusing 0.9% NaCl into the circuit before the filter, may offer benefits. Implementing a triple tap on the arterial line before the filter and applying a 100 mL/hour infusion of 0.9% NaCl. When patients are anticoagulated with sodium chloride, it's crucial to consider the infusion rate of 0.9% NaCl when calculating the UF rate.

8. Solution Selection

If CRRT systems operate on the principle of diffusion (CVVHD), dialysate is utilized. Conversely, if they function on the principle of convection (CVVH), replacement fluid is employed. In cases where both methods are to be combined (CVVHDF), both dialysis and replacement solutions are utilized. Solutions utilized in CRRT facilitate solute transfer, aid in correcting metabolic disorders, and play a crucial role in providing renal support. Solutions used in CRRT should ideally possess the following characteristics:

(a) Physiological: Mimicking the composition of bodily fluids to maintain electrolyte balance and osmolarity.

(b) Inexpensive: Cost-effective to ensure affordability and accessibility.

(c) Easy to administer: Simple to prepare and administer to facilitate efficient treatment delivery.

(d) Easy to store: Stable under appropriate storage conditions to maintain efficacy.

(e) Accessible: Readily available to ensure uninterrupted therapy.

Preference should be given to commercially produced solutions, which typically contain sodium, buffer, calcium, and magnesium in concentrations resembling plasma levels. Solutions employing bicarbonate as a buffer are preferable.

In cases where citrate anticoagulation is planned, dialysate and replacement solutions should not contain calcium.

Adding Electrolytes to Solutions

In long-term CRRT applications, phosphorus can either be incorporated into the solutions or administered separately through additional vascular access.[44,45] If phosphorus supplementation is chosen to be included in CRRT solutions, it is crucial to maintain the total phosphorus concentration within the solutions below 2 mmol/L. In cases where potassium addition is required, the total potassium concentration in CRRT solutions should not exceed 4.5 mmol/L.[44] In patients

with elevated levels of potassium and phosphorus, it is advisable not to add additional potassium and phosphorus to the solutions used in CRRT.

For patients diagnosed with tumor lysis syndrome, if blood biochemistry reveals potassium levels below 4 mmol/L, potassium chloride may be introduced into the solutions, with careful attention to maintaining the total potassium concentration within the solutions below 4.5 mmol/L. However, it's important to note that phosphate should not be included in solutions for patients with tumor lysis syndrome.

In patients with congenital metabolic disease or systemic inflammatory response syndrome, potassium chloride can be added up to 3 mmol/L and potassium phosphate up to 1.5 mmol/L as needed. However, it is crucial to ensure that the total potassium concentration in the solutions does not exceed 4.5 mmol/L.[44]

The solutions available in our country and their contents are presented in Table 7. Figure 2 shows an example CRRT algorithm in children.

Cardio-renal Pediatric Emergency Dialysis Device

The cardio-renal pediatric emergency dialysis device (CARPEDIEM) is the first CRRT device produced specifically for pediatric patients weighing between 2.5 and 10 kg.[46] When utilizing this device, double-lumen catheters ranging from 4Fr to 7Fr are preferred for vascular access. Its advantages include an extracorporeal set volume of 27 mL and a variety of surface area options for the dialysis membranes, ranging from 0.075 m^2 to 0.25 m^2. Additionally, other benefits of the device include the ability to adjust the BFR within the range of 5-50 mL/min, its compatibility with low prime volume, and low pump flow rate requirements. In CRRT applications with the CARPEDIEM device, only heparin is utilized for anticoagulation.

Table 7. Solutions and their ingredients available in our country

Product	Volume (L)	Na (mmol/L)	K (mmol/L)	Ca (mmol/L)	Inorganic phosphate (mmol/L)	Mg (mmol/L)	Cl (mmol/L)	HCO_3 (mmol/L)	Glucose (mmol/L)	Lactate (mmol/L)
Multibic- 0[#]	5	140	0	1.5	0	0.5	109	35	5.55	0
Multibic- 2[#]	5	140	2.0	1.5	0	0.5	111	35	5.55	0
Multibic- 3[#]	5	140	3.0	1.5	0	0.5	112	35	5.55	0
Multibic- 4[#]	5	140	4.0	1.5	0	0.5	113	35	5.55	0
MultiPlus-dialysate with phosphate	5	140	2.0	1.5	1.0	0.75	109.7	35	5.55	0
Ci-Ca Dialysate K2	5	133	2.0	0	0	0.75	116.5	20	5.55	0
Ci-Ca Dialysate K4	5	133	4.0	0	0	0.75	118.5	20	5.55	0
Ci-Ca Dialysate K2 Plus	5	133	2.0	0	1.25	1	115.75	20	5.55	0
Ci-Ca Dialysate K4 Plus	5	133	4.0	0	1.25	1	117.75	20	5.55	0
Dialisan[&]	5	140	2.0	1.75	0	0.50	111.5	32	6.1	3
Prism0cal[+]	5	140	0	0	0	0.5	106	32	0	3
Prism0calB22[+]	5	140	0	0	0	0.75	130.5	22	6.1	3
HDF SM 35[%]	5	140	1.5	1.75	0	0.5	11.5	35	3	0.61
MD042*	2	140	2.5	1.5	0	0.75	115	32	5.55	0
Sodium citrate 4%[^]	Citrate 136 mmol/L, bag volume 1 and 1.5 L									
Prismocitrate 10/2	Citrate 10 mmol/L, citric acid 2 mmol/L, Na 136 mmol/L, Cl- 106 mmol/L									
Prismocitrate 18/0	Citrate 18 mmol/L, citric acid 0 mmol/L, Na 140 mmol/L, Cl- 86 mmol/L									

[#]: It has received FDA approval as a dialysis and replacement solution, [%]: It has received CE approval as a dialysis and replacement solution in Europe, [&]: It has received FDA approval only as a dialysis solution, but it is also used as a replacement fluid in practical application, [^]: Citrate solution. If citrate anticoagulation is to be applied, there should be no calcium in the dialysate solution. Ci-Ca Dialysate solutions are used together with citrate anticoagulation, [+]: Prism0cal and Prism0cal B22 solutions are dialysate solutions used during anticoagulation with Prismocitrate solutions. Since PrismOcal B22 solution contains 4 mmol/L potassium, additional potassium is not added to this solution. Solutions no. 1-9, 15 have been made available by Fresenius, solutions no. 10, 11, 12, 16, 17 have been made available by Baxter, and solution no. 13 has been made available by Medica. Solution number 14 has been made available for use abroad by Meditronic.
*: It is offered for use as the dialysate solution of the cardio-renal pediatric emergency dialysis device (CARPEDIEM), CARPEDIEM: Cardio-renal pediatric emergency dialysis device

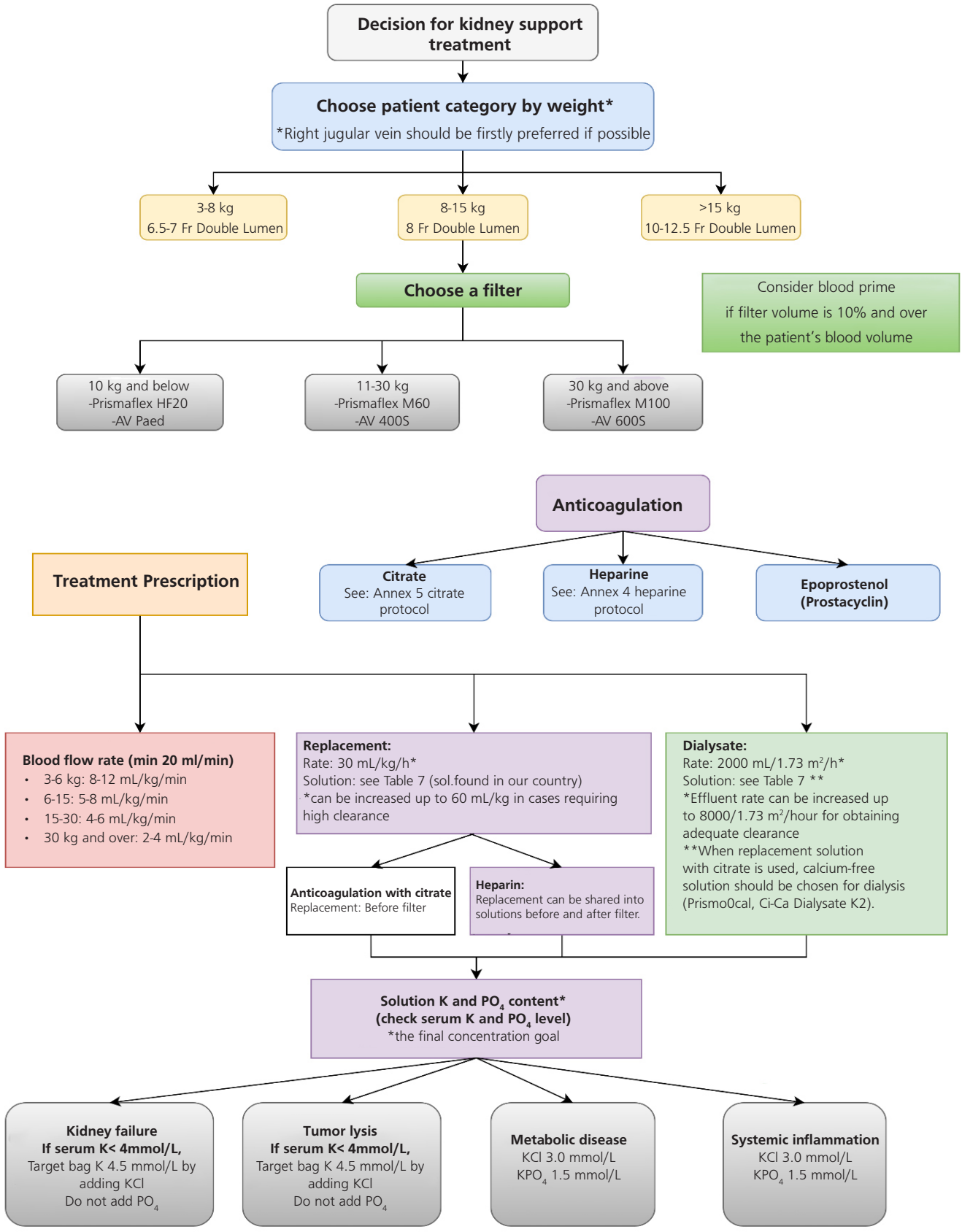

Figure 2. Sample CRRT algorithm in children

Since the data on clearance in CRRT applications with the CARPADIEM device is limited, it is not recommended to be used in cases where rapid clearance is desired, such as hyperammonemia and leucine toxicity.

9. Nutrition

Malnutrition is frequently observed in patients with AKI. This condition arises due to various factors including malabsorption, increased protein degradation, insulin resistance, and impaired hormonal regulation. In patients undergoing CRRT, essential nutrients such as amino acids, carnitine, trace elements, glucose, and water-soluble vitamins are removed. Moreover, beyond these losses, CRRT may serve as a significant yet overlooked source of exogenous energy.

There are no specific guidelines for the nutrition of patients undergoing CRRT in the PICU.

Energy Requirements in Patients Receiving Continuous Renal Replacement Therapy

It has been shown that intensive parenteral hyperalimentation has a positive effect on the prognosis in patients diagnosed with AKI who receive CRRT.[47] The daily calorie requirement of these patients is 25-35 kcal/kg (60-70% from carbohydrates and 30-40% from lipids). It should be noted that hypothermia due to inadequate heating of fluids during CRRT can significantly increase the caloric requirement.

However, CRRT can serve as a significant yet often overlooked source of exogenous energy. It's estimated that 35-45% of the dextrose in dialysis solutions is absorbed during CRRT. Additionally, lactate present in lactate-based solutions can serve as an additional energy source, providing approximately 3.62 kcal/g. Lactate in CRRT solutions may correspond to a caloric intake of approximately 500 kcal/day, which should be considered when calculating the patient's energy balance. Daily calories gained from lactate-based dialysis solutions can vary widely, ranging from 120 to 2300 calories, depending on factors such as blood flow and UF rates.

Another source of calories in CRRT patients is citrate. Once citrate enters the mitochondria via the Na/citrate transporter, it undergoes rapid metabolism in the citric acid cycle, providing approximately 0.59 kcal/mmol of energy. The caloric gain from citrate can be calculated by multiplying the citrate load by the citrate bioenergetic equivalent of 0.59/mmol.

The citrate load can be calculated using the formula (mmol/min) = [(flow rate x 1000) x citrate dose) x (1-(filtration fraction/100)]. Here, the flow rate represents the effluent flow in mL/min, the citrate dose is in mmol/L, and the filtration fraction is expressed as a percentage.

Daily energy gain from citrate can be determined by multiplying the citrate load (mmol/min) by 60 and then multiplying the hourly value by the number of hours citrate anticoagulation is administered.

Amino Acid Requirement in Patients Receiving Continuous Renal Replacement Therapy

ASPEN's recommendation for protein requirements in critically ill pediatric patients according to age groups: 0-2 years: 2-3 gr/kg/day, 2-13 years: 1.5-2 gr/kg/day, 13-18 years: 1.5 gr/kg/day.[48] During CRRT, there is significant nitrogen loss, primarily in the form of amino acids. To counteract these losses, it is recommended to increase the intake of amino acids in the diet by 10-20%. Specifically, glutamine should constitute approximately 25% of the amino acid losses. This adjustment helps maintain nitrogen balance and supports proper protein metabolism during CRRT.

Lipid Requirement in Patients Receiving Continuous Renal Replacement Therapy

In AKI, hepatic lipase and lipolysis activities are negatively affected and the triglyceride content of lipoproteins increases and HDL level decreases. With the deterioration in lipid metabolism, lipid clearance, especially triglycerides, decreases by nearly 50%. Hypertriglyceridemia and hyperglycemia are common, especially in patients receiving parenteral nutrition. The lipid levels of patients should be monitored. L-carnitine is lost at a considerable rate during CRRT, and its deficiency contributes to lipid accumulation in critically ill patients. It is important to be mindful that carnitine deficiency may develop, especially in patients who receive CRRT for an extended period (≥3 weeks). Since the metabolism of medium-chain fatty acids does not require carnitine, their use can compensate for L-carnitine deficiency.

Trace Element Requirements in Patients Receiving Continuous Renal Replacement Therapy

Trace element deficiencies may develop in patients undergoing CRRT, but the necessity of their replacement is controversial. The general opinion is that micronutrients should be replaced. Although the optimal dose for multicomponent trace element preparations in pediatric patients undergoing CRRT has not yet been determined, the standard daily doses recommended for parenteral nutrition, excluding selenium, are thought to be sufficient. Selenium is the element most lost during CRRT, and 100 micrograms/day intravenously is recommended in adults.[49]

Vitamin Requirements in Patients Receiving Continuous Renal Replacement Therapy

The risk of water-soluble vitamin deficiency is high in patients receiving CRRT with high clearance/high flow or for a long time. Although there are no specified dosage recommendations for

children, ESPEN recommends 100 mg of thiamine (vitamin B1), 2 mg of vitamin B2, 20 mg of vitamin B3, 10 mg of vitamin B5, 100 mg of vitamin B6, 200 µg biotin (vitamin B7), 1 mg in adult patients undergoing CRRT. It recommends giving mg folic acid, 4 µg vitamin B12, and 250 mg vitamin C supplements.[49] Although the elimination levels of fat-soluble vitamins are lower, they are recommended to be supplemented during the CRRT process, except for vitamin A. Vitamin E and vitamin K supplements should be provided during CRRT. During CRRT in children, it is recommended to continue vitamin support at recommended daily standard doses and to monitor blood levels of water-soluble vitamins and trace elements in long-term applications.

10. Continuous Renal Replacement Therapy in Patients Undergoing Extracorporeal Membrane Oxygenation

The prevalence of combined CRRT and Extracorporeal Membrane Oxygenation (ECMO) applications in critically ill pediatric patients is on the rise. Patients undergoing ECMO monitoring face a heightened risk of AKI and fluid overload. AKI affliction occurs in approximately 70-80% of ECMO-receiving patients.[50] Given the nature of ECMO support, patients may necessitate substantial fluid resuscitation and considerable volumes of blood products.

If AKI develops in patients monitored on ECMO, PD, IHD, and CRRT can be applied. Although each method has advantages and disadvantages, CRRT is the frequently preferred method in ECMO patients. For this, a separate vascular line can be used or the CRRT circuit can be integrated into the system using existing ECMO cannulas. The development of AKI during ECMO is an independent risk factor for mortality and failure to wean from ECMO. However, if there is no underlying primary kidney disease, renal recovery is seen in over 90% of surviving patients after ECMO and the need for chronic RRT is low.

Indications for Combination of ECMO and CRRT

Indications for starting RRT in ECMO patients are similar to patients not on ECMO. In the study conducted by the kidney interventions during the membrane oxygenation study group in neonatal and pediatric intensive care patients in 2020, it was shown that the primary indication was the treatment or prevention of fluid overload.[51] Reasons for performing CRRT in ECMO patients, in order of frequency:

1. Fluid overload (43%)
2. AKI (35%)
3. Preventing fluid overload (16%)
4. Electrolyte disorders (4%)
5. Others (2%)

Advantages of ECMO-CRRT Combination

The concurrent utilization of ECMO and CRRT offers notable advantages in enhancing tissue and organ oxygenation as well as perfusion. By rectifying hypoxia through ECMO support, lactic acidosis can be mitigated, potentially expediting renal recovery. Introducing CRRT, particularly with bicarbonate-based solutions, alongside ECMO in hemodynamically unstable patients, serves to forestall fluid overload, promote favorable fluid balance, and ameliorate cardiac and pulmonary functions. This combined approach facilitates the prompt correction of severe lactic acidosis and its metabolic ramifications, thereby averting hypocalcemia. Moreover, CRRT's maintenance of fluid balance ensures adequate nourishment for the patient, obviating restrictions on medication and blood product administration. Furthermore, this strategy reduces inflammatory cytokine levels, dampening the systemic inflammatory response syndrome instigated by ECMO. The ECMO-CRRT synergy proves beneficial in addressing electrolyte imbalances and mitigating kidney damage attributable to ECMO.

Timing of Initiating CRRT in ECMO Patients

Although there is no clear data for the timing of CRRT, literature information has shown that fluid overload negatively affects the prognosis in ECMO patients. It has been found that early initiation of CRRT in patients on ECMO support has a positive effect on the outcome.[50] CRRT decision should be made based on the cumulative fluid load and fluid status of the patient, whose fluid status is evaluated daily.

A Combination of CRRT and ECMO

There are several ways to perform CRRT in a patient using ECMO support. The first way is to use separate vascular access and circuits for CRRT and ECMO. The other option is to connect the CRRT device to the ECMO circuit.

1. CRRT with Separate Vascular Pathway

This option requires additional vascular access and is generally preferred if CRRT is already used before ECMO. The application of this method is no different from CRRT applications in patients not on ECMO.

However, when the indication for CRRT is placed while the patient is on ECMO, the placement of a new large-lumen catheter in the patient receiving high-dose anticoagulants increases the risk of complications. Multiple vascular access sites may be required to perform ECMO, limiting the number of access sites available to establish the CRRT circuit. In these cases, CRRT should be integrated into the ECMO circuit.

2. Combining Two Independent Extracorporeal Circuits

There are various methods for integrating the CRRT circuit with the ECMO circuit. Typically, the CRRT device is linked to the venous line of the ECMO circuit, with options to position the input to the CRRT circuit either before or after the oxygenator or centrifugal pump. Similarly, the outlet line of the CRRT can be connected before the centrifugal pump or between the centrifugal pump and the membrane oxygenator. Each connection method depicted in Figures 3 to 7 offers distinct advantages and disadvantages.

However, in our country, leading ECMO centers with extensive experience recommend connecting both the inlet and outlet of CRRT to the venous line before the centrifugal pump. This particular configuration may be favored due to its perceived advantages in terms of circuit simplicity, ease of monitoring, and potentially lower risk of hemolysis or clotting issues.

