TÜRK YOĞUN BAKIM DERGİSİ

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AMAÇ VE KAPSAM

Türk Yoğun Bakım Dergisi (eski adı Türk Yoğun Bakım Derneği Dergisi ISSN: 2146-6416), Türk Yoğun Bakım Derneği'nin süreli yayın organı olup yoğun bakım içerikli, yayın dili Türkçe ve İngilizce olan, bağımsız ve önyargısız hakemlik ilkelerine dayanan ulusal, periyodik bir dergidir. Türk Yoğun Bakım Dergisi Mart, Haziran, Eylül, Aralık aylarında olmak üzere yılda dört sayı çıkar. Ayrıca yılda bir kez özel sayı yayınlanır.

Türk Yoğun Bakım Dergisi'nin hedefi nitelikli, sürekli ve yoğun bakım konusunda özgün bir periyodik olarak klinik ve bilimsel açıdan en üst düzeyde derlemeler, olgu sunumları ve araştırmalar yayınlamaktır. Dergi, yoğun bakım alanı ile ilgili olan hekimler, anestezistler, cerrahlar, pediatristler ve bu alanla ilgili diğer uzmanlara yöneliktir.

Türk Yoğun Bakım Dergisi, **Emerging Sources Citation Index (ESCI), ProQuest Health & Medical Complete, EBSCO Database, Gale, Index Copernicus, CINAHL, Tübitak/Ulakbim, Türk Tıp Dizini, Türkiye Atıf Dizini, Hinari, GOALI, ARDI, OARE, AGORA, J-Gate, IdealOnline** ve **Türk Medline**'da indekslenmektedir.

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Dergide açık erişim politikası uygulanmaktadır. Açık erişim politikası Budapest Open Access Initiative (BOAI) http://www.budapestopenaccessinitiative.org/ kuralları esas alınarak uygulanmaktadır.

Açık Erişim, "[hakem değerlendirmesinden geçmiş bilimsel literatürün], İnternet aracılığıyla; finansal, yasal ve teknik engeller olmaksızın, serbestçe erişilebilir, okunabilir, indirilebilir, kopyalanabilir, dağıtılabilir, basılabilir, taranabilir, tam metinlere bağlantı verilebilir, dizinlenebilir, yazılıma veri olarak aktarılabilir ve her türlü yasal amaç için kullanılabilir olması"dır. Çoğaltma ve dağıtım üzerindeki tek kısıtlama yetkisi ve bu alandaki tek telif hakkı rolü; kendi çalışmalarının bütünlüğü üzerinde kontrol sahibi olabilmeleri, gerektiği gibi tanınmalarının ve alıntılanmalarının sağlanması için, yazarlara verilmelidir.

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AIMS AND SCOPE

Turkish Journal of Intensive Care (formerly called Journal of the Turkish Society of Intensive Care ISSN: 2146-6416) is the periodical of the "Turkish Society of Intensive Care" and it covers subjects on intensive care, being published in Turkish and English languages, and is an independent national periodical based on unprejudiced peer-review principles. Turkish Journal of Intensive Care is regularly published four times a year; in March, June, September and December In addition, an annual special issue is published.

The aim of the Turkish Journal of Intensive Care is to publish original periodic research papers of highest scientific and clinical value on intensive care, reviews, case reports. It is directed towards for interested in intensive care, physicians, anesthesists, surgeons, pediatricians, and any other specialists concerned with these fields.

Turkish Journal of Intensive Care is indexed in **Emerging Sources Citation Index (ESCI), ProQuest Health & Medical Complete, EBSCO Database, Gale, Index Copernicus, CINAHL, Tübitak/Ulakbim Turkish Medical Database, Turkiye Citation Index, Hinari, GOALI, ARDI, OARE, AGORA, J-Gate, IdealOnline** and **Turk Medline**.

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YAZARLARA BİLGİ

Türk Yoğun Bakım Dergisi, Türk Yoğun Bakım Derneği'nin yayın organıdır. Dergi dört ayda bir (Nisan, Ağustos, Aralık) yayınlanan bağımsız, uluslararası hakemli bir dergidir.

Türk Yoğun Bakım Dergisi'ne gönderilen yazılar çift-kör hakemliğe tabi tutulur. Dergi Türkçe ve İngilizce dillerinde makaleler yayınlar.

Türk Yoğun Bakım Dergisi'nin kısa adı "Turk J Intensive Care"dir. Kaynaklarda kullanılırken bu şekilde belirtilmelidir.

Yoğun bakım alanına ilişkin özgün deneysel ve klinik araştırmaları, olgu sunumlarını, yayın kurulu kararı ile istenmiş derlemeleri, editöryal yorumları, editöre mektupları ve ulusal yoğun bakım kongrelerinde sunulan bildiri özetlerini yayımlar. Dergide yayınlanacak yazıların seçimine temel teşkil eden hakem heyeti, dergide belirtilen danışmanlar ve gerekirse yurt içi/dışı otörler arasından seçilir.

Türkçe yazılarda Türk Dil Kurumu'nun Türkçe Sözlüğü ve Yazım Kılavuzu temel alınmalıdır.

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Türk Yoğun Bakım Dergisi makale başvuru ücreti ve ya makale işlem ücreti uygulamamaktadır.

Yazılar sadece online olarak kabul edilmektedir. Yazarların makale gönderebilmesi için web sayfasına (http://www.journalagent.com/tybdd/) kayıt olup şifre almaları gereklidir. Bu sistem online yazı gönderilmesine ve değerlendirilmesine olanak tanımaktadır.

Makale gönderimi yapılırken sorumlu yazarın ORCID (Open Researcher and Contributor ID) numarası belirtilmelidir. http://orcid.org adresinden ücretsiz olarak kayıt oluşturabilir.

Bu sistem ile toplanan makaleler International Committee of Medical Journal Editors (ICMJE), Index Medicus (Medline/PubMed) ve Ulakbim-Türk Tıp Dizini kurallarına uygun olarak sisteme alınmakta ve arşivlenmektedir.

Yayına kabul edilmeyen yazılar, sanatsal resimler hariç geriye yollanmaz.

Editör veya yardımcıları tarafından, etik kurul onayı alınması zorunluluğu olan klinik araştırmalarda onay belgesi (etik onay numarası ile birlikte), talep edilmektedir. Yazıların içeriğinden ve kaynakların doğruluğundan yazarlar sorumludur.

Yazarlar, gönderdikleri çalışmanın başka bir dergide yayınlanmadığı ve/veya yayınlanmak üzere incelemede olmadığı konusunda garanti vermelidir. Daha önceki bilimsel toplantılarda 200 kelimeyi geçmeyen özet sunumlarının yayınları, durumu belirtilmek koşulu ile kabul edilebilir. Tüm otörler bilimsel katkı ve sorumluluklarını bildiren toplu imza ile yayına katılmalıdırlar.

Hastalar mahremiyet hakkına sahiptirler. Belirleyici bilgiler, hasta isimleri ve fotoğraflar, bilimsel olarak gerekli olmayan durumlarda ve hasta (ebeveyn veya koruyucu) tarafından yayınlanmasına yazılı olarak bilgilendirilmiş bir onay verilmediği sürece yayınlanmamalıdır.

Bu amaçla, bilgilendirilmiş onay, hastanın yayınlanacak belirli bir taslağı görmesini gerektirir. Eğer gerekli değilse hastanın belirleyici detayları yayınlanmayabilir. Tam bir gizliliği yakalamak oldukça zordur ancak eğer bir şüphe varsa, bilgilendirilmiş onay alınmalıdır. Örneğin, hasta fotoğraflarında göz bölgesini maskelemek, yetersiz bir gizlilik sağlanmasıdır.

Yazarlar, takip edilen standartların, insan deneylerinden sorumlu komitenin (kurumsal ve ulusal) etik standartlarına ve 2013'de gözden geçirilmiş 1964 Helsinki Beyannamesine uygun olduğunu belirtmelidirler. Deney hayvanı ile olan çalışmalarda, yazarlar takip edilen standartların hayvan haklarına (laboratuvar hayvanlarının bakım ve kullanımı için rehber www.nap.edu/catalog/5140.html) uygun olduğunu ve hayvan etik komitesinin onayını aldıklarını belirtmelidirler. Etik kurul onayı ve bilgilendirilmiş onam formu alındığı araştırmanın "Gereç ve Yöntem" bölümünde belirtilmelidir.

Yazıların bilimsel ve etik sorumlulukları yazarlara, telif hakkı ise Türk Yoğun Bakım Dergisi'ne aittir. Yazıların içeriğinden ve kaynakların doğruluğundan yazarlar sorumludur. Yazarlar, yayın haklarının devredildiğini belirten onay belgesini (Yayın Hakları Devir Formu) yazıları ile birlikte göndermelidirler. Bu belgenin tüm yazarlar tarafından imzalanarak dergiye gönderilmesi ile birlikte yazarlar, gönderdikleri çalışmanın başka bir dergide yayınlanmadığı ve/veya yayınlanmak üzere incelemede olmadığı konusunda garanti vermiş, bilimsel katkı ve sorumluluklarını beyan etmiş sayılırlar.

Makale Değerlendirmesi

Dergiye yayımlanmak üzere gönderilen tüm yazılar 'iThenticate' programı ile taranarak intihal kontrolünden geçmektedir. İntihal taraması sonucuna göre yazılar red ya da iade edilebilir.

Tüm yazılar, editör ve ilgili editör yardımcıları ile en az iki danışman hakem tarafından incelenir. Yazarlar, yayına kabul edilen yazılarda, metinde temel değişiklik yapmamak kaydı ile editör ve yardımcılarının düzeltme yapmalarını kabul etmiş olmalıdırlar.

Makalelerin formatı Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication (http://www.icmje.org/) kurallarına göre düzenlenmelidir.

İncelemeye sunulan araştırmada olası bir bilimsel hata, etik ihlal şüphesi veya iddiasıyla karşılaşılırsa, bu dergi verilen yazıyı destek kuruluşların veya diğer yetkililerin soruşturmasına sunma hakkını saklı tutar. Bu dergi sorunun düzgün biçimde takip edilmesi sorumluluğunu kabul eder ancak gerçek soruşturmayı veya hatalar hakkında karar verme yetkisini üstlenmez.

Yayın Politikası ve Makale Yazım Kuralları aşağıda belirtilen maddeler "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" (2016, http://www.icmje.org/) temel alınarak hazırlanmıştır.

Araştırma makalelerinin hazırlığı, sistematik derleme, meta-analizleri ve sunumu ise uluslararası kılavuzlara uygun olmalıdır.

Randomize çalışmalar için; CONSORT (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285:1987-91) (http://www.consort-statement.org/).

Sistematik derleme ve meta-analizlerin raporlamaları için; PRISMA [Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097] (http://www.prisma-statement.org/).

Tanısal değerli çalışmalar için; STARD (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al, for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4) (http://www.stard-statement.org/).

Gözlemsel çalışmalar için; STROBE (http://www.strobe-statement.org/).

Meta-analizleri ve gözlemsel çalışmaların sistematik derlemeleri için; MOOSE [Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting "Meta-analysis of observational Studies in Epidemiology" (MOOSE) group. JAMA 2000; 283: 2008-12].

YAZI ÇEŞİTLERİ

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Yazının tümünün 5000 kelimeden az olması gerekmektedir. İlk sayfa hariç tüm yazıların sağ üst köşelerinde sayfa numaraları bulunmalıdır. Yazıda, konunun anlaşılmasında gerekli olan sayıda ve içerikte tablo ve şekil bulunmalıdır.

Başlık sayfası, kaynaklar, şekiller ve tablolar ile ilgili kurallar bu dergide basılan tüm yayın türleri için geçerlidir.

1) Başlık Sayfası (Sayfa 1)

Yazı başlığının, yazar(lar)ın bilgilerinin, anahtar kelimelerin ve kısa başlıkların yer aldığı ilk sayfadır.

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Türkçe yazılarda, yazının İngilizce başlığı da mutlaka yer almalıdır; yabancı dildeki yayınlarda ise yazının Türkçe başlığı da bulunmalıdır.

Türkçe ve İngilizce anahtar sözcükler ve kısa başlık da başlık sayfasında yer almalıdır.

Yazarların isimleri, hangi kurumda çalıştıkları ve açık adresleri belirtilmelidir. Yazışmaların yapılacağı yazarın adresi de ayrıca açık olarak belirtilmelidir. Yazarlarla iletişimde öncelikle e-posta adresi kullanılacağından, yazışmaların yapılacağı yazara ait e-posta adresi belirtilmelidir. Buna ek olarak telefon ve faks numaraları da bildirilmelidir.

Çalışma herhangi bir bilimsel toplantıda önceden bildirilen koşullarda tebliğ edilmiş ya da özeti yayınlanmış ise bu sayfada konu ile ilgili açıklama yapılmalıdır.

Yine bu sayfada, dergiye gönderilen yazı ile ilgili herhangi bir kuruluşun desteği sağlanmışsa belirtilmelidir.

2) Özet (Sayfa 2)

İkinci sayfada yazının Türkçe ve İngilizce özetleri (her biri için en fazla 200 sözcük) ile anahtar sözcükler belirtilmelidir.

Özet bölümü; Amaç, Gereç ve Yöntem, Bulgular, Sonuç şeklinde alt başlıklarla düzenlenir. Derleme, olgu sunumu ve eğitim yazılarında özet bölümü alt başlıklara ayrılmaz. Bunlarda özet bölümü, 200 kelimeyi geçmeyecek şekilde amaçlar, bulgular ve sonuç cümlelerini içermelidir.

Özet bölümünde kaynaklar gösterilmemelidir. Özet bölümünde kısaltmalardan mümkün olduğunca kaçınılmalıdır. Yapılacak kısaltmalar metindekilerden bağımsız olarak ele alınmalıdır.

3) Metin (Özetin uzunluğuna göre Sayfa 3 veya 4'den başlayarak)

Metinde ana başlıklar şunlardır: Giriş, Gereç ve Yöntem, Bulgular, Tartışma.

Giriş bölümü, çalışmanın mantığı ve konunun geçmişi ile ilgili bilgiler içermelidir. Çalışmanın sonuçları giriş bölümünde tartışılmamalıdır.

Gereç ve Yöntem bölümü, çalışmanın tekrar edilebilmesi için yeterli ayrıntılar içermelidir. Kullanılan istatistik yöntemler açık olarak belirtilmelidir.

Bulgular bölümü de çalışmanın tekrar edilebilmesine yetecek ayrıntıları içermelidir.

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e) Elektronik Formatta Makale: Morse SS. Factors in the emergence of infectious disease. Emerg Infect Dis [serial online] 1995 1(1):[24 screens]. Available from:s URL:http://www/cdc/gov/ncidoc/EID/eid.htm. Accessed December 25, 1999.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Usefulness of Bispectral Index Monitoring for the Detection and Diagnosis of the Brain Death

Beyin Ölümü Tespiti ve Tanısında Bispektral İndeks Monitorizasyonunun Yararlılığı

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Presented in: This study was presented at the 22nd International Congress of Intensive Care in 2019, in İstanbul.

ABSTRACT *Objective:* Bispectral index (BIS) is a parameter generated from a mathematical analysis of frontal cortex activity. BIS monitoring has been widely used in cerebral pathologies such as traumatic brain injury, brain death, metabolic coma and barbiturate coma and some studies have reported a good correlation between neurological status and BIS values. We evaluated the validity of BIS monitoring for the detection and diagnosis of brain death in our study.
Materials and Methods: Our study was a methodological prospective study. Twenty-eight patients with severe coma [Glasgow coma scale score (GCS)<8] at intensive care unit (ICU) admission are monitored by BIS. Eight patients were excluded from the study due to varies reasons. Data of twenty patients with brain death were evaluated.
Results: The most common diagnoses were intracranial hemorrhage (8 patients-40%) and subarachnoid hemorrhage (8 patients-40%). The most common used ancillary method was computed tomography angiography. BIS and suppression ratio (SR) were determined as 0 and 100 respectively at the moment of brain death diagnosis in 12 of 20 patients, whereas BIS was determined >0 in the remainders. When the receiver operating characteristic curve analysis was performed for the 34041 BIS values of 20 patients, the area under curve was found as 0.582 (0.576-0.588), which was statistically significant (p<0.05). There was a strong negative correlation between BIS and SR and it was statistically significant (R:-0.959, p<0.05).
Conclusion: BIS is a non-invasive method and it may be used in the ICU. BIS monitoring may be useful, especially in patients with head trauma and GCS =3. BIS monitoring provides information about the neurological prognosis. We consider that BIS monitoring can prevent the loss of time by providing to detect the moment of the brain death and thus facilitating the organ transplantation process and however it can not take the place of the other ancillary methods.
Keywords: Bispectral index monitoring, brain death, ancillary method

ÖZ *Amaç:* Bispektral indeks (BİS) frontal korteks aktivitesinin matematiksel analizi ile elde edilen bir parametredir. BİS monitorizasyonu travmatik beyin hasarı, beyin ölümü, metabolik koma ve barbitürat koması gibi serebral patalojilerde yaygın olarak kullanılmaktadır ve bazı çalışmalar nörolojik durum ve BİS değerleri arasında iyi bir korelasyon olduğunu bildirmektedir. Çalışmamızda BİS monitorizasyonunun beyin ölümü tespiti ve tanısındaki geçerliliğini incelemeyi amaçladık.
Gereç ve Yöntem: Çalışmamız metodolojik prospektif bir çalışmadır. Ağır komalı [Glasgow koma skala skoru (GKS)<8] 28 hastaya yoğun bakım ünitesi (YBÜ) kabulü ile birlikte BİS monitorizasyonu uygulandı. Sekiz hasta farklı sebeplerle çalışmadan çıkartıldı. Beyin ölümü tanısı olan 20 hastanın verileri değerlendirildi.
Bulgular: En sık görülen tanı intrakraniyal kanama (8 hasta-%40) ve subaraknoid kanamaydı (8 hasta-%40). En sık kullanılan yardımcı yöntem bilgisayarlı tomografik anjiyografiydi. Yirmi hastanın 12'sinde beyin ölümü teşhis anında BİS 0 ve supresyon oranı (SR) 100 olarak bulundu. Geri kalan hastalarda BİS >0 olarak tespit edildi. Yirmi hastanın 34041 BİS değeri için alıcı işletim karakteristik eğri analizi yapıldığında eğri altındaki alan değeri 0,582 (0,576-0,588) olarak bulundu ve istatistiksel olarak anlamlıydı (p<0,05). BİS ve SR arasında istatistiksel olarak anlamlı olan güçlü negatif korelasyon vardı (R:-0,959, p<0,05).
Sonuç: BİS non-invaziv bir metottur ve YBÜ'de kullanılabilir. BİS monitorizasyonu özellikle GKS =3 olan kafa travmalı hastalarda yararlı olabilir. BİS monitorizasyonu nörolojik prognoz hakkında da bilgi vermektedir. BİS monitorizasyonunun beyin ölümü anının tespitini sağlayarak zaman kaybını önleyeceğini ve organ transplantasyon sürecini hızlandıracağını ancak diğer yardımcı yöntemlerin yerini alamayacağını düşünüyoruz.
Anahtar Kelimeler: Bispektral indeks monitorizasyonu, beyin ölümü, yardımcı yöntem

Introduction

It is among the duties and responsibilities of intensive care physicians in our country as well as in the world to determine and report brain death which means the end of life medically and legally (1). Brain death is a clinical diagnosis of irreversible loss of cerebral hemisphere and brainstem functions. There are three fundamental findings in brain death. These include the presence of irreversible coma, absence of brainstem reflexes, and positive apnea test characterized by the absence of respiratory response to severe hypercapnia (2,3).

Ancillary tests are essential legally to confirm the brain death in some countries when brain death is suspected or prediagnosed clinically (4). Electrophysiological studies [electroencephalography (EEG), somatosensory evoked potentials] and tests measuring cerebral blood flow [cerebral angiography, computed tomography angiography (CTA), transcranial Doppler ultrasonography (TCD), radionuclide cerebral scintigraphy] are used as ancillary tests (3). Cerebral angiography is considered to be the most important test evaluating cerebral circulation (5). In cases where a clinical diagnosis of brain death is made, an ancillary test evaluating the cerebral circulation is performed and if this test is compatible with brain death, there is no need for a second neurological examination (3). Thus, an ancillary test seems to be a more practical way to save time in the diagnosis of brain death. The requirement to transfer the patient out of the intensive care unit (ICU) for these procedures carries a risk for the patients. In addition, the use of contrast media during cerebral angiography may potentially jeopardize the kidney and other organs of the potential donor candidate (4,5).

Bispectral index (BIS) monitoring, approved by the United States Food and Drug Administration for the measurement of hypnotic effects of anesthetics and sedative drugs in 1996, was developed for the measurement of sedation depth and consciousness level during and after general anesthesia. BIS monitoring, which has expanded in use over time, has been widely used in cerebral pathologies such as traumatic brain injury (TBI), brain death, metabolic coma and barbiturate coma (6,7). BIS is a parameter generated from mathematical analysis of frontal cortex activity with 2-channel EEG. BIS values are between 0 and 100, 100 means complete conciousness, 0 means full electrical silence of the brain (8). BIS values between 65-85 means appropriate sedation level (7). It is stated that BIS monitoring is a noninvasive method and can be used in ICU for the measurement of sedation depth (9). Some studies have reported a good correlation between neurological status and BIS values in non-sedated comatose patients (10,11). Dunham et al. (12) reported that BIS monitoring in head trauma patients with a low Glasgow coma scale score (GCS) may be useful to determine the appropriate timing for a comprehensive neurological examination, apnea assessment, or an ancillary test. Vivien et al. (10) suggested that BIS monitoring could be used to ensure proper programming of EEG and cerebral angiography to confirm brain death by determining the onset of brain death in comatose patients. Okuyaz et al. (13), in their study, reported that decreasing BIS to 0 in patients with suspected brain death may support the brain death diagnosis in children and thus that expensive tests such as cerebral angiography can be planned at the appropriate time. We aimed to evaluate the validity of BIS monitoring for detecting and diagnosis of brain death in our study.

Materials and Methods

Study Groups

Our study is a methodological prospective study to determine the validity of BIS application in the clinical course of coma patients and the diagnosis of brain death. Study was performed between 2016-2017 in Dokuz Eylül University (DEU) Faculty of Medicine ICU after DEU Non-Interventional Research Ethics Committee approval (decision no: 2016/19-05, date: 14.07.2016). No additional consent was obtained from the patient relatives for the study.

Twenty-eight patients admitted to our clinic with severe coma (GCS <8) due to TBI, spontaneous intracranial hemorrhage (ICH), subarachnoid hemorrhage, ischemic stroke and hypoxic brain injury were included in the study. Eight patients were excluded from the study, because 3 patients without brain death diagnosis were died, 3 patients were not diagnosed with brain death and BIS records of 2 patients were not appropriate. Data of 20 patients with brain death were evaluated (Figure 1). The cause of the coma in each patient was evaluated and patients with reversible coma reasons (hypothermia, hypovolemic or hypotensive shock, intoxications, barbiturate or other sedative-narcotic drugs, metabolic disorders) or impaired forehead integrity were not included in the study.

