Blood Purification

Pediatric Section – Research Article

Blood Purif
DOI: 10.1159/000530446

Received: October 6, 2022
Accepted: March 23, 2023
Published online: May 25, 2023

The Role of Blood Purification by HA330 as Adjunctive Treatment in Children with Septic Shock

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Keywords
Pediatric patient · Septic shock · HA330 hemoperfusion · PELOD-2 score · PRISM-3 score

Abstract
Introduction: Despite advances in supportive care for critically ill patients, sepsis remains an important cause of death worldwide in the PICU. One of the hallmarks of sepsis is hyperinflammation due to the excessive release of inflammatory mediators. Recently, new therapeutic approaches, such as immune modulation and blood purification, have been tried to improve outcomes in patients with septic shock. ***Methods:*** This study is a prospective observational study composed of children with septic shock and the PELOD-2 score ≥10 or the PRISM-3 score ≥15. All received 2–4 h of HA330 treatment on 2 consecutive days, used as adjunctive therapy. The effectiveness of HA330 hemoperfusion was evaluated by improving the PELOD-2 and PRISM-3 scores, the vasoactive inotropic score (VIS), and inflammatory markers from baseline to 72 h after the use of HA330 hemoperfusion. ***Results:*** Twelve patients hospitalized in the PICU and diagnosed with septic shock between July 2021 and May 2022 were included in this study and received hemoperfusion with HA330. The average PELOD-2 and PRISM-3 scores decreased significantly from 9.5 (IQR: 6.5–13.0) at baseline to 2.0 (IQR: 0–6.5) at 72 h (p = 0.002) and from 16.5 (IQR: 15.0–20.5) at baseline to 5.5 (IQR: 2.0–9.5) at 72 h (p = 0.002), respectively. The VIS decreased significantly from baseline to 72 h (p = 0.003). IL-6, procalcitonin, and lactate levels also decreased significantly from baseline to 72 h (p = 0.005, 0.03, and 0.03, respectively). Two of 12 patients expired due to their underlying condition (2/12, 16.7%). Device-related adverse events did not occur in this study. ***Conclusions:*** Our observational case series suggests a possible role for HA330 hemoperfusion as an adjunctive treatment of refractory septic shock in children with high severity scores in the context of rapid improvement in organ dysfunction, without serious adverse effects.

Introduction

Sepsis is one of the leading causes of death in infants and children. Despite advances in supportive care for critically ill patients, sepsis remains an important cause of death worldwide in the PICU [1]. Overall, the incidence of sepsis peaked in early childhood. There were an estimated 20.3 million incident sepsis cases worldwide among children younger than 5 years [1–3]. The Surviving Sepsis Campaign (SSC), which standardized the evidence-based approach to the treatment of septic shock and other organ dysfunction associated with sepsis in

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children, was recently updated [3]. However, mortality and costs are still high [1–4].

One of the hallmarks of sepsis is characterized by hyperinflammation and dysregulated host responses to a microbial pathogen, which can result in life-threatening multiorgan dysfunction [5]. Endotoxin and proinflammatory cytokines play an important role in the pathogenesis of septic shock [6–10]. High levels of endotoxin and proinflammatory cytokines are associated with a multiorgan failure and a high mortality rate [11].

According to the SSC guideline, treatment strategies in pediatric septic shock include adequate fluid resuscitation, early use of broad-spectrum antibiotics with source control, and vasopressors or inotropic support when indicated [3]. Immune modulation and blood purification have been tried to improve outcomes in patients with sepsis and septic shock. Blood purification using the hemoperfusion technique aims to restore the balance of the immune response to infection, by removing triggers for the response and the cytokines produced, thereby achieving immune homeostasis [9]. Elimination of inflammatory cytokines would be an effective adjunctive approach to the treatment of severe sepsis [7, 12].

Direct hemoadsorption (HA) is an extracorporeal technique used for blood purification [13]. Over the years, new adsorption cartridges with improved characteristics have been developed [14]. Resin-directed HA is associated with improved oxygenation, hemodynamic status, and cardiac function [15]. However, most studies include only adults, and little information is available on the clinical experience and efficacy of blood purification for pediatric septic shock. This study aimed to evaluate clinical results among children admitted to the PICU who received direct HA as an adjunctive treatment for refractory septic shock in children with high severity scores.

