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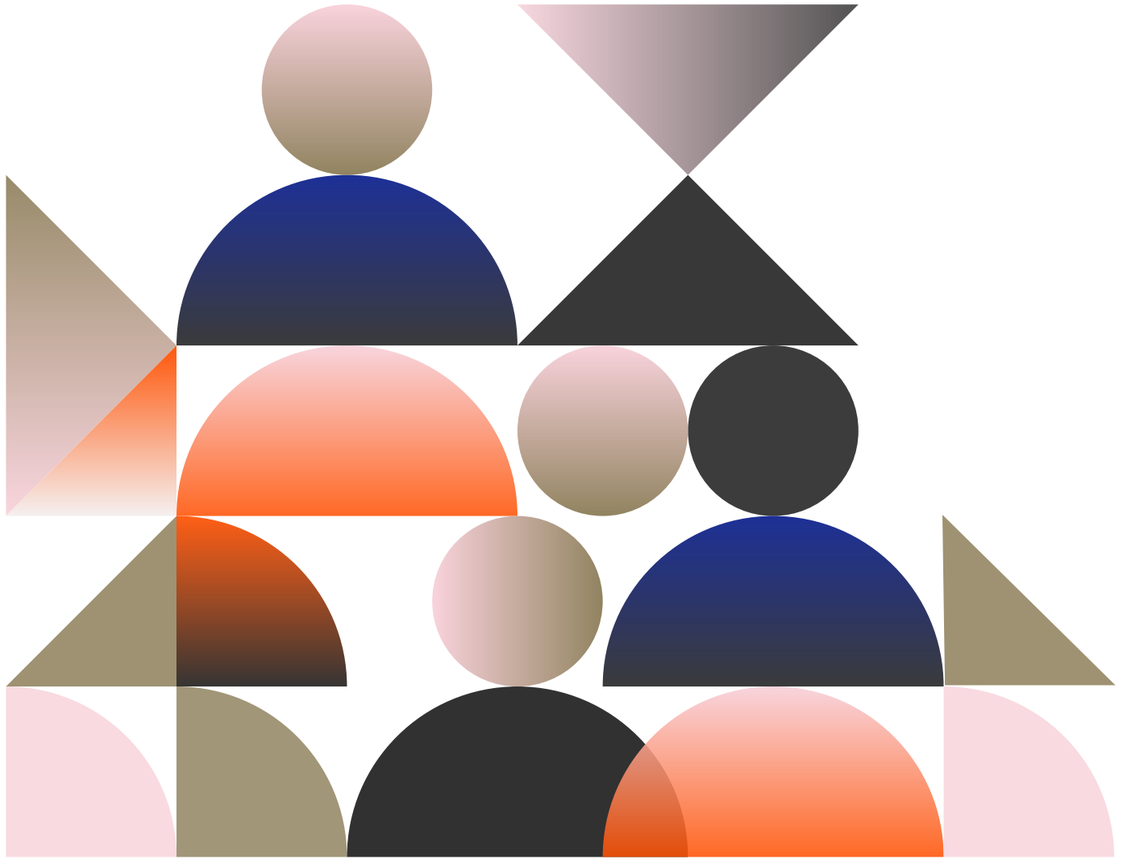

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Aims and Scope

Archives of Pediatric Critical Care (abbreviated as Arch Pediatr Crit Care, APCC) is the official journal of Korean Society of Pediatric Critical Care Medicine. This is a peer-reviewed scientific journal that considers articles on all aspects of pediatric intensive and critical care medicine. It publishes current clinical and research works and ideas in these fields. The journal aims to accumulate evidence and rapid dissemination of recently updated knowledge from clinical and experimental results through the prompt publication to inform all pediatricians, pediatric intensivists, pediatric critical care nurses, and other healthcare professionals, researchers, and policy makers related to pediatric critical care to improve the field of pediatric critical care. Additionally, it will initiate dynamic, international, and academic discussions concerning the major topics related to pediatric critical care. The journal is published biannually on the last day of June and December. It publishes editorial, original articles, review articles, case reports, and letters to the editor in the field of pediatric intensive and critical care medicine.
Its regional focus is mainly Korea, but it welcomes submissions from researchers all over the world.

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Shining forward: small steps toward a brighter future in pediatric critical care—Launching *Archives of Pediatric Critical Care* (APCC)

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Editor-in-chief, *Archives of Pediatric Critical Care*

At the cutting edge of pediatric critical care medicine, the Korean Society of Pediatric Critical Care Medicine (KSPCCM) has been making significant strides toward the advancement of this important field. Now, after years of dedication and hard work, we have launched *Archives of Pediatric Critical Care* (APCC), an international, peer-reviewed scientific journal dedicated to publishing the most recent clinical and research articles in the field of pediatric intensive and critical care medicine.

As the official journal of the KSPCCM, APCC will play a leading role in raising awareness of the clinical and academic aspects of pediatric critical care. The journal aims to facilitate the rapid dissemination of up-to-date knowledge derived from clinical and experimental results to inform all healthcare professionals involved in pediatric critical care and advance the field.

APCC will publish a diverse range of articles, including editorials, original articles, review articles, case reports, and letters to the editor. Each of these articles will aim to provide new and exciting insights concerning the major topics related to pediatric critical care. Above all, APCC will serve as a platform for facilitating scholarly discussions and idea exchanges among experts, ultimately contributing to ongoing efforts to enhance clinical practice and patient outcomes.

In conclusion, this marks a historic moment in the field of pediatric critical care medicine, as APCC begins its journey to illuminate and shape the discipline. APCC aspires to be the premier journal for the most recent research developments in this field and invites contributions from authors and readers across the globe.

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Review Article

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신경보정 환기보조의 적용과 효과

박성종

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The application and effect of neurally adjusted ventilatory assist

Seong Jong Park

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Although mechanical ventilation is a life-saving intervention for the management of acute respiratory failure, it can cause complications such as ventilator-induced lung injury and ventilator-induced diaphragmatic dysfunction, adversely affecting the outcomes of critically ill patients. Hence, methods of implementing lung- and diaphragm-protective ventilation are currently a major topic of discussion in intensive care medicine. Unlike other modes of partial ventilator assistance, which adopt conventional pneumatic signals (flow, volume, and airway pressure) to drive and control the ventilator operation, neurally adjusted ventilatory assist (NAVA) uses the electrical activity of the diaphragm, which is the best signal for estimating the respiratory drive, to control triggering, cycling, and the magnitude of assistance. Based on this concept, NAVA has the ability to avoid over- and under-assistance, improve patient-ventilator interaction and synchrony, and potentially play a role in lung-and diaphragm-protective ventilation. However, it remains to be determined whether these advantages translate into improved clinical outcomes.

Keywords: Mechanical ventilation; Neurally adjusted ventilatory assist; Lung-protective ventilation; Diaphragm-protective ventilation

서론

기계환기는 호흡부전 환자들에게 생명을 구하는 중재술이다. 그러나 기계환기 자체가 호흡부전에 대한 치료는 아니며 기계환기로 인하여 폐손상이나 횡격막손상과 같은 유해한 영향을 초래할 수 있다. 폐손상은 폐의 과팽창으로 신전손상을 일으키는 압력상해(barotrauma) 또는

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용적상해(volutrauma)와 폐포의 허탈과 팽창이 반복되면서 전단력으로 야기되는 허탈상해(atelectrauma)가 주요한 두 가지 기전이다[1]. 기계환기의 부적절한 설정은 횡격막을 비롯한 호흡근의 손상을 야기하게 된다[2,3]. 부족한 환기 보조는 과도한 흡기 노력으로 호흡근의 염증반응을 유발하며 과도한 환기 보조는 호흡 욕구의 저하로 불사용 위축을 초래한다[4-7]. 또한 과소한 호기말양압(positive end expiratory pressure [PEEP])은 횡격막의 편심성 수축으로 손상을 줄 수 있으며 반대로 과도한 PEEP은 횡격막 근섬유의 단축을 일으키기도 한다[8,9]. 자발호흡과 기계호흡의 부조화 또한 기계환기로 인한 폐와 횡격막 손상의 원인이 되고 환자의 예후에 영향을 미치게 된다[10-12]. 따라서 호흡부전 환자에서 기계환기 적용 시 그들의 예후를 호전시키기 위해서는 이러한 기계환기로 인한 폐손상과 횡격막손상을 최소로 하는 폐와 횡격막 보호 기계환기를 시행하는 것이 필요하다[13,14].

신경보정 환기보조(neurally adjusted ventilatory assist [NAVA])는 환아 자신의 신경호흡구동(neural respiratory drive)에 따라 환기 보조의 시기와 정도가 조절되는 기계환기의 방식이다[15,16]. 호흡중추로부터의 흡기 유발 신호는 횡격막신경를 통해 횡격막에 전기활성(electrical activity of the diaphragm [EAdi])을 유발하게 되는데 이 EAdi에 따라 기계호흡 흡기의 시작과 강도 및 호기의 시작을 결정하게 된다. NAVA의 이러한 작동원리는 호흡 보조가 과도하거나 과소해지는 것을 막고 환자와 기계환기기 사이의 상호작용을 개선하고 자발호흡과 기계호흡 사이의 부조화를 줄여줌으로써 폐와 횡격막 보호 기계환기를 이룰 수 있는 잠재성을 가지고 있다. 본 종설에서는 NAVA의 기본 원리를 이해하고 그 적용 및 효과에 대하여 살펴보고자 한다.

NAVA의 기본 원리

자발호흡과 횡격막의 전기활성

자발호흡은 중추신경계 뇌간의 호흡중추에서 기원하며 폐와 호흡근의 기계수용기, 동맥혈의 산소, 이산화탄소 농도 및 pH에 대한 화학수용기, 진정, 자발적인 조절, 감정적인 자극 등 여러 기관으로부터의 피드백에 따라 주기적인 호흡의 속도와 깊이가 조절된다[17]. 호흡중추로부터의 호흡 신호는 횡격막신경을 통해 횡격막으로 전달되고 신경-근 전달 후 횡격막 근섬유들에 활동전위가 전파되고 횡격막이 수축하게 된다. 수축한 횡격막과 호흡근은 흉강 내 내압을 떨어뜨려 폐를 팽창시키고 결국 폐포 내 압력이 떨어짐으로써 기도를 통해 공기가 흡입되게 된다(Fig. 1). 이러한 과정을 신경환기 연결이라 하며 횡격막의 전기활성의 강도와 빈도에 따라 활성화되는 근섬유의 수와 근수축의 강도가 결정되게 된다.

NAVA는 EAdi에 따라 작동하는 호흡 보조이다. EAdi는 호흡중추에서 기시되는 신경 호흡 구동을 비침습적으로 호흡중추에서 가장 가까운 위치에서 측정할 방법으로 작은 센서들이 배열되어 장착된 특정 식이 튜브를 통하여 측정하게 된다. 튜브의 센서들의 위치를 위식도 경계 부위 즉 횡격막에 근접한 부위에 위치시키고 각부 횡격막(crural diaphragm)의 전기활성을 측정하게 된다. 자발호흡 시 호흡 신호가 강할수록 EAdi 값이 커지며 횡격막의 수축도 강하게 된다.

EAdi 파형의 특성

EAdi 파형은 횡격막의 근전도를 신호 여과와 신호조정 등의 과정을 통해 파형으로 나타낸 것이다[16,18]. 다양한 최대 EAdi (peak EAdi)와 최소 EAdi (min EAdi)가 반복적으로 나타나는 형태를 보인다(Fig. 2) [19]. EAdi 파형에서 상승 편향은 신경 흡기를 나타내고 EAdi파형의 하락 편향은 신경호기를 나타낸다. EAdi가 상승하는 시작점부터 peak EAdi에 도달하는 시간이 신경흡기시간이며 peak EAdi부터 다음 EAdi 상승 시점까지가 신경호기시간이 된다. 흡기 시 EAdi값이 증가하는 진폭(phasic EAdi)은 전체 횡격막의 전기활성 및 횡격막의 수축 동력과 연관이 있다. EAdi 진폭은 호흡기계의 악화, 감소한 호흡 보조, 감소한 진정, 증가된 호흡 요구, 증가한 사강(dead space) 등에서 증가하게 되며 반대의 경우는 감소하게 된다. 흡기가 끝난 후에도 EAdi 신호가 지속될 경우(tonic EAdi) 이는 호기시에도 횡경막이 완전히 이완되지 못하고 지속적으로 전기활성이 상승하여 있는 것을 의미하며 호기시 폐의 허탈(derecruitment)을 막고 호기말 폐용적(end-expiratory lung volume)을 유지하기 위한 것으로 PEEP을 적용함으로써 tonic EAdi를 낮출 수 있다[20].

NAVA의 작동 원리

통상적인 기계환기기는 기계환기기의 회로에서 기도압, 기류, 또는 용

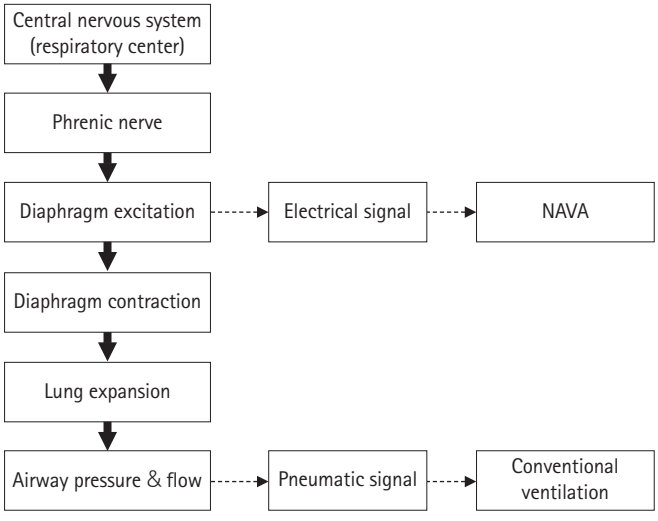

Fig. 1. Chain of events involved in spontaneous breathing and the different levels of signaling for ventilator control. During neurally adjusted ventilatory assist (NAVA), electrical activity of the diaphragm is used to control the ventilator.

적을 측정함으로써 환자의 흡기 시작 또는 끝을 인식하고 조절한다. 그러나 이러한 공기의 흐름을 통한 조절은 환자의 신경 호흡 노력과 기계환기기의 호흡 보조를 시간상으로 동기화하는데 한계가 있다. 또한 환자의 호흡 노력의 강도에 반응하여 호흡 보조의 강도가 조절되거나 Hering-Breuer 반사와 같은 폐 보호 반사의 이점을 얻는데도 제한이 있다. NAVA는 EAdi를 사용하여 호흡 보조의 시기와 강도를 조절함으로써 호흡 보조가 환자의 호흡 노력에 동기화될 뿐 아니라 강도도 호흡 노력에 비례하여 공급됨으로써 환자의 호흡근과 동일한 신경 조절하에 있는 추가적인 인공 호흡근과 같이 작용하게 된다.

NAVA에서 호흡 보조는 EAdi의 절댓값이 아닌 min EAdi에서 특정 한계치 이상의 상승(기본값은 0.5 μV로 설정)이 있을 때 흡기가 시작된다. 흡기 시 전달되는 호흡 보조는 흡기 시기 동안 나타나는 EAdi 값에 비례하여 압력이 전달되며 따라서 호흡 보조의 압력파형은 흡기 시 보이는 EAdi 파형의 형태를 따라가게 된다. EAdi 값과 그에 비례하는 흡기압력의 매칭은 매 16 ms마다 업데이트되면서 이루어지게 된다. EAdi 값과 그에 비례하여 공급되는 흡기압력과의 비례상수가 NAVA level이다. 즉 호흡 보조는 다음식과 같이 PEEP에 더해서 EAdi 값에 NAVA level (cm H_2O/μV)의 배율로 곱하여진 압력으로 공급되게 된다.

$$Paw = (NAVA\ level \times EAdi) + PEEP$$

호흡 보조의 흡기는 EAdi 값이 최고치의 70%까지 떨어졌을 때 끝나게 되고 호기로 넘어가게 된다. 만일 흡기시간이 과도하게 길어질 경우 영아에서는 1.5초, 성인에서는 2.5초에서 흡기가 끝나도록 설정되어 있다.

NAVA의 적용

NAVA 카테터(catheter) 위치시키는 방법

NAVA의 적절한 호흡 보조를 위해서는 전형적인 EAdi 신호를 얻어야 하며 이를 위해서는 NAVA 카테터를 올바르게 위치시키는 것이 필요하다. 카테터의 삽입은 먼저 비강 혹은 구강을 통해 예측되는 깊이로 삽입하고 이후 기계환기기 모니터의 EAdi catheter positioning 창에서 정확한 위치로 조정하게 된다. 예측되는 카테터의 삽입 깊이는 코-귓볼-검상돌기 길이를 측정하여 Table 1에서와 같은 공식으로 구하여 삽입한다. EAdi catheter positioning 창에서 네 개의 심전도 기록 중 중간 두 개의 기록에서 흡기 시 나타나는 EAdi 신호에 맞춰 파란색으로 강조되어 표시되는 깊이로 조절한다[21,22]. 카테터가 얕게 삽입되었을 경우에는 네 개의 심전도 중 아래쪽 심전도가 강조되게 되고 깊게 삽입되었을 경우에는 위쪽 심전도가 강조되어 나타나게 된다. 중간 두 개의 심전도에서 강조되어 나타나는 삽입 위치가 횡격막의 전기신호를 카테터에 배열된 전극 중 중심에 위치한 전극에서 가장 잘 인식하게 되는 위치이다.

NAVA level의 설정

초기 NAVA level의 설정은 목표로 하는 압력을 공급하기 위해서 다음과 같은 식을 이용하여 구할 수 있다. Target pressure (above PEEP) in cm H_2O = (peak EAdi–min EAdi) in μV × NAVA level (cm H_2O/μV). 구해진 NAVA level로 설정하고 기계호흡을 NAVA 양식으로 전환하였을 때 EAdi 파형이 바뀔 수 있고 목표했던 압력과 다를 수 있다.