All patients included in the study were followed-up for possible brain death. Critical cares of patients with brain trauma in ICU were performed according to the standard

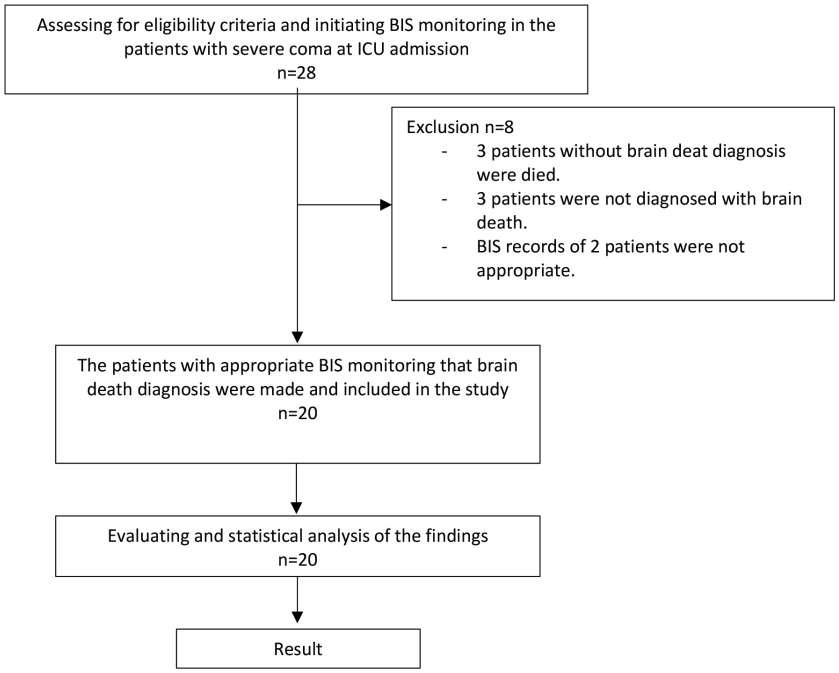

Figure 1. Study flow-chart
BIS: Bispectral index, ICU: intensive care unit

procedures of Brain Trauma Foundation Guidelines (14) and BIS monitoring was performed in all patients included in the study. The skin was cleaned before placing the BIS sensor and BIS sensors were used for a maximum of 72 hours. Sensors were changed if necessary.

Neurological examination was performed at 6 hour intervals each day. If clinical findings were not consistent with brain death, monitoring was continued as afore planned. But if a patient showed GCS regression, the neurological examination was performed hourly. Clinical evaluation of brain death was performed in patients with suspected brain death in the neurological examination. CTA, TCD, and digital subtraction angiography (DSA) were performed as an ancillary test in patients who were both clinically compatible with brain death and in whom apnea test positive. Consistency of BIS values with the brain death diagnosis was evaluated in patients whose brain death diagnosis was confirmed by an ancillary test. A significant change in BIS values accompanying GCS regression and its association with prognosis were also evaluated.

Brain Death Diagnosis

The brain death diagnosis was performed by the absence of brainstem reflexes and apnea test positivity in patients with irreversible coma according to the recommendations of the Ministry of Health Organ and Tissue Transplantation Services Regulation updated in 2014 (01.02.2012-28191) (15).

Data Collection

Demographic data, cause of coma, GCS and neurological examination findings at the admission of 28 patients were recorded. BIS monitorization was started in all patients admitted to ICU and neurological examination was done routinely every six hours, but upon regression of GCS of the patient, neurological examination frequency was increased and performed every hour. Suppression ratio (SR), signal quality index (SQI) and electromyographic activity (EMG) were recorded by BIS monitoring continuously.

BIS Monitoring

BIS and EMG of patients were monitored continuously by VISTA device (Aspect Medical System Inc., MA, USA). Four channel sensor (Quattro, Aspect Medical System Inc., MA, USA) was used in BIS device. Data were transferred to a computer for analysis and artifacts generated by devices such as cardiac pacing and air heating systems that could affect BIS recordings were removed.

Statistical Analysis

In our study, when the power analysis for receiver operating characteristic (ROC) with 80% power, 95% confidence interval and area under curve (AUC) =0.75, the number of samples to be included in the study was calculated as 20. For correlation analysis, 80% power 95% confidence interval and 0.70 correlation between two measurements were found to be 23 samples.

Data obtained from the patients were expressed as mean ± standard deviation if showed normal distribution in continuous characteristics, and median [minimum-maximum (min-max)] if not a normal distribution. The normal distribution of data was evaluated by the Kolmogorov-Smirnov test. Categorical data were defined by frequency and percentages.

In order to determine the validity of BIS, the clinical and ancillary test and brain death decision were accepted as the gold standard reference, the statistical significance of AUC obtained from ROC curve analysis for BIS values of 20 patients at the time of brain death diagnosis was tested. 34041 repeated BIS measurement data of 20 patients were evaluated. The optimal cut-off point was determined from the ROC curve for BIS with the highest sensitivity and specificity, and sensitivity and specificity values were determined according to this point. Spearman correlation analysis was performed between BIS and SQI, SR, EMG values. In the Spearman correlation $p<0.01$ and in the other evaluations $p<0.05$ were considered statistically significant.

Results

Mean age of 20 patients (13 males and 7 females) in the study was 61.9±17.7 years. Mean ICU length of stay was 4.1±5.6 days. The most common diagnosis at ICU admission were ICH (8 patients-40%) and subarachnoid hemorrhage (8 patients-40%). Mean GCS of patients with brain death at ICU admission was 3.3±0.9 (Table 1). The most common used ancillary method for the brain death diagnosis was CTA [75% (n=15)]. TCD was used in 2 patients (10%) and DSA was used in 1 patient (5%). Also two patients (10%) were diagnosed with brain death without ancillary test.

BIS and SR were determined as 0 and 100 respectively at the moment of brain death diagnosis in 12 of 20 patients, whereas BIS was determined >0 in the remainders. BIS median value was identified 0 (min-max 0-69) at the moment of brain death diagnosis. The median (min-max) values of BIS, SQI, EMG and SR data were as follows; 0 (0-97), 100 (0-100), 26 (20-80), 100 (0-100). 34041 repeated BIS measurement data of 20 patients were evaluated. In order to determine the validity of BIS, the clinical and ancillary tests and brain death decision were accepted as gold standard, when the ROC curve analysis was performed for the BIS values of 20 patients at the moment of brain death diagnosis, the AUC was found as 0.582 (0.576-0.588) which was statistically significant ($p<0.05$) (Figure 2). The sensitivity and specificity of ROC curve analysis for BIS were 0.752, 0.384 consecutively and the optimal diagnostic value

Table 1. Demographic and clinical information of patients

Characteristics	**n=20**
Age (years) (mean ± SD)	61.9±17.7
Gender n (%)	
Male	13 (65%)
Female	7 (35%)
GCS (at ICU admission) (mean ± SD)	3.3±0.9
Time from ICU admission to brain death (days) (mean ± SD)	3.4±5.6
Hospital lenght of stay (days) (mean ± SD)	6.4±5.7
ICU length of stay (days) (mean ± SD)	4.1±5.6
Diagnosis n (%)	
ICH	8 (40%)
ICM	1 (5%)
SAH	8 (40%)
Methanol intoxication	2 (10%)
Firearm injury	1 (5%)

GCS: Glasgow coma scale score, SD: standard deviation, ICU: intensive care unit, ICH: intracranial hemorrhage, ICM: intracranial mass, SAH: subarachnoid hemorrhage

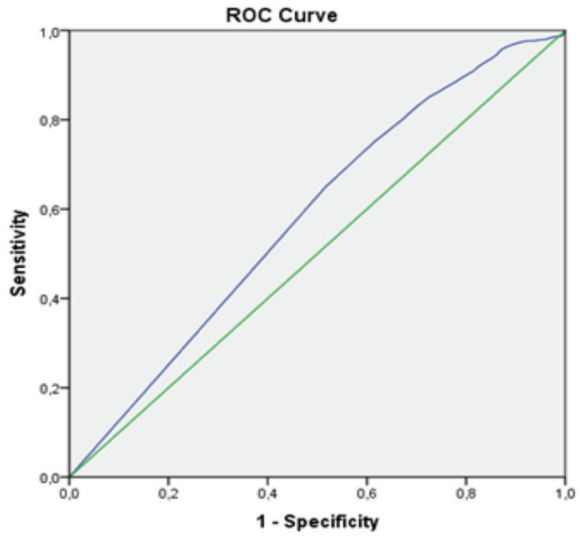

Figure 2. ROC curve of BIS measurements for brain death decision
BIS: Bispectral index, ROC: receiver operating characteristic

was 1.5. There was a negative correlation between BIS and SQI and it was statistically significant (R: -0.118, p<0.05). Although there was a statistically significant correlation, since R<0.20, there was no mention of the correlation. There was a positive correlation between BIS and EMG and it was statistically significant (R: 0.679, p<0.05). There was a strong negative correlation between BIS and SR and it was statistically significant (R: -0.959, p<0.05).

Discussion

In our study BIS and SR were determined as 0 and 100 respectively at the moment of brain death diagnosis in 12 of 20 patients, whereas BIS was determined >0 in the remainders. BIS median value was identified 0 (min-max 0-69) at the moment of brain death diagnosis.When the ROC curve analysis of BIS values was performed the AUC was found as 0.582 (0.576-0.588) which was statistically significant (p<0.05). At the same time, there was a positive correlation between BIS and EMG and it was statistically significant (R: 0.679, p<0.05). In addition, there was a strong negative correlation between BIS and SR and it was statistically significant (R: -0.959, p<0.05).

BIS monitoring is a non-invasive and easy to use method for critically ill patients in ICU. Some studies have reported that BIS monitoring can be useful to determine the timing for performing a comprehensive neurological examination, apnea test and an ancillary test in patients with head trauma and suspected brain death (12). In addition, some studies reported that BIS monitoring can be used for the brain death diagnosis in patients with severe coma admitted to ICU (10,16). Vivien et al. (10), in their prospective study, reported that 44 patients without brain death at ICU admission and who had BIS values ranging from 20 to 79 did progress to brain death and their BIS values decreased to 0. In contrast, in 17 patients with persistent electrocortical activity detected by EEG who did not progress to brain death after ICU admission, mean BIS values was over 35. Escudero et al. (17), in their study evaluated 19 patients, reported a gradual decrease in BIS values and an increase in SR with clinical deterioration. It was reported that BIS and SR were 0 and 100 consecutively in all patients with confirmed brain death diagnosis. We detected BIS and SR values as 0 and 100 respectively in 12 patients at the moment of brain death whereas BIS >0 and SR <100 values were recorded in the remainders. Vivien et al. (10) emphasized two important limitations of their study. Firstly, BIS values can drop to 0 before onset of the brain death in patients with major intracranial hypertension, secondly, significant EMG activity and cardiovascular hyperpulsatility may increase BIS values falsely. Escudero et al. (17), reported that low-frequency EMG activity may increase BIS values falsely in the absence of EEG activity, especially in brain death. Fyntanidou et al. (8), in their study including 35 patients, reported that BIS values consistently gave a value of 0 in 12 patients with brain death diagnosis, but in 23 patients, BIS values were >30 for more than 30 minutes. They emphasized that this change was not due to brainstem electrical activity, but it might be due to external factors such as nearby equipment or internal factors such as heartbeat. Mayr et al. (18) reported "tetaniform" muscle activity during EEG recording in five potential organ donors, suggesting that increased EEG activity may be due to hyperstability of the neuronal membrane caused by artificial hyperventilation in brain death patients. In our study, we recorded BIS values >0 in 8 patients with brain death diagnosis. This may be related to low EMG activity at the moment of brain death diagnosis, interference of nearby devices or heartbeat. In clinical practice, some studies suggested that EMG activity should always be considered for the interpretation of BIS values in severely comatose patients and even neuromuscular blockers may be used in some cases (10). But we did not use neuromuscular blockers during BIS monitoring. In our study, there was a positive

correlation between BIS and EMG and it was statistically significant (R: 0.679, p<0.05). Dunham et al. (12), performed a study including 27 patients, and compared BIS values of the patients with brain death and without brain death. They reported that BIS values of the patients with brain death were significantly lower. They reported that BIS value was <5 in 83% of the patients with brain death diagnosis. In the same study, they reported the sensitivity of BIS <20 as 100%, positive predictive value as 82%, negative predictive value as 100% and accuracy as 87%. Jouffroy et al. (19), prospectively evaluated 46 patients, identified that mean BIS value was 4 in 29 patients with brain death under therapeutic hypothermia and it was 0 after warming. BIS values were found to be significantly different between patients with and without brain death. The sensitivity and specificity of the BIS <30 cut-off value during the ICU stay were 96% and 82% respectively for brain death.

In our study, when ROC analysis of BIS values was performed during the brain death diagnosis, AUC was 0.582 (0.576-0.588) and it was statistically significant (p<0.05). Although AUC was as low as 0.58, it was found to be statistically significant since BIS values were measured many times (34041 repetitive BIS data) from the time of ICU admission in 20 patients with brain death. The sensitivity and specificity of ROC curve analysis for BIS were 0.752, 0.384 respectively and optimal diagnosis value was identified 1.5. While the sensitivity is 0.752, it is unacceptable that the specificity is 0.384. As the value of n was 34041 (repeated BIS values) and the confidence interval was 95% (0.576-0.588), the ROC value may be statistically significant. Although this value is an acceptable level for the validity of a diagnostic test in the field of health, it was not considered statistically significant (20).

Miao et al. (21), used BIS monitoring in 90 patients with coma, reported AUC of BIS values as 0.841 (p<0.001, 95% CI =0.751-0.931). They suggested that BIS may reflect the degree of brain injury and it may help clinicians predict brain death in patients whose BIS value <32.5. On the other hand, Dou et al. (16), evaluated 208 patients with coma, they found that AUC of BIS was <0.5 in their study. In addition, they stated that BIS values <42.5 can not differentiate vegetative state and brain death.

Conclusion

BIS is a non-invasive method and it may be used in ICU. BIS monitoring may be useful especially in patients with head trauma and GCS =3. BIS monitoring provides an information about the neurological prognosis and may be used to determine the moment of brain death. When BIS dropped to 0 in patients with brain death suspect, the neurological examination should be repeated and if it is necessary, the brain death diagnosis should be confirmed by ancillary methods such as TCD and CTA. However, EMG activity that may affect BIS values should be considered. We consider that BIS monitoring can prevent loss of time by providing to detect the moment of the brain death and so facilitate the organ transplantation process and however it can not take the place of the other ancillary methods.

Ethics

Ethics Committee Approval: Study was performed between 2016-2017 in Dokuz Eylül University (DEU) Faculty of Medicine ICU after DEU Non-Interventional Research Ethics Committee approval (decision no: 2016/19-05, date: 14.07.2016).

Informed Consent: No additional consent was obtained from the patient relatives for the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.A., Y.L.U., T.Ç., Concept: K.A., Y.L.U., T.Ç., P.K., A.N.G., Design: K.A., Y.L.U., T.Ç., B.E., T.M., Y.S., E.Y., B.C., U.K., P.K., A.N.G., Data Collection or Processing: K.A., Y.L.U., T.Ç., T.M., Y.S., E.Y., B.C., U.K., A.N.G., Analysis or Interpretation: K.A., Y.L.U., T.Ç., B.E., T.M., Y.S., E.Y., B.C., U.K., P.K., A.N.G., Literature Search: K.A., Y.L.U., T.Ç., B.E., T.M., Y.S., E.Y., B.C., U.K., P.K., A.N.G., Writing: K.A., Y.L.U., T.Ç., B.E., T.M., Y.S., E.Y., B.C., U.K., P.K., A.N.G.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Pain Behaviors and Physiological Parameters During Painful Procedures in Surgical Intensive Care Patients

Cerrahi Yoğun Bakım Hastalarının Ağrılı İşlemler Sırasında Ağrı Davranışları ve Fizyolojik Parametreleri

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Presented in: The abstract of this study was presented as an oral presentation at the 3rd International 11th National Congress of Turkish Surgery and Operating Room Nursing held between 3-6 October 2019.

ABSTRACT *Objective:* This research was conducted to determine the pain behaviors and physiological parameters of patients connected to mechanical ventilators in the postoperative surgical intensive care unit.
Materials and Methods: This study was conducted descriptively and observationally with 176 patients. The introductory information form, physiological parameters follow-up form, behavioral pain scale (BPS), and Ramsey sedation scale were used to collect data. Descriptive statistics, Two-Way variance in repeated measures, Friedman analysis, post-hoc Bonferroni analysis, One-Way variance analysis, Kruskal-Wallis analysis, and Spearman correlation analysis were used.
Results: The mean arterial pressure (MAP), heart rate and mean BPS scores increased ($p<0.001$), and oxygen saturation decreased during aspiration, wound care, and position change ($p<0.001$). Additionally, while a moderate, positive correlation was found between BPS and MAP and heart rate during wound care ($r=0.447$; $p=0.001$, $r=0.306$; $p=0.033$). A moderate negative correlation was found between oxygen saturation and BPS during aspiration ($r=-0.389$; $p=0.000$).
Conclusion: It has been revealed that individuals connected to mechanical ventilators experience pain during wound care, position change and aspiration. Physiological parameters and behavioral symptoms resulting from pain should be analyzed together. Pain should be relieved with pharmacological and non-pharmacological nursing interventions in pain management.
Keywords: Intensive care, pain, painful procedure, pain assessment, physiological parameters

ÖZ *Amaç:* Bu araştırma ameliyat sonrası cerrahi yoğun bakımda mekanik ventilatöre bağlanmış hastaların ağrı davranışlarının ve fizyolojik parametrelerinin belirlenmesi amacıyla yürütülmüştür.
Gereç ve Yöntem: Yüz yetmiş altı hasta ile tamamlanan araştırma, tanımlayıcı ve gözlemsel tiptedir. Verilerin toplanmasında hasta tanıtım formu, fizyolojik parametreler takip formu, davranışsal ağrı ölçeği (DAÖ) ve Ramsey sedasyon skalasından yararlanılmıştır. Verilerin analizinde; tanımlayıcı istatistikler, tekrarlı ölçümlerde İki-Yönlü varyans, Friedman analizi, post-hoc Bonferroni analizi, Tek-Yönlü varyans analizi, Kruskal-Wallis analizi ve Spearman korelasyon analizi kullanılmıştır.
Bulgular: Pozisyon değişikliği, yara bakımı ve aspirasyon, yapılırken DAÖ ortalaması, nabız ve ortalama arter basıncı (OAB) yükselmiştir; oksijen satürasyonu ise düşmüştür ($p<0,001$). Yara bakımı yapılırken DAÖ ortalaması ile nabız ve OAB arasında pozitif yönlü orta düzeyde bir ilişki saptanmıştır (sırasıyla $r=0,306$; $p=0,033$; $r=0,447$; $p=0,001$). Aspirasyon yapılırken ise sadece DAÖ ortalaması ile oksijen satürasyonu arasında negatif yönlü orta düzeyde bir ilişki bulunmuştur ($r=-0,389$; $p=0,000$).
Sonuç: Mekanik ventilatöre bağlanmış bireylerin yara bakımı, pozisyon değişikliği ve aspirasyon yapılırken ağrı yaşadıkları ortaya konmuştur. Ağrı sonucu ortaya çıkan fizyolojik parametreler ve davranışsal belirtiler beraber analiz edilmelidir. Ağrı yönetiminde farmakolojik ve farmakolojik olmayan hemşirelik girişimleri ile ağrı dindirilmelidir.
Anahtar Kelimeler: Yoğun bakım, ağrı, ağrılı işlem, ağrı değerlendirmesi, fizyolojik parametreler

Introduction

The surgical intensive care patients can experience discomfort due to a range of procedures such as surgical intervention, diagnostic procedures that involve invasiveness, post-operative monitoring, use of mechanical ventilation, physical therapy, suctioning of airways, regular dressing changes, shifts in position, and transfer to other locations for medical purposes (1,2). Uncontrolled pain is an important

physiological and psychological stressor for intensive care unit (ICU) patients and can negatively affect the healing processes. It is stated that inadequate pain management causes physiological and psychological complications, such as pulmonary complications, severe vasoconstriction, increased oxygen consumption, tissue ischemia, depression, and anxiety. In addition, inadequate pain management negatively affects mortality and morbidity, increases the cost of care, and decreases the quality of life (1-3). Therefore, pain assessment and pain management in ICU patients are of great importance.

The most accurate and valid diagnosis of pain is the verbal expression of the pain. Therefore, verbal or visual comparison scales are used in the diagnosis of pain in communicative patients. However, it must be noted that individuals in the ICU who are dependent on mechanical ventilation are unable to verbally communicate their experience of pain. When verbal communication cannot be established with ICU patients, health professionals should observe behavioral responses while evaluating pain (4,5). Behavioral responses due to pain include symptoms such as contraction, pulling the damaged organ or area away from the stimulus, supporting the incision site, immobility, pulling the legs towards the abdomen, grimacing, chewing the intubation tube (5,6). In addition, physiological parameters such as blood pressure, heart rate, and oxygen saturation can be used in pain assessment (7). However, pain assessment may not be reliable because ICU patients often experience many hemodynamic problems that cause changes in their vital signs. For example, tachycardia may be due to pain, as well as fever or hypovolemia. For this reason, it is recommended to use validated pain assessment scales in patients who cannot express their pain and to use physiological parameters as supportive data (8).

In the literature, it has been documented that procedures such as endotracheal aspiration, oral care, vascular catheterization, and repositioning are commonly associated with causing discomfort or pain (9-11). It has been documented that only one study has been conducted to evaluate the experience of pain during wound care among patients who are unable to verbally communicate their experience of pain in the ICU. In that study, pain assessment during wound care in both conscious and unconscious patients after neurosurgery was performed on different scales, and this was reported as a limitation of the study (12). Our research was conducted to examine the pain behavior and the effect of pain on physiological parameters during aspiration, wound care, and position change in surgical ICU patients followed up on mechanical ventilation support and sedated.

Materials and Methods

Design and Sample

This study was conducted to descriptively and observationally. The data were collected between 2017-2018 in a university hospitals' general surgery intensive care, neurosurgery intensive care and anesthesia intensive care services in the Central Anatolia region of Turkey. There is no routine analgesic and sedation protocol in clinics. Analgesic and sedative drugs are administered according to the patient and clinical situation.

All patients who were hospitalized in neurosurgery intensive care, general surgery intensive care and anesthesia ICUs, underwent surgery and were on mechanical ventilation support constituted the population of the research. The study sample comprised of individuals who met the inclusion criteria: Followed on mechanical ventilation support, undergone surgery and 24 hours have passed, Ramsey sedation scale (RSS) 4 and 5 points, and patients with consent from their families. Patients with traumatic brain injury, quadriplegia, excessive postoperative bleeding, continuous analgesic infusion, and aneurysm patients whose blood pressure should be kept high against the risk of vasospasm after surgery were excluded from the study.

The study was completed with 176 patients. Sampling adequacy was decided according to post-hoc power analysis. Based on the mean behavioral pain scale (BPS) score in a study (12), the effect size was found to be 1.430, and when the type I error was 5% and the sample size was 176, the study's statistical power was determined as 99%.

Data Collection Tool

The data were collected using descriptive information form, physiological parameters follow-up form, BPS, and RSS.

The descriptive information form was created by scanning the literature (9,11,12). This form includes introductory data such as age, gender, occupation, diagnosis and the drugs used, the duration of stay in the ventilator.

BPS: It was developed in 2001 by Payen et al. (13). In this scale, there are three items: facial expression, upper extremities, and compliance with the ventilator, and four

variables for each item, including behavioral responses to pain. Each variable is rated on a scale of 1 (absent response) to 4 (full response). The scale ranges from 3 to 12, with a score of 6 or above indicating an unacceptable level of pain (9,10). In 2003, the scale was translated into Turkish and the Cronbach's alpha coefficient was found to be in the range of 0.71 to 0.93 (9). In our study, Cronbach's alpha was determined as 0.84.