Materials and Methods

Study Design and Patients

This study is a prospective observational study in a ten-bed PICU in a university referral hospital. Children with septic shock who meet the inclusion criteria were included. The patients were enrolled between July 2021 and May 2022. The protocol was started after receiving approval from the Institutional Review Board (IRB) of King Chulalongkorn Memorial Hospital (IRB No. 046/64, March 23, 2021). This study was registered in the Thai Clinical Trials Registry (TCTR20220602002), and we obtained informed consent from patients and parents or legal guardians of all enrolled patients under 18 years of age to participate in this study. The study protocol was approved by the Institute's Committee on Human Research.

The patients included children with sepsis, as defined by the SSC guideline [3], who were admitted to our PICU during the study period. All children initially received routine treatment for septic shock following the 2020 SSC guideline [3]. Inclusion criteria were: 1 month to 15 years of age; required any dose of at least one vasopressor; and have a Pediatric Logistic Organ Dysfunction (PELOD)-2 score ≥10 or Pediatric Risk of Mortality (PRISM)-3 score ≥15. Exclusion criteria were patients receiving end-of-life support and those with uncontrolled bleeding.

Hemoperfusion Treatment

An HA330 disposable hemoperfusion cartridge (HA330; Jafron, Zhuhai City, China) was used with a continuous renal replacement therapy (CRRT) machine (Prismaflex® or Aquarius®). A blood circuit was selected according to the patient's body weight for each machine. Four types of blood circuit with the Prismaflex machine including the Prismaflex HF20 set (60 mL blood volume) were used for weight <3–11 kg, the Prismaflex M60 set (93 mL blood volume) used for weight 11–30 kg, and the Prismaflex M100 set (152 mL blood volume) used for weight >30 kg. For the Aquarius machine, Aqualine S (64 mL blood volume) was used for body weight <30 kg and Aqualine (105 mL blood volume) was used for weight ≥30 kg. Vascular access was established by ultrasound-guided insertion of a double-lumen venous catheter into the right internal jugular or femoral vein. The size of the double-lumen catheter was selected according to the patient's body weight and vascular diameter.

We primed the circuit and an HA330 cartridge with normal saline with heparin solution. When the volume of the extracorporeal circuit is greater than 10% of the circulatory volume of the patient, we primed the circuit and an HA330 cartridge with 5% albumin or packed red cells to avoid hemodynamic instability. All patients were monitored by continuous invasive arterial pressure monitoring, electrocardiography, and pulse oximetry throughout the treatment period. HA330 hemoperfusion was started as soon as possible within 24 h when the patients met the inclusion criteria and performed for 2–4 h on 2 consecutive days (total of 2 sessions). The second session started approximately 12–24 h after the end of the first session.

Data Collection and Study Endpoints

The demographic data of the patient, the underlying disease, and the source of infection were recorded. The type of respiratory support, the dose of vasopressors, and laboratory data were recorded at 0 h (the time before the HA330 hemoperfusion started), 24 h, 48 h, and 72 h after the beginning of the HA330 hemoperfusion. The PELOD-2 score and PRISM-3 score were recorded at the four times above. The dose of vasoactive/vasopressor agents was expressed as the vasoactive inotropic score (VIS). The effectiveness of HA330 hemoperfusion was evaluated by reducing the PELOD-2 and/or PRISM-3 scores, VIS, interleukin 6 (IL-6), procalcitonin (PCT), high-sensitivity C-reactive protein (hs-CRP), base excess, lactate levels and oxygenation index from baseline to 72 h after HA330 treatment. The length of stay in the PICU, mechanical ventilation (MV), and mortality at 28 days were also recorded.

All statistical analyzes were evaluated using STATA software version 15.1 (StataCorp LLC, College Station, TX, USA). Descriptive analysis was presented as frequency with percentage, median with interquartile range (IQR). Differences in continuous data

between hour follow-up and baseline were assessed using a Wilcoxon signed-rank test. The p value <0.05 was considered statistically significant.