When the ECMO circuit and CRRT are combined, the blood flows of both systems may interact with each other. The combination of the two circuits can cause some technical problems, most of which are related to the CRRT device inlet and outlet pressure alarms. Pressure levels of different segments of the ECMO circuit may not be compatible with CRRT device pressure alarm limits. CRRT devices are designed to provide connection in the range of 0-20 mmHg, compatible with central venous pressure. While the pressures of the ECMO circuit before the centrifugal pump are significantly negative compared to these values, the pressures between the pump and the oxygenator are significantly positive. Detecting pressure outside the alarm limits in the CRRT device may stop the CRRT device. If the output line of the CRRT machine is connected to the ECMO circuit before the centrifugal pump,

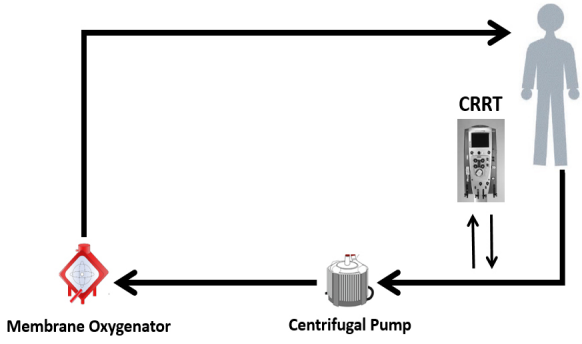

Figure 3. The inlet and outlet of the CRRT are on the venous line before the centrifugal pump
CRRT: Continuous renal replacement therapy

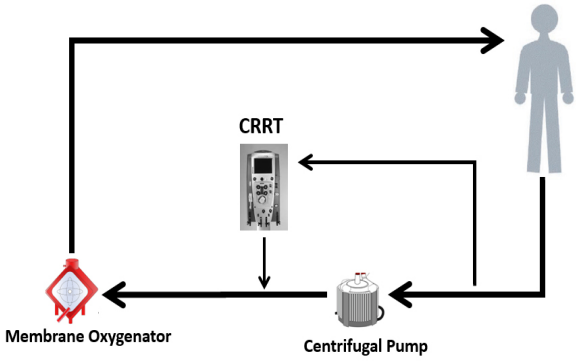

Figure 4. CRRT inlet on the venous line before the centrifugal pump, CRRT outlet after the centrifugal pump
CRRT: Continuous renal replacement therapy

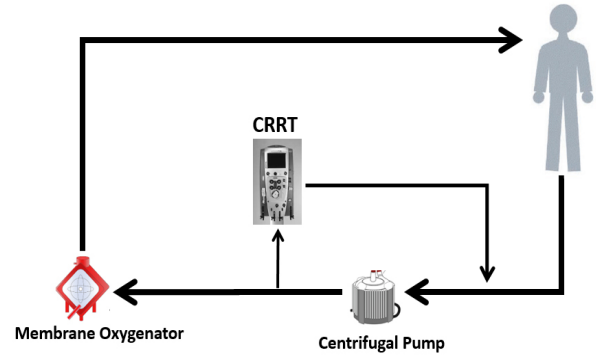

Figure 5. The inlet of the CRRT is after the centrifugal pump, and the outlet is on the venous line before the centrifugal pump
CRRT: Continuous renal replacement therapy

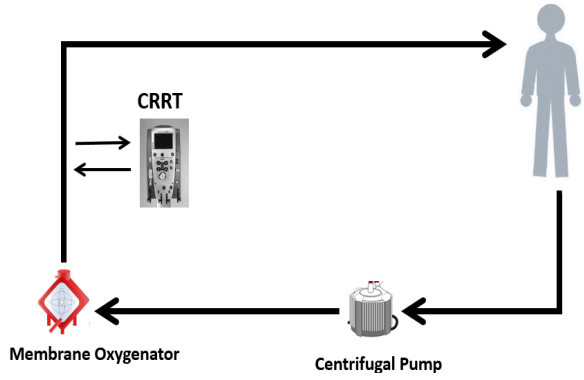

Figure 6. The inlet and outlet of the CRRT are after the oxygenator
CRRT: Continuous renal replacement therapy

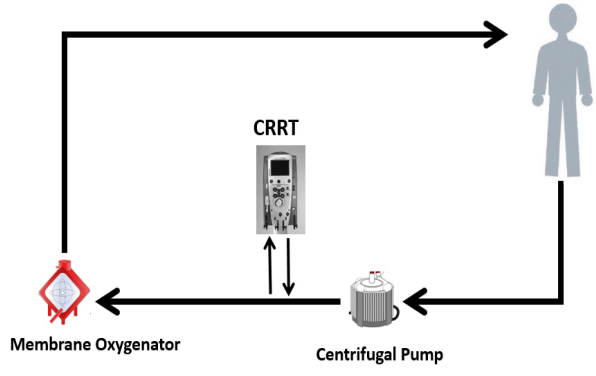

Figure 7. The inlet of the CRRT is after the centrifugal pump, and the outlet is before the oxygenator
CRRT: Continuous renal replacement therapy

blood from the CRRT returns to the negative pressure portion of the ECMO circuit. This creates a low return pressure alarm on the CRRT machine and may automatically shut down over time. Ignoring the limits may lead to excessive negative pressures, causing hemolysis and microembolization. Patients with severe hypoxemia often require high blood flow, thus ECMO pump speeds above 3000 rpm. This leads to excessive negative pressures, especially in patients with borderline ECMO input flow. To prevent this situation, it would be appropriate to convert the return pressure towards 0 or positive by placing small clamps on the venous line going from the CRRT machine to the ECMO set.

Incorporating the CRRT circuit into the ECMO circuit has advantages.

1. Cost-effectiveness
2. Easy circuit installation
3. Working with lower blood volume
4. Easy management
5. Low resource usage
6. No need for additional vascular access and no complications related to catheter placement
7. When the CRRT device is placed before the oxygenator, possible embolism due to air and blood clots is retained by the oxygenator.

Anticoagulation

Anticoagulation is administered via two distinct methods: citrate and heparin. As systemic heparinization is standard practice during ECMO, additional routine anticoagulation for the CRRT circuit is typically unnecessary. However, in exceptional circumstances such as instances of excessive bleeding during ECMO, aiming for low ACT targets, or temporary cessation of heparin, it becomes crucial to implement regional anticoagulation with CRRT citrate. This approach ensures appropriate anticoagulation within the CRRT circuit while minimizing systemic implications and complications associated with systemic anticoagulation.

Bivalirudin serves as an alternative option for anticoagulation management in patients undergoing ECMO. This medication operates by inhibiting thrombin activity. Notably, bivalirudin offers several advantages over other anticoagulants. It boasts a lower propensity for side effects associated with heparin usage, such as heparin-induced thrombocytopenia (HIT). Moreover, it can be effectively employed in cases of heparin-related thrombocytopenia (HIT), as well as instances of heparin resistance and non-HIT-related thrombocytopenia. Bivalirudin exhibits a relatively short half-life, lasting approximately 25 minutes.[52] It binds directly to thrombin, acts independently of the antithrombin level, and does not induce the formation of antibodies against platelets.[53] Its disadvantage is that there are no antidotes that can reverse its effects. Approximately 20% of bivalirudin excretion occurs via renal elimination, with the remainder being metabolized by proteolytic enzymes. While various sources suggest a broad starting dose range, the average recommended dosage falls between 0.045 and 0.48 mg/kg/min. Notably, there is typically no requirement for an initial bolus dose when initiating bivalirudin therapy.[54] Close monitoring of patients undergoing bivalirudin therapy is essential. Regular assessment of parameters such as ACT, aPTT, thromboelastography (TEG) or rotational thromboelastometry (ROTEM), and platelet counts is imperative. This vigilant monitoring plays a crucial role in fine-tuning bivalirudin dosage and evaluating the efficacy of anticoagulation.

Antibiotic Dosage in CRRT and ECMO

Limited data exist regarding the separate impacts of ECMO and CRRT on antibiotic pharmacokinetics. Individuals undergoing treatment on extracorporeal circuits frequently exhibit alterations in volume of distribution and clearance rates, which can vary considerably. Clinical investigations have revealed notable modifications in pharmacokinetics, potentially resulting in inappropriate dosing practices, including both suboptimal and excessive dosages of medications. Guidelines for medication dosing should take into account the specific mode of RRT, the dosage administered, BFRs, filter material composition, and surface area of the filter.

11. Complications That May Occur During Continuous Renal Replacement Treatment

While CRRT is recognized as an effective intervention for managing acute renal failure in critically ill patients, its implementation poses challenges, particularly in infants and children. The complexity of CRRT administration in pediatric populations often leads to an increased risk of complications.[26,55-57]

CRRT-related complications are shown in Table 8.

In general, complications associated with CRRT can be categorized as mechanical, hemodynamic, metabolic, nutritional, and pharmacological complications. Knowing CRRT systems, possible complications, and causes of alarms minimizes side effects.

A. Mechanical complications: Under this category, we encounter complications related to vascular access and extracorporeal circuits.

Vascular Complications and Alarms

Complications of vascular access include vascular damage and infection. It has been reported that it develops in 5-19% of its patients. Arterial interference, hematoma, hemothorax, and pneumothorax are the most common vascular problems.

Table 8. Complications associated with CRRT
A. Mechanical complications
Catheter-related complications Bleeding Infection Venous thrombosis Venous stenosis Traumatic arteriovenous fistula Pneumothorax Hemothorax Air embolism Organ injury Extracorporeal circuit-related complications Allergic reaction to hemodialyzer/hemofilter Circuit thrombosis Hemolysis Air embolism
B. Hemodynamic complications
Hypothermia
Hypotension
C. Metabolic complications
Acid base disorders Electrolyte disorders Hypophosphatemia Hypokalemia Hypocalcemia Hypomagnesemia Hyponatremia
D. Nutritional complications
E. Pharmacological complications
CRRT: Continuous renal replecement therapy

Arteriovenous fistula, aneurysm, thrombus formation, and retroperitoneal bleeding have been reported. Vascular complications are more common in patients <10 kg and in infancy.

Vascular spasms may develop due to a high blood flow rate at the beginning of the procedure, movement of the catheter in the opposite direction on the vessel wall, or the catheter being longer than necessary.

A low arterial pressure alarm is a mechanical complication during CRRT that indicates a mechanical problem with blood flow. It is caused by a physical obstruction such as a clamp remaining closed, bending in the catheter or tubes, or a clot in the system. In addition, it should be considered that the pump speed is high compared to the catheter size, the catheter pulls against the vessel wall and causes flow obstruction. In pediatric patients, it means that the pump speed is higher than the central venous pressure or right atrium blood volume.

A low venous pressure alarm occurs when the system cannot detect venous flow or there is positive pressure in the return line of the circuit. In the presence of this problem, it should be considered that the system is disconnected from the venous line, there is an obstruction between the filter and the venous pressure sensor, or the pump speed is not at a level to create the necessary positive pressure in the venous catheter. The transmembrane pressure alarm reflects changes in membrane pressure between the blood and ultrafiltrate compartments. It is an indication that the filter is clogged. In some systems, this alarm is also activated when the clamp on the UF line is left closed incorrectly.

Excessive Ultrafiltration

It has been shown to develop in 30% of patients undergoing CRRT. The patient's fluid balance should be closely monitored (see monitoring of fluid balance).

Balance, Bag Volume, or Weighing Alarm

Ultrafiltrate is activated when replacement fluid or dialysate falls outside the target volume. The main reasons for the alarm to occur are replacement or dialysate solutions remaining clamped or scales moving while the process is in progress.

Infection

It is the most serious complication that may develop during CRRT application. It can develop in 50% of patients receiving CRRT and results in death in 70%.

Filter Clogging

Thrombosis is the most important cause of loss of vascular access. Hypotension and hypovolemia are common, especially in infants. Hypotension, hypovolemia, and low UF rate increase the likelihood of filter clogging.

To minimize possible complications, the pressures in the device should be closely monitored and the procedure should be terminated in case of an increase in pressure. Pressure upper limits:

1. Pre-filter pressure >270 mmHg
2. Transmembrane pressure >250 mmHg
3. Filter life >72 hours

Membrane Reaction

Patients with severe metabolic acidosis prior to undergoing CRRT may encounter a sudden release of bradykinin when their blood interacts with the membrane. This can manifest clinically with symptoms ranging from vomiting to life-threatening anaphylaxis. In high-risk patients, it is recommended to prime the filter with blood before initiating the procedure. This precautionary measure helps mitigate the risk of adverse reactions associated with bradykinin release (see Appendix 5).

B. Hemodynamic Complications

Hypothermia

Hypothermia is a frequent complication during CRRT since the patient's blood is circulated outside the body and exposed to

cold dialysate or replacement solution. Prolonged hypothermia is undesirable as it can result in energy depletion, heightened oxygen demand due to shivering, vasoconstriction, impaired leukocyte function, and coagulopathy. If relying solely on the integrated heating system within the CRRT machine proves insufficient, supplementary external heating should be administered to maintain the patient's body temperature at 37 °C.

Hypotension

Hypotension is one of the important complications seen during the initiation of CRRT, especially in pediatric patients. The solution may be to start with a low blood flow rate and gradually increase the blood flow rate according to the patient's tolerance.

C. Metabolic Complications

Metabolic complications associated with CRRT include acid-base abnormalities, electrolyte disturbances, and hypoglycemia.

Correction of Metabolic and Electrolyte Disorders That May Occur During CRRT

Additional recommendations regarding these complications are also described in the section on adding electrolytes to CRRT solutions (see solution). Situations that need to be taken into consideration and examples of additional applications that can be applied are summarized below:[44]

- Azotemia; increase dialysis/replacement rate

- Hyponatremia; add 70 mL of 3% hypertonic saline to a 5-liter bag

- Hypernatremia; start intravenous infusion of 5% dextrose 0.45% saline

- Metabolic acidosis; start a bicarbonate infusion or replace the replacement solution with a solution containing 3 ampoules of sodium bicarbonate added to 5% dextrose or add 20 mL of bicarbonate per liter to the dialysis solution.

- Metabolic alkalosis; replace the replacement solution with isotonic fluid to which potassium chloride has been added.

- Hypercalcemia; increase the rate of replacement or dialysate fluid.

- Hypocalcemia; add 24 g of calcium gluconate into 1000 mL of isotonic and infuse at 5 mg/kg/hour, aiming for Cai to be 1.1-1.3 mmol/L.

- Hypophosphatemia; start phosphorus infusion, check phosphorus level every 2-4 hours.

- Hypokalemia; give potassium infusion.

- Hyperkalemia; administer potassium-free fluid or increase the rate of dialysis/replacement solution.

D. Nutritional Complications: Described in the nutrition section (see nutrition).

E. Pharmacological Complications: Adjusting the dosage of antimicrobial drugs in critically ill patients undergoing CRRT presents a significant challenge. Most antimicrobials have a molecular weight below 1500 daltons, and their blood levels can fluctuate with convective treatments, leading to increased clearance. For drugs that are highly protein-bound and have a large volume of distribution, such as amphotericin and macrolides, clearance may be reduced. Conversely, water-soluble antimicrobials with a low volume of distribution, such as aminoglycosides and β-lactam antibiotics, are easily cleared via CRRT.

Although guidelines offer recommendations for adjusting antimicrobial dosages, these recommendations are not foolproof due to the multitude of variables influencing clearance. Therefore, a personalized approach to dose adjustment should be adopted, based on therapeutic levels if available, to ensure optimal treatment outcomes.

12. Follow-up of the Patient on Continuous Renal Replacement Therapy

The cornerstone of effective and uninterrupted CRRT in pediatric intensive care relies on comprehensive training of the medical staff. This training should encompass both didactic components (covering reasons for implementation, treatment modalities, patient scenarios, and documentation) and practical simulations (including proficiency assessments, machine setup, and troubleshooting). Regular bedside visits for CRRT supervision and periodic proficiency checks are essential for identifying and rectifying any potential deficiencies in practice.[58,59]

Patients undergoing CRRT necessitate meticulous monitoring to uphold hemodynamic equilibrium, ensure the smooth operation of the system, and promptly address any arising issues. Ideally, daily weighing should be conducted, and vital signs ought to be recorded hourly. Regular physical examinations, focusing on fluid status and detection of bleeding complications, should be performed in 6 to 8-hour intervals.

Adjustments to ultrafiltration, dialysate, and replacement fluid volumes should be made as necessary throughout treatment, considering sensitive losses when calculating fluid status. This comprehensive monitoring regimen is crucial for optimizing patient care and treatment outcomes during CRRT.

Electrolytes (glucose, Na, K, Cl, bicarbonate, Ca), blood urea nitrogen, and creatinine levels should be assessed every 6-8 hours. Magnesium, phosphorus, and blood count should be checked every 12-24 hours. For patients receiving heparin, aPTT or ACT should be monitored. In cases where

citrate is administered, ionized calcium levels and blood gas parameters should be monitored and documented according to the protocol.

Hypothermia is a common occurrence, particularly during high-flow CRRT procedures. If feasible, this issue can be addressed by incorporating a heater into the system or implementing active external heating measures. Additionally, inlet pressure, return pressure, and filter pressure should be monitored hourly and documented using the standardized form (Figure 8).

During CRRT, the patient should be monitored by an intensive care nurse with experience in monitoring CRRT patients, if possible. The responsibilities of the health care providers are as follows:

a) The entry site of the catheter must be regularly assessed and documented. Additionally, the nurse should promptly notify the physician of any signs of bleeding, infection, or other potential issues. This proactive communication ensures timely intervention and optimal management of the patient's condition.

b) Hourly monitoring of fluid intake and output is essential for the patient, who should actively participate in maintaining fluid balance.

c) The nurse is responsible for monitoring and documenting the continuation of CRRT according to the prescribed renal replacement therapy doses.

d) Throughout CRRT, it is essential to regularly monitor and document the patient's vital signs. The caregiver must ensure that alarm limits are appropriately set on the monitoring equipment.

e) It is imperative for nurses to remain vigilant and responsive to potential alarms during CRRT. They should actively engage in addressing alarm triggers and swiftly undertake necessary interventions, such as altering solutions, emptying waste bags, or preparing heparin syringes. This proactive approach is crucial for ensuring the safety and efficacy of CRRT procedures.

f) The nurse should also monitor complications that may not be directly related to CRRT, such as bleeding, convulsions, and hypothermia.

Patient's Name-Surname: **Method:** **Date:**

Hour	Blood flow rate mL/min	Dialysis rate mL/h	Replacement rate mL/h	Fluid intake/h	Ca rate mL/h	Citrate/ Heparin rate	aPTT/ ACT	PostF Cai	PreF Cai	UF rate /h	Amount of urine/h	Net amount of fluid drawn	Arrival pressure	Return pressure	Filter pressure
09:00															
10:00															
11:00															
12:00															
13:00															
14:00															
15:00															
16:00															
17:00															
18:00															
19:00															
20:00															
21:00															

Heparin titration protocol

ACT level(sec)	PTT level (sec)	Heparin dose
180-220	60-80	No change
>220	>80	Stop heparin for an hour
<180	<60	Start by reducing the dose by 10% after one hour.

Citrate – calcium infusion rate according to PreFCai level

Prefilter-Cai level (mmol/L) *	Calcium infusion rate regulation	
	>20kg	<20kg
>1.3	Rate 5 ml/hour ↓	Rate 2.5 ml/hr ↓
1.1-1.3	No change	
0.9-1.1	Rate 5ml/hour ↑	Rate 2.5 ml/hr ↑
<0.9	Rate 10ml/hour ↑	Rate 5 ml/hr ↑

Citrate-calcium infusion rate according to postFCai level

Post-filter Cai level (mmol/L) *	Citrate infusion rate regulation	
	>20 kg	<20kg
<0.35	Citrate rate 10% ↓	Citrate rate 5% ↓
0.35-0.5	No change	
0.5-0.6	Citrate rate 10% ↑	Citrate rate 5%↑
>0.6	Citrate rate 20% ↑	Citrate rate 10%↑

*: It should be taken from the blue port located at the outlet of the dialysis membrane.

Figure 8. CRRT follow-up chart

g) Any fluctuations in arterial, venous pressure, transmembrane, and dialysate pressures, possibly arising from thrombosis within the set, filter, or catheter, as well as blood flow-related issues, should be closely monitored. Any detected abnormalities should be promptly communicated to the attending physician for early resolution.

h) At the end of the treatment, the catheter lumens should be filled with heparin solution at a concentration appropriate to the patient's age, ensuring readiness for the next treatment. Heparinized fluid should be administered in an amount equal to the volume of the catheter lumen, and a notation should be made on the catheter indicating that it has been filled with heparinized fluid.) Must ensure that the catheter entry site dressing is done appropriately and regularly.

Device Alarms and Clinical Trouble Prevention and Troubleshooting in CRRT Tracking

On CRRT machines, alarms are colored according to the urgency of the situation:

Green: Machine operation is OK

Orange: The pumps are working, but there is a situation that is not urgent but needs to be corrected, for example, the waste bag is full, the dialysate/replacement bag is empty.