RSS: This scale was developed by Ramsay in the mid-1970's. This scale consists of a total of six items, three in each section including the level of wakefulness and sleep level. These are, respectively, "The patient is restless and/or agitated, patient-oriented, calm and cooperative, the patient only follows orders, obvious response, decreased response and no response". The first three responses are assessed in the awake patient, and the other three responses in the sleeping patient by hitting the glabella or by high verbal stimulation (9). The validity and reliability of the scale were made in 2015 and it was stated that it can be used safely (14). This scale is recommended to be used together with the BPS in sedated ICU patients (15).

Data Collection

It has been shown that physiological parameters such as mean arterial pressure immediately return to their baseline values 5 minutes after aspiration (16). Therefore, in our study, data collection forms were filled 3 times: 10 minutes before aspiration, wound care and position change (T1), during aspiration, wound care and position change (T2), and 10 minutes after the aspiration, wound care and position change (T3). The respiratory rate was not evaluated because the patients were followed up on a mechanical ventilator. Physiological parameters were recorded on the monitor, and BPS was filled in by observation.

Data were collected by researchers and observers who responsible for patient care. For the observers to follow-up with the same protocol, joint meetings were held and data were collected by exchanging information.

Ethical Considerations

Before starting the study, Erciyes University Clinical Research Ethics Committee approval (decision no: 2017/355, date: 16.06.2017) and approval from the institutional authority of the institution in which the study was conducted was obtained. Because of intubation and sedation, which is one of the sampling criteria, the aim of the study and the method was explained to the first-degree relatives of the patients, and permission was obtained. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

The data was analyzed using SPSS 24.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test and Q-Q plots were utilized to assess the normality of the numerical data. Descriptive statistics were given as number, percentage, and mean ± standard deviation. Two-Way variance in repeated measures, Friedman analysis, One-Way analysis of variance, Kruskal-Wallis analysis, and the Spearman correlation analysis was employed, and results were considered statistically significant if $p<0.05$ in all cases.

Results

In the study, it was determined that 64.2% of the patients were male, 57.4% were 51 years and older, and 60.8% had cranial surgery. The mean duration of the patients on followed up on mechanical ventilation support was 9.81±15.11 days. As a painful procedure, aspiration was performed for 46% of the patients, wound care for 27.8%, and position change for 26.1%. In addition, 83.0 % of the patients use analgesics, 48.3% of the patients use sedative drugs (Table 1).

Table 2 shows the vital signs and mean BPS of the patients before, during, and after the painful procedure. It was determined that during aspiration, wound care, and position change, MAP, heart rate and mean BPS scores increased ($p<0.001$), and oxygen saturation decreased ($p<0.001$).

The comparison of the procedures of wound care, aspiration and position change revealed that there was no significant difference between the groups in terms of mean BPS scores and heart rate ($p>0.05$). However; it was found that MAP increased during wound care and oxygen saturation decreased during aspiration ($p<0.05$) (Table 3).

A significant negative correlation was found between the oxygen saturation during aspiration and BPS ($r=-0.389$; $p=0.000$). As the BPS mean score increases, the oxygen saturation decreases. In addition, a significant positive correlation was found between BPS and MAP and pulse rates during wound care ($r=0.447$; $p=0.001$, $r=0.306$; $p=0.033$, respectively). As the mean BPS mean score increases, the MAP and heart rate increase (Table 4).

Table 1. Descriptive characteristics of the patients		
Descriptive characteristics	**n**	**%**
Gender		
Female	63	35.8
Male	113	64.2
Age (years)		
≤30	28	15.9
31-40	25	14.2
41-50	22	12.5
≥51	101	57.4
Mean age ± SD (min-max)	53.67±19.78 (18-95)	
Operation type		
Cranial surgery	107	60.8
GIS surgery	28	15.9
Cancer surgery	13	7.4
Trauma and orthopedic surgery	28	15.9
Painful procedures		
Aspiration	81	46.0
Wound care	49	27.8
Position change	46	26.1
Occupation		
House wife	48	27.3
Retired	57	32.4
Worker	46	26.1
Self-employed	25	14.2
Duration on mechanical ventilation (days)		
1-5	90	51.1
6-10	43	24.4
11-15	15	8.5
≥16	28	15.9
Mean duration on mechanical ventilation ± SD	9.81±15.11	
Use of analgesic medication*		
Yes	146	83.0
No	30	17.0
Use of sedative medication**		
Yes	85	48.3
No	91	51.7

SD: Standard deviation, min-max: minimum-maximum. *Paracetamol, diclofenac sodium, dexketoprofen trometamol, **dormicum, fentanly + propofol, rocuronium bromide

Table 2. Distribution of physiological parameters and mean BPS score before, during and after the procedure according to painful procedures

Painful procedures	Variables	Time			Test
		T1	T2	T3	
Aspiration (n=81)	Vital signs	Mean ± SD Median (min-max)	Mean ± SD Median (min-max)	Mean ± SD Median (min-max)	
	MAP	84.49±17.11[a]	103.06±20.53[b]	90.65±16.37[c]	p=0.000*
	Heart rate	94.61±18.48[a]	110.96±20.73[b]	97.88±16.70[c]	p=0.000*
	Oxygen saturation	94.92±6.69[a]	87.18±10.46[b]	96.17±4.00[a]	p=0.000*
	BPS mean score	3.97±1.27[a] 3 (4-5)	6.40±2.03[b] 5 (6-8)	4.19±1.20[c] 3 (4-5)	p=0.000**
Wound care (n=49)	Vital signs				
	MAP	87.38±10.85[a]	105.72±17.43[b]	94.17±15.28[c]	p=0.000*
	Heart rate	94.73±19.14[a]	111.32±26.14[b]	97.26±18.70[c]	p=0.000*
	Oxygen saturation	96.93±3.53[a]	93.08±5.88[b]	97.20±2.97[a]	
	BPS mean score	3.85±1.00[a] 3 (4-4)	6.32±1.95[b] 5 (6-8)	4.16±1.14[c] 3 (4-5)	p=0.000**
Position change (n=46)	Vital signs				
	MAP	83.56±16.99[a]	94.10±19.19[b]	87.49±18.44[c]	p=0.000*
	Heart rate	89.54±17.68[a]	105.69±22.54[b]	93.26±17.92[c]	p=0.000*
	Oxygen saturation	95.63±3.73[a]	91.10±5.70[b]	96.32±3.75[a]	p=0.000*
	BPS mean score	4.15±0.98[a] 3 (4-5)	6.56±1.79[b] 5 (7-8)	4.34±1.03[a] 4 (4-5)	p=0.000**

SD: Standard deviation, min-max: minimum-maximum, MAP: mean arterial pressure, BPS: behavioral pain scale. *Two-Way variance in repeated measures was used. **Friedman analysis has been done. [a, b, c]: Different letters show statistically difference between the groups. Post-hoc Bonferroni analysis was performed

Table 3. Distribution of physiological parameters and mean BPS score during the procedure (T2) according to the painful procedures

Physiological parameters	Painful procedures			
	Aspiration (T2) Mean ± SD Median (min-max)	Wound care (T2) Mean ± SD Median (min-max)	Position change (T2) Mean ± SD Median (min-max)	p-value
MAP	103.06 ±20.53[a]	105.72±17.43[a]	94.10±19.19[b]	**0.009***
Heart rate	110.96±20.73	111.32±26.14	105.69±22.54	0.386*
Oxygen saturation	87.18±10.46[a]	93.08±5.88[b]	91.10±5.70[b]	**0.000***
BPS mean score	6.40±2.03 6 (5-8)	6.32±1.95 7 (5-8)	6.56±1.79 6 (5-8)	0.716**

SD: Standard deviation, min-max: minimum-maximum, MAP: mean arterial pressure, BPS: behavioral pain scale. *One-Way analysis of variance was used. Post-hoc Tukey analysis was performed. **Kruskal-Wallis analysis was used. [a, b, c]: Different letters show statistically difference between the groups

Table 4. Relationship between vital signs and BPS mean scores of patients during painful procedures

Vital signs	BPS scores in painful procedures (T2)					
	Aspiration		Wound care		Position change	
	r*	p	r*	p	r*	p
MAP	0.113	0.314	0.447	0.001	0.078	0.604
Heart rate	0.193	0.084	0.306	0.033	0.096	0.526
Oxygen saturation	-0.389	0.000	-0.247	0.086	-0.191	0.205

MAP: Mean arterial pressure, BPS: behavioral pain scale. *Spearman correlation analysis were used

Discussion

The evaluation of pain in non-verbal patients undergoing mechanical ventilation is crucial for ensuring consistent care and patient comfort (17). In this study, the correlation between physiological parameters and behavioral indicators of pain was assessed in non-verbal patients who underwent surgery. In the study, it was found that the heart rate, MAP and BPS mean score increased and oxygen saturation decreased during aspiration, wound care, and position change in patients who were unconscious and followed up on a mechanical ventilator. Our study results are in line with some studies investigating the vital signs and pain levels of intensive care patients during the painful procedure (11,12,18). In the studies, Erden et al. (12), reported that both conscious and unconscious patients had an increase in heart rate during the painful procedure, Al Sutari et al. (11), reported that the mean BPS score increased, Arbor and Gélinas (18), reported that MAP and heart rate showed an increase, while oxygen saturation demonstrated a decrease. These results can be considered as a reason for tachycardia and an increase in blood pressure as a result of the release of catecholamines by the pain experienced during painful procedures stimulating the sympathetic nervous system.

In ICU patients, pain may develop at rest, depending on surgical procedures, or during procedures such as endotracheal aspiration, wound care, change of position, and withdrawal of drain tubes and catheters (19,20). In our study, when the pain behavior and physiological parameters of the patients were compared during aspiration, position change, and wound care procedures; it was determined that there was no significant difference in terms of mean BPS scores and heart rate according to the procedures, but the MAP increased significantly during wound care. The reason for this situation may be the tissue damage caused by the recent surgical procedure and the skin integrity has not yet reached its former strength and the pain experienced is more. Furthermore, it was discovered that oxygen saturation significantly decreased during the process of aspiration. Complications such as injury to the tracheal tissue, hypoxia, and reduced oxygen saturation may arise during endotracheal aspiration (21). In this study, it was hypothesized that the decrease in oxygen saturation during aspiration could have resulted from both the procedure itself and the accompanying pain.

In the study, while there was a moderately negative correlation between BPS score and oxygen saturation during aspiration, a moderate positive correlation was observed between BPS and heart rate and MAP during wound care. There are conflicting results on this subject in the literature. Erden et al. (12), found a moderate association with pain score and heart rate during wound care. Similarly, in another study, it was reported that there was a relationship between pain score and heart rate and MAP during painful procedures (11). On the contrary, in the Chen and Chen (22) study, no relationship was found between heart rate and blood pressure and pain level. As intensive care patients may experience many hemodynamic problems that cause changes in their vital signs, pain assessment using physiological parameters alone may not be reliable (12). Therefore, physiological parameters such as heart rate, MAP, respiratory rate, and oxygen saturation should be used in combination with BPSs.

The dose of sedative drugs administered to the patients during the study and the related change in the patient's consciousness were applied according to their clinical routines and the decision was made beyond our control. In addition, the presence of more than one researcher and observer in the study is one of the limitations of the study.

When considered ethically, every individual has the right to have his/her pain evaluated and relieved (3). Defining pain is a pre-requisite for effective pain management. Consequently, it is crucial to assess the level of pain experienced by patients dependent on mechanical ventilation, who are unable to verbally communicate their pain (23).

Conclusion

The results of this study demonstrated an increase in the BPS scores, MAP, and heart rate, along with a decrease in oxygen saturation levels in surgical intensive care patients during procedures such as suctioning of airways, dressing changes, and shifts in position.

In this patient group, it may be suggested that intensive care nurses should understand the importance of identifying pain with BPSs as well as vital signs to maintain the critical role they play in the assessment and management of pain. In addition, case discussions and training sessions on the physiological effects of pain may be recommended to intensive care nurses.

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Ethics

Ethics Committee Approval: Before starting the study, Erciyes University Clinical Research Ethics Committee approval (decision no: 2017/355, date: 16.06.2017) and institutional permission from the institution where the study was conducted was obtained.

Informed Consent: Consent was obtained from their families.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Y.S., Ö.C., Design: Y.S., Ö.C., Data Collection and Process: Y.S., Analysis or Interpretation: Y.S., H.Y.K., Literature Search: Y.S., H.Y.K., Writing: Y.S., H.Y.K., Ö.C., İ.Y.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Evaluation of Patients with Hematological Malignancies Admitted to the General Intensive Care Unit - Should There be Dedicated Hematological ICUs?

Genel Yoğun Bakım Ünitesine Kabul Edilen Hematolojik Maligniteli Hastaların Değerlendirilmesi - Özelleşmiş Hematolojik YBÜ Olmalı mı?

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ABSTRACT *Objective:* With new treatment modalities, the overall survival of patients with hematological malignancies (HM) has increased over the years. However, intensive care unit (ICU) mortality is still high. This study aimed to evaluate the clinical characteristics, treatment methods, and results of HM patients admitted to the ICU at a center in Turkey.
Materials and Methods: Patients with HM admitted to the ICU between January 2013 and 2020 were retrospectively evaluated. A total of 172 adult patients with HM were included in the study.
Results: The median (interquartile range) age of patients was 60 (47-67) years, admission Acute Physiology Assessment and Chronic Health Evaluation-II score was 30 (26-32), Sequential Organ Failure Assessment score was 10 (7-12). Results of the 172 patients, 60 (34.9%) had newly diagnosed malignancies, 16 (9.3%) were in remission, and 96 (55.8%) had relapsed/refractory disease. The ICU admission was mostly required for acute respiratory failure (62.5%) and/or shock (42.3%). Forty-seven (27.3%) patients had stem cell transplantation, and 59 (34.3%) were neutropenic. Of them, 143 (83.2%) patients were admitted to intensive care after intubation and 159 (92.4%) patients needed vasopressors during intensive care stay. Thirteen (7.5%) patients were diagnosed with fiberoptic bronchoscopy-bronchoalveolar lavage sampling only, and treatment was changed in 85% according to the results. We observed that the patients were admitted to the ICU at the 28th hour (11-55) after determining the need for ICU follow-up. Intensive care mortality was 94.3% (163).
Conclusion: Early detection of critical illness and rapid admission to the ICU are important for the patients with HM. Collaborative studies determining early admission criteria to ICUs should be performed by the intensivists and hematologists to improve survival. This may be achieved by allocating special ICUs for these patients within the hematology clinics.
Keywords: Hematological malignancies, intensive care, mortality, admission time

ÖZ *Amaç:* Yeni tedavi modaliteleri ile birlikte, hematolojik maligniteli (HM) hastaların genel sağkalımı yıllar içinde artmıştır. Ancak yoğun bakım ünitesi (YBÜ) mortalitesi hala yüksektir. Bu çalışmanın amacı, Türkiye'de bir merkezde YBÜ'ye yatırılan HM hastalarının klinik özelliklerini, tedavi yöntemlerini ve sonuçlarını değerlendirmektir.
Gereç ve Yöntem: Ocak 2013 ve 2020 tarihleri arasında YBÜ'ye yatırılan HM'li hastalar geriye dönük olarak değerlendirildi. HM'li toplam 172 erişkin hasta çalışmaya dahil edildi.
Bulgular: Hastaların ortanca yaşı 60 (47-67), başvuru Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-II skoru 30 (26-32), Sıralı Organ Yetmezliği Değerlendirmesi skoru 10 (7-12) idi. Yüz yetmiş iki hastanın 60'ı (%34,9) yeni tanı, 16'sı (%9,3) remisyon ve 96'sı (%55,8) relaps/refrakter hastalık olarak değerlendirildi. YBÜ'ye yatış nedeni çoğunlukla akut solunum yetmezliği (%62,5) ve/veya şok (%42,3) nedeniyleydi. Kırk yedi (%27,3) hastaya kök hücre nakli yapıldığı ve 59 (%34,3) hastanın nötropenik olduğu saptandı. Bunların 143'ünün (%83,2) yoğun bakıma entübe olarak kabul edildiği ve 159'unun (%92,4) yoğun bakımdayken vazopressör ihtiyacının olduğu saptandı. On üç (%7,5) hastaya sadece fiberoptik bronkoskopi-bronkoalveolar lavaj örneklemesi ile tanı konuldu ve sonuçlara göre %85 oranında tedavinin değiştiği saptandı. Hastaların yoğun bakım ihtiyacı belirlendikten sonra 28. saatte (11-55) yoğun bakıma alındıkları görüldü. Yoğun bakım mortalitesi %94,3 (163) idi.

Sonuç: HM hastaları için, kritik hastalığın erken tespiti ve YBÜ'ye hızlı kabulü önemlidir. Yoğun bakım uzmanları ve hematologlar tarafından sağkalımı artırma açısından YBÜ'ye erken kabul kriterlerini değerlendirmek için ortak çalışmalara ihtiyaç vardır. Hematoloji kliniklerinde bu hastalara özel YBÜ'leri tahsis edilerek sağkalım artabilir.
Anahtar Kelimeler: Hematolojik maligniteler, yoğun bakım, mortalite, kabul süresi

Introduction

Although there are new treatment regimens and supportive treatments, overall survival in patients with hematological malignancies (HM) is still high. In previous studies, mortality in patients with HM admitted to the intensive care unit (ICU) ranged from 37.6% to 90% (1-3).

High Acute Physiology Assessment and Chronic Health Evaluation-II (APACHE-II) (4,5) and Sequential Organ Failure Assessment (SOFA) (6) scores, invasive mechanical ventilation (IMV) (7), neutropenia (8), prior history of stem cell transplantation (SCT) (3) and sepsis (5) are several factors associated with poor prognosis in critical patients with HM during ICU stay. The presence of positive blood culture with neutropenia has also been shown to be associated with an increase in mortality over 28 days (9).

The possible short- and long-term poor prognosis in patients with HM, as well as the necessity of time and costly treatments, has also led to the reluctance of intensive care professionals to accept and treat patients with HM (4). In addition, patients with advanced and refractory hematologic malignancies were found to be referred to palliative care services less frequently and received more aggressive treatments than patients with end-stage treatment-resistant solid tumors (10,11). Therefore, given high ICU and in-hospital mortality and limited ICU resources, identifying factors affecting mortality will help hematologists and intensivists to identify patients who may benefit from ICU treatment and to decide on treatment options. However, careful monitoring and early detection of these patients in terms of the critical disease process and rapid ICU transfer are important for survival (12).

The aim of this study is to evaluate the clinical characteristics, treatment methods and outcomes of critical patients with HM admitted to the general ICU.

Materials and Methods

Study Population and Design

Patients over 18 years with HM who were admitted to ICU from January 2013 to January 2020 were included in this study. Patients under the age of 18, patients who were followed up with HM but in complete remission and were admitted to ICU for another reason, and whom length of ICU stay less than 24 hours were excluded. The study was approved by the Non-Interventional Research Ethics Committee of Dokuz Eylül University (decision no: 2019/19-36, date: 31.07.2019).

The decision to admit the patient to the ICU was made by the intensive care specialist. In all consultations, the hematologist's opinion on the course and condition of the disease was asked and the ICU admission decision process were finalized accordingly. Treatment of HM was planned by the attending hematologist for each patient.

Definitions

The diagnoses of HM were classified as acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma (NHL), multiple myeloma and myelodysplastic syndrome. The type of SCT was identified as autologous or allogenic.

Disease status was determined by hematologists before ICU admission and categorized as "new diagnosis", "in remission" and "relapsed/refractory" according to each HM's specific criteria. Patients were categorized based on ICU admission reason as; disease-related, septic shock, graft-versus-host disease, acute respiratory failure (ARF), neurologic, gastrointestinal, and post cardiopulmonary resuscitation.

ARF was defined as less than 90% of oxygen saturation in room air or below 60 mmHg of arterial partial oxygen pressure (PaO_2) and severe shortness of breath during resting, as well as symptoms of inability to speak of a full sentence or respiratory rate or clinical respiratory distress of more than 30 breaths per minute (13). Sepsis and septic shock are defined according to the 2016 Third International Definition of Sepsis and Septic Shock Consensus (14). Neutropenia was defined as absolute neutrophil count $<0.5x10^3/\mu L$ and thrombocytopenia as platelet count $<50x10^3/\mu L$. The diagnosis of systemic fungal infection was clinically determined according to the revised definition

of invasive fungal disease (15). The use of inotropes and vasopressors was defined as the use of dobutamine, noradrenaline, adrenaline, and vasopressin in any dose.

Data Collection and Medical Records

Hospital records and laboratory data were examined in each patient and the following data were collected: Age, gender, Charlson comorbidity index (CCI), HM type, SCT and related complications, disease status, causes of admission, APACHE-II and SOFA scores, treatment types and supportive measures used during ICU stay including the use of [high-flow nasal oxygen therapy (HFNOT), non-invasive mechanical ventilation (NIMV), IMV, renal replacement therapy (RRT), vasoactive therapy, plasmapheresis, leukapheresis, blood product replacements, chemotherapy, fiberoptic bronchoscopy (FOB)]; laboratory parameters on the first day of ICU admission including arterial blood gas results PaO_2, $PaCO_2$; arterial partial carbon dioxide pressure, FiO_2; fraction of inspired oxygen, PO_2/FiO_2, HCO_3; bicarbonate, SO_2; oxygen saturation, lactate, complete blood count, C-reactive protein (CRP), procalcitonin, serum creatine, and fibrinogen. Length of ICU and hospital stay and ICU mortality were recorded. All microbiological results of the included patients were obtained from the hospital database. For each patient, all cultures sampled 24 hours before and after admission to the ICU were screened. Bronchoalveolar lavage (BAL) sampling was performed by experienced experts with fiberoptic bronchoscope (FOB, Olympus, Japan) in patients with >20,000/μL platelet count. The diagnosis of *pneumocystis jirovecii* pneumonia (PcP) was detected in tracheal secretion or BAL sampling, while cytomegalovirus (CMV) DNA was detected in BAL and peripheral blood by studying real-time polymerase chain reaction (PCR).

Statistical Analysis

Categorical variables were expressed as numbers and percentages. Continuous variables were expressed as the median and interquartile range (IQR). Statistical analysis was performed with SPSS (Statistical Package for the Social Sciences Version 26.0; IBM Corporation, Armonk, NY, USA) program.

Results

Patient Characteristics

Between January 2013 to January 2020, 172 patients [median age 60 (47-67), 60.5% male] with HM who were admitted to ICU were included in the study. The median APACHE-II score was 30 (26-32), SOFA score on the day of admission was 10 (7-12) and CCI was 7 (5-8). NHL was the most common HM (30.2%). It was determined that 47 (27.3%) patients had a history of SCT. Of them, 26 (15.1%) were autologous and 21 (12.2%) were allogeneic transplants. Sixty (34.9%) patients had novel diagnosis of HM (Table 1).

The most common reason of ICU admission was ARF (36.0%), the most common reasons of ARF were pneumonia (23.2%) and alveolar hemorrhage (4.6%). It was followed by septic shock (28.4%) and disease-related causes (13.3%). The most common reasons of septic shock were respiratory tract infection (16.9%) and catheter-related infection (4.75%). Thirteen patients (7.6%) were admitted after cardiac arrest and resuscitation (Table 2).