또 다른 NAVA level 설정 방법은 통상적인 기계호흡 중 최고 흡기압과 NAVA의 최고압력을 일치시키는 방법이다. NAVA preview window 창은 현재 적용 중인 통상적인 기계호흡의 압력곡선과 NAVA 양식으로 변경했을 때 보일 압력곡선이 다른 색깔로 표시되어 나타난다. 적용 중인 기계호흡 양식의 최고 흡기압과 NAVA 최고 흡기압이 일치되도록 NAVA level을 조정하여 설정한 후 기계호흡 양식을 NAVA 양식으로 변경하게 된다.

NAVA level을 낮은 수준에서 단계적으로 증가시키면서 적정할 수도 있다[23]. NAVA level을 낮은 수준에서 점차 증가시키면 처음에는 NAVA level이 올라감에 따라 흡기압과 일회환기량이 증가하다가(일차 반응) 이후에는 NAVA level의 증가에도 기도압과 일회환기량의 변화가 없어지게 된다(이차 반응). 일차 반응의 NAVA level은 불충분한 호흡 보조를 나타내고 이차 반응의 NAVA level 수준은 환자의 신경 호흡 요구를 충족하는 수준을 의미한다. 일차 반응에서 이차 반응으로 넘어가는 수준의 NAVA level이 적정한 NAVA level이 된다. 그러나

Table 1. Predicted insertion distance of EAdi catheter

Catheter size (Fr/cm)	Patient height (cm)/weight (kg)	Insertion distance (cm)	
		Nasal insertion	Oral insertion
16/125	>140	NEX×0.9+18	NEX×0.8+18
12/125	75–160	NEX×0.9+15	NEX×0.8+15
8/125	>140	NEX×0.9+18	NEX×0.8+18
8/100	45–85	NEX×0.9+8	NEX×0.8+8
6/50	<55/1.0–2.0	NEX×0.9+3.5	NEX×0.8+3.5
6/49	<55/0.5–1.5	NEX×0.9+2.5	NEX×0.8+2.5

EAdi, electrical activity of the diaphragm; NEX, distance from the bridge of the nose to the earlobe and to the xiphoid process.

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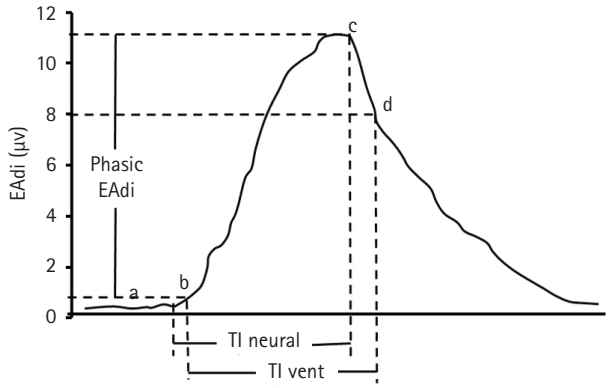

Fig. 2. Electrical activity of the diaphragm (EAdi) waveform. a, minimum EAdi; b, trigger EAdi (default setting: 0.5 μV above min EAdi); c, peak EAdi; d, cycle-off EAdi (70% of peak EAdi); TI neural, neural inspiratory time; TI vent, inspiratory time of ventilator.

일차 반응과 이차 반응 부분 간의 구분이 모호해서 인식하기가 어려운 경우가 있어 임상 적용에는 논란이 있다. 그 외 매일 자발호흡 시도(spontaneous breathing trial [SBT])를 해서 SBT 중 나타나는 EAdi 진폭의 60% 수준으로 EAdi 값이 나오도록 NAVA level을 설정하거나 호흡근이 흡기압력과 용적을 만들어 내는 능력을 나타내는 지표인, 호흡보조가 없는 상태(NAVA level 0)에서의 일회환기량과 EAdi 값의 비율, 즉 neuro-ventilatory efficiency index를 구하고 그 값의 적정수준(40%)으로 호흡보조가 이루어지도록 NAVA level을 설정하는 방법들이 제시되었다[24,25].

이탈

호흡 기능의 상승이나 호흡 요구의 감소는 EAdi 파형을 감소시키게 된다. NAVA 적용 중 공급되는 흡기압은 EAdi를 따라가기 때문에 환자의 호흡 상태가 호전되면 EAdi가 감소하게 되고 NAVA level이나 진정이 일정하다면 공급되는 흡기압 또한 감소하게 된다. 따라서 환자의 호흡 상태가 호전된다면 NAVA는 자동으로 자가 이탈되는 양식으로 생각할 수 있다. 환자의 호흡 상태가 호전되어 EAdi가 감소되면 NAVA level을 낮추어 조정해 준다. 가장 쉬운 방법은 환자가 편안한 상태에서의 EAdi 값(기준 EAdi)을 확인하고 만일 EAdi 값이 감소하면 EAdi 값이 기준 EAdi 값으로 돌아오도록 NAVA level을 낮추는 것이다.

적응증 및 금기증

NAVA는 자발호흡이 있고 부분적으로 호흡 보조를 필요로 하는 모든 연령의 환자들에게 적응증이 된다. 특히 장기간의 기계환기 적용의 위험이 있거나 SBT들에서 실패하여 발관을 못 하는 환자들에게 유용하게 사용될 수 있다. EAdi 모니터링은 침습적 또는 비침습적 기계환기의 모든 양식에서 적용될 수 있으며 환자-기계환기기 상호작용 또는 환자의 신경 호흡 양상, 자발호흡의 존재 등을 판정하는 데 이용될 수 있다.

NAVA의 금기증은 호흡중추나 횡격막 신경의 이상 등 신경계 질환, 과도한 진정제 또는 신경근 차단제의 사용, 횡격막 탈장이나 심한 척추측만증 등 어떠한 원인이든 EAdi를 적절히 얻기 어려운 경우, 식도폐색과 같이 비강과 구강 삽관이 금기되어 있는 경우 등이 있겠다.

NAVA의 효과

폐보호 환기 측면에서 NAVA의 효과

정상적으로 폐의 과도한 신장은 (1) 흡기시간을 제한하는 반사(Hering-Breuer reflex)와 (2) 증가한 폐용적에서는 횡격막의 단축으로 흡기압력을 생성하는 흡기 근육의 능력이 점진적으로 저하되는 두 가지 기전에 의해 방지되게 된다[26-28]. 그러나 이러한 흡기시간 및 흡기압력의 감소를 통해 폐를 보호하는 기전은 통상적인 기계환기 양식의 호흡 보조에서는 제한되게 된다. 용적 또는 압력 보조 환기의 경우 환자의 신경흡기시간이나 환자의 흡기 근육이 생성하는 압력과 관계없이 설정된 시간 동안 설정된 용적이나 압력을 공급하며 압력지지환기는 설정된 흡기 종료 조건의 시간 동안 설정된 일정한 압력을 공급하게 된다. 결국 폐의 과도한 신장을 예방하는 두 기전이 효율적으로 작동하지 못하게 된다. 반면에 NAVA에서는 호흡보조의 흡기시간이 환자의 흡기노력에 밀접하게 따르므로 Hering-Breuer 반사로 환자의 흡기시간이 짧아지면 기계호흡의 흡기시간도 짧아지게 되고 결과적으로 전달되는 일회환기량이 감소되게 된다. 또한 폐용적의 증가에 따라 환자가 생성하는 압력이 감소하면 NAVA 호흡보조의 흡기압력도 흡사하게 반영되어 감소하게 된다. 또한 NAVA 양식의 호흡보조에서는 NAVA level을 증가시키더라도 환자의 호흡노력이 감소하여 결국 안정된 일회환기량을 유지하게 된다[29].

횡격막 보호 환기 측면에서 NAVA의 효과

용적지향 보조환기나 압력지향 보조환기는 환자의 호흡노력과 관계없이 정해진 일회환기량을 유지하거나 정해진 압력을 전달해 주게 된다. 만일 이들의 정해진 설정이 과도할 경우 환자의 호흡 노력은 저하되고 반대로 과소할 경우엔 환자의 호흡 노력이 과도해지게 된다. 과도하거나 과소한 호흡 노력은 환자의 횡격막 상해를 유발할 수 있다. 용적지향 환기나 압력지향 환기 양식을 적용 중인 환자에서 환자의 호흡 요구가 높아져 호흡 노력이 증가될 경우 용적지향 환기에서는 자발 호흡의 증가로 인해 늘어난 환기량만큼 기계환기는 오히려 적은 양의 호흡보조를 해주게 되고 압력지향 환기의 경우는 호흡 노력의 변화와 관계없이 일정한 압력의 호흡 보조만 하게 된다. 따라서 이들 기계환기 양식에서 환자의 호흡 노력은 지속적으로 상승하게 된다. 반대로 환자의 호흡 요구가 낮아져 호흡 노력이 감소하였을 경우 용적지향 환기에서는 오히려 호흡 보조가 증가하게 되고 압력지향 환기에서는 호흡노력

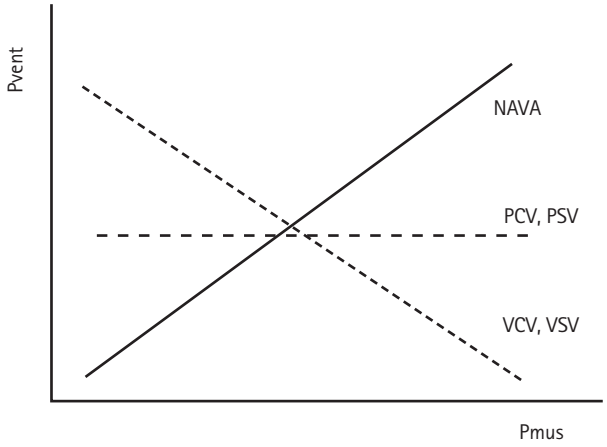

Fig. 3. Relationship between patient effort and ventilator-delivered pressure during various modes of mechanical ventilation. Pressure-targeted modes of ventilation deliver same level of pressure whatever the patient's effort. Airway pressure with volume targeted modes decrease when patient's effort increases. PVent, pressure delivered by the ventilator; NAVA, neurally adjusted ventilatory assist; PCV, pressure controlled ventilation; PSV, pressure support ventilation; VCV, volume controlled ventilation; VSV, volume support ventilation; Pmus, pressure generated by patient respiratory effort.

과 관계없이 일정한 흡기압력이 유지되어 환자의 호흡 노력은 계속 감소하게 된다. 결국 용적지향 또는 압력지향 환기에서는 환자의 호흡노력과 기계호흡의 호흡 보조가 적절히 조화되지 않기 때문에 환자는 계속 호흡노력이 증가되거나 감소하게 되고 이는 횡격막상해의 원인이 될 수 있다(Fig. 3) [30]. NAVA에서는 적정 NAVA level을 설정해 주면 호흡노력의 증가 또는 감소는 그에 따라 호흡보조가 동조되어 증가 또는 감소하므로 안정된 호흡 노력을 유지하도록 해줌으로써 횡격막 보호 환기를 이루게 된다.

환자–기계환기기 상호작용 측면에서 NAVA의 효과

기계환기기의 호흡 보조를 받는 자발호흡이 있는 환자들에게서 자발호흡과 기계호흡의 완전한 동조화를 이루기는 어렵다. 모든 양식의 기계호흡에서 부동조화가 발생할 수 있고 이는 폐와 횡격막의 손상을 야기할 수 있으며 기계호흡의 기간을 증가시키고 사망률을 증가시킬 수 있다[10,11,31]. 조기 흡기 종료나 기계호흡의 흡기를 촉발하지 못한 호흡노력과 같은 특정 부동기화는 횡격막의 신장 시 수축을 일어나게 하고 횡격막 근섬유의 파열과 염증을 야기하게 된다. 지연된 흡기 종료나 특히 이중 흡기 촉발과 같은 부동기화의 경우는 높은 일회환기량을 공급하여 폐손상을 야기할 수 있다.

NAVA의 경우 기계호흡이 환자의 자발호흡에 더 긴밀하게 따라감으로써 부동기화를 감소시키게 된다[32-36]. 환자와 기계환기 기간의 상호작용이 개선되고 부동기화가 감소하는 것은 폐 횡격막 보호 환기의 중요한 요소이다.

결론

NAVA는 자발호흡이 있는 환자들에서 호흡 보조를 하는 기계호흡의 양식으로 환자의 호흡 요구를 적절히 반영하는 횡격막의 전기활성을 이용하여 호흡 보조의 시기와 강도가 조절되게 된다. 이러한 작동원리는 환자-기계환기기 간의 동조화를 개선하고 기계호흡의 과도하거나 과소한 호흡 보조로 인한 폐와 횡격막의 손상을 줄일 수 있는 폐와 횡격막 보호 기계환기의 가능성을 제공해 준다. 그러나 NAVA가 실제 임상적으로 호흡부전 환자들의 예후에 긍정적인 영향을 보일 것인지에 대해서는 앞으로 추가적인 연구가 필요하다.

CONFLICT OF INTEREST

Seong Jong Park is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Development of an estimating equation for the baseline creatinine level in critically ill pediatric patients

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Background: The current diagnostic criteria for acute kidney injury mainly rely on baseline serum creatinine (SCr-base). However, this information is frequently missing or unavailable for a significant number of hospitalized patients. In this study, we developed an estimating equation (EE) for SCr-base and validated its performance in critically ill pediatric patients.

Methods: This single-center retrospective study included patients admitted to the pediatric intensive care unit (PICU) at a tertiary care children's hospital between January 2016 and July 2020. These patients had a measured SCr-base (mSCr-base) within 3 months prior to admission and initial SCr value at PICU admission (SCr-adm). The patients were divided by admission date into a derivation cohort and a validation cohort for the development and validation of the EE.

Results: In total, 761 children were included in the study (605 in the derivation cohort and 156 in the validation cohort). We employed linear regression analysis to develop the following EE: eSCr-base=0.159+(−0.031)×sex+(0.355×SCr-adm)+(0.006×weight for height z-score). Compared to other imputation methods for SCr-base, such as SCr-adm and SCr-base determined by back-calculation with an assumed estimated glomerular filtration rate of 75 mL/min/1.73 m^2 (SCr-eGFR75), eSCr-base demonstrated higher agreement with mSCr-base, exhibiting less bias (0.005) and narrower limits of agreement (LOA) interval (0.506).

Conclusion: eSCr-base calculated through an EE showed better agreement with mSCr-base, with less bias and a smaller LOA interval than other currently used methods (SCr-adm and SCr-eGFR75). Further large-scale studies are necessary for validation and widespread adoption.

Keywords: Acute kidney injury; Critical illness; Pediatrics; Creatinine

INTRODUCTION

Acute kidney injury (AKI) is characterized by abruptly deteriorating renal function and is a common condition associated with elevated morbidity and mortality in critically ill pediatric patients [1-4]. It is defined and diagnosed using standardized diagnostic criteria, most of which primarily rely on the elevation of serum creatinine (SCr) from baseline serum creatinine (SCr-base) values [5-9]. Therefore, having a reliable and available SCr-base value is essential for accurately evaluating AKI.

However, this value is often missing or unavailable in a large number of hospitalized patients, which can hinder the precise

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evaluation of AKI and related researches [10-12].

To solve this problem, several efforts have been made to identify an ideal imputation method for missing SCr-based values, including the use of initial SCr value at pediatric intensive care unit (PICU) admission (SCr-adm), minimum SCr values during hospitalization, dynamic SCr values during a 48-hour or 7-day time window, or back-calculation of SCr values by assuming an estimated glomerular filtration rate (eGFR) of 75 mL/min/1.73 m^2 using the modification of diet in renal disease (MDRD) equation or the Chronic Kidney Disease Epidemiology Collaboration formula [11,13-16]. Furthermore, recent research has adopted and proposed multiple imputation methods as a substitute [17]. However, no consensus-based gold standard method has been established. Additionally, these methods have been primarily studied in adult populations, with few studies focusing on SCr-based imputation in critically ill children.

In this study, we hypothesized that the simple imputation of a uniform value by extrapolating methods used in adults may be unsuitable for critically ill children. Instead, estimating the SCr-base while taking into account individual characteristics and adjusting for relevant clinical parameters could enhance the accuracy of the estimation. Therefore, our objective was to develop an estimating equation (EE) for SCr-base and validate its performance in estimating SCr-base for critically ill pediatric patients.

METHODS

This retrospective chart review study, which involved human participants, adhered to the ethical standards of both the institutional and national research committees, as well as the 1964 Helsinki Declaration and its subsequent amendments or equivalent ethical guidelines. The Institutional Review Board of Asan Medical Center granted approval for this study (No. 2020-0878). Due to the study's retrospective nature, the requirement for informed consent was waived.

Study Population

This was a single-center, retrospective cohort study. We screened all critically ill children who were consecutively admitted to a 14-bed multidisciplinary PICU of a tertiary care academic referral hospital between January 2016 and July 2020 for enrollment. The inclusion criteria were patients aged 1 month to 18 years with a measured SCr-base (mSCr-base), defined as the lowest value within 3 months prior to PICU admission, and a SCr value at PICU admission (SCr-adm). We excluded patients aged under 1 month or over 18 years, those without available mSCr-base or SCr-adm, those with pre-existing chronic renal failure, those on dialysis prior to PICU admission, and those who stayed in the PICU for less than 24 hours. The study population was divided into derivation and validation cohorts based on the admission period. The derivation cohort, which was used to develop the EE for SCr-base, consisted of patients admitted from January 2016 to June 2019. The validation cohort, which was used to evaluate the EE, consisted of patients admitted from July 2019 to July 2020.

Data Collection

We retrospectively reviewed the electronic medical records of all included patients and collected data on baseline demographic characteristics, underlying disorders, reasons for PICU admission, the duration of PICU stay, and laboratory findings. Using body weight (W) and height (H) data, the weight for height (WFH) z-scores were evaluated in accordance with the 2017 growth standards for Korean children. We defined moderate to severe malnutrition as a z-score ≤ -2. T o evaluate disease severity and organ dysfunction, the Pediatric Risk of Mortality III and the pediatric Sequential Organ Dysfunction Assessment scores were calculated using the worst documented values within the first 24 hours of PICU admission [18,19].

