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The Use of Methylene Blue in Children with Catecholamine-resistant Shock: A Retrospective Case Series

Katekolamin Dirençli Şok Tanılı Çocuklarda Metilen Mavisi Kullanımı: Retrospektif Olgu Serisi

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Abstract

Introduction: Shock is a common and life-threatening condition in pediatric intensive care units (PICUs). In catecholamine-resistant shock, current guidelines suggest adjunctive therapies such as hydrocortisone, vasopressin, angiotensin II, or extracorporeal membrane oxygenation (ECMO). Methylene blue (MB) has emerged as a potential alternative or adjunct therapy. We report our clinical experience administering MB to children who had refractory shock unresponsive to standard inotropes and vasopressors.

Methods: We retrospectively reviewed children who were treated with MB between March and November 2023 at a tertiary PICU. Pre- and post-MB variables included vasoactive-inotropic score (VIS), systolic blood pressure (SBP), vasopressor requirements, concurrent continuous renal replacement therapy/ECMO use, and mortality. Hemodynamic parameters were evaluated before MB administration and up to 24 hours thereafter.

Results: Ten patients were included (mean age 9.4 years; 70% with chronic comorbidities). Baseline VIS was 116.4±90.5 and SBP was 81.3±19 mmHg. At 24 hours after MB administration, VIS decreased to 109.9±74.6 and SBP increased to 96.5±18.2 mmHg, corresponding to an average absolute change of -6.5 points in VIS and +15 mmHg in SBP. Hemodynamic responses were heterogeneous: VIS decreased in five patients, remained unchanged in two, and increased in three, while SBP improved in all patients. No MB-related adverse effects were observed. Overall survival to hospital discharge was 10%.

Conclusion: In children with catecholamine-resistant shock, MB administration was associated with short-term improvement in blood pressure, although the reduction in vasoactive burden was inconsistent and mortality remained high. Larger prospective studies are needed to define the optimal timing, dosing, safety, and efficacy of MB in pediatric vasodilatory shock.

Keywords: Catecholamine-resistant shock, methylene blue, pediatric intensive care, septic shock, vasoactive-inotropic score, sepsis

Öz

Giriş: Şok, çocuk yoğun bakım ünitelerinde sık görülen ve yaşamı tehdit eden bir tablodur. Katekolamin dirençli şokta kılavuzlar hidrokortizon, vazopressin, anjiyotensin II veya ekstrakorporeal membran oksijenizasyonu (ECMO) kullanımını önermektedir. Metilen mavisi (MM), potansiyel bir ek tedavi seçeneğidir. Bu çalışmada, standart inotrop ve vazopressör tedavilere yanıtsız, refrakter şoklu çocuklarda MM kullanımına ilişkin deneyimimizi sunuyoruz.

Yöntemler: Mart-Kasım 2023 tarihleri arasında MM ile tedavi edilen çocuklar geriye dönük olarak incelendi. MM uygulaması öncesi ve sonrasında değerlendirilen değişkenler; vasoaktif-inotropik skor (VIS), sistolik kan basıncı (SKB), inotrop/vazopressör dozları ve süreleri, eşzamanlı sürekli renal replasman tedavisi/ECMO uygulamaları ve mortalite olarak belirlendi.

Bulgular: Çalışmaya on hasta dahil edildi (ortalama yaş: 9,4 yıl; %70'inde kronik komorbidite mevcuttu). Başlangıçta VIS 116,4±90,5 ve SKB 81,3±19 mmHg idi. MM uygulamasından 24 saat sonra VIS 109,9±74,6 ve SKB 96,5±18,2 mmHg olarak saptandı. Bu değerler, VIS'te yaklaşık %6,5'lik bir azalma ve SKB'de yaklaşık 15 mmHg'lik bir artışa karşılık gelmekteydi. Hemodinamik yanıtlar heterojen bulundu: VIS beş hastada azaldı, iki hastada değişmedi, üç hastada arttı; SKB ise tüm hastalarda yükseldi. MM'ye bağlı herhangi bir advers etki gözlenmedi. Yalnızca bir hasta taburculuğa kadar sağ kaldı.

