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Extremity Ischemia after Peripheral Vascular Intervention in Newborns with Congenital Heart Disease: Our Single Center Experience

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SOUHRN

Kontext: Akutní končetinová ischemie (acute limb ischemia, ALI) je v dětské populaci vzácné, avšak závažné postižení s významnou celoživotní morbiditou nebo mortalitou. Zpravidla se jedná o posttraumatický stav nebo je příčina iatrogenní.
Výsledky: V této studii bylo retrospektivně vyšetřeno 127 novorozenců s invazivním monitorováním hodnot arteriální krve na naší jednotce intenzivní péče v letech 2019–2021. Monitorování se provádělo na horních končetinách u 83 pacientů a na dolních končetinách u 44 pacientů. Akutní končetinová ischemie byla zjištěna u tří (6 %) pacientů s monitorováním dolní končetiny a u osmi (9 %) s monitorováním horní končetiny. Primárně se u pacientů prováděl zahřívání končetiny, infuze heparinu (10 μ/kg/h) i infuze perlinganitu (glycerol-trinitrátu) (0,5 μg/kg/h). Pokud to stav pacienta dovolil, neaplikovaly se vazokonstriktory (adrenalin, noradrenalin atd.). Všichni pacienti reagovali na farmakoterapii a konzervativní léčbu, takže ani v jednom případě nebylo nutno volit chirurgické řešení. U žádného pacienta ani nebylo nutno provést amputaci, protože se krevní oběh v končetinách postupně obnovil.
Závěry: Časná a správně zvolená a provedená intervence může významně snížit mortalitu a morbiditu ALI, která se ve skupině novorozenců vyskytuje vzácně. Stále se ještě vyvíjejí různé strategie léčby a množství zkušeností je omezené. I když se zdá, že chirurgické řešení je častější u dospělých pacientů, pozitivních výsledků u akutní končetinové ischemie – vzhledem k technické obtížnosti chirurgického výkonu a odlišné základní patofyziologii dětské populace – lze dosáhnout i u novorozenců důsledným sledováním jejich klinického stavu a farmakologicky.

Keywords:
Acute limb ischemia
Iatrogenic arterial trauma
Pediatric arterial access

ABSTRACT

Background: Acute limb ischemia (ALI) is a rare but serious condition that can cause significant lifetime morbidity or mortality in the pediatric population. It is usually post-traumatic or iatrogenic.
Results: In the study, 127 newborns who were followed up with arterial monitoring in our intensive care unit between 2019–2021 were screened retrospectively. Invasive arterial monitoring was performed on the upper extremities in 83 patients and the lower extremities in 44 patients. Acute extremity ischemia was observed in three (6%) patients who underwent lower extremity monitoring and eight (9%) patients with upper extremity ischemia. Primarily, extremity warming, heparin infusion (10 μ/kg/h), perliganit (Glycerol Trinitrate) infusion (0.5 μg/kg/h) were applied to the patients. Vasoconstrictor agents (adrenaline, noradrenaline etc.) have been avoided in patients whenever possible. All of the patients responded to medical and conservative treatment, and no surgical treatment was applied. Amputation was not applied to any of the patients, and their limb circulations were gradually restored.
Conclusions: Early and correct intervention can significantly reduce mortality and morbidity in ALI, which is rare in the newborn group. Management strategies are still evolving and experience is limited. Although the surgical approach seems to be more prominent in adult patients, positive results can be obtained in newborn acute limb ischemia with close clinical follow-up and medical approach due to technical difficulties and different underlying pathophysiology in the pediatric population.

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Background

Acute limb ischemia (ALI) is a rare but serious condition that can cause significant lifetime morbidity or mortality in the pediatric population. It is usually post-traumatic or iatrogenic. Because of the rarity of ALI in pediatric patients, physicians and surgeons caring for these patients are often guided by consensus guidelines that mostly extrapolate from the adult literature rather than well-designed prospective studies in the pediatric population.[1]

Clinical manifestations of ALI include pale or cold extremities, weak or absent pulse, and decreased or undetectable blood pressure.[2] Arterial catheters inserted for hemodynamic monitoring in the intensive care unit are one of the most common causes of iatrogenic limb ischemia in newborns with congenital heart disease. There is a 2% risk of arterial injury after femoral arterial catheterization.[3]

Little is known about the optimal management algorithm for limb salvage and morbidity prevention in patients with pediatric ALI. Given the historically poor outcomes of early surgical revascularization, anticoagulant therapy or observation may be the most appropriate first line of treatment.[4] In our study, we would like to share our experience with the literature in extremity ischemia after peripheral vascular intervention in newborns with congenital heart disease in our clinic.

