Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1576395

J Health Sci Med. 2025;8(2):249-253

Evaluation of intravenous iloprost use in critically ill pediatric patients: a single-center experience

Merve Mısırlıoğlu[1], Mehmet Alakaya[1], Ali Ertuğ Arslanköylü[1], Abdulkadir Bilgiç[2]

[1]Department of Pediatric Intensive Care, Faculty of Medicine, Mersin University, Mersin, Turkiye
[2]Department of Cardiovascular Surgery, Faculty of Medicine, Mersin University, Mersin, Turkiye

Cite this article as: Mısırlıoğlu M, Alakaya M, Arslanköylü AE, Bilgiç A. Evaluation of intravenous iloprost use in critically ill pediatric patients: a single-center experience. *J Health Sci Med.* 2025;8(2):249-253.

Received: 30.10.2024 ◆ **Accepted**: 06.02.2025 ◆ **Published**: 21.03.2025

ABSTRACT

Aims: Iloprost is a prostacyclin analog that has vasodilatation properties at the systemic level, inhibiting platelet aggregation and adhesion and triggering angiogenesis. Our experience with intravenous (IV) administration of iloprost as a vasodilator in pediatric intensive care units is limited. The present study investigates the characteristics of patients subjected to IV iloprost therapy and their response to treatment.

Methods: A 15-month period, all patients who received IV iloprost treatment were included. Data including age, gender, reason for hospitalization, cause of vascular damage, affected vessel, iloprost dosage, treatment duration, necessity of surgery, and occurrence of treatment-related complications were retrieved from retrospective patient files.

Results: During the study, IV ten patients receiving iloprost treatment were examined. The starting dose of the drug was 0.5 ng/kg/min in all patients, and the initial dose was continued in seven patients. Duration of iloprost use was 17.8±10.8 (min 1, max 28) days. 50% (n=5) of the reasons for hospitalization were non-traumatic reasons. Amputation was performed in three patients (30%). In the clinical classification of those with damage to the extremities, there were four patients in stage 1 (44.5%), two patients in stage IIa (22.2%), and three patients in stage IIb (33.3%). Amputation was applied to three patients in stage IIb, and this is the patient group where the dose was started at a dose of 0.5 ng/kg/min and the dose was increased.

Conclusion: Intravenous iloprost treatment is a safe therapeutic option with minimal side effects, beneficial for preventing hypoxia and tissue cellular damage in cases of vascular injury.

Keywords: Child, iloprost, pediatric intensive care, vasodilation

INTRODUCTION

Iloprost is a prostacyclin analog that has vasodilatation properties at the systemic level and triggers angiogenesis by inhibiting platelet aggregation and adhesion. The administration of intravenous (IV) iloprost infusions has come to the fore as a new treatment alternative in acute arterial occlusive diseases in recent years.[1,2] Although iloprost is commonly used as an inhaler for treating pulmonary hypertension in pediatric intensive care units (PICU), there is insufficient experience regarding its use in vasodilator therapy. This lack of experience is particularly pronounced with its IV administration.

Acute arterial occlusive diseases are clinical syndromes that occur as a result of arterial tissue or organ ischemia. Acute limb ischemia develops as a result of a sudden decrease in arterial perfusion in the limb. Symptoms and signs of acute limb ischemia vary depending on the duration of ischemia and the location of arterial obstruction. Vasculopathies occur secondary to septic shock, peripheral artery disease, iatrogenic vascular injury, or as a result of acute traumatic ischemia.[1,2]

Acute traumatic ischemia is the general definition of injuries caused by a high-energy trauma that can cause skin, soft tissue, bone, tendon, nerve, or vascular damage that blocks blood flow to the tissue and is a part of crush syndrome. It appears as a result of many situations that threaten tissue integrity, such as open fractures, gunshot and sharp object injuries, and frostbites. Acute limb ischemia also occurs as a serious complication of septic shock. Ischemia in the extremities may occur as a result of local inflammation of the skin, hypoperfusion, severe vasoconstriction, hypoxia, and disseminated intravascular coagulation.[1,2]