Sonuç: Katekolamin dirençli pediatrik şokta MM, kan basıncında düzelme ve inotrop/vazopressör ihtiyacında azalma ile ilişkili bulundu ancak sağkalım oranı düşük saptandı. Septik/vasodilatör şokta MM'nin optimal kullanım zamanı, dozu, güvenilirliği ve etkinliğinin belirlenmesi için daha geniş, prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Katekolamin dirençli şok, metilen mavisi, çocuk yoğun bakım, septik şok, vazoaktif-inotropik skor, sepsis

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Introduction

Shock is a life-threatening syndrome of acute circulatory failure that results in inadequate oxygen delivery to tissues. It affects nearly one-third of patients admitted to intensive care units and is associated with high mortality.[1-4] Four major types of shock—distributive, hypovolemic, cardiogenic, and obstructive—may occur alone or in combination.[4,5] Distributive shock, most commonly due to sepsis, predominates in pediatric intensive care units (PICUs). Early recognition and stabilization, including airway, breathing, and circulation assessment, prompt antibiotic therapy, intravenous fluid resuscitation, and initiation of vasopressors when indicated, remain the standard of care.[6]

Despite these measures, a subset of patients develops catecholamine-resistant shock, in which hemodynamic stability cannot be achieved even with escalating doses of conventional vasopressors. Because prolonged exposure to high-dose catecholamines is associated with significant adverse effects, interest has grown in alternative or adjunctive therapies aimed at improving vascular responsiveness.[7,8]

Methylene blue (MB), a heterocyclic aromatic compound, interferes with nitric oxide-dependent signaling pathways by inhibiting soluble guanylate cyclase (sGC), thereby reducing cyclic guanosine monophosphate production and attenuating pathological vasodilation.[9,10] In addition, MB inhibits inducible nitric oxide synthase and scavenges nitric oxide, typically producing measurable hemodynamic effects within 30-60 minutes of intravenous administration.[11-13] Because it is inexpensive, widely available, and generally well tolerated, MB has been proposed as a adjunctive therapy in catecholamine-resistant shock. However, pediatric data remain limited, and its role in routine clinical practice has not been clearly defined.[14,15]

This study aimed to evaluate our clinical experience with MB administration in critically ill children with catecholamine-resistant shock, focusing on short-term hemodynamic effects and clinical outcomes in a highly selected, severely ill patient population.

Materials and Methods

This retrospective observational study was conducted in the PICU of Ankara University between March and November 2023. Children with catecholamine-resistant shock who received MB were included. Demographic and clinical data, including age, sex, underlying conditions, inotrope and vasopressor dosages, MB administration details (loading and maintenance doses, duration), and concurrent therapies were recorded.

Catecholamine-resistant shock was defined as persistent hypotension and/or clinical signs of inadequate tissue perfusion despite adequate fluid resuscitation and treatment with vasoactive agents. Persistent catecholamine-resistant shock was operationally defined as ongoing hemodynamic instability despite the administration of two or more vasoactive agents at escalating doses. In our clinical practice, MB administration was considered when high-dose vasoactive support was required, typically corresponding to a vasoactive-inotropic score (VIS) greater than 30, despite optimization of conventional therapies.[16,17]

The VIS and systolic blood pressure (SBP) were documented before MB initiation and at 4, 8, 12, and 24 hours post-treatment. Mortality outcomes were recorded. Disease severity was assessed using the pediatric risk of mortality III (PRISM III) and pediatric logistic organ dysfunction (PELOD) scores.[18-23] The VIS was calculated as follows: VIS=dopamine (μg/kg/min)+dobutamine(μg/kg/min)+100×epinephrine (μg/kg/min)+10×milrinone (μg/kg/min)+10.000×vasopressin (U/kg/min)+100×norepinephrine (μg/kg/min).