Table 1. Baseline clinical characteristics patients with haematological malignancy (n=172)

Clinical characteristics	All patients (n=172)
Age (years)	60 (47-67)
Male sex	104 (60.5)
APACHE-II score	28 (24-32)
SOFA score	10 (7-12)
CCI	7 (5-8)
ICU admission from	
Emergency department	12 (7)
Hematology clinic	160 (93)
Haematological malignancy	
Non-Hodgkin's lymphoma	52 (30.2)
Acute myeloid leukaemia	44 (25.6)
Multiple myeloma	33 (19.2)
Acute lymphoblastic leukaemia	16 (9.3)
Chronic lymphocytic leukaemia	12 (7.0)
Hodgkin's lymphoma	11 (6.4)
Chronic myelogenous leukaemia	3 (1.7)
Myelodysplastic syndromes	1 (0.6)
Previous stem cell transplantation	
Autologous stem cell transplant	26 (15.1)
Allogeneic stem cell transplant	21 (12.2)
Disease status	
Newly diagnosed	60 (34.9)
Relapsed/refractory	96 (55.8)
In remission	16 (9.3)

All values are expressed as numbers (percentages) or median (interquartile range). APACHE-II: Acute Physiology Assessment and Chronic Health Evaluation-II, CCI: Charlson comorbidity index, SOFA: Sequential Organ Failure Assessment, ICU: intensive care unit

Laboratory Results

The median hemoglobin level on the day of admission was 8.4 (7.5-9.6) gr/dL, platelet count was 37.5 (18.0-84.0) x10^3/μL, and neutrophil count was 2.4 (0.2-8.2)x10^3/μL. Neutropenia and thrombocytopenia were detected in 59 (34.3%) and 108 (62.8%) patients, respectively. Median (IQR) CRP and procalcitonin levels were 178 (92-271) mg/L, 2.82 (0.9-12) ng/mL, respectively. In arterial blood gas analysis, median PaO_2 and $PaCO_2$ were 69 (44-98) and 35 (28-40) mmHg, respectively. Additionally, The median SaO_2 and PO_2/FiO_2 were 92% (89-94) and 122 (108-172), respectively. The median lactate level was detected as 2.3 (1.3-4.2) mmol/L (Table 3).

Treatments and Outcomes

One hundred forty three (83.2%) patients were transferred to ICU after intubation. Amongst the others 26 (15.1%) patients were treated with NIMV, 3 patients (1.7%) were treated with HFNOT. Of them, 22 (84.6%) patients needed escalation of respiratory support and were intubated during ICU follow-up. Sixty four (37.2%) patients were started on vasopressors in ICU, while 159 (92.4%) patients needed vasopressors at any time during ICU stay.

FOB was planned for 55 (32.0%) patients for microbiological sampling, but it has only been performed on 28 (16.2%) patients (due to resistant thrombocytopenia and hemodynamic instability FOB could not be performed). Tracheostomy was performed in 9 (5.2%) patients on the median 14th day (IQR 6-23) of ICU stay.

Fourteen (8.1%) patients received chemotherapy for a median of 2 days (2-4). Six (3.5%) patients received 5 days (4-6) of plasmapheresis, five (2.9%) patients received 2 days (1-4%) of leukapheresis, and one (0.5%) patient received 5 days of photopheresis during ICU stay.

Table 2. Reason for ICU admission of patients with haematological malignancy

Reason for ICU admission	All patients (n=172)
ARF	**62 (36.0)**
Pneumonia	40 (23.2)
Alveolar hemorrhage	8 (4.6)
Tumor progression causing pleural effusion	7 (4.0)
Pulmonary edema	5 (2.9)
Superior vena cava syndrome	1 (0.5)
Pulmonary embolism	1 (0.5)
Septic shock	**49 (28.4)**
Respiratory tract infection	29 (16.9)
Catheter-related infection	8 (4.7)
Unknown source of infection	7 (4.1)
Urinary tract infection	5 (3.6)
Malignancy related	**23 (13.3)**
Hyperviscosity syndrome	10 (5.8)
Graft-versus-host disease	9 (5.2)
Tumor lysis syndrome	4 (2.3)
Disturbed consciousness	**19 (11)**
Intracranial bleeding	12 (7.0)
Malignant central nervous system infiltration	4 (2.4)
Seizure	3 (1.7)
Post-CPR	13 (7.6)
Gastrointestinal bleeding	6 (3.6)

All values are expressed as numbers (percentages). ARF: Acute respiratory failure, CPR: cardiopulmonary resuscitation, ICU: intensive care unit

Table 3. Laboratory findings of patients with haematological malignancy on ICU admission

Variables	
Hemoglobin, gr/dL	8.4 (7.5-9.6)
Neutrophil, 10^3/μL	2.4 (0.2-8.2)
Neutropenia (<500/μL)	59 (34.3%)
Platelet, x10^3/μL	37.5 (18.0-84.0)
Thrombocytopenia (<50x10^3/μL)	108 (62.8)
CRP, mg/L	178 (92-271)
Procalcitonin, ng/mL	2.82 (0.9-12)
INR	1.4 (1.2-1.7)
Fibrinogen, g/L	4.5 (2.81-6.07)
Creatinine, mg/dL	1.28 (0.77-2.18)
Arterial blood gas analysis	
pH	7.38 (7.30-7.43)
PaO_2, mmHg	69 (44-98)
$PaCO_2$, mmHg	35 (28-40)
FiO_2, %	0.50 (0.45-0.60)
PO_2/FiO_2	122 (108-172)
SaO_2, %	92 (89-94)
HCO_3, mmol/L	21 (18-24)
Lactate, mmol/L	2.3 (1.3-4.2)

All values are expressed as numbers (percentages) or median (interquartile range). INR: International normalized ratio, PaO_2: arterial partial oxygen pressure, $PaCO_2$: arterial partial carbon dioxide pressure, CRP: C-reactive protein, FiO_2: fraction of inspired oxygen, HCO_3: bicarbonate, SO_2: oxygen saturation, Scr: serum creatinine, ICU: intensive care unit

Patients were admitted to ICU median 28 (11-55) hours after the first consultation. Median ICU stay was 5 (2-12) days and median length of hospital stay was 26 (12-44) days. ICU mortality was 94.3% (n=163), hospital mortality was 98.3% (n=169), overall (Table 4).

Microbiological Examinations

Positive cultures were detected in tracheal secretions of 58 patients (33.7%) and the most common bacterial pathogens were *Acinetobacter* spp. (17.4%) and *Klebsiella* spp. (5.2%). Positive BAL cultures were detected in 21 patients, of which 5 (2.9%) were *Aspergillus* spp., 5 (2.9%) were *Candida* spp., 4 (2.3%) were *Acinetobacter* spp. compared to tracheal cultures, *Aspergillus* spp. in 3 patients and *Candida* spp. in 2 patients was detected only with BAL culture and not with tracheal culture. PcP PCR tested on BAL sampling was positive in 8 (4.6%) patients. Positive results were detected in the blood culture of 48 (27.9%) patients and the most common factors were *Acinetobacter* spp. (10.5%) and *Klebsiella* spp. (4.1%). CMV DNA was found to be significantly higher in the blood of 22 (12.8%) patients and in BAL of 3 (1.7%) patients in the samples examined with clinical and radiological suspicion (Table 5).

Discussion

In this study, clinical characteristics, supportive and hematologic treatments, and outcomes of HM patients admitted to ICU were examined in detail and important results were deduced. The median duration of delay in ICU admission was 28 hours. ICU mortality of patients with HM was 94.3% and hospital mortality was 98.3%, which is significantly higher than the date presented in the literature.

Many studies examined the factors affecting the prognosis and outcomes of patients with HM after ICU admission and although the results varied over the years with developing treatment regimens and significant improvement in ICU mortality (3), the high mortality rates in our study were notable.

First of all, in our study, the most common reasons for ICU admission of patients with HM were ARF and septic shock and this is compatible with the literature (3,6,16). The high APACHE-II and SOFA scores, which are significantly associated with ICU mortality, are consistent with other studies in the literature but our hospital and ICU mortality rates are higher than the data presented in the literature. In a study by Demandt et al. (6), the mean APACHE-II score was 29.5±7.4 and the mean SOFA score at admission was 10.9±3.4 while ICU mortality was 52% and hospital mortality was 60%. In another study, which showed an ICU mortality rate of 33.7%, the non-survivors group's median APACHE-II score was 27, and SOFA score was 11 (17).

Table 4. Types of pathogens isolated from various sites

Tracheal secretion sample culture	**58 (33.7)**
Acinetobacter spp.	30 (17.4)
Klebsiella spp.	9 (5.2)
Stenotrophomonas spp.	7 (4.1)
Pseudomonas spp.	4 (2.3)
Candida spp.	3 (1.7)
Staphylococcus spp.	3 (1.7)
Aspergillus spp.	2 (1.2)
Blood culture*	**48 (27.9)**
Acinetobacter spp.	18 (10.5)
Klebsiella spp.	14 (4.1)
Enterobacter spp.	6 (3.5)
Pseudomonas spp.	5 (2.0)
Stenotrophomonas spp.	2 (1.2)
Candida spp.	1 (0.6)
Urine culture	**10 (5.8)**
Candida spp.	5 (2.0)
Escherichia coli	3 (1.7)
Klebsiella spp.	2 (1.2)
Central catheter culture	**7 (4.1)**
Acinetobacter spp.	2 (1.2)
Klebsiella spp.	2 (1.2)
Pseudomonas spp.	2 (1.2)
Candida spp.	1 (0.6)
BAL sample	21 (12.2)
Aspergillus spp.	5 (2.9)
Candida spp.	5 (2.9)
Acinetobacter spp.	4 (2.3)
Klebsiella spp.	3 (1.7)
Stenotrophomonas spp.	2 (1.2)
Pseudomonas spp.	2 (1.2)
Bronchoalveolar lavage sample	
BAL PcP PCR	8 (4.6)
BAL CMV PCR	3 (1.7)
Blood CMV PCR	22 (12.8)

*Collected percutaneously or via a central vein. All values are expressed as numbers (percentages). PcP: *Pneumocystis carinii* pneumonia, BAL: bronchoalveolar lavage, CMV: cytomegalovirus, PCR: polymerase chain reaction

The high ICU and hospital mortality can be explained by the delayed admission of patients to the ICU and the high rates of need for IMV and vasopressor support in the first 24 hours.

Table 5. Treatments and outcomes of patients with haematological malignancy

Variables	All patients (n=172)
Treatments	
Respiratory support within 24 h of ICU admission	
MV	143 (83.2%)
NIMV	26 (15.1%)
HFNO	3 (1.7%)
Vasopressors on ICU admission day	64 (37.2%)
Vasopressors during ICU admission	159 (92.4%)
RRT	39 (22.7%)
RRT, days	4 (2-6)
Bronchoscopy for microbiological sampling	22 (12.8%)
Chemotherapy before ICU admission*	35 (20.3%)
Chemotherapy in ICU	14 (8.1%)
Chemotherapy in ICU, days	2 (2-4)
Plasmapheresis	6 (3.5%)
Plasmapheresis, days	5 (4-6)
Leukapheresis	5 (2.9%)
Leukapheresis, days	2 (1-4)
Photopheresis	1 (0.5)
Photopheresis, days	5 (5-5)
Tracheostomy	9 (5.2)
Tracheostomy day from admission	14 (6-23)
Total erythrocyte transfusion, unit	4 (2-8)
Apheresis platelets transfusion, unit	2 (1-5)
Pooled platelets transfusion, unit	12 (8-21)
Cryoprecipitate transfusion, unit	12 (8-14)
Fresh frozen plasma, unit	5 (2-8)
Outcomes	
Duration of IMV, days	4 (2-9)
Time from consultation to ICU admission, hours	28 (11-55)
Length of hospital stay, days	26 (12-44)
Length of ICU stay, days	5 (2-12)
Hospital mortality	169 (98.3%)
ICU mortality	163 (94.3%)

*Chemotherapy within 15 days of ICU hospitalization, all values are expressed as numbers (percentages) or median (interquartile range). HFNO: High flow nasal oxygen, ICU: intensive care unit, MV: mechanical ventilation, IMV: invasive mechanical ventilation, NIMV: non-invasive mechanical ventilation, RRT: renal replacement therapy

As shown in other studies (3,7,16,18) IMV is the most important factor affecting mortality in patients with HM. Irie et al. (17) emphasized that mortality is high in patients who need IMV within the first 24 hours of ICU admittance. Depuydt et al. (19) found that 48.9% of patients with HM needed IMV within the first 24 hours, and this group had ICU mortality rate of 63% and hospital mortality rate of 80%. In another study, hospital mortality was 75% in patients who needed IMV, 21.6% in patients who didn't receive IMV, compared to 90.6% in patients receiving IMV support with a history of SCT (20).

In our study, 108 patients (62.7%) were intubated on ICU admission. It was determined that 143 (83.7%) patients received IMV support within 24 hours of ICU acceptance and this group had 100% mortality. The most common reason for admission is ARF and median PaO_2/FiO_2 on the day of hospitalization is consistent with moderate acute respiratory distress syndrome. Considering the time passed between acceptance to ICU and admittance, we determined that admittance was delayed, especially for patients who required IMV within the first 24 of ICU admittance. In cancer patients, 84% of whom had HM, who was admitted to ICU with ARF the time between the onset of respiratory failure symptoms and transfer to the ICU has been shown to directly affect mortality (12). In previous studies, prolonged NIMV administration and delayed intubation have been associated with increased mortality and early management and treatment of ARF in ICU have been shown to reduce the risk of intubation (1,13).

The need for vasopressors during ICU hospitalization is another risk factor for mortality in patients with HM (2,20). In our study, it was determined that 49 (28.4%) patients needed vasopressors during ICU admittance and 159 (92.4%) patients needed vasopressors during ICU stay and vasopressor use is associated with increased mortality. In our study, it can be said that the incidence of sepsis and septic shock was high in this patient group when we consider median lactate, CRP, and procalcitonin values. This can also be explained by a delay in the transfer of ICU patients with HM. In a study, which examined critical neutropenic cancer patients, 83.6% of whom had HM, septic shock was detected in 59% of patients at ICU admission, and ARF was the most common cause of sepsis-related ICU admission indications. In the same study, it was emphasized that early ICU acceptance reduced the incidence of septic shock in

neutropenic patients (21). In our study, ARF and septic shock were the most common reasons of ICU admission.

FOB and BAL sampling are frequently used in ICU and are important diagnostic tools for patients with HM who have ARF. Azoulay et al. (13), who investigated the strategies of ARF diagnosis in patients with HM, sampled FOB-BAL in 32.7% of patients and changed treatment according to the results in all patients. In addition, 18% of patients were only diagnosed with FOB-BAL (13). For this purpose, it is recommended that this procedure, which is performed safely in critical patients with ARF, be added to non-invasive tests immediately after ICU hospitalization (13). In our study, it was determined that 16.2% of patients were diagnosed with FOB-BAL, 85% had treatment changes according to the results and only 13 (7.5%) patients were diagnosed with FOB-BAL. Therefore, early ICU admission and early treatment modification, especially antimicrobials are very important. Especially invasive aspergillosis is associated with increased mortality in patients presenting with ARF (1). In our study, *Aspergillus* spp. was detected in tracheal secretion culture in 2 (1.2%) patients and FOB-BAL culture in 5 patients (2.9%), and treatment was started. *Aspergillus* was identified as the most common pathogen in the study evaluating the BAL results of patients with HM and is consistent with our study. Other opportunistic infections such as PcP and CMV are especially common in patients with SCT and are associated with increased mortality (22,23). In our study, 8 (4.6%) patients were diagnosed with PcP, and 3 (1.7%) patients were diagnosed with CMV by FOB-BAL, and treatment was started.

Each hour of delay for ICU admission is associated with increased mortality in critically ill patients (24). Early ICU transfer of patients reduces mortality after diagnosis of critical illness (25).

In a multicenter study involving general ICU patients, the time from triage to admission was 2.1±3.9 hours (26). In our study, the median time between the evaluation of patients with HM and the admission to the ICU was 28 (11-55) hours. Lack of a separate ICU for HM patients may be an important reason for the delay in ICU admission. In a multicenter study, ICU mortality in all patients was 70.4%, compared to 66% in hematology centers with their ICU (27). Another reason for the delayed admission of the patients with HM to ICUs is the attiribution lower chance of benefit of the ICU treatment in patients with advanced or relapsed/refractory HM by intensivist. Hence, these patients might have been positioned last in triage due to the limited ICU sources.

Communication and cooperation between the hematologist and the intensivist are very effective in determining which patient will benefit from ICU. Costly treatments of HM patients continue at ICU and primary disease treatments are continuing with leukapheresis, plasmapheresis, chemotherapy protocols, blood product replacements ordered by hematologists. In our study, it was seen that these treatments are applied to a significant number of ICU patients and when possible, it is very important to determine beforehand which patients would benefit from these treatments (in ICU) and use them accordingly, in terms of both cost and using the limited ICU resources efficiently. A study showed that aggressive treatments continued in the last months of the lives of patients with HM, highlighting the need for better and earlier integration of palliative care approaches in standard hematology practice (28).

There are some limitations in our study. First of all, this is a retrospective single-center study and our results are not generalizable. Second, due to high mortality, the causes affecting mortality could not be evaluated statistically. However, there are some strengths: Our study is the first to comprehensively examine the characteristics and treatments of patients with HM admitted to the general ICU.

Conclusion

Patients with HM still have high ICU and hospital mortality. The HM disease and current treatment regimens are risk factors for critical illness. Delayed ICU admission time may increase mortality in patients with critical HM. Considering the high treatment costs and limited ICU bed capacity, the establishment of specialized ICUs for hematological patients in hematology clinics and early recognition of critical illness, and rapid intervention and transfer to intensive care may improve outcomes.

Ethics

Ethics Committee Approval: The study was approved by the Non-Interventional Research Ethics Committee of Dokuz Eylül University (decision no: 2019/19-36, date: 31.07.2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.K., M.C.Ö., M.N.Y., B.C., A.N.G., İ.A., B.E., Design: M.K., M.C.Ö., B.Y., Bi.E., M.N.Y., B.C., A.N.G., İ.A., B.E., Data Collection and Process: M.K., M.C.Ö., B.Y., Bi.E., M.N.Y., A.N.G., İ.A., Analysis or Interpretation: M.K., M.C.Ö., B.Y., Bi.E., B.C., İ.A., B.E., Literature Search: M.K., M.C.Ö., B.Y., Bi.E., M.N.Y., B.C., A.N.G., İ.A., B.E., Writing: M.K., Bi.E., M.N.Y., B.E.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Stewart's Approach for Acid-base Disorders: Does the Strong Ion Difference and Effects Have an Impact on Intensive Care Unit Mortality?

Asit-baz Bozukluklarına Stewart Yaklaşımı: Güçlü İyon Farkı Yoğun Bakım Mortalitesini Etkiler mi?

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ABSTRACT *Objective:* The diagnosis and treatment of electrolyte and acid-base imbalances in intensive care unit (ICU) patients have critical importance. The value of Stewart's approach in revealing acid-base disorders is known. There are parameters defined according to this approach. This study investigates the impact of the chloride effect (Cl_{Effect}), sodium effect (Na_{Effect}), sodium-chloride effect ($Na\text{-}Cl_{Effect}$), strong ion difference (SID_{nl}) and Cl/Na ratio values calculated according to Stewart's approach on ICU mortality.

Materials and Methods: Two thousand patients whose Na, Cl, K, standard base excess (SBE), pH values were recorded and SID_{nl}, Cl_{Effect}, Na_{Effect}, $Na\text{-}Cl_{Effect}$, Acute Physiology Assessment and Chronic Health Evaluation-II (APACHE-II) and Sequential Organ Failure Assessment (SOFA) scores calculated are included in this study. Cl_{Effect}, Na_{Effect}, $Na\text{-}Cl_{Effect}$, SID_{nl}, Cl/Na ratio values were evaluated with a multivariable logistic regression model in terms of ICU mortality.

Results: Abnormal ranges of SID_{nl} (SID_{nl} <30 or SID_{nl} ≥43) were significantly increased in non-survivors than survivors (p=0.026). Cl_{Effect}, Na_{Effect}, $Na\text{-}Cl_{Effect}$, Cl/Na ratio and their percentages of abnormal ranges were similar between survivor and non-survivor patients.In the multivariate logistic regression model, the likelihood of mortality was 3.5-fold (2.9-4.3), 1.7-fold (1.4-2.1) and 1.2-fold (1.0-1.5) increased by APACHE-II ≥26, SOFA >7, and SID_{nl} <30 or SID_{nl} ≥43 (p<0.001, p<0.001, p=0.041, respectively).

Conclusion: SID_{nl} is associated with ICU mortality, but pH, SBE, Cl_{Effect}, Na_{Effect}, $Na\text{-}Cl_{Effect}$ and Cl/Na ratio is not. SID_{nl} is one of the independent variables of Stewart's approach and is a valuable parameter in blood gas evaluations.

Keywords: Acid-base, strong ion difference, sodium, chloride, base excess, intensive care unit, mortality

ÖZ *Amaç:* Yoğun bakım ünitesi (YBÜ) hastalarında elektrolit ve asit-baz bozukluklarının tanı ve tedavisi kritik öneme sahiptir. Asit-baz bozukluklarını açıklamada Stewart yaklaşımının önemi bilinmektedir. Bu yaklaşıma göre tanımlanmış çeşitli parametreler vardır. Bu çalışmanın amacı, Stewart'ın yaklaşımına göre hesaplanan klorür etki (Cl_{Effect}), sodyum etki (Na_{Effect}), sodyum-klorür etki ($Na\text{-}Cl_{Effect}$) güçlü iyon farkı (SID_{nl}), Cl/Na oranı değerlerinin YBÜ mortalitesi üzerindeki etkilerini değerlendirmektir.

Gereç ve Yöntem: Bilgisayar destekli karar destek sistemine Na, Cl, K, standart baz fazlalığı (SBE), pH değerleri kaydedilen ve sisteme tanımlı formüller aracılığıyla SID, Na_{Effect}, Cl_{Effect}, $Na\text{-}Cl_{Effect}$, Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-II (APACHE-II) ve Sıralı Organ Yetmezliği Değerlendirmesi (SOFA) skorları hesaplanan 2.000 hasta bu çalışmaya dahil edilmiştir. Cl_{Effect}, Na_{Effect}, $Na\text{-}Cl_{Effect}$, SID_{nl}, Cl/Na oranı değerleri multivariable lojistik regresyon modeli ile YBÜ mortalitesi açısından değerlendirildi.

Bulgular: Anormal SID_{nl} aralıkları (SID_{nl} <30 veya SID_{nl} ≥43), ölen hastalarda hayatta kalanlara göre anlamlı olarak yüksekti (p=0,026). Cl_{Effect}, Na_{Effect}, $Na\text{-}Cl_{Effect}$, Cl/Na oranı ve bunların anormal aralıkları, hayatta kalan ve ölen hastalarda benzerdi. Multivariable lojistik regresyon modelinde, ölüm olasılığı APACHE-II ≥26, SOFA >7 ve SID_{nl} <30 veya SID_{nl} ≥43 olan hastalarda sırasıyla 3,5 kat (2,9-4,3), 1,7 kat (1,4-2,1) ve 1,2 kat (1,0-1,5) artmış olarak bulundu (p<0,001, p<0,001, p=0,041).

Sonuç: SID_{nl}, YBÜ mortalitesi ile ilişkili iken, pH, SBE, Cl_{Effect}, Na_{Effect}, $Na\text{-}Cl_{Effect}$ ve Cl/Na oranı değildir. Stewart yaklaşımının bağımsız değişkenlerinden biri olan SID_{nl}, kan gazı değerlendirmelerinde önemli bir parametredir.

Anahtar Kelimeler: Asit-baz, güçlü iyon farkı, sodyum, klorür, baz açığı, yoğun bakım ünitesi, mortalite

Introduction

Acid-base disorders are commonly found in patients admitted to the intensive care unit (ICU) as a consequence of the underlying disease or inappropriate fluid resuscitation. They are associated with high mortality and morbidity, often accompanying critical diseases (1). Therefore, the assessment of acid-base disorders is critical for accurate diagnosis and effective treatment.