Results

Twelve patients hospitalized in the PICU and diagnosed with septic shock and multiorgan dysfunction between July 2021 and May 2022 were included in this study and received HA330 hemoperfusion. Tables 1, 2 show the baseline characteristics of the patients with details on the individual diagnosis, source of infection, type of mechanical and respiratory support, PELOD-2 and PRISM-3 scores, and laboratory parameters. Eight (66.7%) of the patients were male. The median age was 6.5 years (IQR: 6.0–14.4). All patients had a source of infection. Five patients (41.7%) had COVID-19 infection and developed a multisystemic inflammatory syndrome in children with acute respiratory distress syndrome, 3 patients (25%) had gastrointestinal and hepatobiliary tract infection with septic shock, and 2 patients (17%) had invasive pulmonary aspergillosis. Ten of the patients (83.3%) required invasive MV, 5 patients (41.7%) received CRRT, and 1 patient (8.3%%) required extracorporeal membrane oxygenation. The median time to HA330 was 12.5 h (IQR: 5.0–23.0). The median scores for PELOD-2 and PRISM-3 were 9.5 (IQR: 6.5–13.0) and 16.5 (IQR: 15.0–20.5), respectively. The median duration of stay in the PICU was 10.5 days (IQR: 6.0–21.5) and the median duration of hospital stay was 33.5 days (IQR: 22.0–63.0). The median duration of MV was 4 days (IQR: 2.5–12.0). Two of 12 patients (16.7%) expired and 10 patients (83.3%) were transferred from the intensive care unit (ICU) to other services and fully recovered. The average of PELOD-2 and PRISM-3 scores decreased significantly from 9.5 (IQR: 6.5–13.0) at baseline to 2.0 (IQR: 0–6.5) at 72 h (p = 0.002) and from 16.5 (IQR: 15.0–20.5) at baseline to 5.5 (IQR: 2.0–9.5) at 72 h (p = 0.002), respectively (shown in Fig. 1, 2).

The median VIS decreased significantly from 17.5 (IQR: 9.8–46.0) at baseline to 1.5 (IQR: 0–6.0) at 72 h (p = 0.003). A significant reduction in IL-6 was detected from 206.4 pg/mL (IQR: 111.0–412.5) at baseline to 37.4 pg/mL (IQR: 6.4–146.8) at 72 h (p = 0.005). The PCT, lactate and oxygenation index were significantly reduced from baseline to 72 h after HA330 hemoperfusion (p = 0.03, 0.03, and 0.04, respectively). There was no significant change in hs-CRP and base excess from baseline to 72 h (Table 3).

Two of 12 patients expired. The first one that expired was diagnosed with fulminant myocarditis with dilated cardiomyopathy and multiorgan failure. Another patient was diagnosed with biliary atresia with post-liver transplantation and developed posttransplant lymphoproliferative disorder. He was sent to our PICU for septic shock with small bowel perforation. After resuscitation, correcting the cause of septic shock, and receiving HA330 hemoperfusion, the patient improved and was discharged from our PICU on day 11 of admission to the PICU. Due to the progressive development of posttransplant lymphoproliferative disorder, he had marked abdominal distension and developed hemophagocytic lymphohistiocytosis. He eventually died from his underlying condition. No device-related adverse events and hemodynamic instability occurred from the beginning to the end of HA330 hemoperfusion in the 12 patients.

Discussion

Direct HA is an extracorporeal technique utilized for blood purification. The HA using the HA330 cartridge was studied in multiple cohorts in the context of inflammatory conditions such as sepsis, septic shock, and inflammatory diseases [13, 14, 16–18]. We evaluated the effects of HA330 as an adjunctive therapy in pediatric patients with septic shock and multiorgan dysfunction. In this study, we prospectively enrolled 12 children with septic shock and multiorgan dysfunction with high baseline clinical severity scores (PELOD-2 ≥10 or PRISM-3 ≥15) who were treated with the HA330 hemoperfusion technique in addition to standard sepsis therapy. The PELOD-2 and PRISM-3 scores decreased significantly during the first 24 h after HA330 hemoperfusion (p = 0.002 and 0.002, respectively). Furthermore, another study found a notable reduction in inflammatory mediators [16]. In an animal model of acute lung injury and acute respiratory distress syndrome [19], the HA significantly reduced circulating and alveolar levels of proinflammatory cytokines, improved oxygenation, and attenuated lung injury. In human studies, Huang et al. [20] evaluated the effectiveness of the HA330 cartridge in septic adult patients, showed improvement in hemodynamic and respiratory parameters, shorter stay in the ICU, reduced mortality in the ICU, and had no safety concerns. Few reports described clinical experience with HA330 hemoperfusion in pediatric patients. In 2021, Sazonov V et al. [21] reported case series of three septic children using extracorporeal blood purification therapy with HA330 cartridge. They showed rapid improvement