Red: This is an emergency alarm situation where the pumps will halt until the issue is rectified. Failure to address the problem promptly may result in filter coagulation. Examples of issues triggering this alarm include air in the return line, blood leakage, excessive negative inlet pressure, or excessively high return pressure.

Below, the main CRRT machine alarms, prevention, and troubleshooting methods are summarized (Table 9).

Clinical Troubleshooting

The venous catheter or patient-related inlet/return pressure alarms:

- Please ensure that the patient's position, entry, and return lines are checked thoroughly for any signs of pinching or twisting around the patient or clamps.

- Temporarily decreasing blood flow can help alleviate pressure on the vessel wall.

- Aspirate and rinse the lumens to inspect for any clots. Aspirated blood can be sprayed onto gauze to assess for clot presence.

- In instances of negative arrival pressures, consider rotating the temporary dialysis catheter 180 degrees around its axis. This procedure should be carried out by a skilled CRRT nurse in collaboration with the PICU physician.

- If blood supply remains poor despite previous measures, the final option is to replace the inflow-return lumens. However,

Table 9. Clinical problem prevention and resolution in CRRT monitoring

Clinical problem/alarm	Prevention	Troubleshooting
Inlet pressure is too negative and/or return pressure too positive	-Use appropriate size catheter -Adjust the blood flow rate appropriately -Make sure the clamps are opened after each procedure.	-Check patient position -Temporarily reduce blood flow rate -Check/flush catheter lumens for clots -Change input-return lumens
Trans membrane pressure and filter pressure rising	-Use an appropriate dosage of anticoagulant -Adjust blood flow rate, UF rate appropriately -Keep filtration fraction <25%	-If TMP >300 despite appropriate settings and anticoagulation, consider set replacement -Check the return pressure, if it is high, troubleshoot. -Check replacement fluid speed, reduce speed if too high -Consider additional factors such as sepsis, lipid and/or propofol infusion
Loss/gain fluid limit reached	-Use the "change bags" button when changing dialysate/ replacement/waste bags -When the bags are tied, make sure the safety valves are broken properly and the clamps are opened. -Make sure the bags are not touched from the bottom or sides.	-Change set
There's air on the set	-Check the set for air after prime -Make sure all connections in the set are made correctly -Check that the fluid/blood level in the air chamber is at the appropriate height.	-Fill the air chamber with liquid by pressing and holding the "up arrow" button. -Replace the set if there is still air in the return line to the patient.
Blood leak detected	-Clean the blood detector compartment before set installation	-Change the set
Bag volume and/or weighing alarm	- Make sure the safety valves are broken properly when the bags are tied - Make sure the clamps are open after each procedure. - Make sure nothing touches the bags from the bottom or sides	- Check the set for errors in the prevention section

it's essential to acknowledge that this manipulation carries a risk of recirculation, estimated at approximately 25%, which could consequently reduce clearances by around 10%.

Filter alarms [trans membrane pressure (TMP) and filter pressure rising]:

Extending filter life can be attained through several measures including using properly sized catheters and sets, adjusting blood flow rates based on the patient's weight, maintaining the filtration fraction below 25%, optimizing anticoagulation levels, and promptly addressing alarms-particularly those flagged as red. Typically, normal filter pressure ranges between 100 to 250 mmHg.

The maximum filter pressure is +450 mmHg. Nevertheless, when the pressure reaches 300 mmHg, the device will trigger a TMP high alarm, indicating significant clotting. At this point, there's a risk that blood may be returned to the patient before clotting is complete, necessitating consideration for filter replacement.

- If the filter pressure remains static while TMP increases, this could indicate adsorption, such as in cases of sepsis or accumulation of fat particles from infusions like propofol or lipids. In such scenarios, careful monitoring and appropriate interventions are essential.

- An increase in return pressure correlates with an increase in TMP, indicating a need to inspect the return path. It's crucial to investigate and address any issues in the return path promptly.

- High-flow replacement, especially post-dilution, can elevate TMP. In such cases, it's advisable to consider reducing the replacement rush rate to alleviate the TMP increase.

- If there is a sudden increase in both filter and TMP, it may be prudent to consider discontinuing the treatment.

Table 10. Determination of heparin concentration

Weight of the patient (kg)	Heparin concentration (U/mL)
<10 kg	40
11-25 kg	100
16-60 kg	250
>60 kg	500

Table 11. Heparin titration protocol

ACT level (sec)	PTT level (sec)	Heparin dosage
180-220	60-80	No change
>220	>80	Stop heparin for an hour. Start by reducing the dose by 10% after one hour
<180	<60	Increase the dose by 10%

ACT: Activated clotting time, PTT: Partial thromboplastin time

Table 12. Citrate solutions and their ingredients commonly used in the world

Content (mmol/L)	Acid-Citrate-Dextrose A	4% sodium citrate	Prismocitrate 18/0
Citric acid	38	0	0
Citrate	75	136	18
Sodium	225	408	140
Dextrose	124	0	0

Blood Leak Detected

This protocol is solely applicable in the event of a sudden rupture in the filter, permitting blood passage into the filtrate. Replacement of the entire circuit becomes imperative. While

Table 13. Solutions that do not contain calcium

Solution	Volume (L)	Sodium (mmol/L)	Potassium (mmol/L)	Calcium (mmol/L)	Magnesium (mmol/L)	Chloride (mmol/L)	Bicarbonate (mmol/L)
Prismocal	5	140	0	0	0.5	106	32
Prismocal B22	5	140	4	0	0.75	130.5	22
Ci-Ca Dialysate K2	5	133	2	0	0.75	116.5	20
Ci-Ca Dialysate K4	5	133	4	0	0.75	118.5	20

Table 14. Adjustment of citrate-calcium infusion rate according to the patient's ionized calcium level

Ionized calcium level of the patient (mmol/L) *	Calcium infusion rate regulation	
	>20 kg	<20 kg
>1.3	Rate 5 mL/hour ↓	Rate 2.5 mL/hour ↓
1.1-1.3	No change	No change
0.9-1.1	Rate 5 mL/hour ↑	Rate 2.5 mL/hour ↑
<0.9	Rate 10 mL/hour ↑	Rate 5 mL/hour ↑

*: Blood sample should be taken from the draw line (red port) or from the peripheral vene

Table 15. Citrate-calcium infusion rate adjustment according to the ionized calcium level of the filter

Post-filter Cai (mmol/L) *	Citrate infusion rate regulation	
	>20 kg	<20 kg
<0.35	Citrate rate 10% ↓	Citrate rate 5% ↓
0.35-0.5	No change	No change
0.5-0.6	Citrate rate 10% ↑	Citrate rate 5% ↑
>0.6	Citrate rate 20% ↑	Citrate rate 10% ↑

*: Blood sample should be taken from the blue port located at the outlet of the dialysis membrane

Table 16. Management of metabolic complications that may develop with citrate use

	Citrate accumulation	Excess citrate use	Insufficient citrate use
Mechanism	Presence of high amounts of citrate-calcium complex in the circulation because of inadequate citrate-bicarbonate conversion	Development of alkalosis because of excessive use of citrate and citrate bicarbonate conversion	Failure to correct acidosis due to acute kidney injury because of insufficient citrate use and citrate bicarbonate conversion
Diagnosis	Metabolic acidosis and total Ca/iCa>2.5	Metabolic alkalosis and total Ca/iCa <2.5	metabolic acidosis and total Ca/iCa<2.5
Management	-Reduce blood flow rate or -Increase dialysate speed or -Consider alternative anticoagulation.	-Reduce blood flow rate or -Increase dialysate speed or -Reduce alkaline buffer concentration in other solutions.	-Increase blood flow rate or -Reduce dialysate speed or -Increase the alkaline buffer concentration in other solutions.

such occurrences are uncommon, if encountered, securely store the ruptured filter in a waste bag for subsequent return to the manufacturer for evaluation.

Anaphylactic Reaction

In rare instances, the patient may experience an anaphylactic reaction to the filter membrane or to the ethylene oxide utilized for filter sterilization. Priming the set with albumin or blood may mitigate this risk. However, if the priming process was conducted more than 30 minutes before patient connection, there's a potential for ethylene oxide accumulation, heightening the risk. In such scenarios, it's imperative to re-prime the set before connecting it to the patient.

- If anaphylaxis develops, it typically manifests with the hallmark symptoms of tachycardia, hypotension, urticarial or maculopapular skin rash, and bronchospasm.

- If the circuit is filled with blood, it can mimic and be difficult to distinguish from a transfusion reaction.

- In very mild cases, treatment typically involves administering antihistamines.

- In the majority of cases, hemofiltration will need to be discontinued.

• Blood in the extracorporeal circuit should not be returned to the patient.

• Blood sample should be separated for Igs, IgE, mast cell tryptase.

Drug Clearance

During CRRT, drugs may be filtered out to a degree that could compromise the treatment of underlying conditions, such as sepsis or hypotension. It may be necessary to adjust doses of vasopressors, inotropes, sedative-analgesics, and antibiotics in patients undergoing CRRT. When renewing drug dosages, considerations should include factors like the patient's renal clearance, residual renal function, distribution volumes, molecular weight, and protein binding. Clearance may also be influenced by the location of drug infusion relative to the vascular access of the CRRT circuit. Therefore, careful attention should be paid to the location of drug infusion concerning proximity to CRRT access.

Ethics

Authorship Contributions

Concept: A.Y., M.D., N.A., D.D., Design: A.K., T.D., D.D., Data Collection or Processing: E.A., T.B., Analysis or Interpretation: D.D., Literature Search: A.K., A.Y., E.A., M.D., N.A., T.D., T.B., D.D., Writing: A.K., A.Y., E.A., M.D., N.A., T.D., T.B., D.D.

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

Financial Disclosure: The authors declared that this study received no financial support.

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Appendix 1. Protocol for Filling the Filter with Blood (Blood Priming) and Preventing Bradykinin Release

1. In cases where the filter volume constitutes 10% or more of the patient's blood volume, filling the filter with blood may be considered to mitigate potential hemodynamic issues at the onset of treatment.

2. If the filter is to be filled with erythrocyte suspension, verify the hematocrit level of the provided suspension, and dilute it accordingly to achieve the target hematocrit level. If the hematocrit level cannot be measured, a ratio of 9 parts erythrocyte suspension to 5 parts isotonic solution can be used.

3. Heat the diluted erythrocyte suspension to 37 °C.

4. Transfer the heated erythrocyte suspension into the total parenteral nutrition bag.

5. Once the standard priming program of the machine is completed, attach a dispensing spike (Braun) to the end of the total parenteral nutrition bag.

6. Add a three-way stopcock to the end of the installed dispensing spike.

7. Connect the arterial end of the extracorporeal circuit to one end of the three-way stopcock.

8. Open the three-way stopcock in the direction that allows blood to fill the circuit. Operate the device in either CVVHD or CVVHDF mode, setting the blood flow rate to 70 mL/min and the dialysis rate to 2000 mL/hour.

9. Operate the device until the blood reaches the waste bag attached to the venous end.

10. Once blood reaches the waste bag, stop the pump to fill the system with blood. However, note that the pH and calcium levels in the filled blood may be very low. Therefore, conducting short-term dialysis on the filled blood helps prevent potential issues arising from acidic blood flowing to the patient (bradykinin release syndrome).

11. Clamp and separate the venous end from the waste bag.

12. Connect the venous end to the empty end of the three-way stopcock previously connected to the arterial end.

13. Close the triple tap at the arterial end to prevent blood from flowing into the circuit.

14. Through the triple tap, allow the blood in the venous pathway of the circuit to pass to the arterial side, thus forming a closed circuit circulating within itself.

15. At this stage, ensure that the venous line is not clamped and verify its integrity.

16. Open the triple tap in the direction that allows blood to fill the circuit. Operate the device in CVVHD or CVVHDF mode, running it for 7.5 minutes* with the blood flow rate set to 70 mL/min and the dialysis rate set to 2000 mL/hour.

17. Upon completion of the procedure, check the pH and calcium levels of the blood inside the filter, which often reach physiological limits.

18. Stop the device, clamp the artery and venous lines, disconnect them from the three-way stopcock, and connect them to the patient.

19. Open the clamps and restart the device, initiating renal replacement therapy by adjusting the target blood flow, replacement, and dialysate rates.

Appendix 2. Returning the set within itself (recirculation=recirculation) protocol

If CRRT needs to be temporarily interrupted, recirculation with blood or saline can be considered to facilitate set reuse. If ***the set has been in use for less than 24 hours*** and is free of clots, it can be preserved by following the steps outlined below during treatment interruption:

Recirculation with saline:

1. Press the "Stop Treatment" button.
2. Select "Refill".
3. Press the "Saline Recirculation" option button.
4. Suspend 1000 mL of 0.9% sodium chloride in the device and attach a distribution spike to the end.
5. Clamp and disconnect the red access line from the patient, connecting it to the distribution spike at the end of the saline bag, then open the clamp.
6. Select the volume of blood to be returned to the patient (equivalent to the volume of the set and accessories) and adjust the return speed.
7. After the patient's blood is returned, clamp and disconnect the blue access line from the patient, connecting it to the distribution spike at the end of the saline bag, then open the clamp.
8. Restart circulation with saline.
9. Solutions are not consumed during recirculation; adjustments are made only to the blood flow rate during this process, which can be tailored according to the specific set used.
10. When the set is to be reused, stop recirculation, reconnect the filter to the patient, and perform a new priming process.
11. With the saline recirculation method, the set can be maintained for **up to 2 hours.**

Recirculation with blood:

1. Press the "Stop Treatment" button.
2. Select "Refill".
3. Press the "Blood Refill" option button.
4. Clamp and disconnect the blue access line from the patient.
5. Create a closed circuit with the blue access line and the red access line through the three-way tap, ensuring circulation within itself.
6. Initiate recirculation with blood.
7. Solutions are not consumed during recirculation; adjustments are made only to the blood flow rate during this process, which can be tailored according to the specific set used.
8. The set can be reconnected to the patient without requiring re-priming in this method.
9. With the blood recirculation method, the set can be maintained for **up to 1 hour.**

Appendix 3. Heparin Protocol

1. Before initiating anticoagulation, it's essential to check the PT/PTT or ACT and platelet count.

2. In patients undergoing ACT monitoring, aPTT should be measured at least once daily.

3. Heparin should not be initiated if the initial ACT level is >200 sec, or aPTT is >60 sec, or PT-INR is >2.5 times the normal value, or the platelet count is <50,000/mm^3.

4. If there is no coagulopathy (ACT<180 sec or aPTT<60 sec), administer 20 units/kg of intravenous heparin.

5. Twenty minutes later, recheck the ACT or aPTT level (sample taken from the blue port after the filter). If ACT <180 sec or PTT <60 sec, repeat the heparin loading dose (maximum 2 times).

6. Target ACT level should be 180-220 seconds, and PTT level should be 60-80 seconds.

7. After the loading dose, start a continuous intravenous infusion of heparin at a rate of 10 units/kg/hour. Maximum heparin concentrations per liter according to age are shown in Table 10.

8. If possible, monitor activated clotting time (ACT) every 20-30 minutes for the first hour.

9. Check ACT or aPTT level one hour after each heparin dose change.

10. Follow the heparin dose adjustment protocol as outlined in Table 11.

11. Once a stable heparin infusion rate is achieved, monitor ACT or aPTT every four hours.

12. Check ACT or aPTT 20 minutes after each circuit change or blood transfusion.

Appendix 4. Citrate Anticoagulation Management

1. The recommended initial citrate dose is 2.5 mmol/L.

2. In certain devices, when dose information (mmol/L) is inputted, the device can automatically determine the citrate flow rate. However, in other devices, the initial citrate flow rate can be calculated manually using the formula:

Citrate dose = $Q_{citrate}$ x $C_{citrate}$/blood flow rate (mL/hour)

Where:

- $Q_{citrate}$ represents the citrate flow rate

- $C_{citrate}$ denotes the citrate concentration of the solution used

The contents of commonly used citrate solutions worldwide are detailed in Table 12. Among these solutions, acid-citrate-dextrose (ACD-A) A solution has been demonstrated by studies to be safe for use in children. While the content of 4% trisodium citrate solution closely resembles that of ACD-A solution, its sodium concentration is elevated. Despite this, it can still be utilized in pediatric patients with careful monitoring. Pediatric studies have been conducted on prismocitrate 18/0 solution. However, the challenge with prismocitrate 10/2 and 18/0 in pediatrics is that their concentrations per liter are low, necessitating high rates to achieve the effective citrate concentration in the extracorporeal circuit.

3. The solution intended for use as the dialyzer (second solution bag) should not contain calcium. However, there is no restriction for the solution designated as replacement (third solution bag) to contain calcium. Solutions devoid of calcium are outlined in Table 13.

4. Calcium infusion should ideally be administered through a separate central venous catheter. If this isn't feasible, a Y connector/triple tap system can be placed on the return line of the dialysis (blue line) to initiate calcium infusion to the patient. Calcium gluconate preparations, available in our country, are commonly used for calcium infusion, containing calcium at a concentration of 232 mmol/L. In pediatric patients, it is often diluted to a 1:1 ratio, resulting in a concentration of 116 mmol/L.

The calcium infusion rate can be calculated using the formula:

Calcium infusion rate = Citrate flow rate ×0.03.

For example, if the blood flow rate of a patient is determined to be 50 mL/minute, and the citrate flow rate is adjusted to provide a citrate dose of 2.5 mmol/liter concentration using 18/0 prismocal solution, the calculated citrate flow rate would be 416 mL/hour. Thus, the calcium infusion rate would be:

Calcium infusion rate =416 mL/hour × 0.03=12.5 mL/hour.

Dosage adjustment recommendations based on ionized calcium levels before (preFCai) and after (postFCai) the filter are provided in Tables 14 and 15, respectively.

5. Magnesium infusion guidelines:

- The magnesium level should be within a normal range (>0.7 mmol/L) before initiating citrate anticoagulation.

- If the magnesium level is low, 0.4 mmol/kg magnesium sulfate ($MgSO_4$) should be infused over 30-60 minutes prior to treatment.

- During citrate anticoagulation, $MgSO_4$ can be administered through a separate central venous catheter at a dose of 0.4 mmol/kg every 6-12 hours.

- Magnesium sulfate should not be infused through the same route as calcium.

- Plasma magnesium levels should be monitored every 12 hours. If the level falls below 0.7 mmol/L, an additional dose of $MgSO_4$ should be administered at a dose of 0.4 mmol/L, and magnesium levels should be checked at intervals of 6-8 hours.

6. Patients receiving citrate anticoagulation should be monitored as follows:

- Check patient and filter ionized calcium levels 30 minutes after the start of dialysis.

- Simultaneously measure ionized calcium levels from the patient and the filter.

- Monitor ionized calcium levels every hour for the first 3 hours and then every 4 hours after achieving balanced levels.

- Urea, creatinine, magnesium, phosphorus, calcium, and sodium levels should be checked at least every 12 hours.

- Management of acid-base imbalances due to citrate is detailed in Table 16.

Acknowledgment is extended to all team members, especially Oğuz Dursun and Bülent Karapınar, for their valuable contributions to both the creation of this new protocol and the utilization of information from the previous protocol.

Appendix 5. Protocol for the Prevention of Bradykinin Release Syndrome

The steps in Annex-1 of the protocol are followed. However, for patients at risk of bradykinin release syndrome, the filter should fill with erythrocyte suspension diluted with physiological saline to achieve the target hematocrit level.

1. The venous end is clamped and separated from the waste bag.

2. The venous end is connected to the empty end of the three-way tap that was previously connected to the arterial end.

3. The direction of the triple tap at the arterial end is closed to prevent blood from flowing into the circuit.

4. The blood in the venous pathway of the circuit is then passed to the arterial side through the triple tap, creating a closed circuit that circulates within itself.

5. At this stage, the venous line should remain unclamped and checked.

6. The triple tap is opened to allow blood to fill the circuit. The device is operated in CVVHD or CVVHDF mode. The system is run for 7.5 minutes, setting the blood flow rate to 40 mL/min and the dialysis rate to 200 mL/min.

7. At the end of the procedure, the pH and calcium levels of the blood inside the filter should be checked, as they often reach physiological limits.