Debates on which approach is more logical and holistic in the analysis of acid-base balance have continued for many years (2). However, Stewart's approach is more comprehensive than the others, it can define subtle or combined acid-base disorders that cannot be detected using only the Henderson-Hasselbalch or base excess (BE) approaches (3,4). Traditional approaches are insufficient to reveal causal mechanisms (5). Gilfix et al. (6) devised an original Fencl concept showing the impact of changes in strong ion difference (SID) and the total amount of weak acids (A_{TOT}) on BE and designed simple formulas that do not require computers or calculators, aiming to make Stewart's approach accessible (7). With this approach, complex acid-base abnormalities can be detected at the bedside, and early treatment targeting underlying causes can be started (8,9).

This study aims to investigate the impact of the chloride effect (Cl_{Effect}), sodium effect (Na_{Effect}), sodium-chloride effect ($Na\text{-}Cl_{Effect}$), non-lactate strong ion difference (SID_{nl}), chloride/sodium ratio (Cl/Na ratio) values calculated according to Stewart's approach by a computer-based decision support system on ICU mortality.

Materials and Methods

The retrospective observational study was approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee with a protocol code. 2019/49 (decision no: 2019-02-25, date: 21.01.2019). During the admission of all patients to the ICU, information and consent forms were signed by the relatives of the patients, stating that the patient data would be used in retrospective scientific studies.

Definitions and Calculations of the Effects and SID

The physicochemical approach is based on four mechanisms (6):

1) Na_{Effect}: Changes in the amount of solvent (i.e. water) concentrate or dilute the solution, changing the SID (8). This diluting effect of water is called the "free water effect".

2) Cl_{Effect}: Indicates the amount of change from normal serum chloride (Cl_s) concentration. First of all, the correction should be made by considering the dilution effect on chloride. This correction ($Cl_{corrected}$) is obtained by multiplying the measured serum chloride concentration (Cl_s) by the ratio of standard sodium (140 mmol/L) to the measured sodium (Na_s).

3) Protein effect: It shows the change of dominant weak acids such as albumin.

4) Other effects: The effect of negative ions (lactate, ketoacids, formate, oxalate, salicylate, sulfate, and phosphate), most of which cannot be measured and cause strong ion gap metabolic acidosis.

In our study, SID was calculated from the differences of strong ions other than lactate, also known as SID_{nl} (10). (See Electronic Supplement for formulas used in effects and SID_{nl} calculations).

Study Population

Data of 9,038 patients hospitalized in University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Anesthesiology and Reanimation General ICU between 01.01.2013-31.12.2019 and registered with 'ImdSoft-Metavision/QlinICU Clinical Decision Support Software (Israel)' were obtained by Structured Query Language inquiries. Radiometer ABL 800 (Denmark) was used for blood gas analysis. Patients who stayed in the ICU for less than 48 hours (3,234) and patients whose Acute Physiology Assessment and Chronic Health Evaluation-II (APACHE-II) score was not calculated (2,101) were excluded from the study. Out of 3,703 patients, 2000 patients whose Na_s, Cl_s, K_s, standard base excess (SBE), pH values were recorded and SID_{nl}, Cl_{Effect}, Na_{Effect}, $Na\text{-}Cl_{Effect}$, Cl/Na ratio, APACHE-II, and Sequential Organ Failure Assessment (SOFA) scores calculated are included in this study (Figure 1).

Inclusion criteria: All patients older than 17 years were admitted to the medical or surgical ICU.

Exclusion criteria: Patients hospitalized for less than 48 hours and whose Na_s, Cl_s, K_s, SBE, pH values were not recorded or effects, SID_{nl}, scores not calculated.

Statistical Analysis

Data were analyzed using SPSS 22 for Windows (IBM Corp., Armonk, NY, USA). Mean ± standard deviation, median (interquartile range), frequencies and percentages were used for descriptive data. The conformity of the quantitative data to the normal distribution was tested with the Kolmogorov-Smirnov test and graphical examinations.

Student's t-test and Mann-Whitney U test were used for comparisons between two groups (survivors and nonsurvivors) of quantitative variables. Pearson chi-square test was used to compare qualitative data. The optimal cut-off level for APACHE-II score, SOFA score, SBE and pH to affect mortality was evaluated with receiver operating characteristic analysis using the Youden index. Multivariate logistic regression analysis was used for the likelihood of mortality. APACHE-II score, SOFA score, SID_{nl}, SBE and pH were added to the multivariate model. A p-value of <0.05 was used to determine the significance.

Results

The study was conducted with 2,000 patients, 40.1% (n=803) female and 59.9% (n=1197) male (Table 1). The median age of the patients was 67 years. The median values

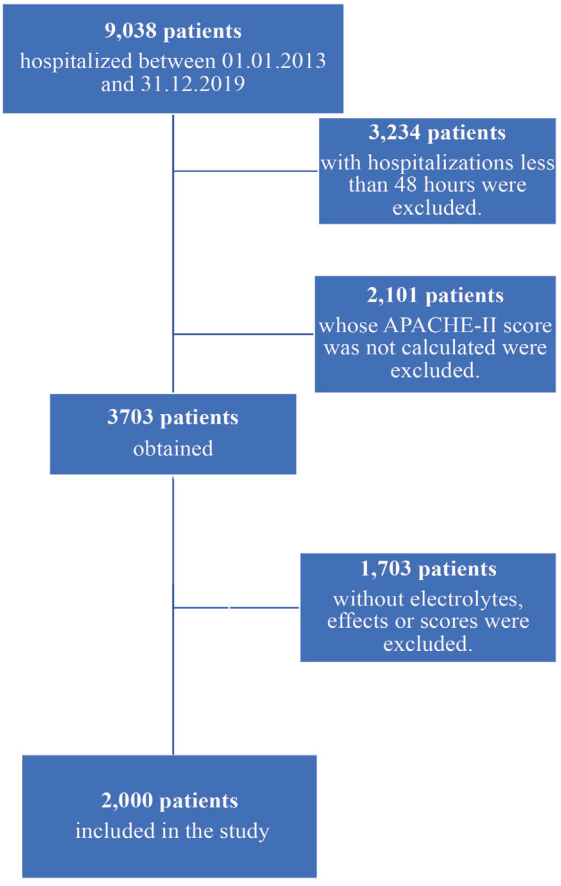

Figure 1. Flow chart of study participants
APACHE-II: Acute Physiology Assessment and Chronic Health Evaluation-II

Table 1. Patients' chracteristics and outcomes	
Patients, n	**2,000**
Age, years	67 (55-78)
Male, n (%)	1,197 (59.9)
BMI, (kg/m^2)	26.1 (24.2-29.4)
SOFA score	8 (6-11)
APACHE-II	26 (21-31)
Diagnosis, n (%)	
Medical	1,862 (93.1)
Surgery	138 (6.9)
pH	7.33 (7.23-7.40)
$PaCO_2$, (mmHg)	40.2 (33.4-49.0)
SBE, (mmol/L)	-4.5 (-9.2; -0.2)
Cl_s, (mmol/L)	107 (103-112)
Na_s, (mmol/L)	139 (136-144)
K, (mmol/L)	4.0 (3.6-4.4)
Cl_{Effect}, (mmol/L)	-5.1±9.0
$-14.1 \leq Cl_{Effect} \leq 4.9$	1,465 (73.2)
$Cl_{Effect} < -14.1$ or $Cl_{Effect} > 4.9$	535 (26.8)
Na_{Effect}, (mmol/L)	0.0 (-1.2-1.2)
$-1.2 \leq Na_{Effect} \leq 1.2$	1,127 (56.3)
$Na_{Effect} < -1.2$ or $Na_{Effect} > 1.2$	873 (43.7)
$Na\text{-}Cl_{Effect}$, (mmol/L)	-4.9±10.5
$-15.5 \leq Na\text{-}Cl_{Effect} \leq 4.6$	1,384 (69.2)
$Na\text{-}Cl_{Effect} < -15.5$ or $Na\text{-}Cl_{Effect} > 4.6$	616 (30.8)
SID_{nl}, (mmol/L)	37 (30-43)
$30 \leq SID_{nl} \leq 43$	1,092 (54.6)
$SID_{nl} < 30$ or $SID_{nl} \geq 43$	908 (45.4)
Cl/Na ratio	0.77 (0.72-0.81)
0.72≤ Cl/Na ratio ≤0.81	1,161 (58.1)
Cl/Na ratio <0.72 or Cl/Na ratio >0.81	839 (41.9)
Lactate, (mmol/L)	1.4 (1.0-2.0)
Urea, (mg/dL)	44 (27-70)
Creatine, (mg/dL)	0.7 (0.5-1.13)
Duration of IMV, (h)	88 (20-272)
Length of ICU stay, (h)	124 (48-306)
AKI, n (%)	796 (39.8)
Mortality, n (%)	1,069 (53.5)

AKI: Acute kidney injury, APACHE-II: Acute Physiology Assessment and Chronic Health Evaluation-II, BMI: body mass index, ICU: intensive care unit, IMV: invasive mechanical ventilation, $PaCO_2$: partial carbon dioxide pressure, $_s$: serum, SBE: standard base excess, SID_{nl}: non-lactate strong ion difference, SOFA: Sequential Organ Failure Assessment, Cl_{Effect}: chloride effect, Na_{Effect}: sodium effect, Cl/Na ratio: chloride/sodium ratio

of SOFA and APACHE-II scores were 8 (6-11) and 26 (21-31), respectively (Table 1). The mortality rate was 53.5% (n=1,069). The percentages of abnormal ranges of Cl_{Effect}, Na_{Effect}, $Na\text{-}Cl_{Effect}$, SID_{nl} and Cl/Na ratio were differently found (Table 1).

In non-survivors, SBE, pH, duration of invasive mechanical ventilation and length of ICU stay (LOS-ICU) were significantly decreased whereas SOFA and APACHE-II scores were significantly increased than survivors (p<0.001, p<0.001, p=0.034, p<0.001, p<0.001 and p<0.001 respectively) (Table 2).

Although median values of SID_{nl} were similar between the two groups, the percentage of abnormal ranges of SID_{nl} (SID_{nl} <30 or SID_{nl} ≥43) were significantly increased in non-survivors than survivors (p=0.390, p=0.026) (Table 2).

On the other hand, Cl_{Effect}, Na_{Effect}, $Na\text{-}Cl_{Effect}$, Cl/Na ratio and their percentages of abnormal ranges were also similar between survivor and non-survivor patients (p=0.846, p=0.309; p=0.072, p=0.612; p=0.981, p=0.903; p=0.706, p=0.218) (Table 2).

Cut-off and area under curve values of SOFA score, APACHE-II, SBE and pH were >7 [0.66 (0.64-0.69)], ≥26 [0.74 (0.72-0.76)], ≤-4.4 mmol/L [0.59 (0.56-0.61)] and <7.33 [0.57 (0.54-0.59)], respectively (p<0.001 for all) (Table 3).

In the multivariate logistic regression model, the likelihood of mortality were 3.5-fold (2.9-4.3), 1.7-fold (1.4-2.1) and 1.2-fold (1.0-1.5) increased by APACHE-II ≥26, SOFA >7, and SID_{nl} <30 or SID_{nl} ≥43, respectively (p<0.001, p<0.001, p=0.041) (Table 4).

Discussion

In the present study, it was shown that SOFA score, APACHE-II and abnormal SID_{nl} values (<30 or ≥43) at the ICU admission were associated with mortality. This highlights the importance of the Stewart approach and its metabolic component, SID. Unlike some studies, we didn't find any relationship between SBE, pH and mortality (11-14). SBE and pH are known as dependent variables, hence, we think that it can be the reason for this result. Discussions on the superiority of approaches to the diagnosis and treatment of acid-base disorders continue today (15-18). However, the physicochemical approach is thought to provide a broader perspective. In patients with normal pH and SBE values, it was shown that low SID, which can only be detected by Stewart's approach, is associated with prolonged hospitalization even at neutral pH (19). Furthermore, it is also known that SID and SID_{nl} were associated with increased ICU mortality and length of stay in ICU (10,20,21). For this reason, SID, especially SID_{nl}, is a more important blood-gas parameter which affects outcomes in the ICU.

Actually, SID_{nl} is a parameter which is used to detect electrolyte effect on acid-base status. And, a few electrolyte evaluation approaches are defined in the literature such as Fencl's corrections, base excess chloride (BE_{Cl}) and Cl/Na ratio (6,7,22,23). In our study, we didn't observe any relationship among all serum levels of electrolytes (Cl_s, Na_s, K_s), effect values of them (Cl_{Effect}, Na_{Effect}, $Na\text{-}Cl_{Effect}$), Cl/Na ratio and ICU mortality except for SID_{nl}. Effect values (Cl_{Effect}, $Na\text{-}Cl_{Effect}$), which are suitable for the Fencl concept that we used in our study, take into account the $Cl_{corrected}$ instead of the Cl_s in chloride measurements (6,7). The lack of mention of any correction in Stewart's approach has caused the Fencl concept to be criticized in this respect (23,24). Gucyetmez et al. (23) claimed that the best chloride evaluation approach was the BE_{Cl}. Indeed, SID_{nl} and BE_{Cl} mainly refer to the difference between Na and Cl in accordance with their formulas (23). Our results obviously show that approaches based on the difference between Na and Cl such as SID_{nl} and BE_{Cl} are also more valuable parameters to lead electrolyte effects on mortality in the ICU. For this reason, we can argue that the serum values of electrolytes should be evaluated without any correction.

Surprisingly, the median lactate value (1.4 mmol/L) was higher in survivor patients than in non-survivor patients (1.3 mmol/L) in our study. Therefore, no relationship was found between lactate and mortality. However, it is known that high lactate levels are associated with high mortality (25-28).

In this study, it was also found that APACHE-II ≥26 and SOFA score >7 were associated with higher mortality. This result is consistent with previous studies (29-31). In addition, as expected, the duration of mechanical ventilation and the LOS-ICU were found to be longer in non-survivor patients.

Although all parameters of the quantitative method have been previously defined in the software, it is not known how effectively these data are used by intensive care physicians and how they affect the treatment of patients. Also, due to the retrospective nature of our study, we could not test the adequacy of the sample size.

Table 2. Comparison between survivors and non-survivors			
	Survivors (n=931)	**Non-survivors (n=1069)**	**p-value**
Age, years	67 (54-77)	68 (56-78)	0.100
Male, n (%)	564 (60.6)	633 (59.2)	0.534
BMI, (kg/m^2)	26.1 (24.5-29.4)	26.1 (24.2-29.4)	0.329
SOFA score	7 (5-9)	9 (7-12)	<0.001
APACHE-II	23 (18-27)	29 (24-33)	<0.001
Diagnosis, n (%)			
Medical	860 (92.4)	1,002 (93.7)	0.232
Surgery	71 (7.6)	67 (6.3)	
pH	7.34 (7.26-7.41)	7.31 (7.21-7.40)	<0.001
$PaCO_2$, (mmHg)	40.4 (33.8-48.4)	40.1 (33.0-49.6)	0.827
SBE, (mmol/L)	-3.6 (-7.3; 0.0)	-5.6 (-10.8; -0.7)	<0.001
Na_s, (mmol/L)	139 (137-143)	139 (136-144)	0.682
Cl_s, (mmol/L)	108 (103-112)	107 (102-112)	0.152
K_s, (mmol/L)	4.0 (3.6-4.5)	3.9 (3.5-4.4)	0.144
Cl_{Effect}, (mmol/L)	-5.2±8.8	-5.1±9.2	0.846
-14.1≤ Cl_{Effect} ≤4.9	692 (74.3)	773 (72.3)	0.309
Cl_{Effect} <-14.1 or Cl_{Effect} >4.9	239 (25.7)	296 (27.7)	
Na_{Effect}, (mmol/L)	0.0 (-0.9; 1.2)	-0.3 (-1.2; 1.2)	0.072
-1.2≤ Na_{Effect} ≤1.2	519 (55.7)	608 (56.9)	0.612
Na_{Effect} <-1.2 or Na_{Effect} >1.2	412 (44.3)	461 (43.1)	
Na-Cl_{Effect}, (mmol/L)	-5.0 (-11.6; 1.3)	-5.1 (-11.7; 2.0)	0.981
-15.5≤ Na-Cl_{Effect} ≤4.6	643 (69.1)	741 (69.3)	0.903
Na-Cl_{Effect} <-15.5 or Na-Cl_{Effect} >4.6	288 (30.9)	328 (30.7)	
SID_{nl}, (mmol/L)	36 (31-43)	37 (30-44)	0.390
30≤ SID_{nl} ≤43	533 (57.3)	559 (52.3)	0.026
SID_{nl} <30 or SID_{nl} ≥43	398 (42.7)	510 (47.7)	
Cl/Na ratio	0.76 (0.73-0.81)	0.77 (0.72-0.81)	0.706
0.72≤ Cl/Na ratio ≤0.81	554 (59.5)	607 (56.8)	0.218
Cl/Na ratio <0.72 or Cl/Na ratio >0.81	377 (40.5)	462 (43.2)	
Lactate, (mmol/L)	1.4 (1.1-2.1)	1.3 (1.0-1.9)	0.068
Urea, (mg/dL)	44 (27-70)	44 (28-71)	0.587
Creatinine, (mg/dL)	0.71 (0.47-1.15)	0.72 (0.46-1.11)	0.979
AKI, n (%)	540 (58.0)	664 (62.1)	0.085
Duration of IMV, (h)	89 (0-272)	88 (26-272)	0.034
Length of ICU stay, (h)	139 (52-328)	111 (48-286)	<0.001

AKI: Acute kidney injury, APACHE-II: Acute Physiology Assessment and Chronic Health Evaluation-II, BMI: body mass index, ICU: intensive care unit, IMV: invasive mechanical ventilation, $PaCO_2$: partial carbon dioxide pressure, $_s$: serum, SBE: standard base excess, SID_{nl}: non-lactate strong ion difference, SOFA: Sequential Organ Failure Assessment, Cl_{Effect}: chloride effect, Na_{Effect}: sodium effect, Cl/Na ratio: chloride/sodium ratio

Table 3. Cut-off and area under curve values of significantly difference variables in non-survivors			
	Cut-off values	AUC (95% CI)	p-value
APACHE-II	≥26	0.74 (0.72-0.76)	<0.001
SOFA score	>7	0.66 (0.64-0.69)	<0.001
SBE, (mmol/L)	≤-4.4	0.59 (0.56-0.61)	<0.001
pH	<7.33	0.57 (0.54-0.59)	<0.001
APACHE-II: Acute Physiology Assessment and Chronic Health Evaluation-II, AUC: area under curve, CI: confidence interval, SBE: standard base excess, SOFA: Sequential Organ Failure Assessment			

Table 4. Multivariate logistic regression model for likelihood of mortality		
	OR (95% CI)	p-value
APACHE-II≥26	3.5 (2.9-4.3)	<0.001
SOFA score >7	1.7 (1.4-2.1)	<0.001
SID_{nl}<30 or SID_{nl}≥43, (mmol/L)	1.2 (1.0-1.5)	0.041
SBE ≤-4.4, (mmol/L)	1.2 (0.9-1.5)	0.102
pH<7.33	0.9 (0.8-1.2)	0.872
APACHE-II: Acute Physiology Assessment and Chronic Health Evaluation-II, CI: confidence interval, OR: odds ratio, SBE: standard base excess, SID_{nl}: non-lactate strong ion difference, SOFA: Sequential Organ Failure Assessment		

Conclusion

The importance of Stewart's approach, especially in defining complex acid-base disorders, is known. The results of our study show that SID_{nl} is associated with ICU mortality, but pH, SBE and Na-Cl_{Effect} are not. Therefore, SID_{nl} is a valuable parameter in blood gas evaluations.

Ethics

Ethics Committee Approval: The retrospective observational study was approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee with a protocol code. 2019/49 (decision no: 2019-02-25, date: 21.01.2019).

Informed Consent: During the admission of all patients to the ICU, information and consent forms were signed by the relatives of the patients, stating that the patient data would be used in retrospective scientific studies.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.T., S.A., K.A.T., Concept: F.T., S.A., Z.Ç., Design: F.T., S.A., Data Collection and Process: F.T., S.A., B.Ö.B., K.A.T., Z.Ç., Analysis or Interpretation: F.T., S.A., B.Ö.B., G.Ö.Y., K.A.T., Z.Ç., Literature Search: F.T., Z.Ç., Writing: F.T., S.A., G.Ö.Y., K.A.T., Z.Ç.

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Electronic Supplement

Supplementer Data

SID (strong ion difference), Sodium Effect, Chloride Effect, Sodium Chloride Effect were calculated using the formulas defined in ImdSoft-Metavision/QlinICU Clinical Decision Support Software over the laboratory parameters of the patients with the software language as shown below (1-4):

Chloride Effect

```
If Parameters.Uvalue("Cl")>0 then
cl=Parameters.Uvalue("Cl")
Else
cl=0
End If
If Parameters.Uvalue("Na+")>0 then
na=Parameters.Uvalue("Na+")
Else
na=0
End If
If na>0 and cl>0 then
Return_Value=Round(((140/na)*cl),2)
Else
Return_Value="–"
End If
If Parameters.Uvalue("Cl")>0 then
cl=Parameters.Uvalue("Cl")
Else
cl=0
End If
If Parameters.Uvalue("Na+")>0 then
na=Parameters.Uvalue("Na+")
Else
na=0
End If
If cl>0 and na>0 then
Return_Value=102-(Round(((140/na)*cl),2))
Else
Return_Value="–"
End If
```

Sodium Effect

```
If Parameters.Uvalue("Na+")>0 then
Na=Parameters.Uvalue("Na+")
Else
Na=0
End If
If na>0 then
Return_Value=Round((0.3*(Na-140)),2)
Else
Return_Value="–"
End If
```

Sodium Chloride effect

```
Value"Sodium Effect"+ Value" Chloride Effect"
```

Chloride /Sodium Ratio

```
a=("Klor")
b= ("Sodyum")
if  a>0 and  b>0 then
result=Round((a/b),2)
else
result=" "
end if
Return_Value =result
```

SID_{nl}

```
if ("Na+")>0 then
s=("Sodyum")
k=("Klor")
p=("Potasyum")
Return Value=Round(((s+p)-k),0)
```

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Analysis of Heart Rate Variability in Patients Undergoing Mechanical Ventilation

Mekanik Ventilasyon Uygulanan Hastalardaki Kalp Hızı Değişkenliğinin İncelenmesi

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Presented in: The summary of this study was orally presented at the Balkan States Anesthesia Days-II Congress (Tirana, Albenia, May 2015).