Study Design

Given that mSCr-base values are missing for some patients, we developed an EE for mSCr-base, taking into account the association between various clinical parameters and SCr. This EE was derived from the results of a linear regression analysis conducted on the derivation cohort. Using the EE, we estimated the baseline SCr (eSCr-base) and compared it to mSCr-base. We also evaluated the agreement between mSCr-base and either SCr-adm or SCr-base, which were back-calculated assuming an eGFR of 75 mL/min/1.73 m^2 (SCr-eGFR75) using the Schwartz formula for eGFR.

Statistical Analysis

Data were analyzed using IBM SPSS ver. 21.0 (IBM Corp.). Continuous variables are reported as means with standard deviations (SDs) or medians with interquartile ranges. Categorical variables are expressed as numbers and proportions. We performed multiple linear regression analysis to identify clinical parameters associated with mSCr-base. Based on the results, we developed an EE for SCr-base. Correlation analysis was performed, and Pearson correlation coefficients were used to measure the strength of associations between pairs of normally distributed continuous variables. Agreement between two variables was assessed using Bland-Altman plots. Bland-Altman plots were visually described

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with the bias (the mean difference between two parameters) and limits of agreement (LOA), defined as the bias ± 1.96 × SD . For all analyses, variables with a two-sided p-value of < 0.05 were considered statistically significant.

RESULTS

Baseline Characteristics of the Study Population

In accordance with the inclusion and exclusion criteria of this study, 1,228 potentially eligible patients were evaluated, and 761 patients were ultimately included in the study and separated into derivation and validation cohorts (Fig. 1). The derivation cohort comprised 605 patients with 337 boys and 268 girls. The validation cohort included 156 patients, with 83 boys and 73 girls. Comparison between two groups are presented in Table 1.

Development of the EE

Based on the results of multiple linear regression analysis (Table 2), we developed an EE for SCr-base from the derivation cohort as follows:

$$\text{eSCr-base} = 0.159 + (-0.031) \times \text{sex} + (0.355 \times \text{SCr-adm}) + (0.006 \times \text{WFH z-scores})$$

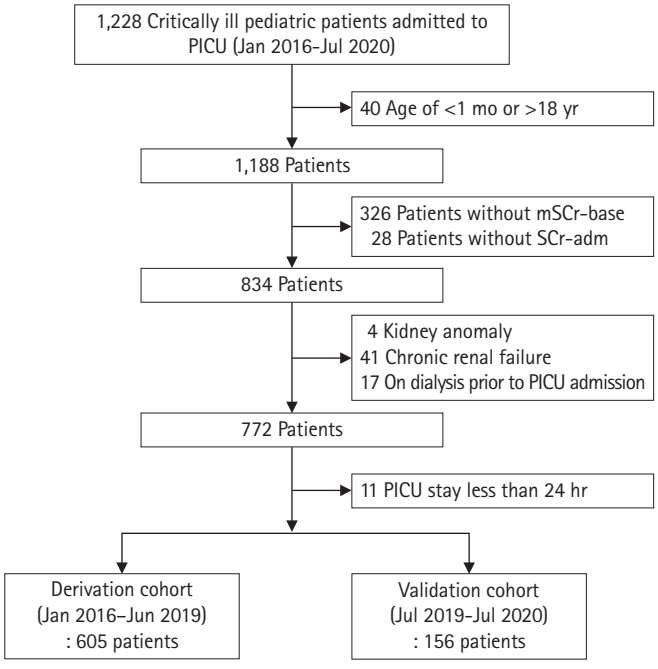

Fig. 1. Flowchart of the study population. PICU, pediatric intensive care unit; SCr, serum creatinine; mSCr-base, measured SCr-base within 3 months prior to admission; SCr-adm, initial SCr value at PICU admission.

The Pearson correlation coefficients between mSCr-base and eSCr-base, SCr-adm, and SCr-eGFR75 were 0.753, 0.750, and 0.354, respectively ($p < 0.001$). The agreement between mSCr-base and eSCr-base, SCr-adm, and SCr-eGFR75 was demonstrated graphically using Bland-Altman plots. The arrangement of data points visually indicates the degree of agreement. eSCr-base showed better agreement with mSCr-base than SCr-adm and SCr-eGFR75, with lower bias (0.0004) and narrower LOA (0.760).

Validation of EE

The performance of EE was evaluated in terms of the agreement of eSCr-base with mSCr-base in the validation cohort. The bias and LOA interval of eSCr-base were 0.005 and 0.506, which were lower and narrower, respectively, than the corresponding values of SCr-adm and SCr-eGFR75. The Bland-Altman plots between mSCr-base and eSCr-base, SCr-adm, and SCr-eGFR75 visually showed that eSCr-base had the best agreement with mSCr-base (Fig. 2). The Pearson correlation coefficients between mSCr-base and eSCr-base, SCr-adm, and SCr-eGFR75 were 0.659, 0.654, and 0.642, respectively ($p < 0.001$).

DISCUSSION

In this study, we developed an EE for SCr-base using multiple linear regression analysis as a more accurate and reliable imputation approach for missing SCr-base values. As most AKI diagnostic criteria are heavily dependent on SCr-base, it is crucial to use an appropriate SCr-base value to accurately evaluate AKI. Ideally, SCr-base should reflect the patient's steady state before admission or development of AKI. However, there have been some debates and inconsistencies in the absence of a definitive, consensus-based method for deriving SCr-base. Furthermore, it has been reported to be missing in up to 40% of cases [12,20-23]. In fact, in this study, 326 patients were excluded due to the unavailability of mSCr-base, which accounted for 26.5% of the screened (evaluated) study population. Considering that AKI is common and significantly associated with short and long-term prognosis in critically ill children, it is crucial not to exclude these patients without an mSCr-base in order to assess the prevalence of AKI accurately and promptly in this population in clinical studies, as well as to provide timely and appropriate interventions to improve clinical outcomes. For patients with an unavailable mSCr-base, there are no universally accepted imputation methods; however, several approaches have been evaluated and suggested for adult populations [11,13,14,16]. Among these meth-

Table 1. Baseline characteristics of the study population

Variable	Derivation cohort (n=605)	Validation cohort (n=156)	*p*-value
Male	337 (55.7)	83 (53.2)	0.576
Age (mo)	22.3 (7.2 to 81.3)	27.1 (8.8 to 104.6)	0.477
Weight (kg)	9.8 (5.8 to 19.3)	10.5 (5.6 to 25.2)	0.316
Height (cm)	80.0 (62.5 to 115.3)	82.0 (65.0 to 123.8)	0.595
WFH z-score	–1 (–3 to 1)	–1 (–2 to 2)	0.192
Duration of PICU stay (day)	7 (3.0 to 16.5)	5 (3.0 to 9.0)	0.005
Underlying disease			0.386
Cardiac	173 (28.6)	45 (28.8)	
Hematologic-oncologic	130 (21.5)	36 (23.1)	
Gastrointestinal/hepatic	109 (18.0)	25 (16.0)	
Respiratory	69 (11.4)	23 (14.7)	
Neurologic	41 (6.8)	10 (6.4)	
Genetic	39 (6.4)	5 (3.2)	
Endocrinologic	17 (2.8)	7 (4.5)	
Nephrologic	9 (1.5)	4 (2.6)	
None	18 (3.0)	1 (0.6)	
Cause of PICU admission			0.541
Respiratory problems	243 (40.2)	57 (36.5)	
Gastrointestinal/hepatic problems	117 (19.3)	25 (16.0)	
Cardiac problems	91 (15.0)	24 (15.4)	
Shock	47 (7.8)	20 (12.8)	
Neurological problems	38 (6.3)	14 (9.0)	
Hematologic-oncologic problems	24 (4.0)	6 (3.8)	
Nephrologic problems	22 (3.6)	4 (2.6)	
Post-cardiopulmonary arrest	10 (1.7)	2 (1.3)	
Others	13 (2.1)	4 (2.6)	
CRRT within 7 days of PICU admission	44 (7.3)	6 (3.8)	0.121
Moderate to severe malnutrition state	279 (46.1)	62 (39.7)	0.497
28-Day mortality	56 (9.6)	13 (8.3)	0.628
mSCr-base	0.29±0.29	0.28±0.16	0.520
SCr-adm	0.52±0.62	0.45±0.44	0.159
SCr-eGFR75	0.66±0.34	0.69±0.36	0.481
PRISM III score	10.0±6.3	9.7±6.0	0.650
pSOFA score	6.3±3.5	7.0±3.5	0.023

Values are presented as number (%), median (interquartile range), or mean±standard deviation.
WFH, weight for height; PICU, pediatric intensive care unit; CRRT, continuous renal replacement therapy; SCr, serum creatinine; mSCr-base, measured SCr-base within 3 months prior to admission; SCr-adm, initial SCr value at PICU admission; SCr-eGFR75, back-calculation of SCr assuming an estimated glomerular filtration rate of 75 mL/min/1.73 m^2; PRISM, Pediatric Risk of Mortality; pSOFA, pediatric Sequential Organ Failure Assessment.

Table 2. Multiple linear regression analysis of several clinical factors used in the estimating equation

Model	B coefficient	95% CI	*p*-value
SCr-adm	0.355	0.330 to 0.380	<0.001
WFH z-score	0.006	–0.001 to 0.014	0.110
Sex	–0.031	–0.062 to 0.0001	0.053
Constant	0.159	0.109 to 0.209	<0.001

R^2=0.567, adjusted R^2=0.565, MSE=0.038, RMSE=0.195, F score=262.76 (p<0.001). Sex: 1=male, 2=female.
CI, confidence interval; SCr-adm, initial serum creatinine value at pediatric intensive care unit admission; WFH, weight for height.

ods, we compared eSCr-base to SCr-adm and SCr-eGFR75.

The SCr-eGFR75 method is the most widely used and recommended approach for imputing missing mSCr-base values, as suggested by the Acute Dialysis Quality Initiative and the Kidney Disease: Improving Global Outcomes. This approach involves back-calculating the SCr value using the MDRD equation, assuming an eGFR of 75 mL/min/1.73 m^2 [11,14,24]. However, there are numerous formulas for estimating GFR, which are often categorized by population specificity. It is well known that

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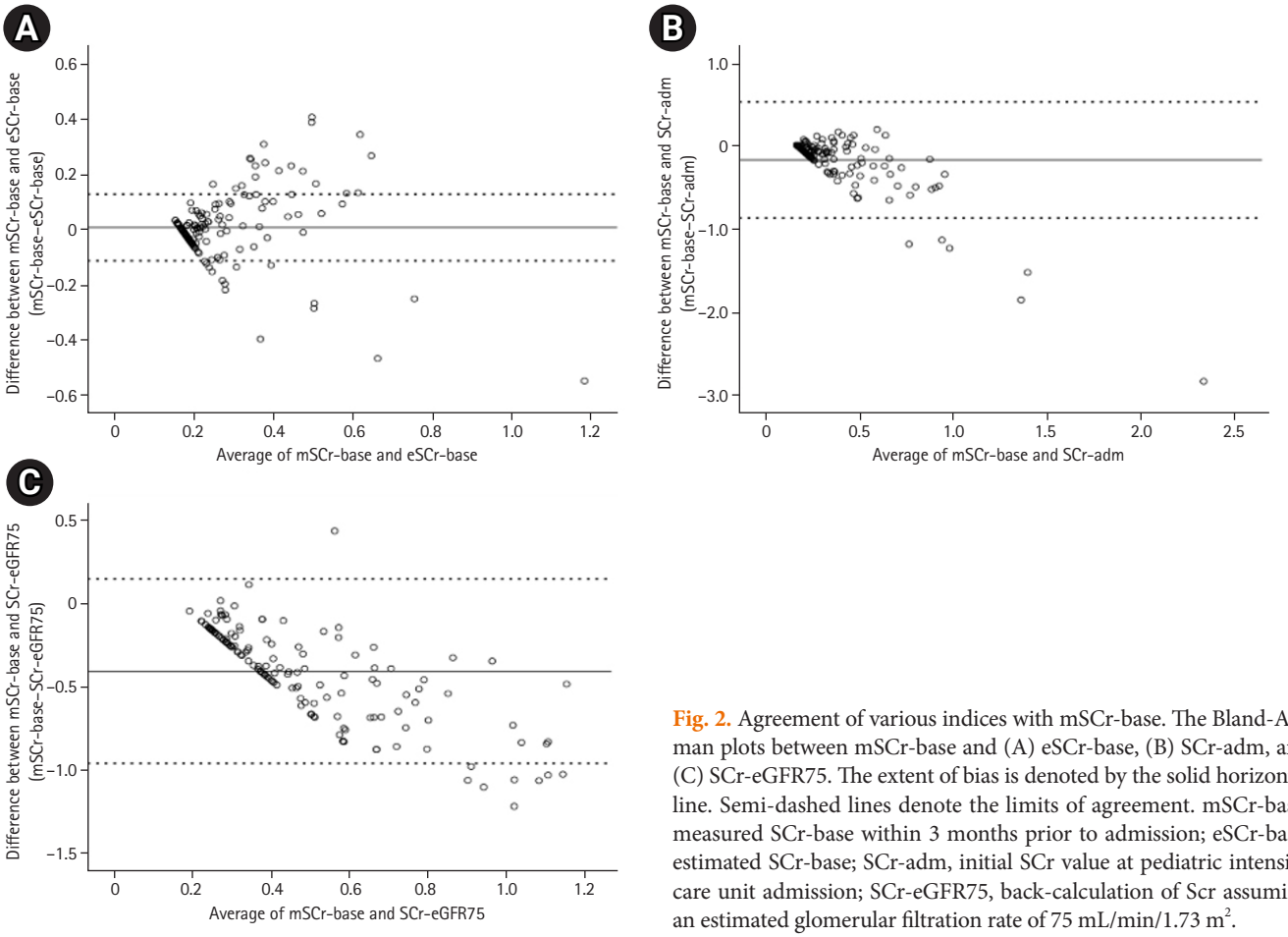

Fig. 2. Agreement of various indices with mSCr-base. The Bland-Altman plots between mSCr-base and (A) eSCr-base, (B) SCr-adm, and (C) SCr-eGFR75. The extent of bias is denoted by the solid horizontal line. Semi-dashed lines denote the limits of agreement. mSCr-base, measured SCr-base within 3 months prior to admission; eSCr-base, estimated SCr-base; SCr-adm, initial SCr value at pediatric intensive care unit admission; SCr-eGFR75, back-calculation of Scr assuming an estimated glomerular filtration rate of 75 mL/min/1.73 m^2.

different equations are applied to various age groups, such as pediatric and adult populations. As a result, the choice of EE for eGFR can affect the back-calculated SCr value, leading to a range of possible values.

In this study, we used the Schwartz formula for back-calculating SCr, as it is the most commonly used method for estimating GFR in pediatric populations. However, this may result in a different SCr value compared to that obtained using the MDRD formula. Additionally, this approach assumes a fixed eGFR value of 75 mL/min/1.73 m^2, which may not be appropriate for all study participants. Moreover, pediatric patients have a wide range of normal eGFR values, and critically ill children may have unique clinical situations that affect their SCr values. Consequently, the use of a "universal value" may be inaccurate in these cases.

Another widely used approach for imputing missing SCr-base values is to use SCr-adm as a substitute, which offers the advantages of being easily accessible, time-saving, and enabling prompt evaluation of AKI. In fact, the Acute Kidney Injury Network recommends diagnosing and classifying AKI based on SCr-adm. However, as previously noted, this method has limitations in detecting community-acquired AKI. It may fail to diagnose patients whose SCr has already increased above the true baseline at the time of admission, potentially underestimating the actual prevalence and significance of AKI. In line with this, the current study found poor agreement between the two methods, SCr-eGFR75 and SCr-adm, in comparison to mSCr-base.

In order to impute a reliable SCr-base, we aimed to develop an EE that takes various factors into account. It is well-known that SCr value measurements are significantly influenced by methods and laboratory settings, as well as factors such as age, sex, muscle mass, nutritional state, and diet [25-27]. Therefore, we developed an EE for eSCr-base that considers several associated clinical factors based on statistical analysis. While incorporating more parameters can improve the accuracy of estimates, there are existing multiple imputation methods that consider up to 15 parameters in adults [17]. However, increased complexity may reduce the practicality of an estimation method. Considering the impor-

tance of prompt, easy, and precise assessment of AKI, as well as the general usefulness of the method, we opted to include only the minimum parameters necessary for estimating SCr-base. These parameters were SCr-adm, sex, and the WFH z-score.

In the correlation analysis, mSCr-base and SCr-adm demonstrated a significant correlation, which was stronger than that between mSCr-base and SCr-eGFR75. This suggests that the assumption of "normal" may not be appropriate for replacing mSCr-base in these critically ill patients. Although SCr-adm exhibited a strong correlation with mSCr-base, it also displayed a significant bias compared to mSCr-base. We further adjusted this by incorporating several associated clinical factors, such as sex and WFH z-score. Sex is a well-known factor associated with SCr. As for the WFH z-score, we utilized it as an indirect indicator of nutritional status and related muscle mass. Since SCr values are influenced by skeletal muscle mass, a loss of muscle mass alters the amount of creatinine generated in the body. A substantial reduction in creatinine generation has been observed in patients with chronic illness, critical illness, and those with longer hospital stays [28-30]. Therefore, considering these factors may be essential, particularly in critically ill patients.

In this study, the EE performed well in predicting eSCr-base, exhibiting the highest agreement with mSCr-base, the lowest bias, and the narrowest LOA interval in comparison to other currently used imputation methods (SCr-adm and SCr-eGFR75). This finding is consistent with previous results suggesting that taking individual factors into account and adjusting for clinical factors are crucial for achieving a more accurate estimation than general, undifferentiated approaches.