Patients who received continuous renal replacement therapy (CRRT) or extracorporeal membrane oxygenation (ECMO) during their PICU stay were also evaluated.[24-26]

Blood pressure measurements were obtained as part of routine clinical monitoring; however, the use of invasive versus non-invasive measurement methods was not standardized across patients and was not consistently documented. Diastolic blood pressure and mean arterial pressure values were not systematically available for all patients and were therefore not included in the analysis.

Ethical Considerations

The study protocol was approved by the Ankara University Human Research Ethics Committee (approval no: I04-406-24, date: 11.06.2024). Written informed consent for treatment and data use was obtained from the families of all participants.

Statistical Analysis

Analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation and/or median with interquartile range, as appropriate. Changes in VIS and SBP before and after MB were analyzed using the Wilcoxon signed-rank test, and time-dependent variations at 0, 4, 8, 12, and 24 h were analyzed using the Friedman test with Dunn-Bonferroni correction. Correlations between MB dose, duration, and hemodynamic changes were examined using Spearman's rho. A two-sided $p<0.05$ was considered statistically significant.

Results

Ten children with catecholamine-resistant shock received MB therapy during the study period. Seven patients (70%) were female; the mean age was 9.4 years (range: 3 months-19 years). Most patients (70%) had chronic comorbidities, including bone marrow transplantation, neuromuscular disease with multiple organ dysfunction syndrome, liver transplantation, cystic fibrosis, cerebral palsy, and severe congenital or acquired infections. Baseline clinical characteristics, treatments, and outcomes are summarized in Table 1; mean values are presented in Table 2.

At PICU admission, the mean PRISM III score was 9.0±3.3, and the mean PELOD score was 10.6±5.9, indicating high disease severity. All patients were receiving multiple vasopressors, including norepinephrine, epinephrine, dopamine, and hydrocortisone before MB initiation. The mean baseline VIS was 116.4±90.5, and the mean SBP was 81.3±19.0 mmHg.

Following MB administration, SBP demonstrated a consistent upward trend over the 24-hour observation period, whereas changes in VIS were variable. At 24 hours post-treatment, the mean VIS decreased to 109.9±75.8, corresponding to a mean relative reduction of 6.5%, while mean SBP increased to 96.5±17.3 mmHg, representing a mean relative increase of 18.7%. Statistical testing demonstrated a significant increase in SBP (Wilcoxon signed-rank test, Z=-2.03, p=0.04), whereas the change in VIS did not reach statistical significance (Z=-1.06, p=0.29). A time-series analysis using the Friedman test showed a significant rise in SBP across time points [$\chi^2(4)=9.6$, p=0.048], whereas variations in VIS were not significant [$\chi^2(4)=5.3$, p=0.26].

Individual hemodynamic responses varied: VIS decreased in 5 patients (50%), remained unchanged in 2 patients (20%), and increased in 3 patients (30%). However, SBP improved in all patients, with the greatest relative increase (+142.8%) observed in a patient with amlodipine intoxication. No MB-related adverse effects (e.g., hemolysis, serotonin syndrome, methemoglobinemia) were observed.

The duration of MB therapy ranged from 1 to 6 days (mean 2.6±1.4). A loading dose (1-2 mg/kg) was administered to 6 patients, followed by a continuous infusion at 0.25-1 mg/kg/h. Six patients (60%) underwent CRRT, and four (40%)

Table 1. Clinical characteristics, therapies, and outcomes of patients receiving methylene blue (MB)