Methods

In the study, 127 newborns who underwent arterial monitoring in our intensive care unit between 2019–2021 were retrospectively screened. The neonatal period includes the first 28 days of each baby's birth, regardless of the gestational week.

Invasive arterial monitoring was performed on the upper extremities in 83 patients and the lower extremities in 44 patients. Acute extremity ischemia was observed in 3 (6%) patients who underwent lower extremity monitoring and in 8 (9%) patients with upper extremity ischemia (**Fig. 1**).

When diagnosing the patients, a hand-held Doppler Huntleigh Diagnostic Doppler (Model No. SD2, manufactured by Huntleigh Healthcare, Cardiff UK, 2010) with 8 MHz probe was used primarily for detailed physical examination, distal pulse control, and to determine and follow the course of the arteries. The diagnosis was confirmed by the bedside Doppler USG for the suspected patients by the radiologist.

Extremity warming, heparin infusion (10 μg/kg/h), perliganide infusion (0.5 μg/kg/h) were applied primarily to the patients, and vasoconstrictor agents (adrenaline, noradrenaline etc.) were tried to be avoided in patients where possible. All of the patients responded to medical and conservative treatment, and no surgical treatment was applied.

Our study is a retrospective, observational, single-center case series study. Permission was obtained from the hospital administration for the study. It was done retrospectively, in accordance with the Declaration of Helsinki, taking into account the ethical rules.

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. While evaluating the study data, descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used.

Results

Ischemia was detected in 3 (6%) of 44 patients who underwent lower extremity monitoring (**Fig. 1**). The weight of patients who developed lower extremity ischemia ranged from 2.9 to 4 kg, with an average of 3.43±0.55 kg. Their ages ranged from 6 to 15 days, with a mean of 10±4.58 days. The length of stay in the intensive care unit of these patients ranged from 9 to 20 days, with an average of 14.66±5.50 days. Out of the patients, 2 (66.6%) were male and 1 (33.4%) was female. Norwood stage 1, arterial switch and coarctation operations were performed on the patients. One of the patients (33.4%) died due to low cardiac output after Norwood stage 1.

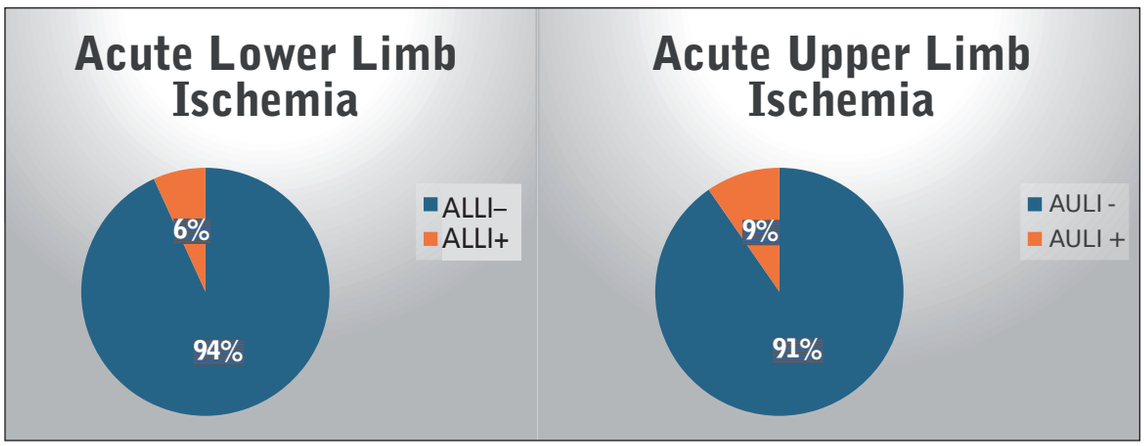

Fig. 1 – Figure showing the rate of development of limb ischemia after lower and upper extremity arterial monitoring.

Fig. 2 – Image of a 9-day-old patient who developed lower extremity ischemia.

Fig. 3 – The view of the 28-day-old patient who developed upper extremity ischemia.