Our study possesses several strengths. To date, few studies have focused on the evaluation of SCr-based measurements in pediatric patients. To the best of our knowledge, this is the first study to develop an EE for SCr-based measurements in children, particularly in critically ill pediatric patients. We developed this EE using multiple linear regression analysis, taking into account associated clinical parameters from a derivation cohort of 605 critically ill children, which is a substantial number. We then validated the EE using eSCr-based measurements in a separate validation cohort, distinct from the derivation cohort. Additionally, we compared the eSCr-based measurements to widely used and evaluated imputation methods in the adult population, which facilitates an understanding of the degree of improvement achieved by using the EE compared to previously employed methods.

Despite the aforementioned advantages, this study has several limitations. It was a single-center retrospective study. Although we divided the enrolled patients by admission date, the characteristics of the derivation and validation cohorts were so similar that there could have been an overfitting issue in the validation of EE. Since we designed this study to include pediatric patients with mSCr-base, 326 patients were excluded due to the absence of mSCr-base, which could have resulted in selection bias. Given the limited number of patients included in this study, it was necessary to selectively include certain parameters in the development of EE, which could have also potentially introduced some bias. In addition, due to the nature of our institution as a tertiary academic referral hospital, the study population is also subject to selection bias, limiting the generalizability of the results.

In conclusion, the accurate evaluation of AKI—encompassing diagnosis, staging, and the prediction of mortality risk—is significantly influenced by SCr-base. Therefore, reliable imputation methods for missing SCr-base values are crucial. To address this need, we developed an EE based on statistical analysis, taking into account associated clinical parameters. This method demonstrated excellent performance for eSCr-base, showing better agreement with mSCr-base than SCr-adm and SCr-eGFR75. It is essential to consider individual characteristics, particularly in critically ill children. Further large-scale studies are needed to validate this EE for widespread use in general practice.

CONFLICT OF INTEREST

Won Kyoung Jhang is an Editor-in-Chief, and Seong Jong Park is an editorial board member of the journal, but they were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: WKJ, SJP. Data curation: WKJ. Formal analysis: WKJ. Investigation: WKJ. Methodology: WKJ, SJP. Validation: SJP. Writing - original draft: WKJ. Writing - review & editing: WKJ, SJP.

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지속적 신대체 요법을 적용한 소아 중환자의 사망 위험요인

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Risk factors for mortality in critically ill pediatric patients receiving continuous renal replacement therapy

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Background: Continuous renal replacement therapy is administered increasingly often in pediatric cases of acute kidney injury. However, the mortality rate remains quite high in these patients. Therefore, this study aimed to investigate the risk factors for mortality in critically ill pediatric patients receiving continuous renal replacement therapy.

Methods: A retrospective review was conducted on 96 patients who were admitted to a pediatric intensive care unit and underwent continuous renal replacement therapy from January 2013 to December 2022.

Results: Of the 96 patients, 47 survived and 49 died, resulting in a mortality rate of 51%. Multivariate analysis showed that each additional vasoactive inotropic agent yielded an odds ratio (OR) of 5.233 (95% confidence interval [CI], 1.804–15.176) for mortality (p=0.002). Additionally, higher risks of mortality were found for each increase of 1 mmol/L in the lactate level (OR, 1.076; 95% CI, 1.023–1.131; p=0.004) and each 1-day increase in the duration of continuous renal replacement therapy (OR, 1.043; 95% CI, 1.004–1.084; p=0.030).

Conclusion: An increased number of vasoactive inotropic agents, higher lactate levels, and a longer duration of continuous renal replacement therapy were associated with an increased risk of mortality. The management of hypotension and therapeutic interventions for high lactate levels are expected to shorten the duration of continuous renal replacement therapy, thereby reducing the risk of mortality.

Keywords: Continuous renal replacement therapy; Pediatrics; Critical illness; Mortality; Risk factors

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서론

소아 중환자는 생명에 위험을 초래하며 매우 불안정하고 아주 복잡한 내과적 혹은 외과적 치료를 요하는 질환을 앓는 소아를 말한다[1]. 소아 중환자실에 입실한 환자의 30%에서 급성 신손상이 발생하며 이는 사망률과 밀접한 관련이 있다[2]. 급성 신손상은 그 자체가 소아 환자의 발병률과 사망률의 원인이 될 수 있으며 소아 중환자실에서 급성 신손상이 발병할 경우 사망률은 66%–90%로 상대적으로 높다[3]. 지난 10여 년간 소아에서 급성 신손상 발생빈도는 급격하게 증가하였고, 이로 인한 다장기부전과 같은 심각한 문제로 이어져 사망률을 증가시킨다[4].

소아 중환자실에서 급성 신손상으로 치료 중인 환자에게 지속적 신대체 요법은 일차적으로 적용하는 방법으로 많이 선택되고 있으며 시행하는 비율 또한 증가하고 있는 추세이다[5]. 1955년 Mateer 등에 의해 급성 신부전 소아에서 성공적으로 혈액 투석이 시행된 이래, 혈액투석법은 급성 신부전 환아 치료의 주된 치료로 이용되어 왔다. 소아 중환자의 급성 신손상에 사용하기 위해서는 신대체 기능인 혈장 내 용질과 수분을 제거하는 능력이 효과적이면서 적용 중 안전해야 한다. 지속적 신대체 요법은 혈액에서 용질과 수분을 직접 제거할 뿐만 아니라 24시간 동안 천천히 이루어지기 때문에 충분한 수분 제거가 용이하고 혈역동학적으로 불안정한 소아에 적용하기에 적합한 방법[6]으로 소아 중환자실에서 대부분 적용하는 투석 방법이다.

중환자실에 입원한 소아의 급성 신손상은 다양한 원인에 의해 발생한다. 지난 몇 년 동안 소아의 급성 신손상의 주요 원인은 신장 질환이기보다는 선천성 심질환과 패혈증 같은 질환으로 변화되었으며[5], 심정지, 패혈증, 쇼크, 심부전, 약물중독, 급성 저산소성 호흡부전, 심장수술, 다장기부전, 간질환의 이차적인 증상으로 나타날 수 있다[3].

소아에서 지속적 신대체 요법 적용 시 적은 체중, 다장기부전, 중증도, 심한 수분 과다가 사망률을 증가시키는 위험 요소로 보고되고 있음을 고려할 때 소아의 급성 신손상을 조기에 인지하고 빠른 치료의 시작으로 사망률 감소를 위해 지속적 신대체 요법의 치료 원칙을 다시 세밀하게 검토하고 정리할 필요가 있다[4]. 선행 연구에서 패혈증을 동반한 급성 신손상의 경우 높은 사망률을 보이는데[7], 패혈증이 동반되면 혈역학적으로 불안정하여 지속적 신대체 요법을 적용하게 된다. 이때 급성 신손상의 요인을 인지하여 조기에 적용한 경우 사망률이 감소하게 된다는 연구 보고가 있다[8]. 따라서 급성 신손상의 발병 요인을 조기에 파악하고 지속적 신대체 요법을 적절한 시기에 적용한다면 더 좋은 임상 결과를 얻을 수 있을 것이다.

우리나라에서 소아의 지속적 신대체 요법과 관련된 선행 연구에서 치료 결과와 예후 및 사망률을 분석하였으나 그 수가 미미한 실정이다. 따라서 본 연구에서는 소아 중환자실에서 지속적 신대체 요법을 적용한 환자를 대상으로 사망위험 요인을 파악하여 이후 환자들의 예후 예측 및 임상 양상 호전에 도움이 되고자 한다.

방법

본 연구는 서울아산병원 소아 중환자실에서 지속적 신대체 요법을 적용한 소아 중환자의 사망위험 요인을 분석하기 위한 후향적 조사연구이다.

연구 대상

2013년 1월에서 2022년 12월까지 서울아산병원 소아 중환자실에 입실하여 지속적 신대체 요법을 적용한 환자 전수인 96명을 대상으로 하였다. 중환자실 재실 기간 중 두 번 이상 지속적 신대체 요법을 적용한 대상자의 경우 처음 적용한 시점을 기준으로 자료를 수집하였다.

연구 방법

본 연구는 서울아산병원의 임상 연구 심의위원회(Institutional Review Board)의 심의 통과(승인번호: 2023-0224) 후 연구를 진행하였다. 대상자의 전자의무기록을 토대로 대상자의 일반적 특성, 임상적 특성 및 사망 여부에 대한 자료를 수집하여 조사하였다. 본 연구는 후향적 조사 연구로 임상 연구 심의위원회의 판단에 따라 대상자의 동의가 면제되었다.

일반적 특성

대상자의 일반적 특성으로는 나이, 성별, 체질량지수, 기저질환, 소아 중환자실에서의 재실 기간을 조사하였다.

임상적 특성

대상자의 임상적 특성은 지속적 신대체 요법을 적용한 시점을 기준으로 적용하기 전 가장 가까운 시점에 해당하는 자료를 수집하였다. 진단 검사로는 백혈구(cells/mm^3), 혈소판(cells/mm^3), C-반응성 단백(mg/dL), 사구체여과율(mL/min), 혈액 요소 질소(mg/dL), 혈장 크레아티닌(mg/dL), 포타슘(mEq/L), 나트륨(mEq/L), 뇌나트륨이뇨펩티드(pg/mL), 프로트롬빈시간(second), 활성화부분트롬보플라스틴시간(second), 젖산(mmol/L), 혈당(mg/dL)을 조사하였다.

소아 중증도 분류인 Pollack 등[9]이 개발한 Pediatric Risk of Mortality (PRISM) Ⅲ score를 조사하였고(Supplementary Table 1), 승압제의 사용 개수, 인공호흡기의 적용 유무 및 적용 일수, 체외막산소화장치의 적용 유무 및 적용 일수를 조사하였다. 인공호흡기와 체외막산소화장치는 대상자가 입실 후 적용한 총기간을 조사하였다. 중심정맥관의 적용 일수는 적용 시작 시점에 조사하였고, 중심정맥관을 2개 이상 유지하고 있는 경우 적용 일수가 더 긴 일수를 조사하였다. 지속적 신대체 요법의 적용 일수와 시작 일수를 조사하였으며 시작 일수는 소아 중환자실에 입실한 시점으로부터 지속적 신대체 요법을 적용하기까지의 일수로 조사하였다. 또한 지속적 신대체 요법의 시작 이유를 조사하였고 적용 후 중환자실 재실 중 사망 여부를 조사하였다.

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자료 분석

본 연구에서 수집된 자료는 IBM SPSS 27.0 프로그램(IBM Corp.)을 이용하여 분석하였으며 통계학적 유의수준은 95%로 하여 p 값이 0.05 미만일 때 유의하다고 판단하였다. 대상자의 일반적 특성 및 임상적 특성은 실수와 백분율, 정규성을 만족하지 않는 변수는 중위수와 사분위수 범위로 나타내었고, 지속적 신대체 요법의 사망위험 요인을 확인하기 위해 생존군과 사망군 간의 일반적, 임상적 특성 비교는 chi-square test 또는 Fisher's exact test, Mann-Whitney test로 분석하였다. 지속적 신대체 요법을 적용한 대상자의 사망에 영향을 미치는 요인은 로지스틱 회귀분석(logistic regression)으로 분석하였다.

결과

대상자의 일반적 특성

연구 대상자는 총 96명으로 생존군은 47명, 사망군은 49명이며 사망률은 51%로 나타났다. 총대상자 연령의 중앙값은 11세(interquartile range [IQR], 3.08–15.00세)로 생존군의 중앙값은 11세(IQR, 3.42–14.00세), 사망군의 중앙값은 11세(IQR, 2.17–15.50세)이며 두 군 간의 유의한 차이가 없었다(Z = –0.139, p = 0.889). 사망군 중 남성은 29명(59.2%), 여성은 20명(40.8%)으로 성별에서 두 군 간의 유의한 차이가 없었다(X^2 = 0.030, p = 0.863).

기저질환이 백혈병인 대상자가 35명(36.5%)으로 가장 많았고 다음으로는 심부전이 26명(27%)으로 나타났으며 만성신부전인 대상자는 4명(4.2%), 기타 질환은 31명(32.3%)이었다. 소아 중환자실에 입실하여 퇴실하기까지 총대상자의 재원 일수의 중앙값은 25일(IQR, 10.00–50.75일)로 생존군의 중앙값은 19일(IQR, 8.00–42.00일), 사망군의 중앙값은 26일(IQR, 10.50–55.00일)이며 두 군 간의 유의한 차이가 없었다(Z = –0.931, p = 0.352) (Table 1).

대상자의 임상적 특성

연구 대상자들의 PRISM Ⅲ score는 14.5점(IQR, 8.00–21.75점), 지속적 신대체 요법을 적용하는 시점 전 6시간 동안의 시간당 체중당 소변량은 0.38 mL/kg/hr (IQR, 0.07–1.02 mL/kg/hr)이었다. 승압제 사용 개수의 중앙값은 2개(IQR, 0–3.00개)였다. 연구 대상자 중 인공호흡기를 적용한 대상자는 67명(69.8%), 인공호흡기 적용 일수는 24일(IQR, 10.00–45.00일)이었다. 체외막산소공급장치를 적용한 대상자는 28명(29.2%)으로, 체외막산소공급장치 적용 일수는 22.5일(IQR, 7.00–35.50일)이었다.

지속적 신대체 요법 적용 일수는 14일(IQR, 4.00–26.75일), 소아 중환자실에 입실하여 지속적 신대체 요법의 적용 시점까지 시작 일수는 2일(IQR, 1.00–3.00일)이었다. 지속적 신대체 요법의 적용 사유 중 소변량 감소가 원인인 경우가 총 52명(54.2%)으로 가장 많았고 그다음으로는 체액 과다로 29명(30.2%)이었다(Table 2).

지속적 신대체 요법을 적용한 소아 중환자의 사망위험 요인에 대한 단변량 분석

지속적 신대체 요법을 적용한 소아 중환자의 사망에 유의한 영향을 미치는 요인으로는 기저질환이 백혈병인 경우, 사망 위험은 기타 질환에 비해 odds ratio (OR)가 3.244 (95% Confidence interval [CI], 1.219–8.629; p = 0.018)였다. PRISM Ⅲ score, 승압제 사용 개수, 인공호흡기를 적용한 경우, 체외막산소공급장치를 적용한 경우로 나타났다. 진단 검사 결과에서는 혈소판 수치, C반응성단백질 수치, 뇌나트륨이뇨펩티드 수치, 프로트롬빈시간, 활성화부분트롬보플라스틴시간, 젖산 수치가 유의한 관련성을 보였다. 지속적 신대체 요법의 적용 일수, 지속적 신대체 요법의 적용 사유 중 패혈증이 원인인 환자의 경우가 유의한 관련성을 보였다(Table 3).

지속적 신대체 요법을 적용한 소아 중환자의 사망위험 요인에 대한 다변량 분석

본 연구의 단변량 분석 결과를 토대로 양측 검정 수준의 유의수준 0.1을 기준으로 통계적으로 유의한 차이를 나타낸 변수를 선택하여 다변량 로지스틱 회귀분석을 시행하였다. 후진 likelihood ratio 방법으로

Table 1. General characteristics of survivors and non-survivors among pediatric patients receiving CRRT

Variable	Total (n=96)	Survivor (n=47)	Non-survivor (n=49)	X^2 or Z	p-value
Age (yr)	11.00 (3.08–15.00)	11.00 (3.42–14.00)	11.00 (2.17–15.50)	–0.139	0.889
Sex					
Male	56 (58.3)	27 (57.4)	29 (59.2)	0.030	0.863
Female	40 (41.7)	20 (42.6)	20 (40.8)		
BMI (kg/m^2)	19.04 (15.98–23.34)	18.65 (16.43–23.28)	19.33 (15.92–23.41)	–0.029	0.977
Underlying disease					
Leukemia	35 (36.5)	13 (27.7)	22 (44.9)	6.348	0.042
Others	31 (32.3)	19 (40.4)	12 (24.5)		
Heart failure	26 (27.0)	11 (23.4)	15 (30.6)		
Chronic kidney disease	4 (4.2)	4 (8.5)	0		
Length of stay in PICU (day)	25.00 (10.00–50.75)	19.00 (8.00–42.00)	26.00 (10.50–55.00)	–0.931	0.352

Values are presented as median (interquartile range) or number (%).
CRRT, continuous renal replacement therapy; BMI, body mass index; PICU, pediatric intensive care unit.