It has been reported that iloprost therapy has positive effects on healing trophic lesions, relieving rest pain, decreasing amputation rates, and reducing overall mortality.[1,2] These positive effects are achieved by increasing iloprost microcirculation. The ideal dose for iloprost treatment should be one that minimally affects blood pressure and has minimal side effects. In many clinical studies, it has been demonstrated

Corresponding Author: Merve Mısırlıoğlu, mervemisirlioglu@gmail.com

that administering IV iloprost infusion at a dose of 0.5-2 nanograms (ng)/ kilogram (kg)/ minute (min) for six hours daily achieves the desired optimal results safely and without serious side effects.[1-3] This retrospective study aimed to contribute to the literature by examining the characteristics and treatment response of IV iloprost administered patients who were followed up and treated as inpatients in PICU over 15 months.

METHODS

All patients aged between one month and 18 years who received IV iloprost treatment during a 15-month period starting from January 2023 were included in our tertiary PICU. Data on patients' age, gender, reason for admission to the PICU, duration of PICU and hospital stay, cause of vascular damage, affected vessel, iloprost dose, treatment duration, clinical classification of extremity ischemia, treatment outcomes, use of anticoagulants, necessity of surgery and treatment-related complications were obtained from retrospective patient files. Approval for the study was received from Mersin University Non-interventional Clinical Researches Ethics Committee (Date: 22.04.2024, Decision No: 2024/364). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The reasons for admission to PICU were classified as trauma and non-traumatic causes. Causes of vascular damage were categorized into acute traumatic ischemia, damage secondary to septic shock and iatrogenic vascular injury. Amputation, if performed, was further divided into minor and major categories. Minor amputation refers to limb loss that occurs distal to the metatarsophalangeal joint in the lower extremities and metacarpophalangeal joint in the upper extremities, without significant impact on daily function or work capacity. Major amputation was defined as all amputations starting from the transmetatarsal level in the lower extremity and the metacarpal level in the upper extremity. Acute limb ischemia is a decrease in blood supply that endangers tissue viability. Clinical classification is made by evaluating loss of sensation, muscle dysfunction, and arterial and venous Doppler findings (Table 1).[4,5]

Statistical Analysis

Statistical Package for Social Sciences (SPSS for Windows 20.0 version) statistical program was used for statistical evaluation. Number and percentage values are used in categorical data; minimum, maximum, and mean±standard deviation values are given for descriptive statistical measurements.

RESULTS

Included in the study were 10patients aged between 1 month and 18 years who received IV iloprost therapy in the tertiary pediatric intensive care unit over a 15-month period, as of January 2023, 60% (n=6) of whom were female. The age was 9.7±5.3 (min 1, max 16) years and the body weight was 35.0±21.87 (min 6, max 70) kg. The PICU stay was 54.8±62.2 (min 5, max 180) days and the hospital stay was 68.4±59.3 (min 15, max 185) days. Initially, all patients started iloprost at a dose of 0.5 ng/kg/min. During treatment, the dose was increased to 2.0 ng/kg/min for 1 patient, 1.0 ng/kg/min for 2 patients, while 7 patients continued with the initial dose. No complications related to the drug were detected and the duration of iloprost use was 17.8±10.8 (min 1, max 28) days.

The reasons for admission to the PICU were 50% (n=5) trauma and 50% (n=5) non-traumatic reasons. Forty percent (n=4) of the patients had compartment syndrome and 50% (n=5) crush syndrome. When the areas where vascular damage develops are examined, 20% (n=2) are in the upper extremities, 70% (n=7) are in the lower extremities, and one patient is in the abdomen. The injured vessel in the abdominal area was the portal vein (V. portae hepatitis), while the other injuries (n=9, 90%) were arterial vessel injuries. Among the damaged arteries, 3 of them (30%) were arteria (A) tibialis anterior, 2 (20%) were A. tibialis posterior, 2 (20%) were A. poplitea, 1 (10%) was A. radialis and 1 (10%) was A. ulnaris.

Anticoagulant treatment could be given to five of the patients (50%); low molecular weight heparin was used in anticoagulant therapy. Amputation was performed in three patients (30%), minor amputation was performed in one (10%) patient, and major amputation was performed in two (20%) patients. The characteristics of the patients are shown in Table 2. When nine patients with damage to the vessels in the extremities were examined in terms of clinical classification, it was found that there were four patients in stage 1 (44.5%), two patients in stage IIa (22.2%), and three patients in stage IIb (33.3%). Amputation was applied to three patients in stage IIb, and this is the patient group in which the dose was started at a dose of 0.5 ng/kg/min and the dose was increased.