ABSTRACT *Objective:* In this study, the purpose was to determine the changes in the activity of the autonomic nervous system by analyzing the parameters of heart rate variability (HRV) among patients who underwent invasive mechanical ventilation.
Materials and Methods: A total of 83 patients who had been followed up in the intensive care unit for at least 24 h, without a diagnosis of any known heart disease or arrhythmia, and aged over 18 years were included in the study. Mechanically ventilated patients were included in group M (n=41) and others in group K (n=42). The electrocardiography (ECGs) of the patients was recorded for 24 h through a Holter device, which records ambulatory ECG with 3 channels.
Results: There was no significant difference between the groups regarding the HRV parameters, atrial arrhythmia numbers, heart rates, RR interval times, as well as intervals of QT and QTc. It was found that the number of ventricular arrhythmias was significantly higher in the mechanically ventilated group compared to the non-mechanically ventilated group (p=0.0083).
Conclusion: In conclusion, based on the results of this study, we believe that invasive mechanical ventilation did not lead to changes in the HRV parameters of the patients who were hemodynamically stable without any cardiac disease.
Keywords: Ventilation, respiration, intensive care unit, heart rate, electrocardiography

ÖZ *Amaç:* Bu çalışmada, invaziv mekanik ventilasyon uygulanan hastalarda kalp hızı değişkenliği parametrelerini analiz ederek otonom sinir sistemi aktivitesindeki değişiklikleri belirlemeyi amaçladık.
Gereç ve Yöntem: Bilinen herhangi bir kalp hastalığı veya aritmi tanısı olmayan, en az 24 saat yoğun bakımda izlenmiş olan 18 yaş üstü toplam 83 hasta çalışmaya dahil edildi. Mekanik ventilasyon uygulanan hastalar grup M'ye (n=41), uygulanmayanlar grup K'ye (n=42) dahil edildi. Hastaların elektrokardiyografileri (EKG), 3 kanallı EKG kaydeden Holter cihazı ile 24 saat boyunca kaydedildi.
Bulgular: Kalp hızı değişkenlik parametreleri, atriyal aritmi sayıları, kalp hızları, RR interval süreleri, QT ve QTc aralıkları açısından gruplar arasında anlamlı fark yoktu. Ventriküler aritmi sayısının mekanik ventilasyon uygulanan grupta mekanik ventilasyon uygulanmayan gruba göre anlamlı derecede yüksek olduğu saptandı (p=0,0083).
Sonuç: Çalışmamızın sonuçlarına dayanarak, herhangi bir kalp hastalığı olmayan hemodinamik olarak stabil olan hastalarda invaziv mekanik ventilasyonun kalp hızı değişkenlik parametrelerinde değişikliğe yol açmadığına inanıyoruz.
Anahtar Kelimeler: Ventilasyon, solunum, yoğun bakım, kalp hızı, elektrokardiyografi

Introduction

Mechanical ventilation may cause changes in cardiac parameters such as heart rate, preload, contraction, and afterload by affecting parameters such as lung volume, intrathoracic pressure, and autonomic nervous system tone (1). Changes in lung volume during invasive mechanical ventilation can cause sinus arrhythmia, decreased heart rate, and reflex arterial vasodilation (2). These changes might not be determined through standard monitoring techniques unless they cause severe arrhythmias.

Heart rate variability (HRV) consists of very low frequency (VLF), low frequency (LF), high frequency (HF), and total

power (TP) components. HRV analysis is a simple and non-invasive technique, which is utilized to assess autonomic function and sympathovagal balance at the sino-atrial level (3). In this regard, an increase in sympathetic activity or a decrease in vagal activity on cardiac functions can be assessed through HRV. Values of the normalized high frequency (HFn), which is one of the autonomic nervous system parameters, account for parasympathetic activity, while normalized low frequency (LFn) are considered to be the indicators of sympathetic activity (4). The decrease in HRV is considered to be correlated with increased sympathetic modulation and has been associated with an increased risk of cardiovascular disease, arrhythmia, and sudden cardiac death (3,4). Moreover, decreased HRV and autonomic changes are correlated with an increase in malignant ventricular arrhythmias (3). Thanks to Holter monitoring, electrocardiography (ECG) parameters can be recorded for 24 hours, and these records can be analyzed by a computer. In our study, we aimed to investigate comparatively the parameters of HRV and activities of the autonomic nervous system among intensive care patients who had undergone invasive mechanical ventilation and those who had not through continuous Holter monitoring technique.

Materials and Methods

After obtaining Ankara Training and Research Hospital Education, Planning and Coordination Board approval (decision no: 4032, date: 19.02.2013), patients who met the study criteria in Ankara Training and Research Hospital tertiary intensive care unit (ICU) within two years were included in the study. Written consent was taken to participate in the study of the patient's relatives. The study was performed according to the Declaration of Helsinki. Patients aged over 18, who had undergone invasive mechanical ventilation and those who had not, were divided into two groups, each of which consisting of 50 patients. The demographic characteristics of the patients, their pre-admission characteristics to the ICU, and the duration of intensive care hospitalization until they were included in the study were recorded. Patients aged under 18, pregnant, patients who stayed in the ICU for less than 24 hours, and those who had been receiving medications that affect the interval of corrected QT (QTc) (antiarrhythmic drugs, beta-blockers, tricyclic antidepressants, phenothiazines), who had arrhythmias, bundle branch blocks or preexcitation, as well as those who had not normal sinus rhythm, who had a medical history of myocardial infarction, congestive heart failure, and the patients with the diagnosis of secondary or idiopathic long QT syndrome were excluded from the study. In addition, patients who had been receiving sedation and inotropic support were excluded from the study. Intubated patients who underwent mechanical ventilation for at least 24 hours were included in the study.

In the study, the mechanical ventilator mode had been set as Pressure-Synchronized Intermittent Mandatory Ventilation, and parameters of the patients who underwent mechanical ventilation throughout the follow-up period had been set to generate a frequency of 14/min, positive end-expiratory pressure (PEEP): 5 cm H_2O and tidal volume of 6-8 mL/kg. The same brand and model of mechanical ventilators were used in all patients (Galileo Classic, Hamilton Medical AG, Switzerland). To exclude the changes, which occurred during the weaning period, patients who did not undergo mechanical ventilation in group K were selected from those who had never been intubated since admission to the ICU. The ECGs of the patients in both groups were recorded for 24 hours with a Holter device (NorthEast's DR200/HE, NorthEast Monitoring, Inc., USA.), which recorded a 3-channel ambulatory ECG and transferred to the Holter analysis system (NorthEast's Holter LX Analysis Software New Version 5.4). For the analysis of the Holter records, the minimal, maximal and mean heart rates of the patients, as well as the HRV parameters, HFn and LFn measurements, the LF/HF ratios, and the measurements of the RR durations were assessed. QTc intervals were calculated by using Bazett's formula ($QTc=QT\sqrt{RR}$). Global sympathetic index (GSI) calculations were performed using the formula of LF + VLF/HF (5). The QRS complexes were automatically classified as normal sinus rhythm, atrial or ventricular premature beats, and manually verified. Normal intervals of RR (N-N intervals) were measured based on the normal sinus beats. Analysis of the HRV was conducted based on the records. Values of VLF (0.01-0.04 Hz), LF (0.04-0.15 Hz), HF (0.15-0.4 Hz), and TP (0.01-0.4 Hz) were obtained from the sum of the areas within their range through performing power spectrum density analysis. "Normalized HF" and "LF" components, which are expressions of these components in percentage, were calculated by proportioning these components to the total power.

The sample size was calculated for the student t-test, which was used to test the primary hypothesis of our study. As a result of the sample size analysis performed using Cohen's effect size value of 0.58 (determined by expert opinion as a result of the pilot study) with a minimum of 80% power (1-β=0.20) and α=0.05 error (95% confidence interval), it was found that a minimum of 74 patients (37 patients in both groups) should be included in the study to reveal significant differences between the HRV parameters of two independent research groups. However, it was decided to include 80 patients (an additional 10%) in the study, taking into account the patients who could leave the study during the research process. The G*power software (Version 3.1.9.7, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) was used for sample size estimation.

Holter recordings were assessed by a cardiologist who did not know which group the patients belonged to. Patients who had normal sinus beats as >85% at the time of analysis were included and recordings with intense artifacts were excluded from the study. As a result, the study was performed with 42 patients from the group, which had not undergone mechanical ventilation, and 41 patients from the intubated group, which had undergone mechanical ventilation.

Statistical Analysis

To determine the normality of the distribution, the Kolmogorov-Smirnov test was used for the statistical analysis of all quantitative data. T-test was used for intergroup comparison of quantitative data, which conformed to the normal distribution, and Mann-Whitney U test was used for comparing quantitative data, which did not conform to normal distribution between the groups. Results were presented as the mean +/- standard deviation. The chi-square test was used to compare qualitative data between groups. Results were presented as percentages and were considered statistically significant at p≤0.05.

Results

When the demographic data were examined, it was determined that there was no statistically significant difference between the groups, which had undergone mechanical ventilation and those that had not (Table 1).

It was found that there was no significant difference between the groups concerning the HRV variables including the LF, HF, HFn, LFn, LF/HF ratios, VLF, TP, and GSI values (Table 2).

The normalized HF and LF percentages of both groups are shown in Figure 1.

It was determined that there was no statistically significant difference between the atrial arrhythmia numbers, maximal, minimal, and mean values of the heart rates, durations of RR, as well as durations of QT and QTc. Durations of RR, QT, and QTc of both groups are shown in Figure 2.

When the number of ventricular arrhythmias was examined between the two groups, it was found to be higher in the group that had undergone mechanical ventilation compared to the group, which had no mechanical ventilation (Table 3). It was determined that the mean number of ventricular arrhythmias was 59.537±107.460 in the mechanically ventilated group, while it was 54.952±185 in the group that had not undergone mechanical ventilation (p=0.0083).

Table 1. Demographic data

Group	Group M	Group K
Age	58.14±19.94	57.73±15.96
Number of patients	41	42
Gender M/F	27/14	23/19
Reason of admission to intensive care		
Pneumonia	14	7
GIS surgery	8	4
Trauma	6	6
Other	7	14

Group M: Mechanical ventilated group, group K: non-mechanical ventilated group, M: male, F: female, GIS: gastrointestinal system

Table 2. Mean and standard deviation values of heart rate variability components			
HRV	**Group M**	**Group K**	**p-value**
Total power (msn^2) Mean ± SD	3.77±2.34	3.47±2.06	0.421
VLF (msn^2) Mean ± SD	4.23±2.60	3.25±2.03	0.0974
LF (msn^2) Mean ± SD	4.72±2.69	3.95±2.29	0.2071
HF (msn^2) Mean ± SD	3.65±2.40	3.64±2.69	0.6068
LF/HF ratio	1.91±1.57	2.10±1.99	0.9274
LF nu	53.98±25.79	63.57±29.06	0.0699
HF nu	46.51±25.93	36.87±28.95	0.0735
Global sympathetic index	3.56±2.44	3.27±3.16	0.2088
VLF: Very low frequency, LF: low frequency, HF: high frequency, LF nu: normalized low frequency, HF nu: normalized high frequency, SD: standard deviation, HRV: heart rate variability			

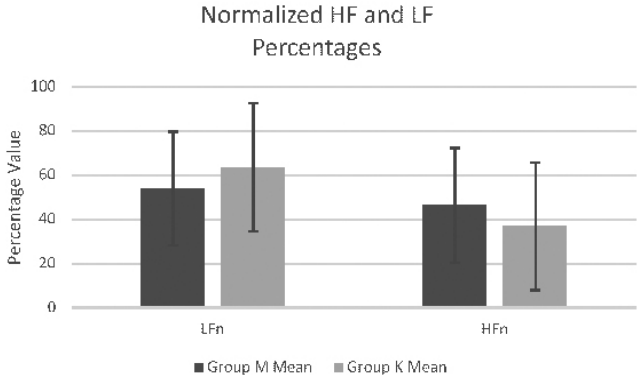

Figure 1. Mean values of HFn and LFn, and standard deviation values in the group
HFn: Normalized high frequency, LFn: normalized low frequency

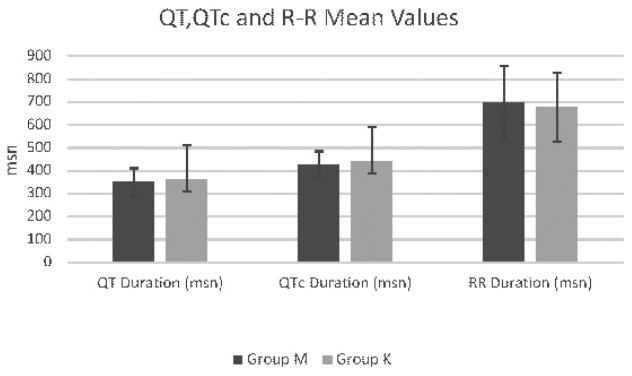

Figure 2. Mean ± SD values for QT, QTc, and RR durations of the groups
SD: Standard deviation

Table 3. Mean values of heart rate, QT durations, and arrhythmia numbers for the groups			
	Mechanical ventilation group	**Non-mechanical ventilation group**	**p-value**
Maximum heart rate	131.70±31.77	138.97±27.31	0.1282
Minimum heart rate	61.09±15.52	60.57±18.46	0.6099
Average heart rate	89.90±18.51	86.23±18.64	0.3718
QT duration (msn)	351.22±59.37	360.95±51.02	0.4252
QTc duration (msn)	425.70±58.67	438.78±48.94	0.2730
RR duration (sec)	0.696±0.16	0.677±0.15	0.4661
Ventricular arrhythmia (VES)	59.53±107.46	54.95±185.14	0.0083
Atrial arrhythmia (AES)	34.58±90.56	40.78±120.84	0.1282
Number of supraventricular tachycardia attacks	1.17±3.54	0.35±1.26	0.3249
Number of ventricular tachycardia attacks	0.56±1.76	0.14±0.92	0.1124
VES: Ventricular extrasystoles, sec: second, AES: atrial extrasystoles			

Discussion

In this study, which investigated the effect of mechanical ventilation on HRV between two demographically similar groups, no significant differences were found between the two groups. There was no significant difference between the groups concerning the HRV variables including the LF, HF, HFn, LFn, LF/HF ratios, VLF, TP, and GSI values. Also, there was no statistically significant difference between the atrial arrhythmia numbers, maximal, minimal, and mean values of the heart rates, durations of RR, as well as durations of QT and QTc. Different from these results, the number of ventricular arrhythmias was found to be higher in the group that had undergone mechanical ventilation compared to the group which had no mechanical ventilation. It was determined that the mean number of ventricular arrhythmias was 59.537±107.460 in the mechanically ventilated group, while it was 54.952±185 in the group that had not undergone mechanical ventilation (p=0.0083).

The HF component of HRV primarily indicates parasympathetic modulation (4,6-9). Although the LF component is thought to demonstrate both sympathetic and parasympathetic activity, recent studies are showing that the LF component is not a measure of cardiac sympathetic tone (4,6,8,10,11). Moreover, the LF/HF ratio is regarded to demonstrate the sympathetic-parasympathetic balance (5). However, due to the complex and uncertain situation in the LF component, the accuracy of the thought that the LF/HF ratio indicates sympathovagal balance is controversial (12). No significant difference was determined in this study regarding the HRV variability and GSI components among patients who underwent ventilation and control groups. In this respect, our study contradicts the results of Macefield (13) and Wallin (14) who revealed that high intrathoracic pressure caused an increased sympathetic response in the muscles, and the results of Garet et al. (15), which indicated indicated that positive pressure ventilation causes a decrease in the LF band and an increase in the HF band.

Increases in respiratory frequency and tidal volume may affect both high and low-frequency spectral components (16). In a study carried out by Thungton et al. (17) in a rat model with acute lung injury, biological variable ventilation (BVV) and continuous mechanical ventilation (CMV) modes were compared and no HRV variability was detected. In this study, when the RR intervals were examined, no change was observed, but when the periodic repetitions (periodicity) of the intervals were examined, it was determined that there were more RR interval changes in BVV mode than in the CMV mode. Variable lung volumes in BVV mode have been noted to lead to this result. It was found in the study that there was no statistically significant difference when the two groups were compared in this regard by making RR measurements, which is the indicator of parasympathetic tone. Based on the results of Thungton et al.'s (17) study, it was thought that the reason why HRV changes were not observed in our study may be due to the low volume changes in the selected mode and settings. The results of our research are in line with the study of Elinoff et al. (18), which demonstrated that there are no major ECG changes in mechanically ventilated patients.

In hemodynamically unstable critically ill patients in whom heart rate can change rapidly, erroneous conclusions about HRV are possible if the heart rate is not taken into account (16). The results of studies on this subject show that changes in HRV and autonomic nervous system during mechanical ventilation are dependent on the current cardiovascular status (19). According to the general opinion revealed in the results of studies on this subject, HRV changes are not expected in hemodynamically stable patients, like the patients in our study.

There are reports in the literature stating that there may be changes in HRV and autonomic nervous system function depending on the level of sedation (20,21). According to the results of one of them, deep sedation, especially with benzodiazepines, may be associated with suppression of parasympathetic function in patients receiving mechanical ventilation (21). Similarly, Kasaoka et al. (22), suggested that mechanical ventilation combined with sedation could reduce autonomic nervous system function in intensive care patients. To exclude HRV changes due to sedation, patients were not sedated in our study.

It was found in the study of Güntzel Chiappa et al. (23), which compared the acute effects of spontaneous breathing with T-piece and ventilation with pressure support ventilation in intensive care patients, that there was an increase in LF values among patients who spontaneously breathing with a T-piece, whereas there was a decrease in HF values, and hence an increased LF/HF ratio (23). In a different study, Crescimanno et al. (24) compared the same ventilator parameters and different PEEP values, and higher sympathetic activity was observed in the examination of HRV in patients who underwent PEEP. Based on this result, it was thought that different ventilator settings may increase

sympathetic activity. Besides different ventilator settings, the weaning process also changes the normal ventilation mechanics. Studies on this subject have shown that HRV changes that occur in weaning failure are a decrease in HRV and vagal withdrawal in autonomic nervous system activity (25). A recent study examined the relationship between HRV change and weaning outcomes in critically ill patients. The results of this study showed that HRV changes can be used as a guide for successful extubation (26). To exclude these changes, patients in the weaning period were not included in our study. It was determined in our study that there was no significant difference between the two groups regarding the HRV variables.

GSI is one of the sympathovagal balance indicators and has a positive correlation with the increase in sympathetic tone, as in the LF/HF ratio (5). The GSI was calculated in our study as well, and there was no difference in GSI values because there was no difference between the two groups in HRV values.

The prolongation of the QT (QTc) interval, which is corrected based on the heart rate, is considered to be pathological (27). Arai et al. (28) investigated the correlation between the QT interval and HRV among youngsters, and they found out that the QTc interval was negatively correlated with parasympathetic activity. In our study, there was no statistically significant difference between the two groups, regarding the QTc intervals.

The impacts of the autonomic nervous system on ventricular arrhythmias have been examined both in various heart diseases and in individuals without structural heart disease. Ventricular tachycardias, which occur typically during sympathetic tone increase or isoproterenol infusion, are considered to be the result of the triggered activity (29). In the study by Shen and Zipes (30), which investigates the relationship between the autonomic nervous system and arrhythmias, it was revealed that the sympathetic activity was proarrhythmic and the parasympathetic effect was antiarrhythmic. In our study, the number of ventricular arrhythmias was determined to be significantly higher (p=0.0083) in the mechanically ventilated group; the publications, demonstrate that ventricular arrhythmias are associated with sympathetic activity (29,30), and the publications, which put forwards that HRV has deficiencies in showing the sympathetic effect (31), made us think that sympathetic activity could not be monitored thoroughly in our study.

Our failure to detect HRV changes, which are linked to mechanical ventilation in our study, might be resulting from various reasons and limitations. First, positive pressure ventilation might not generate consistent HRV changes in individuals who are hemodynamically stable and have no active cardiac disease. The second likelihood is that the difference between the tidal volume of the patients and the tidal volume, which was applied in our study, may not be great enough to reveal the ECG and HRV changes, which were specified previously, that occur with hyperinflation. When compared with the studies consisting of different patient groups that we examined due to the design of the study, it was found that our patient group was more stable in terms of hemodynamically than the other groups; and there was no active cardiac disease in our group. Even though including patients who had no active cardiac disease seems to limit the study, it strengthened our study since it enabled us to determine the impact of mechanical ventilation by isolating other variables that might be encountered. Another limiting factor was that we used only a single ventilator parameter. Various tidal volumes and PEEP applications could induce ECG and HRV changes that we could not detect. Given that the ventilator settings, which we preferred, are often used clinically, we consider that these settings do not have a major impact, but we cannot state the same for other ventilator settings.

Conclusion

Consequently, we believe that there is no significant change in the activity of the autonomic nervous system and HRV variables during invasive mechanical ventilation in ICU patients who have not any active cardiac disease and who are hemodynamically stable.

Ethics

Ethics Committee Approval: The study was approved by the Ankara Training and Research Hospital Education, Planning and Coordination Board (decision no: 4032, date: 19.02.2013).

Informed Consent: Written consent was taken to participate in the study of the patient's relatives.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.Y., Ç.K., N.N.Ö., H.B., Concept: R.Y., Ç.K., S.N.M., H.B., A.Ö., Design: R.Y., Ç.K., H.B., A.Ö., M.S.K., Data Collection and Process: R.Y., N.N.Ö., A.Ö., A.K., Analysis or Interpretation: R.Y., Ç.K., N.N.Ö., S.N.M., H.B., A.Ö., A.K., M.S.K., Literature Search: R.Y., Ç.K., N.N.Ö., A.K., M.S.K., Writing: R.Y., Ç.K., N.N.Ö., S.N.M., H.B., A.Ö., A.K., M.S.K.

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

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Evaluation of Trauma Patients Followed Up and Treated in Intensive Care Unit: The Sample of İstanbul Province Training and Research Hospital

Yoğun Bakım Ünitesinde Takip ve Tedavisi Yapılan Travma Hastalarının Değerlendirilmesi: İstanbul İli Eğitim ve Araştırma Hastanesi Örneği

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ABSTRACT *Objective:* Trauma is an important cause of functional limitation, disability, and mortality. This study investigated the clinical characteristics of trauma patients and the factors affecting mortality in intensive care unit (ICU).
Materials and Methods: The data of patients who were followed up due to trauma in the ICU of University of Health Sciences Turkey, İstanbul Kanuni Sultan Süleyman Training and Research Hospital between January 2019-2020 were evaluated retrospectively. Demographic data, comorbidities, trauma etiologies, Glasgow coma score (GCS), Acute Physiology Assessment and Chronic Health Evaluation-II (APACHE-II) score, revised trauma score (RTS), lactate levels, and mortality were investigated.
Results: Two hundred fifty (25.2%) patients were followed up in the ICU with a trauma diagnosis. 60.4% of the patients were male, and the median age was 58.5 (1-97). 71.6% of the patients had no systemic disease. While blunt trauma was observed in 94% of the patients, the most common type of trauma was falling, with 64.4%. ICU and mechanical ventilation (MV) stay median lengths were 4 (1-86) and 1 (0-53) days. The median ICU admission GCS was 11 (3-15), APACHE-II score was 22 (5-56), RTS of 7 (2-10) and lactate value was 1.66 (0.7-19.8) mmoL. While 85.6% of the patients were discharged, 14.4% died. Age, duration of stay in ICU and MV, lactate levels, and APACHE-II scores were significantly higher in patients with mortality. GCS and RTS scores were significantly lower ($p<0.05$). In multiple logistic regression analyses, RTS and lactate values were independent risk factors for mortality.
Conclusion: We think that high lactate levels and low RTS help predict mortality in trauma patients in the ICU.
Keywords: Trauma, intensive care unit, mortality, scoring systems, lactate

ÖZ *Amaç:* Travma fonksiyonel kısıtlılık, sakatlık ve mortalitenin önemli bir sebebidir. Bu çalışmada, yoğun bakım ünitesinde (YBÜ) takip edilen travma hastalarının klinik özellikleri ile mortaliteyi etkileyen faktörler araştırılmıştır.
Gereç ve Yöntem: Ocak 2019-2020 tarihleri arasında Sağlık Bilimleri Üniversitesi, İstanbul Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi YBÜ'sünde travma nedeniyle takip edilen hastaların verileri retrospektif olarak değerlendirildi. Hastaların demografik verileri, komorbiditeleri, travma etiyolojileri, yatış sırasındaki Glasgow koma skoru (GKS), Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-II (APACHE-II) skoru, revize travma skoru (RTS), laktat düzeyleri ve mortaliteler araştırıldı.
Bulgular: YBÜ'de travma nedenli 250 (%25,2) hasta takip edilmiştir. Hastaların %60,4'ü erkek ve medyan yaş 58,5 (1-97) idi. Hastaların %71,6'sının sistemik hastalığı yoktu. Hastaların %94'ünde künt travma gözlenirken, en sık travma şekli %64,4 ile düşme idi. YBÜ ve mekanik ventilatörde (MV) ortanca kalış süresi 4 (1-86) ve 1 (0-53) gün idi. Giriş GKS medyan 11 (3-15), APACHE-II skoru 22 (5-56), RTS 7 (2-10) ve laktat değeri 1,66 (0,7-19,8) mmoL idi. Hastaların %85,6'sı taburcu edilirken, %14,4'ü vefat etti. Mortalite gelişenlerde yaş, YBÜ ve MV'de kalma süreleri, laktat düzeyleri, APACHE-II skorları, anlamlı olarak yüksek saptanırken, GKS ve RTS skorları anlamlı düşük bulundu ($p<0,05$). Çoklu lojistik regresyon analizinde RTS ve laktat değerlerinin mortalite üzerine bağımsız risk faktörleri olduğu saptandı.
Sonuç: YBÜ'deki travma hastalarında yüksek laktat düzeyi ve düşük RTS'nin mortalitenin öngörülmesinde yol gösterici olduğunu düşünüyoruz.
Anahtar Kelimeler: Travma, yoğun bakım ünitesi, mortalite, skorlama sistemleri, laktat

Introduction

Trauma; is a broad term that can include traffic accidents, falls, injuries, acts of violence and war, burns, drowning, and poisoning. It is generally classified as blunt and penetrating.