Table 2. Clinical characteristics of survivors and non-survivors among pediatric patients receiving CRRT

Variable	Total (n=96)	Survivor (n=47)	Non-survivor (n=49)	X^2 or Z	*p*-value
PRISM III score	14.50 (8.00–21.75)	9.00 (7.00–17.00)	20.00 (14.00–28.00)	–4.806	<0.001
Urine output for 6 hours (mL/kg/hr)	0.38 (0.07–1.02)	0.38 (0.15–1.53)	0.38 (0.05–0.65)	–1.604	0.109
Number of vasoactive inotropic agents	2.00 (0–3.00)	0 (0–2.00)	3.00 (3.00–4.00)	–7.127	<0.001
Application of mechanical ventilation	67 (69.8)	19 (40.4)	48 (98.0)	37.665	<0.001
Length of mechanical ventilation (day)	24.00 (10.00–45.00)	25.00 (16.00–53.00)	23.00 (7.00–44.00)	–1.134	0.257
Application of ECMO	28 (29.2)	7 (14.9)	21 (42.9)	9.080	0.003
Length of ECMO (day)	22.5 (7.00–35.50)	11.00 (7.00–24.00)	24.00 (7.50–38.50)	–1.009	0.313
Duration of central venous line (day)	33.50 (17.25–73.50)	29.00 (13.00–60.00)	45.00 (23.50–101.50)	–1.158	0.247
Laboratory data					
WBC (cells/mm^3)	12,350 (6,500–19,725)	10,400 (7,300–16,600)	13,500 (4,700–24,950)	–0.755	0.450
Platelets (cells/mm^3)	71,000 (36,500–171,750)	130,000 (70,000–269,000)	44,000 (24,000–79,500)	–5.167	<0.001
CRP (mg/dL)	7.22 (2.41–21.19)	2.46 (0.70–5.26)	18.22 (10.80–26.54)	–6.996	<0.001
eGFR (mL/min)	40.58 (26.11–68.75)	43.00 (19.00–93.00)	39.00 (28.00–54.78)	–0.194	0.846
BUN (mg/dL)	42.00 (21.00–67.75)	47.00 (18.00–79.00)	39.00 (25.00–59.00)	–0.183	0.855
Creatinine (mg/dL)	1.57 (0.90–3.06)	1.59 (0.81–4.23)	1.56 (1.02–2.80)	–0.150	0.881
Potassium (mEq/L)	4.10 (3.40–5.20)	3.90 (3.40–4.80)	4.50 (3.40–5.40)	–1.661	0.097
Sodium (mEq/L)	139.00 (136.25–144.00)	139.00 (136.00–142.00)	140.00 (136.50–147.00)	–1.608	0.108
BNP (pg/dL)	560.00 (151.25–3,500.50)	182.00 (96.00–560.00)	1,528.00 (512.00–4,419.00)	–5.136	<0.001
PT (sec)	18.05 (14.50–29.65)	15.30 (13.30–21.70)	20.70 (16.60–36.70)	–3.903	<0.001
aPTT (sec)	48.90 (31.60–64.68)	32.50 (27.80–56.00)	61.40 (45.20–98.25)	–5.014	<0.001
Lactic acid (mmol/L)	4.00 (1.80–7.93)	1.80 (1.20–3.50)	7.40 (4.40–11.95)	–6.988	<0.001
Glucose (mg/dL)	123.00 (91.25–167.00)	146.00 (110.00–172.00)	109.00 (86.00–155.00)	–2.345	0.019
CRRT					
Duration of CRRT (day)	14.00 (4.00–26.75)	8.00 (4.00–21.00)	22.00 (8.00–33.50)	–2.388	0.017
Interval from admission to CRRT application (day)	2.00 (1.00–3.00)	2.00 (1.00–3.00)	2.00 (1.00–4.00)	–1.921	0.055
Reason for CRRT application					
Decrease in urine output	52 (54.2)	22 (46.8)	30 (61.2)	2.008	0.156
Fluid overload	29 (30.2)	12 (25.5)	17 (34.7)	0.955	0.328
Metabolic acidosis	25 (26.0)	8 (17.0)	17 (34.7)	3.89	0.049
Sepsis	18 (18.8)	2 (4.3)	16 (32.7)	12.699	<0.001
Others	16 (16.7)	14 (29.8)	2 (4.1)	-	0.158[a]

Values are presented as median (interquartile range) or number (%).
CRRT, continuous renal replacement therapy; PRISM, Pediatric Risk of Mortality; ECMO, extracorporeal membrane oxygenation; WBC, white blood cell; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; BNP, brain natriuretic peptide; PT, prothrombin time; aPTT, activated partial thromboplastin time.
[a]Fisher's exact test.

시행한 최종 회귀모형은 통계적으로 유의하였고(X^2=97.362, p<0.001), Nagelkerke 결정계수에 의한 설명력은 85%로 나타났다. 분류 정확도는 93.9%, 모형의 적합성은 Hosmer와 Lemeshow 검정 결과 자료에 잘 부합하는 것으로 나타났다(X^2=2.825, p=0.945).

지속적 신대체 요법을 적용한 소아 중환자의 사망위험 요인은 승압제 사용 개수, 젖산 수치, 지속적 신대체 요법의 적용 일수로 나타났으며 승압제 사용 개수가 1개 증가 시 OR은 5.233 (95% CI, 1.804–15.176; p=0.002)이었다. 젖산 수치 1 mmol/L 증가 시 OR은 1.076 (95% CI, 1.023–1.131; p=0.004)이었으며 지속적 신대체 요법의 적용 일수가 1일 증가 시 OR은 1.043 (95% CI, 1.004–1.084; p=0.030)이었다(Table 4).

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Table 3. Univariate analysis of factors associated with mortality in pediatric patients receiving CRRT

Variable	OR	95% CI	*p*-value
Underlying disease			
Leukemia	3.244	1.219–8.629	0.018
Heart failure	2.614	0.919–7.433	0.072
PRISM III score	1.129	1.064–1.198	<0.001
Number of vasoactive inotropic agents	4.996	2.762–9.036	<0.001
Application of mechanical ventilator	70.737	8.978–557.328	<0.001
Application of ECMO	4.286	1.605–11.446	0.004
Laboratory data			
Platelets (/1,000 cells/mm^3)	0.988	0.982–0.994	<0.001
C-reactive protein (mg/dL)	1.264	1.146–1.394	<0.001
Potassium (mEq/L)	1.335	0.971–1.889	0.074
Brain natriuretic peptide (/100 pg/dL)	1.055	1.026–1.084	<0.001
PT (sec)	1.043	1.006–1.082	0.024
aPTT (sec)	1.038	1.017–1.061	0.001
Lactic acid (mmol/L)	2.394	1.648–3.476	<0.001
Glucose (/10 mg/dL)	0.969	0.914–1.028	0.293
Duration of CRRT application (day)	1.026	1.004–1.048	0.023
Interval from admission to CRRT application (day)	1.021	0.968–1.078	0.441
Reason for CRRT application			
Sepsis	10.909	2.346–50.738	0.002
Metabolic acidosis	2.590	0.990–6.775	0.052

CRRT, continuous renal replacement therapy; OR, odds ratio; CI, confidence interval; PRISM, Pediatric Risk of Mortality; ECMO, extracorporeal membrane oxygenation; PT, prothrombin time; aPTT, activated partial thromboplastin time.

고찰

본 연구 결과 지속적 신대체 요법을 적용한 소아 중환자의 사망에 유의한 위험 요인으로는 승압제 사용 개수가 많을수록, 젖산 수치가 높을수록, 지속적 신대체 요법의 적용 일수가 길수록 사망위험이 높은 것으로 나타났다. 이는 선행 연구에서 승압제 사용 시 사망률이 증가한다는 결과[2,5,10,11]와 유사하였고, 승압제 사용 개수가 많을수록 사망률이 증가한다는 결과[2,4,11,12]와도 일치하였다. 저혈압은 패혈증의 병태생리 중 중요한 특징 중 하나로 저혈압 기간이 길어질수록 패혈성쇼크 및 다장기부전이나 사망률의 위험이 증가한다[13]. 따라서 지속적 신대체 요법을 적용 중인 환자들에게서는 적절한 승압제를 조기에 적용하여 혈역학적 안정성을 유지해 주는 것이 임상 예후에 중요한 영향을 미치는 요소가 된다.

본 연구에서 젖산 수치가 높을수록 사망위험이 증가한다는 결과는 선행 연구에서 젖산 수치가 생존군과 사망군에서 유의한 차이를 보였다는 결과[5]와 유사하였다. 소아의 지속적 신대체 요법을 다룬 선행 연구에서 젖산 수치에 대한 연구의 수가 적어 정확한 결과를 비교하기는 어려웠으나 높은 젖산 수치가 사망률에 영향을 줄 수 있다는 선행 연구들은 많았다. 중환자실에서 평가된 젖산 수치가 병원 내 사망률을 예측하는 인자로 유용하다는 결과[14]가 있었고, 혈장 내 높은 젖산 수치가 심각한 패혈증 환자의 사망률을 예측하는 임상적 진단 검사임

Table 4. Multivariate analysis of factors associated with mortality in pediatric patients receiving CRRT (n=96)

Variable	OR	95% CI	*p*-value
Number of vasoactive inotropic agents	5.233	1.804–15.176	0.002
Brain natriuretic peptide (/100 pg/dL)	0.948	0.896–1.004	0.066
Lactic acid (mmol/L)	1.076	1.023–1.131	0.004
Duration of CRRT application (day)	1.043	1.004–1.084	0.030
Sepsis	6.910	0.794–60.133	0.080

CRRT, continuous renal replacement therapy; OR, odds ratio; CI, confidence interval.

[15]이 보고된 바 있다. 또한 저혈압을 동반한 패혈증 및 젖산 수치의 상승은 사망률을 높일 수 있다는 선행 연구의 결과[16]와 승압제를 사용하는 대상자의 경우 높은 젖산 수치를 나타낼 때 더 높은 사망률을 보인 선행 연구 결과[17], 그리고 승압제 사용과 높은 젖산 수치가 사망률을 예측하는 인자로서 유용하다는 선행 연구 결과[13,15]로 보아 지속적 신대체 요법을 적용한 소아 중환자에 있어서도 동일하게 혈장 내 높은 젖산 수치와 승압제를 필요로하는 저혈압은 유의한 사망위험 요인으로 볼 수 있다.

또한, 본 연구에서 지속적 신대체 요법 적용 일수가 길수록 사망위험이 증가한다는 결과는 적용 일수가 짧을수록 임상 결과와 예후가 좋다는 결과[18]의 선행연구와 유사하였다. 다른 선행 연구에서는 지속

적 신대체 요법의 적용 시간이 사망률에 유의한 차이가 없었다는 결과[4,10]가 나타났는데 이는 선행 연구의 연구 대상자의 연령대와 기저질환의 분포가 본 연구와 다르기 때문이라고 생각한다. 급성 신손상은 기저질환으로 인한 이차적인 증상으로 나타나 지속적 신대체 요법을 적용하는 경우가 많은데 선행 연구의 연구 대상자는 소아와 신생아를 포함하였고 신생아가 21.1%의 분포를 보였다. 적용 사유 또한 고질소혈증이 81.9%로 가장 많았으며 이는 본 연구의 가장 많은 적용 사유인 패혈증과는 다르게 나타났다. 소아는 체중과 연령대의 범위가 넓고 연령에 따른 기저질환 자체가 다르며 질환의 경과가 다르기 때문에[19] 더 세분화된 분류를 통한 지속적 신대체 요법에 대한 연구가 필요하다.

본 연구에서 체내 수분 저류 정도를 나타내는 수치인 뇌나트륨이뇨펩티드의 낮은 수치가 사망위험 요인으로 유의하지 않다는 결과는 수치가 높을수록 사망 위험 요인이 될 수 있음을 알 수 있다. 선행 연구에서 뇌나트륨이뇨펩티드에 대한 연구가 적어 정확한 결과를 확인하기 어려움이 있어 체액 과다가 사망률에 유의한 차이를 보였던 연구와 비교하였다. 선행 연구에서 지속적 신대체 요법 시작 시점에 체액 과다가 나타나는 경우 사망률이 증가한다는 결과[2,20]가 있었고 체내 수분의 저류 정도가 심할수록 사망률이 증가한다는 결과[12]와 유사하였다. 또한 지속적 신대체 요법의 적용 사유가 체액 과다인 경우 사망률에 유의한 차이를 보였던 선행 연구 결과[10], 지속적 신대체 요법 시작 시점에 체액 과다가 나타나는 경우 사망률이 증가한다는 결과[2,20]와 유사하였다. 또한 체내 수분의 저류 정도가 심할수록 사망률이 증가한다는 결과[12], 지속적 신대체 요법의 적용 사유가 체액 과다인 경우 사망률에 유의한 차이를 보였던 선행 연구[10]의 결과와 유사하였다. 체내 수분 저류 정도인 체액 과다를 측정하는 계산법이 있긴 하지만 실제 임상에서는 적용하기 어려운 실정이다. 대상자가 입실하기 전 병동에 있었다면 섭취량과 배설량의 정확한 확인이 가능하지만, 응급실을 통해서 온 대상자의 경우에는 정확한 체액 과다 정도를 알기 어렵기 때문에 측정이 어려워 본 연구에서는 뇌나트륨이뇨펩티드로 확인하는 방법이 가장 적절하다고 판단하여 자료를 수집하였다. 현재의 체액 과다 계산법은 쉽게 확인 가능한 방법이라고 보기 어려우므로 임상에서 쉽게 확인할 수 있는 진단 검사 수치로 체내 수분 저류를 정확하게 확인할 수 있는 지표가 마련된다면 체액 과다를 판단할 기초자료로 유용하게 활용될 수 있을 것이다. 또한 소아의 지속적 신대체 요법 연구에서 뇌나트륨이뇨펩티드 수치에 대한 선행연구가 적어 본 연구와 비교하기 어려움이 있었으므로 이에 대한 추가 연구가 필요하다.

본 연구는 몇 가지 제한점을 가지고 있다. 첫째, 서울 시내 단일 의료 기관에서 진행된 연구이며 둘째, 대상자 수가 적어 연구 결과를 일반화하기 어렵다는 점, 그리고 셋째, 소아의 지속적 신대체 요법에 대한 선행 연구의 수가 적어 본 연구의 결과와 비교할 수 있는 부분이 제한적이었다는 점이다. 또한 2013년 1월부터 2022년 12월까지 10년의 기간에 의료 발전으로 인한 소아 중환자실에서의 치료 과정과 방법에 많은 변화가 있었을 것으로 생각되나 이에 따른 결과를 알기 어렵다는 점이다. 그럼에도 불구하고 단일 기관의 소아 중환자실에서 적은 대상자 수로 자료를 수집하였기 때문에 치료 과정과 결과에 외적인 변수들이 최소화되었고 모든 대상자에게 치료 방법의 변화가 동일하게 적용되었을 것으로 생각해 볼 수 있기 때문에 의미 있는 결과라고 볼 수 있다. 본 연구에서 지속적 신대체 요법을 적용한 소아 중환자 사망률의 경향을 확인할 수 있었으며 10년 동안의 초기 자료에서는 적용률이 대부분 한 자릿수로 적어 정확한 사망률을 알기 어려웠지만 최근 5년 동안의 자료에서 살펴보면 2018년 75%, 2019년 70%, 2020년 78%, 2021년 56%, 2022년 24%로 사망률이 감소하는 경향을 나타내는 것을 알 수 있다.

위와 같은 제한점이 있음에도 본 연구는 지속적 신대체 요법을 적용한 소아 중환자의 사망위험 요인을 파악하여 이에 대한 이해를 도와 긍정적인 임상 결과를 나타낼 것으로 생각한다. 또한 소아의 지속적 신대체 요법에 대한 연구의 수가 적기 때문에 이에 대한 기초 자료를 제공했다는 데에 의의가 있다. 본 연구는 지속적 신대체 요법을 적용한 소아 중환자의 사망위험 요인을 파악하기 위한 후향적 조사연구로, 승압제 사용 개수가 많을수록, 젖산 수치가 높을수록, 지속적 신대체 요법의 적용 일수가 길수록 사망위험이 높은 것으로 나타났다.

본 연구에 대한 몇 가지 제언을 하고자 한다. 첫째, 본 연구는 서울 시내 일개 상급종합병원에서 조사한 연구로 연구 결과의 일반화에 제한이 있으므로 다기관에서의 여러 대상자를 포함한 반복 연구가 필요하며, 둘째, 소아의 특성상 연령대와 체중의 범위가 넓고 연령대에 따른 기저질환의 분포가 다르며 지속적 신대체 요법을 적용한 사유 또한 연령대별로 특징적이므로 더 세분화된 분류를 하여 지속적 신대체 요법에 대한 연구가 필요하다. 셋째, 본 연구의 결과와 비교할 선행 연구가 많지 않아 결과 해석의 제한이 있으므로 소아의 지속적 신대체 요법에 대한 반복 연구가 필요하다.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: SYK, HRC. Methodology: SYK, HRC. Formal analysis: SYK, HRC. Data curation: SYK. Visualization: SYK,

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HRC. Project administration: SYK, HRC. Writing - original draft: SYK. Writing - review & editing: SYK, HRC.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.32990/apcc.2023.00031.

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The effect of fluid therapy during the first 12 hours after septic shock onset in pediatric patients

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Background: Initial fluid therapy is the cornerstone of hemodynamic resuscitation in pediatric patients with septic shock. This study investigated the association between fluid therapy during the first 12 hours after septic shock onset and the outcomes of pediatric patients.

Methods: This retrospective, observational study included consecutive pediatric patients with septic shock who were admitted to a multidisciplinary pediatric intensive care unit between January 2012 and December 2019. Data on total fluid administration within the first 12 hours of septic shock onset, patient characteristics, and outcome measurements were collected from validated electronic medical records.

Results: In total, 144 cases were included (overall 28-day mortality rate, 20.1%). Significant differences were found between survivors and non-survivors in the proportion of fluid received within the first 3 hours (36.9% vs. 25.4%, p=0.004) and within the last 3 hours (18.9% vs. 21.3%, p=0.031). The mortality rate was lower in patients who received a higher proportion of fluid within the first 3 hours (13.9% vs. 26.4%, p=0.048). Conversely, those with a higher proportion of fluid in the last 3 hours had a significantly higher mortality rate (29.6% vs. 14.4%, p=0.025). Multivariable logistic regression analysis revealed that a higher proportion of fluid within the first 3 hours was associated with decreased mortality (odds ratio [OR], 0.951; 95% confidence interval [CI], 0.918–0.986; p=0.028), while a higher proportion within the last 3 hours was associated with increased mortality (OR, 2.761; 95% CI, 1.175–6.495; p=0.020).

Conclusion: Higher fluid intake during the initial 3 hours after septic shock onset was linked to a reduction in 28-day mortality among pediatric patients; conversely, higher fluid volume during the final 3 hours of the 12-hour period post-onset was correlated with worse survival outcomes. Providing an adequate fluid volume within the first 3 hours, followed by a more conservative approach to fluid administration, may contribute to decreased mortality.

Keywords: Sepsis; Shock; Resuscitation; Fluid therapy; Critical illness

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INTRODUCTION

Septic shock remains a leading cause of morbidity and mortality in children, with fatality rates reaching up to 60% [1]. In severe cases of sepsis and septic shock, the primary therapeutic treatment approaches include intravenous fluids, appropriate antibiotics, source control, vasopressors, and ventilator support [2]. A study by Carcillo et al. [3] in 1991 demonstrated that higher volumes of initial fluid resuscitation were associated with decreased mortality in pediatric septic shock. Specifically, patients who received a volume of resuscitation fluid equal to or greater than 40 mL/kg in the first hour after septic shock onset exhibited better survival rates than those who received smaller initial fluid amounts. Subsequent evidence led to a consensus statement in 2002, providing guidelines for hemodynamic support in pediatric and neonatal patients with septic shock [4]. These guidelines recommended aggressive fluid resuscitation with the aim of normalizing vital signs and evidence of perfusion within the first hour, followed by titration of inotropes and vasopressors along with ongoing volume resuscitation. The recommendations were updated in 2007 and 2017, maintaining the focus on early and aggressive normalization of perfusion through aggressive volume resuscitation, followed by the addition of vasopressors [5]. However, the 2020 Surviving Sepsis Campaign (SSC) guidelines recommended a bolus fluid of 40–60 mL/kg over the first hour if hypotension is present but did not provide distinct recommendations for subsequent fluid therapy [6].