DOI: 10.4274/cayd.galenos.2024.35248
J Pediatr Emerg Intensive Care Med 2024;11:57-76

Sedation-analgesia, Muscle Relaxant Applications in Pediatric Intensive Care Units and Guidelines for the Management and Environment Optimization of Clinical Statements Such as Withdrawal, Delirium Developed During These Applications

Çocuk Yoğun Bakım Ünitelerinde Sedasyon-analjezi, Kas Gevşetici Uygulamaları ve Bu Uygulamalar Esnasında Gelişen Yoksunluk, Deliryum gibi Klinik Tabloların Yönetimi ve Ortam Optimizasyonuna Yönelik Rehber

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Keywords: Pediatric intensive care, sedation, analgesia, muscle relaxant, delirium, deprivation, environment optimization
Anahtar Kelimeler: Çocuk yoğun bakım, sedasyon, analjezi, kas gevşetici, deliryum, yoksunluk, ortam optimizasyonu

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Regardless of the patient's age or underlying clinical condition, painful interventions are frequently performed during admission and follow-up in intensive care units. Pain may be caused by the underlying disease or may develop due to care. In intensive care units, pain caused by endotracheal tubes and mechanical ventilation is important. Factors such as separation from family, disturbances in the day and night cycles, noise of machines and monitors, unfamiliar people, and fear of death may cause emotional stress, anxiety, and insomnia in pediatric intensive care units (PICU). The aim of using sedation and analgesia in pediatric patients is to ensure that the patient is comfortable, to minimize physical discomfort and pain, to prevent psychological trauma by reducing anxiety, to create amnesia, to increase the success of assisted ventilation by keeping the level of consciousness and movement of the patient under control, and to ensure a safe return to the pre-consciousness level after the application.[1-3]

Methodology

"Pediatric Intensive Care Sedation-Analgesia and Muscle Relaxant Group" was established, and a guideline was planned to be prepared in order to make a common regulation in light of current information in the sedation-analgesia management,

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Received/Geliş Tarihi: 07.11.2023 **Accepted/Kabul Tarihi:** 08.01.2024

the use of muscle relaxants and the management of clinical pictures in PICUs, to provide standardization among centers and to prepare a resource that will shed light on new studies. For this purpose, the "Pediatric Intensive Care Sedation-Analgesia and Muscle Relaxants Group" met for six times. While forming the recommendations, firstly, the literature on the subject was reviewed in order to create evidence, the results of the surveys conducted in our country were evaluated, and the evidentiary data obtained were grouped with the GRADE methodology. In order to ensure consensus, voting was held for a maximum of two times. Finally, these recommendations and statements were renewed to be compatible with each other. As a result, recommendations with 80% or more consensus were considered strong recommendations, while 50-80% were considered weak recommendations.

Sedation is used to describe the reduction of consciousness or awareness: analgesia is used to describe the reduction of pain sensation; and amnesia is used to describe the absence of subsequent recollection of events. The American Society of Anesthesiologists defines interventional sedation on a scale from the mildest sedation to general anesthesia. Medically induced mild loss of cognitive and motor functions is anxiolysis. Moderate sedation and analgesia, also defined as conscious sedation, is a state of moderate sedation in which children can respond appropriately to verbal commands with mild tactile stimulation or alone. Respiratory and cardiovascular functions are not affected in these two stages. Deep sedation and analgesia are a medically induced suppressions of consciousness in which the child can only respond to repetitive or painful stimuli. General anesthesia is a medically induced loss of consciousness with no response to painful stimuli (Table 1). Respiration is affected in deep sedation and general anesthesia.[1-3]

In recent years, the negative effects of inadequate sedation-analgesia in intensive care units, especially in mechanically ventilated patients, have been frequently emphasized. Failure to provide effective sedation-analgesia in patients monitored in intensive care units may lead to an increase in oxygen consumption and carbon dioxide production. Changes in respiratory parameters such as increased respiratory rate and minute ventilation, decreased tidal volume, maximum expiratory volume and vital capacity may develop. Neuroendocrine events developing with the release of catecholamine, cortisol, glucagon and other catabolic hormones may lead to negative nitrogen balance and catabolic state with hyperglycemia. Hemodynamically, heart rate and blood pressure may increase.[4-7]

All these findings are related to the sensation of pain as a result of inadequate sedation-analgesia. Therefore, pain and sedation levels should be measured. Assessment and measurement of pain in children is difficult. Especially for infants, non-verbal (2-7 years old) and pediatric patients in intensive care, it is difficult to define pain. This difficulty causes some of the available tests to be inapplicable to children, and adequate pain control cannot be achieved. Many objective and observation-based methods are used in the assessment of pain. The methods used to determine the level of pain are based on the observer's assessment or measurement of certain characteristics or changes in the patient (Type I measurements) or on the patient's self-rating of pain (Type II measurements). Type I methods include physiological (increased plasma cortisol and catecholamine levels, changes in cardiovascular and respiratory parameters), non-pharmacological (inverse relationship with plasma β-endorphin levels, changes in skin temperature) and neurological (nerve conduction velocity, evoked responses, special micrographs and tomographs) measurements. Type II methods include category numerical and visual analog scales, the McGill Pain Questionnaire or Wesh Haven-Yale Inventory, rehabilitation tests. The choice of method should be based on the child's general condition, age and level of pain recognition. In infants, body response, facial expression, crying and pulling reflex can be used to get an idea. Among these, facial expression is considered to be the most reliable. While evaluating facial expression, eyebrow raising, eye squeezing, nasolabial groove formation, opening of the lips, vertical or horizontal stretching of the mouth, puckering of the lips, stretching of the tongue, and trembling of the chin are taken into consideration. The duration and tone of the crying sound can also be evaluated. However, these symptoms indicate the presence of pain rather than its degree. Most children over the age of three years can express their pain and its degree, and can indicate the intensity of pain by choosing from a series of colors or pictures, or by selecting

Table 1. Sedation and analgesia stages

State	Anxiolysis/mild sedation	Conscious sedation/moderate sedation and analgesia	Deep sedation/analgesia	General anesthesia
Non-response	Normal response to verbal stimulation	Appropriate response to verbal or mild tactile stimulation	Appropriate response to repetitive or painful stimuli	Unresponsive to painful stimuli
Airway patency	Maintained	Maintained	Can require intervention	Often require intervention
Respiration	Normal	Sufficient	Can require support	Often require support
Cardiovascular functions	Normal	Maintained	Generally maintained	Can impair

one of the rungs of a ladder. The intensity and severity of pain can be assessed in children aged three years and older using the Oucher scale or the visual scales developed by McGrath. The applicability of these tests is difficult especially for the patients hospitalized in intensive care units.[4-7]

Determining the level of sedation during sedation-analgesia use is also necessary for dose adjustment in non-cooperative PICU patients. The most commonly used sedation scores in the PICU are scales assessing physiologic variables or depth of sedation or both. The most commonly used scale is the COMFORT score, which is assessed by patient response or physiologic parameters. Here, patient alertness, respiration, blood pressure, muscle tone, agitation, mobility, heart rate and facial tension are assessed (Table 2). Tachycardia or hypertension may not be observed despite pain and agitation, especially in patients with cardiovascular instability and those taking vasoactive drugs. COMFORT-B scoring was developed due to the limitations mentioned. In the COMFORT scoring, which is most commonly used in children, a score between 6 and 10 indicates excessive sedation, and a score between 23 and 30 indicates inadequate sedation levels. The other sedation grading system is the RAMSAY scoring used in adults (Table 3). Many scoring systems are subjective and adversely affected by differences in assessment between observers. Methods with high objectivity may be difficult to apply routinely. Based on this, the Brussels sedation scale, which was developed as a simple scoring system, is easy to use and reduces subjectivity and inter-observer variability (Table 4). Scoring systems have been shown to be cost-effective for PICUs. With good control of the sedation level of the patient, weaning from the ventilator is accelerated and the number of ventilator-dependent days decreases.[5-8]

A major problem with clinical sedation systems is the difficulty in determining the depth of sedation in patients receiving paralytic agents. A bispectral index (BIS) is a monitor that measures the hypnotic effects of sedative and anesthetic agents based on the electroencephalogram. The measurement of brain electrical activity with the BIS monitor is integrated into a single numerical value between 0 and 100. The results are not clear, but most reports have found a good correlation between the COMFORT score and the BIS. The BIS has been found to correlate particularly well in patients undergoing inhalation anesthesia or in assessing the efficacy of some specific agents.[9,10]

The BIS can be applied to a group of patients for whom intensive care scoring systems using muscle relaxants and/or agents that can alter the heart rate and blood pressure response would be difficult to assess. The main problem associated with the use of BIS is the recording of highly variable values.

Table 2. Comfort and comfort B sedation scales

Comfort scale	Score
Alertness	
Deeply asleep	1
Lightly asleep	2
Drowsy	3
Fully awake and alert	4
Hyperalert	5
Calmness	
Calm	1
Slightly anxious	2
Anxious	3
Very anxious	4
Panicky	5
Heart rate	
Heart rate below baseline	1
Heart rate consistently at baseline	2
Infrequent elevations of 15% or more above baseline (1-3 during observation)	3
Frequent elevations of 15% or more above baseline (more than 3 during observation)	4
Sustained elevations of 15% or more	5
Facial appearance	
Facial muscles totally relaxed	1
Facial muscle tone normal, no facial muscle tension evident	2
Tension evident in some facial muscles	3
Tension evident throughout muscles	4
Facial muscles contorted and grimacing	5
Blood pressure baseline	
Blood pressure below baseline	1
Blood pressure consistently at baseline	2
Infrequent elevations of 15% or more above baseline (1-3 during observation)	3
Frequent elevations of 15% or more above baseline (more than 3 during observation)	4
Sustained elevations of 15% or more	5
Respiratory response (only in patients undergoing mechanical ventilation)	
No coughing and no spontaneous respiration	1
Spontaneous respiration with little or no response to ventilation	2
Occasional cough or resistance to ventilator	3
Active respiration against ventilator	4
Fights ventilator, coughing or choking	5
Muscle tone	
Muscles totally relaxed, no muscle tone	1
Reduced muscle tone	2
Normal muscle tone	3
Increased muscle tone and flexion of fingers and toes	4
Extreme muscle rigidity	5
Physical movement	
No movement	1
Occasional, slight movements	2
Frequent, slight movements	3
Vigorous movement limited to extremities	4
Vigorous movements including torso and head	5

Main Principles for the Selection of Drugs

Adequate control of pain and/or anxiety requires an accurate assessment of patient and environmental factors. Before sedation and increasing analgesia doses, it is imperative to determine that the agitation is treatable and not due to life-threatening causes such as hypoxemia, hypercarbia, cerebral hypoperfusion, necrotic bowel syndrome or compartment syndrome. Non-pharmacologic interventions are very important for pain control, sedation and the prevention of physical and emotional stress.

It is important to identify the factor causing the stress in determining the correct agent. Analgesic drugs should be used in the presence of tissue damage or pain, and sedative, anxiolytic and amnestic agents should be used in times of emotional stress. Unfortunately, a very limited number of drugs have both sedative and analgesic effects. The half-life of the agent to be used should be taken into consideration when choosing the right drug. Some interventions may take days and weeks starting in 5 minutes and lasting 12 hours. In addition, there are not enough studies on the pharmacology and pharmacodynamics of sedative/analgesic drugs in critically ill children and they are not evidence-based. Especially in the PICU, organ damage, respiratory and circulatory imbalance, low protein levels and drug interactions make this situation more complex. In addition to pharmacokinetic and pharmacodynamic properties, pharmacogenic factors should also be considered in agent selection. The efficacy and side effects of sedatives and analgesics may vary individually. In some patients, adequate efficacy can be achieved with low doses, whereas high doses may be needed in others. Drug doses should be adjusted according to the patient's level of sedation and analgesia. Drugs with few side effects should be preferred. Incorrect use of sedatives and analgesia without examination of the patient and effective monitoring may lead to negative results. Institutions should make a sedation-analgesia plan, have monitoring criteria, personnel accreditation and quality improvement protocols to ensure safe sedation and analgesia practices in children.[1-5] The use of guidelines published by the American Pediatric Association in the management of sedation and analgesia in these patients may increase efficacy and safety.[9,10]

Table 3. RAMSAY scale

Grade	Describing
1	Patient is awake, anxious, restless and/or disturbed
2	Patient is awake, cooperative, oriented and calm
3	Patient awake, responding only to commands
4	Patient is asleep, responds vividly to loud vocalization and glabellar stimulation
5	Patient is asleep, responds poorly to loud vocalization and glabellar stimulation
6	The patient is asleep, unresponsive to loud vocalization and glabellar stimulation

Table 4. Brussels sedation scale

Grade	Describing
1	Unable to wake up
2	No response to verbal stimuli, responds to painful stimuli
3	Responds to verbal stimuli
4	Awake and alert
5	Agitated

Clinics of Turkey; Non-invasive and Invasive mechanical ventilation special issue: Sedation and Analgesia During Non-invasive and Invasive Mechanical Ventilation pages; 51-60

The parameters to be considered in patients planned to be sedated in PICUs are:

1. Always exclude the treatable cause of agitation

- Hypoxia and hypercarbia
- Cerebral hypoperfusion
- Bladder distortion
- Surgical lesion: Necrotic bowel and compartment syndrome

2. Adequate sedation-identify the cause of pain and agitation if you want to provide analgesia

3. Follow the recommendation of the American Pediatric Association

4. Administer the first loading dose, and then the infusion dose according to the clinical response

5. Monitor for physiological effects, including the development of tolerance, and increase the dose or switch to another drug if necessary.

Agent, Route and Management Procedure

The choice of medication should be based on the type of intervention and the patient's underlying medical condition. Procedures that are not painful but require the child to remain still can usually be performed with sedation alone. Children undergoing painful procedures require additional analgesia in addition to sedation. Before starting sedation-analgesia treatments, three basic issues should be decided: 1) the agent to be used, 2) the route of administration, 3) the method of administration. There is no single agent that will be effective for every patient. The intravenous route is usually chosen. Very rarely, inhaled anesthetics or subcutaneous drugs can be used for analgesia. The inhaled route is preferred if there are side effects or problems with the intravenous route. Not every drug may have an alternative route. Chlorhydrate is administered orally and rectally, isoflurane is inhaled, and propofol is administered only intravenously. Midazolam and ketamine can be used by any route. Finally, the method of administration (continuous, intermittent or patient-controlled) should be decided. In a mechanically ventilated children, long-

acting agents (lorezepam, phentobarbital, and morphine) may provide adequate sedation when administered intermittently and bolus. However, the most common and best practice is to infuse short-acting agents (midozalom-fentanyl) continuously to provide normal serum concentrations. Patient-controlled analgesia is more commonly used outside of intensive care.

Various drugs with advantages and disadvantages are used for sedation and analgesia in the PICU. Healthcare workers should select the agents that they think will be effective based on the clinical characteristics of the patient and should know the characteristics of all of them in order to be able to switch between drugs when necessary.

Pharmacological Agents Used for Sedation and Anesthesia

Opioids

The limbic system, periaquaductal structures and posterior laminae of the spinal cord contain specific pain receptors and are involved in pain perception. The identified sites are stereospecific binding sites for opioids and opioid-related drugs. There are multiple types of receptors specific to these drugs. Table 5 shows the physiologic effects of opioids.

Morphine

It means "god of sleep" in Greek. It provides analgesia by agonist effect on μu receptors in the central nervous system. Because morphine is a lipid soluble drug, and the blood-brain barrier is immature in newborns, its permeability to morphine is high. It is metabolized in the liver. Its half-life is three hours but it is prolonged in neonates and premature infants. Morphine can cause nausea, vomiting, pruritus, miosis and convulsions at high doses. The likelihood of side effects is high, especially in neonates. Although morphine causes peripheral vasodilatation and venous pooling, it has little effect on hemodynamic parameters. It may cause hypotension when used with the sedative drug diazepam. It may cause respiratory depression by decreasing the sensitivity of the respiratory center in the brain stem to hypoxia and hypercarbia. It causes biliary colic, contraction of the ureter, bladder, and bladder detrusor muscles and increased tonus. It is contraindicated in asthma crises because it increases histamine release.[11]

Fentanyl

Its effect starts quickly and its duration of action is short; for these reasons, it is used quite frequently. It is the most commonly used opioid group drug in mechanically ventilated patients. It is 100 times stronger than morphine. There are four commonly used agents: fentanyl, sulfentanil, alfentanil and remifentanil. When they are compared clinically, they have no obvious superiority over each other. Fentanyl-sulfentanil-alfentanil are hepatically metabolized. Their half-lives are prolonged in the presence of hepatic dysfunction. Sulfentanil is 10 times more potent than fentanyl. Alfentanil is 5-10 times less potent than fentanyl. Fentanyl has little negative effect on the cardiovascular system. Remifentanil, one of the new opioids, is less affected by liver dysfunction than other opioids. Remifentanil's half-life is 5-10 minutes. It causes deep sedation. When the drug is discontinued, its effect subsides rapidly and the patient wakes up in a short time.

Opioids may increase intracranial pressure and cause chest wall rigidity. Studies in adults have shown that they decrease mean arterial pressure, increase intracranial pressure and decrease cerebral perfusion pressure. These effects are explained by reflex cerebral vasodilation in response to decreased mean arterial pressure. Chest wall rigidity is dose, rate of administration-, and age-related. The side effect of chest wall rigidity is reversed with the administration of naloxone and muscle relaxants. Fentanyl and similar group drugs are highly lipophilic and cross the blood brain barrier rapidly. Fentanyl's half-life is 233±137 minutes in infants and

Table 5. Physiological effects of opioids

Totally delete this sentence please				
CNS	**Respiratory system**	**Cardiovascular system**	**Gastrointestinal system**	**Urinary system**
Analgesia, sedation	Antitussive	Bradycardia (fentanyl-morphine)	Motility-persistaltism ↓	Ureter, bladder, bladder detrusor muscle tone ↑
Nausea, vomiting	Minute ventilation ↓	Histamine release (morphine)	Sphincter tone ↑	
Myosis	Respiratory rate-tidal volume ↓	Little effect on cardiac output		
Seizure	Suppresses the response to CO_2 and O_2			
Dysphoria				
Euphoria				

CO_2: Carbon dioxide, O_2; Oxygen, CNS: Central nervous system, Clinics of Turkey; Non-invasive and Invasive mechanical ventilation special issue: Sedation and analgesia during non-invasive and invasive mechanical ventilation pages; 51-60

244±79 minutes in older children. Fentanyl can be easily used as a continuous infusion in intensive care units. It can be administered as a bolus dose or continuous infusion as needed. Other fentanyl group drugs have recently started to be used in pediatric patients, and information on their efficacy and side effects is limited.[1-3,11]

Benzodiazepines

Benzodiazepines are the most commonly used agents to provide sedation in the PICU. Benzodiazepines provide sedation, anxiolysis and amnesia and do not have analgesic properties. They bind to the alpha-subunit of the inhibitory amino acid gamma-aminobutyric acid (GABA) receptor. This association leads to tight binding of the GABA molecule to the beta-subunit, chloride transmission through the neuronal membrane is accelerated and hyperpolarization occurs.

Midazolam

Midazolam is a water-soluble benzodiazepine with a rapid onset of action and a short half-life after bolus administration. It has good anxiolytic, amnestic and muscle relaxant properties. Midazolam is often used to provide mild sedation in children or combined with fentanyl or dexmedetomidine in patients targeting moderate sedation. Midazolam is metabolized by the hepatic P450 enzyme system to 1-OH midazolam, which has the same potency as the parent compound. Subsequently, 1-OH midazolam-glucronide is formed in the liver by the glucronyl transferase system, which dissolves in water and is excreted through the kidneys. Midazolam pharmacokinetics can be altered by many factors, including age and underlying disease. The metabolism of midazolam is dependent on the hepatic P450 system, and the half-life is shortened while clearance increases from infancy to adulthood. The presence of hepatic insufficiency increases the free fraction 2-3-fold, leading to the accumulation of active metabolites and prolonged duration of drug action. Renal dysfunction leads to the accumulation of 1-OH midazolam-glucronide, which increases the efficacy of midazolam. Midazolam has a high protein binding rate. Free levels of midazolam may vary significantly with various factors such as heparin affecting its protein binding. Awakening time is fast in short-term use (<12 hours) and slow in long-term use. Midazolam clearance is decreased by many commonly used drugs such as calcium channel blockers, erythromycin and triazole antifungals. Midazolam is water soluble and can be administered parenterally (intravenously or intramuscularly), rectally (PR), intranasally (IN), sublingually (SL) or orally (PO). Doses, onset and duration of action vary depending on the patient's age and route of administration. Midazolam has the fastest onset of action via the V route.