It has been reported that deaths from trauma exceed 5 million annually worldwide, constituting 9% of all deaths. Trauma is the most common cause of death among young people aged 1-44 worldwide. It ranks sixth among all deaths in our country (1). It has been reported that approximately 400,000 patients in Turkey have been exposed to traumatic injuries due to falls, traffic accidents, stab wounds, and beatings (2). Mortality in trauma patients; is affected by many parameters such as age, current medical history, interventional procedures, scoring systems in the first 24 hours, length of stay in the intensive care unit (ICU), and need for mechanical ventilation.

Treating trauma patients with a multidisciplinary approach, starting from the emergency services, is important in reducing mortality and morbidity (3,4). This study aims to investigate the clinical features, mortality rates, and factors affecting mortality in trauma patients followed in the ICU of a tertiary center in İstanbul.

Materials and Methods

This retrospective cross-sectional study was approved by the University of Health Sciences Turkey, İstanbul Kanuni Sultan Süleyman Training and Research Hospital Ethics Committee (decision no: 200, date: 30.06.2021). The study was started following the principles of the Declaration of Helsinki. All patients followed up and treated in the Istanbul Kanuni Sultan Süleyman Training and Research Hospital ICU between 01.01.2019 and 01.01.2020 for one year were retrospectively analyzed through the hospital information system.

The Anesthesiology and Reanimation Clinic provided ICU service with 36 beds on the relevant dates. Clinical and laboratory results were included in the study for patients from all age groups who stayed in the ICU for more than 24 hours and did not have deficiencies in scoring systems. In this descriptive study, no sample was selected, and all patients diagnosed with trauma between the relevant dates were tried to be reached.

Demographic data of patients such as age and gender, indications for admission to ICUs, comorbidities, operation, and re-operation requirements, length of stay in intensive care, mechanical ventilator and hospital, renal replacement therapy (RRT) requirements, percutaneous tracheostomy opening status and duration, thorax tube availability, microorganism growth status in blood, urine, tracheal aspirate and other cultures in the ICU, Glasgow coma score (GCS), Acute Physiology Assessment and Chronic Health Evaluation-II (APACHE-II) score, revised trauma score (RTS) and blood gas lactate levels and 28 and 90-day mortality were investigated. Data were analyzed by categorizing the mortality group and the discharge group patients.

Statistical Analysis

Percentage, median, and range of distribution values were used to generate descriptive statistics using SPSS Inc., Chicago, IL, USA (SPSS v22.0) program. The conformity of the variables to the normal distribution was evaluated analytically (Shapiro-Wilks test) and visually (histogram). Pearson chi-square test and Fisher's Exact test evaluated categorical data between groups. The Mann-Whitney U test was used to determine the difference between groups in quantitative data. Multiple logistic regression analysis was applied to the significant variables in univariate analysis. The statistical significance limit was accepted as $p<0.05$.

Results

Nine hundred ninety-two patients were followed up and treated between the relevant dates in our ICU. A total of 250 (25.2%) patients who were followed up for trauma and whose data were not missing were included in the study. 60.4% (n=151) of the patients were male. While 85.6% (n=224) of the patients were discharged after their treatment, 14.4% (n=36) died. 50% (n=18) of 36 patients in the mortality group were male. The median age in the overall discharge group and mortality group was 58.5 (1-97), 55.5 (1-97), and 77 (4-95) years, respectively. 47.2% (n=118) of the patients were transferred from the clinical services, 34.8% (n=87) from the operating room, and 18% (n=45) from the emergency service. Of the patients, 85.5% (n=101) were transferred to the ICU from orthopedics and traumatology, 9.3% (n=11) from neurosurgery, and 5.2% (n=6) from general surgery.

There was no systemic disease in 71.6% of the patients. 12% had cardiac, 8.4% had metabolic and renal diseases, 5.6% had the respiratory system, and 2.4% had neurological and psychiatric disorders.

All of the patients who died were exposed to blunt trauma. While 88.4% (n=221) of the patients underwent

surgery, 11.6% (n=29) were followed up without surgery. More than one operation was performed on the patients' 4.4% (n=11).

One or more RRTs were applied to 6% (n=15) of the patients during their follow-up. 3.2% (n=8) of the patients had a thoracic tube during hospitalization. Percutaneous tracheostomy was performed in 6% (n=15) of the patients by the ICU team. The median duration of tracheostomy opening was 12 (1-20) days. Growth was detected in blood, urine, or tracheal aspirate cultures in 24% (n=60) of the patients.

The median length of stay in ICU was 4 (1-86), the median length of stay on a mechanical ventilator was 1 (0-53), and the median length of stay in the hospital was 11 (1-87) days. The median GCS for admission to the ICU was 11 (3-15), APACHE-II score was 22 (5-56), RTS was 7 (2-10), and lactate value was 1.66 (0.7-19.8) mmoL.

After the treatment, 84.4% (n=211) of the patients were discharged to the service, and 2.2% (n=3) were discharged home. While two patients (0.8%) were diagnosed with brain death, no organ transplantation was performed. In our study, 28 and 90-day mortality rates were 12.4% (n=31) and 14.4% (n=36), respectively.

Age, length of stay in ICU and mechanical ventilator, lactate levels, and APACHE-II scores were significantly higher in the mortality group. In contrast, GCS and RTS scores were significantly lower at admission (p=0.011 and p<0.001, respectively). Similarly, RRT requirements and microorganism growth status in cultures were significantly higher in this group (p<0.001). Demographic data and clinical and laboratory characteristics of the patients are shown in Table 1.

Multiple logistic regression analyses of factors associated with patients' 28-day mortality status showed that RTS and lactate values continued to be associated with 28-day mortality (p<0.001 and p=0.003, respectively). An increase in RTS was found to reduce the risk of 28-day mortality by approximately 27% [(p<0.001, odds ratio (OR): 0.277; 95% confidence interval (CI): 0.154-0.496]. Multiple logistic regression analysis of factors associated with 28-day mortality is given in Table 2.

Table 1. Demographic data of patients, distribution of some clinical and laboratory characteristics

	Total (n=250)	Discharge group (n=214)	Mortality group (n=36)	p-value
Age (years)*	58.5 (1-97)	55.5 (1-97)	77 (4-95)	0.011
Gender, n (%)				0.198
Female	99 (39.6)	81 (32.4)	18 (7.2)	
Male	151 (60.4)	133 (53.2)	18 (7.2)	
Trauma type, n (%)				0.138
Blunt	235 (94)	200 (79.6)	15 (20.4)	
Penetrating	15 (6)	15 (100)	0	
GCS*	11 (3-15)	12 (3-15)	6 (3-14)	<0.001
APACHE-II score*	22 (5-56)	21 (5-56)	36 (14-56)	<0.001
Laktat level (mmoL)*	1.66 (0.7-19.8)	1.60 (0.7-7.6)	3.96 (2.3-19.8)	<0.001
RTS*	7 (2-10)	7 (3-10)	3 (2-8)	<0.001
Duration of ICU (days)*	4 (1-86)	4 (1-85)	8 (1-86)	<0.001
Duration of MV (days)*	1 (0-53)	1 (0-50)	7.5 (0-53)	<0.001
Duration of hospital (days)*	11 (1-87)	11 (1-85)	13.5 (1-87)	0.355
Need of RRT, n (%)	15 (6)	5 (2)	10 (4)	<0.001
Reproduction in culture, n (%)	60 (24)	39 (15.6)	21 (8.4)	<0.001
Tracheostomy requirement, n (%)	15 (6)	11 (4.4)	4 (1.6)	0.243
Admission thorax tube, n (%)	8 (3.2)	6 (2.4)	2 (0.8)	<0.001
Operation, n (%)	221 (88.4)	189 (75.6)	32 (12.8)	1.000

*Values are given as median and range of distribution (minimum-maximum). GCS: Glasgow coma score, APACHE-II: Acute Physiology Assessment and Chronic Health Evaluation-II, RTS: revised trauma score, ICU: intensive care unit, MV: mechanical ventilation, RRT: renal replacement therapy

Table 2. Multiple logistic regression analysis of factors associated with patients' mortality status			
Variables	**OR**	**p-value**	**95% CI (min-max)**
Age	1.005	0.769	0.970-1.043
GCS	1.111	0.452	0.844-1.463
RTS	0.277	<0.001	0.154-0.496
Laktat	2.565	0.003	1.376-4.781
APACHE-II	1.059	0.150	0.979-1.146
Constant	0.363	0.698	-

OR: Odds ratio, CI (min-max): confidence interval (minimum-maximum), GCS: Glasgow coma scale, RTS: revised trauma score, APACHE-II: Acute Physiology Assessment and Chronic Health Evaluation-II

Discussion

Trauma is a public health problem and a cause of functional limitation, disability, and mortality, especially in young people. Falls, traffic accidents, beatings, and stab wounds are important reasons for patient admission to the ICU. In a study from the USA, it was reported that approximately 15% of patients admitted to the ICU were trauma patients (5). In studies reported from Turkey, trauma patients' rates are between 10.4% and 26.2%. In our study, the rate of trauma patients admitted to the ICU was 25.2%. Reporting trauma rates at different rates in ICUs necessitates the establishment of standardization for trauma follow-up. We think that the rate of trauma patients is above the average since our hospital functions as a trauma center.

Trauma has been reported more frequently in males (1-5). Although 60.4% of trauma patients were male in our study, there was no significant difference between the genders (p=0.198). When the literature was searched, it was reported that mortality was higher in the elderly population in trauma patients (6-8). In a study from our country, Ünlü et al. (8) reported no significant difference. In our research, while the median age was 55 in the discharged group, it was 77 in the mortality group. Consistent with the literature, age was significantly higher in the mortality group in our study (p=0.011). However, age was not found to be an independent risk factor for mortality (p=0.769, OR:1.005, CI: 0.970-1.043).

Mortality in trauma patients can vary according to many factors such as age, gender, location and severity of the injury, and response to treatment. In the literature, mortality rates of trauma patients in patients hospitalized in the ICU have been reported to be between 15-and 61.3% (6-9). It is often used to evaluate treatment outcomes of 28 or 30-day mortality trauma patients. It has been reported that deaths occurring in a more extended period may not be directly related to the first injury (9). Kara et al. (10) reported a 28-day mortality of 19.4% in their study. In our study, 28-day mortality rates were below the average and were found to be 12.4%. We think mortality is lower because 71.6% of our patients do not have comorbidities. The literature has reported no significant gender difference between discharged and deceased patients (8,10). In our study, half of the 36 patients who developed mortality were male and half female, and following the literature, no difference was found in gender (p=0.198).

It is known that the risk of infection and mortality increases as the patients' length of stay in the ICU increases (10). Adıyaman et al. (11), in their study from our country, stated that prolonged stay in the ICU of trauma patients did not affect mortality. They explained this situation by prolonging hospitalization in multiple trauma, primarily infection, initiation of early enteral nutrition, implementation of ventilator-associated pneumonia preventive protocols, and early initiation of appropriate antibiotics (11). In the same study, Kara et al. (10) found that the median length of stay in ICU was three days, and Ünlü et al. (8) reported the median as five days in the same study. Render et al. (12), in their study, which included 46,053 patients, reported the average duration of stay in the ICU as 3.1 days. In our study, the median length of stay in the ICU was found to be 4 (1-86) days, similar to the literature, and the duration of stay in the group with mortality was significantly higher (p<0.001).

It has been reported in the literature that there is a significant relationship between the duration of stay on a mechanical ventilator in trauma patients and mortality (10-13). In our study, the duration of mechanical ventilation was significantly higher in the mortality group (p<0.001). The duration of mechanical ventilation is a risk factor for mortality in trauma patients, so the duration of mechanical ventilation should be kept as short as possible.

Trauma is the most common cause of death in the first four decades of life globally and in our country. When the causes of trauma are examined, it is seen that the most common cause in developed countries is traffic accidents. On the other hand, traffic accidents, beatings, falls, and stab wounds come to the fore in developing countries. In our country, Ateşçelik and Gürger (14) stated that traffic accidents are the most common reason for trauma admission to emergency services. Keskinoglu and İnan (15) reported the most common reason for admission as falling. In our study, falls from a height of 64.4% or the same level and traffic accidents by 20.8% were the most common trauma causes. While falls from height are more common in young people, falls from the same level are more common in geriatric patients. The diagnoses of patients admitted to the ICU are shown in Table 3.

Trauma scoring systems have been defined to determine the severity of trauma and predict mortality. In the follow-up of trauma patients in ICUs, physiological scoring systems such as APACHE-II or scoring systems such as GCS and RTS where clinical and physiological evaluation can be performed together are often preferred (16). GCS is frequently selected to evaluate consciousness and estimate mortality, and the relationship between GCS and mortality is known (17). The RTS is a physiologically based triage score. RTS; consists of 3 variables: respiratory rate, systolic blood pressure, and GCS (18). Table 4 shows the RTS.

Table 3. Distribution of patients according to trauma etiologies

	n=250
Falls	161 (64.4%)
Traffic accidents	52 (20.8%)
Assault	14 (5.6%)
Gunshot wound	11 (4.4%)
Penetrating stab wounds	6 (2.4%)
Suicidal	5 (2%)
Others	1 (0.4%)

The literature has emphasized that high APACHE-II and low GCS and RTS increase mortality (1,2,7,9,18). Ünlü et al. (8) found a higher APACHE-II score in the patient group with mortality in their same study. They reported a statistically significant relationship between APACHE-II values and the need and duration of mechanical ventilation. Consistent with the literature, the APACHE-II score was significantly higher in our study, with a median of 36 in the mortality group ($p<0.001$). Similarly, the GCS was significantly lower in the group with a median mortality of 6 ($p<0.001$). Öner et al. (2) reported that one of the RTS variables is GCS and the other is the respiratory rate so it may be more beneficial in patients with head trauma. In our study, RTS scores were significantly lower in the mortality group with a median of 3 ($p<0.001$). At the same time, RTS has been identified as an independent risk factor for mortality. RTS increase reduces mortality by 27% ($p<0.001$, OR: 0.277, CI: 0.154-0.496). Following the literature, we think RTS may be more useful in predicting mortality, especially in patients with head trauma.

It is known that high blood lactate levels can predict mortality. Quellet et al. (19) stated in their study that blood lactate level is an indicator of tissue perfusion disorder and is associated with mortality. In our country, Adıyaman et al. (11) reported high blood lactate levels as an independent risk factor for mortality in the same study. Consistent with the literature, in our study, blood lactate level was significantly higher in the mortality group ($p<0.001$). Like RTS, elevated lactate was an independent risk factor for mortality ($p=0.003$, OR: 2.565, CI: 1.376-4.781). We think early hemodynamic resuscitation and adequate oxygen supply to tissues and organs in treating trauma patients are essential in preventing organ failure and death.

The human body is divided into four central regions in trauma: head-face-neck, chest, abdomen, and extremities. The presence of trauma in at least two of these regions is defined as multi-trauma. Multi-traumas, usually life-

Table 4. Revised trauma score

GCS	Respiratory rate	Systolic blood pressure	Score
13-15	10-29	>89	4
9-12	>29	76-89	3
6-8	6-9	50-75	2
4-5	1-5	1-49	1
3	0	0	0

GCS: Glasgow coma scale

threatening, require immediate surgical intervention (20). Kara et al. (10) reported that 42.6% of trauma patients were operated on in their same study. In our study, 88.4% of patients who were followed up for trauma had an operation. 4.4% of the patients had more than one operation. There was no significant difference between the groups regarding operation requirements (p=1.000).

Podoll et al. (5) reported the prevalence of acute kidney injury as 5.7% and the need for RRT as 4.3% in patients followed in the ICU. In our study, RRT was applied to 6% of the patients. RRT requirement was significantly higher in the mortality group (p<0.001).

Dur et al. (16) reported that invasive procedures such as tracheostomy increased mortality in patients with multi-trauma. In our study, the ICU team performed tracheostomy with percutaneous technique in 6% of the patients. No significant difference was found in tracheostomy compared to the groups (p=0.243).

Thoracic wall injuries significantly increase morbidity and mortality due to the proximity of the thorax to the cardiopulmonary system. Although it is mainly related to blunt trauma, it has been reported as the leading cause of death in 25% of trauma-related deaths (21). A thoracic tube was inserted in 3.2% of the patients admitted to the ICU in our study. In the comparison between the groups, the presence of a thorax tube was significantly higher in the mortality group (p<0.001).

The limitation of our study is that it is retrospective and single-center.

Conclusion

Trauma is a significant cause of mortality, although it indicates that many patients are admitted to the ICU. During the follow-up of these patients, high lactate levels and low RTS scores were directly related to mortality. We think that using RTS with proven scores such as APACHE-II and GCS for use in trauma patients will contribute to patient evaluation, selection, follow-up, and treatment.

Ethics

Ethics Committee Approval: This retrospective cross-sectional study was approved by the University of Health Sciences Turkey, İstanbul Kanuni Sultan Süleyman Training and Research Hospital Ethics Committee (decision no: 200, date: 30.06.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.A., Concept: K.A., A.S.Ş., N.Y., E.K., Design: K.A., A.S.Ş., N.Y., E.K., Data Collection and Process: K.A., E.K., Analysis or Interpretation: K.A., A.S.Ş., N.Y., Literature Search: K.A., A.S.Ş., E.K., Writing: K.A., N.Y.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Evaluation of Variants and the Effect of Vaccine on Mortality in Pregnant and Postpartum Women Infected with COVID-19

COVİD-19 ile Enfekte Gebe ve Lohusalarda Varyantların ve Aşının Mortalite Üzerindeki Etkisi

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ABSTRACT *Objective:* Due to the anatomical, physiological, and immunological changes associated with pregnancy, pregnant women are a population at risk of coronavirus disease-2019 (COVID-19) disease-related morbidity and mortality. There aren't enough studies on the conditions of pregnant and puerperal women who are being followed up in intensive care. The goal of this study was to determine if there was a link between variant status, vaccination status, and mortality in pregnant and puerperal women who were monitored in the intensive care unit during the transition from the alpha to the delta variation.

Materials and Methods: The study was designed as a 6-month prospective observational study that occurred between August 1, 2021, and February 1, 2022. Age, present comorbidities, vaccination status, gravida, parity, gestational age (for pregnant women), variant status, birth style (cesarean section or normal delivery), and COVID-19 medical therapies in the critical care unit were all recorded.

Results: During the observation period, forty patients were enrolled in the study. The patients average age was 30.9±5.2. The pregnant patients' median gestational week was 32 weeks and 2 days. While 30 of the patients had no concomitant conditions, two had gestational diabetes, four had hypothyroidism, three had chronic hypertension, and one had Wilson's disease. In 37.5% of the patients, intubation was required. During the follow-up in intensive care, ten individuals died. The patients in the intensive care unit spent an average of 12.1±11.8 days there. While 7 (19.4%) of the 36 patients with alpha variants died, 3 (75%) of the 4 patients with delta variants died, a statistically significant difference (p=0.042).

Conclusion: In the pregnant population admitted to the intensive care unit, the delta variant was associated with a greater mortality rate. In our research, we discovered that the vaccination rate among pregnant women admitted to the intensive care unit was quite low.

Keywords: COVID-19 vaccine, COVID-19 variants, mortality, pregnancy, SARS-CoV-2

ÖZ *Amaç:* Gebelikle ilişkili anatomik, fizyolojik ve immünolojik değişiklikler nedeniyle gebeler koronavirüs hastalığı-2019'a (COVİD-19) bağlı morbidite ve mortalite açısından risk altındaki popülasyonlardan biridir. Yoğun bakımda takip edilen gebe ve lohusa kadınların durumları ile ilgili yeterli çalışma bulunmamaktadır. Bu çalışmanın amacı, toplumda alfa varyasyonundan delta varyasyonuna geçiş sırasında yoğun bakım ünitesinde izlenen hamile ve lohusa kadınlarda varyant durumu, aşı durumu ve mortalite arasında bir bağlantı olup olmadığını görmekti.

Gereç ve Yöntem: Çalışma 1 Ağustos 2021 ile 1 Şubat 2022 tarihleri arasında gerçekleştirilen 6 aylık prospektif gözlemsel bir çalışma olarak tasarlandı. Yaş, mevcut komorbiditeler, aşılanma durumu, gravida, parite, gebelik haftası (hamileler için), varyant durumu, doğum şekli (sezaryen veya normal doğum) ve yoğun bakım ünitesindeki COVİD-19 tıbbi tedavilerinin tümü kaydedildi.

Bulgular: Gözlem süresi boyunca, çalışmaya kırk hasta alındı. Hastaların yaş ortalaması 30,9±5,2 idi. Gebe hastaların medyan gebelik haftası 32 hafta 2 gündü. Hastaların 30'unda eşlik eden hastalık bulunmazken, ikisinde gestasyonel diyabet, dördünde hipotiroidi, üçünde kronik hipertansiyon ve birinde Wilson hastalığı vardı. Hastaların %37,5'inde entübasyon gerekti. Yoğun bakımda yapılan takipte on hasta hayatını kaybetti. Yoğun bakım yatış süresi burada ortalama 12,1±11,8 gün olarak tespit edildi. Alfa varyantı olan 36 hastanın 7'si (%19,4), delta varyantı olan 4 hastanın 3'ü (%75) mortaliteyle sonuçlandı ve aradaki fark istatistiksel olarak anlamlıydı (p=0,042).

Sonuç: Yoğun bakım ünitesine kabul edilen gebe popülasyonda delta varyantı daha yüksek bir ölüm oranı ile ilişkilendirilmiştir. Araştırmamızda yoğun bakım ünitesine kabul edilen gebelerde aşılanma oranının oldukça düşük olduğunu tespit ettik.