Table 1. Baseline characteristics, clinical features, and outcome of patients

	HA330 hemoperfusion (n = 12)
Sex, *n* (%)	
Male	8 (66.7)
Age, median (IQR), years	9.5 (6–14.4)
Underlying disease, *n* (%)	5 (41.7)
Mechanical support, *n* (%)	
CRRT	5 (41.7)
TPE	2 (16.7)
ECMO	1 (8.3)
None	6 (50)
Respiratory support, *n* (%)	
Invasive	10 (83.3)
Noninvasive	2 (16.7)
PELOD-2 score, median (IQR)	9.5 (6.5–13)
PRISM-3 score, median (IQR)	16.5 (15–20.5)
VIS, median (IQR)	17.5 (9.8–46)
IL-6, median (IQR), pg/mL	206.4 (111–412.5)
PCT, median (IQR), pg/mL	8.4 (1.3–21.6)
hs-CRP, median (IQR), mg/L	87.6 (16.3–135.2)
Lactate levels, median (IQR), mmol/L	3.1 (1.9–5.1)
Time to HA330, median (IQR), h	12.5 (5.0–23.0)
PICU-LOS, median (IQR), days	10.5 (6–21.5)
Length of hospital stay, median (IQR), days	33.5 (22–63)
MV-LOS, median (IQR), days	4 (2.5–12)
Outcome, *n* (%)	
Death	2 (16.7)

CRRT, continuous renal replacement therapy; TPE, therapeutic plasma exchange; ECMO, extracorporeal membrane oxygenation; BIVAD, biventricular assist device, PELOD, Pediatric Logistic Organ Dysfunction; PRISM, Pediatric Risk of Mortality; VIS, vasoactive inotropic score; IL-6, interleukin 6; PCT, procalcitonin; hs-CRP, high-sensitivity C-reactive protein; LOS, length of stay; MV, mechanical ventilation.

in all inflammatory parameters. These patients were also able to quickly wean themselves off ventilatory support, and vasoactive medications were gradually discontinued. Similarly, in our study, we found a significant reduction in VIS, IL-6, PCT, and lactate levels from baseline to 72 h after HA330 treatment.

In our study, significant reductions were detected in PELOD-2 and PRISM-3 scores in the first 24 h after HA330 use. These results may be mainly attributed to the rapid improvement in hemodynamics and organ dysfunctions with hemoperfusion from HA330, as reflected in the PELOD-2 scores. In adult studies, there were few reports that demonstrated that mortality scores were lower in the hemoperfusion group in patients with Sequential Organ Failure Assessment (SOFA) scores <8 at admission to the ICU [16, 20, 22]. They showed that an early and non-delayed hemoperfusion treatment can effectively improve the clinical outcomes of septic patients. Similarly to our study, HA330 treatment was used early as soon as possible within 24 h when patients met the inclusion criteria. Our study recruited children with sepsis who had high predicted mortality scores of more than 20% (PELOD-2 score ≥10 or PRISM-3 score ≥15) as inclusion criteria. The median PELOD-2 score was 9.5 (IQR: 6.5–13.0); the predicted mortality was approximately 18–30% [23]. Only two of 12 patients (16.7%) died. Both died of their underlying conditions. Overall, there were no device-related adverse events and hemodynamic instability occurred from the beginning to the end of hemoperfusion of HA330 in all patients. Therefore, adjunctive treatment of HA330 hemoperfusion could be used safely in children with septic shock with high predictive mortality scores.

In addition to improvement in hemodynamics, the hemoperfusion of HA330 also improves oxygenation parameters, such as the PaO_2/FiO_2 ratio [16, 19, 20]. The hemoperfusion of HA330 has been shown to improve oxygenation in patients with sepsis and various lung diseases [16, 20]. Similarly in our study, there was a significant reduction in the oxygenation index from baseline to 72 h after HA330 treatment.