Midazolam may cause respiratory depression and apnea, especially when used in combination with opioid drugs such as fentanyl or morphine. When midazolam is used as a single agent, paradoxical reactions such as inconsolable crying, hyperactivity and aggressive behavior may occur in approximately 1% to 3% of patients. Both respiratory depression and paradoxical reactions can be reversed with flumazenil.[1-5,12-14] Flumazenil should not be used in patients with seizure disorders or who are taking chronic benzodiazepines because of the risk of triggering withdrawal symptoms.[1-3,11]

Lorazepam

Lorazepam is metabolized by glucuronyl transferase and is a water-soluble benzodiazepine with no active metabolites. It is well absorbed orally and intramuscularly. It shows sedation effect for 4-8 hours after a single dose. Its half-life is approximately 14 hours. Lorazepam pharmacokinetics are not altered by drugs known to affect the P450 system (e.g., anticonvulsants, rifampicin, and cimetidine). Its metabolism is not affected by age and critical illness.

Due to the toxic effects of propylene glycol, which is a diluent in the intravenous form of lorazepam, caution should be exercised in high doses or in the newborn population. In propylene glycol toxicity, symptoms and signs such as metabolic acidosis, renal failure, mental changes, hemolysis and an increased osmolar gap are observed. Propylene glycol is metabolized to lactic and pyruvic acid in the liver; it should be used with caution in the presence of lactic acidosis. Propylene glycol is also excreted unchanged in the urine and the risk of toxicity increases in the presence of renal insufficiency. Neonatal infants, especially preterm ones, cannot metabolize propylene glycol sufficiently due to hepatic and renal immaturity; continuous infusion of lorazepam is not recommended in this population.[12]

Etomidate

It is an intravenous anesthetic agent. Its half-life is 2.9-5.3 hours. It decreases cerebral metabolic O_2 requirement, blood flow and intracranial pressure. The induction dose in children is 0.2-0.3 mg/kg. Especially at doses of 0.2-0.4 mg/kg, cardiovascular effects are low. The infusion dose is 40-50 µg/kg/min. Respiratory suppression and apnea may develop dose-dependently and may be prominent when used in combination with other drugs. It may cause myoclonus. Its myoclonus side effect can be prevented by administering low doses of fentanyl-benzodiazepine and etomidate before treatment. With prolonged use, etomidate reduces endogenous corticosteroid production by blocking the enzyme 11 β hydroxylase. This enzyme is required for the production of cortisol, aldosterone and corticosterone. Even a single dose reduces corticosteroid production but is of no clinical significance. In addition, it suppresses neutrophil function. A continuous infusion of etomidate is known to

increase the development of infection and mortality. It may cause pain, anaphylaxis, nausea and vomiting. Etomiodate is the frequently preferred agent for rapid sequence intubation because it has no adverse effects on the cardiovascular system. It is also an ideal sedative agent for the patients with increased intracranial pressure. However, prolonged infusions and repeated doses are not recommended.[2,3]

Ketamine

Ketamine is a sedative, amnesic and analgesic drug. It increases mean arterial pressure, heart rate and cardiac output regardless of the route of administration and can be used in shock and in hemodynamically unstable patients. Ketamine is a potent bronchial smooth muscle relaxant, making it an ideal sedative-analgesic agent for asthmatic patients. Its effect on pulmonary vascular resistance is controversial. It may increase intracranial pressure due to its effect on CO_2 or directly on cerebral vascularity. For years, ketamine was not used in patients with increased intracranial pressure because it was thought to increase intracranial pressure further by vasodilatation. However, recent experimental studies have shown no change or even a decrease in intracranial pressure following ketamine injection in mechanically ventilated subjects. Ketamine may cause vertical or horizontal nystagmus and hallucinations. Administration of benzodiazepine before ketamine treatment prevents hallucinations. It increases salivary and bronchial mucus secretion; atropine can be used in cases where it causes an increase in secretions.

Ketamine has high lipid solubility; it rapidly crosses the blood-brain barrier with a single intravenous dose and causes loss of consciousness. It has a half-life of 2-3 hours and is metabolized in the liver by microsomal enzymes. There are few studies on its use in mechanically ventilated patients. The ketamine bolus dose is 0.5-1 mg/kg and infusion dose are 1-2 mg/kg/hour. Ketamine is not the first agent to be used in patients undergoing mechanical ventilation in PICUs. Ketamine should be used especially 1) when cardiovascular side effects due to opioid and benzodiazepine use have developed, 2) when spontaneous breathing needs to be maintained while applying non-invasive ventilation, 3) due to its bronchodilator properties in the presence of status asthmaticus 4) as a low dose in cases where increasing the opioid dose and developing tolerance is not desired and 5) in short painful interventions where spontaneous breathing is desired.[2,3,13]

Propofol

It is a general anesthetic agent. Its chemical structure is similar to etomidate and barbiturate but the mechanism of action is different. It has sedative and amnestic effects, but no analgesic effect. In recent years, it has been frequently used in intensive care units because its onset and termination are rapid, and it has no active metabolites. This agent causes cerebral vasoconstriction like barbiturates, and decreases cerebral metabolic oxygen demand and intracranial pressure. Propofol has been reported to decrease intracranial pressure and improve cerebral perfusion pressure in vasogenic edema, but not in cytotoxic edema. In human studies, it was found that it decreased intracranial pressure but mean arterial pressure and cerebral perfusion pressure decreased simultaneously. However, it has been shown that if mean arterial pressure is kept normal by using vasopressors, intracranial pressure decreases and cerebral perfusion pressure is maintained. Propofol is one of the agents used in rapid sequence intubation; it reduces airway reactivity. Propofol is used in the treatment of refractory status epilepticus.

It causes peripheral vasodilation, it is a negative inotrope and hypotension may develop during administration. This side effect is prominent in patients with rapid injections and suppressed cardiovascular function. Adverse hemodynamic effects may improve with calcium therapy. Propofol may increase vagal tone and cause bradycardia, conduction disturbances and asystole. The possibility of these side effects increases when used with other drugs (such as fentanyl, succinylcholine). Propofol may cause respiratory suppression-apnea and airway obstruction. It may cause neurologic side effects such as opisthotonos, myoclonic movements and seizure-like activity. Propofol is diluted with a lipid emulsion. Lipid emulsion content is 10% lipid compound used in parenteral nutrition fluids. The daily caloric intake of the patient should be calculated taking into account the lipid content of propofol. Lipid content may cause anaphylactic reactions, pain during administration, an increase in triglyceride levels in prolonged infusions and may create a favorable environment for the growth of bacteria. Pain during administration may be reduced if given with lidocaine or low dose ketamine. It may cause a trace element deficiency. Due to propofol infusion syndrome, it is not recommended for use in children aged 3 years and younger. Syndrome may develop in patients receiving a propofol infusion for more than 48 hours and at a dose of more than 4 mg/kg/hour. Propofol is thought to impair mitochondrial function. The findings of this syndrome include metabolic acidosis, bradycardia, dysrhythmia, rhabdomyolysis and fatal heart failure. Blood gas, creatine phosphokinase and lactate levels should be checked in patients receiving propofol. If the syndrome develops, propofol infusion should be terminated and supportive therapies should be administered. If long-term use of propofol is required, a cost-benefit analysis should be performed carefully.[2,3]

Barbiturates

Barbiturates are classified according to their chemical structure or duration of action. Hepatic metabolism of short-acting

agents is slow, but their redistribution-induced effects end rapidly. The clinical duration of action of short-acting agents such as methohexital, thiopental and thiamylal is between 5 and 10 minutes. Long-acting agents such as phenobarbital and pentobarbital have half-lives of 6-12 hours. Short-acting barbiturates are used in situations where rapid onset and termination of action are targeted, such as induction of anesthesia and endotracheal intubation.

The cardio-respiratory effects of barbiturates are similar to those of propofol. In healthy subjects, sedative doses minimally affect cardiovascular function, respiration and airway protective reflexes, while higher doses may cause respiratory depression, apnea and hypotension, especially in patients with myocardial dysfunction. Hypotension is caused by peripheral vasodilation and direct negative inotropic effects. Pentobarbital is an alkaline solution; it is incompatible with other medications and parenteral nutrition fluids and should be administered through a separate infusion line. The high pH of the barbiturate solution may cause localized erythema with subcutaneous infiltration and thrombophlebitis. It is not recommended to use barbiturate as the first agent for sedated patients to be monitored in the PICU. However, they may be preferred in cases where the agents used are not effective or undesirable side effects occur. In the retrospective evaluation of 50 infants and children aged between 1 month and 14 years who were on mechanical ventilation and who could not achieve the desired level of sedation despite the combination of benzodiazepines (midazolam dose 0.4 mg/kg/h) and opioids (fentanyl dose 10 micrograms/kg/h, morphine dose 100 micrograms/kg/h), it was shown that effective sedation was achieved with pentobarbital treatment, and the dose of other agents was reduced. Barbiturates do not have analgesic properties and should be used together with opioids in patients requiring pain treatment.[2,3]

Alpha-2 Adrenergic Agonists

Alpha-2 adrenergic agonists achieve their sedative effects by stimulating central parasympathetic signals and inhibiting central sympathetic signals. Noradrenergic impulses originating from the locus coeruleus decrease, a number of inhibitory neurons involving the GABA system are stimulated, and sedative and anxiolytic effects begin. This effect is similar to the changes seen during the non-REM period of sleep. The mechanism of action of alpha-2 adrenergic drugs is different from that of other agents used for sedation in the PICU. When other agents are used for prolonged periods, non-REM sleep periods are reduced and the likelihood of delirium increases significantly. Alpha-2 adrenergic agonists exert analgesic effects by regulating the release of substance P and enhancing the effects of opioids. The affinity of dexmedetomidine for alpha-2 adrenergic receptors is 8 times higher than that of clonidine, the alpha 1/alpha 2 agonism ratio is 1:1600, and the half-life is two hours, allowing dose adjustment in intravenous infusion. Dexmedetomidine is approved by the FDA for short-term (less than 24 hours) sedation in mechanically ventilated adults. Dexmedetomidine has been used for sedation in adult patients requiring mechanical ventilation after cardiac surgery and general surgery caused an 80% reduction in midazolam dose and a 50% reduction in morphine dose compared to placebo. Currently, there is no prospective study using dexmedetomidine in pediatric patients undergoing mechanical ventilation. In this study, dexmedetomidine, when administered at a dose of 0.25 microgram/kg/h, provided a similar level of sedation to midazolam administered at an infusion rate of 0.22 mg/kg/h, and was more effective than midazolam when administered at a higher dose (0.5 microgram/kg/h). Dexmedetomidine is less effective in children younger than 6-12 months. Five of the six patients who could not achieve the desired level of sedation during dexmedetomidine use were younger than 12 months. In the same study, it was reported that bradycardia developed in one patient who was using digoxin as a side effect. Dexmedetomidine may have a negative effect on respiratory and cardiovascular function. Clonidine has a low probability of respiratory depression side effects. There are different results on the effects of dexmedetomidine on ventilatory function. There are studies reporting mild respiratory depression, decreased minute ventilation, suppression of CO_2 response and no adverse effect. In PICUs, clonidine can be administered orally to prevent the development of withdrawal symptoms during discontinuation of other sedative drugs.[2,3,14]

Withdrawal Syndrome

Hospitalization periods in PICUs can be long. Sedation-analgesia applications in patients requiring long hospitalization may lead to long-term effects. It was first described in 1980-1990 that withdrawal or withdrawal syndrome developed after the discontinuation of most sedation-analgesia drugs.[15]

Tolerance, withdrawal and physical dependence develop after prolonged sedation-analgesia. Withdrawal syndrome symptoms are drug-independent and similar. The time of onset of withdrawal symptoms varies depending on the half-life and active metabolites of the sedative and/or analgesic drug administered. Some of the withdrawal symptoms and signs include CNS irritability, GI dysfunction and autonomic dysfunction (Table 6). Convulsions have also been described. Withdrawal syndrome remains a serious problem in long-term hospitalizations despite the development of new sedation techniques.[1,15]

Guidelines should be used to recognize withdrawal syndrome early in patients taking sedation-analgesic drugs for a long-time.[1,15,16] The presence of withdrawal symptoms should be evaluated at twenty-four hour intervals (Table 7) and an appropriate treatment strategy should be determined (Table 8).

Table 6. Typical signs of withdrawal syndrome

CNS irritability	GIS dysfunction	Autonomic dysfunction
Poor sleep pattern	Diarrhea	Tachypnea
Tremor	Vomiting	Piloerection
Convulsion	Abdominal pain	Fever
Fever	Inadequate nutrition	Tachycardia
Myoclonic pulse		Hypotension
		Tachypnea
		Sneezing

GIS: Gastrointestinal, CNS: Central nervous system

Table 7. Sedation withdrawal score

Tremor	Sneezing
Irritability	Respiratory distress
Hypertonicity	Fever
Hyperactivity	Diarrhea
Vomiting	Sweating
Loud crying	Convulsion

For each parameter none=0, mild=1, severe=2. Clinics of Turkey; non-invasive and invasive mechanical ventilation special issue: Sedation and analgesia during non-invasive and invasive mechanical ventilation pages; 51-60

The protocols used in our unit are summarized in Table 9, Figures 1 and 2.

Improper use of sedation-analgesic drugs leads to prolonged mechanical ventilation and intensive care unit stays and increased mortality and morbidity. The quality of sedation-analgesia is improved, and side effects are reduced with the administration of appropriate drugs based on the correct protocols and careful monitoring. Different sedative-analgesic drugs have advantages and disadvantages. The ideal sedative analgesic drug should have a rapid onset of action, a short half-life, low metabolism and elimination, limited hemodynamic or respiratory side effects, a specific antidote and should not interact with other drugs. Pharmacodynamics, route of administration, secondary effects, patient's age, other diseases, need for mechanical ventilation, nutritional status, renal and hepatic function and cost should be taken into consideration when choosing the right agent.

In recent years, it has been reported that daily awakenings can be performed in children receiving sedation and analgesia as well as in adults. However, there are still no clear data on this issue.

There is no single ideal agent for sedation analgesia. In most cases, treatment is started with a combination of benzodiazepines and opioids. The most preferred drugs are midazolam and fentanyl. Hemodynamic balance is maintained during fentanyl treatment, and the risk of developing tolerance is low in morphine treatment. Opioid infusion may be useful in the modulation of pulmonary vascular resistance. Especially in patients with pulmonary hypertension, opioid infusion may prevent the development of crisis. Ketamine, pentobarbital and dexmedetomidine may be used if first-line drugs are inadequate. Ketamine may be useful in patients with hemodynamic instability or airway reactivity. There are very limited reports on the use of pentobarbital for sedation. Propofol is a commonly used agent in adult intensive care units. Propofol is not preferred in PICUs because of the risk of propofol infusion syndrome. Doses of sedative and analgesic drugs are given in Tables 10 and 11.

Table 8. Strategy to be implemented

Score (6 hours)	Strategy
<6	Continue with the current application
6-12	Do not reduce current practice
12-18	Turn back to previous status
>18	Get suggestion

Table 9. Scoring of withdrawal syndrome

Criteria	Score
Crying/agitation	
25%> of the 4-hour period	2
26-75% of the 4-hour period	3
75%< of the 4-hour period	5
Sleeping	
25%> of the 4-hour period	1
26-75% of the 4-hour period	2
75%< of the 4-hour period	3
Hyperactivated moro (for newborns)	2
Apparent hyperactivity (for newborn)	3
Tremor	
Mild	1
Moderate	3
Severe	5
Tonic-clonic seizure	5
Hallucinations (in verbal children)	1
Extubated or IMV-ventilated patient	
Respiratory rate 60< for <2 years	2
Respiratory rate 60< for >2 years	2
Vomiting	2
Diarrhea	2
Other symptoms	1
Total score	32

IMV: Intermittent mandatory ventilation. Clinics of Turkey; non-invasive and invasive mechanical ventilation special issue: Sedation and analgesia during non-invasive and invasive mechanical ventilation pages; 51-60

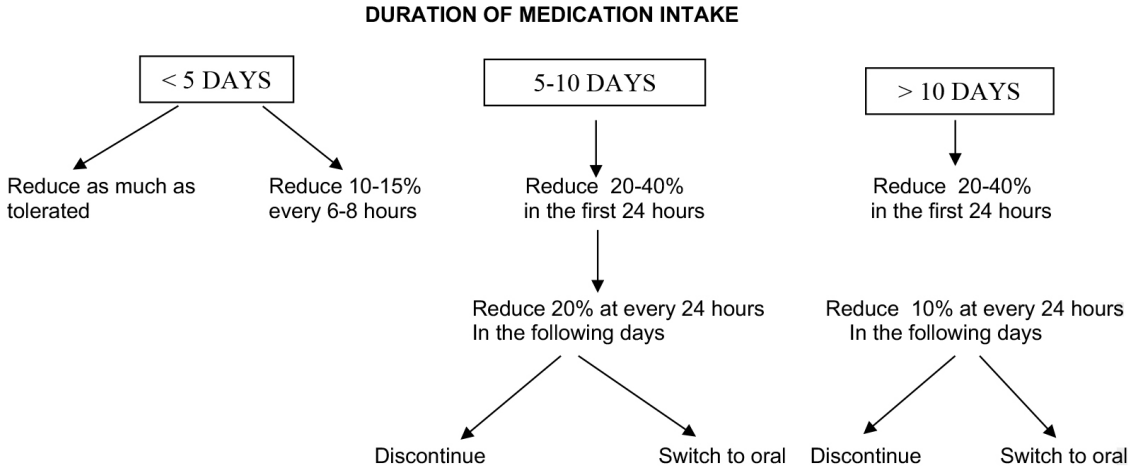
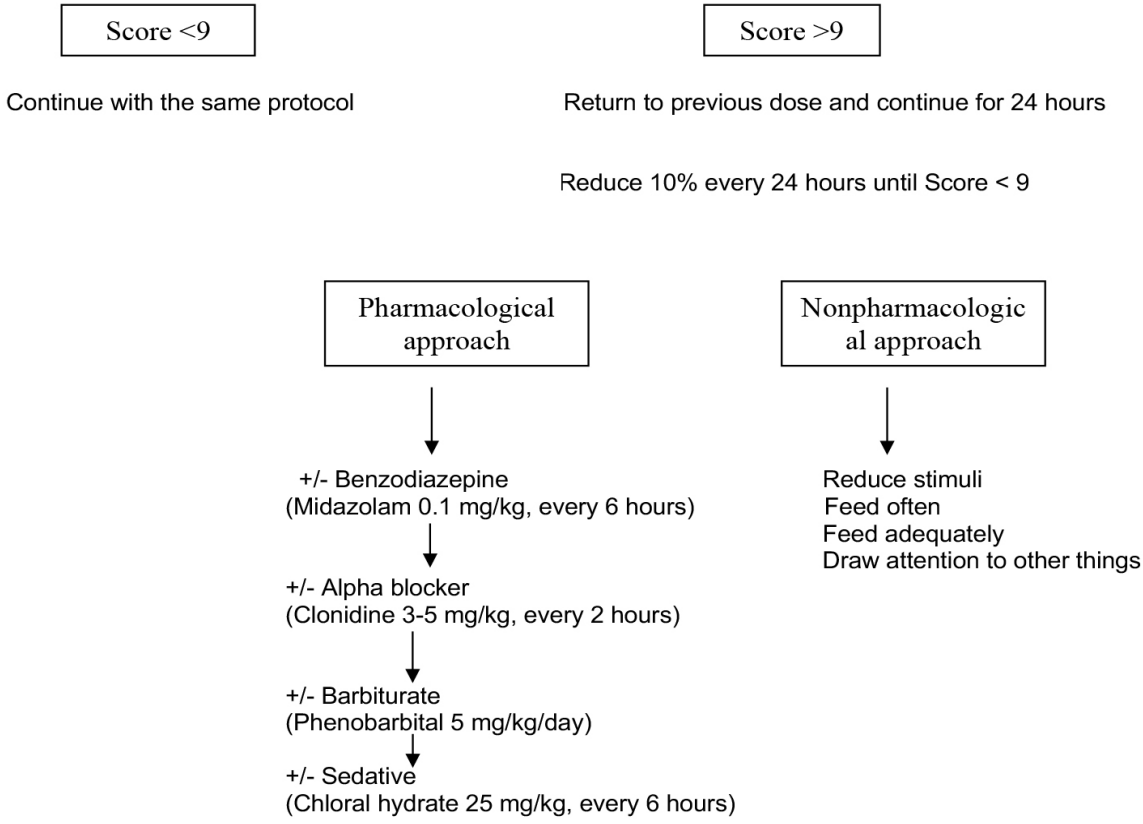


Figure 1. Strategies to prevent withdrawal syndrome during the discontinuation period of sedation and analgesic drugs
Clinics of Turkey; non-invasive and invasive mechanical ventilation special issue: Sedation and analgesia during non-invasive and invasive mechanical ventilation pages; 51-60



Clinics of Turkey; non-invasive and invasive mechanical ventilation special issue: Sedation and analgesia during non-invasive and invasive mechanical ventilation pages; 51-60.