Upper extremity monitoring was performed in 83 of the patients and acute extremity ischemia was observed in 8 (9%) patients. The weight of patients who developed upper extremity ischemia ranged from 2.4 to 4.1 kg, with an average of 3.46±0.61 kg. Their ages ranged from 7 to 28 days, with a mean of 16.75±5.92. The length of stay in the intensive care unit of these patients ranged from 8 to 48 days, with a mean of 19.87±16.65. Of the patients, 5 (62.5%) were male and 3 (37.5%) were female.

One of the patients underwent Norwood stage 1, two of them arterial switch, two of them modified Blalock-Taussig shunt, one of them aortico-pulmonary window repair, 1 of them pulmonary artery band ligation, 1 of them total abnormal pulmonary venous return anomaly (TAPVD) repair (**Figs 2, 3**).

Two patients (25%) died; the patient who underwent TAPVD due to renal problems and sepsis, and the patient who underwent shunt operation due to low cardiac output.

Amputation was not applied to any of the patients, and the circulation of the extremities was provided gradually.

Discussion

Newborns are at risk for in situ thrombosis and embolic events. There is a hypofibrinolytic neonatal state characterized by an immature coagulation mechanism with a deficiency of antithrombin III, protein C, and protein S, placing the neonate at risk for thrombotic disease until this balance is corrected. Polycythemia, which often accompanies the congenital patient group, increases the tendency to microthrombosis by creating hyperviscosity. The most common cause of peripheral ischemia in this group are iatrogenic traumas.[5,6] When 127 newborns who underwent arterial monitoring in our clinic between 2019–2021 were examined, we found acute extremity ischemia in 11 patients.

Arterial catheters are frequently used for hemodynamic monitoring and blood gas analysis after congenital heart surgery. Ischemia may occur after catheterization and with both well-placed and misplaced catheters. The mechanism of this ischemia is due to vasospasm, thrombosis, or embolism from the distal aorta and its branches after catheterization. The first step in treatment should be removal of the responsible catheter.[5] In our clinical practice, we always remove the arterial catheter in extremity ischemia that develops after arterial catheterization. We monitor patients who we think are hemodynamically unstable by making new arterial interventions from different regions.

If medical treatment fails, surgical thrombectomy or embolectomy can be considered to improve extremity perfusion and good results can be obtained.[7] In our clinical practice, we did not have any patient who did not respond to medical treatment, and we did not have any patient who underwent amputation. However, one of the patients (33.4%) who developed lower extremity ischemia died due to low cardiac output after Norwood stage 1. One of the patients who developed upper extremity ischemia, who underwent TAPVD, died due to renal problems and sepsis. The other patient who underwent shunt operation died due to low cardiac output.

Ultrasound-guided arterial cannulation can reduce the risk of incorrect puncture and increase the success rate of cannulation. This technique may reduce the risk of bleeding from the puncture site, pseudoaneurysm, and arteriovenous fistula, which are among the common non-ischemic complications, but it probably does not reduce the risk of ischemic complications. Ischemic complications are closely related to the general and physiological condition of the patient.[8] In our clinical practice, we use USG in both arterial and venous interventions of all our patients. We believe that blinded punctures may have serious consequences in this patient group.

In this patient group, supportive treatment begins with adequate intravenous hydration and appropriate antibiotics should be given to patients with suspected infection. Hyperbaric oxygen therapy can be tried to reduce tissue loss after recanalization.[9] Our patient group

was receiving surgical prophylaxis and appropriate antibiotic therapy in the postoperative period. We did not have any patients who received hyperbaric oxygen therapy.

Fraken and colleagues argue that catheter size relative to vessel diameter makes a significant contribution to arterial spasm in infants. They found that femoral artery spasm was more likely to occur when the catheter diameter was 50% or more of the femoral artery diameter.[10] We use catheters with as small diameter as possible in the neonatal patient group because we think that intimal flaps caused by punctures contribute to acute arterial occlusion.

Biopsy samples from arteries with catheter-associated thrombosis show thin fibrin-platelet fresh thrombi with intracellular neutral fat deposits in macrophage-like cells in early stages associated with sites of injury to the vascular endothelium. As the catheterization time increases, the thrombus begins to organize.[11] We tend to remove arterial catheters as soon as we are sure that the patient does not need them, because these catheters pose a risk for infection as well as embolism.