It is now recognized that a positive fluid balance in the intensive care unit (ICU) is associated with an increased risk of mortality in adult septic shock patients [7-10]. This has challenged the idea that aggressive volume resuscitation is universally beneficial and has suggested potential harm in certain patient populations. As a result, the concept of optimal fluid resuscitation has gained attention as a critical component of clinical interventions and an essential factor in the initial management of sepsis. While the appropriate timing and quantity of fluid resuscitation in the ICU have been emphasized for improving survival, there is a scarcity of studies examining the relationship between fluid balance, timing of fluid resuscitation, and outcomes in pediatric patients with septic shock.

In our present study, we aimed to describe the characteristics of children experiencing septic shock and examine the potential association between the volume and distribution of resuscitation fluid administered during the initial 12 hours and the mortality rates in this patient population.

METHODS

This study received approval from the Institutional Review Board of Asan Medical Center (No. 2019-1269). Due to the retrospective and observational nature of the study, the requirement for informed consent was waived. Patients were treated following our institution's pediatric septic shock management protocol.

Data were collected through a review of electronic patient records from January 2012 to December 2019 at the Asan Medical Center Children's Hospital, a tertiary pediatric ICU in Seoul, Korea. We included consecutive admissions of patients under 18 years of age who were diagnosed with septic shock and required vasoactive agents.

The diagnosis of septic shock was based on the 2017 guidelines of the American College of Critical Care Medicine (ACCM) committee [3,5]. We identified patients who met the following criteria: (1) suspected infection accompanied by clinical signs of hypothermia or hyperthermia, (2) findings suggestive of inadequate tissue perfusion, such as altered mental status, prolonged capillary refill (> 2 seconds), diminished pulses, cool mottled extremities, flash capillary refill, bounding peripheral pulses, wide pulse pressure, or urine output of less than 1 mL/kg/hr, and (3) the need for inotropics or vasopressors to maintain sufficient perfusion or blood pressure. We excluded patients who (1) were unable to receive fluid resuscitation according to the septic shock protocol due to severe pulmonary hypertension or increased intracerebral pressure and (2) had insufficient medical data available.

Data Collection

We carried out a retrospective analysis of electronic medical records to collect data on baseline demographics, Pediatric Risk of Mortality (PRISM) III score, duration of mechanical ventilation support, requirement for renal replacement therapy, length of ICU stay, 28-day mortality, and initial lactate concentration. The onset of septic shock was defined as the moment when fluid resuscitation or vasoactive drugs were first administered to enhance insufficient tissue perfusion.

Fluid intake and output volumes were obtained from electronic medical records to determine the amount of fluid administered during the first 3 hours, and then every 3 hours within the initial 12-hour period following the onset of septic shock. The intake volume encompassed all fluids given, including nutritional fluids, medications, resuscitation bolus fluids, and blood transfusions. The output volume was calculated based on urine, dialysis, drainage, stools, and vomitus.

To evaluate the distribution of fluid intake during the initial 12 hours, the percentage of fluid administered every 3 hours was calculated and compared between survivors and non-survivors. The group with a higher proportion was defined as having a larger distribution than the median distribution of fluid administered for each 3-hour interval, while the group with a lower proportion was defined as having a smaller distribution. Following this, the 28-day mortality rates were compared between the higher-proportion group and the lower-proportion group within each time interval.

Statistical Analysis

Statistical analyses were performed using IBM SPSS ver. 21.0 (IBM Corp.). Categorical variables were represented as numbers and percentages and analyzed using either the Fisher exact test or the chi-square test. Continuous variables were expressed as medians (interquartile range). Two-tailed *t*-tests were employed for normally distributed continuous variables, while the Mann-Whitney *U*-test was utilized for non-parametric data. Multivariable logistic regression was performed to identify the variables associated with 28-day mortality rates. The variables incorporated into the multivariable models were chosen based on a priori clinical rationale and included age, sex, and the PRISM III score. A significance level of $p < 0.05$ (two-sided) was deemed statistically significant for all tests.

RESULTS

From the initial cohort of 167 children who met the inclusion criteria, 23 were subsequently excluded from the study. Of these, 15 patients had incomplete detailed data, while the remaining 8 patients were excluded due to contraindications for fluid resuscitation, specifically severe pulmonary hypertension and increased intracerebral pressure.

A total of 144 patients with septic shock were included in the study cohort. Table 1 displays the characteristics of these cases, as well as the results of the univariable analysis comparing survivors and non-survivors. The median age was 9.1 years, and the median weight was 20.6 kg. The overall 28-day mortality rate in the study population was 20.1%. Hematological/oncological disor-

Table 1. Baseline characteristics of the enrolled pediatric patients with septic shock

Variable	Total (n=144)	Survivor (n=115)	Non-survivor (n=29)	*p*-value
Age (yr)	9.1 (1.6–14.3)	9.8 (1.6–14.4)	4.1 (1.6–13.9)	0.222
Boy	89 (61.8)	61 (61.7)	18 (62.1)	0.576
Body weight (kg)	20.6 (7.7–43.0)	24.6 (7.4–44.0)	14.4 (9.2–42.8)	0.274
Underlying disease				0.323
Hematology-oncology	61 (42.4)	47 (40.9)	14 (48.3)	
Neurology	23 (16.0)	21 (18.3)	2 (6.9)	
Cardiology	18 (12.5)	14 (12.2)	4 (13.8)	
Respiratory	16 (11.1)	14 (12.2)	2 (6.9)	
Gastro-intestinal	12 (8.3)	8 (7.0)	4 (13.8)	
Others	14 (9.7)	11 (9.6)	3 (10.3)	
Microorganism				0.138
Fungus	10 (6.9)	6 (5.3)	4 (13.8)	
Gram-positive	36 (39.6)	31 (38.6)	5 (44.8)	
Gram-negative	57 (25.0)	44 (27.2)	13 (17.2)	
Mycoplasma	1 (0.7)	1 (0.9)	0	
Unproven	40 (27.8)	33 (28.9)	7 (24.1)	
PRISM III score	11.0 (8.0–17.0)	11.0 (8.0–15.0)	14.0 (11.0–20.0)	0.013
VIS at 24 hours	10.0 (0.0–25.0)	10.0 (0.0–20.4)	20.0 (3.5–63.4)	0.024
CRP (mg/dL)	10.0 (2.8–18.3)	9.9 (3.2–18.7)	10.0 (2.4–16.7)	0.673
Lactic acid (mmol/L)	2.1 (1.0–4.5)	2.0 (1.0–4.2)	3.8 (1.4–8.5)	0.052
Mechanical ventilation	79 (54.9)	53 (46.1)	26 (89.7)	0.000
CRRT	29 (20.1)	14 (12.2)	15 (51.7)	0.000
ECMO	7 (4.9)	2 (1.7)	5 (17.2)	0.004

Values are presented as median (interquartile range) or number (%).
PRISM, Pediatric Risk of Mortality; VIS, vasoactive inotropic score; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

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Table 2. Fluid administration patterns after the onset time of septic shock

Variable	Total (n=144)	Survivor (n=115)	Non-survivor (n=29)	*p*-value
Amount of fluid received (mL/kg)				
During the first 12 hours	56.5 (40.8 to 79.6)	54.7 (39.0 to 79.4)	57.3 (43.0 to 85.3)	0.357
In the first 3 hours	21.4 (11.3 to 30.7)	21.9 (12.1 to 31.5)	16.1 (10.6 to 30.5)	0.239
In 3–6 hours	12.0 (7.4 to 17.9)	12.0 (7.2 to 16.4)	12.0 (9.9 to 21.6)	0.163
In 6–9 hours	11.2 (7.6 to 17.7)	10.9 (6.8 to 17.8)	13.9 (9.7 to 17.7)	0.189
In 9–12 hours	10.1 (6.6 to 15.0)	9.4 (6.0 to 14.4)	13.1 (9.6 to 17.7)	0.014
Net fluid balance (mL/kg)				
During the first 12 hours	20.9 (4.9 to 41.5)	20.7 (4.4 to 39.1)	23.9 (6.3 to 53.2)	0.404
In the first 3 hours	14.8 (4.3 to 27.3)	16.7 (4.8 to 27.7)	12.4 (3.6 to 23.0)	0.199
In 3–6 hours	4.0 (–2.9 to 10.0)	3.1 (–4.7 to 10.0)	4.9 (0.8 to 11.1)	0.044
In 6–9 hours	3.0 (–2.2 to 9.3)	3.1 (–2.8 to 9.4)	2.8 (–0.2 to 9.5)	0.363
In 9–12 hours	1.4 (–3.1 to 7.3)	0.8 (–3.6 to 6.5)	3.1 (–1.7 to 11.8)	0.156

Values are presented as median (interquartile range).

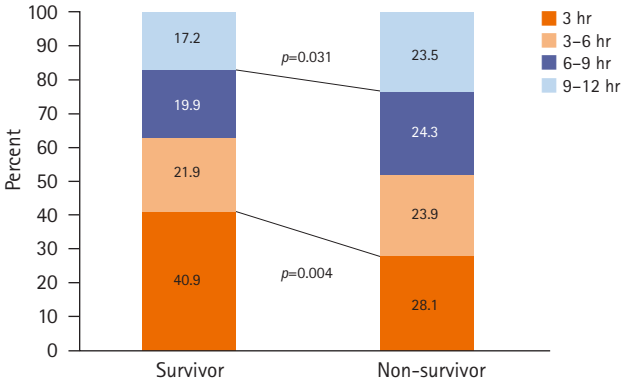

Fig. 1. Distribution of fluid volumes administrated to the study patients during the 12-hour period after the onset of septic shock.

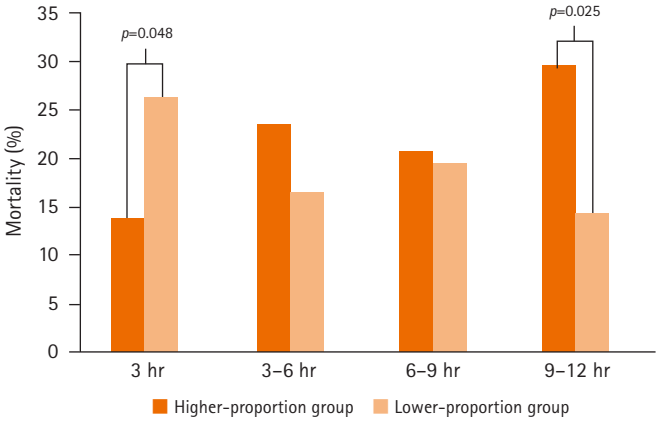

Fig. 2. Comparison of mortality between the higher-proportion group and the lower-proportion group stratified by the time from septic shock onset. The higher-proportion group included patients in whom the volume of fluid administered exceeded the median value for a given 3-hour period. The lower-proportion group included patients in whom the volume of fluid administered was less than the median value for a given 3-hour period.

ders were the most common underlying diseases, while patients with gastrointestinal diseases experienced the highest mortality rate at 33.3%. Significant differences were observed in the PRISM III score on the day of onset and the vasoactive inotropic score at 24 hours between survivors and non-survivors.

Table 2 demonstrates that similar amounts of fluid were administered to both survivors and non-survivors within the initial 12-hour period. However, when divided into 3-hour intervals, survivors received a significantly smaller volume of fluids during the last 3 hours than non-survivors (9.4 vs. 13.1 mL/kg, $p=0.014$). Additionally, although the difference was not statistically significant, a higher volume of fluid was administered to survivors during the initial 3 hours compared to non-survivors (21.9 vs. 16.1 mL/kg, $p=0.239$). There was no significant difference in overall net fluid balance between survivors and non-survivors during the initial 12-hour period. Fig. 1 displays the distribution of fluid administered every 3 hours over the course of 12 hours. Among survivors, the largest proportion of fluid was given during the first 3 hours, followed by a gradual decline. In contrast, non-survivors exhibited a consistent distribution of fluid administration throughout the entire 12-hour period. As illustrated in Fig. 2, when comparing the distribution of fluid within each 3-hour interval to the total amount administered within the initial 12 hours, the group with a higher proportion of fluid during the first 3-hour interval had a significantly lower 28-day mortality rate. However, the group with a higher proportion of fluid administered during the last 3-hour interval experienced a significantly higher 28-day mortality rate.

Table 3 displays the results of a multivariable logistic regression

Table 3. Multivariable logistic regression analysis of 28-day mortality risk factors in the critically ill study children with septic shock

Variable	Odds ratio	95% Confidence interval	*p*-value
PRISM III score	1.069	1.012–1.130	0.017
Group with a higher proportion of fluid intake during the first 3-hour period	0.951	0.918–0.986	0.028
Group with a higher proportion of fluid intake during the 9–12 hour period	2.761	1.175–6.495	0.020

PRISM, Pediatric Risk of Mortality.

analysis that investigates potential risk factors, such as the PRISM III score, the group with a higher proportion of fluid intake during the initial 3 hours, and the group with a higher proportion of fluid intake during hours 9–12. The group with a higher proportion of fluid intake during the first 3 hours demonstrated a significant association with a reduced risk of 28-day mortality (odds ratio [OR], 0.951; 95% confidence interval [CI], 0.918–0.986; $p = 0.028$). In contrast, the group with a higher proportion of fluid intake during hours 9–12 had a significantly elevated risk of 28-day mortality (OR, 2.761; 95% CI, 1.175–6.495; $p = 0.020$).

DISCUSSION

The aim of this study was to investigate the effect of fluid management within the first 12 hours following the onset of septic shock in pediatric patients on clinical outcomes. Our results show that the total volume of fluid administered during the initial 12 hours was similar between survivors and non-survivors, with no significant differences in net fluid balance between the two groups. However, the distribution of fluid administration within the first 12 hours served as a distinguishing factor. Survivors received approximately 40% of the total fluid volume within the first 3 hours, followed by a gradual decrease. In contrast, non-survivors displayed a more consistent distribution of fluid administration throughout the entire 12-hour period. Notably, among the subgroup receiving a relatively higher proportion of fluid during the first 3 hours, there was a significant reduction in 28-day mortality. Conversely, during the last 3 hours of the initial 12-hour period, the higher-proportion group exhibited a significant association with increased mortality rates.

The ACCM guidelines emphasize the importance of initiating aggressive fluid resuscitation, up to 60 mL/kg, within the first hour following the diagnosis of severe septic shock. This is followed by adjusting vasoactive medications based on the specific shock phenotype and potentially administering additional fluids if necessary [4,5,11]. The most recent update of the SSC guidelines did not introduce any changes to this recommended fluid therapy [6]. However, recent research has drawn increased attention to the potentially harmful effects of excessive volume overload beyond the initial resuscitation period [7,8,12]. Fluid resuscitation is a crucial aspect of septic shock management, and the importance of early initiation of fluid resuscitation in the initial phases of septic shock is widely acknowledged and supported by numerous previous studies [2-4,13-15]. In our study, the survival rate was higher among patients who received a greater amount of fluid within the first 3 hours than among those who did not, highlighting the significance of optimizing blood pressure during the early stages of septic shock management. However, determining the appropriate fluid volumes and optimal hemodynamic targets in pediatric patients remains challenging. Fluid responsiveness is a crucial factor guiding fluid resuscitation strategies, yet accurately estimating this parameter remains difficult, and no consensus currently exists on assessment tools specifically tailored for pediatric patients [16-19]. In the present study, a smaller volume of resuscitation fluid was administered than the recommended amount by the ACCM guidelines (i.e., approximately 25 mL/kg within the first 3 hours). Notably, however, the mortality rate was not higher than that reported in other studies. While our institute adheres to ACCM or SSC guidelines, fluid resuscitation strategies in septic shock cases are determined by the treating physicians, who take into account various factors influencing fluid responsiveness and potential adverse effects on cardiac, respiratory, and renal function.

To minimize adverse reactions associated with fluid resuscitation, we implemented a comprehensive evaluation of organ function, including cardiac echocardiography, a chest X-ray examination, and various blood tests (e.g., B-type natriuretic peptide), while administering fluid therapy. For these reasons, adherence to the guideline-recommended fluid volumes in all septic shock patients was not achievable. The primary objective of fluid resuscitation is to raise the mean circulating pressure and stroke volume, leading to an improvement in tissue perfusion pressure. However, crystalloids have a limited capability to expand the intravascular volume, as shown by previous studies where less than 5% of a crystalloid bolus was found to remain in the intravascular space 1 hour after an infusion was completed [20,21]. Macrocirculatory parameters, such as blood pressure or central venous pressure, are currently recognized as poor indicators of microcir-

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culation, especially in patients with sepsis and septic shock. Instead, the microvasculature plays an independent role in tissue perfusion and oxygenation that may not be influenced by macrovascular alterations [22,23]. Hence, fluid therapy aimed at macrocirculatory indicators can lead to fluid overload, which has been consistently associated with harm in critically ill children.

In our study, we discovered that even though the administered fluid volumes did not meet the levels recommended by the guidelines, there was a significant difference in fluid distribution between the survival and non-survival groups. Both groups received comparable total fluid volumes over a 12-hour period; however, the survival group received a larger volume of fluid during the initial 3 hours. In contrast, the non-survival group received a consistent amount of fluid throughout the entire 12-hour period. These findings indicate that the distribution pattern of fluid administration is important, not only the total volume of administered fluid. Aggressive fluid administration during the early phase, followed by a more conservative approach in later hours, seems to be crucial for optimal fluid management.