Figure 2. Withdrawal syndrome treatment protocol

As a result, the ideal level of sedation is when the patient is conscious, breathing in compliance with the ventilator and tolerant to therapeutic interventions. The ideal level of sedation in each patient varies according to the underlying disease and its severity. The ideal level of sedation is achieved by titrating the doses of sedative drugs using observational sedation scales. The steps to be followed in the clinic to ensure the ideal individual sedation level and to recognize and treat withdrawal symptoms early are summarized in Table 12.

Recommendations for Sedation:

1- We recommend that sedation assessments of critically ill children in the pediatric intensive care unit be performed every 4-8 hours (STRONG RECOMMENDATION)

2- We recommend the use of comfort B or state behavioral scale (SBS) scales in the sedation assessment of intubated patients in the pediatric intensive care unit (STRONG RECOMMENDATION)

Table 10. Characteristics of sedative agents used in PICUs

Drug	Dose (mg/kg)	Beginning	Indication	Suggestion
Midazolom	Or, Rec: 0.5-0.75 IN, SL: 0.2-0.5 IV: 0.2 Inf: 0.05-0.6 mg/kg/h	2-3 min	Short intervention Prolonged mechanical ventilation	Tolerance Abstinence Liver and kidney failure, reduce dose Risk of hypotension with bolus dose
Lorezepam	IV loading: 0.02-0.06 Inf: 0.02-0.1 mg/kg/h	5-20 min	Prolonged mechanical ventilation Withdrawal syndrome	Limited
Propofol	IV loading: 2-3 Inf: 1-4 mg/kg/h	1-2 min	Short mechanical ventilation Short intervention	Propofol infusion syndrome Hypertriglycemia
Ketamine	IM: 3-5 IV loading: 1-3 Inf: 0.7-3 mg/kg/h	0.5-1	Short intervention During intubation in an acute asthma attack	Endogenous catecholamine release
Etomidate	IV 0.2-0.3	Immediately	Intubation in hemodynamic instability	Surrenal insufficiency
Thiopental	IV loading: 3-5 Inf: 1-5 mg/kg/h	Immediately	Intubation at ICP ↑	(-) Inotrope vasodilation
Dexmedetomidine	IV loading 1 µg/kg Inf: 0.2-1.0 µg/kg/h	2-5	Short intervention At withdrawal syndrome	
Chloralhydrate	OR, PR: 25-75 mg/kg	5-20	Short intervention	Agitation
Clonidine	OR, IV 1-4 µg/kg Inf: 0.1-02 µg/kg/h	5-20	Prolonged mechanical ventilation Withdrawal syndrome	At sudden withdrawal
Chlorpromazine	OR, PR: 0.5-1.5 mg/kg IV: 0.5 mg/kg	-	Agitation Delirium	Extrapyramidal reaction

ICP: Intracranial pressure, Clinics of Turkey; non-invasive and invasive mechanical ventilation special issue: Sedation and analgesia during non-invasive and invasive mechanical ventilation pages; 51-60

Table 11. Characteristics of analgesic drugs used in PICUs

Drug	Dose (mg/kg)	Beginning	Indication	Suggestion
Morphine	IV: 0.1-0.2 mg/kg Inf: 10-40 µg/kg/h	20	Mechanical ventilation Acute and chronic pain Pulmonary edema	Liver and kidney failure, reduce dose Histamine release Nausea and vomiting
Fentanyl	IV: 1-3 µg/kg Inf: 1-10 µg/kg/h	1-2	Short procedures Similar to morphine	Prolonged clearance Good hemodynamics Thoracic rigidity after rapid bolus
Remifentanil	IV: 1 µg/kg Inf: analgesic 0.5-6 µg/kg/s Sedation: 6-12 µg/kg/h	1	Mechanical ventilation Postoperative	Fast clearance Good hemodynamics Thoracic rigidity
Alfentanyl	IV: 15-25 µg/kg Inf: 0.4-2 µg /kg/h	1-2	Short procedure	High price Do not use in liver failure
Methadone	IV: 0.1-0.2 mg/kg/4-6 h	45	Withdrawal syndrome Chronic pain	Nausea and vomiting
Tramadol	IV: 1-2 mg/kg/4-6 h Inf: 0.2-0.4 mg/kg/h	10	Acute pain	Good hemodynamics Less respiratory depression
Paracetamol	IV 10-15 mg/kg/6 h	30	Moderate pain Hyperthermia	Hepatotoxicity

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3- We recommend that a written sedation protocol should be available for patients monitored on mechanical ventilators in the intensive care unit (STRONG RECOMMENDATION)

4- We recommend the use of dexmedetomidine and/or ketamine (STRONG RECOMMENDATION) in the first order and midazolam (WEAK RECOMMENDATION) in the second order as the first choice sedative agent in patients we monitor using non-invasive mechanical ventilation.

5- We recommend the use of midazolam or dexmethothimidine as the first choice sedative agent in intubated patients on mechanical ventilator (WEAK RECOMMENDATION)

6- We recommend adding a new agent in patients who are monitored on mechanical ventilator and who are not sufficiently sedated despite reaching the adequate dose for the agent we use (WEAK RECOMMENDATION). We recommend the use of ketamine as an adjuvant drug (STRONG RECOMMENDATION).

7- In patients intubated on mechanical ventilator, if only a sedative drug is used, we recommend adding a drug with analgesic effect to the treatment (STRONG RECOMMENDATION)

8- If you think that your team has sufficient experience and expertise, we recommend routine awakening on a daily basis in patients who are sedated in the intensive care unit (WEAK RECOMMENDATION)

9- We suggest that ketamine can be used in patients with increased intracranial pressure (WEAK RECOMMENDATION)

Recommendations for Pain/Analgesia

10- We recommend routine pain assessment in patients monitored in the intensive care unit (STRONG RECOMMENDATION)

11- We recommend that pain assessments be performed every 4-8 hours in patients monitored in the intensive care unit (STRONG RECOMMENDATION)

12- We recommend the use of the Wong-Baker face scale and visual analog scale (VAS) for pain assessment in patients aged 6 years and older who can communicate (STRONG RECOMMENDATION)

13- We recommend the use of FLACC and COMFORT- B facial scales for pain assessment in patients younger than 6 years of age or in patients who cannot communicate (STRONG RECOMMENDATION)

14- We recommend that a written protocol regarding analgesic applications in the intensive care unit be established/available (STRONG RECOMMENDATION)

15- We recommend the use of iv opioids as the primary analgesic in the treatment of moderate to severe pain in pediatric critically ill patients (STRONG RECOMMENDATION), and we recommend the use of fentanyl as the opioid agent of first choice (STRONG RECOMMENDATION).

16- We recommend that ketamine should be administered first as a sedoanalgesic agent in short-term interventions (catheter insertion, lumbar puncture, thoracic tube application, etc.) in pediatric patients who are extubated in the intensive care unit (STRONG RECOMMENDATION)

Table 12. Approach steps for ideal sedation in clinical practice

First step: Evaluate
Use a sedation scale with proven efficacy and train your nurses in its use
Determine the level of sedation every eight hours in a critically ill child
Define the targeted level of sedation in the patient according to individual needs, avoid excessive or inadequate sedation
Second step: Non-pharmacological treatment
Minimize stress by ensuring nurse care and parental presence
Third step: Pharmacological treatment
Titrate doses of sedative medications to provide the ideal level of sedation for the patient according to individual needs
Start with one drug
If under stress, add the second drug
If the goal of sedation level is not achieved, add one more drug. If there is no hemodynamic instability in the patient, increase the infusion rate of the drugs and make a bolus dose to reach the stable blood level quickly
Consider pentobarbital if adequate sedation is not achieved despite all medications. Stop other sedative drugs when pentobarbital is started
Fourth step: Discontinuation and delirium
Reduce doses of sedative drugs according to targeted sedation score
Assess withdrawal and delirium scores at regular intervals
If the patient has been sedated for more than five days, slowly reduce doses or add a long-acting oral medication
If delirium is diagnosed, consult with psychiatry
If antipsychotic treatment is needed, start with a low dose, increase slowly and monitor side effects

17- We recommend the use of dexmedetomidine and ketamine as sedative and sedoanalgesic if needed in patients with respiratory failure in the intensive care unit who are followed up with respiratory failure and YANKOT (STRONG RECOMMENDATION)

18- We recommend the use of Paracetamol or NSAIDs for mild-to-moderate pain in pediatric surgical patients followed postoperatively in the intensive care unit (STRONG RECOMMENDATION)

19- We recommend the use of Paracetamol or NSAIDs for mild to moderate pain in trauma patients monitored in the intensive care unit (STRONG RECOMMENDATION)

20- We recommend the use of Dexmedetomidine as the first line sedation and sedoanalgesic in postoperative cardiac surgery patients monitored in the intensive care unit (STRONG RECOMMENDATION)

21- In critically ill children being monitored in the intensive care unit, if sedative and analgesic drugs are used in the form of continuous infusion for more than 3-5 days and at high doses, we recommend that these drugs should be discontinued carefully and gradually decreased during the termination of treatment (STRONG RECOMMENDATION)

Recommendations for Withdrawal

22- We recommend that withdrawal assessment should be routinely performed in critically ill pediatric patients followed in the intensive care unit (STRONG RECOMMENDATION)

23- We recommend withdrawal assessment every 12-24 hours (STRONG RECOMMENDATION)

24- We recommend the use of the withdrawal assessment tool-1 (WAT-1) scale for withdrawal assessment in critically ill pediatric patients followed up in the intensive care unit (STRONG RECOMMENDATION)

25- We recommend the establishment of a written protocol to prevent the development or mitigate the effects of withdrawal (STRONG RECOMMENDATION)

26- We recommend opioid replacement therapy to alleviate opioid-related withdrawal symptoms, regardless of previous dose and/or duration or opioid exposure (WEAK RECOMMENDATION)

27- We recommend that non-pharmacologic methods (breastfeeding, swaddling, music, watching TV in appropriate patients, etc.) should be applied first to patients observed in the intensive care unit with withdrawal symptoms (STRONG RECOMMENDATION)

28- We recommend benzodiazepine replacement therapy to alleviate symptoms regardless of the benzodiazepine-related pre-withdrawal dose and/or duration of benzodiazepine exposure (WEAK RECOMMENDATION)

DELIRIUM

Delirium is a neuropsychiatric syndrome that can be triggered by various medical, surgical, pharmacologic and traumatic causes. While it can be seen at any age, it develops especially in critically ill patients. The pathogenesis has not yet been elucidated, but a decrease in acetylcholinergic activity is blamed. Patients should be evaluated carefully because iatrogenic withdrawal syndrome, excessive sedation and pain may be confused with the findings.[1,17,18]

While the frequency of delirium has been reported to be high in adult studies, the frequency of studies evaluating the frequency, management and long-term outcomes of delirium in children is increasing day by day. While delirium develops at a rate of 10-30% in pediatric intensive care units, this rate reaches 50% in patients receiving invasive mechanical ventilation support. There are various risk factors that may contribute to the development of delirium. Factors such as disease severity, age <5 years, mechanical ventilation, vasopressors, benzodiazepines, antiepileptic and narcotic agents, and physical restraint increase the risk of delirium.[18-20]

Various scoring systems have been produced to be used in screening for childhood delirium. Among these, the Cornell Assessment of Pediatric Delirium (CAP-D) scoring, which is most commonly used, has been presented as a Grade A recommendation by the European Society for Pediatric and Neonatal Intensive Care (ESPNIC). Patients with ≥9 points in CAP-D scoring are considered to have delirium (Table 13).[1,20]

There are three types of delirium: hypoactive, hyperactive and mixed. Hypoactive delirium is the most difficult type to diagnose; it needs to be differentiated from mood disorders, nonconvulsive status epilepticus and catatonia. The patient has slowed or infrequent speech, slow motor activity, lethargy, decreased awareness and apathy. In hyperactive delirium, hyperactivity, talkativeness, psychomotor agitation, irritability, paranoid delusions, and visual and auditory hallucinations may be observed. In mixed type delirium, findings of hypoactive and hyperactive delirium develop in the same patient.[21]

Delirium is controlled with the treatment of the underlying disease, psychosocial interventions and pharmacologic agents. The aim of treatment is to reduce agitation, treat psychosis, prevent harm, and increase comfort. Psychosocial practices constitute the most important step in the prevention and treatment of delirium. Reducing intensive care lighting at night to ensure the sleep cycle, waking children at the same time in the morning, placing the beds in a sitting position, preventing unnecessary alarm sounds of medical devices, providing television and tablets are environmental arrangements that can be applied. Allowing family members to stay with the patient, ensuring active participation of family members in the treatment process, bringing the child's favorite toys and

Table 13. Cornell assessment of pediatric delirium scoring

	Never 4	Rarely 3	Sometimes 2	Often 1	Always 0	Score
Does the child make eye contact with the caregiver?						
Are the child's actions purposeful?						
Is the child aware of his/her surroundings?						
Does the child communicate needs and wants?						
	Never 0	**Rarely 1**	**Sometimes 2**	**Often 3**	**Always 4**	
Is the child restless?						
Is the child inconsolable?						
Is the child underactive-very little movement while awake?						
Does it take the child a long-time to response to interactions?						
					Total	

photographs of family members, ensuring that they use glasses and hearing aids, and calling patients by their names are psychosocial interventions that can be implemented.[18-21]

Pharmacologic treatment should be applied in case of delirium that cannot be controlled with psychosocial interventions. Haloperidol (0.05-0.25 mg/dose for loading, 0.05-0.5 mg/kg/day 3-4 doses for maintenance) in hyperactive delirium and risperidone (0.1-0.2 mg/dose once daily for <5 years, 0.5-2.5 mg/day 2-4 doses for ≥5 years) in hypoactive delirium are recommended agents. However, patients on antipsychotic treatment should be carefully monitored for acute dystonia, swallowing problems, dysarthria, akathisia, neuroleptic malignant syndrome and QT prolongation. Cardiac side effects of antipsychotic treatment should be considered in patients with existing cardiac disease, and the necessity of treatment should be questioned. In patients who develop side effects, biperiden (50 mcg/kg, IV over 15 minutes) should be administered.[20-22]

The development of delirium increases the length of hospitalization, costs, morbidity and mortality. It has been shown to affect social life even after hospital discharge. Neurocognitive impairment may develop in the long term, and one third of patients develop post-traumatic stress disorder. Patients should be evaluated every 8-12 hours for delirium from the 24-48th hour of pediatric intensive care unit admission. Early recognition and treatment of delirium will increase the patient's compliance with treatment and decrease the duration of intensive care unit stay, morbidity and mortality.[20-23]

Recommendations for Delirium

29- We recommend that delirium evaluation should be performed routinely in critically ill pediatric patients followed up in the intensive care unit (STRONG RECOMMENDATION)

30- We recommend delirium assessment every 12-24 hours (STRONG RECOMMENDATION)

31- We recommend the use of the Preschool and Pediatric Confusion Assessment Methods (ps/pCAM- ICU) or Cornell Assessment for Pediatric Delirium (CAPD) scales as the most valid and reliable delirium monitoring tool for delirium assessment in critically ill pediatric patients followed up in the intensive care unit (STRONG RECOMMENDATION)

32- Given the potential patient benefit to reducing the incidence, duration and/or severity of delirium, we recommend non-pharmacological peripheral implementation strategies; such as optimization of sleep quality, and direct family involvement in patient care (STRONG RECOMMENDATION)

33- We recommend early mobilization if possible to reduce the development of delirium in critically ill pediatric patients followed in the intensive care unit (STRONG RECOMMENDATION)

34- We recommend minimizing the use of benzodiazepine-based sedation whenever possible in critically ill pediatric patients to reduce the incidence, duration and/or severity of delirium (STRONG RECOMMENDATION)

35- Considering possible drug side effects in critically ill pediatric patients with refractory delirium, we recommend that haloperidol or antipsychotics be considered for the treatment of severe delirium symptoms (WEAK RECOMMENDATION)

Environmental Optimization

The environment in the PICU can negatively affect patients during critical illness management and recovery. Although the technological environment of the PICU provides benefits in terms of biological balance, it also has negative physical and psychological effects. Critically ill infants and children are at high risk of developing stress-related behavioral disorders, and the PICU environment contributes significantly to these changes.

Although data on the effects of environmental optimization is limited, the risks of implementing such changes are generally low, with potentially beneficial effects for patients and their families. Providing family-centered care and sleep hygiene can contribute significantly to environmental optimization.[24]

Presence of the Family

Promoting an environment of parent and caregiver interaction with patient care is likely to directly benefit patients and may reduce parents' levels of stress and anxiety. Studies specific to pediatric intensive care show that when parents/caregivers are involved in family-centered care, their anxiety and stress levels are reduced, they are more satisfied with the care their child receives, and when they are allowed to be present for procedures or resuscitations, it helps the parent or caregiver to cope with the situation while maintaining both quality care and patient safety.[25,26]

The presence of parents or caregivers in the PICU during routine care and interventional procedures is recommended for providing comfort to the child, decreasing the stress and anxiety levels of parents and increasing the level of satisfaction with care.[1] However, we think that this is difficult to achieve under the current conditions in our country.

Sleep Hygiene

The environment directly affects the quality and quantity of a patient's sleep. Sleep deprivation is a major stressor reported by survivors of critical illnesses. In addition to patient-related factors such as the presence of invasive devices and procedures, the need for mechanical ventilation, immobility, drug effects and poorly controlled pain, environmental factors such as ambient noise and light levels can also negatively affect sleep.[1,27]

PICU teams are recommended to make environmental and/or behavioral changes to reduce excessive noise and thus improve sleep hygiene and comfort in critically ill pediatric patients.[4] To reduce the effect of ambient noise that cannot be changed, patients are recommended to use noise-reducing devices such as earplugs or headphones. Adjusting the lights in patient rooms in accordance with daylight and using a sleep mask may also contribute to sleep patterns.[1]

Early Mobilization

Early mobilization defines rehabilitation exercises of varying degrees as any passive or active activity that is initiated within the first 72 hours of the patient's admission to the pediatric intensive care unit, is clinically safe and appropriate to the patient's development, and aims to maintain or restore musculoskeletal strength and function. The feasibility of implementing early mobilization has been demonstrated in various ways in pediatric medical, neurological and postoperative patients, including cardiac ones.[28]

Mobilization of critically ill children is associated with potential risks and complications associated with central catheters, endotracheal tubes and other life-saving devices. Safety concerns often drive staff perceptions. Conditions such as hemodynamic instability, accidental tube dislodgement, and falls create anxiety in staff. It is important to educate all healthcare personnel who have a role in patient care about the harms of immobilization.[28-30]

Early mobilization is a complex and multi-step process that facilitates PICU culture. A multicomponent and interdisciplinary approach to early mobilization can be applied to minimize the effects of immobility in critically ill pediatric patients. Early mobilization planning that prioritizes patient safety, sedation minimization, delirium recognition and family participation should be encouraged.[28]

Recommendations for Optimization of the Environment

36. In the care of critically ill pediatric patients in the intensive care unit, we recommend the presence of a parent-caregiver during routine care in appropriate patients (STRONG RECOMMENDATION)

37. We recommend early mobilization to minimize the effects of immobility in critically ill children (STRONG RECOMMENDATION)

38. We recommend environmental and/or behavioral modifications to reduce excessive noise and thus improve sleep hygiene and comfort in the care of critically ill children in the intensive care unit (STRONG RECOMMENDATION)

39. To reduce the impact of ambient noise that cannot be modified, we recommend that patients wear noise-reducing devices such as earplugs or headphones (WEAK RECOMMENDATION)

40. Since the doses, duration of use and costs of sedative and analgesic agents used by providing an appropriate environment in the follow-up of critically ill children followed up in the intensive care unit will be significantly reduced, we recommend that the necessary importance should be given to environmental optimization (STRONG RECOMMENDATION)

Muscle Relaxants

Neuromuscular blockers are drugs that cause paralysis in skeletal muscles by blocking impulse transmission at the neuromuscular junction and do not have sedative, amnestic or analgesic properties. In intensive care, these agents are used for purposes other than intubation preparation, such as decreasing patient-ventilator incompatibility and intra-abdominal pressure in patients receiving mechanical ventilator support, and facilitating gas exchange by increasing chest wall compliance, decreasing the risk of barotrauma in the lungs, decreasing the contribution of muscles to oxygen

Table 14. Indications for the use of muscle relaxants during mechanical ventilation

To prevent patient ventilator incompatibility
To prevent hyper- or hypoventilation
In patients on non-conventional mechanical ventilation,
To reduce respiratory work and metabolic demand
In agitated patients who do not respond to maximum sedation and analgesia
During therapeutic hypothermia
To facilitate the treatment of increased intracranial pressure
Status epilepticus>facilitating treatment*

*: If continuous (24 hours) EEG monitoring is available, EEG: Electroencephalogram

consumption by preventing tremor, and limiting retching and consequently intracranial pressure. Muscle relaxants can be used as continuous infusions or intermittent doses. Since these agents do not have sedative and analgesic properties, sedative and analgesic agents should be used concomitantly. Hypo-hyperventilation is prevented with the administration of muscle relaxants; oxygen consumption decreases and gas exchange improves.[31,32] Indications for muscle relaxants during mechanical ventilation are given in Table 14.