DISCUSSION

At 15-month period, IV parenteral ten patients receiving iloprost treatment were examined. The starting dose of the drug was 0.5 ng/kg/min in all patients, and the initial dose was continued in seven patients. Duration of iloprost use was min 1 days, and max 28 days. 50% (n=5) of the reasons for hospitalization were non-traumatic reasons. Amputation was performed in three patients. In the clinical classification of

Table 1. Clinical classification of acute limb ischemia[4,5]

Stage		Loss of sensation	Muscle dysfunction	Arterial Doppler flow	Venous Doppler flow
1. Alive	No direct threat	No	No	Yes	Yes
2a. Threat at the border	Can be saved with urgent intervention	None/minimal	No	None	Yes
2b. Serious threat	Can be saved with very urgent intervention	Common, with rest pain	Mild	None	Yes
3. Irreversible ischemia	Major tissue damage, permanent nerve damage	Deep, anesthetic	Deep	None	None

Table 2. Assessment of patients receiving iloprost therapy

Patients	Age (years)	Gender	Reason for hospitalization	Affected vessel	Initial iloprost dose (ng/kg/min)	Max Iloprost dosage (ng/kg/min)	Number of days using iloprost	Anticoagulant treatment	Amputation
Patient 1	1	Female	Septic shock, menigococcemia	Bilateral popliteal artery	0.5	2.0	21	+	Bilateral minor amputation
Patient 2	15	Male	Trauma	Left ulnar artery	0.5	0.5	21	+	-
Patient 3	8	Male	Traumatic pancreatitis	Portal vein	0.5	0.5	1	-	-
Patient 4	6	Male	Septic shock, autoimmune encephalitis	Bilateral radial artery	0.5	0.5	28	+	-
Patient 5	12	Female	Septic shock, purpura fulminans	Left tibilias anterior artery	0.5	0.5	28	-	-
Patient 6	16	Female	Trauma	Left tibialis posterior artery	0.5	0.5	28	+	-
Patient 7	13	Female	Septic shock, purpura fulminans	Bilateral tibialis posterior	0.5	0.5	28	+	-
Patient 8	2	Female	Trauma	Right popliteal artery	0.5	1.0	6	-	Right major amputation
Patient 9	15	Female	Trauma	Left tibialis anterior artery	0.5	0.5	5	-	-
Patient 10	8	Male	Trauma	Left tibialis anterior artery	0.5	1.0	12	-	Left major amputation

ng: Nanogram, kg: Kilogram, min: Minute

those with damage to the extremities, there were four patients in stage 1, two patients in stage IIa, and three patients in stage IIb. Amputation was applied to three patients in Stage IIb, and this is the patient group where the dose was started at a dose of 0.5 ng/kg/min and the dose was increased. In this study, we aimed to present our experiences with parenteral iloprost use to the literature.

Damage to vessels, whether caused by trauma, iatrogenic factors or shock, leads to a slowdown or deterioration of circulation, resulting in hypoxia and cellular damage in the tissue supplied by the affected vessel. Our goal in treatment is to increase tissue oxygenation of the damaged area and improve perfusion.[6,7]

In vasodilator treatment in the adult age group, there are studies and experiences regarding IV iloprost.[2,3] Although iloprost is frequently used as an inhaler in the treatment of pulmonary hypertension in PICU, our experience with IV administration in vasodilator therapy is limited.[1,4,8,9] In this study, we present our experiences with ten critically ill pediatric patients who received IV iloprost treatment due to vascular damage.

In a study conducted by Zulian et al.,[1] IV treatment was administered to 15 pediatric patients with severe finger ischemia due to connective tissue disease. It has been reported that iloprost infusion is a safe and effective treatment for ischemic finger and digital ulcers. Tanyıldız et al.,[9] in their 2023 publication on managing earthquake victims in PICU, reported administering vasodilator treatment to eight patients. Although they mentioned using nitroglycerin, milrinone, and iloprost infusion, they did not specify the number of patients treated with iloprost. IV iloprost was administered as an infusion at a rate of 0.5-1 ng/kg/min.