The Fluid Expansion as Supportive Therapy study, a randomized controlled trial involving over 3,000 acutely ill African children with sepsis and impaired perfusion, has played a crucial role in highlighting concerns about the potential harm associated with fluid bolus therapy. This study showed that children who received fluid boluses in response to impaired perfusion experienced higher early mortality rates (within 48 hours) as well as higher late mortality rates (4 weeks) compared to those who did not receive fluid [9]. Notably, a post hoc analysis revealed that although fluid boluses initially offered short-term benefits by resolving the state of shock, children who received fluid boluses faced increased mortality due to the worsening of cardiovascular dysfunction following the initial improvement [24,25].

Abulebda et al. [26] discussed the influence of volume balance on the clinical course of pediatric septic shock patients during the post-ICU admission period. The authors conducted a stratified analysis based on mortality risk using their risk stratification tool and discovered that increased fluid intake and positive fluid balance after ICU admission were linked to worse outcomes in pediatric septic patients with a low initial mortality risk. However, these associations were not observed in patients with moderate or high mortality risk. The findings of that study somewhat diverge from previous reports in adult septic shock patients [7,8,27-29]. The authors attributed this discrepancy to the absence of pre-ICU admission fluid balance data, which made it challenging to predict the overall impact on their results if such data were available. In contrast, our study boasts a significant strength in that the total fluid intake was estimated from the onset of shock, irrespective of the patient's location (emergency room or general ward). This approach has enabled a more transparent illustration of the effects of early fluid therapy in our study.

Existing literature reviews have consistently shown that a positive fluid balance, identified at various time points within the first 24 hours of ICU admission and culminating in a cumulative positive balance at discharge, is associated with higher mortality rates [10,12,30-34]. It is also important to emphasize that our current findings, in line with previous studies, show that an increase in fluid intake volumes starting 3 hours after the onset of septic shock is associated with increased mortality. Notably, our present data reveal that a high intake volume between 9 and 12 hours post-onset is strongly linked to higher mortality in children with septic shock. These findings suggest that a positive fluid balance beginning 3 hours after the onset of septic shock may have detrimental effects.

Our study had several significant limitations. First, it was conducted at a single center, potentially limiting the generalizability of our findings. Second, our observational design covered a brief period of only 12 hours, and our sample size was relatively small compared to other studies on fluid therapy. As a result, our capacity to determine a definitive relationship between fluid resuscitation and patient outcomes was limited. Furthermore, other factors, such as antibiotic therapy, source control, and unmeasured clinical parameters, may have impacted our results.

We found that a higher fluid intake during the initial 3 hours of septic shock onset is associated with a reduced 28-day mortality rate. Conversely, an increased fluid intake in the last 3 hours of the first 12-hour period following onset is linked to poorer outcomes. As a result, we cautiously propose that administering an adequate amount of fluid within the first 3 hours, followed by a more conservative approach to fluid administration, may help decrease mortality. However, given the absence of consensus on these strategies, future high-quality studies involving specific patient populations will be of vital importance.

CONFLICT OF INTEREST

Won Kyoung Jhang is an Editor-in-Chief, and Seong Jong Park is an editorial board member of the journal, but they were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Sufentanil use in critically ill children: a single-center experience

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Background: Critically ill children often require pain management or sedation due to their underlying conditions or the need for intensive care. However, the available drug options and their clinical reliability are frequently limited for these patients. This study explored the utility of sufentanil as an analgosedative in critically ill pediatric patients, drawing on clinical experience.

Methods: This single-center retrospective observational cohort study included patients under 19 years of age admitted to the pediatric intensive care unit (PICU) in a tertiary care children's hospital between March 2021 and September 2022, in whom sufentanil was used as the first-choice continuous analgosedative drug.

Results: In total, 225 patients were included. The most common reason for PICU admission was postoperative care (34.7%), followed by respiratory failure (20.0%), and cardiac problems (17.3%). The initial median starting and maximum doses of sufentanil were 0.5 μg/kg/hr (interquartile range [IQR], 0.3–1.0). The median durations of sufentanil use, mechanical ventilation support, and PICU stay were 1 days (IQR, 4–12), 6 days (IQR, 1–17) and 9 days (IQR, 5–27), respectively. In 199 (88.4%) patients, an appropriate analgesia/sedation level was achieved with sufentanil alone. However, 26 patients required additional drugs such as midazolam and ketamine infusion after administering the maximum dose of sufentanil, indicating the necessity for supplementary agents. No significant adverse effects or withdrawal symptoms were associated with sufentanil use.

Conclusion: Sufentanil may be a promising option for analgesia/sedation in critically ill pediatric patients, as it demonstrated no significant side effects or withdrawal symptoms. However, larger-scale randomized controlled research is necessary to generalize these results.

Keywords: Critically ill; Pediatrics; Sedation; Sufentanil

INTRODUCTION

Critically ill patients frequently require highly complex medico-surgical procedures, painful interventions, testing, and invasive monitoring, which can be extremely stressful and provoke agitation and anxiety for both the patient and the care team [1-4]. To alleviate this stress and promote early recovery, proper pain control and sedation management are essential.

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However, this can be particularly challenging in critically ill children due to factors such as varying ages, developmental stages, clinical statuses, and their unique pharmacokinetics and pharmacodynamics [2,5,6]. Furthermore, limited analgosedative options are available for these patients [5-7].

Sufentanil, a synthetic analog of fentanyl, is a potent analgesic that acts as a highly selective μ-opioid receptor agonist [8-10]. Since its initial development and introduction into clinical practice, sufentanil has primarily been used for anesthesia induction in high-risk surgical procedures. Consequently, most of the existing research on sufentanil has focused on its perioperative applications [11-19]. There remains a dearth of knowledge regarding its efficacy and safety as an analgosedative in critically ill pediatric patients, with few published reports detailing its use in pediatric intensive care units (PICUs) [5].

However, considering the pharmacologic properties of sufentanil published to date and several reports of its use in critically ill adults and neonates, sufentanil seems to hold promise as a potential analgosedative option for critically ill pediatric patients [20-23]. In this study, therefore, we aimed to evaluate the clinical utility of sufentanil as an analgosedative in critically ill pediatric patients, drawing from our own experiences with this drug at our institution's PICU.

METHODS

This study received approval from the Institutional Review Board of Asan Medical Center (No. 2020-0878). Due to the retrospective nature of the study, the requirement for informed consent was waived. The study was conducted in accordance with the principles of the 1964 Declaration of Helsinki and its subsequent amendments. Additionally, this study adheres to the Strengthening the Reporting of Observational (STROBE) guidelines for reporting observational studies.

Study Design and Subjects

This was a single-center, retrospective observational cohort study. We screened all critically ill pediatric patients who were consecutively admitted to a 25-bed multidisciplinary PICU at a tertiary care academic referral hospital between March 2021 and September 2022 for enrollment. Our inclusion criteria were patients under 19 years of age who received sufentanil as the first-choice continuous analgosedative drug.

Data Collection

In this study, we conducted a retrospective review of electronic medical records for all included patients, gathering data on various baseline demographics such as underlying disorders, reasons for PICU admission, mechanical ventilator (MV) support usage, and the need for continuous renal replacement therapy (CRRT) or extracorporeal membrane oxygenation (ECMO). Additionally, we collected information on the duration of MV support and PICU stay, pain and sedation assessment scores, and all relevant aspects of sufentanil use, including the initial starting dose, maximum dosage for optimal pain control and sedation, duration of use, any withdrawal symptoms, adverse effects, and the requirements for additional analgosedative drugs.

Pain and sedation assessments were performed using various tools according to the patients' ages, such as the Neonatal Pain, Agitation and Sedation Scale (N-PASS); Face, Legs, Activity, Cry, Consolability (FLACC) scale; numeric rating scale (NRS); State Behavioral Assessment Scale (SBS), COMFORT Scale; and Richmond Agitation Sedation Scale (RASS) [24]. We established daily targeted goals for pain control and sedation levels. Based on the assessment scores, drug doses were adjusted. To evaluate withdrawal symptoms, we used the Withdrawal Assessment Tool-1 [25].

Statistical Analysis

Data were analyzed using IBM SPSS ver. 21.0 (IBM Corp.). Continuous variables are reported as medians with interquartile ranges. Categorical variables are expressed as numbers and proportions.

RESULTS

Baseline Characteristics of the Study Population

A total of 225 patients were included in the study, with 142 (55.7%) being boys. The median age and body weight of the patients were 1.9 years (0.6–6.8 years) and 10.9 kg (6.0–20.3 kg), respectively. Cardiac disorders were the most frequently encountered underlying conditions, affecting 70 patients (31.1%). The most common reason for PICU admission was postoperative care, accounting for 78 cases (34.7%). MV support was required for 196 patients (87.1%), while 26 patients (11.6%) needed CRRT. ECMO was applied to 15 patients (6.7%) during the study period (Table 1).

Sufentanil Use

Sufentanil was initiated without a loading dose, and the median initial starting dose was 0.5 μg/kg/hr (0.3–1 μg/kg/hr). The maximum dose required for optimal pain control and sedation level

Table 1. Baseline characteristics of the study population

Variable	Value (n=225)
Male	142 (55.7)
Age (yr)	1.9 (0.6–6.8)
Weight (kg)	10.9 (6.0–20.3)
Duration of PICU stay (day)	6 (1.0–17.0)
Duration of hospital stay (day)	5 (9.0–27.0)
Underlying disease	
Cardiac	70 (31.1)
Gastrointestinal/hepatic	55 (24.4)
Respiratory	41 (18.2)
Hematologic-oncologic	35 (15.6)
Neurologic	12 (5.3)
Genetic/endocrinologic	7 (3.1)
Nephrologic	5 (2.2)
Others	3 (1.3)
Causes of PICU admission	
Postoperative care	78 (34.7)
Respiratory failure	45 (20.0)
Cardiac problems	39 (17.3)
Hematologic-oncologic problems	17 (7.6)
Neurologic problems	16 (7.1)
Gastrointestinal/hepatic problems	14 (6.2)
Shock	11 (4.9)
Acute kidney injury	3 (1.3)
Others	2 (0.9)
Number of patients with MV	196 (87.1)
Duration of MV (day)	6 (1–17)
Number of patients with CRRT	26 (11.6)
Number of patients with ECMO	15 (6.7)
Duration of PICU stay (day)	9 (5–27)
Use of sufentanil	
Initial starting dose (μg/kg/hr)	0.5 (0.3–1)
Maximum dose (μg/kg/hr)	0.5 (0.3–1)
Duration of use (day)	1 (4–12)

Values are presented as number (%) or median (interquartile range).
PICU, pediatric intensive care unit; MV, mechanical ventilation; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

was also 0.5 μg/kg/hr (0.3–1 μg/kg/hr). The optimal dose for targeted pain control and sedation level after initiation was achieved within 4 hours. The median duration of sufentanil use was 4 days (1–12 days). When tapering, a total period of more than 1 week was needed to decrease the dose by 0.1 μg/kg/hr per day. If continuous usage was less than 1 week, tapering was performed at a faster rate according to the patient's condition and targeted pain control and sedation level.

In our study, vecuronium was started simultaneously with sufentanil in 38 patients requiring a secure neuromuscular blocking agent (NMB) effect. These patients underwent operations or procedures that required secure immobilization, such as tracheal anastomosis, esophageal reconstruction and anastomosis, facial flap operation, central-type ECMO catheter placement, or high risk of operation site bleeding. Patients with severe acute respiratory distress syndrome, severe bronchopulmonary dysplasia, and severe pulmonary hypertension crises also required additional NMB due to deteriorating clinical conditions.

Additionally, 23 patients required midazolam as a supplementary agent even after the maximum dosage of sufentanil was administered. In five patients, ketamine was also required as an adjunct to sufentanil, and two patients required both midazolam and ketamine. Notably, no significant adverse effects related to the use of sufentanil were observed during the study period, including respiratory depression or hemodynamic instability. Furthermore, we did not observe any significant withdrawal symptoms.

DISCUSSION

The results of the present study showed that sufentanil was safe and effective as an analgosedative drug in critically ill pediatric patients with substantial variation in their age, size and clinical conditions. In our study, we did not conduct a direct comparison between the effects of sufentanil and other analgesic sedatives, such as fentanyl. However, our findings can be partially supported and corroborated by previous reports on the physiochemical and pharmacological properties of sufentanil [8,10,21,22,26,27].

Previous research on pediatric patients has shown that sufentanil has a lower volume of distribution compared to fentanyl, necessitating less medication to achieve the desired drug concentration. The higher lipid solubility of sufentanil relative to fentanyl results in a shorter distribution time, faster onset, more rapid peak effect, and briefer distribution and elimination half-lives [26]. As a result, sufentanil is a more potent analgesic than fentanyl.

It was previously believed that a longer infusion duration led to a longer recovery time due to saturation and increased drug concentration in the peripheral compartment. The context-sensitive half-time refers to the time it takes for the drug concentration in the blood to decrease by 50% after stopping the infusion over varying time intervals [28]. Sufentanil exhibits a consistent, low context-sensitive half-time regardless of infusion duration, and its effect-site concentration decrement time is also consistently low. As a result, sufentanil is an ideal medication for prolonged use, as it allows for rapid elimination without the risk of cumulative effects. In our study, the median duration of sufentanil use

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was 4 days (1–12 days). However, no significant adverse effects were observed during the study period. Regarding withdrawal, when sedatives are used for more than 5 days, withdrawal symptoms may occur, which can be alleviated by carefully weaning and tapering medication use [25,29]. Nevertheless, our results demonstrated no significant withdrawal symptoms during the tapering process, and there was no need to increase medication use, as a smooth and successful taper was achieved throughout.

Sufentanil offers several advantages for use in critically ill patients. It is metabolized via hepatic cytochrome P450 CYP3A4 through oxidative N-dealkylation into inactive metabolites, with only a small portion (2%) excreted unchanged via the kidneys (2%) [30]. It does not produce active or toxic metabolites, nor is it eliminated through renal clearance. Consequently, accumulation does not occur in cases of renal insufficiency, which is frequently observed in critically ill pediatric patients [31,32]. This characteristic makes sufentanil a safe option for pain management in critically ill patients, even in instances of renal failure. In our study, 26 patients required CRRT due to acute kidney injury, yet no sufentanil-related adverse effects were observed compared to other patients.

Sufentanil is well-known for maintaining hemodynamic stability during infusion, more so than other opioids. Respiratory depression has also been rarely reported. Consistent with this, no adverse effects were observed in patients with hemodynamically unstable shock or those not receiving mechanical ventilation support. This, in contrast to most other sedative drugs, could be an incredibly significant advantage, as sufentanil has demonstrated the ability to be safely administered to critically ill children with multiple organ failure without causing hemodynamic instability or respiratory depression.

In our study, 88.4% of patients did not require additional analgesia/sedative medication, a result that can be attributed to the wide range of available doses and rapid onset of action associated with sufentanil use. This enabled easy and efficient adjustments of medication as needed, tailored to each patient's specific target goals. This flexibility in medication management proved to be an invaluable asset in the successful treatment of critically ill children, setting sufentanil apart as an exceptional analgesia/sedative option.

However, there are several limitations to this study. First, this was a single-center, retrospective observational cohort study with a relatively small sample size and a highly heterogeneous patient group. As a result, the findings may not be generalizable without further validation in a larger, prospective randomized case-control study. It is important to note that a significant number of patients in our study were administered NMB agents concurrently due to their clinical characteristics. This suggests a potential confounding factor in our results, and further investigation is needed to fully understand the implications of these findings. Therefore, caution should be exercised when drawing definitive conclusions about the efficacy of sufentanil administration in critically ill children.

In this study, the diversity in age, disease, and clinical condition profiles of the patients made it challenging to consistently measure pain and sedation using numerical methods. Instead, individually tailored approaches were employed using various tools, which may have introduced some differences in medication control. Our study did not utilize a protocol-based, nurse-driven approach for managing analgosedative medications. Rather, it primarily relied on the physician's discretion to set daily targeted goals and control analgesic/sedation, which could introduce bias.

Despite its limitations, this study is of considerable significance, as it represents one of the few systematic accounts of clinical experience using sufentanil for pain management and sedation in critically ill pediatric patients. Furthermore, there is a need for additional large-scale randomized controlled trials to compare the safety and efficacy of sufentanil with other analgosedative agents in this vulnerable patient population.

In conclusion, our study offers significant insights into the clinical application of sufentanil for pain management in critically ill pediatric patients. We propose that sufentanil can be utilized as a safe and effective analgosedative in critically ill pediatric patients across various age groups and with a wide range of clinical conditions. The findings of this study may lay the groundwork for future research on pediatric pain management in the intensive care unit.

CONFLICT OF INTEREST

Won Kyoung Jhang is an Editor-in-Chief, and Seong Jong Park is an editorial board member of the journal, but they were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: WKJ, SJP. Data curation: WKJ. Formal analysis: WKJ. Investigation: WKJ. Methodology: WKJ, SJP. Validation: SJP. Writing - original draft: WKJ. Writing - review & editing: WKJ, SJP.

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Instructions to authors

APCC
Archives of Pediatric Critical Care

Enacted June 2023

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5.2. Categories of Manuscripts

APCC publishes editorials, original articles, review articles, case reports, and letters to the editor.