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DOI: 10.1159/000530446

Table 2. Demographic data, source of infection, micro-organisms, type of MV, procedure, and outcomes of 12 patients

Case No.	Baseline characteristics							Type of mechanical support			HA330 hemoperfusion			Outcomes		
	age, years	source of infection	micro-organisms	MV	PELOD-2	PRISM-3	VIS	RRT	TPE	ECMO	time to HA330, h	priming	blood flow rate at start/stable, mL/min	PICU-LOS, days	MV-LOS, days	mortality
1	14	Pulmonary	*P. aeruginosa*	Invasive	13	28	15	N	N	N	21	NSS	100/200	7	5	S
2	5	Blood stream	*A. baumannii* (XDR)	Invasive	10	15	70	N	N	Y	23	NSS	50/150	36	36	D
3	7	Hepato-biliary	*K. pneumoniae* (ESBL)	Invasive	15	22	8	Y	Y	N	17	NSS	50/150	10	8	S
4	11	Pulmonary	*A. baumannii*	Noninvasive	7	15	20	N	N	N	11	NSS	50/200	4	2	S
5	14	Wound infection	*P. aeruginosa*	Invasive	3	20	15	Y	N	N	14	NSS	100/200	10	3	S
6	15	Hepato-biliary	Unclear	Invasive	9	15	5	Y	Y	N	19	NSS	100/200	22	2	S
7	8	Pulmonary	*A. baumannii*	Invasive	15	15	5	Y	N	N	12	NSS	50/150	37	16	S
8	4	Gastrointestinal	*E. coli* (ESBL)	Invasive	12	18	150	N	N	N	5	5% albumin	50/150	11	3	D
9	5	Pulmonary	*P. aeruginosa*	Invasive	6	15	52	N	N	N	13	NSS	50/150	5	3	S
10	3	Pulmonary	*Aspergillus* spp.	Noninvasive	4	15	12	N	N	N	8	5% albumin	50/150	5	3	S
11	13	Pulmonary	*Aspergillus* spp. and *S. maltophilia*	Invasive	13	21	40	Y	N	N	10	NSS	100/200	19	12	S
12	8	Pulmonary and catheter-related	*K. pneumoniae* (ESBL)	Invasive	9	18	20	N	N	N	7	NSS	50/150	21	12	S

MV, mechanical ventilation; PELOD, Pediatric Logistic Organ Dysfunction; PRISM, Pediatric Risk of Mortality; VIS, vasoactive inotropic score; RRT, renal replacement therapy; TPE, therapeutic plasma exchange; ECMO, extracorporeal membrane oxygenation; LOS, length of stay; NSS, normal saline solution; S, survived; D, died; XDR, extensively drug resistant; ESBL, extended spectrum beta-lactamase.

Table 3. Comparison score and laboratory results at hour follow-up from baseline

	HA330 hemoperfusion (n = 12)	
	median (IQR)	p value
VIS		
At baseline	17.5 (9.8–46)	Ref
At 24 h	10 (2.5–25)	0.003
At 48 h	5 (0–7)	0.003
At 72 h	1.5 (0–6)	0.003
IL-6, pg/mL		
At baseline	206.4 (111–412.5)	Ref
At 72 h	37.4 (6.4–146.8)	0.005
PCT, pg/mL		
At baseline	8.4 (1.3–21.6)	Ref
At 72 h	1.6 (1.1–8.8)	0.03
hs-CRP, mg/L		
At baseline	87.6 (16.3–135.2)	Ref
At 72 h	25.2 (6.8–120.4)	0.53
Lactate, mmol/L		
At baseline	3.1 (1.9–5.1)	Ref
At 72 h	1.7 (1–2.3)	0.03
Base excess		
At baseline	−6.7 (−8.9 to −0.7)	Ref
At 72 h	−0.1 (−1.9–3.7)	0.47
Oxygenation index		
At baseline	7.7 (2.2–13.3)	Ref
At 72 h	2.3 (2–3.2)	0.04

VIS, vasoactive inotropic score; IL-6, interleukin 6; PCT, procalcitonin; hs-CRP, high-sensitivity C-reactive protein.

This pilot study was the first prospective observational study to evaluate the effectiveness of HA330 hemoperfusion as adjunctive therapy in pediatric patients with septic shock and multiorgan dysfunction in Thailand. However, this study is an observational study lacking a control group for comparison. The number of patients was small, which limits the generalization of the results and the analysis. The multiple therapeutic approaches and interventions (i.e., antibiotics, HA330, CRRT, extracorporeal membrane oxygenation) used to treat complex conditions make it difficult to draw definitive conclusions from our data. However, our results provide promising preliminary data on the clinical benefit of HA330 hemoperfusion as an adjunctive therapy for pediatric sepsis with multiple organ dysfunction. We intend to address these limitations in our larger future clinical trial.