Patient no	Age/sex	Primary diagnosis	PRISM III	PELOD	Pre-MB VIS	Steroid	Pre-MB SBP (mmHg)	ECMO	CRRT	MB dose	Duration (days)	Post-MB VIS	Post-MB SBP (mmHg)	Adverse effects	Outcome
1	11 y, F	BMT and septic shock	11	22	80	Yes	102	Yes	Yes	LD 1 mg/kg+MD 0.25 mg/kg/h	6	30	112	None	Died (day 1)
2	17 y, M	Septic shock, MODS	8	12	35	Yes	67	Yes	Yes	MD 1 mg/kg/h	1	35	72	None	Died (day 1)
3	17 y, M	Crush syndrome	8	3	90	Yes	56	No	Yes	MD 0.5 mg/kg/h	1	30	136	None	Died (day 20)
4	3 m, F	Atypical teratoid rhabdoid tumor	8	12	216	Yes	72	No	No	MD 1 mg/kg/h	1	216	78	None	Died (day 1)
5	1 y, F	Liver transplantation	14	12	135	Yes	73	No	Yes	LD 1 mg/kg+MD 1 mg/kg/h	3	135	86	None	Died (day 1)
6	8 y, F	Crush syndrome	6	1	114	Yes	119	No	Yes	MD 1 mg/kg/h	1	114	120	None	Died (day 1)
7	19 y, F	Cystic fibrosis, CRF, pulmonary HT	4	1	154	Yes	104	Yes	No	MD 1 mg/kg/h	2	55	110	None	Died (day 28)
8	6 y, M	Hydrocephalus, CP, septic shock	8	12	100	Yes	72	No	No	LD 1 mg/kg+MD 1 mg/kg/h	3	88	103	None	Died (day 11)
9	22 m, M	Hirschsprung disease, sepsis	15	20	140	Yes	65	Yes	No	LD 1 mg/kg+MD 1 mg/kg/h	4	212	106	None	Died (day 1)
10	14 y, F	Amlodipine intoxication	8	11	100	Yes	101	No	No	LD 1 mg/kg+MD 1 mg/kg/h	3	15	119	None	Survived

PRISM III: Pediatric risk of mortality III, PELOD: Paediatric logistic organ dysfunction, VIS: Vasoactive-inotropic score, SBP: Systolic blood pressure, ECMO: Extracorporeal membrane oxygenation, CRRT: Continuous renal replacement therapy, BMT: Bone marrow transplantation, LD: Loading dose, MODS: Multiple organ dysfunction syndrome, MD: Maintenance dose, CRF: Chronic respiratory failure, HT: Hypertension, CP: Cerebral palsy

Table 2. Average clinical characteristics, therapies, and outcomes of patients receiving methylene blue (MB)

Variable	Minimum	Maximum	Mean ± SD
Age (years)	0.25	19	9.4±6.5
PRISM III score	4	14	9±3.2
PELOD score	1	20	10.6±5.9
Pre-MB VIS	35	216	116.4±90.5
Pre-MB SBP (mmHg)	56	119	81.3±19.0
Duration of MB use (days)	1	6	2.5±1.4
Post-MB VIS	30	216	109.9±75.8
Post-MB SBP (mmHg)	72	120	96.5±17.3

SD: Standard deviation, PRISM III: Pediatric risk of mortality III, PELOD: Paediatric logistic organ dysfunction, VIS: Vasoactive-inotropic score, SBP: Systolic blood pressure

received venoarterial ECMO. In all patients receiving CRRT or ECMO, SBP increased after MB administration, whereas reductions in VIS were inconsistent. Two ECMO patients demonstrated reductions in VIS and improvements in perfusion parameters, while others required stable vasopressor support. Despite short-term hemodynamic improvement, overall mortality remained high. Nine patients (90%) died during their PICU stay, whereas one patient—diagnosed with amlodipine intoxication—survived and was discharged in good clinical condition.

Figures 1 and 2 illustrate individual temporal changes in VIS and SBP following MB administration over the first 24 hours.