Topical nitroglycerin therapy has been used with some success in a case series for the treatment of acute limb ischemia. It has been suggested that it may be beneficial in acute vasospasm after arterial catheterization.[12] We do not use topical nitroglycerin in our clinical practice, but we use low-dose glyceryl trinitrate (perlinganit), warming and vasoconstrictor drug dose reduction for peripheral vasodilation.

Interventional radiological management of acute limb ischemia can be difficult, but systemic heparinization with or without thrombolysis may be beneficial in selected patients. When using tPA, doses of 0.1–0.5 mg/kg/h have been described, with no clear benefit from using higher doses as previously described. It is not recommended in the patient group undergoing cardiovascular surgery because the risk of bleeding due to thrombolysis is unacceptably high.[13] In our clinical practice, we do not apply thrombolysis due to the high risk of bleeding in the postoperative period. We start heparin perfusion (10 µg/kg/h), monitor the heparin infusion with activated clotting time (ACT) and Aptt, and adjust the heparin dose according to ACT and Aptt.

Boyd et al. said that Milrinone, a PDE3 inhibitor, plays a role in improving ischemia-reperfusion injury in many organs, including kidney and liver, in animal studies. They also focused on the fact that its inhibitory effect on platelet aggregation and its anti-inflammatory properties may have additional benefits to PDE inhibition in reducing thrombus formation. However, there is no current evidence to support a beneficial effect of milrinone in attenuating ischemia-reperfusion injury in an extremity through a c-AMP-mediated mechanism.[14] In our routine practice. We use it very frequently because of its pulmonary and systemic arterial vasodilator effects. However, we are skeptical of its effects on limb ischemia and instead follow the literature.

In these patients, patients should undergo serial examinations to assess changes in limb perfusion and repeat Doppler USG within three to four weeks. It has been recommended to stop anticoagulation if adequate perfusion is achieved in the limb with examination and USG.[15] We evaluated the arterial patency of the patients in our patient group with Doppler USG before discharge. We adjusted the anticoagulation and other drugs of patients with adequate perfusion and no thrombus detected on USG according to their existing cardiac pathologies.

Surgical repair of arterial injuries in neonatal patients is difficult due to their small vascular size and frequent spasms. Currently, surgical treatment options for ALI include: thromboembolectomy using a balloon catheter, bypass surgery, thromboendarterectomy, patch plasty, and intraoperative thrombolysis.[16] In our last three years of experience, we did not have to apply any of these surgical methods.

It has been concluded that management by a multidisciplinary team including vascular surgeons, haematologists, medical imaging, and pediatric intensive care physicians and conservative treatment with anticoagulation is necessary to achieve a successful outcome in pediatric patients presenting with ALI.[1,17] In our clinical practice, we make decisions with our team of pediatric intensive care physician, pediatricians, anesthesiologists, and pediatric cardiovascular surgeons. We believe that leaving responsibility and management to one person will slow down this complex process and reduce its success.

Wang et al. argued that non-operative management of infants with ALI with anticoagulation or, in certain cases, observation alone, is safe and effective. They recommended non-surgical management as the first-line treatment for their babies with ALI.[4] In our clinical practice, we argue that medical treatment has positive results in this patient group and that surgical treatment should be reserved as the last option. In the literature, compartment syndrome and shortening of the limbs are listed among the complications and potential risks of medical follow-up. However, Wang et al. argued that this is similar with risks secondary to surgery.[4]

Limitations

Our study is a single-center retrospective study, and studies with appropriate and large designs evaluating possible strategies for the management of these conditions are required.

Conclusions

Early and correct intervention in ALI, which is rare in the newborn group, can significantly reduce mortality and morbidity in this patient group. Management strategies are still evolving and limited experience is available. Although the surgical approach seems to be more prominent in adult patients, positive results can be obtained in newborn acute limb ischemia with close clinical follow-up and medical approach due to technical difficulties and different underlying pathophysiology in the pediatric population.

Conflict of interest
None.

Funding
No funding was obtained for this study.

Ethical statement and consent to participate
The study protocol was approved by the hospital management. The study is retrospective, and consent to participate was waived by the IRB. The committee's reference number is not applicable. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication
Specific research consent was not obtained and waived. Before surgery, written informed consent to publish this information was obtained from study participants next of kin and/or parent/legal guardian.

Contributions
Study design by EA, KAK; data collection by EA and NÇ; writing by EA, FY, and KAK; supervising by HC, NÇ, and ET; final approval by all authors. All authors have read and approved the manuscript.

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