Muscle relaxants are divided into two groups: Depolarizing and non-depolarizing. Succinylcholine is the only depolarizing agent available. This drug, which may have serious side effects, is contraindicated in some cases, and its use in pediatric intensive care is extremely rare because of the potential hazards (Table 15). Non-depolarizing muscle relaxants are used during mechanical ventilation in intensive care units. Non-depolarizing drugs are competitive antagonists of acetylcholine receptors. When they compete with acetylcholine and bind to the 2 alpha subunit of the acetylcholine receptor, they do not cause structural changes in the receptor and the ion channel in the middle is not opened.[31-33]

Therefore, acetylcholine cannot trigger contractions. The most commonly used of these are medium- and long-acting non-depolarizing muscle relaxants. In this group, d-tubocurarine, doxacurium and pancuronium are long-acting, while atracurium, cisatracurium, vecuronium and rocuronium are intermediate-acting. Tables 16 and 17 show the properties and potential side effects of non-depolarizing drugs.

Long-acting non-depolarizing drugs may cause hypotension and tachycardia-bradycardia. Doxacurium does not cause histamine release and has no harmful effects on the cardiovascular system. Pancuronium causes tachycardia, hypotension and increased cardiac output.

Medium-acting drugs are the most commonly used group of drugs during mechanical ventilation. Their effects start in 1-3 minutes and last for 30-60 minutes. Atracurium can cause histamine release and hypotension. When it causes histamine release, the patient develops itching and increased bronchial secretion and wheezing. Vecuronium is the most commonly used drug during mechanical ventilation in intensive care units. Unlike pancuronium, vecuronium does not cause

Table 15. Conditions in which succinylcholine is contraindicated

Burns 3 days to 6 months
Massive trauma: 3 days to 1 year
Stroke/paraplegia: 3 days to 1 year
Myotonia
Duchene muscular dystrophy
Friedreich's ataxia
Amyotropic lateral sclerosis
Multiple sclerosis
Guillain-Barré syndrome
Spinal cord trauma
Penetrating injuries of the ocular globe
History of malignant hyperthermia
Increased intracranial pressure
Chronic renal failure
Hyperkalemia
Prolonged effect expected due to pseudocholinesterase deficiency, hypomagnesemia, malnutrition and hepatic failure

histamine and catecholamine release. Cisatracurium is a steroisomer of atracurium and is 3-4 times more potent than atracurium in humans. Unlike atracurium, it does not cause histamine release.

If very high doses are not used, it does not change heart rate and blood pressure. Rocuronium has been increasingly used in intensive care units in recent years. Even very high doses do not cause histamine release and side effects in the cardiovascular system. Therefore, it can be used in very high doses.

There are a number of drugs that decrease and increase the effects of muscle relaxants. The interaction between muscle relaxants and other drugs should be well known in mechanically ventilated patients because they may increase the existing complications of muscle relaxants. Corticosteroids are the most frequently interacting agents with muscle relaxants, followed by other drugs. Drugs that antagonize or potentiate the effect of muscle relaxants are given in Table 18.

One of the biggest problems caused by muscle relaxants is muscle weakness. This problem is more common in patients with renal failure and in the female gender. Muscle weakness

Table 16. Dosage and duration of action of non-depolarizing muscle relaxants

Drug	Initial dose (µg/kg)		Infusion dose (µg/kg)		Start time of the effect (min)		Duration of clinical effect (min)		Time to return of clinical effects (min)	
	Infant	Older	Infant	Older	Infant	Older	Infant	Older	Infant	Older
Doxacurium	-	50	-	0.1-0.2	-	3-6	-	44	-	107
Pancuronium	100	150	0.4-0.6	0.5-0.1	2-5	2-4	-	24	-	33
Atracuronium	300	500	10-20	10-20	1-3	1-3	22	25	33	40
Vecuronium	100	150	1-1.5	1.5-2.5	-	1-3	-	22	73	35
Rokuronium	500	800	-	-	-	0.8-1.5	-	27	-	42

Table 17. Potential side effects of drugs used in mechanical ventilation

Drugs	Histamine release	Cholinergic properties	Ganglion blockade	Active metabolite	Prolonged blockage
Doxacurium	-	-	-	No	?
Pancuronium	-	Moderate	-	Yes	Yes
Atracuronium	Mild	-	Mild	No	Rarely
Vecuronium	-	-	-	Yes	Yes
Rokuronium	-	-	-	?	?
Cisatracurium	-	-	-	No	?

Table 18. Interaction of muscle relaxants with other drugs

Drugs/conditions that antogonize the effect	Drugs/conditions that potentiate the effect
• Hyperkalemia	• Inhalation anesthetics
• Alkalosis	· Antibiotics
• Phenytoin	· Vancomycin
• Carbamazepine	· Aminoglycosides
• Motor neuron lesions	• Others (clindamycin-tetracycline)
• Burn	• Antiarrhythmics
• Cerebral palsy	· Procainamide
• Sympathomimetic drugs	· Quinidine
• Theophylline	• β Adrenergic blockers
	• Calcium channel blockers
	• Hypermagnesemia
	• Local anesthetics
	• Myastenia gravis
	• Lithium carbonate
	• Diuretics
	· Furosemide
	· Thiazide
	• Cyclosporine

Table 19. Complications of muscle paralysis during mechanical ventilation

Complications caused by immobilization
Deep venous thrombosis and pulmonary embolism
Peripheral nerve injuries
Decubitus ulcer
Complications of cough reflex disappearance Secretion accumulation and atelectasis
Prolonged paralysis after muscle relaxant withdrawal
Resistant neuromuscular blockade
Steroid-related myopathy
Motor neuropathy **Neuromuscular dysfunction** **Central nervous system effects**

can easily develop in patients who use vecuronium for more than two days. This is caused by the active metabolite 3-deacetyl vecuronium. Besides myopathy, muscle relaxants can also cause motor neuropathy. Especially vecuronium and pancuronium used for a long-time can cause this condition. There is a loss of deep tendon reflexes and muscle wasting in the affected upper and lower extremities. Motor neuropathy is correlated with dose increase and duration. Another problem with muscle relaxants is prolonged paralysis. The risk factors for this are renal failure, female gender, concomitant use with high dose corticosteroids and high dose and prolonged use of muscle relaxants.[34-36] Other complications are given in Table 19.

Non-depolarizing Drugs

Short Effects

Mivacurium (Mivacron)

Since it is completely hydrolyzed in plasma by pseudocholinesterase, its duration of action is short. Mivacurium 0.2-0.25 mg/kg intravenously allows intubation within 1 minute and reverses its effect within 20 minutes. It is metabolized by plasma cholinesterases. Its effect may be prolonged in patients with severe renal or hepatic insufficiency due to plasma cholinesterase activity. It may cause histamine

release. Its typical uses are: Rapid sequential intubation or laryngospasm.

Moderate Effects

Vecuronium

It is an analog of pancuronium. When 0.1 mg/kg is used intravenously, it allows intubation within 1.5 minutes and reverses its effect within 20 minutes. At a dose of 0.4 mg/kg, the initial effect is shorter than 30 seconds, and the reversal time is within 90 minutes. In infants and newborns, this effect is longer. It is metabolized mainly in the liver. Metabolites accumulate in the presence of renal failure and prolonged paralysis. Its advantage is that it has few hemodynamic effects and does not cause tachycardia.

Atracurium

Like vecuronium, it is a moderately effective muscle relaxant. It is highly metabolized in circulation. It is metabolized in two different ways: Ester hydrolysis (non-specific esterases) and Hoffman elimination (spontaneous non-enzymatic chemical degradation at physiologic pH and temperature). Paralysis develops 2 minutes after intravenous administration of atracurium 0.4 mg/kg and reverses in 30 minutes. When metabolites accumulate, it causes central nervous system depression. High doses may cause histamine release, which may result in bronchospasm or hypotension. The duration of action may be prolonged in hypothermic and acidotic patients. It may form precipitate when administered intravenously with alkaline drugs such as thiopental.[1,37]

Long Effects

Pancuronium

An intravenous dose of 0.06-0.1 mg/kg causes paralysis within 3 minutes and reverses within 1 hour. It is primarily eliminated from the kidney, and its effect may be prolonged in renal failure. In hepatic failure, drug resistance may develop and prolong its effect. Tachycardia and hypertension are common side effects.

Metocurine

The dose of metocurine is 0.2-0.3 mg/kg. Its action and elimination are similar to pancuronium but without cardiovascular side effects.

Pipecuronium

It is a derivative of pancuronium and 20-30% more potent than pancuronium. It is preferred in operations that do not require early extubation that last >3-4 hours and requires cardiovascular stability because it has no vagolytic effect, does not affect the autonomic ganglia, and does not cause histamine release. It is not metabolized. Its main excretion is by the kidneys and to a lesser extent by the liver.[38] There are insufficient data on its pediatric use.

Reversing the Effects of Muscle Relaxants

When residual paralysis develops secondary to muscle relaxants, it is possible to antagonize their effects (e.g., extubation). For this, less than 90% of the receptors must be blocked.

Neostigmine 0.05-7 mg/kg or edrophonium 1 mg/kg combined with atropine 0.02 mg/kg or glycopyrrolate 0.01 mg/kg is used for this procedure, and reverses the effect of muscle relaxants in 10 minutes.[39]

Among the non-depolarizing muscle relaxants, the specific antagonist of vecuronium and rocuronium is Bridion (sugammadex), which is very effective in eliminating neuromuscular block, especially in non-intubated cases. If repeated applications of rocuronium and vecuronium are necessary in patients receiving Bridion, these applications should be performed after 24 hours, but if muscle relaxants are required before 24 hours, non-steroidal muscle relaxants (atracurium or cisatracurium) can be tried. Bridion is currently of limited use in children under two years of age due to a lack of sufficient data. It is recommended to use 2-4 mg/kg by dilution (1 mL drug + 9 mL saline) in the reversal of rocuronium-induced block only in children aged 2-17 years.[40]

Recommendations for Muscle Relaxants

41. We do not recommend the routine use of muscle relaxants in patients on Mechanical Ventilation in the intensive care unit (STRONG RECOMMENDATION).

42. If it is necessary to use muscle relaxants for various reasons (patient-ventilator incompatibility, to reduce work of breathing and metabolic demand in ARDS, bronchospasm, during rapid successive intubation, etc...) in patients undergoing mechanical ventilation in the intensive care unit, we recommend the use of rokuronium, vekuronium at the lowest required doses (STRONG RECOMMENDATION).

43. We recommend the use of bispectral index instead of validated clinical scoring tools to assess the depth of sedation in patients receiving muscle relaxants (STRONG RECOMMENDATION).

44. We recommend routine passive eyelid closure and use of lubricant to prevent corneal abrasions in critically ill pediatric patients receiving muscle relaxants (STRONG RECOMMENDATION).

As a result, it is the duty and obligation of all physicians and auxiliary health personnel working in these units to ensure the

correct sedation and analgesia application in the treatment management of the sick child hospitalized in the PICU, the use of appropriate muscle relaxants when necessary, the prevention and/or correct management of withdrawal and delirium pictures that may occur, and the correct arrangement of intensive care units in order for all these applications to be more effective under appropriate conditions, in other words, to ensure the correct "environmental optimization". When all these practices are carried out in accordance with certain standards based on up-to-date information, improvement and recovery in the clinical picture of the patient will be faster, unwanted situations and complications will be minimized, and the treatment and management of the patient will become easier for the intensive care team. We hope that the guideline we have prepared in order to organize all these practices and regulations in the most up-to-date and best conditions in the PICUs in our country will be a guide and will be beneficial to our patients by helping all healthcare professionals.

Ethics

Authorship Contributions

Concept: D.Y., Design: D.Y., Data Collection or Processing: G.B., E.K., A.K., Ü.A., Analysis or Interpretation: G.B., E.K., A.K., Ü.A., D.Y., Literature Search: G.B., E.K., A.K., Ü.A., Writing: G.B., E.K., A.K., Ü.A., D.Y.

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

Financial Disclosure: The authors declared that this study received no financial support.

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Case Report / Olgu Sunumu

DOI: 10.4274/cayd.galenos.2023.48568
J Pediatr Emerg Intensive Care Med 2024;11:77-80

Candida utilis: A Rare Cause of Septicemia in Two Immunocompetent Patients in the Pediatric Intensive Care Unit

Candida utilis: Çocuk Yoğun Bakım Ünitesinde İzlenen İki İmmünokompetan Hastada Nadir Bir Sepsis Etkeni

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Abstract

In recent years, an evident rise in the frequency of candidaemia caused by non-albicans Candida species has been reported. *Candida utilis* is a low-virulence fungus that is commonly used in the food processing industry. Only a few studies have reported invasive infection due to *C. utilis*. In this paper, we present two cases of clinically manifested candidaemia and sepsis caused by *C. utilis*. This was a retrospective study carried out at a tertiary intensive care center in Turkey. Two *C. utilis* were isolated from blood culture over a 6-month period. *C. utilis* fungemia has mainly been reported in immunocompromised patients, neonates, and following surgical intervention. The two cases discussed here did not have a defined immunodeficiency. Both patients had common risk factors such as prolonged stay in the pediatric intensive care unit and the presence of a central venous catheter. Our aim in reporting these cases is to highlight *C. utilis* as a probable cause of candidemia in hospitalized pediatric patients and can be mortal.

Keywords: Invasive fungal disease, *Candida utilis*, candidemia, sepsis, pediatric intensive care, children

Öz

Son yıllarda, albicans dışı Candida türlerinin neden olduğu kandidemi sıklığında belirgin bir artış bildirilmiştir. *Candida utilis*, gıda işleme endüstrisinde yaygın olarak kullanılan düşük virülanslı bir mantardır. Sadece birkaç çalışmada *C. utilis*'e bağlı invaziv enfeksiyon bildirilmiştir. Bu yazıda, *C. utilis*'in neden olduğu iki kandidemi/sepsis olgusunu sunuyoruz. Bu, Türkiye'de üçüncü basamak bir yoğun bakım merkezinde gerçekleştirilen geriye dönük bir çalışmadır. Altı aylık bir süre boyunca kan kültüründen iki *C. utilis* izole edildi. *C. utilis* fungemisi esas olarak bağışıklığı baskılanmış hastalarda, yenidoğanlarda ve cerrahi müdahaleyi takiben rapor edilmiştir. Burada tartışılan iki olguda tanımlanmış bir immün yetmezlik yoktu. Her iki hastada da çocuk yoğun bakım ünitesinde uzun süre kalma ve santral venöz kateter varlığı gibi ortak risk faktörleri vardı. Bu olguları bildirmekteki amacımız hastanede yatan çocuk hastalarda olası bir kandidemi nedeni olan ve ölümle sonuçlanabilen *C. utilis*'i vurgulamaktır.

Anahtar Kelimeler: İnvaziv fungal hastalık, *Candida utilis*, kandidemi, sepsis, çocuk yoğun bakım, çocuk

Introduction

Invasive fungal disease is a leading cause of death and morbidity in immunocompromised and hospitalized children. The incidence of candidaemia has been increasing during the past few decades.[1,2] Newborns and infants below the 3 months have an increased risk for candidaemia.[3] Here, we aimed to draw attention to this rare agent by discussing the characteristics of clinical findings and treatment of *Candida utilis* infections in pediatric patients.

Case Reports

Case 1: A 5-month-old male patient who had been coughing and wheezing for ten days and had been taking oral antibiotics for five days was admitted to the pediatric intensive

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Received/Geliş Tarihi: 14.06.2022 **Accepted/Kabul Tarihi:** 13.08.2023

care unit (PICU) due to pneumonia and respiratory distress. Regarding his medical history, he was born at 34 weeks, was hospitalized in neonatal intensive care for three months, and was diagnosed with bronchopulmonary dysplasia. On admission to PICU, he had a fever (axillary temperature 38.7 °C), oxygen saturation of 70%, a heart rate of 160/per minute, tachypnea, common crepitant rales, and drowsy consciousness. PRISM score was 28. We intubated the patient with cyanosis and carbon dioxide retention and placed them on a mechanical ventilator. We initiated empirical piperacillin tazobactam treatment. His echocardiography was normal, and pulmonary hypertension was not detected. According to the blood gas analysis, mechanical ventilator support was gradually increased so that the peak inspiratory pressure was 30 mmHg. Amikacin was started on the 5th day of his admission to the patient, who had a high fever. A furosemide infusion was started due to pretibial edema. He was extubated on the 12th day, and nasal high-flow oxygen was given. Due to peripheral vascular access problems, a central venous catheter has been inserted into the right jugular vein on the 15th day of hospitalization. liposomal amphotericin B (3 mg/kg per day i.v.) was started on the 23rd day because of the presence of a candida signal in the blood culture of the patient with resistant fever and thrombocytopenia (caspofungin was not available in our hospital at the time). Galactomannan antigen was negative. The patient, whose general condition worsened and oxygen saturation decreased to 70-75%, was re-intubated on the 27th day. Due to septic shock, we started an adrenaline infusion. Serum C-reactive protein (CRP) level was 96 mg/L and procalcitonin was 0.5 ng/mL. *Candia utilis* obtained in catheter blood culture (antifungal susceptibility MIC: fluconazole 1, caspofungin ≤0.12, micafungin ≤0.06, voriconazole ≤0.12, amphotericin B ≤0.25). He had full enteral nutrition and no need to use total parenteral nutrition. Ejection fraction 65%, good contraction, no thrombus or verruca in echocardiography. The central venous catheter was removed. The thorax computerized tomography examination revealed chronic changes and pneumonic infiltrations in the lower lobe of the left lung, which was performed due to a history of three previous hospitalizations for pneumonia. Serum immunoglobulin levels and T lymphocyte subgroups were in the normal range for age. After 10 days of liposomal amphotericin B treatment, the blood cultures showed no signs for microorganisms. Liposomal amphotericin B treatment had to be continued for another 15 days, for a total of 25 days of treatment. During the follow-up, the patient's septic findings regressed, and he was extubated on the 36th day of hospitalization, followed by discharge from the PICU on the 42nd day.