Discussion

This study describes one of the few pediatric series evaluating MB in catecholamine-resistant shock. MB administration was associated with a statistically significant short-term increase in SBP, whereas the reduction in the VIS was modest and was not statistically significant. Taken together, these findings indicate

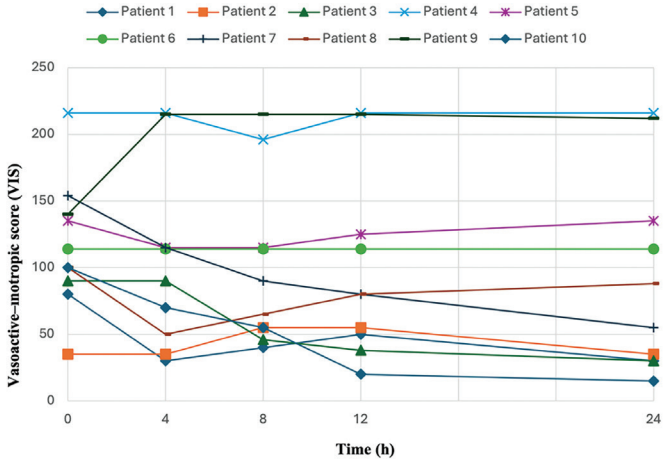

Figure 1. Individual vasoactive-inotropic score trajectories over 24 hours following methylene blue administration

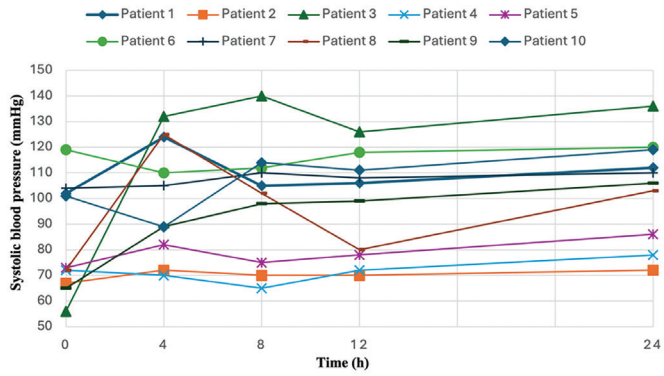

Figure 2. Individual systolic blood pressure trajectories over 24 hours following methylene blue administration

a transient hemodynamic improvement without evidence of a sustained reduction in vasoactive support, and they should be interpreted cautiously, given the small sample size and the lack of a control group.

The hemodynamic response observed after MB use is consistent with its mechanism of action through inhibition of nitric oxide synthase and sGC, which helps restore vascular tone and catecholamine responsiveness.[12,13] However, in our cohort, the limited improvement in VIS and the persistently high mortality rate (90%) likely reflect the advanced stage of shock and extensive multi-organ dysfunction at the time of MB initiation rather than treatment inefficacy.

Although a statistically significant increase in SBP was observed, this improvement did not translate into a survival benefit. This apparent discrepancy between short-term hemodynamic improvement and high mortality highlights the clinical context in which MB was used. In our study, MB was administered predominantly as a late rescue therapy in a highly selected population of critically ill children, many of whom required CRRT and/or ECMO support. Under these circumstances, MB may provide temporary physiological stabilization without altering the overall disease trajectory.

Previous pediatric studies evaluating MB in refractory shock have reported heterogeneous outcomes. Otero Luna et al.[27] reported improved blood pressure and reduced vasopressor requirements following MB administration, with lower reported mortality rates and limited use of advanced organ support. Similarly, Bitterman et al.[28] described favorable short-term hemodynamic responses in selected pediatric patients, most of whom did not require ECMO or CRRT at the time of MB initiation. In contrast, our cohort was characterized by a markedly greater severity of illness, a frequent need for ECMO and CRRT, and predominantly late administration of MB as rescue therapy. These differences likely explain the higher mortality observed in our study and highlight the unique

contribution of our series, which reflects real-world use of MB in the most critically ill pediatric patients.