Anahtar Kelimeler: COVİD-19 aşısı, COVİD-19 varyantları, mortalite, gebelik, SARS-CoV-2

Introduction

Pregnant women are one of the populations at potential risk for coronavirus disease-2019 (COVID-19) disease-related morbidity and mortality due to the anatomical, physiological and immunological changes associated with pregnancy. Several studies have been published with the goal of providing evidence for treatment by describing the clinical features and outcomes of pregnant women infected with COVID-19. COVID-19 infection during pregnancy has been linked to an increased risk of preterm birth, fetal loss, and cesarean delivery, as well as a higher risk of mortality (1-3).

The need for intensive care in COVID-19 infection during pregnancy has been reported as 1% and the need for mechanical ventilation has been reported as 0.3% (4). Hantoushzadeh et al. (5) presented 7 maternal deaths and 9 critically ill cases. Among them, 6 patients began needing mechanical ventilation within 1 week of onset, highlighting the speed of COVID-19 infection in pregnancy. Based on the limited reports above, we learned that in some severe cases, the disease may progress to the point of requiring mechanical ventilation and intensive care after onset, even resulting in maternal death within a very short time (1 to 2 weeks).

It is well known that most pregnancy complications, such as hypertensive disorders of pregnancy, will resolve after termination of pregnancy. However, postpartum exacerbation for COVID-19 has been found to occur soon after birth due to short-term pathophysiological changes (6). Published articles arguing that cytokine storms may be exacerbated by birth (7,8).

As the evidence about the safety of vaccines produced for the prevention of COVID-19 in pregnant women became widespread, vaccines began to be applied in the pregnant population. It has been reported that the rates of admission to hospital, need for intensive care and perinatal death are higher in unvaccinated COVID-19 pregnant women compared to vaccinated women (9). In our country, it is recommended by the Ministry of Health to have the COVID-19 vaccine in every period of pregnancy and in the puerperium (10).

Studies on the effects of omicron and delta variants, which emerged towards the end of 2021, on pregnancy and puerperium are limited. In the study by Sahin et al. (11), when the pre- and post-variant periods were compared, it was reported that the need for maternal intensive care, pregnancy complications and mortality in the post-variant period were higher in the post-variant period. It has also been reported that there was an increase in morbidity in pregnancy with COVID-19, especially in the pregnant population with low vaccine acceptance, during the period when the delta variant was observed (12,13). However, there are not enough studies on variant conditions in pregnant and puerperal women who are under intensive care follow-up.

In this study, we aimed to evaluate the relationship between variant status, vaccination status and mortality in pregnant and puerperal women who were followed in the intensive care unit (ICU) (during the period when the alpha variant changed to the delta variant.

Materials and Methods

The study was designed as a prospective observational study and was conducted after the approval of the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Ethics Committee (approval number: 2021.10.232) between August 1, 2021 and February 1, 2022, in a 6-month period in a 3rd step training and research hospital with intensive care and a separate pandemic service for pregnant women. In this process, our hospital was serving with 2 pandemic ICUs, each with 16 beds. The study included pregnant and postpartum patients who were over the age of 18 in the pandemic ICUs, whose COVID-19 disease was confirmed by polymerase chain reaction (PCR) positivity, and who were followed up due to COVID-19-related pneumonia during the specified period. Patients who were followed up, who had a negative PCR test but suspected COVID-19 according to clinical and imaging were excluded from the study. Patients were included in the study after their written consent was obtained.

Age, current comorbidities, vaccination status, gravida, parity, gestational week (for pregnant women), variant status, mode of delivery (cesarean section or normal delivery), medical treatments for COVID-19 in the ICU were recorded. Extracorporeal therapy (continuous renal replacement therapies and extracorporeal membrane oxygen administration) and pre-intubation oxygen support type (non-invasive mechanical ventilation, high-flow oxygen therapy or mask oxygen with a reservoir) were recorded. The date of symptom onset, the date of positive PCR test, the date of admission to the ICU, the date of intubation, the date of extubation, the date of discharge from the ICU, the date of birth and survival of the patients who gave birth

during or before the follow-up were recorded. According to the recorded dates, the length of stay in the ICU, the intubation time, the time between symptom onset and admission to the ICU, and the puerperium duration for those who were puerperant were calculated as days. Complete blood count, liver and kidney function tests (ure, cre, alt, ast, albumin), C-reactive protein, procalcitonin, ferritin, D-dimer, international normalized ratio values on the day of admission to the ICU and on the day of intubation were obtained retrospectively from the hospital computer system. The blood gas parameters on the day of admission to the ICU and on the day of intubation were recorded in the study data file on the same day.

Statistical Analysis

In our study, according to the distribution of quantitative variables, mean and standard deviation or median (minimum-maximum) expressed as. Student t-test or Mann-Whitney U test was used to compare two groups. Qualitative data were expressed as the number and percentage of cases. Chi-square and Fisher's exact tests were used in the comparison of categorical variables between two groups.

Results

Forty patients were included in the study during the observation period. The mean age of the patients was 30.9±5.2. The median gestational week of the pregnant patients was 32 weeks and 2 days. While 30 patients had no comorbid disease, 2 patients had gestational diabetes mellitus (GDM), 4 patients had hypothyroidism, 3 patients had chronic hypertension and 1 patient had Wilson's disease. During the follow-up, 32 patients were delivered. Eight of these patients gave birth before their admission to the ICU, 11 of them gave birth on the day they were admitted to the ICU, and 13 of them gave birth after they were admitted to the ICU. All patients gave birth by cesarean section. Six of the 32 patients who gave birth gave birth at term (37 weeks and later), 18 patients had premature preterm births under 34 weeks, 8 patients had late preterm births between 34-37 weeks.

During the intensive care follow-up, 10 patients died. The medical treatments and oxygen support treatments given for COVID-19 during the ICU are presented in Table 1. The average length of stay of the patients in the ICU was 12.1±11.8 days. The mean time between PCR positivity and admission to the ICU is 6.7±5.1 days, and there is no statistically significant difference between vaccinated and unvaccinated patients (6.1±3.2 vs. 12.5±13.3; p=0.821). Intubation was required in 37.5% of the patients. While 36 patients were never vaccinated, 1 of the remaining 4 patients was vaccinated with a single dose of inactivated vaccine, 1 with two doses of inactivated vaccine, and 2 with a single dose of mRNA vaccine. While 9 (25%) of the unvaccinated patients died, 1 (25%) of the patients who had any vaccine died. No statistically significant difference was found between the vaccinated and unvaccinated patients in terms of mortality (p=1.000) (Table 2).

Of the 10 patients with exitus, 7 were alpha variant and 3 were delta variant. No Omicron variant was found during the follow-up. While 7 (19.4%) of 36 patients with alpha variants died, 3 (75%) of 4 patients with delta variants died, and this was statistically significant (p=0.042).

Discussion

In our study, we found that mortality was higher in pregnant and puerperal women with delta variant compared to alpha variant. Due to the fact that it was conducted in a population with a low vaccination rate, we could not obtain sufficient information about the vaccine from our study. However, we can conclude that the very low rate of vaccination in pregnant women admitted to the ICU reduces the rate of need for intensive care in the pregnant population.

According to surveillance data published by the Centers for Disease Control and Prevention, among pregnant women hospitalized with symptomatic COVID-19, COVID-19-related hospitalization (41%), ICU admission (16.2%), and mechanical ventilation It was emphasized that (8.5%) (14).

In the study of 252 COVID-19 positive pregnant patients, thirteen women (5%) presented with or developed either severe or critical (moderate and severe) COVID-19 pneumonia. Respiratory support methods included low-flow nasal cannula for 7 women (54%), non-breathing mask for 2 women (15%), high-flow nasal cannula for 2 women (15%), and mechanical ventilation for 2 women (15%). Pregnancy loss or preterm delivery (iatrogenic or spontaneous) occurred in 6 (60%) of 10 severe or critically ill pregnancies diagnosed before 37 weeks of gestation. Intravenous remdesivir was administered to 5 women (38%), dexamethasone to 5 women (38%), convalescent plasma to 2 women (15%), and an interleukin-6 inhibitor to 1 woman (8%). Other non-obstetric bacterial infections were treated in 3 women (23%).

Table 1. Descriptive charactersistics study population		
Variable	**Mean ± SD**	**Min-max**
Age	30.9±5.2	18-42
Gravidity	2.7±1.3	1-7
Parity	1.4±1.1	0-6
Gestational age (days)	225±27.1	168-266
PCR to Admission	6.7±5.1	0-24
LOS	12.1±11.8	1-61
Admission to Intubation	3.2±2.9	0-11
Variable	**n**	**%**
Comorbidities		
None	30	75%
GDM	2	5%
Hypothyroidis	4	10%
Chronic hypertension	3	7.5%
Wilson disease	1	2.5%
Vaccination status		
Non-vaccinated	36	90%
Single dose Sinovac	1	2.5%
Two doses Sinovac	1	2.5%
Single dose Biontech	2	5%
Variant status		
Alpha	36	90%
Delta	4	10%
Delivery type		
Cesarean	32	80%
Vaginal delivery	0	0%
Medical treatment		
Kaletra	29	72.5%
Favipravir	20	50%
Remdesivir	3	7.5%
IVIG	0	0%
Plazmaferez	0	0%
Actemra	4	10%
Anakinra	6	15%
Prednol	40	100%
Pulse prednol	17	42.5%
Continious renal replacement	2	5%
ECMO	3	7.5%
HFNO	25	62.5%
NIMV	9	22.5%
Reservoir mask	34	85%
Intubation	15	37.5%
Exitus	10	25%

LOS: Lenght of stay, GDM: gestational diabetes mellitus, IVIG: intravenous immunoglobuline, ECMO: extracorporeal membrane oxygenation, HFNO: high flow nasal cannula oxygen, NIMV: non invasive mechanical ventilation, min-max: minimum-maximum, SD: standard deviation

Table 2. Vaccinated vs unvaccinated patient's characteristics			
	Vaccinated n=4	Unvaccinated n=36	p-value
Age	34.7±4.2	30.4±5.2	0.124
Gestational age (days)	215.2±18.1	226.7±27.8	0.332
FiO_2 admission	30.3±34.2	89.5±15.8	0.003
Hb admission	11.9±0.5	10.5±1.3	0.040
PLT admission	157.5±10.3	253.7±98.9	0.042
Lymp admission	0.6±0.1	2.5±8.1	0.024
P50 admission	23.2±2.8	26.5±2.5	0.040
CRP admission	37.7±30	91.5±60	0.047
Procalcitonin admission	0.08±0.03	2.8±13.9	0.026
Symtom to admission	13.7±13	7.6±4.0	0.700
PCR to admission	12.5±13.3	6.1±3.2	0.821
LOS	7.7±8.3	12.6±12.1	0.309
Mortality	1 (25%)	9 (25%)	1.000

FiO_2: Fractional inspired oxygen, Hb: hemoglobin, Lymp: lympocite, P50: partial pressure of arterial oxygen when hemoglobin is fifty percent saturated, CRP: C-reactive protein, PCR: polymerase chain reaction, LOS: lenght of stay

Of 13 women presenting or developing severe or critical COVID-19 pneumonia, 2 (15%) were diagnosed at less than 24 weeks, 1 experienced second trimester pregnancy loss during prolonged intubation, and 1 was discharged for spontaneous delivery at 39 weeks (15).

As in our study, it was reported that increased morbidity in pregnancy with COVID-19 was observed during the delta variant-related fluctuation in a population with low vaccine acceptance. However, the vaccination rate in this population was higher than in our study (21.4% vs. 10%). In this study, 82 (5.4%) of 1515 pregnant COVID-19 cases required intensive care, mechanical ventilation was required in 11, and maternal death was observed in 2 patients (12).

In a prospective observational cohort study in the United Kingdom, pregnant women with GDM had delta infection (n=171, 11.1%) to wild-type variant (n=1,435, 10.2%) and Alpha variant (n=1,765, 10%) showed that he was more vulnerable than regardless of the variant, GDM was found to be significantly higher in pregnant women infected with symptomatic COVID-19 than in non-symptomatic women (16,17).

In the literature, the destructive effect of delta variant in pregnant women is explained as follows; delta variant itself is more contagious and effective in infecting host cells, delta variant causes a viral infection that accumulates more rapidly in the respiratory system, pregnant women are more susceptible to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, lower vaccination rates in pregnant women compared to the general population (18).

It concluded that, as reported by the World Health Organization, COVID-19 is associated with an increased risk of admission to intensive care for pregnant women and an increased risk of preterm birth and admission to neonatal care for the baby (19).

We showed that ICU stay with SARS-CoV-2 is associated with an increased risk of cesarean section. This situation has been reported similarly in the literature (20).

The limitation of our study is the small number of vaccinated patients to compare with the unvaccinated. However, this is explained by the fact that vaccinated patients need less intensive care.

Conclusion

As a result, delta variant progressed with higher mortality in the pregnant population admitted to the ICU. Again, in our study, it was seen that the vaccination rate was very low in pregnant women who were taken to the ICU. Although the COVID-19 pandemic has lost its effect, it is a fact that vaccination in pregnant women will reduce maternal deaths for future outbreaks.

Ethics

Ethics Committee Approval: The study was designed as a prospective observational study and was conducted after the approval of the Başakşehir Çam and Sakura City Hospital Ethics Committee (approval number: 2021.10.232).

Informed Consent: Patients were included in the study after their written consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.H.A., D.G., A.Ö., Concept: G.H.A., G.T., Design: G.H.A., G.T., Data Collection and Process: G.H.A., D.G., A.Ö., Analysis or Interpretation: G.H.A., G.T., Literature Search: G.H.A., Writing: G.H.A.

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CASE REPORT / *OLGU SUNUMU*

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Toxic Methemoglobinemia Caused by Prilocaine: Presentation of Two Cases

Prilokaine Bağlı Toksik Methemaglobinemi: İki Olgu Takdimi

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ABSTRACT Prilocaine is a local anesthetic agent used in many areas, but it may cause the methemoglobinemia, a life-threatening side effect. As a result, hypoxia may develop in the tissues. In this study, two toxic methemoglobinemia cases are presented since they develop depending on the local prilocaine used during the invasive intervention by radiology. Methemoglobinemia is a serious hematological disease and occurs when iron in hemoglobin is oxidized and becomes trivalent (Fe+++). Methemoglobinemia should be brought to mind in the differential diagnosis in the case of determining nonconcurrence or cyanosis between PaO_2 and SaO_2 values after using a local anesthetic. In such circumstances, it is appropriate to monitor patients in fully equipped intensive care units in terms of problems that may develop. Methylene blue and ascorbic acid were successfully used in treatment. In this paper, two cases are presented since methemoglobinemia developed depending on the use of prilocaine for local anesthesia and they were treated by intravenous methylene blue and/or ascorbic acid.
Keywords: Interventional radiography, methemoglobinemia, prilocaine, methylene blue, ascorbic acid

ÖZ Prilokain, pek çok alanda kullanılan lokal anestetik bir ajandır, ancak hayatı tehdit edebilen bir yan etki olan methemoglobinemiye neden olabilmektedir. Bunun sonucunda dokularda hipoksi gelişebilir. Bu çalışmada radyoloji tarafından girişimsel işlem sırasında kullanılan lokal prilokaine bağlı gelişen iki toksik methemoglobinemi olgusu sunulmuştur. Methemoglobinemi ciddi bir hematolojik hastalık olup hemoglobindeki demirin okside olup, üç değerli (Fe+++) duruma geçmesiyle oluşur. Lokal anestezik kullanımından sonra, PaO_2 ile SaO_2 değerleri arasında uyumsuzluk veya siyanoz saptanması halinde ayırıcı tanıda methemoglobinemi akla getirilmelidir. Böyle durumlarda hastaların gelişebilecek problemler açısından tam donanımlı yoğun bakım ünitelerinde izlenmesi uygundur. Tedavide metilen mavisi ve askorbik asit başarıyla kullanılmaktadır. Bu yazıda lokal anestezi amacıyla prilokain kullanımına bağlı methemoglobinemi gelişen ve intravenöz metilen mavisi ve/veya askorbik asit ile tedavi edilen iki olgu sunulmuştur.
Anahtar Kelimeler: Girişimsel işlemler, methemoglobinemi, prilokain, metilen mavisi, askorbik asit

Introduction

Methemoglobinemia is a severe haematologic disease (1). The iron found in hemoglobin is bivalent under normal circumstances (Fe++). Methemoglobinemia occurs by oxidizing of iron in the hemoglobin and becoming triad (Fe+++). Methemoglobin (MetHb) level in blood is below 1% under normal circumstances and if it exceeds 10-15%, cyanosis develops. While systemic symptoms such as weakness, tachycardia, respiratory distress, nausea, and vomiting develop as a result of tissue hypoxia if the level exceeds 35%; lethargy, stupor, and syncope occurs when it is above 55%. If the level is above 70% and when methemoglobinemia is not treated, it is fatal (2). Prilocaine is one of the local anesthetics making methemoglobinemia (3). In this article, the literature related to diagnosis and treatment approaches was aimed to review in methemoglobinemia cases in company with two cases, for which prilocaine was administered before the invasive operation in radiology clinic, in which acute methemoglobinemia developed and which were treated.

Case Reports

Case 1

A woman at the age of 54, who had liver metastasis and diagnosed by breast cancer (ca), was operated in the oncology unit due to microwave ablation. The patient was then accepted by the anesthesia intensive care since there was cyanosis on hands and legs and around the mouth after 4-5 hours from ablation operation made by invasive radiology. The patient was dyspneic, cyanotic and agitated in physical examination. Her blood pressure was 96/55 mmHg, heart apex beat was 116/min, respiratory rate was 40/min, fewer 36.4 °C and lung and cardiac auscultation were ordinary. The patient's cyanosis did not get better after giving oxygen as 6 L/min with a nasal cannula since her oxygen saturation was 85%. Her pH was 7.47, PaO_2 was 141.3 mmHg, pCO_2 was 31.2 mmHg and MetHb level was 31.4% in venous blood gas measured. Her hemoglobin was 11.2 g/dL and leukocyte count was 10.100/mm^3 in complete blood count and her polymorphonuclear leukocyte (PMNL) was 68%, lymphocyte was 30% and monocyte was 2% in the peripheral blood smear. With these findings, methemoglobinemia was considered in the patient. At the 8th hour of her hospitalization, methylene blue was given to the patient by intravenous (IV) route at a dose of 1 mg/kg in 5 minutes as a slow push, as a single dose.

Blood MetHb level of the patient, whose cyanosis regressed after methylene blue treatment, was determined as 0.9%. The patient, who was followed up in the unit for observation for 24 hours, was referred to the oncology unit after obtaining her consent for this case report, as her vital signs were stable and cyanosis did not develop in the follow-up.

Case 2

A female patient at the age of 69 diagnosed by cholangiocellular ca was hospitalized in the oncology unit for chemotherapy plan. The patient, whose biliary stent operation was made by invasive radiology in company with local anesthesia, was accepted by the intensive care unit since there was cyanosis on lips, tachypnea, and respiratory distress after 5-6 hours from the operation. Her blood pressure was 121/57 mmHg, heart apex beat was 91/min, respiratory rate was 33/min, fewer 36.4 °C and she was cyanotic in her hospitalization. The patient's cyanosis did not get better after giving oxygen as 5 l/min with a nasal cannula since her oxygen saturation was 89%. Her pH was 7.48, PaO_2 was 104 mmHg, pCO_2 was 33.9 mmHg and MetHb level was 21.9% in venous blood gas measured. Her hemoglobin was 11.9 g/dL and leukocyte count was 4.500/mm^3 in complete blood count and her PMNL was 80% and lymphocyte was 20% in the peripheral blood smear. With these findings, the patient was diagnosed with methemoglobinemia at the 2nd hour of hospitalization, but methylene blue could not be obtained from the hospital pharmacy. Therefore, the patient was given 1000 mg/day ascorbic acid in 5% dextrose intravenously as a single dose over 2 hours. The patient, whose cyanosis regressed within 24 hours, MetHb level of 0.2%, and consent was obtained for this case report, was transferred to the oncology clinic. Thus, it was observed that the efficacy of methylene blue or 1000 mg ascoric acid applications was similar and sufficient.

Discussion

Methemoglobinemia generally develops with toxic reasons in adults. Drugs take an important place for these reasons. Methemoglobinemia may be seen depending on local anesthetic drugs, but cases depending on prilocaine are rare in adults (4). Prilocaine's injectable form (Citanest®) and prilocaine-lidocaine cream (EMLA®) are used in practical application. In our article, two cases were referred since they hospitalized in the oncology unit and transferred to the intensive care unit by methemoglobinemia pre-diagnosis. Shortness of breath, cyanosis on lips and low saturation were detected in the patients after a few hours from local prilocaine given during administered invasive operation. Methemoglobinemia pre-diagnosis was thought and the diagnosis was verified by arterial blood gas analysis in the patients who did not have such symptom previously and had local anesthetic drug usage history in anamnesis. If MetHb level is lower than 20% in acquired methemoglobinemia, recovery is generally seen upon discontinuing causing drug. Close follow up and support treatment of the patients are acceptable approach since they do not have an additional disease, whose general condition is good and whom cardiac, pulmonary or neurologic findings do not develop (5). However, there is a consensus on the elimination of toxic substance or drug, support treatment and giving more aggressive treatments such as ascorbic acid and methylene blue in the cases, which are symptomatic or of which MetHb level quickly increases. In general, methylene blue

and treatment are required in the cases, of which MetHb level is higher than 30% (5). NADPH-MetHb reductase enzyme system quickly activates by methylene blue that is given intravenously and slowly with the dose of 1-2 mg/kg in these patients (6). Response to the treatment should be quantitatively evaluated upon reducing MetHb level or returning to normal in 1-2 hours besides clinical findings. Conversion of MetHb into hemoglobin starts within 15-60 minutes in the patients to whom methylene blue is given (5). But, it should not be forgotten that methylene blue may rarely be the reason of methemoglobinemia (7). For example, in a case report study that had a place in the literature in 2008 and belongs to McRobb and Holt (8) it was determined that methemoglobinemia developed in the patient for whom methylene blue was used and whose hypoxias deepened during cardiac surgery.

1 mg/kg from 1% methylene blue solution was intravenously administered to the first case in treatment for 5 minutes as a slow push. It is known that dextrose treatment increases NADH production through glycolysis and participates in patient's MetHb clearance with NADH-diaphoresis enzyme (7). 100% oxygen and 5% dextrose treatment were concomitantly given to the patient and a quick decrease was determined in MetHb level within two hours.

The primary drug is methylene blue in toxic methemoglobinemia treatment; however, the ascorbic acid infusion may be preferred when it may not be supplied. Ascorbic acid degrades MetHb as in vitro in a non-enzymatic way. Usage of ascorbic acid in methemoglobinemia treatment is thought since it decreases methemoglobin level as *in vitro* in animal and human erythrocytes (9). It also showed a correlation to clinical response with clinical response to IV methylene blue treatment in the literature (10).

In conclusion, prilocaine from local anesthetics may cause acquired methemoglobinemia in adults. Methemoglobinemia pre-diagnosis should be brought to mind in the cases of cyanosis and desaturation. Ascorbic acid or methylene blue administration is lifesaving in early and effective ways. IV methylene blue primarily used in treatment is hard-to-get in our country's conditions. General support treatment was immediately made, methylene blue was given when supplied and ascorbic acid treatment was administered without delay when it could not be supplied in two cases in this article. This drug should be compulsorily kept available in certain centers since it is of vital importance. It is also brought to mind that ascorbic acid was effectively used when it could not be supplied.

Ethics

Informed Consent: The necessary permission and informed consent were obtained from the legal representatives of the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.B., Concept: H.S., Design: Y.B., H.S., Data Collection and/or Processing: Y.B., Analysis and/or Interpretation: H.S., Literature Search: Y.B., H.S., Writing: Y.B.

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