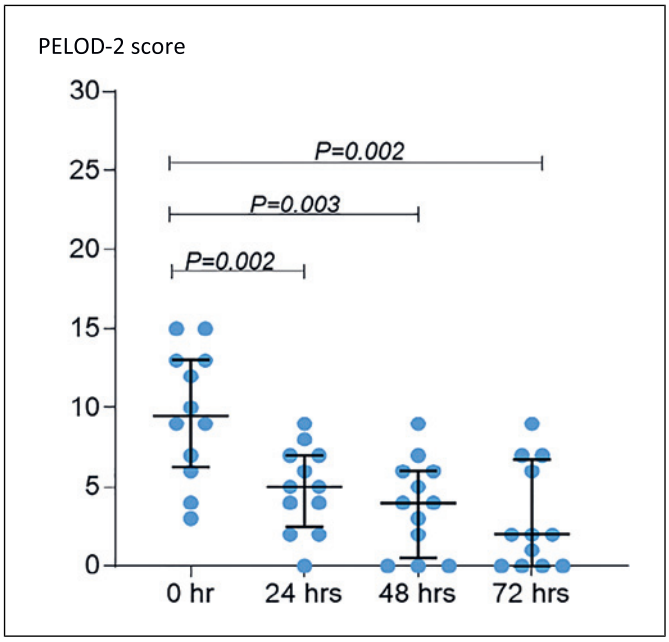

Fig. 1. Comparison of the PELOD-2 score at hour follow-up and baseline (0 h).

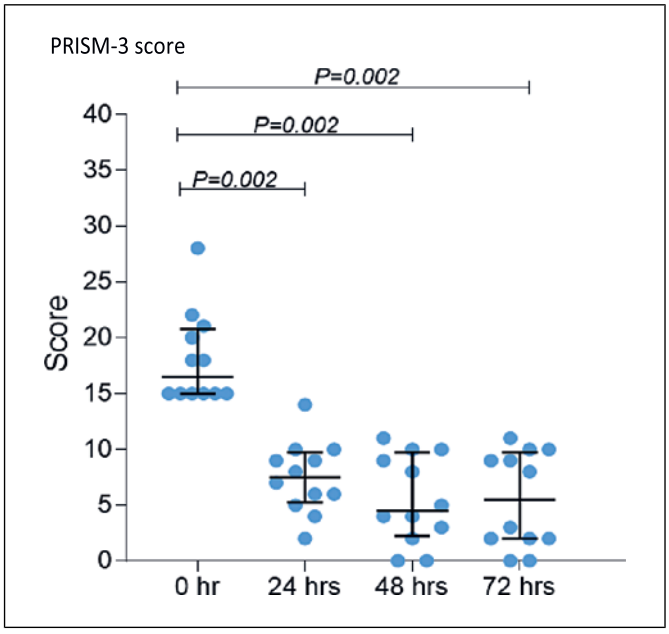

Fig. 2. Comparison of the PRISM-3 score at hour follow-up and baseline (0 h).

Conclusion

Our prospective observational study suggests a possible role for the use of HA330 hemoperfusion as an adjunctive treatment that resulted in the rapid improvement of multiple organ dysfunction in pediatric patients with fluid-refractory septic shock, without serious adverse

effects. Therefore, the use of HA330 hemoperfusion may contribute to improved clinical outcomes in affected children.

Statement of Ethics

This study was initiated after receiving approval from the Institutional Review Board (IRB) of King Chulalongkorn Memorial Hospital (No. 046/64, COA No. 431/2021, March 23, 2021). Written informed content was obtained from the patients and the parents or legal guardians of all enrolled patients under 18 years of age for participation prior to the study. The study protocol was approved by the institute's committee on human research.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was supported by the Ratchadapisek Sompoch Fund, Faculty of Medicine, Chulalongkorn University. Astromed company supported the HA330 cartridge. All companies were not related to the study protocol, data collection, statistical analysis, and discussion.

Author Contributions

T.S. and R.S. were responsible for the protocol and study design. T.S. was responsible for the acquisition, analysis, interpretation of the data, and drafting the manuscript. R.S. edited and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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