The timing of MB appears to be crucial. Early administration, before irreversible endothelial injury occurs, may enhance efficacy.[7,9,12] In our cohort, MB was mostly used as a late rescue therapy, which may have limited its benefit. Nonetheless, no MB-related complications were observed, consistent with previous safety reports.[10,12,27] Particular caution should be exercised in patients with glucose-6-phosphate dehydrogenase deficiency or in those receiving serotonergic medications, as MB may precipitate hemolysis or serotonin syndrome.

MB administration in children with catecholamine-resistant shock was associated with a short-term improvement in SBP, without an observable survival benefit. Larger prospective studies are needed to clarify the optimal timing, dosing, and patient selection for MB therapy in pediatric shock.

Study Limitations

This study has several limitations. It was a retrospective, single-center analysis with a small sample size, thereby limiting the generalizability of the findings and precluding causal inference. The absence of a control group further restricts the interpretation of treatment effects. In addition, the timing and dosing of MB were not standardized, and concomitant therapies such as corticosteroids, vasopressin, CRRT, and ECMO may have influenced outcomes. Hemodynamic assessment was primarily based on changes in SBP and VIS; diastolic blood pressure and mean arterial pressure were not systematically recorded or compared; perfusion or biochemical markers were not available. Furthermore, blood pressure measurements were not standardized with respect to invasive versus noninvasive monitoring, and the cohort's small, heterogeneous composition with respect to inotrope selection and dosing precluded meaningful within-group comparisons of the MB effect. Finally, long-term follow-up data on survival or organ recovery were not available. Larger prospective multicenter studies are needed to confirm the safety and efficacy of MB in pediatric catecholamine-resistant shock.

Conclusion

Methylene blue was associated with a short-term increase in systolic blood pressure in children with catecholamine-resistant shock, but its effect on vasoactive support was inconsistent and mortality remained high. Although no treatment-related adverse events were observed, larger prospective studies are needed to determine its optimal timing, dosing, safety, and clinical benefit.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ankara University Human Research Ethics Committee (approval no: I04-406-24, date: 11.06.2024).

Informed Consent: Written informed consent for treatment and data use was obtained from the families of all participants.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: D.E.D., T.K., Concept: D.E.D., M.H., T.K., Design: D.E.D., A.D.A., T.K., Data Collection or Processing: D.E.D., H.U., B.B., E.E., Analysis or Interpretation: D.E.D., E.E., Literature Search: D.E.D., Writing: D.E.D., M.H., A.D.A.

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References

1. Puntillo F, Giglio M, Pasqualucci A, Brienza N, Paladini A, et al. Vasopressor-sparing action of methylene blue in severe sepsis and shock: a narrative review. Adv Ther. 2020;37:3692-706.
2. Sakr Y, Reinhart K, Vincent JL, Sprung CL, Moreno R, et al. Does dopamine administration in shock influence outcome? Results of the sepsis occurrence in acutely Ill patients (SOAP) study. Crit Care Med. 2006;34:589-97.
3. Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med. 2014;40:1795-815.
4. Vincent JL, De Backer D. Circulatory shock. N Engl J Med. 2013;369:1726-34.
5. Hiemstra B, Eck RJ, Keus F, van der Horst ICC. Clinical examination for diagnosing circulatory shock. Curr Opin Crit Care. 2017;23:293-301.
6. Scheeren TWL, Bakker J, De Backer D, Annane D, Asfar P, et al. Current use of vasopressors in septic shock. Ann Intensive Care. 2019;9:20.
7. Buckley MS, Barletta JF, Smithburger PL, Radosevich JJ, Kane-Gill SL. Catecholamine vasopressor support sparing strategies in vasodilatory shock. Pharmacotherapy. 2019;39:382-98.