Case 2: A 4-month-old girl with no previous health problems, was admitted to the PICU after being hospitalized for 2 days with a diagnosis of pneumonia and undergoing intubation due to respiratory arrest. The patient has severe pediatric acute respiratory distress syndrome (pARDS) with an oxygen saturation of 70%, PaO_2/FiO_2 of 90, bilateral diffuse infiltration, and pulmonary edema on a chest X-ray. Prone position, high positive end-expiratory pressure (14 mmHg), and empirical piperacillin-tazobactam were started. An adrenaline infusion was started for hypotension, and its dose was titrated. We inserted a central venous catheter into the right jugular vein on the first day. The PRISM score was 35. Echocardiography revealed no pathology except for a small central muscular atrial septal defect. We provided early enteral feeding. Vancomycin was added to the treatment of the patient whose CRP elevation continued on the 6th day of his hospitalization, and her general condition was poor. No pathogen was detected in blood culture or a respiratory viral panel at admission. Severe acute respiratory syndrome-coronavirus-2 RNA test was negative on the nasopharyngeal swab by polymerase chain reaction. On the 11th day of hospitalization, her oxygenation improved, and ventilator support was reduced. After a successful spontaneous breathing test, we extubated the patient. However, the patient required re-intubation after 2 hours due to tachypnea and oxygen saturation not exceeding 80%. On the 15th day of hospitalization, a chest tube was placed in the right lung due to pneumothorax. On the 22nd day of hospitalization, caspofungin acetate (loading dose 70 mg/m^2, maintenance dose 50 mg/m^2 per day i.v.) was administered to the patient whose yeast signal in blood culture was detected. *C. utulis* have been reported in both catheter blood and endotracheal aspirate cultures (antifungal susceptibility MIC: fluconazole 1, caspofungin ≤0.12, micafungin ≤0.06, voriconazole ≤0.12, and amphotericin B ≤0.25). *C. utilis* have been reported in two blood cultures taken every 3 days. There was a bilateral ground-glass density appearance in the chest X-ray of the patient, and her oxygen saturation was 66%. In laboratory tests, respiratory acidosis (pH 7, PaO_2 60 mmHg, $PaCO_2$ 88 mmHg, lactate 4 mmol/L), creatinine 1.32 mg/dL, urea 178 mg/dL, thrombocytopenia (83.103/uL), CRP 42 mg/L, procalcitonin 0.6 ng/mL, liver enzymes, and electrolyte values were within the normal limit. We performed continuous veno-venous hemodialysis on the patient, who had edema throughout the body and inadequate urine output with a diuretic. However, our patient died due to candida septicemia and pARDS on the 28th day of her hospitalization.

Methods

The patients' blood cultures in a BACTEC 9050 system (Becton Dickinson) using BACTECPedsPlus/F culture vials. The isolates were identified using the ID 32 C yeast identification

method from BioMérieux, as well as by their morphology on cornmeal agar. *In vitro* antifungal susceptibility testing using the ATB FUNGUS 3 (bioMérieux) microdilution method have been used. Interpretation of the results based on the recommendations provided by the Clinical and Laboratory Standards Institute.

Discussion

Candida species are responsible for around 70-90% of invasive fungal infections and are the primary cause of fungal infections in patients referred to the PICU. Invasive candidiasis has a significant mortality rate, ranging from 40% to 60%. There are a substantial number of clinical trials about bloodstream infections (candidemia) caused by *Candida* spp. in the literature. There are at least 15 candida species that induce infections in humans, with five species accounting for over 90% of invasive infections: *C. albicans, C. glabrata, C. tropicalis, C. parapsilosis,* and *C. krusei*. Based on these trials and studies on the epidemiological characteristics of candidemia, it has been found that non-albicans Candida species make up over 50% of the isolates in individuals with candidemia.[4,5]

Candida utilis is renowned for its fermentation capabilities in the food industry.[6] Infrequently, *C. utilis* causes fungemia. It is exceptionally rare to isolate it from superficial clinical specimens. The occurrence of it in the gastrointestinal system of hospitalized individuals is infrequent rare.[7,8] Alsina et al.[7] documented the occurrence of catheter-associated fungemia. Gaisne et al.[9] documented a case of *C. utilis* fungemia in a patient who had received a solid organ transplant. The fungemia was successfully managed with micafungin as a treatment. Another case was a 68-year-old individual afflicted with Alzheimer's disease who was admitted due to neurological problems and a persistent fever. However, it is worth noting that this patient did not exhibit neutropenia or have a central venous catheter (CVC).[10] The remaining three occurrences were fungemia associated with CVCs.[7,11,12]

In previously neutropenic or immunosuppressive patients, while candidemia is more common, diagnostic possibilities are also increased; it is now frequently encountered in individuals without an underlying disease. Mechanical ventilatotion, delays in enteral feeding, and the use of broad-spectrum antibiotics increase this possibility of candidemia in the PICU.[4,5] Additional factors that increase the likelihood of a condition include the use of antineoplastic drugs and the patient's impaired immune system.[2] Both of our hospitalized children in the critical care unit exhibited risk characteristics such as extended hospitalization in the PICU, CVC, and antibiotic medication. Our first patient, who was delivered preterm, required an extended period of hospitalization in the neonatal critical care unit. Both of our patients had early enteral feeding (within 24-48 hours) and did not have neutropenia. Lukić-Grlić et al.[13] documented three patients of clinically evident candidaemia caused by *C. utilis* who were admitted to the neonatal intensive care unit. The risk factors reported for three cases of newborns include antibiotic medication, total parenteral nutrition, anti-ulcer prophylaxis, CVC, receiving a surgical operation at delivery, and mechanical ventilation. All patients got better and no longer had any *C. utilis* in their blood after taking liposomal amphotericin B or caspofungin. The Infectious Diseases Society of America guidelines suggest using echinocandin drugs (such as caspofungin, micafungin, and anidulafungin) as the initial treatment for invasive candidiasis. If there is intolerance, limited availability, or resistance to existing antifungal drugs, the lipid formulation amphotericin B at a dosage of 3-5 mg/kg daily is an alternative. Fluconazole can be used as an alternative if the patient is not in severe condition and is unlikely to have a fluconazole-resistant *Candida* species.[5] In our first case, we administered liposomal amphotericin B, while in case 2, we used caspofungin. The *C. utilis* strain obtained from our patients showed minimal inhibitory concentrations of <0.25 µg/ml for amphotericin B and ≤0.12 µg/mL for caspofungin. We showed that *C. utilis* was susceptible to both medications. In our study, *C. utilis* was the single cause of the bloodstream infection in two cases. The duration of candidaemia in our patients was between 22 and 23 days. We obtained a sterile blood culture in our first case, but we did not have a sterile blood culture because we lost our second case on the 28th day of hospitalization. The limitation of this report is in the restricted number of cases and the retrospective assessment conducted inside a single center.

Conclusion

By presenting these cases, our intention is to point out *C. utilis*, a low-virulent Candida species, as a possible cause of candidaemia that can be fatal among hospitalized immunocompetent pediatric patients.

Ethics

Informed Consent: Retrospective study.

Authorship Contributions

Concept: E.K., T.E., Design: E.K., Data Collection E.K., Literature Search: E.K., Writing: E.K., T.E.

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

Financial Disclosure: The authors declared that this study received no financial support.

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Case Report / Olgu Sunumu

DOI: 10.4274/cayd.galenos.2023.89266
J Pediatr Emerg Intensive Care Med 2024;11:81-4

A Case of Acute Necrotizing Encephalopathy Associated with SARS-CoV-2 on the Background of Takayasu's Arteritis and Intensive Care Management

Takayasu Arteriti Zemininde SARS-CoV-2 İlişkili Akut Nekrotizan Ensefalopati Gelişen Bir Hasta ve Yoğun Bakım Takibi

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Abstract

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) typically leads to mild infectious disease in children, although both acute infection and multisystem inflammatory syndrome in children can cause severe complications. Additionally, SARS-CoV-2 is a neurotropic virus that can present with a wide spectrum of neurological symptoms. Acute necrotizing encephalopathy of childhood (ANE) is a rare acute encephalitis characterized by symmetrical lesions in the thalamus with variable involvement of the white matter, brainstem, and cerebellum. It usually develops after viral infection in genetically predisposed patients. Although the prognosis is poor, some patients respond to steroid and intravenous immunoglobulin (IVIG) treatment. In this case report, we present the case of an 11-year-old patient with no previously known disease who developed SARS-CoV-2-related ANE that did not respond to steroid and IVIG treatment. Our patient was incidentally diagnosed with Takayasu arteritis, and brain death occurred in the 32nd hour of admission.

Keywords: SARS-CoV-2, acute necrotizing encephalopathy, Takayasu arteritis

Öz

Şiddetli akut solunum sendromu-koronavirüs-2 (SARS-CoV-2) literatürde genellikle çocuklarda hafif bir bulaşıcı hastalık seyrine yol açar, ancak hem akut enfeksiyon hem de çocuklarda multisistem enflamatuvar sendrom ciddi komplikasyonlara neden olabilir ayrıca nörotropik bir virüs olup geniş bir spektrumda nörolojik semptomla prezente olabilir. Çocukluk çağının akut nekrotizan ensefalopatisi (ANE), talamusta tipik, simetrik lezyonlarla, beyaz cevher, beyin sapı ve serebellumun değişken tutulumuyla karakterize, nadir bir akut ensefalittir. Genetik olarak yatkın hastalarda genellikle viral enfeksiyon sonrası gelişebilir. Hastalığın prognozu kötü olmakla beraber bazı hastalarda steroid ve intravenöz immünoglobulin (IVIG) tedavisine yanıt alınmaktadır. Olgu olarak daha önce bilinen bir hastalığı olmayan 11 yaşında SARS-CoV-2 ile ilişkili ANE gelişen, steroid ve IVIG tedavisine yanıt vermeyen, başvurusunun 32. saatinde beyin ölümü gerçekleşen ve insidental olarak Takayasu arteriti tanısı alan hasta sunulmuştur.

Anahtar Kelimeler: SARS-CoV-2, akut nekrotizan ensefalopati, Takayasu arteritis

Introduction

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) usually leads to a mild course of infectious disease in children than in adults, but acute infection and multisystem inflammatory syndrome can cause serious complications. Neurological symptoms are predominantly reported in adults, ranging from mild headaches to seizures, peripheral neuropathy, stroke, demyelinating disorders, and encephalopathy. Acute

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Received/Geliş Tarihi: 02.03.2023 **Accepted/Kabul Tarihi:** 06.09.2023

necrotizing encephalopathy (ANE) of childhood is a rare disease usually characterized as acute encephalitis by typical, symmetrical lesions in the thalamus, white matter, brainstem, and cerebellum. It can usually develop after viral infection in genetically predisposed patients. Although the prognosis of the disease is poor, some patients benefit from steroid and IVIG treatment. Here, we present a patient who developed SARS-CoV-2-associated ANE and did not benefit from any treatment. The patient died at 32 hours of hospitalization and was diagnosed incidentally with Takayasu's arteritis.

Case Report

An 11-year-old male patient with no known disease before complained of high fever, weakness, and headache for two days. He was admitted to the hospital with generalized tonic-clonic seizures on the second day of his symptoms. Due to the patient being of foreign nationality, there is no record within Turkey's vaccination program, and there is no available information regarding their vaccination status abroad. In the emergency department, midazolam was used to the patient due to his seizure; the patient was unconscious, had shallow breathing, and was intubated in the emergency department. In addition, inotropic support was started for fluid-resistant hypotension.

Hypodense areas and signs of cerebral edema were detected on non-contrast cranial computer tomography (CT), and the patient was pre-diagnosed with encephalitis, so anti-edema treatment, ceftriaxone, vancomycin, and oseltamivir started. In the first physical examination after admission to our intensive care unit, his pupils were fixed and dilated, Glasgow Coma scale was 3, and he had no brainstem reflexes.

Cranial magnetic resonance imaging (MRI) showed diffuse, symmetrical edema and signal changes consistent with pathological contrast enhancement in the thalamus, both sides of the cerebral crus of the mesencephalon, and in the pons at the 6th hour of admission to the intensive care unit (Figure 1A, B, E, F-H) and diffusion-weighted MRI showed diffusion restriction only in a focal area in the pons (Figure 1C, D). IVIG and pulse methylprednisolone treatment was started for the patient prediagnosed with ANE.

In cranial CT angiography, diffuse cerebral edema, tonsillar herniation, fourth ventricular hemorrhage, and absence of intracranial blood flow supported brain death. In the arterial phase of CT angiography, concentric stenosis areas and enlargements in the lumen of the left vertebral artery, subclavian artery, left common carotid artery, and cervical segment of the internal carotid arteries on both sides and concentric wall thickening in the stenosis areas were observed (Figure 1I). In addition, there was extravasation and pseudoaneurysm appearance from the left vertebral artery (Figure 1I).

Takayasu arteritis (TA) was considered in the radiological findings. Thoracic abdominal computed tomography also showed a slight increase in vessel wall thickness supporting vasculitis in the thoracic aorta, which is more prominent in the supra-aortic branches. In the viral serology tested for the etiology of acute necrotizing encephalopathy, Coronavirus disease-2019 (COVID-19) IgG, and also the SARS-CoV-2 polymerase chain reaction of the patient was positive (Table 1).

The patient, who developed multiple organ failure secondary to hyper inflammation, died at the 12th hour of his admission to the intensive care unit. In light of this information, the patient was diagnosed with ANE and multi-organ failure due to SARS-CoV-2, which developed underlying Takayasu arthritis.

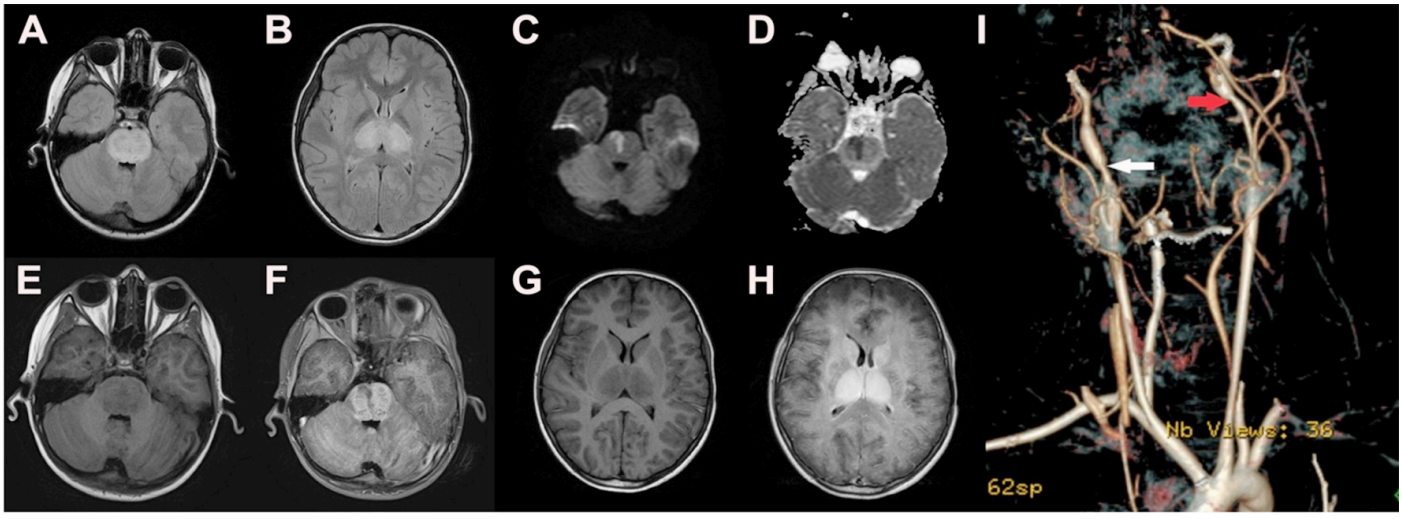

Figure 1. A, B) Diffuse edema in the pons, thalamus, C, D) Diffusion restriction in the pons, E-G) Hypointensity due to edema in the pons, thalamus, caudate nucleus, F-H) Diffusion-limiting area in the thalamus, caudat nucleus, I) Stenosis in both internal carotid arteries

Table 1. Laboratory test findings

Laboratory parameters	Value	Normal range
White blood cell	20.76x10^9/L	4.8-12x10^9/L
Absolute neutrophil count	19.29x10^9/L	1.7-8.1x10^9/L
C-reactive protein	304 mg/L	0-5 mg/L
Interleukin-6	5297.8 pg/mL	0-3.4 pg/mL
Creatinine	2.01 mg/dL	0.4-0.8 mg/dL
Aspartate aminotransferase	23672 U/L	0-37 U/L
Alanine transaminase	9387 U/L	0-32 U/L
Lactate dehydrogenase	17913 U/L	0-298 U/L
Sodium	155 mEq/L	132-146 mEq/L
Brain natriuretic peptide	19083 ng/L	<125 ng/L
Troponin I	>25000 ng/L	<45 ng/L
D-dimer	>10000 ng/mL	<500 ng/mL
Ammonia	228 µmol/L	11.2-35.4 µmol/L
Post-mortem lumbar puncture cerebrospinal fluid parameters	White blood cell: 40 cells/mm^3 Red blood cell: 10,720 cells/mm^3 Protein: >2.500 mg/L Glucose: 70 mg/dL	
Cerebrospinal fluid, polymerase chain reaction test, and culture	Negative	
RANBP2, the mitochondrial disease-specific mutation in exome analysis	Negative	
Metabolic test for inherited metabolic disease	Negative	

Discussion

We present a patient with SARS-CoV-2 related ANE and incidentally diagnosed with TA, who did not benefit from steroid or IVIG treatment, and at the 32nd hour of the hospital administration, brain death occurred. It was aimed to draw attention to the relationship of ANE with SARS-CoV-2 and to elucidate the underlying mechanisms in an undiagnosed and untreated patient with vasculitis that may cause high mortality. The vascular endothelium plays a role in regulating vascular tone in addition to maintaining vascular hemostasis. Therefore, endothelial dysfunction is the primary determinant of microvascular dysfunction. In the literature, it has been shown that SARS-CoV-2 causes direct viral infection and diffuse endothelial inflammation in the endothelial cells.[1]

SARS-CoV-2 infection can cause primer pulmonary disease and complications, venous thromboembolism, acute kidney, and liver injury, cytokine release, septic shock, disseminated intravascular coagulation, and neurological complications.[2] However, most neurological complications result from the systemic effects of SARS-CoV-2, such as cytokine release, immune-mediated inflammatory syndromes, and hypercoagulability.[3]

Maury et al.[4] reported neurologic symptoms in 73% of hospitalized COVID-19 patients, 13-40% had non-specific encephalopathy, less commonly acute demyelinating encephalomyelitis (n=13), and 4 of the patients diagnosed with ANE.ANE is a parainfectious disease primarily reported in pediatric patients. The autopsy of a patient with ANE showed no cellular inflammatory response in areas of necrosis.[5] However, it is accepted that immune-mediated, uncontrolled inflammation after viral infections may cause ANE. There is no standard treatment for ANE, and in the case series of Vanjare et al.[6] ANE, related mortality was reported as 40%; limited studies show that using anti-virals, IVIG, and steroids may increase the effectiveness of the treatment.There are limited cases of COVID-19-associated ANE, and only one resulted in death.[7] Therefore, we think that the rapid progression of the disease in our patient cannot only be explained by the combination of SARS-CoV-2 and ANE. Furthermore, it is considered that accompanying vasculitis may have changed the prognosis of the disease.

TA is a rare idiopathic granulomatous vasculitis in children. The systemic inflammatory response often may not correlate with the vessel wall's inflammatory process. Skipping lesions in affected segments and intact segments seen together along the artery in our patient is characteristic of TA. Although the earliest detectable lesion by imaging methods is localized narrowing or irregularity in the arterial lumen, our patient's stenosis and aneurysm formation may indicate the chronicity of the disease. Since it is not a common vasculitis, clinicians often do not consider TA in the differential diagnosis, and the diagnosis can take even years after the first onset of symptoms.[8]

In this paper, we offer a compelling clinical scenario that describes the development of ANE as a result of SARS-CoV-2

infection in a patient suffering from Takayasu's arteritis, a rare autoimmune vasculitis. This case serves as an illustration of the complex interactions between Takayasu's arteritis, viral infection, and the emergence of severe necrotizing encephalopathy.

Conclusion

The given case demonstrates the necessity for increased awareness and varied management techniques due to the complex relationship between Takayasu's arteritis, SARS-CoV-2 infection, and the resulting severe necrotizing encephalopathy.

This report meets with ethical standards by including informed consent, author contribution clarification, a statement of no conflict of interest, and an assurance that no financial disclosures were made. This commitment emphasizes the equality of all contributions and the lack of external funding.

Ethics

Informed Consent: Informed consent was obtained.

Authorship Contributions

Surgical and Medical Practices: E.U., B.Ç.A., R.B., A.Ö.P., S.Ö., O.P., E.K., S.E., Concept: E.U., G.G., Design: E.U., G.G., Analysis or Interpretation: E.U., B.Ç.A., R.B., A.Ö.P., S.Ö., O.P., E.K., S.E., Literature Search: E.U., G.G., B.Ç.A., R.B., A.Ö.P., S.Ö., O.P., E.K., S.E., Writing: E.U., G.G.

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

Financial Disclosure: The authors declared that this study received no financial support.

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