Headaches, rash, nausea, and vomiting are common drug-related side effects. The ideal dose for iloprost treatment should be the dose that does not affect blood pressure and has minimal side effects.[10] In our study, no drug-related complications were detected in our patients. While no complications were observed in 47% (n=7) of the patients during IV iloprost treatment administered to children with connective tissue disease; drug-related complications seen in other patients have been reported to include nausea, vomiting, headache, and hypotension.[1] In our study, the starting dose of medication was 0.5 ng/kg/min in all patients. The dose was increased to 2.0 ng/kg/min in one patient and 1.0 ng/kg/min in two patients, and the initial dose was continued in seven patients. Studies have shown that the lowest infusion rate at which vasodilatation and platelet aggregation inhibition begins is 0.5 ng/kg/min. It has been reported that high doses of iloprost do not increase the effect. It is believed that doses higher than 0.5-2.0 ng/kg/min do not further enhance the therapeutic effect of iloprost, potentially due to increased vasodilatation and blood leakage from the skin into the muscle tissue.[11-13] In our study, the maximum dose was found to be 2.0 ng/kg/min.

Distal limb ischemia is a serious complication of septic shock. Ischemia may occur in the extremities as a result of local inflammation of the skin, hypoperfusion, severe vasoconstriction, hypoxia and disseminated intravascular coagulation. One therapeutic method used to interrupt this series of events is iloprost, a prostacyclin analogue known for its systemic vasodilatory properties. It inhibits platelet aggregation and adhesion while promoting angiogenesis. It can prevent progression to necrosis and amputation in patients whose lesions are peripheral and have digital involvement.[2,3,8,14] In the article, four patients in the pediatric

age group who developed limb ischemia as a result of septic shock were presented. It was reported that two patients responded to iloprost treatment, while the response to iloprost treatment could not be evaluated in the other two patients who died due to multiple organ failure resulting from meningococcemia.[8] In our study, four patients received vasodilator treatment due to acute extremity ischemia resulting from septic shock. While cure was achieved in three patients, one patient underwent minor amputation. One of our patients received IV iloprost treatment for one day due to iatrogenic injury to the portal vein during an abdominal operation. Iloprost infusion was administered. While our average duration of iloprost use was 17.8±10.8 days, with a maximum of 28 days, this duration aligns with similar studies reported in the literature. Guidelines for critical limb ischemia also recommend parenteral iloprost treatment for 7-28 days.[15]

Acute artery occlusion is followed by clinical findings. Patients are monitored for pain in the relevant area, pulselessness, pallor, sensory impairment, and motor losses.[5] In addition, evaluation is performed with Doppler ultrasonography in the area with a clinical picture of acute limb ischemia. Doppler works on the principle of detecting the movement of blood and is used together with other diagnostic tests to detect vascular diseases. In a normal artery, the waveform is triphasic. During cardiac systole, there is forward flow in the artery. At the beginning of diastole, the flow reverses. The normal triphasic signal changes if stenosis develops in the vessel. If the stenosis is minimal, signal loss distal to the lesion or disappearance of the forward flow component in mid-diastole results in a biphasic signal. As the stenosis becomes more severe, the signal becomes monophasic. The location of the stenosis can be determined by evaluating the Doppler signal in different parts of the extremity.[16] Our patients were followed with repeated clinical examinations and Doppler ultrasonography examinations, and as a result of these evaluations, the number of days and dosage of parenteral vasodilator treatment were determined. Amputation may be life-saving in extremity gangrene that cannot be corrected despite all treatments. It should be performed at the appropriate time above the demarcation line formed in the unfed area. Three of our patients underwent an amputation.

Limitations

In the study, five patients received anticoagulant therapy in addition to iloprost treatment. This may have contributed to the treatment success of these patients. Not comparing the patients who received anticoagulant therapy and those was a limitation of the study. The biggest limitation of our study is that we could not statistically examine the factors that could affect it due to the lack of a sufficient number of cases. However, since there is limited information in the literature about the use of parenteral iloprost in pediatric intensive care patients, we wanted to convey our experiences in this study.