8. Tchen S, Sullivan JB. Clinical utility of midodrine and methylene blue as catecholamine-sparing agents in intensive care unit patients with shock. J Crit Care. 2020;57:148-56.
9. Jentzer JC, Vallabhajosyula S, Khanna AK, Chawla LS, Busse LW, et al. Management of refractory vasodilatory shock. Chest. 2018;154:416-26.
10. Stawicki SP, Sims C, Sarani B, Grossman MD, Gracias VH. Methylene blue and vasoplegia: who, when, and how? Mini Rev Med Chem. 2008;8:472-90.
11. Shapeton AD, Mahmood F, Ortoleva JP. Hydroxocobalamin for the treatment of vasoplegia: a review of current literature and considerations for use. J Cardiothorac Vasc Anesth. 2019;33:894-901.
12. Hosseinian L, Weiner M, Levin MA, Fischer GW. Methylene blue: magic bullet for vasoplegia? Anesth Analg. 2016;122:194-201.
13. Jang DH, Nelson LS, Hoffman RS. Methylene blue for distributive shock: a potential new use of an old antidote. J Med Toxicol. 2013;9:242-9.
14. Peer G, Itzhakov E, Wollman Y, Chernihovsky T, Grosskopf I, et al. Methylene blue, a nitric oxide inhibitor, prevents haemodialysis hypotension. Nephrol Dial Transplant. 2001;16:1436-41.
15. Paciullo CA, McMahon Horner D, Hatton KW, Flynn JD. Methylene blue for the treatment of septic shock. Pharmacotherapy. 2010;30:702-15.
16. Lee EP, Chu SC, Hsia SH, Chen KF, Chan OW, et al. Comparison of predictive powers for mortality between systemic vascular resistance index and serum lactate in children with persistent catecholamine-resistant shock. Biomed Res Int. 2020;2020:1341326.
17. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41:580-637.
18. Gemke RJ, Bonsel GJ, Van Vught AJ. Effectiveness and efficiency of a Dutch pediatric intensive care unit: validity and application of the pediatric risk of mortality score. Crit Care Med. 1994;22:1477-84.
19. Proulx F, Gauthier M, Nadeau D, Lacroix J, Farrell CA. Timing and predictors of death in pediatric patients with multiple organ system failure. Crit Care Med. 1994;22:1025-31.
20. Graciano AL, Balko JA, Rahn DS, Ahmad N, Giroir BP. The pediatric multiple organ dysfunction score (P-MODS): development and validation of an objective scale to measure the severity of multiple organ dysfunction in critically ill children. Crit Care Med. 2005;33:1484-91.
21. Leteurtre S, Martinot A, Duhamel A, Gauvin F, Grandbastien B, et al. Development of a pediatric multiple organ dysfunction score: use of two strategies. Med Decis Making. 1999;19:399-410.
22. Leteurtre S, Martinot A, Duhamel A, Proulx F, Grandbastien B, et al. Validation of the paediatric logistic organ dysfunction (PELOD) score: prospective, observational, multicentre study. Lancet. 2003;362:192-7.
23. Pollack MM, Dean JM, Butler J, Holubkov R, Doctor A, et al. The ideal time interval for critical care severity-of-illness assessment. Pediatr Crit Care Med. 2013;14:448-53.
24. Bock KR. Renal replacement therapy in pediatric critical care medicine. Curr Opin Pediatr. 2005;17:368-71.
25. Garzotto F, Zanella M, Ronco C. The evolution of pediatric continuous renal replacement therapy. Nephron Clin Pract. 2014;127:172-5.
26. Kellum JA, Angus DC, Johnson JP, Leblanc M, Griffin M, et al. Continuous versus intermittent renal replacement therapy: a meta-analysis. Intensive Care Med. 2002;28:29-37.
27. Otero Luna AV, Johnson R, Funaro M, Canarie MF, Pierce RW. Methylene blue for refractory shock in children: a systematic review and survey practice analysis. Pediatr Crit Care Med. 2020;21:e378-86.
28. Bitterman Y, Hubara E, Hadash A, Ben-Ari J, Annich G, et al. Methylene blue administration for distributive shock states in critically ill children. Isr Med Assoc J. 2020;22:404-8.