- **Editorials:** Editorials are commentaries on current topics or manuscripts related to materials within the current issue. they raise challenging questions or explore controversies. The editor solicits such opinion pieces. Editorials are invited by the Editors. The order of the submitted manuscript includes a title page, integrated discussion, and references. The text should be limited to 1,500 words and 10 references. A maximum of 2 figures or tables may be included.
- **Original articles:** Original articles are papers containing the results of clinical or laboratory investigations in areas relevant to pediatric critical care medicine, which are sufficiently well documented to be acceptable to critical readers. The basic structure of manuscripts reporting original articles should include the following: abstract (structured abstract of no more than 300 words); maximum length: 4,000 words in English and 8,000 characters in Korean (not including abstract, tables, figures, acknowledgments, references); no more than a total of 6 tables and/or figures; no more than 50 references.
- **Review articles:** Reviews on clinical topics provide an up-to-date review for clinicians on a topic of general common interest from the perspective of internationally recognized experts in the pediatric critical care field. The focus of review articles will be an update on the current understanding of the physiology of the disease or condition, diagnostic consideration, and treatment. The basic structure of manuscripts reporting review articles should include the following: Abstract (unstructured abstract of no more than 300 words); maximum length: 5,000 words in English and 10,000 characters in Korean (not including abstract, tables, figures, acknowledgments, references); no more than a total of 6 tables and/or figures; no more than 100 references.
- **Case reports:** Case reports describe unique and instructive cases that make an important teaching point or scientific observation, novel techniques, use of new equipment, or new information on diseases that are of importance to the pediatric critical care field. The basic structure of manuscripts reporting case reports should include the following: abstract (unstructured abstract of no more than 250 words); section headings in the main text (introduction, case report, discussion); maximum length: 2,000 words in English and 4,000 characters in Korean of text (not including abstract, tables, figures, acknowledgments, references); no more than a total of 5 tables and/or figures; no more than 20 references.
- **Letters to the editor:** Letters to the Editor should include brief constructive comments that concern a published article; a short, free-standing opinion; or a short, interesting case. Letters discussing a recent article in this journal should be submitted within 6 months of the publication of the article in print. Letters should not exceed 1,000 words in English and 2,000 characters in Korean of text and 10 references, 1 of which should be to the recent article. No abstract is required.

Table 1. Recommended maximums[a] for articles submitted to ACPP

Type	Abstract/ keyword	Text (English & Korean)[b]	Figure & table	Reference
Editorials	-	1,500 Words & 3,000 characters	2	10
Original articles	300 Words/6	4,000 Words & 8,000 characters	6	50
Review articles	300 Words/6	5,000 Words & 10,000 characters	6	100
Case reports	250 Words/6	2,000 Words & 4,000 characters	5	20
Letters to the editor	-	1,000 Words & 2,000 characters	-	10

[a]The requirements for the number of references and length of the main text can be consulted with the Editorial Office; [b]Not including an abstract, tables, figures, acknowledgments, and references.

5.3. Reporting Guidelines for Specific Study Designs

For the specific study design, it is recommended that authors follow the reporting guidelines, such as CONSORT (http://www.consort-statement.org) for randomized controlled trials, STROBE (http://www.strobe-statement.org) for observational studies, PRIS-

MA (http://www.prisma-statement.org) for systematic reviews and meta-analyses, and CARE (https://www.care-statement.org) for case reports. A good source for reporting guidelines is the EQUATOR Network (https://www.equator-network.org/) and the United States National Institutes of Health/National Library of Medicine (https://www.nlm.nih.gov/services/research_report_guide.html).

5.4. Format of Manuscript

(1) Title page

All contents on the title page should be written in English. For manuscripts written in Korean, the title and authors' names must also be written in both Korean and English.

- Title: The title should be concise and precise. Only the first letter of title must be capitalized.
- Running title: A running head of no more than 50 characters including letters and spaces should be included in English.
- Author list and affiliations: Full names of authors and institutional affiliation(s) should be included for each author. If several authors and institutions are listed, it should be made clear with which department and institution each author is affiliated. For a multicenter study, indicate each individual's affiliation using a superscript Arabic number (e.g., [1,2,3]).
- Corresponding author: The corresponding author's name, postal code, address, and email should be included.
- ORCID (Open Researcher and Contributor ID): ORCIDs of all authors are recommended to be provided. They can obtain ORCIDs at the website (http://orcid.org/).
- Author contributions: The contributions of all authors must be described using the Contributor Roles Taxonomy (CRediT; https://credit.niso.org/).
- Conflict of interest: If there are any conflicts of interest, authors should disclose them in the manuscript. Disclosures allow editors, reviewers, and readers to approach the manuscript with an understanding of the situation and background of the completed research. If there are no conflicts of interest, authors should include the following sentence: "No potential conflict of interest relevant to this article was reported."
- Funding statement: Describe the sources of funding that have supported the work. Please include relevant grant numbers and the URL of any funder's website. Also, describe the role of any sponsors or funders.
- Acknowledgments: Any persons that contributed to the study or the manuscript, but not meeting the requirements of authorship could be placed here. If you do not have anyone to acknowledge, please write "Not applicable" in this section.

(2) Abstract and keywords: The abstract of original article should be concise (less than 300 words) and describe concisely the Background, Methods, Results, and Conclusion, in a structured format. In principle, acronyms and informal abbreviations should be avoided, but they, if needed, can be kept to an absolute minimum with proper identifications. The abstracts of review articles and case reports should be in an unstructured format and limited to 300 and 250 words, respectively.

A maximum of 6 keywords should be listed at the end of the abstract to be used as index terms. For the selection of keywords, refer to Medical Subject Headings (MeSH) in Index Medicus, or http://www.nlm.nih.gov/mesh/MBrowser.html.

(3) Introduction: A brief background, references to the most pertinent papers general enough to inform readers, and the relevant findings of others should be included. It is recommended that the introduction includes general and specific background, a debating issue, and the specific purpose of this study.

(4) Methods: When reporting experiments with human or animal subjects, the authors should indicate whether they received approval from the relevant committees for the study. The materials and study design should be presented in detail. The sources of special chemicals or preparations should be given (name of company). The method of statistical analysis and the criteria for determining significance levels should be described.

Clearly describe the selection of observational or experimental participants (healthy individuals or patients, including controls), including eligibility and exclusion criteria and a description of the source population. Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance.

(5) Results: This section should be presented logically using text, tables, and illustrations. Excessive repetition of table or figure contents should be avoided. Results should not be presented in duplicate as table and figure.

(6) Discussion: The discussion should focus on the interpretation and significance of the findings and include the objective comments that describe their relation to other work in the area as well as new and important aspects of the study. The data should be interpreted concisely without repeating materials already presented in the results

section. A summary or conclusion should be included at the end of this section.

(7) References

- References should be listed in the sequence cited in the paper, and sequential numbers should be attached in the middle or at the end of the corresponding sentences in the body of the text.
- References should be identified in the text with full-size Arabic numerals on the line and in square brackets. e.g., In the study by Song et al. [23]...
- All authors up to 6 can be listed. If author number is more than 6, the names of all authors after the first 6 authors should be abbreviated to "et al".

- **Examples of reference style**

Journal article

1. Scumpia PO, Sarcia PJ, Kelly KM, DeMarco VG, Skimming JW. Hypothermia induces anti-inflammatory cytokines and inhibits nitric oxide and myeloperoxidase-mediated damage in the hearts of endotoxemic rats. Chest 2004;125:1483-91.
2. Chakdour S, Vaidya PC, Angurana SK, Muralidharan J, Singh M, Singhi SC. Pulmonary Functions in Children Ventilated for Acute Hypoxemic Respiratory Failure. Pediatr Crit Care Med 2018;19:e464-71.
3. Nam KH, Kang HK, Lee SS, Park SH, Kang SW, Hwang JJ, et al. Effects of high-flow nasal cannula in patients with mild to moderate hypercapnia: a prospective observational study. Acute Crit Care 2021;36:249-55.
4. Ghorbanzadeh K, Ebadi A, Hosseini M, Madah SS, Khankeh H. Challenges of the patient transition process from the intensive care unit: a qualitative study. Acute Crit Care 2021 Jan 28 [Epub]. https://doi.org/10.4266/acc.2020.00626

Book and book chapter

5. Shaffner DH, Nichols DG. Rogers' textbook of pediatric intensive care. 5th ed. Wolters Kluwer; 2016.
6. Ventre KM, Arnold JH. Acute lung injury and acute respiratory distress syndrome. In: Shaffner DH, Nichols DG, editors. Rogers' textbook of pediatric intensive care. 5th ed. Wolters Kluwer; 2016. p.766-93.

Website

7. Extracorporeal Life Support Organization. ECLS registry report & international summary of statistics [Internet]. Extracorporeal Life Support Organization; 2019 [cited on 2021 Dec 15]. Available from: https://www.elso.org/registry/internationalsummaryandreports.aspx

(8) Tables

- Tables should be referenced in the main text in sequential order and uploaded separately with the main text. Each table should be inserted on a separate page, with the table number and table title above the table.
- Titles of tables should be concise using a phrase or a clause. The first character should be capitalized. Table footnotes should be indicated with superscript small letters (e.g., $^{a), b), c)}$) in alphabetical order.
- All symbols and abbreviations should be described below the table. All units of measurements and concentrations should be designated. Unnecessary longitudinal lines should not be drawn.
- If a table has been previously published should be accompanied by the written consent of the copyright holder and the footnote must acknowledge the original source.

(9) Figures and figure legends

- Figure numbers, in Arabic numerals, should appear in the figure legends. Arabic numerals should be used in the order in which the figures are referred to in the main text. In cases where more than two photographs are used with the same number, alphabet characters should be used next to the Arabic numeral (e.g., Fig. 1A, Fig. 1B).
- All pictures and photographs should be described in the legend with complete sentences rather than incomplete phrases or a clause. All symbols and abbreviations should be described below the figure. The description of footnotes below the figure should follow the order of that of acronyms and then symbols. Symbols should be marked with small alphabet letters in the order of their usage such as $^{a), b), c)}$.
- Figures should be submitted separately from the text of the manuscript. APCC publishes in full color and encourages authors to use color to increase the clarity of figures. All pictures and photographs should be of excellent quality and supplied as TIFF, JPEG, GIF, or PPT files with a resolution of more than 300 dpi. Except for particularly complicated drawings that show large amounts of data, all figures are published at one page or one column width. All kinds of figures may be reduced, enlarged, or trimmed for publication by the editor.
- A previously published figure should be accompanied by a footnote acknowledging the original source and the consent of the copyright holder.

(10) Supplemental data

Nonessential tables and figures may accompany articles as online-only supplemental files. All online-only supplementary files

should be combined in one document file (whenever possible) and uploaded separately during the submission process. These files must be referenced in the main text of the manuscript at least once (e.g., Supplementary Table 1). All online-only supplemental files are subject to review, but such files will not be copyedited or proofread by production staff. As such, authors are encouraged to review their supplemental files carefully before submitting them.

6. MANUSCRIPT SUBMISSION AND PEER REVIEW PROCESS

6.1. Online Submission

All manuscripts should be submitted online via the online submission system available at: https://submit.apccjournal.org/. Under this online system, only corresponding authors can submit manuscripts. The process of reviewing and editing will be conducted entirely through this system. Once you have logged into your account, the online system will lead you through the submission process in a step-by-step orderly process. Submission instructions are available on the website. In case of any trouble, please contact the editorial office (Email: kspccm@kspccm.org).

6.2. Screening after Submission

Screening process will be conducted after submission. If the manuscript does not fit the aims and scope of the Journal or does not adhere to the Instructions to authors, it may be returned to the author immediately after receipt and without a review. Before reviewing, all submitted manuscripts are inspected by "Similarity Check powered by iThenticate (https://www.crossref.org/services/similarity-check/), a plagiarism-screening tool. If a too high a degree of similarity score is found, the Editorial Board will do a more profound content screening. The criterion for similarity rate for further screening is usually 15%; however, the excess amount of similarity in specific sentences may be also checked in every manuscript. The settings for Similarity Check screening are as follows: It excludes quotes, a bibliography, small matches of 6 words, small sources of 1%, and the Methods section.

6.3. Peer Review Process

Submitted manuscripts will be reviewed by two or more experts in the corresponding field. The Editorial Board may request authors to revise the manuscripts according to the reviewer's opinion. After revising the manuscript, the author should upload the revised files with a reply to each item of the reviewer's opinion. The revised part should be marked in red font with an underline.

The author's revisions should be completed within 30 days after the request. If it is not received by the due date, the Editorial Board will not consider it for publication again. The manuscript review process can be finished with the second review. If further revision is requested, the Editorial Board may consider it. Editorial Board will make a final decision on the approval of the submitted manuscript for publication and can request any further corrections, revisions, and deletions of the article text if necessary. Statistical editing is also performed if the data requires professional statistical review by a statistician.

6.4. Appeals of Decisions

Any appeal against an editorial decision must be made within 2 weeks of the date of the decision letter. Authors who wish to appeal against a decision should contact the editor-in-chief, explaining in detail the reasons for the appeal. All appeals will be discussed with at least one other associate editor. If consensus cannot be reached thereby, an appeal will be discussed at a full editorial meeting. The process of handling complaints and appeals follows the guidelines of COPE available from (https://publicationethics.org/appeals). APCC does not consider second appeals.

7. MANUSCRIPT PROCESSING AFTER ACCEPTANCE

7.1. Final Version

After a paper has been accepted for publication, the author(s) should submit the final version of the manuscript. The names and affiliations of authors should be double-checked, and if the originally submitted image files were of poor resolution, higher-resolution image files should be submitted at this time. TIFF and PDF formats are preferred for the submission of digital files of photographic images. Files containing figures must be named according to the figure number (ex: Fig. 1. tiff). Symbols (e.g., circles, triangles, squares), letters (e.g., words, abbreviations), and numbers should be large enough to be legible on reduction to the journal's column widths. All symbols must be defined in the figure caption. If references, tables, or figures are moved, added, or deleted during the revision process, they should be renumbered to reflect such changes so that all tables, references, and figures are cited in numeric order.

7.2. Manuscript Corrections

Before publication, the manuscript editor will correct the manuscript such that it meets the standard publication format. The author(s) must respond within 2 working days when the manuscript editor contacts the author for revisions. If the response is delayed, the manuscript's publication may be postponed to the next issue.

7.3. Galley Proof

After corrections have been made, an accepted manuscript will be sent to the publisher for printing. The proof may be revised more than once by the corresponding author, if needed. The author should double-check for corrections in the content, title, affiliation, capitalization, locations of figures, and references. Corresponding authors are responsible for further corrections made after printing.

7.4. Post-publication Discussions

Post-publication discussions can be held through letters to the editor. If any readers have concerns about any articles published, they can submit a letter to the editor related to the articles. If any errors or mistakes are found in an article, they can be corrected through an erratum, corrigendum, or retraction.

8. AUTHOR'S CHECKLIST

- All manuscripts are typed in 12-point font size, double-spaced, and saved as an MS Word file.
- All pages are numbered consecutively starting from the abstract page.
- The order of the manuscript is a title page, abstract, main body, references, and table and legend of figures.
- Figures are inserted into the separated files in the order of citation.
- The title page includes the article title, running title (no more than 50 characters), authors' full name(s) and affiliation, address for correspondence (including address and e-mail), ORCID (all authors), conflict of interest, funding statement, and footnotes, if any.
- The title page states that the manuscript has not been published previously and will not be submitted for publication elsewhere. It discloses conflicts of interest of all listed authors if any.
- The abstract for an original article/review should be less than 300 words, and the abstract for a case report should be less than 250 words.
- The format of an original article is Background, Methods, Results, and Conclusion, and each component should be on the next line.
- A maximum of 6 keywords should be listed at the end of the abstract to be used as index terms. For the selection of keywords, refer to Medical Subject Headings (MeSH) in Index Medicus.
- The order of the main text is Abstract with Keywords, Introduction, Methods, Results, Discussion, References, and Table and Figure legends.
- All pages are numbered consecutively starting from the abstract page.
- Change the author information (Name, Institute) to "OOO".
- The reference items are listed in the correct format and all references listed in the references section are cited in the text.
- Manuscript for original articles should be limited strictly up to 50 references. For reviews, case reports, and editorials and letters to the editor should be limited strictly to 100, 20, and 10 references).
- Tables are provided in English and an Arabic figure. It should be placed at the end of the manuscript.
- All figures are submitted as a separate file in TIFF, JPEG, GIF, or PPT formats higher than 300 dpi.
- All authors must read the manuscript and agree with the submission.

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Author's checklist

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Archives of Pediatric Critical Care

Confirm the checklist before submitting the manuscript. Checking on every point is needed to proceed.

1. Manuscript Form

☐ All manuscripts are typed in 12-point font size, double-spaced, and saved as an MS Word file.
☐ All pages are numbered consecutively starting from the abstract page.
☐ The order of the manuscript is a title page, abstract, main body, references, and table and legend of figures.
☐ Figures are inserted into the separated files in the order of citation.

2. Title Page

☐ The title page includes the article title, running title (no more than 50 characters), authors' full name(s) and affiliation, address for correspondence (including address and e-mail), ORCID (all authors), conflict of interest, funding statement, and footnotes, if any.
☐ The title page states that the manuscript has not been published previously and will not be submitted for publication elsewhere. It discloses conflicts of interest of all listed authors if any.

3. Abstract

☐ The abstract for an original article/review should be less than 300 words, and the abstract for a case report should be less than 250 words.
☐ The format of an original article is Background, Methods, Results, and Conclusion.
☐ A maximum of 6 keywords should be listed at the end of the abstract to be used as index terms. For the selection of keywords, refer to Medical Subject Headings (MeSH) in Index Medicus.

4. Main Body

☐ The order of the main text is Abstract with Keywords, Introduction, Methods, Results, Discussion, References, and Table and Figure legends.
☐ All pages are numbered consecutively starting from the abstract page.
☐ Change the author information (Name, Institute) to "OOO".

5. References

☐ The reference items are listed in the correct format and all references listed in the references section are cited in the text.
☐ Manuscript for original articles should be limited strictly up to 50 references. For reviews, case reports, and editorials and letters to the editor should be limited strictly to 100, 20, and 10 references).

6. Tables and Figures

☐ Tables are provided in English and an Arabic figure. It should be placed at the end of the manuscript.
☐ All figures are submitted as a separate file in TIFF, JPEG, GIF, or PPT formats higher than 300 dpi.

☐ **All authors must read the manuscript and agree with the submission.**

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☐ Editorial ☐ Original article ☐ Review ☐ Case report ☐ Letter to the editor

Title : _____

Each author must read and sign the following statements. Completed statements should be send to the Editorial Office through the online manuscript submission system or e-mail (apcc@apccjournal.org).

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