CONCLUSION

Intravenous iloprost therapy is a safe therapeutic approach with minimal side effects. It effectively prevents hypoxia and cellular damage in tissues supplied by damaged vessels, addressing circulation slowdown or deterioration caused by vessel injury. There is a need for further studies of this issue involving larger patient cohorts.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Mersin University Non-interventional Clinical Researches Ethics Committee (Date: 22.04.2024, Decision No: 2024/364).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Zulian F, Corona F, Gerloni V, et al. Safety and efficacy of iloprost for the treatment of ischaemic digits in paediatric connective tissue diseases. *Rheumatology (Oxford).* 2004;43(2):229-233. doi:10.1093/rheumatology/keg480
2. Martins-Rocha T, Matias JP, Vicente Ferreira M, Mota B, Brito I. Post-infectious digital ischemia successfully treated with iloprost in a child. *Reumatol Clin (Engl Ed).* 2020;16(5 Pt 1):364-365. doi:10.1016/j.reuma.2018.05.003
3. Meini S, Dentali F, Melillo E, de Donato G, Mumoli N, Mazzone A. Prostanoids for critical limb ischemia: a clinical review and consideration of current guideline recommendations. *Angiology.* 2020;71(3):226-234. doi:10.1177/0003319719889273
4. Boga M. Acute limb ischemia. *Turk J Family Pract.* 2009;13(1):11-15. doi:10.54308/tahd.2024.802
5. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg.* 1997;26(3):517-38. doi:10.1016/s0741-5214(97)70045-4
6. Lerner A, Reis D, Soudry M. Primary Treatment. In: Severe Injuries to the Limbs. Springer, Berlin, Heidelberg. 2007, p. 5-11.
7. Meini S, De Franco V, Auteri A, Setacci C, Di Renzo M, Pieragalli D. Short-term and long-term effects of one-week treatment with intravenous iloprost in critical limb ischemia patients (Leriche-Fontaine stage III and IV). *Int Angiol.* 2005;24(1):64-69.
8. García Soler P, Milano Manso G, Camacho Alonso JM, Manuel González J. Iloprost para el tratamiento de la isquemia digital en el shock séptico pediátrico. *Med Clin (Barc).* 2011;136(15):695-696. doi:10.1016/j.medcli.2009.12.012
9. Tanyildiz M, Ozden O, Ozbek L, et al. Management of an earthquake in a pediatric intensive care unit. *J Child.* 2023; 23(3): 21-30. doi:10.26650/jchild.2023.1341364
10. Watson HR, Smith FCT, Shearman P, Hildebrand M. Pharmacokinetics and pharmacodynamics of intra-graft iloprost in femorodistal bypass surgery. *Prostagl Leukotrien Essent Fatty Acids.* 1997;56(5):389-393. doi:10.1016/s0952-3278(97)90589-5

11. Müler B, Krast T, Stürzebecher S, Witt W, Schillinger E, Baldus B. Potential therapeutic mechanisms of stable prostacyclin (PGI2)-mimetics in severe peripheral vascular disease. *Acta Biomed Biochim.* 1988; 47(10-11):S40-S44.
12. Grant SM, Goa KL. Iloprost. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in peripheral vascular disease, myocardial ischemia and extracorporeal circulation procedures. *Drugs.* 1992;43(6):889-924. doi:10.2165/00003495-199243060-00008
13. Caspary L, Creutzig A, Alexander K. Intravenous infusion iloprost in arterial occlusive disease: dose-dependent effects on skin microcirculation. *Eur J Clin Pharmacol.* 1991;41(2):131-136. doi:10.1007/BF00265905
14. Pathan N, Faust SN, Levin M. Pathophysiology of meningococcal meningitis and septicaemia. *Arch Dis Child.* 2003;88(7):601-607. doi:10.1136/adc.88.7.601
15. Rooke TW, Hirsch AT, Misra S, et al. American College of Cardiology Foundation Task Force; American Heart Association Task Force. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013; 61(14):1555-1570. doi:10.1016/j.jacc.2013.01.004
16. Montorfano MA, Montorfano LM, Perez Quirante F, Rodríguez F, Vera L, Neri L. The FAST D protocol: a simple method to rule out traumatic vascular injuries of the lower extremities. *Crit Ultrasound J.* 2017;9(1):8. doi: 10.1186/s13089-017-0063-2